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PRINCIPLES OF HEPATIC SURGERY



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Principles of Hepatic Surgery

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Foreword

The foreword to this superb book has deliberately been written jointly by one old and one young academic surgeon involved in hepatobiliary surgery. The elder of us started his career with more limited access to medical publications, which were only available through printed scientific journals. International exchanges were mainly done during scientific congresses. Nowadays, the widespread use of the internet and the development of more and more sophisticated connected devices have allowed us to always stay updated and with endless amounts of information in our daily medical practice. For the younger of us, while these tools represent an endless source of knowledge, differentiating medical fads from actual scientific breakthroughs remains difficult. In hepatobiliary surgery, with the constant renewal of operative techniques (including the development of mini-invasive surgery), the ongoing evolution in our understanding of the liver regeneration process (which has allowed for the planning of complex operative strategies), and the increasing role of chemotherapeutic regimens in refining the indications for resection, it has become somewhat easy to get lost in the shuffle. This is clearly one of the main reasons why textbooks still play an important part in our medical training and practice. A surgical textbook must contain widely accredited knowledge from around the world and clearly describe state-of-the-art techniques, but it must also provide well-chosen insights regarding forthcoming trends that may represent the future of the field. Hence, the most difficult task is probably to anticipate which techniques and strategies may withstand the test of time and which ones will fade away without trace. By inviting input from some of the most renowned hepatobiliary clinicians in the world, Dr. Balzan and Dr. Gava have ensured the most relevant selection of information. We admire their undertaking of providing such extensive and important information in this "mini-Blumgart"; chapters have been meticulously selected and developed, providing a thorough overview of our specialty both for trainees and for senior surgeons. The relevant selection of suggested readings enables the reader to go even further in their understanding of every chapter, and represents a valuable feature of this book. Finally, the excellent illustrations and overall presentation of the book make it a true masterpiece, one that any reader would want on his or her bookshelf.

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I am delighted to have been asked to write this additional foreword. There is no doubt that this book will make a significant contribution to the development of Hepatobiliary Surgery as a specialty. The editors have managed to produce a text that is comprehensive yet easily readable. I am sure it will be of value to not only the young resident but also a point of reference for the established surgeon.

I congratulate the editors and am confident of the success of this book, which will occupy an important place on the bookshelf of many interested in the special skills needed for successful Hepatobiliary Surgery.

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Preface

The main goal of "Principles of Hepatic Surgery" is to introduce the reader to the modern era of liver surgery and to discuss its current features. This ambitious project was conceived as a means of covering both the fundamentals of liver surgery as well as cutting-edge progress in this exciting surgical area.

We sought to provide a pleasant reading experience through a concise but comprehensive manuscript. To that end, we were fortunate to have an impressive list of contributors including experts from major centers devoted to hepatic surgery around the world. In addition, texts and illustrations were largely edited to avoid excessive overlap and to achieve a standard style. With 350 illustrations and figures, readers are provided with truly effective didactic material.

Hopefully, "Principles of Hepatic Surgery" will not only be of value to those at the beginning of their training in the field, but will also become a key source of up-to-date information for practicing liver surgeons. To address potential differences in approaches to and/or the biology of a given condition, some chapters include a commentary section written by other experts.

In summary, our aim was to publish a textbook providing logical, concise, and clear information in the field of hepatic surgery. As such, this first edition of "Principles of Hepatic Surgery" has exceeded our expectations and also inspired us to look forward to further developments in the field.

Silvio M P Balzan
Vinícius G Gava

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We are deeply grateful to the collaborators that believed in this project and dedicated their valuable time to this textbook.

Thanks to Dr Fábio Girardi, our colleague and illustrator, for his tireless work in providing clear and informative illustrations.

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Thanks to Milton Duarte for his hard work in the typesetting and edition of the figures.

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1 Surgical Anatomy of the Liver

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- *The morphologic anatomy of the liver, based on superficial landmarks, has been replaced by functional anatomy, which is more appropriate for liver surgery.*
- *The liver is divided according to portal pedicles and hepatic veins. Cantlie's line (where the middle hepatic vein is located) divides the liver in right and left hemilivers.*
- *The right hemiliver is divided in anterior (segments 5 and 8) and posterior (segments 6 and 7) sectors by a plan where the right hepatic vein is located.*
- *The left hemiliver is divided in medial (segment 4) and lateral (segments 2 and 3) sectors.*
- *Segment 1 corresponds to the caudate lobe, located around the vena cava.*
- *Vascular and biliary variations are very frequent and they have significant implications on liver resections and/or transplantation.*

INTRODUCTION

Knowledge of hepatic anatomy has evolved since the first anatomic liver resection by Lortat-Jacob in 1952. The anatomy currently used is based on descriptions made by Hjörstsjö and by Couinaud. These comprehensive papers divided the liver in segments or sectors according to its vascularization and biliary drainage. Modern hepatic surgery is based on the concept that the future remnant liver must have enough hepatic parenchyma but also adequate blood inflow (arterial and venous), blood outflow, and biliary drainage. The comprehension of the complex anatomy of the liver allowed the development of highly structured hepatic procedures such as staged resections and living liver donor transplantation.

Liver anatomy can be described using mainly two different aspects: morphological anatomy and functional anatomy. Traditional morphological anatomy (**Figure 1**) is based on the external appearance of the liver and does not take into account internal features such as vessels and biliary duct branching, which are of obvious importance in hepatic surgery. Functional anatomy (**Figure 2**) is based on the internal architecture of the liver and constitutes the basis for modern surgery of the liver.

Total liver volume has a relatively constant relationship to body weight, although liver/body weight ratios are greater in growing individuals than in adults. Various formulas can be used to estimate total liver volume in adults. One that is frequently used in Western subjects is based on the linear correlation between TLV and body surface area (BSA): Total Liver Volume (in cm^3) = -794.41 + 1,267.28 × BSA (in m^2) (see **Chapter 4** – Underlying Liver Disorders in Hepatic Surgery). In general, the left hemiliver comprises about one-third of the total weight of the liver in humans. However, the ratios of the left and right hemiliver volumes to total liver volume vary considerably among individuals. Therefore, the remnant liver volume after a hepatectomy or the volume of the graft in a case of living donor liver transplantation cannot be accurately predicted preoperatively on the basis of the donor body weight alone.

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The liver receives a dual blood supply from the hepatic portal vein and hepatic arteries. Approximately 75% of the liver's blood supply is through the hepatic portal vein, which carries venous blood drained from the spleen, gastrointestinal tract, and its associated organs. The hepatic arteries supply arterial blood to the liver, accounting for the remainder 25% of its blood flow. Oxygen is provided from both sources; approximately half of the liver's oxygen demand is met by the hepatic portal vein, and the hepatic arteries meet the other half. Blood flows through the sinusoids and empties into the central vein of each lobule. The central veins coalesce into hepatic veins, which leave the liver and empty into the inferior vena cava.

The term "biliary tree" derives from the arboreal branches aspect of the bile ducts. The bile produced in the liver is collected in bile canaliculi, which merge to form bile ducts. Within the liver, these ducts are called intrahepatic bile ducts, and once they exit the liver parenchyma they are considered extrahepatic. The intrahepatic ducts eventually drain into the right and left hepatic ducts, which merge to form the common hepatic duct. The cystic duct from the gallbladder joins with the common hepatic duct to form the common bile duct.

MORPHOLOGIC ANATOMY

The liver is located in the right upper quadrant of the abdominal cavity, resting just below the diaphragm and under cover of the lower ribs. Most of the liver lies to the right of the midline, where the lower border coincides with the right costal margins, and a small portion lies immediately behind the anterior abdominal wall in the epigastrium, between the anterior surface of the stomach and the left dome of the diaphragm. The upper surface is boldly convex, molded to the diaphragm, and the surface projection on the anterior body wall extends up to the fourth intercostal space on the right and the fifth intercostal space on the left. The convexity of the upper surface slopes down to a posterior surface, which is triangular in shape. The posterior surface is enclosed by the leaves of the coronary and the triangular ligaments, and lies in contact with the inferior vena cava. It is a relatively soft organ, mostly covered by a thin fibrous capsule – Glisson's capsule (an extension of the peritoneum) – except on the posterior surface, where the peritoneum reflects onto the diaphragm, forming the right and left triangular ligaments (**Figure 1**). The undersurface of the liver is concave and extends down to a sharp anterior border. It contains a fissure (the hilum or *porta hepatis*), by which the major vessels and bile ducts enter and leave the liver. The liver is suspended from the anterior abdominal wall and the diaphragm by the falciform ligament and three other peritoneal folds. The round ligament (*ligamentum teres*), formed by the obliteration of the umbilical vein, arises from the end of the left portal branch and forms the lower, visceral border of the falciform ligament. It is connected to the diaphragm and abdominal walls by five ligaments: the membranous falciform (which also separates the right and left lobes), coronary, right and left triangular ligaments, and the fibrous round ligament. They have no functional importance, but they are easily recognizable surface landmarks.

Traditional gross anatomy divided the liver into four lobes based on surface features. The falciform ligament divides the liver into a left anatomical lobe, and a right anatomical lobe, the right lobe is considerably larger than the left. If the liver is flipped over (**Figure 1C**), or visualized from behind (**Figure 1B**), two morphological additional lobes can be individualized. They are the caudate lobe and quadrate lobe.

From behind, the lobes are divided up by the *ligamentum venosum* and *ligamentum teres* (the parenchyma and other

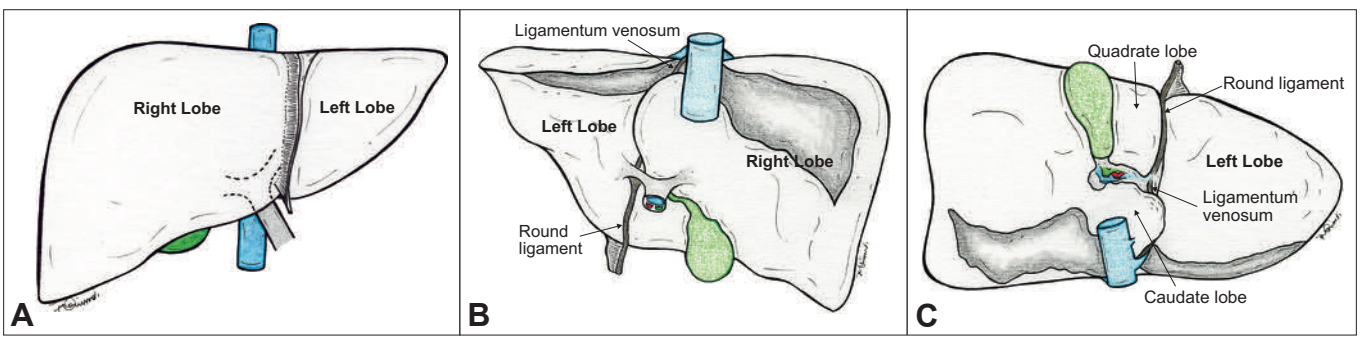


Figure 1. A) Anterior view. The liver is divided in two main lobes by the falciform ligament. The right one is larger than the left one. **B**) Dorsal view. The IVC lies snugly in a deep groove within the bare area; the hepatic veins open directly into it. Occasionally, the liver tissue embraces the vena cava completely so that it runs within a tunnel of parenchyma. **C**) Inferior view. The portion of the right lobe located anterior to the hilar fissure is called the quadrate lobe, limited on the left by the umbilical fissure and on the right by the gallbladder fossa. The caudate lobe is seen posteriorly to the transverse hilar fissure. The gastrohepatic omentum is attached to the ligamentum venosum (or Arantius ligamentum), lying between the caudate lobe (that is placed within the lesser omental sac) and the left hepatic lobe.

hepatic structures on the left of these ligaments pertain to the morphological left lobe). The transverse fissure (or *porta hepatis*) divides the caudate from the quadrate lobe, and the right sagittal fossa, which the inferior vena cava runs over, separates these two lobes from the right lobe.

Occasionally, anatomical variants of a hepatic lobe, such as the Riedel lobe, may be present and confused for a mass (**Figure 3**).

BASIC ANATOMY OF THE HEPATIC HILUM

The hepatic hilum (and the hepatoduodenal ligament) is, for the most part, composed of three layers: the portal vein in its most dorsal aspect, the hepatic artery in the middle, and the bile duct in its most ventral aspect (**Figure 4**). The anatomy of the **portal vein** is generally very regular. Its bifurcation is located on right portion of the hepatic hilum. Its left branch consists of a transverse portion that runs from the bifurcation of the main portal vein to the *ligamentum venosum*, and an umbilical portion that runs upward in the umbilical fissure. The **bile duct** normally follows an extrahepatic course very similar to that of the portal vein. The confluence of right and left hepatic ducts is located more cranially than the main portal vein and proper hepatic artery bifurcation. The intrahepatic right and left biliary ducts are situated on the dorsal aspect of right and left portal branches, but immediately before their confluence in the hilar plate they pass anteriorly and the common bile duct and main bile duct assume an anterior situation in the hepatoduodenal ligament. Anomalies of the bile duct are much more common than those of the portal vein. The **hepatic artery** normally divides into a large right branch and a thinner left (and middle) branch more inferiorly in the hepatoduodenal ligament than the division of the portal vein and confluence of right and left hepatic biliary ducts. As a result, both right and left arterial branches have a relatively long extrahepatic course that differs from those of the portal vein and bile duct, especially in regard to the left and middle branch. The right hepatic artery is usually larger and passes behind the bile duct immediately after branding off the proper hepatic artery. The left and middle hepatic arteries travel along the left side of the hepatoduodenal ligament, with no close relationship to the bile duct until the end of the transverse portion of the hilar plate. The hepatic arteries, like the bile duct, are subject to many anomalies, as described below in this chapter, which can necessitate a variety of surgical modifications, especially during liver transplantation and resections.

FUNCTIONAL ANATOMY

The term functional anatomy refers to the description of hepatic segmentation based on the internal architecture of the liver (**Figure 2**) and constitutes the real anatomic basis for modern hepatic surgery. This approach was first made by Cantlie in 1898 and further clarified by the publications of McIndoe and Counseller[1] (1927), Ton That Tung[2] (1939), Hjörstsjö[3] (1951), Healey and Schroy[4] (1953), Goldsmith and Woodburne[5] (1957), Couinaud[6] (1957), Bismuth et al.[7] (1982), and more recently by Takasaki[8] (1998). The description by Couinaud is the most used, and although an increasing number of surgical and radiological observations call Couinaud's concept of eight liver segments into question[9–12], it is still very useful for surgeons. In this functional anatomy, eight segments are numbered in a clockwise direction from an anterior viewpoint, starting with the caudate lobe as segment 1.

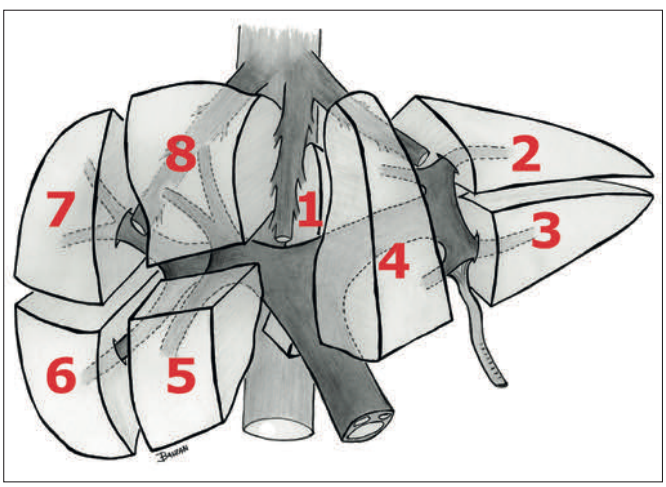


Figure 2. Segmental anatomy of the liver proposed by Couinaud. The middle hepatic vein divides the right hemiliver (segments 5,6,7 and 8) from the left hemiliver (segments 2,3 and 4).

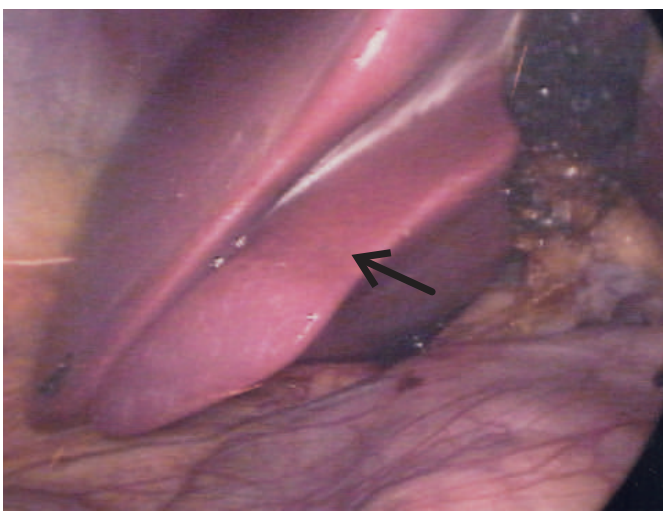


Figure 3. Surgical aspect of a Riedel lobe (arrow), inferior projection of the right lobe, during a laparoscopic cholecystectomy.

The central area where the Glissonean pedicles (also called portal pedicles or portal canals) enter the liver is the hilum or *porta hepatis* (**Figure 4**). The Glissonean pedicles consist of the triad of portal vein, hepatic artery, and bile ducts inside a sheath formed by an extension of Glisson's capsule. At the right of the hilum, the Glissonean pedicle with the biliary duct, portal vein, and artery divide into left and right branches, and the portions of the liver supplied by these branches constitute the functional left and right hemilivers.

An imaginary plane joining the gallbladder fossa to the inferior vena cava, called Cantlie's line, separates the functional lobes. This plane separates the liver into true right and left hemilivers. The middle hepatic vein runs in this plane. The right lobe is further divided into an anterior and posterior segment by the right hepatic vein. The left lobe is divided into the medial and lateral segments by the left hepatic vein. The fissure for the *ligamentum teres* also separates the medial and lateral segments. The medial segment is also called the quadrate lobe. In this widely used Couinaud (or "French") system, the functional lobes are further divided into a total of eight subsegments based on a transverse plane through the bifurcation of the main portal vein. The caudate lobe is a separate structure, which receives blood flow from both the right- and left-sided vascular branches.

A schematic representation of the liver segments through different transverse levels can be seen in **Figure 5**. The middle hepatic vein divides the liver in right and left hemilivers. The right hepatic vein divides the right hemiliver in two sectors: anterior (segments 5 and 8) and posterior (segments 6 and 7). A transverse plane at the level of the right portal vein divides the superior from the inferior segments (segment 7 from 6 and segment 8 from 5). At the level of the left portal vein the left hemiliver is divided in superior (segments 2 and 4a) and inferior (segments 3 and 4b) segments. The left portal vein is at a higher level than the right portal vein. At the level of the splenic vein, which is below the level of the right portal vein, only the inferior segments are seen.

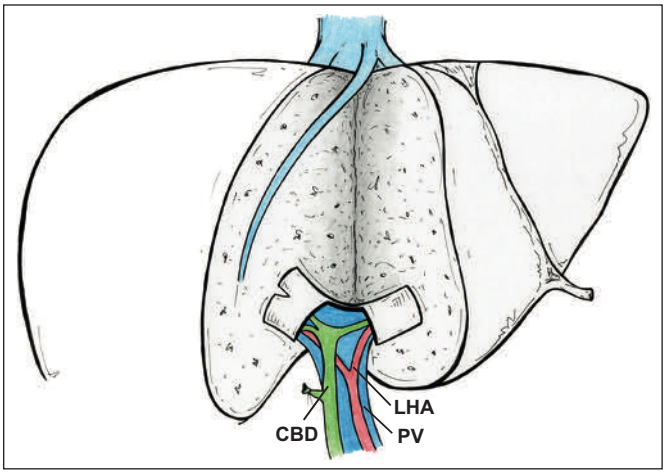


Figure 4. Schematic representation of usual anatomy of the hilar structures. The bile duct (green) is located anteriorly and the portal vein (blue) posteriorly. The right hepatic artery usually runs between the common bile duct and the portal vein. The gallbladder was removed and the cystic duct ligated. CBD: common bile duct; LHA: left hepatic artery; PV: portal vein

The classification of Bismuth et al.[7] is very similar to the Couinaud classification, although there are small differences. According to Bismuth three hepatic veins divide the liver into four sectors, further divided into segments (**Figure 6**). These sectors are termed portal sectors as each is supplied by a portal pedicle in the centre. The separation line between sectors contains a hepatic vein. The hepatic veins and portal pedicles are intertwined, as are the fingers of two hands.

The left portal scissura divides the left liver into two sectors: anteromedial and posterolateral. Left anterior (anteromedial) sector consists of two segments: segment 4, which correspond to the quadrate lobe, and segment 3, which is anterior part of anatomical left lobe. These two segments are separated by the left hepatic fissure or umbilical fissure. Left posterior (posterolateral) sector consists of only one segment (segment 2). It is the posterior and superior part of the left lobe.

The right liver is divided into two portions by the right

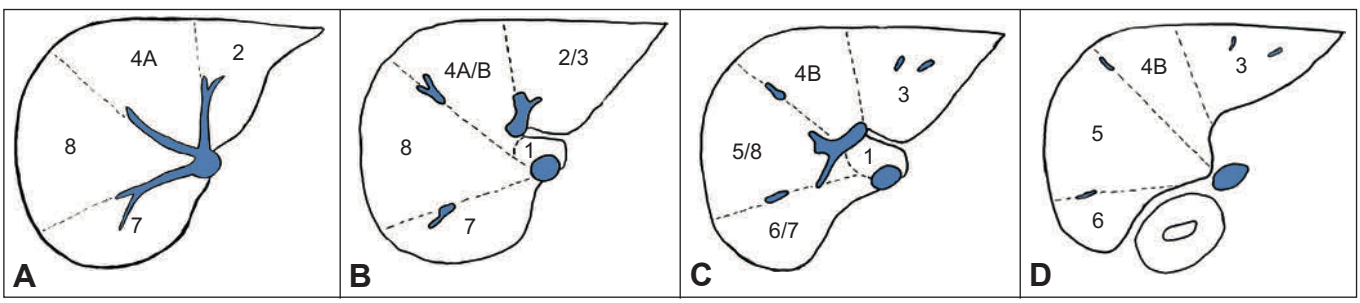


Figure 5. Transverse images through different levels of the liver. **A**) Transverse section of superior segments of the liver divided by the hepatic veins. **B**) Tansverse section at the level of the left portal vein. **C**) Transverse section at the level of the right portal vein. **D**) Transverse section at the level of the splenic vein. Only the inferior segments of the liver are seen. Numbers indicate the Couinaud segments.

portal scissura, which contain the right hepatic vein. The right portal scissura divides the right liver into anteromedial and posterolateral sectors, clearly seen when the liver is placed on a flat table. In situ, however, the liver is molded around the spine, and these two sectors are better described as anterior and posterior sectors. The right portal scissura is inclined approximately 40 degrees to the right. According to Couinaud, it extends from the anterior surface of the liver at the anterior border, midway between the right angle of the liver and the right side of the gallbladder bed, to the confluence of the inferior vena cava and the right hepatic vein posteriorly.

A new concept of liver segmentation on the basis of the Glissonean pedicle proposed by Takasaki [8] describes the blood supply of the liver as derived from three secondary branches of the Glissonean pedicle, and each secondary branch feeds one segment. Consequently, the liver can be separated into three segments: right, middle, and left. There is one additional area, called the caudate area, which is nourished directly from the primary branch. The three segments are almost the same size, each accounting for about 30% of the total liver volume, with the remaining 10% occupied by the caudate area (**Figure 7**).

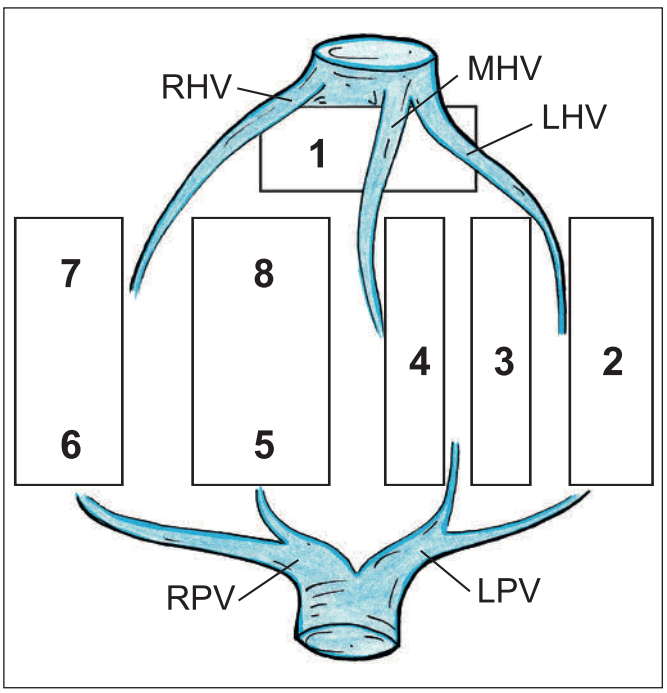


Figure 6. Schematic representation of the liver functional anatomy based on the division by the hepatic veins. Hepatic sectors are delimited by the three main hepatic veins. Note that the caudate (Spiegel) lobe constitutes an independent sector (dorsal) which is not delimited by the hepatic veins (Numbers indicate the Couinaud segments). RHV: Right hepatic vein; MHV: Middle hepatic vein; LHV: Left hepatic vein; RPV: Right portal vein; LPV: Left portal vein. (Modified from Bismuth et al.[7])

HEPATIC VEINS AND INFERIOR VENA CAVA

The venous drainage of the liver comprises three main hepatic veins that drain into the suprahepatic part of the inferior vena cava, and a variable number of accessory hepatic veins that drain into the retrohepatic vena cava. The right hepatic vein, the longest vein in the liver, is single in about 94 percent of cases.[13] The main trunk is formed by the convergence of an anterior trunk situated in the right portal fissure, which drains mainly segments 5 and 6, and a posterior trunk that chiefly drains segment 7.[14] The middle hepatic vein courses along Cantlie's line in the principal portal fissure and forms a common trunk with the left hepatic vein in about 85% of cases.[13,14] It drains the central sector of the liver, receiving constant tributaries from segment 4

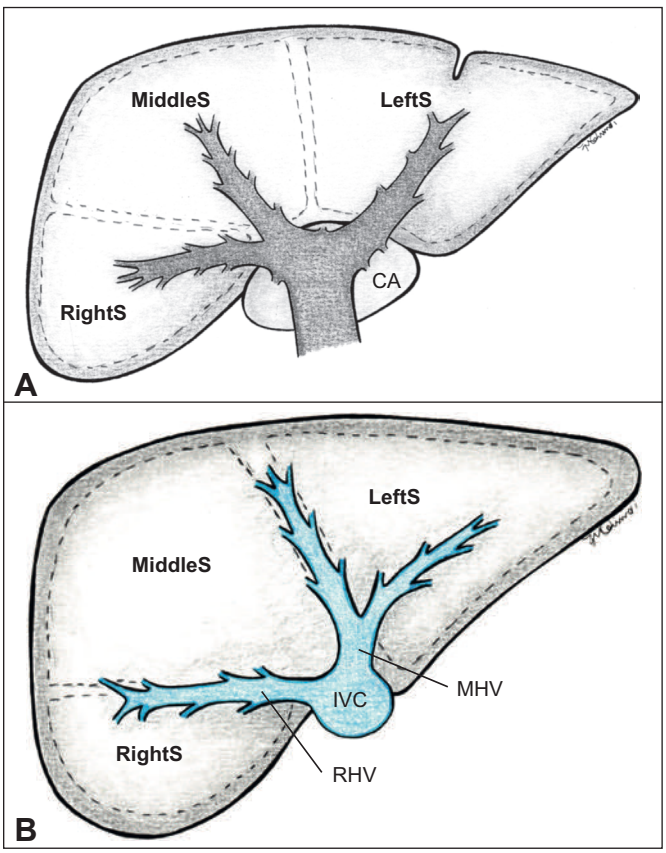


Figure 7. Takasaki's liver segmentation. Differently than other classifications, this segmentation is based on the two major venous trunks (right hepatic vein and middle/left hepatic vein trunk). **A**) Three segments and a caudate area. The left hemiliver of Couinaud's classification corresponds to the left segment. The right anterior sector and right posterior sector of Couinaud correspond to the medial and right segments, respectively. **B**) Relationship between the hepatic veins and the three segments according to Takasaki. RightS: Right segment; MiddleS: Middle segment; LeftS: Left segment; CA: Caudate area; IVC: inferior vena cava; RHV: right hepatic vein; MHV: middle hepatic vein.

on the left, and from segments 5 and 8 on the right.[15] It is often the main vein draining the anterior segment of the right lobe. The left hepatic vein arises from the confluence of a transverse vein, draining segment 2, and a sagittal vein, draining segment 3.[14] It occasionally receives a contribution from segment 4.

Short accessory (dorsal) right hepatic veins, not to be mistaken with the caudate lobe veins, drain the dorsal sector of the liver (mainly segments 6 and 7) and empty directly into the retrohepatic inferior vena cava on its right.

In 1981, Nakamura and Tsuzuki [13] made an extensive study of the patterns of the ramifications of the hepatic veins, and observed that the size of the main right hepatic vein seemed to determine the number of accessory hepatic veins and their diameters. In the presence of a large hepatic vein draining a wide area of the right lobe, only a small posterior vein drains a small area of the posterior sector of the right lobe, with occasional absence. If the main right hepatic vein is medium sized, a posterior or posteroinferior vein, 0.5 to 1 cm in diameter, drains the posteroinferior segment (segment 6) of the right lobe separately into the vena cava. In just under a quarter of livers, however, the right hepatic vein is small and short, and drains only segment 7, while a large posterior or posteroinferior vein, up to 1.8 cm in diameter, drains the bulk of the posteroinferior area of the right lobe. In such circumstances the anterior segments can drain solely into the middle hepatic vein. The peripheral course of the hepatic veins appears to be the most important cue for the identification of the portal segments, because these veins are thought to run along the sectorial and/or segmental borders. The right hepatic vein runs between the anterior and posterior sectors, i.e., between segments 5 and 6 and between segments 7 and 8. However, some researchers have reported that when the right hepatic vein is poorly developed it does not reach the border of segments 5 and 6.[13,16] In addition, Masselot and Laborgne [16] found a well-developed middle hepatic vein draining segment 6 in 23% of the cases they examined. Hepatic bisegmentectomies 7-8 (with ligature of the right hepatic vein) were thought to be possible only in the presence of an accessory (posterior or posteroinferior) right hepatic vein,[17] but recently Machado et al.[18] have published the feasibility of this technique in four consecutive cases in the absence of a large inferior right hepatic vein and without venous reconstruction.

The middle and left hepatic veins form a common trunk in the majority of cases. After examination of 140 specimens Onishi et al.[19] found a common trunk in 88.5% and independent trunks in 11.5% of the specimens, almost the same proportion found by Nakamura and Tsuzuki [13] (84.3%). The length of the common trunk was 0.2 to 1.5 cm (mean: 0.78 cm), whereas Nakamura and Tsuzuki reported 0.2 to 1.7 cm, with those having a length of 1 cm or longer comprising 31.5% of the specimens. The confluence pattern of the middle hepatic vein was also investigated,[19] and eight major types were recognized (**Figure 8**). In addition, small individual veins, draining segment 3 or the superior part of segment 4 (Segment 4a), may empty directly into the suprahepatic inferior vena cava close to the main left hepatic trunk, a feature usually absent on the right side.[13] The intersegmental area between segment 4 and the left lateral segment forms a watershed between the drainage territories of the middle and left hepatic veins. This is drained in more than 60% of livers by a tributary of the left hepatic vein that run across the falciform ligament, and in up to 30% of cases equally between tributaries of the left and the middle veins. In less than 10% the entire segment 3 is drained by its vein,

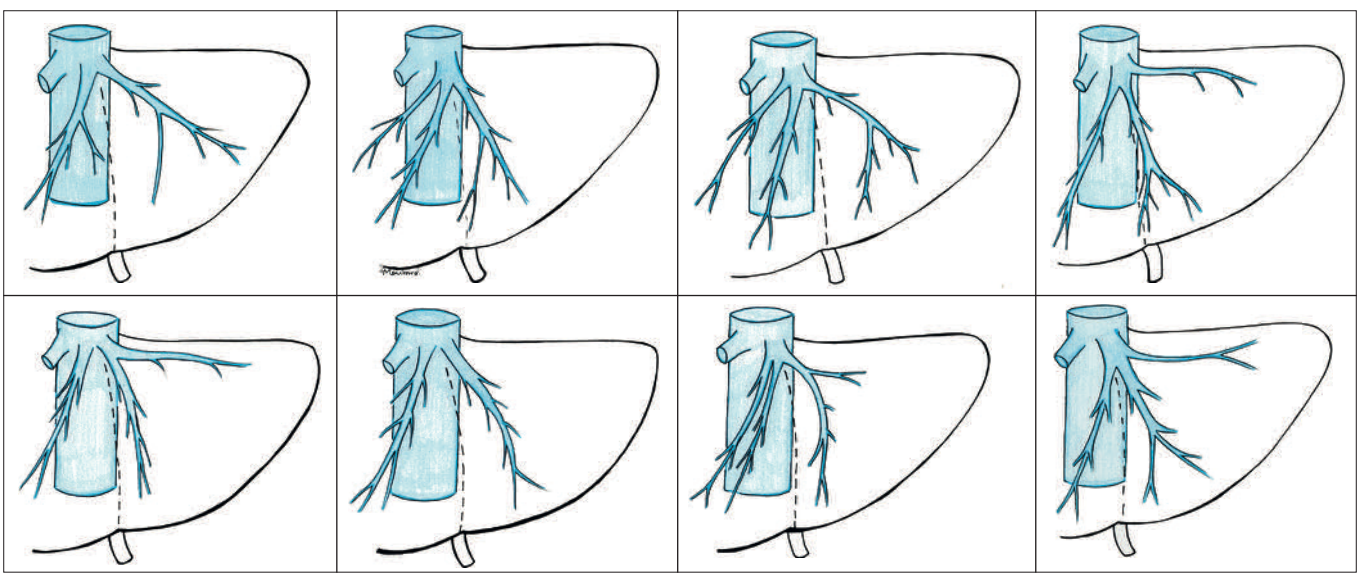


Figure 8. Anatomical variations of the left and middle hepatic veins (8 major types), according to Onishi et al.[19] Note that in most of cases the left hemiliver is drained by a common trunk. Only the trunk of the right hepatic vein is shown on the schemas.

which joins the middle hepatic vein instead of uniting with the segment 2 vein.[13] Concerning the left hepatic vein itself, Reichert et al.[20] found three distinct anatomical variants. The most common variant, observed in 73% of specimens, was a union of segment 2 and 3 veins to form a principal left hepatic vein at the umbilical fissure. Notably, this variant would receive significant tributaries draining the posterior aspects of segment 4 as it approached the inferior vena cava. The second most commonly (14%) observed pattern was separate large veins, each draining an individual segment that united to form the left hepatic vein at the level of the inferior vena cava. In this pattern, each venous channel received tributaries from the posterior aspects of segment 4 before uniting just before the inferior vena cava. The third anatomical variant, identified in 13% of specimens, was a union of segment 2 and 3 draining veins in the parenchyma of the graft to form the left hepatic vein medial to the umbilical fissure. In this variant, the left hepatic vein is a large single vessel that directly empties into the inferior vena cava without receiving significant tributaries from segment 4.

Although the liver segments based on the position of rigid planes along vascular main stems are well described by Couinaud [6], the volume, position, and shape of venous segments are barely understood. Masselot and Leborgne [16] and Gupta and Gupta [21] characterized the principle drainage area of the hepatic veins. According to their work, the left liver vein drains the left lateral sector (segments 2 and 3) in up to 95% of all analyzed livers. Besides draining segments 4 and 5, the middle hepatic vein is also described as essential in creating overlapping drainage areas and, thereby, forming functional anastomosis between the left and right hepatic vein. The right liver vein with its two main branches predominantly drains segments 6 and 7. In general, both describe the right hepatic vein as the largest venous system within the human liver.[16,21]

Using three-dimensional images based on CT/MRI scan to obtain accurate volumetric data and a better anatomical understanding, Fischer et al.[11] were able to identify three venous segments and six venous subsegments, which they have compared with the Couinaud segmental approach. They found that the left hepatic vein drains the smallest part of the liver with 20.4% of total liver volume. The middle hepatic vein has a drainage area of 32.5%, and the right hepatic vein drains 47.1% of the total liver volume. They showed that segments 2 and 3 are positioned only within the left hepatic vein area of drainage, that segments 4a and 4b are covered by the drainage area of the left (40.3%, 39.8%) and middle (53.6%, 50.3%) hepatic veins. For segment 5 there is a distribution between the area of the middle (42.5%) and right (54.5%) hepatic veins. In contrast, segments 6 (99.1%) and 7 (99.8%) are only within the drainage area of the right hepatic vein. Segment 8 shows a 53.6% drainage by the middle hepatic vein and 45.4% drainage by the right hepatic vein.

Although the findings outlined above represent the most common anatomical pattern, there are a great number of inter-individual differences in the drainage pattern of the liver, in terms of which of these veins or tributaries are the dominant drainage veins of the respective segments. It is generally acknowledged that there is overlapping between these venous drainage territories, and that interruption of the tributaries of a single vein does not result in serious congestion, probably because of the development of preexisting venous collaterals.[16,22]

The relative position of the hepatic vein and Glissonean pedicles differs depending upon their location in the liver. In the upper part of the liver, almost all branches of the Glissonean pedicle tree intersect those of the hepatic vein, while in the lower part of the liver almost all branches of the Glissonean pedicle tree tend to run parallel to the hepatic vein (**Figure 9**).[23]

The suprahepatic IVC and extrahepatic segments of the major hepatic veins can be exposed by completely freeing the liver from its attachments and the retrohepatic IVC. Freeing the liver from the retrohepatic IVC is completed by dividing the short hepatic veins and the IVC ligament, also called "Makuuchi's ligament".

Another key anatomical point is the inferior phrenic veins. Both the right and left inferior phrenic veins flow into

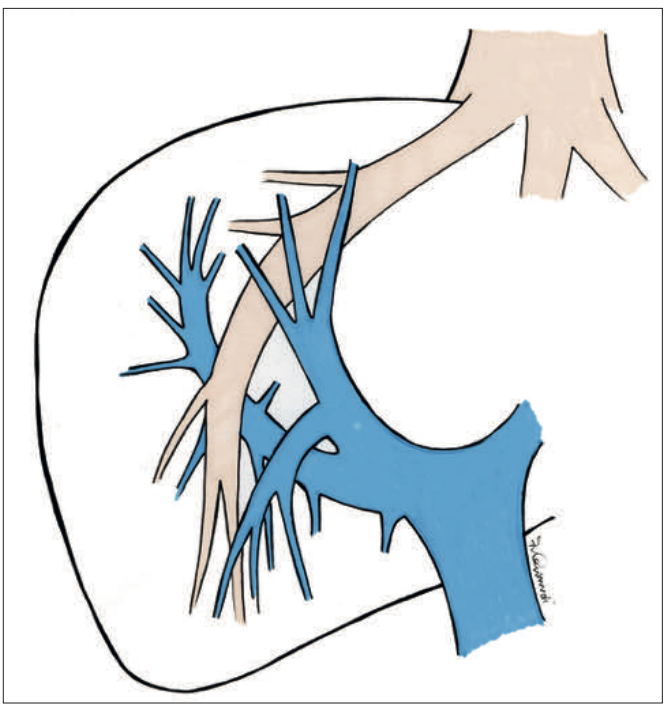


Figure 9. Relationship between Glissonean pedicles and right hepatic vein. Note that on superior segments (7 and 8) of the liver most of Glissonean pedicles run perpendicularly to right hepatic venous branches. Contrarily, on inferior segments (5 and 6) Glissonean and hepatic venous branches run more parallel.

the right hepatic veins and the common trunk at their most cranial points, respectively. Therefore, the division veins and subsequent dissection of the more proximal connective tissue becomes an important procedure in fully exposing the right hepatic vein or the common trunk and facilitating extensive clamping of these veins. This procedure becomes particularly important for left-sided grafts in living-donor liver transplantation, because the extrahepatic portion of the hepatic vein is shorter than in right hemiliver grafts.

PORTAL VEIN

The portal vein divides at the hepatic hilum into right and left pedicles, on which the right and the left lobes of the liver are respectively based. A theoretical plane, the main portal fissure, separates the two lobes. The right portal vein, the shorter of the two, lies anterior to the caudate process and enters the liver through the hilar plate to divide into anterior and posterior branches (**Figure 10A**). The anterior branch curves forward, lies in a vertical plane, and divides into ascending and descending branches for segments 8 and 5 respectively. The posterior branch curves posterolaterally, lying in a horizontal plane and then superiorly in an arch-like pattern, giving branches to segments 6 and 7, or the posterior branch divides in two main branches, similarly to anterior portal branch, for segments 6 and 7.[15] The left portal vein is much longer than the right and its course consists of two parts: a transverse part 3-5 cm long in the hilum, and a part that curves anteriorly and to the left as an arch towards the base of the umbilical fissure where it is joined anteriorly by the round ligament. The anatomy of the left portal venous system is remarkably constant. The segment 2 vein is usually solitary, whereas segment 3 can have up to three veins.[15] The arch then curves forward and distributes a varying number of ascending and descending branches to segment 4, which lies between the falciform ligament and the main portal fissure. The caudate lobe is most commonly vascularized by the left branch of the portal vein and only occasionally by the right.[14] The right portal vein has more variations (**Figure 10**). A trifurcation of the main portal vein occurs in 10-15% of cases, where the right portal vein immediately divides into two sectorial branches (**Figure 10B**). Occasionally one of the sectorial veins, usually the one supplying the right anterior segments 5 and 8, comes from the left portal vein in a short distance after its origin (**Figure 10C**). A third variation is the caudal shift of the right posterior segments resulting in the right posterior portal vein arising directly from the main portal trunk, before its bifurcation (**Figure 10D**). In all of these circumstances the transverse portion of the left portal vein is usually shorter than normal. Finally, the left portal vein may rarely be absent. In such cases, the main portal trunk is undivided as it enters the liver, gives off its right segmental branches and then turns left, crossing the umbilical fissure intraparenchymally as the left portal vein and then supplies branches to the left lobe segments.[24] Chaib et al.[25] found that the portal vein trunk been divided into right and left branches in 98.3% of specimens, a median branch appeared in 15.2%, and no bifurcation of the portal vein occurred in 1.6%. Concerning living donor liver transplantation, one key to obtaining sufficient length and mobility of the graft portal vein is to divide portal tributaries to the caudate lobe (segment 1). Although some researchers insist that this necessitates the resection of segment 1, it can be left intact with no adverse effect in the absence of afferent bloody supply.[26]

Some researchers have reported that portal branches to segment 4 originating from the right portal trunk are not uncommon, and have insisted that care must be taken to preserve the viability of segment 4 during donor hepatectomy;[22] however, many authors believe this is based on a misinterpretation of angiographic images.[19,26] Onishi et al.[19] investigated the ramification patterns of portal branches to segment 4 in a total of 166 specimens. Portal vein branches to segment 4b were observed to branch from the right angle and upper portion of the right border of the umbilical portion of the portal vein in every specimen, and one or two branches were given off by the inferior portion of the right border by the transverse portion of the vein in only five specimens. There were three to six branches in every specimen; in the

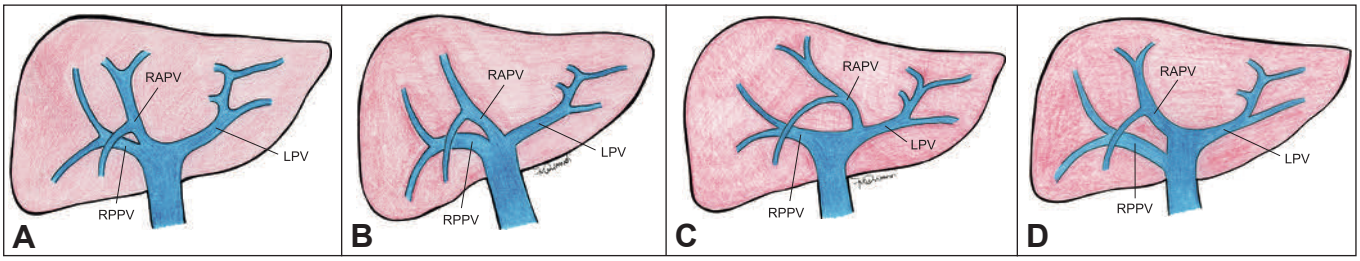


Figure 10. Portal vein variations. **A**) Normal (classic) main portal vein branching pattern. **B**) Portal vein trifurcation. **C**) Right anterior portal vein as a branch of the left portal vein. **D**) Right posterior portal vein as the first branch of the main portal vein. RPPV: Right posterior portal vein; RAPV: Right anterior portal vein; LPV: Left portal vein.

overwhelming majority of specimens, there was one large (> 2 mm in thickness) and two or three small branches (< 2 mm in thickness) (41% of specimens) or two large and one or two small branches (35.6% of specimens). Portal vein variations in the superior area of the medial segment (segment 4a) showed almost all of the portal branches to segment 4a branching lower than those for segment 4b posteriorly to the umbilical portion on the left portal vein. Portal branches to segment 4b consisted most of the time of one large and one (or no) small branch (57.8%) or two large and no small branches (29%).

It is well known that the pattern of intrahepatic vessel ramification in the right posterior hepatic sector varies considerably.[5–7] According to Kinoshita et al.[27] simple bifurcation of the posterior sectorial trunk occurred in only 37.6% of their 202 portography cases. Couinaud [28] (1989) reported that the most common type of ramification (63.1%) is an arch-like pattern in which a thick posterior sectorial trunk issues several branches in succession at almost equal intervals, which supply segments 6 and 7. Hata et al.[29] classified the portal ramification patterns of the posterior sector of the liver into four groups (**Figure 11**): 1) the arch-like group (32%), showing plurality of portal branches to segment 6; in this group the posterior sectorial trunk showed a curved course upward and backward without a sudden change or turn in direction, thus the branch for segment 7 looked like a direct continuation of the posterior sectorial trunk; 2) the simple bifurcation group (27.9%), in which the posterior sectorial trunk simply divided into two branches for segments 6 and 7; 3) the trifurcation group (6.6%), which was characterized by an intermediate branch that supplied a territory between segments 6 and 7; notably, the intermediate branch originated from the wedge-shape region between the two main branches of the posterior sectorial trunk; and 4) variations involving the anterior segmental branches (33.5%), where the most common variation was a trifurcation of the right portal vein into P6 (portal vein to segment 6), P7, and the anterior sectorial trunk. They also found P5 and P6 issued from a common trunk (3.5%), and in only one specimen the right portal trunk and the posterior

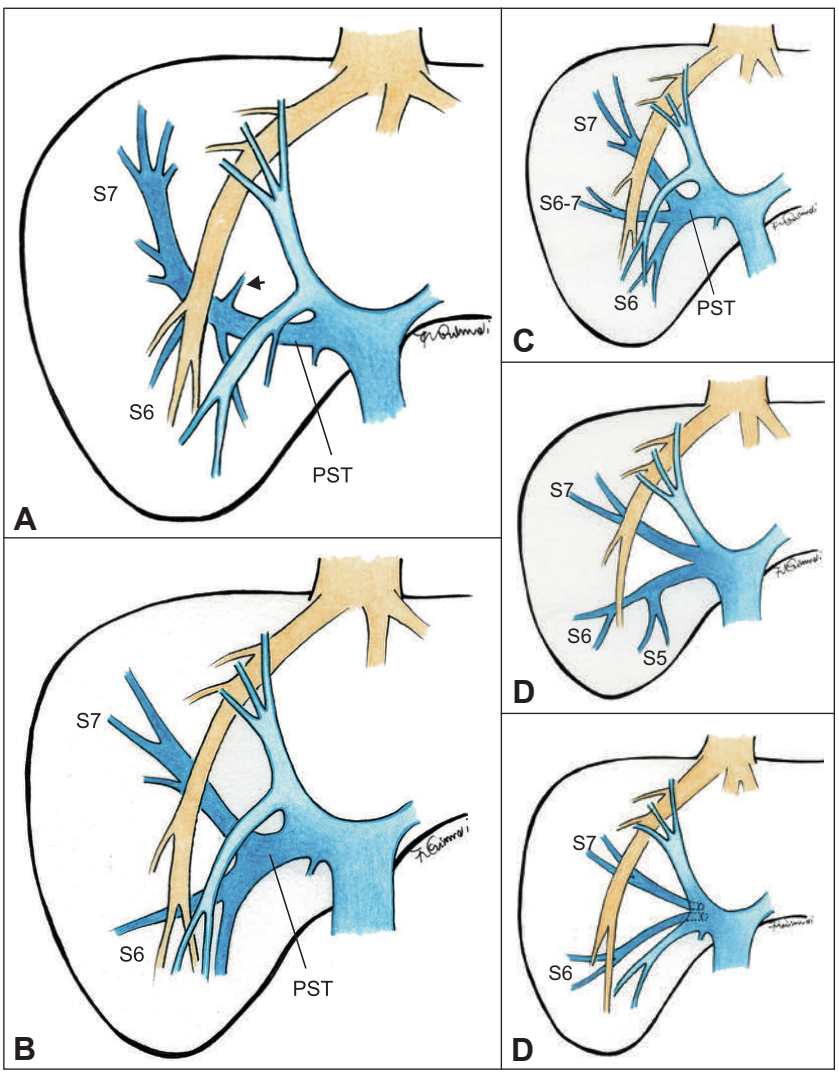


Figure 11. Portal vein patterns of branches from the right posterior sector. **A**) Arch-like ramification of the posterior sectorial trunk (PST), present in nearly 32% of cases. Arrowhead: upward branch for paracaval region of segment 7. **B**) Bifurcation of the posterior sectorial trunk, present in nearly 28% of cases. Figures C, D and E represent examples of less common distribution of right portal branches. **C**) Intermediate branch between those for segment 6 and 7. **D**) Branches to segment 5 and 6 share a common trunk in the absence of anterior sectorial trunk. **E**) Absence of PST, branches to segment 6 and to segment 7 originate separately from the right portal vein. PST: Posterior sectorial trunk. (Adapted from Hata et al.[29])

sectorial trunk were absent, with the left portal vein, the anterior sectorial trunk, P6, and P7 arising simultaneously from the porta hepatis.

Using computed tomography during arterial portography, Cho et al.[30] concluded that the right anterior portal vein did not bifurcate into P8 and P5, but into a ventral and a dorsal branch, which were approximately equal in size. Based on these findings, they have proposed a new classification for the liver anatomy, in which the right liver is divided longitudinally along the anterior fissure of the right liver, demarcated by the anterior fissure vein.[12,30]

These apparent discrepancies with Couinaud's scheme have been very recently discussed in an interesting way by Fasel et al.[10], where they performed helical CT scans of 25 portal veins showing that the number of branches originating from the right and left portal vein was never eight, but in fact many more (mean 20, ranging from 9 to 44). The differences seen between Couinaud's system and others may be simply the result of gathering (or not gathering) various branches of the same order to one territory for the sake of obtaining a rigid number of segments, while the underlying reality does not differ.

ARTERIAL ANATOMY

The common hepatic artery, a branch of the celiac trunk, but occasionally of the superior mesenteric pedicle, supplies the liver with arterial blood through its right and left hepatic branches (**Figure 12**). However, the origins of these two vessels are subject to considerable variation, the most common being a left hepatic branch from the left gastric artery and a right hepatic branch from the superior mesenteric artery (**Figure 12**).[31] Under variant patterns, the lobes may receive blood supply from the superior mesenteric artery, left gastric artery, aorta, or other visceral branches. These vessels may be accessory, occurring in addition to the normal arterial supply, or replaced, representing the primary arterial supply to the lobe. The common hepatic artery may divide into its terminal branches anywhere between its origin and the hilum of the liver. The division usually takes place to the left of the hilum, resulting in a slightly longer right artery.[15] The right hepatic artery then courses laterally, posterior to the common bile duct and right hepatic duct, and enters the liver parenchyma. The left hepatic artery courses along the

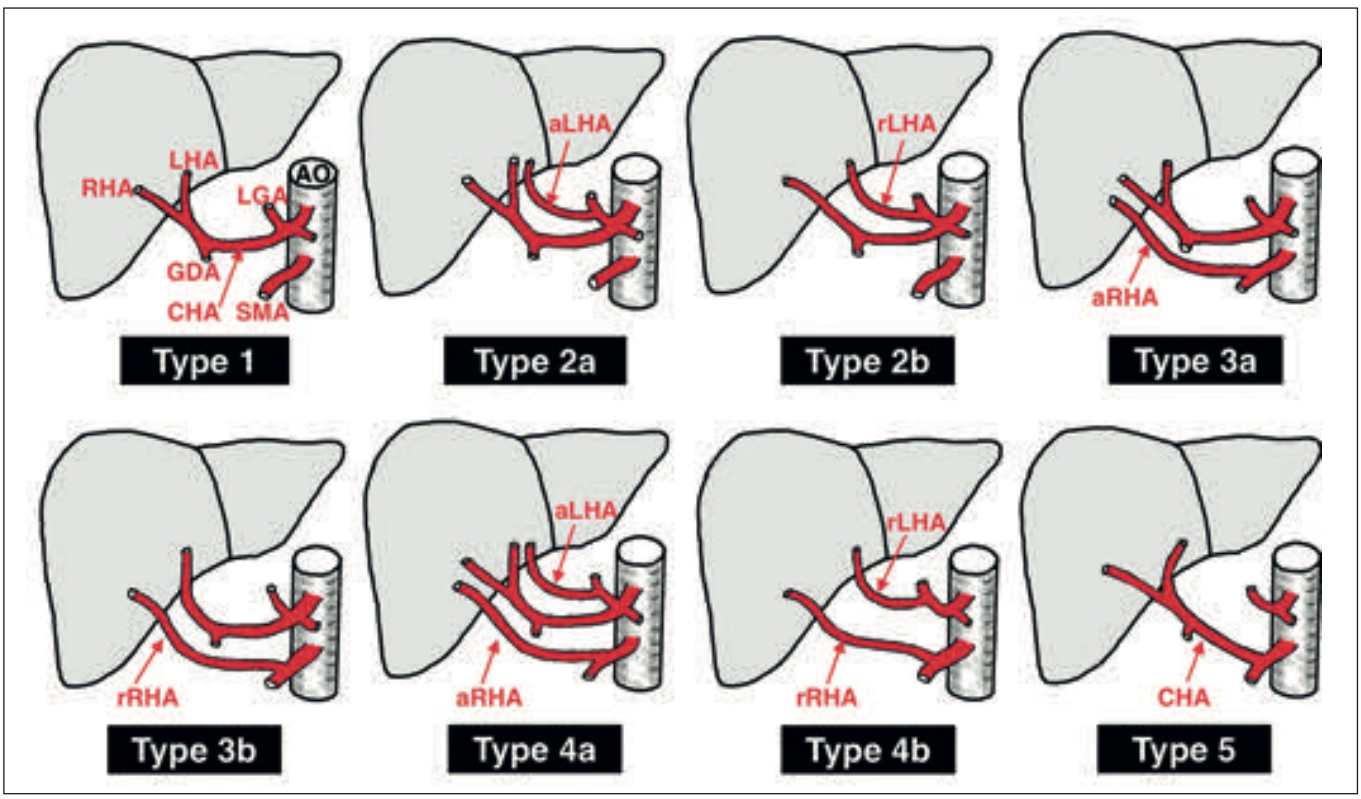


Figure 12. Hepatic artery anatomy variations. **Type 1** – standard presentation; **Type 2** – an accessory or replaced left hepatic artery from left gastric artery; **Type 3** – an accessory or replaced right hepatic artery from superior mesenteric artery (SMA); **Type 4** – both right and left hepatic arteries arising from the superior mesenteric and left gastric arteries, respectively; **Type 5** - common hepatic artery from SMA; **Type 6** (not shown) – common hepatic artery originating directly from the aorta. RHA: right hepatic artery; LHA: left hepatic artery; LGA: left gastric artery; GDA: gastroduodenal artery; CHA: common hepatic artery; SMA: superior mesenteric artery; aLHA: accessory left hepatic artery; rLHA: replaced left hepatic artery; aRHA: accessory right hepatic artery; rRHA: replaced right hepatic artery. (Adapted from Hiatt et al.[33])

inferior aspect of the lobe, with the left hepatic duct and left portal vein, for a varying distance before entering the left lobe at the level of the umbilical fissure.

The anomalies of the arterial system rival those of the biliary tract but, unlike biliary anomalies, they are important in both segmental and whole liver transplantation. Extrahepatic anomalies are recognized readily at standard multiorgan retrieval, and arterial reconstruction is a relatively routine procedure although it increases the likelihood of complications. Arterial anomalies in the donor and recipient may occur and influence graft implantation. Modifications of the dominant scheme, in which the liver receives its total inflow from the hepatic branch of the celiac axis, occur in 25-75% of cases.[32]

Hiatt et al.[33] analyzed the records of 1,000 patients who underwent liver harvesting for orthotopic transplantation and could classify arterial variations as one of six types (**Figure 12**): Type 1 (75.7%), the normal pattern in which the common hepatic artery arose from the celiac axis to form the gastroduodenal and proper hepatic arteries; the proper hepatic artery divided distally into right and left branches; Type 2 (9.7%), in which a replaced or accessory left hepatic artery arose from the left gastric artery; Type 3 (10.6%), in which a replaced or accessory right hepatic artery originated from the superior mesenteric artery; Type 4 (2.3%), a double-replaced pattern in which the right hepatic artery arose from the superior mesenteric artery and the left hepatic artery was a branch of the left gastric artery; Type 5 (1.5%), in which the entire common hepatic artery originated as a branch of the superior mesenteric artery; and Type 6 (0.2%), in which the common hepatic artery took direct origin from the aorta.

BILE DUCTS

Although consequential anomalies of the bile ducts are much more common than those of the portal vein, they less frequently necessitate surgical modifications. So many variations of the biliary tree exist that the "normal" anatomy is present in only about 50% of people [34] (**Figure 13**). Usually, a short vertical right hepatic duct and a longer horizontal left hepatic duct join at the hilum to form the common hepatic duct. The right duct is formed by the fusion of the right anterior and posterior sectorial ducts at a variable point in its intrahepatic course. These individual ducts, in turn, course along the vascular pedicles, draining the anterior (5 and 8) and posterior (6 and 7) segments of the right lobe of the liver. The left duct is formed by fusion of segment 2 and 3 ducts. The segment 4 duct is more variable, but most commonly drains into the left hepatic duct. The biliary confluence is separated from the posterior aspect of the quadrate lobe of the liver by the hilar plate, which is the fusion of connective tissue enclosing the biliary and vascular elements with Glisson's capsule (**Figure 14**).[35] Because of the absence of any vascular interposition, it is possible to open the connective tissue constituting the hilar plate at the inferior border of the quadrate lobe and by elevating it to display the biliary convergence and left hepatic duct.

Knowledge of the blood supply of the extrahepatic biliary apparatus is important when performing hilar dissections. The epicholedochal plexus receives its blood supply from three arterial branches [4,34]: a branch of the posterior superior pancreatoduodenal artery, a branch of the right hepatic artery arising at the point where it passes behind the common bile duct, and a branch running caudally from the arteries of the hepatic hilum. Although these branches usually communicate with each other, division of any one of them may occasionally result in severe bile duct ischemia. Approximately 60% of the vessels that supply the supraduodenal duct run upwards from the gastroduodenal arcade below, while 38% run down, mainly from the hepatic artery. The remaining 2% have a non-axial supply arising from the common hepatic artery.

Couinaud [6] has classified biliary anatomy variations into six main types **(Figure 13)**. In Type A (57%), the anatomy is normal. In Type B (12%), there is a trifurcation of the common bile duct into right anterior, right posterior, and

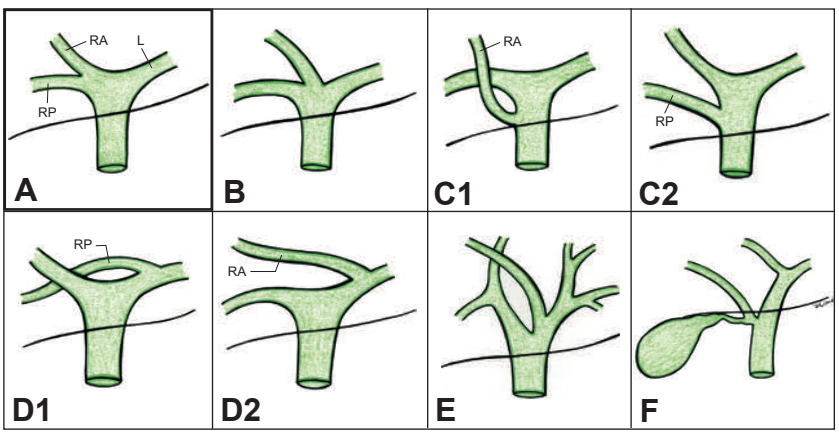


Figure 13. Main variations of the hepatic biliary duct confluence. **A**) Typical anatomy of the confluence. **B**) Triple confluence. **C**) Ectopic drainage of a right sectorial duct into the common hepatic duct (C1, right anterior duct draining into the common hepatic duct; (C2, right posterior duct draining into the common hepatic duct. **D**) Ectopic drainage of a right sectorial duct into the left hepatic ductal system (D1, right posterior sectorial duct draining into the left hepatic system). **E**) Absence of the hepatic duct confluence. **F**) Absence of right hepatic duct and ectopic drainage of the right posterior duct into the cystic duct. RP: right posterior duct; RA: right anterior duct; L: left duct.

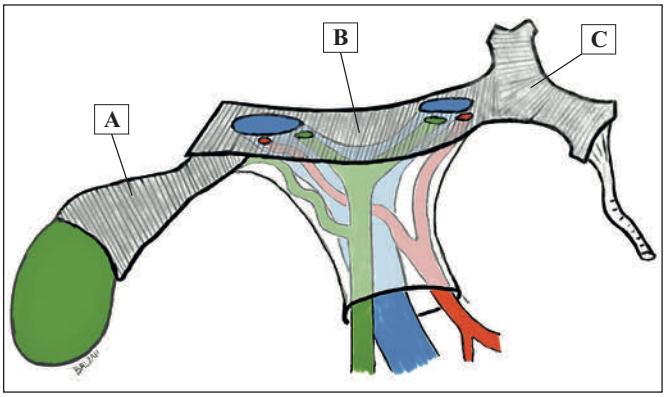


Figure 14. Sketch of the anatomy of the plate system. The cystic plate (**A**) above the gallbladder, the hilar plate (**B**) above the biliary confluence and at the base of the quadrate lobe, and the umbilical plate (**C**) above the umbilical portion of the portal vein.

the left hepatic duct, with an absence of a demonstrable length of the right hepatic duct. In Type C (20%), there is an aberrant drainage of the right segmental ducts into the common hepatic duct. In Type D (6%), there is an aberrant drainage of the right segmental ducts into the left hepatic duct. The right posterior duct is more commonly aberrant than the right anterior duct in both Type C and Type D. In Type E (3%), there is absence of hepatic duct confluence, there being convergence of two more ducts from either lobe to form the common hepatic duct. Finally, in Type F (2%), there is an absence of the right hepatic duct with ectopic drainage of right posterior duct into the cystic duct.

Concerned about the relatively high incidence of biliary complications in reduced-organ liver transplantations, Reichert et al.[20] found four distinct patterns of left bile duct anatomy. The most common pattern was the union of segment 2 and 3 ducts to form the left lateral segment duct close to the umbilical fissure. The incidence of this pattern was 55%. The union of segment 2 and 3 ducts was at the umbilical fissure in 5% of specimens, to the right of the umbilical fissure in 50% of specimens, and to the left of the umbilical fissure in 45% of specimens with this specific anatomical pattern. The left lateral segment duct was then joined by a single segment 4 duct between the umbilical fissure and the hilum to form the left hepatic duct. The second most common (30%) anatomical pattern was creation of the left lateral segment duct close to the umbilical fissure with two parallel ducts from segment 4 joining to form the left hepatic duct. Typically, one segment 4 duct is on the umbilical portion of the left portal vein, and one is close to the union of the right hepatic duct. The third biliary pattern (10%) identified was a single segment 3 duct that receives the duct from segment 4 and joins segment 2 close to the hilum. In this variant, a left lateral segment duct was absent. The fourth pattern (5%) was defined by segment 2 and 3 ducts joining immediately to the right of the umbilical fissure to form a short left lateral segment duct that receives the segment 4 duct just after crossing the umbilical fissure to form the left hepatic duct. Notably, in 10% of specimens, at least one distinct duct from the right liver was observed to cross Cantlie's line and join the left duct system.

Ohkubo et al.[36] classified the confluence patterns of the right intrahepatic bile ducts into three patterns according to the anatomic relation between the right posterior sectional bile duct and the portal vein (**Figure 15**): supraportal pattern (82.7%), in which the right posterior sectional bile duct ran dorsally and cranially to the right of the right anterior portal vein and joined with the distal bile duct at its cranial side; infraportal pattern (11.8%), in which the right posterior sectional bile duct ran ventrally and caudally to the right or the right anterior portal vein and drained into the distal bile duct at its caudal side; and a combined pattern (5.5%), in which some parts of the right posterior sectional bile duct entered the distal bile duct supraportally and the remaining parts of the right posterior sectional bile duct joined with the distal bile duct infraportally.

SEGMENT 1 (CAUDATE LOBE)

Analysis of anatomy, comparative anatomy, and embryology of the liver led to recognition of the modern hepatic or Couinaud segments, with the Spiegel lobe designated as an independent hepatic segment, termed the dorsal sector, caudate lobe, or Couinaud segment 1. The lobe was described as containing two (left and right) or three subsegments (the left or Spiegel lobe, the medial paracaval portion, and the right portion or caudate process).[37] Couinaud and other investigators [38,39] have reported that the right caudate

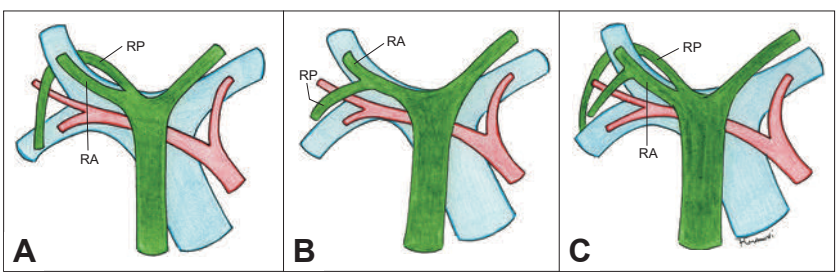


Figure 15. Anatomic relationship of the right posterior sector bile ducts with the right portal vein **A**) supraportal, **B**) infraportal, and **C**) combined pattern. RP: right posterior bile duct; RA: right anterior bile duct.

represents the separate segment 9. Confusion regarding terminology arises from the proximity of the caudate lobe to the portal confluence, proximal hepatic arteries, and the main hepatic veins-vena cava confluence.

The caudate lobe or dorsal liver sector, with its intimate and extended contact with the inferior vena cava, is independent of the two hemilivers from a functional point of view. It is the mid portion of the posterior liver (**Figure 16**). It lies between the main liver and the anterior surface of the inferior vena cava (below the entrance of the main hepatic veins into the vena cava and behind the transverse portal arch). Anteriorly, the dorsal sector or caudate lobe is connected (from left to right) to segments 4, 8, and 7; the limit is represented by a quadro-dorsal (i.e., quadro-caudal) and a dorso-paramedian fissure, and is difficult to identify (**Figure 16**).[39] Rarely, the caudate lobe completely encircles the vena cava (**Figure 16**).

The Spiegel lobe is the most readily identified portion of segment 1 (**Figure 16**). It is protuberant and can be seen through the gastrohepatic ligament to the left of the vena cava. Three major structures surround the Spiegel lobe: to the right, the anterior lateral aspect of the vena cava; anteriorly, the left main portal pedicle; and superiorly, the left hepatic vein. The true division, or intersegmental plane, between the Spiegel lobe and the paracaval portion is defined by the first- or second-order segmentation of the portal branches near the left edge of the vena cava, as described by Kogure and collegues.[40] An external notch is evident at the caudal edge of the caudate lobe in 54% of examined livers.[40] A dominant portal branch (up to 2 mm) from the right may cross this plane (the intersegmental plane) to the Spiegel lobe on the left, and the proper hepatic vein consistently is found deep in the intersegmental plane. Division of the parenchyma of the caudate lobe is performed best along the sagittal plane toward the left margin, not through the middle point, of the vena cava.[41]

The left border of the paracaval portion is defined as the intersegmental plane near the left margin of the vena cava. The posterior border is the vena cava, and the anterior border is the main right portal pedicle at its caudal aspect, although the parenchyma merges with segments 4 and 8, and sometimes 7, at the confluence of the main hepatic veins with the vena cava. Because the right and anterior margins of the right portion of posterior sector are incorporated completely into the posterior surface of the right liver, the precise right margin of the caudate process is obscure. Kitagawa et al.[42] reported a careful analysis of 55 cadaveric dissections, where they defined the right paracaval plane as a reference for the position of the right border of the caudate process. The plane is marked by three landmarks: (i) the bifurcation of the right portal vein, (ii) the end of the right hepatic vein, and (iii) the notch in the gallbladder fossa. In 80% of livers, the caudate extended no more than 1 cm to the right of the right paracaval plane, and never extended more than 3 cm to the right of this landmark. The caudate process never touched the right hepatic vein (except at its confluence with the vena cava). This finding reveals that a significant mass of the right hemiliver can be preserved with the right hepatic vein pedicle when complete caudate resection is required without concomitant right hepatectomy. The ventral or anterior margin is more difficult to define. Kwon et al.[43] described the ventral margin as a horizontal curvilinear plane that is defined by the hilar plate and *ligamentum venosum*; however, Couinaud's

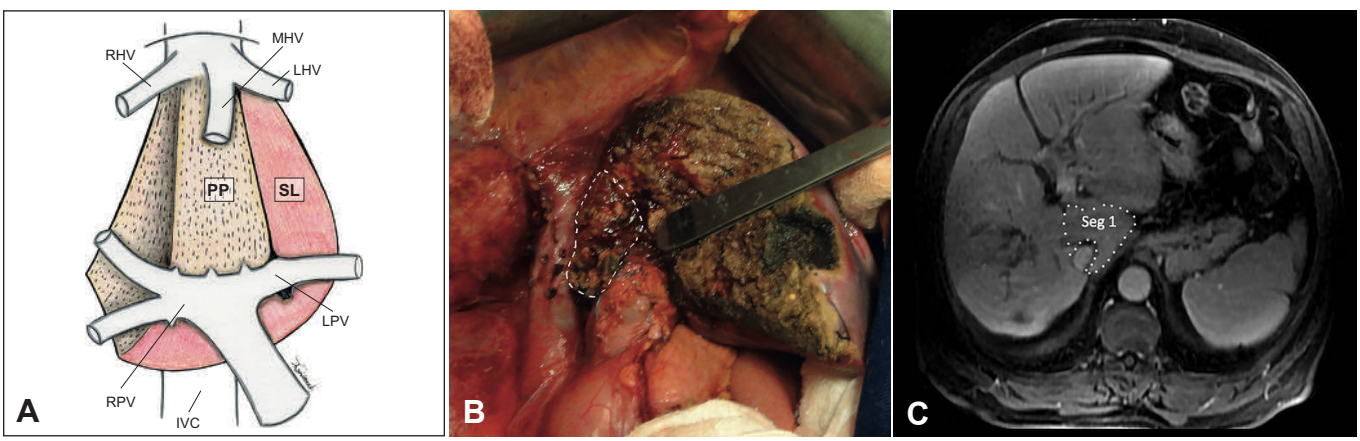


Figure 16. The caudate lobe lies between the hilar structures and the vena cava. It has a roughly pyramidal form. The Spiegel lobe corresponds to the portion on the left of the inferior vena cava. Note the lack of a defined border between the right border and the anterior border of the caudate process with the main right liver. **A**) Schematic representation. **B**) Surgical aspect showing the right paracaval plane of segment 1 (Dashed area). The right hemiliver was resected and the segment 1 visualized between the portal bifurcation and retrohepatic vena cava. **C**) Magnetic resonance imaging showing hepatic segment 1 (dashed area) encircling the retro-hepatic vena cava. RPV: right portal vein; LPV: left portal vein; RHV: right hepatic vein; MHV: middle hepatic vein; LHV: left hepatic vein; IVC: inferior vena cava; SL: Spiegel lobe; PP: paracaval portion.

use of the plane of the middle and right hepatic vein as a guide is equally helpful and simpler. Kwon et al.[43] found that the caudate interdigitated between the origins of the three main hepatic veins and abutted the diaphragm in nearly 50% of studied cadavers. Small branches to each major hepatic vein required meticulous attention to avoid injury to the main veins. Makuuchi et al.[44] and Takayama et al.[45] described a counterstaining technique in which dye is injected into the portal venous branches to aid in identification of the otherwise undefined border of the right caudate and the right lobe.

The caudate lobe is drained predominantly on the left by a single vein in 50% of livers and by two or three veins in the rest. In addition, there may be up to 20 small short venules attaching the caudate lobe to the retrohepatic inferior vena cava.[46] Heloury et al.[47] also described small veins that directly enter the left and middle hepatic veins. The network of hepatic veins communicates within the caudate lobe to form a rich anastomosis between the main hepatic veins and vena cava within the lobe. Usually there are three major veins at most,[47,48] a few intermediated-sized veins, and anywhere from nine to more than 30 tiny accessory branches. The largest vein usually drains anterolaterally into the vena cava from the caudate process (a single proper vein in up to 88%).[40] The Spiegel lobe is usually drained by one large and a few accessory veins and rarely is drained only by several small veins. The paracaval portion is drained by three groups of veins: a large-sized group, a middle-sized group (mainly right-side drainage), and a group of thread-like veins (caudal drainage). The caudate process has the most variable anatomy, but rarely has larger veins and usually has only small accessory veins.[40] The middle anterior surface of the vena cava is generally lacking of any branches from the caudate lobe. Surgeons use this anatomic constancy when using an anterior parenchymal transection approach to major resections (**Figure 17**).[49–51]

An average of three (one to six) portal branches supply the entire caudate [40,41] and may arise from the left, right, bifurcation, or a combination of the portal branches. Although the vessels to the left supply the caudate, the deeper veins on the right, which ascend above the plane of the hepatic vein, may supply the posterior portion of segment 4 or 8. The pedicles supplying the left and right portions of the caudate [48] and a third pedicle [47] have been described, but surgical experience and Couinaud's comparative analysis of liver casts have shown that the high variation prevents precise definition of pedicles.[41]

The distribution of hepatic arterial branches to the caudate lobe is highly variable. The caudate lobe and caudate process receive separate branches from the right and left hepatic arteries in what has been described as an "arcade" or "tree" pattern.[52] Resection of the lobe along Glisson's sheaths [53] minimizes the need to describe every known variation, because all variations occur beneath the hilar plates and because when the vein, artery, and duct join together, a sheath arises from the transverse portal arch and enters the dorsal sector.[54]After the hilar plate is lowered, dissection permits identification of branches, ligation under direct vision, and avoidance of bleeding and bile leaks.[53] The left branches are more constant, and the right branches are more variable and more often are absent.[41]

Caudate bile ducts are also variable.[55] The dominant left branch often is recognized at surgery. Branches to the hilum or right branches occur frequently and may arise from the posterior-superior surface of the portal arch, superficially, or deeply within the lobe. By lowering the hilar plate or by approaching the inflow through the umbilical fissure, identification of the often-dominant biliary radical to the left caudate can be visualized and ligated.[41] Because biliary drainage from the caudate lobe can flow into the right duct, left duct, or hepatic bifurcation, cancer of the hilar bile duct

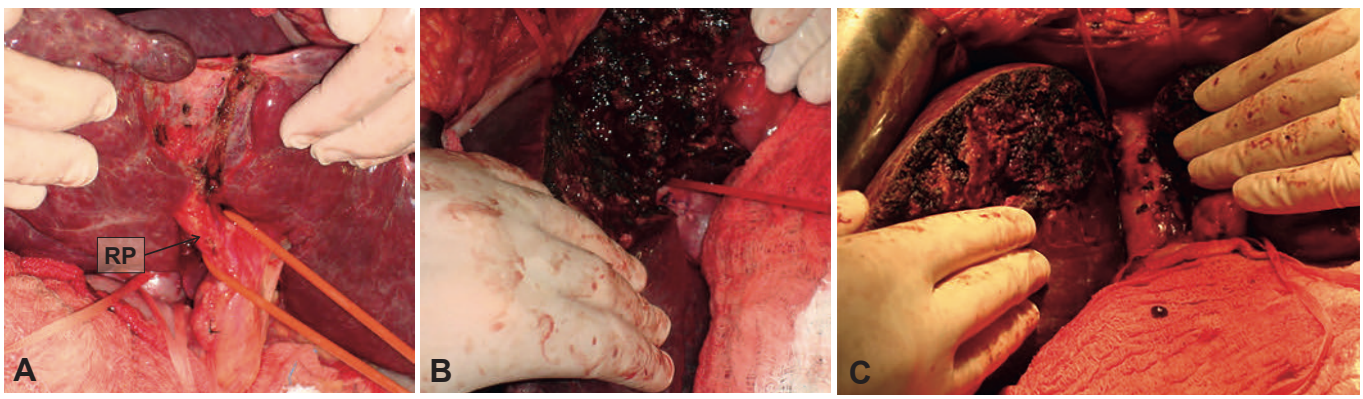


Figure 17. Surgical aspect during liver resections using anterior approach. **A**) Vascular control before the anterior approach for a right hepatectomy due to a large HCC. The right Glissonean pedicle is encircled. **B**) Note the umbilical tape, which runs between the posterior aspect of the liver and the inferior vena cava (IVC), representing the so-called "hanging maneuver". **C**) View after parenchyma transection, the anterior surface of the IVC is completely exposed. RP, right Glissonean pedicle.

can extend into the lobe regardless of its invasion of the left or right main branch of the bile duct.

TERMINOLOGY FOR HEPATIC RESECTIONS

According to the hepatotomy plan, liver resections can be anatomically based or not. Three or more anatomic segments resected (contiguous or not) should be designated a major hepatectomy while minor ones are those with less than three anatomical segments resected including wedge resections.

As a surrogate of the functional hepatic reserve, the resected liver volume and mainly the estimated remnant liver volume should be reported (see **Chapter 4** - Underlying Liver Disorders in Hepatic Surgery - and **Chapter 5** - Liver Function Assessment Before and After Hepatic Resection). Also, in order to make a fair comparison among series and estimate the morbidity and mortality associated with the liver surgery, every associated procedure (resections of other organs, vascular and/or biliary reconstruction, use of combined ablative methods) should be described.

In an attempt to standardize the terminology of liver resections, the Brisbane 2000 Terminology of Hepatic Anatomy and Resection [56] divided the liver into eight segments and four sections: the right anterior section (segments 5 and 8), right posterior section (segments 6 and 7), left medial section (segment 4), and left lateral section (segments 2 and 3). Some of the multiple possibilities of resection and proper terminology can be seen in **Figure 18.** Of course segmentectomies, isolated or combined - contiguous or not – are also possible, and should be reported according to segment number (segment is indicated in short form as "Sg" followed by the corresponding Couinaud segment number).

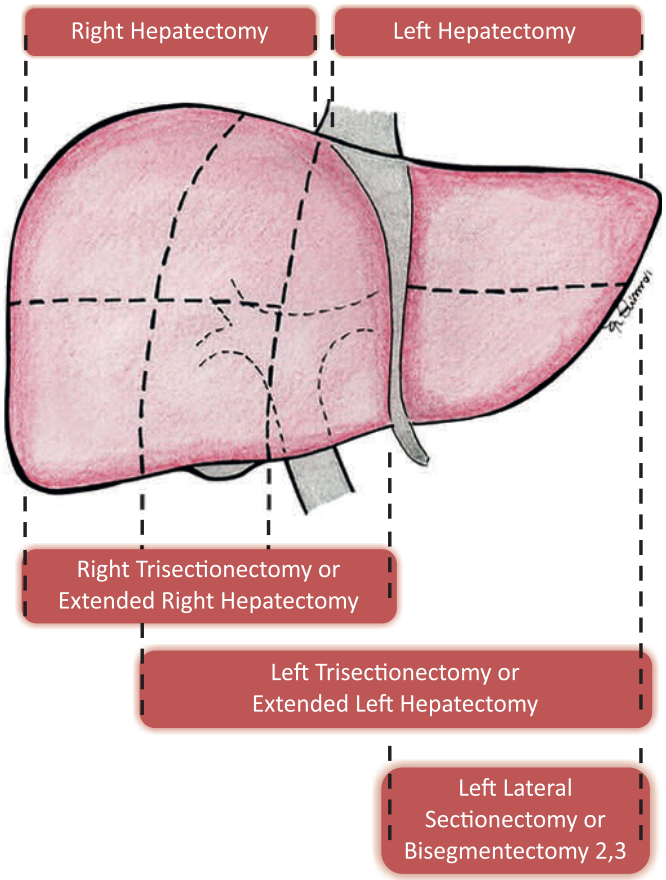


Figure 18. Examples of liver resections using the IHPBA (International Hepato-Pancreato-Biliary Association) 2000 Brisbane terminology of liver resections. The resection of the caudate lobe should be reported whenever done. (Adapted from Strasberg et al.[56])

In fact, it is always correct to refer to any resection by its segments; e.g., for a resection of Couinaud segments 5 to 8, the terms "right hepatectomy" and "resection Sgs 5-8" are equally acceptable.

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2 Radiological Anatomy of the Liver

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- *Perioperative imaging is fundamental in modern hepatic surgery. Accurate knowledge of the regular anatomy of the liver and its variations is essential for planning hepatectomy or transplantation.*
- *A minority of patients has the classical vascular and/or biliary anatomy and some normal radiological findings can be misinterpreted as disease.*
- *The liver is divided in two hemi-livers by a sagittal plane from the gallbladder fossa to the inferior vena cava. The Cantlie line is better delimited by radiology and includes the middle hepatic vein.*
- *Modern multislice computed tomography can scan the whole liver in 5-10s and provides precise parenchymal and vascular anatomy using three phases (arterial, portal, and venous).*
- *Magnetic Resonance Imaging (MRI) is free of ionizing radiation and especially useful to evaluate focal and diffuse parenchymal diseases. Cholangio MRI plays a major role in the assessment of the biliary tree.*

INTRODUCTION

Liver surgery is undertaken for both diffuse and focal liver diseases. Liver resection is frequently the only curative treatment for primary or secondary focal liver diseases, such as hepatocellular carcinoma or metastases. On the other hand, diffuse chronic liver disease leading to irreversible liver failure is the most common indication for liver transplantation. In adults, causes of liver failure include alcohol abuse, primary biliary cirrhosis, viral hepatitis, and sclerosing cholangitis. In the pediatric population, biliary atresia and inborn errors of liver metabolism are common causes.

Preoperative and postoperative imaging is of utmost importance for planning hepatic surgery. In the majority of cases, the differential diagnosis of focal liver lesions, a foremost indication for hepatic resection, is based on radiological findings. Moreover, the staging of malignant disease is driven by imaging techniques.

Precise knowledge of the liver anatomy and the exact location, number, and distribution of the lesions is crucial to plan any hepatic resection. Although minor hepatectomies are rarely challenging, extensive resections are usually complex with the future liver remnant, the vascular supply, and the venous and biliary drainage determining the surgical plan. The presence of diffuse parenchymal changes (e.g. cirrhosis or diffuse fatty infiltration) may indicate chronic liver impairment, which can lead to liver dysfunction after hepatectomy. All of the aforementioned can be obtained or inferred with a careful imaging study.

Preoperative imaging plays a critical role in appropriate patient selection for liver transplantation and includes evaluation of both the transplantation candidate, as well as the potential donor. In assessing a potential donor imaging is important in estimating liver volume, and in defining a "roadmap" of the arterial, venous, and biliary anatomy. Careful imaging enables the identification of variant vascular anatomy, which is critical for safe and effective surgical

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planning. Prior knowledge of liver volumes will avoid donor-recipient volume mismatch. Preoperative assessment of the liver parenchyma will identify any significant incidental lesions, such as a primary tumor or metastasis. Although malignant lesions within a donor are clearly a contraindication, small benign lesions can still allow for successful transplantation.[1]

Imaging techniques employed for the evaluation of the liver include ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), radionuclide studies and interventional angiography, either alone or in combination.

In this chapter, we describe the basic radiological anatomy of the liver, including the system of segmental division that is used to localize hepatic lesions. The radiological techniques commonly used in liver assessment are discussed, together with the salient normal imaging features of the liver. The imaging techniques employed to demonstrate normal vascular and biliary anatomy are highlighted, together with normal variants, which are pertinent for liver surgery. We will also discuss the relevance of anatomical information derived from imaging to liver transplantation surgery, liver resection and gallbladder surgery. Radiological findings of liver diseases will be discussed in other chapters whenever relevant.

NORMAL GROSS ANATOMY OF THE LIVER

The gross anatomy of the liver is described in detail in **Chapter 1** (Surgical Anatomy of the Liver). In this section, we summarize the features that are relevant to imaging. The liver is the largest and also heaviest organ in the body. It varies with gender and body mass, and is also known to decline in size from the fifth and sixth decades of life onwards.[2,3] The majority of the liver lies to the right of the sagittal plane, and its wedged shape follows the contours of the diaphragm as it tapers towards the left. The diaphragmatic (anterosuperior) surface is smooth and convex, whereas the visceral (posteroinferior) surface is flat and irregular. The main feature of the diaphragmatic surface is the sagittal groove or umbilical fissure. Within this is the *ligamentum teres* (representing a fibrous remnant of the left umbilical vein), which itself lies within the free margin of the falciform ligament (**Figure 1**). The main feature of the visceral surface is the porta hepatis, which is a depression containing the portal vein, hepatic artery and common bile duct. The space inferior to the right liver lobe is the hepatorenal space (Morrison's pouch), whereas the space inferior to the left liver is occupied by the lesser sac. Reidel's accessory lobe describes an extension of the right lobe inferiorly to meet or pass beyond the costal cartilage – the term is actually a misnomer as it is not a true accessory lobe but merely represents a normal variant. The quadrate lobe of the liver is defined by the area bounded by the porta hepatis, the gallbladder fossa, the fissure for the *ligamentum teres*, and the inferior liver edge (**Figure 1**). The caudate lobe is defined by the region between the fissure for the *ligamentum venosum* (also known as *Arantius' ligament* – a thin fibrous cord between the left portal vein and the vena cava originating from the remains of the ducts venosum of the fetus) and the groove for the inferior vena cava (IVC).

A large proportion of the posterior surface of the right liver lobe is devoid of a peritoneal lining, and is termed the "bare area" of the liver (**Figure 1**). This does mean that the

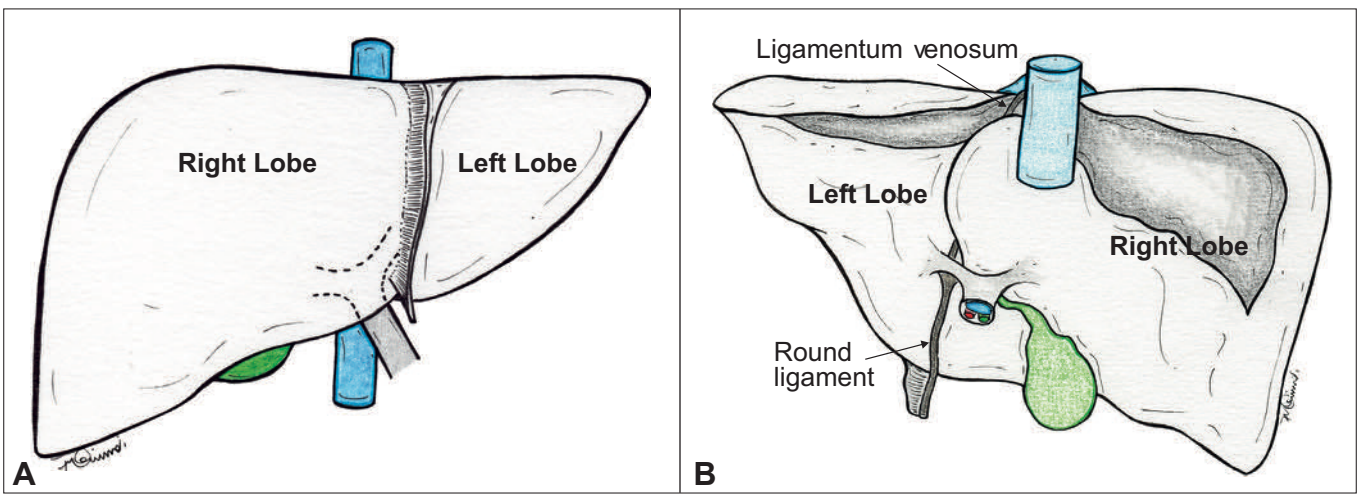


Figure 1. A) Anterior view. The liver is divided in two main lobes by the falciform ligament. The right one is larger than the left one. **B**) Dorsal view. The IVC lies snugly in a deep groove within the bare area; the hepatic veins open directly into it. Occasionally, the liver tissue embraces the vena cava completely so that it runs within a tunnel of parenchyma. The portion of the right lobe located anterior to the hilar fissure is called the quadrate lobe, limited on the left by the umbilical fissure and on the right by the gallbladder fossa. The caudate lobe is seen posteriorly to the transverse hilar fissure. The gastrohepatic omentum is attached to the ligamentum venosum (or Arantius ligamentum), lying between the caudate lobe (that is placed within the lesser omental sac) and the left hepatic lobe.

upper pole of the right kidney, as well as the right adrenal gland, is in direct contact with the liver with no intervening peritoneal covering. Therefore, it is not possible to see free peritoneal fluid between the liver and either the upper pole of the right kidney or the right adrenal gland unless there has been prior liver transplantation or surgical dissection.

The liver can be divided into approximately equivalent halves by a so called "principal plane", which travels in a cranio-caudal direction and separates the liver into two anatomical halves (i.e. the right and left hemilivers). Although not directly visualized on imaging, this imaginary parasagittal line runs posteriorly from the IVC notch to the gallbladder fossa antero-inferiorly. The right side of the liver receives blood from the right portal vein and hepatic artery, with biliary drainage via the right bile duct. The left side of the liver has a similar reciprocal arrangement.

IMAGING OF THE LIVER: TECHNIQUES AND NORMAL APPEARANCES

In clinical practice, imaging of the liver is most frequently performed using ultrasound, a technique that is fast and widely available. When liver visualization is deemed suboptimal or inadequate, or when an indeterminate lesion is detected on ultrasound, CT or MRI is usually employed for further assessment. Radionuclide imaging techniques are usually used in specific indications, such as for the evaluation of hepatocytes tracer uptake, biliary excretion or glucose uptake activity.

ULTRASOUND

Ultrasound (US) images are formed by sound waves transmitted into the body by an ultrasound transducer, which are subsequently reflected back to the transducer. Differences in the acoustic impedance of tissues allow these to be visualized on ultrasound. In order to allow the sound waves to be transmitted from the transducer into the body, an acoustic coupling material in the form of aqueous gel is applied to the skin. Typically, a 3.5MHz phased array ultrasound transducer is used to evaluate the liver, which provides good resolution at an appropriate depth.

On ultrasound, the normal liver demonstrates a homogenous echotexture, which has a slightly higher reflectivity compared with the adjacent right renal cortex (**Figure 2A**). On the sagittal view, the hepatorenal angle and subhepatic space are both well demonstrated. The contour of the liver should appear smooth. Blood vessels within the liver are seen as echo-free branching structures traversing the liver parenchyma (**Figure 2B**). At the porta hepatis, the triad of structures comprising the common bile duct, main portal vein and the hepatic artery are readily identified (**Figure 2C**). The gallbladder is usually visible as a fluid-filled, echo-free sac, with a thin wall (< 3 mm) when normally distended (**Figure 2D**). The liver itself may also be used as an acoustic

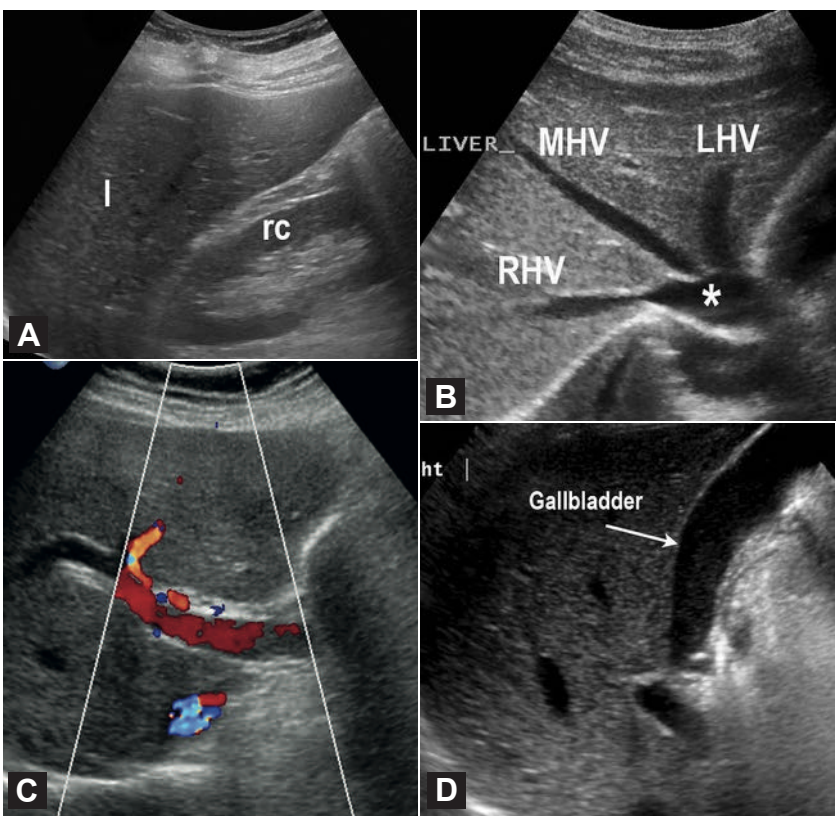


Figure 2. Ultrasound examination of the normal liver. **A**) Sagittal view showing the homogenous echotexture of the liver (l), which is slightly more echogenic (brighter) than the adjacent right renal cortex (rc). **B**) Subcostal view showing the tri-radiate hepatic veins draining into the inferior vena cava (asterisk). The hepatic veins appear as echo free dark structures within the hepatic parenchyma. LHV: left hepatic vein; RHV: right hepatic vein; MHV: middle hepatic vein. **C**) Intercostal oblique view obtained with Doppler technique demonstrating structures at the porta hepatis. The common bile duct (CBD) is seen to run parallel and anterior to the portal vein, with the right branch of the hepatic artery between these two structures. **D**) Intercostal oblique view of the gallbladder. A normal gallbladder appears as a relatively echo-free fluid filled sac with a thin wall (<3 mm).

window for the interrogation of adjacent intra-abdominal organs and great vessels. The size and volume of the liver is difficult to assess accurately with ultrasound, and is at best a subjective impression. Ultrasound may also be employed intraoperatively to identify the plane of surgical dissection by identifying the middle hepatic vein (the principal plane) in order to plan lobar resection.

COMPUTED TOMOGRAPHY (CT)

Computed tomography imaging employs a ring of x-ray tubes and detectors mounted on a circular gantry as the basis for image acquisition. Each x-ray beam generated is attenuated to different extent as it passes through the body placed within the circular gantry and is detected on the opposite side. The differential tissue attenuation of the x-ray is used to compute a transverse cross-sectional image of the body.

Using state-of-the-art multidetector CT allows for breath hold liver scanning in less than 5-10 seconds, even in patients with respiratory difficulties. Imaging of the liver may be performed with or without administration of intravenous contrast medium, although the former is usually utilized in clinical practice. Images obtained without intravenous contrast medium can reflect diffuse changes, such as fat or iron deposition or identify focal areas of calcification or hemorrhage. However, contrast enhanced CT imaging is usually employed for the detection and characterization of focal liver lesions. When contrast is administered, imaging in the arterial phase of enhancement (typically from 20 to 40 seconds after contrast administration) is essential for the detection of hypervascular lesions such as focal nodular hyperplasia, adenoma, hepatocellular carcinoma, and hypervascular metastases (e.g. from neuroendocrine tumors). By comparison, lesions that are relatively hypovascular compared to the normal liver are usually best seen in the portovenous phase of contrast enhancement (typically at 60 to 80 seconds after contrast administration). The density of a tissue on CT imaging can be quantified by measuring its CT attenuation value, which is expressed in Hounsfield Units (HU). Thin section imaging in the arterial or portovenous phases of enhancement is also utilized for CT angiography to evaluate vascular anatomy. This is discussed in greater detail later in the chapter.

When CT is performed without intravenous contrast medium, the normal liver should show a smooth outline. The parenchyma is homogenous and typically demonstrates attenuation values of about 54 to 60 HU, which is usually 8 to 10 HU higher than that of the spleen.[4] This difference is attributed to the glycogen content of the liver (**Figure 3A**). Diffuse fat infiltration will reduce the CT attenuation values of the liver (**Figure 3B**), whereas iron infiltration will increase them. Recent advances in dual energy CT have the potential to improve the quantification of hepatic steatosis and iron deposition disease,[5] by comparing the relative CT attenuation of the liver using x-ray beams of different energies.

On contrast enhanced CT imaging, the normal liver enhances uniformly. In the portovenous phase of contrast enhancement, the intrahepatic vasculature is usually higher density (brighter) than the normal parenchyma. On axial CT imaging sections of the liver in a craniocaudal direction, the following features may be noted. Immediately below the right hemidiaphragm, the liver outline may appear irregular due to indentation by diaphragmatic slips (**Figure 4A**). The tri-radiate hepatic veins draining into the inferior vena cava can be seen cephalad to the plane of the porta-hepatis (**Figure 2B**). The fissure for the *ligamentum venosum* may be used as a landmark for the identification of the gastroesophageal junction (**Figure 4B**). At the level of the porta-hepatis, the main portal vein and its branches are visualized, as well as the fissure for the falciform ligament (**Figures 4C** and **4C**). Note that the hepatic artery is usually not visible in the portovenous phase of contrast enhancement. There should not be any significant dilatation of the intrahepatic ducts although the common bile duct may trace as a low-density tubular structure at the porta. More inferiorly, the gallbladder comes into view as a low-density structure (**Figure 4E**), which is variably distended according to prandial state.

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging (MRI) employs a strong magnetic field (typically 1.5 or 3.0 Tesla) to create images of the body. By applying radiofrequency pulses, the behaviors of water protons in tissues in response to these energy pulses are used to construct the MR images. Compared with CT imaging, MRI is free from ionizing radiation and

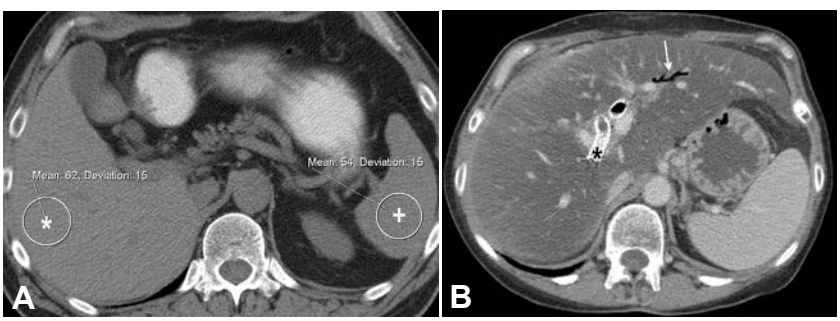


Figure 3. Axial CT. **A**) Without intravenous contrast, the normal liver parenchyma appears homogenous with a CT attenuation value of approximately 60 HU (asterisk), which is 8-10HU higher than the spleen (+). **B**) Portovenous phase in another patient. There is diffuse fat infiltration of the liver, which reduces the CT attenuation value of the liver parenchyma. Compare this image with Figure 3A. There is also a biliary stent in situ (asterisk) resulting in aerobilia in the left lobe of the liver (arrow).

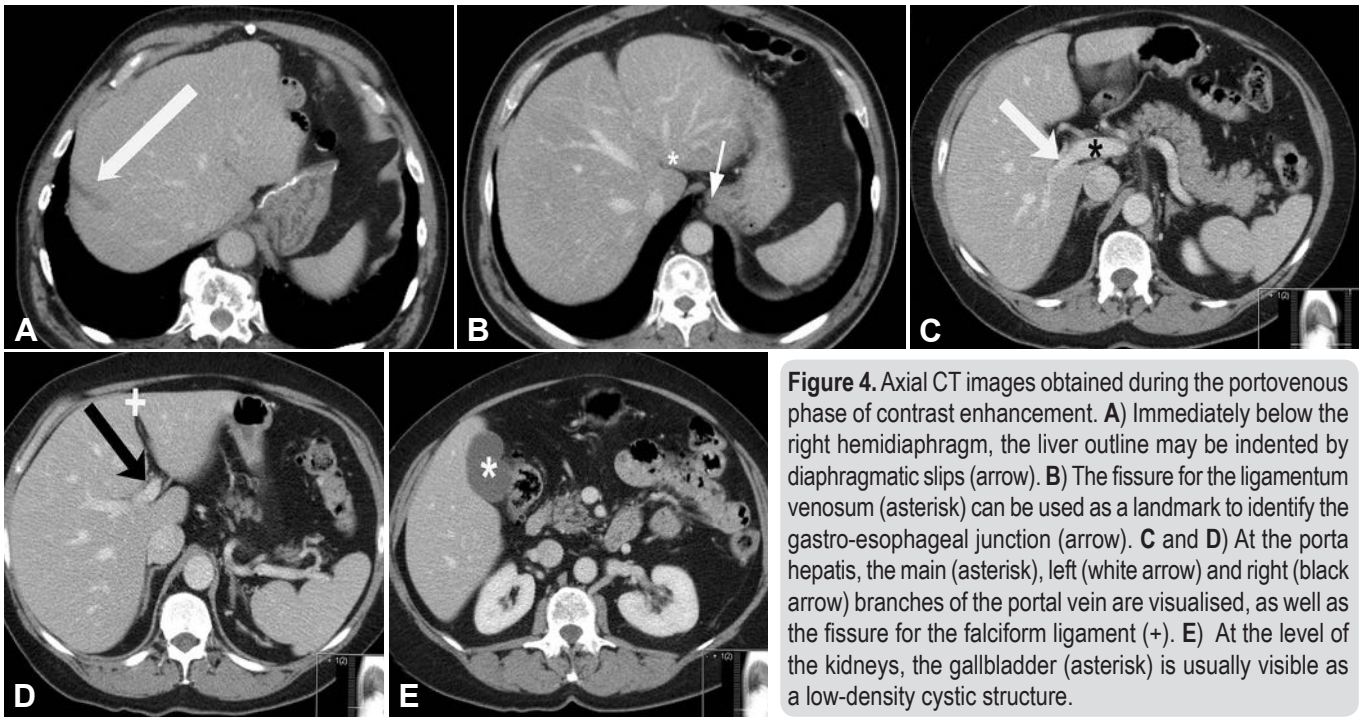


Figure 4. Axial CT images obtained during the portovenous phase of contrast enhancement. **A**) Immediately below the right hemidiaphragm, the liver outline may be indented by diaphragmatic slips (arrow). **B**) The fissure for the ligamentum venosum (asterisk) can be used as a landmark to identify the gastro-esophageal junction (arrow). **C** and **D**) At the porta hepatis, the main (asterisk), left (white arrow) and right (black arrow) branches of the portal vein are visualised, as well as the fissure for the falciform ligament (+). **E**) At the level of the kidneys, the gallbladder (asterisk) is usually visible as a low-density cystic structure.

may be safely repeated. Furthermore, MRI has superior soft tissue contrast, which is harnessed for disease detection and characterization. Two basic types of images are widely used to evaluate the liver: T1-weighted and T2-weighted images.

On a T1-weighted image of the liver, the liver parenchyma appears grey, with intrahepatic vascular structures appearing even darker (**Figure 5A**). Note that the spleen also appears darker than the liver on the T1-weighted image. On a T2-weighted image, fluid-containing structures such as the gallbladder, the biliary tree, cerebrospinal fluid surrounding the spinal cord and luminal contents of the gastrointestinal tract appear high signal intensity or bright (**Figures 5B** and **5C**). By observing the relative signal intensity of a lesion on T1-weighted and T2-weighted images, as well as the behavior of the lesion following MR contrast administration; it is possible to characterize focal liver lesions with a high degree of confidence and diagnostic accuracy in the majority of cases. The key anatomical landmarks described under CT imaging can all be easily discerned on MRI.

MRI is a versatile imaging technique that can also be used to study the biliary tree or the hepatic vasculature. Using T2-weighted imaging in magnetic resonance cholangio-pancreaticography (MRCP), the fluid-containing structures of the gallbladder, bile ducts and pancreatic ducts are rendered highly visible and can be displayed as projection images to reveal the ductal anatomy of the liver and pancreas (**Figure 6A**). Such a technique is particularly helpful for the detection of biliary stones or for identifying the presence and level of biliary tree obstruction (**Figure 6B**).

Following intravenous injection of low molecular

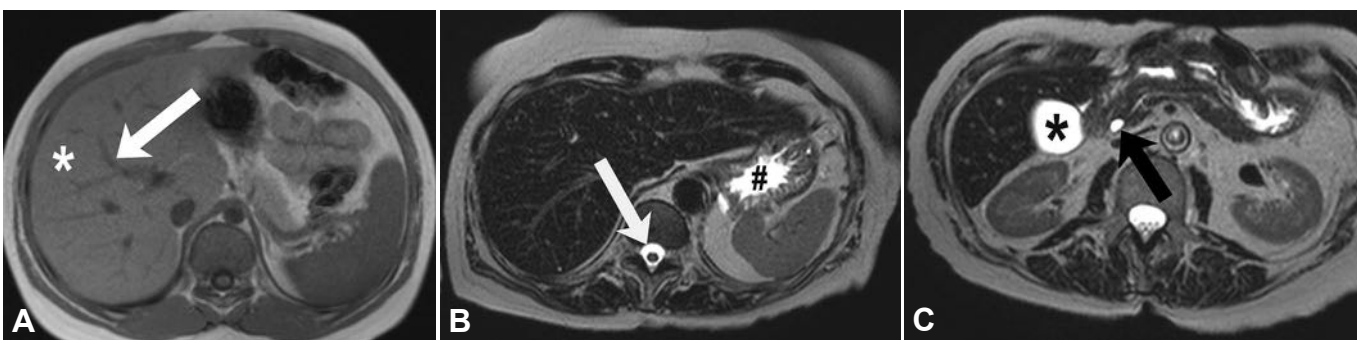


Figure 5. A) T1 weighted axial magnetic resonance (MR) image of the liver. Note that the spleen appears darker than the liver (asterisk), which returns intermediate grey signal intensity. The intrahepatic vasculature appears as dark signal void structures (arrow). **B** and **C**) T2 weighted axial MR images of the liver. Fluid containing structures such as the gallbladder (asterisk), the biliary tree (black arrow), cerebrospinal fluid surrounding the spinal cord (white arrow) and luminal contents of the gastrointestinal tract (#) appear bright (or high signal intensity).

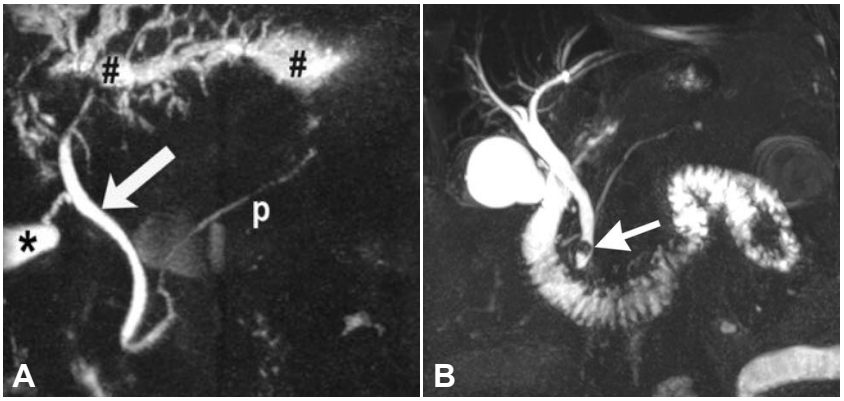


Figure 6. MRCP maximum intensity projection images demonstrating the ductal anatomy of the liver and pancreas. **A**) In this man with a hilar cholangiocarcinoma, the fluid containing gallbladder can be identified (asterisk), as well as the normal common bile duct (white arrow) and pancreatic duct (p). Note however, the abnormally dilated left intrahepatic ducts (#) resulting from the obstructing tumor (not directly visualized). **B**) In this man with a common bile duct stone (arrow), there is a low signal intensity rounded structure surrounded by high signal intensity biliary fluid in the distal common bile duct.

weight gadolinium-based MR contrast medium injection, the passage of contrast through the liver can be tracked using MR angiographic techniques, which allow the hepatic artery, portal vein and hepatic veins to be assessed. Some disadvantages of MR angiography compared with CT angiography include poorer spatial resolution (small vessels may not be seen), the possibility that the technique may not be successful in patients with metallic implants (which induce artifacts) and the fact that some patients may experience claustrophobia whilst in the MR scanner.

More recently, opacification of the biliary tree using contrast media such as mangafodipir trisodium, gadolinium-BOPTA or gadolinium-EOB-DTPA have been shown to be useful for demonstrating the biliary system,[6,7] especially for the detection of bile leaks following liver surgery.

RADIONUCLEAR IMAGING

Radionuclear imaging has the advantage over cross-sectional imaging techniques in that it provides functional information, albeit usually at a low spatial resolution.

Liver imaging commonly employs 99mTc-sulphur colloid or albumin colloid, which is taken up by the reticuloendothelial system. The liver takes up 80-90 per cent of the injected dose, 5-10 per cent is taken up by the spleen, and the small remaining portion is taken up within the bone marrow.[4] Imaging is performed approximately 5-10 minutes after intravenous injection of the radiopharmaceutical as it is rapidly cleared from the bloodstream in patients with normal hepatic function (**Figure 7**). The spleen will appear more prominent during the "arterial" phase, with the liver dominating during the "portal-venous" phase. Single photon emission computed tomography (SPECT) could lead to more accurate localization of a lesion within the liver. A "colloid" shift will occur when there is increased uptake of radiopharmaceutical by the bone marrow, for example with cases of hepatic dysfunction such as hepatitis. Here the spleen will appear relatively more prominent than the liver. Kupffer cell component lesions such as focal nodular hyperplasia (FNH) should appear as "hotspots". Focal liver defects can result from lesions without a normal liver tissue component, such as primary liver tumors, metastases, or simple cysts. A diffuse pattern of liver uptake can be observed in cirrhosis or lymphoma.

Positron emission tomography (PET) using ^{18}Fluoro-deoxyglucose (^{18}FDG) is now widely used in oncology for the staging of malignancies. ^{18}FDG–PET/CT has been shown to be useful for the detection of both hepatic and extrahepatic diseases, which may be radiologically occult on other diagnostic imaging tests.

SEGMENTAL ANATOMY OF THE LIVER

Hepatic surgery, and in particular hepatic resection, is based on a segmental approach to liver anatomy described by Couinaud.[8] This has functional implications, as each segment has its own independent vascular supply and

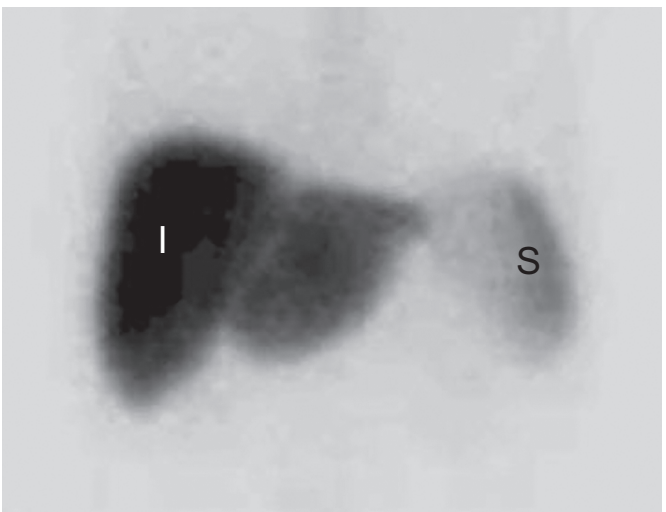


Figure 7. Normal Technetium sulphur colloid scan showing normal tracer uptake in the liver (l), and to a lesser extent within the spleen (s). (*Image courtesy of Ms. Bernadette Cronin, Royal Marsden Hospital, UK*)

can be resected without adversely affecting the other liver segments. The nomenclature proposed by Couinaud divides the liver into eight segments, with the caudate lobe designated as segment I. The remaining segments are defined by their relationship to the branches of the portal vein and hepatic veins, and numbered sequentially in a clockwise fashion. The hepatic veins provide sagittal boundaries, with the portal vein branches acting as the axial (superior/inferior) boundary (**Figure 8**). The "left liver" is separated from the "right liver" by the middle hepatic vein. These are further subdivided into medial and lateral sections by the left hepatic vein as well as anterior and posterior sections by the right hepatic vein.

The left liver is therefore separated sagittally into medial and lateral sectors by the left hepatic vein. Posteriorly, the left hepatic vein separates segment 2 (lateral) from segment 4a (medial). Anteroinferior to the left hepatic vein, segment 3 (lateral) is separated from segment 4b (medial) by the umbilical fissure and falciform ligament. The left portal vein branch will separate the left liver into superior and inferior segments; therefore dividing segment 2 (superior) from segment 3 (inferior). Similarly, it divides segment 4 into two further segments: segment 4a (superior) and segment 4b (inferior).

The anterior right liver segments (5 and 8) are separated from the posterior segments (6 and 7) by a plane containing the right hepatic vein. In a similar fashion to the left liver, the right portal vein branch separates the superior (7 and 8) from the inferior (5 and 6) segments (**Figure 8**).

For further details refer to **Chapter 1** (Surgical Anatomy of the Liver).

The hepatic segments are very well visualized on CT or MR imaging as the planes for the hepatic veins and the portal veins are clearly delineated. On transverse axial CT images, the hepatic segments according to Couinaud

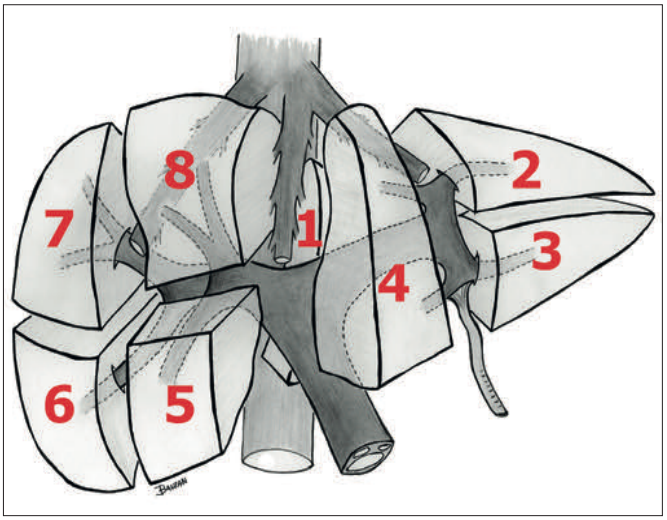


Figure 8. Segmental anatomy of the liver proposed by Couinaud. The middle hepatic vein divides the right hemiliver (segments 5,6,7 and 8) from the left hemiliver (segments 2,3 and 4).

are readily identified. Above the plane of the portal veins, segments 7, 8, 4A and 2 are visible (**Figure 9A**), whereas below the plane of the portal veins, segments 5, 6, 4B, 1 and 3 are identified (**Figure 9B**). Coronal reformats can be helpful to assess lesions sitting at boundary zones between segments for more accurate lesion localization.

HEPATIC BLOOD SUPPLY OF THE LIVER: AN OVERVIEW

The liver has a dual blood supply from the hepatic artery and the portal vein. The liver receives approximately two thirds of its blood supply from the portal vein, with one third from the hepatic artery. The hepatic artery and portal

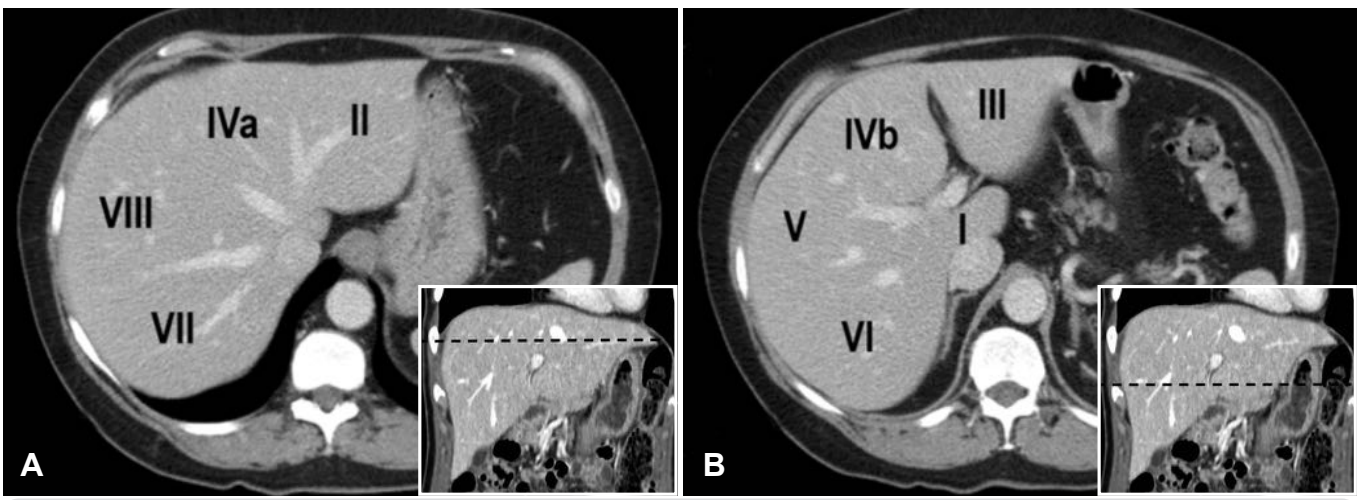


Figure 9. Segmental anatomy of the liver as seen on axial CT imaging. **A**) Above the plane of the portal vein, segments 7, 8, 4a and 2 can be seen. **B**) Note the positions of segments 5, 6, 4b, 1 and 3 below the plane of the portal vein.

vein (together with the common hepatic duct) divides early within the porta hepatis into left and right branches. This is followed by regular sub-divisions into segmental and finally interlobular vessels. Together, these dividing vessels and biliary ducts within the liver are known as portal triads. The quadrate and most of the caudate lobe are supplied by the left vessel branches and therefore belongs to the "functional" left hemiliver. Furthermore, there are few anastomotic connections between vessels supplying the functional left and right livers.[9,10] An important additional point to note is that with the exception of the hepatic veins, branches of the hepatic artery, portal vein, or biliary vessels do not cross to adjacent segments.

Functional segments supplied by the main vascular branches are also recognized. The left liver can be divided into left lateral and left medial sectors. The left lateral sector corresponds to the left anatomical lobe (equivalent to segments 2 and 3), whereas the left medial sector corresponds to the caudate and quadrate lobes (equivalent to segments 4 ± 1). The fissures for the *ligamentum teres* and venosum divide the left medial from the lateral sectors. The right liver can be divided into a functional right anterior and a right posterior sector, although the plane of demarcation is less defined on imaging.

The caudate lobe is a unique liver segment, as it receives arterial blood from both left and right hepatic branches as well as the portal vein. In addition, it drains directly into the IVC via small tributaries. The significance is that in disease states affecting a particular component of the liver venous architecture (e.g. Budd-Chiari syndrome affecting the hepatic veins), the caudate lobe may show reactive hypertrophy (**Figure 10**).

In a minority of patients, perfusion defects can be seen within the caudate and quadrate lobe during CT imaging during the portal venous phase (**Figure 11).** Their significance lies in the fact that they can mimic disease, such as metastatic deposits, but are in fact a result of aberrant venous drainage from the left gastric vein or pericardiophrenic vein.[11] This is thought to occur because segments 1 and 4 embryologically develop after the portal vein, which can thus lead to aberrant patterns of venous drainage.[12]

A blood vessel that supplies a segment in addition to its normal supply is termed an *accessory* vessel, whereas a vessel that solely supplies a segment and does not originate from a conventional location is termed a *replaced* vessel. The classic vascular anatomy only exists in a minority of patients, with a study of 107 patients demonstrating that 65% of the recipients and donors had some form of anatomic vascular variant.[13] As vascular complications account for considerable morbidity and mortality, accurate preoperative assessment of any variant vascular anatomy is therefore essential.

IMAGING EVALUATION OF HEPATIC VASCULATURE

Ultrasound

On ultrasound, the portal vein and its branches will demonstrate hyperechoic or bright fibrous walls, distinguishing them from the hepatic veins, which do not have such an appearance (**Figure 12**). The portal vein and its branches will radiate out from the porta hepatis, whereas the hepatic veins will radiate out from superior aspect of the intrahepatic IVC and they will therefore run approximately perpendicular to each other (**Figure 12C**). The portal tracts will also contain branches of the hepatic artery and biliary tree, but whilst



Figure 10. Budd-Chiari syndrome. Axial CT image of the liver obtained in the portovenous phase of contrast enhancement. Note heterogeneous enhancement of the liver with hypertrophy of the caudate lobe (arrows).

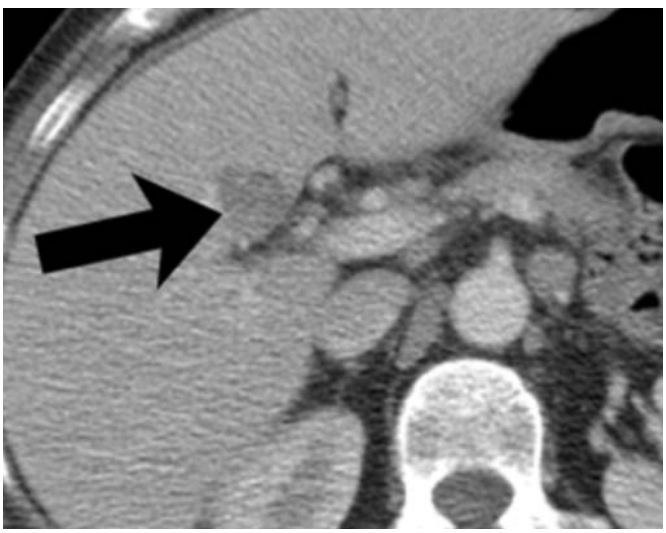


Figure 11. Axial computed tomography image of the abdomen at the level of the celiac artery in the late arterial phase of enhancement. A perfusion defect is visible within segment 4 (black arrow) appearing as a geographical focal area of low density. This is a normal variant, which can mimic disease.

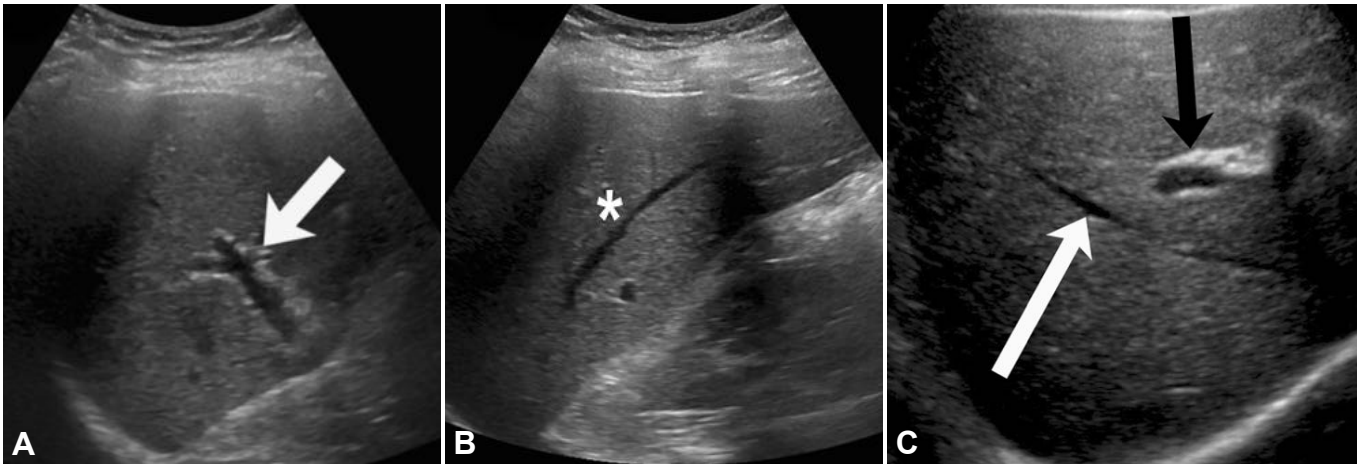


Figure 12. Sonographic appearances of the portal versus the hepatic veins. **A**) Intercostal oblique view showing the hyperechoic (bright) walls of the portal vein (arrow). **B**) The normal hepatic veins lack this appearance (asterisk). **C**) Oblique sonographic view of the right liver lobe. The main portal vein and its branches radiate out from the porta hepatis (black arrow), whereas the hepatic veins drain into the superior aspect of the intrahepatic inferior vena cava (white arrow). On this view, the orientation of these structures appears approximately perpendicular to each other.

these can be separately identified near the porta hepatitis, they are progressively more difficult to appreciate as they taper towards the liver periphery.

Doppler ultrasound technique is routinely used to assess the vascular status of the liver. The portal vein and its main branches are best imaged using a right oblique approach through the ribs thereby ensuring that the flow is towards the transducer and maintaining a good Doppler angle. The normal portal venous waveform is continuously anterograde (**Figure 13A**), but can vary slightly with the respiratory and cardiac cycles [4] reflecting the normal elasticity of the liver parenchyma, which can be lost with fibrosis. Although the normal portal vein diameter is variable, it will not usually exceed 16 mm, and will usually demonstrate a mean velocity between 12 and 20 cm per second.[14] Flow within the portal venous system is usually hepatopetal (towards the liver) and by convention assigned a red color (**Figure 13B**). If there is portal hypertension, and the direction of blood flow is away from the liver (hepatofugal flow), then convention changes to a blue color.

Doppler ultrasound flow within the hepatic veins will show a triphasic waveform, reflecting the transmitted right heart pressure changes with flow reversal during right atrial systole (**Figure 14A**).[15] This occurs because the hepatic veins drain directly into the left atrium with no intervening venous valve. For this reason, the hepatic veins will appear predominantly "blue" by normal convention at color Doppler (**Figure 14B**), with a brief flash of red as blood is redirected back into the liver during atrial systole.

Doppler interrogation of the hepatic artery reveals a pulsatile vessel that demonstrates continuous forward flow as the liver represents a low resistance system (**Figure 15**). On occasion, it can be difficult to visualize as it is a small caliber vessel, but is usually seen to course anterior to the

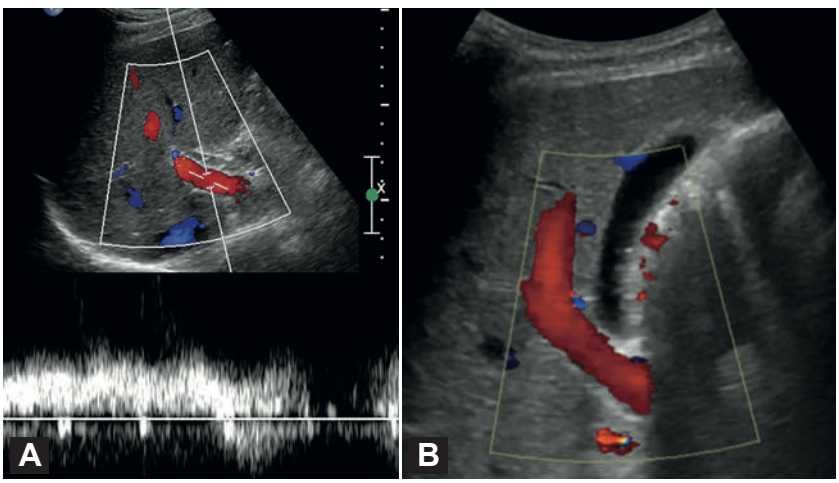


Figure 13. Doppler ultrasound of the portal vein. **A**) The normal portal venous waveform is continuously anterograde, but there can be slight phasic variation with the respiratory cycle. **B**) Portal venous flow is normal hepatopetal (anterograde or towards the liver). By convention, this is assigned a red color on color Doppler examination.

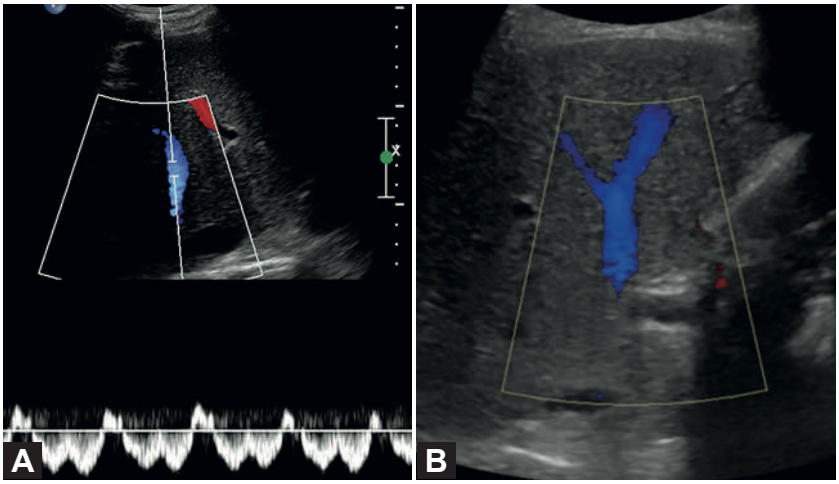


Figure 14. Doppler ultrasound of a hepatic vein. **A**) Hepatic venous flow is triphasic, reflecting the transmitted right heart pressure changes. **B**) As the flow is towards the inferior vena cava (and away from the liver), the hepatic veins are usually colored blue at color Doppler ultrasound examination.

portal vein and posterior to the common hepatic duct at the porta hepatis (**Figure 2C**).

Computed tomography (CT) / Magnetic resonance imaging (MRI)

CT angiography can be performed non-invasively using the appropriate phase of vascular enhancement, without the morbidity associated with conventional transcatheter angiography. CT angiography can assess a number of vascular phases of the liver that together can characterize the vascular nature of a lesion and aid its diagnosis, as well as generating an anatomical "roadmap" of liver vascular anatomy. It is usually performed after injection of 150 ml (at 3 ml/s) of a non-ionic iodinated contrast material, typically of a concentration of 300 mg of iodine per milliliter. Real time bolus tracking systems targeted over the aorta can be employed to ensure timely image acquisition using thin (1.5 mm) axial image sections. Although the normal liver parenchyma receives the majority of its blood supply from the portal vein, solid liver lesions often derive their blood supply from the hepatic artery. Therefore hepatic tumors will become relatively hyperdense to normal liver parenchyma during the arterial phase of enhancement, becoming isodense or hypodense during the portal phase of enhancement. In order to assess the arterial phase of liver enhancement, images are typically obtained 20-40 seconds after injection of contrast medium, with the portal phase of liver enhancement demonstrated at 60-80 seconds after injection. Further delayed imaging can be helpful in characterizing lesions – for example the delayed centripetal enhancement seen with hemangiomas. Furthermore, the image data set can also be routinely reconstructed in either the coronal or sagittal planes, and images manipulated with volume rendering or maximum intensity projection (MIP) techniques, which are particularly useful for demonstrating the vascular anatomy (**Figure 16**). Unfortunately, CT angiography can place a significant burden on the computer software and hardware, but high quality vascular maps can be generated in a few minutes on modern imaging systems. The large data sets generated may also place strains on the picture archiving and communication system (PACS) used for data archiving.

The principles of MRI angiography are similar to those of CT imaging, the difference being that the bolus of contrast injected is typically of a smaller volume (e.g. 10 to 20 ml versus 100 to 150 ml). Multi-phase dynamic T1-weighted imaging is performed, and bolus tracking at the aortic arch can be used to trigger timely image acquisition in the arterial, portovenous and interstitial phases of hepatic enhancement. The dataset can be then post-processed in a similar fashion as CT, using multiplanar reconstruction or MIP to display the vascular anatomy of the liver.

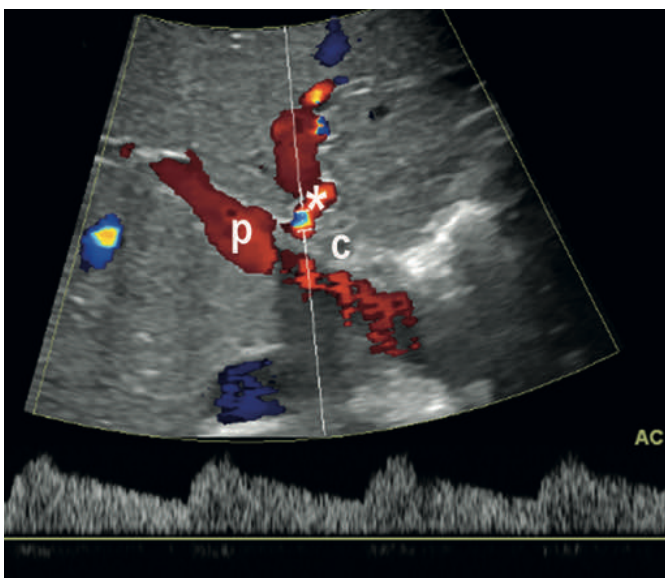


Figure 15. Doppler ultrasound of the hepatic artery at the porta hepatis. The hepatic artery (asterisk) is seen to course anterior to the portal vein (p) and posterior to the common duct (c). Note that the hepatic artery is also red color by normal convention to indicate hepatofugal flow.

Interventional Radiology

Diagnostic transcatheter angiography has largely been replaced by cross sectional imaging techniques, and is usually only employed when lesion embolization is considered. The hepatic arteries are best visualized by selective catheterization, with the arterial and parenchymal phases of greatest diagnostic value (**Figure 17**). The celiac and superior mesenteric arteries are usually selectively cannulated and studied. Portal venography can be performed directly by catheterization of the portal vein, or indirectly via contrast passage through the splenic pulp. Hepatic veins can also be directly assessed retrogradely via a femoral or jugular venous approach. This approach is not unfamiliar to interventional radiologists as it provides the access route for the transjugular intrahepatic portosystemic shunt (TIPS) procedure. Secondary liver tumors are usually hypovascular, whereas vascular tumors will demonstrate neovascularity, typically in the arterial phase. A tumor mass will displace vessels, but the presence of vascular occlusion can suggest invasion.

IMAGING ANATOMY OF THE HEPATIC ARTERY

Normal anatomy

The common hepatic artery is usually a branch of the celiac artery, which itself arises anteriorly from the aorta at approximately the level of L1 (**Figure 18**). After giving the left gastric artery, and as it passes over the superior border of the pancreatic head, the celiac artery then divides into the proper hepatic artery and the gastroduodenal artery, just prior to the opening of the lesser sac. The proper hepatic artery then passes upwards along the free edge of the lesser omentum (anterior to the portal vein and to the left of the common bile duct) to enter the porta hepatis. At the porta hepatis, the proper hepatic artery divides into the left (supplying the left lobe), middle (supplying the quadrate lobe), and right (supplying the right liver) branches.[11]

Common vascular variants

The common hepatic arterial variants were described by Michels[16] in 1966. Hiatt et al.[17] analyzed the records of 1,000 patients who underwent liver harvesting for orthot-



Figure 17. Diagnostic angiogram following selective catheterization of the celiac axis. The common hepatic artery (arrow) and its branches are clearly identified.

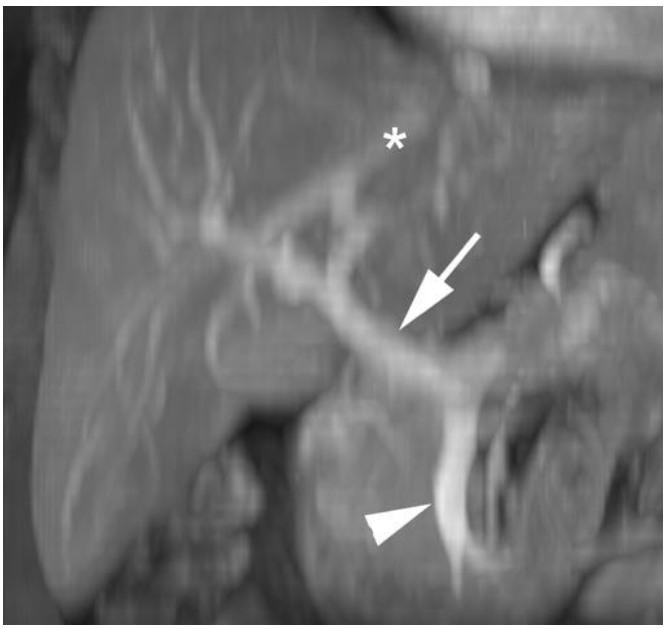


Figure 16. Contrast-enhanced coronal T1 weighted magnetic resonance image (using maximum intensity projection), which demonstrates the normal right hepatic vein (*) and portal veins (arrow) and superior mesenteric vein (arrowhead).

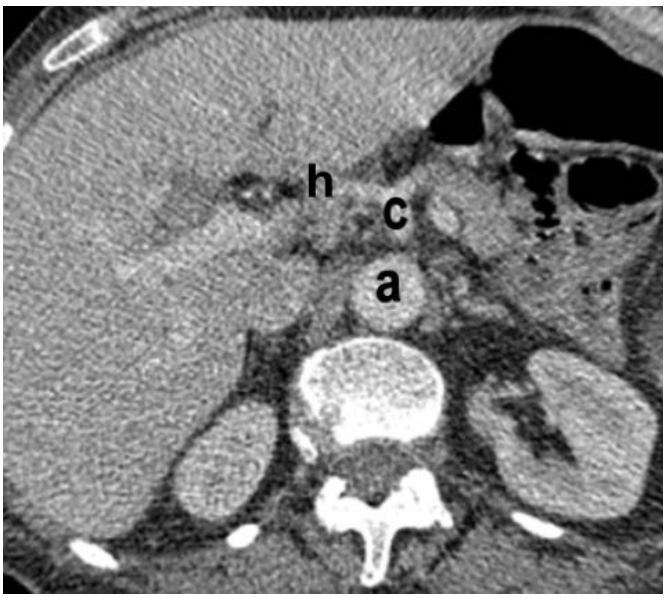


Figure 18. Axial CT image of the abdomen at the level of the celiac axis during the portovenous phase of contrast enhancement. The common hepatic artery (h) can be seen arising from the coeliac artery (c), the celiac artery arising from the anterior aspect of the abdominal aorta (a).

opic liver transplantation and classified arterial variations in six types (**Figure 19**).

Clearly, knowledge of common hepatic arterial variants is critical to the surgeon, and, for example, unfavorable hepatic arterial anatomy may preclude transplantation. Atherosclerosis of the celiac artery may prevent liver donation (or require revascularization), and complex anatomy (e.g. a variant course of the RHA) requires more extensive dissection with increased risk of postoperative ischemia and bile duct injuries. Generally the lengths of the left and right hepatic arteries are quite short for surgical reconstruction, and it is therefore important to determine the arterial length between the common hepatic arterial bifurcation and the next branch. A replaced left or right hepatic artery (**Figure 20**) is usually longer, and may facilitate safer anastomotic reconstruction.[18] Accessory vessels will require at least two arterial anastomoses and may increase the risk of postoperative complications. If these vessels measure less than 2-3 mm in diameter, then the risk of post operative thrombosis is increased.[19] The surgical significance of the hepatic arterial variant will also depend on whether it is in the donor or recipient.

The origin of the artery to segment 4 is of critical importance. This is usually a branch of the left hepatic artery, but in 11% of cases there is a variant supply from the right hepatic artery (**Figure 21**).[20] For a right liver resection, transection of this vessel as it passes through the hepatectomy plane can lead to ischemia of the remaining segment 4 leading to hepatic dysfunction.[21] This aberrant supply to the left liver will be of little significance in the recipient, but it may put the remaining segment 4 at risk of vascular compromise in the donor.[22] For left liver resection in transplantation, such a variant right hepatic artery supply may necessitate the construction of double anastomoses (the left hepatic artery and variant artery).[1]

If the RHA or LHA arises from the common hepatic artery before the origin of the gastroduodenal artery, or if the common hepatic artery trifurcates into the gastroduodenal artery and left and right hepatic arterial branches, then donor perfusion to the stomach or duodenum may be compromised. A replaced hepatic artery that arises from the SMA and passes behind the portal vein will alter the surgical approach in the recipient.

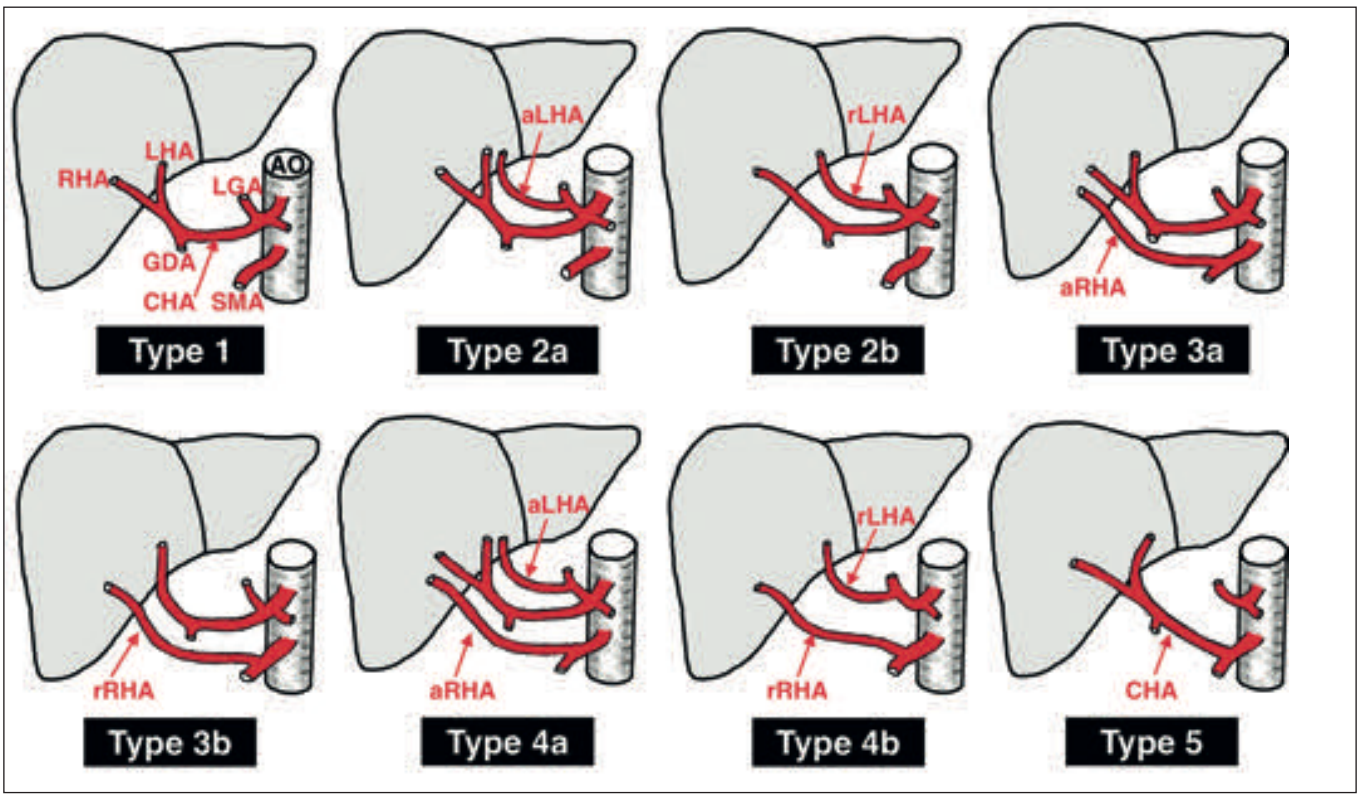


Figure 19. Hepatic artery anatomy variations. **Type 1** – standard presentation; **Type 2** – an accessory or replaced left hepatic artery from left gastric artery; **Type 3** – an accessory or replaced right hepatic artery from superior mesenteric artery (SMA); **Type 4** – both right and left hepatic arteries arising from the superior mesenteric and left gastric arteries, respectively; **Type 5** - common hepatic artery from SMA; **Type 6** (not shown) – common hepatic artery originating directly from the aorta. RHA: right hepatic artery; LHA: left hepatic artery; LGA: left gastric artery; GDA: gastroduodenal artery; CHA: common hepatic artery; SMA: superior mesenteric artery; aLHA: accessory left hepatic artery; rLHA: replaced left hepatic artery; aRHA: accessory right hepatic artery; rRHA: replaced right hepatic artery. (Adapted from Hiatt et al.[17])

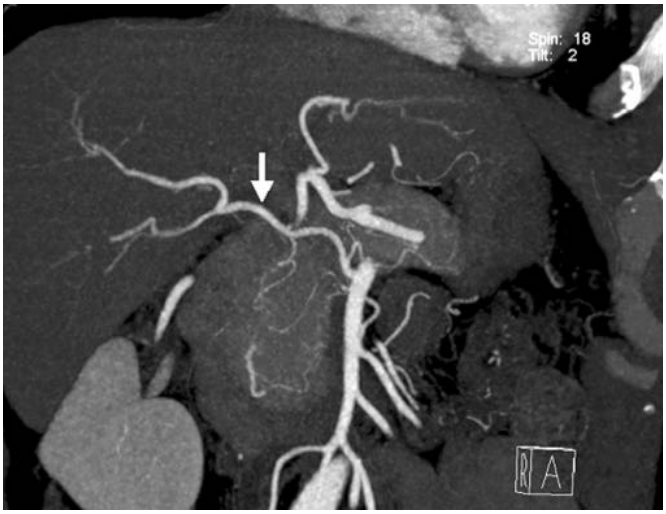


Figure 20. Maximum intensity projection (MIP) of a CT angiogram study. This shows a replaced right hepatic artery (arrow) arising from the superior mesenteric artery.

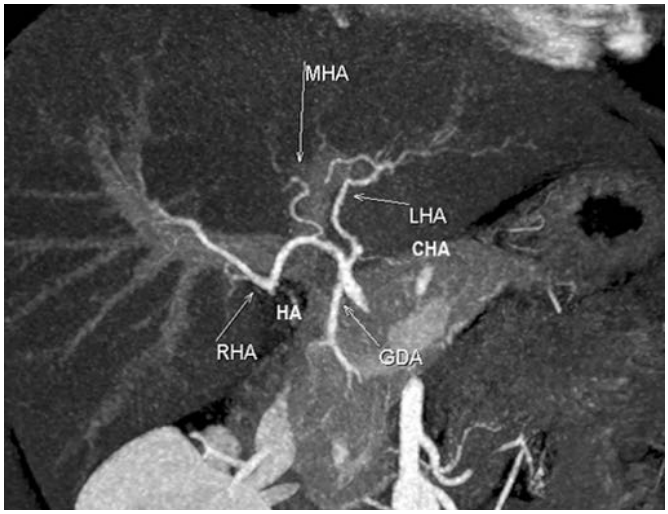


Figure 21. Maximum intensity projection (MIP) of a computed tomography angiogram study. The common hepatic artery (CHA) divides into the gastroduodenal artery (GDA) and hepatic artery proper (HA). The hepatic artery gives rise to the left hepatic artery (LHA) and right hepatic artery (RHA). A middle hepatic artery (MHA) is seen to arise from the RHA.

IMAGING ANATOMY OF THE PORTAL VEIN

Normal anatomy

The portal vein is formed by the confluence of the splenic and superior mesenteric veins behind the pancreatic neck. It divides into left and right branches before entering the liver parenchyma at the porta hepatis (**Figure 22**). The right branch is usually regarded as a continuation of the main portal vein [23] and is shorter than the left, travelling anterior to the caudate lobe (giving a branch to the caudate lobe near its origin). It then divides into an anterior and posterior branch, each further subdividing into superior and inferior branches (supplying the respective liver segments following the distribution of the right hepatic arterial branches). The left portal vein is longer than the right, and initially forms a transverse portion (which gives off a caudate branch). At the level of the umbilical fissure it turns sharply anteriorly in the direction of the round ligament. It then further divides into segmental branches, along with the left hepatic artery (**Figure 23)**.[24] The IVC passes close to and posterior to the portal vein, allowing the surgical construction of a porto-caval anastomosis in patients with portal hypertension.

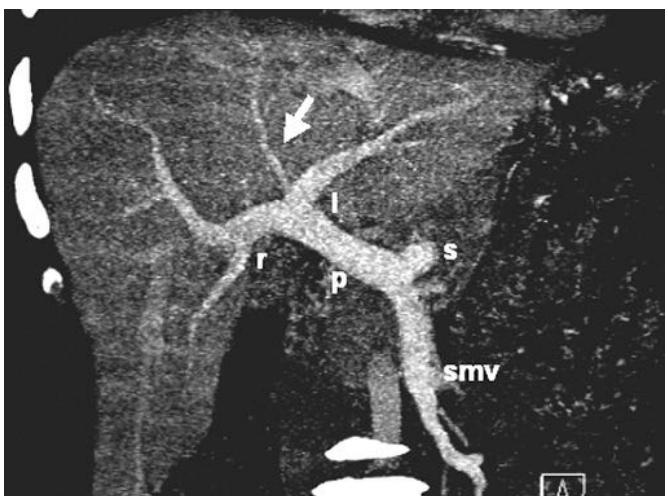


Figure 22. Maximum intensity projection (MIP) coronal CT image at the portovenous phase of enhancement. The portal vein (p) is formed by the confluence of the splenic vein (s) and superior mesenteric vein (smv) behind the pancreatic neck. The portal vein (p) divides into left (l) and right (r) branches before entering the liver parenchyma at the porta hepatis. Note that in this example, there is an accessory portal vein branch (arrow) to segment 8 of the right lobe arising from the left portal vein.

Common vascular variants

Portal venous variants are less common than those involving the hepatic artery or veins, occurring in approximately 20% of the population [25] and usually affecting the right liver. Radiologically, it is important to measure the length of the right portal vein from the main trunk bifurcation to its bifurcation into anterior and posterior branches. Additionally, in cases of left lateral segment donation between an adult donor and pediatric recipient, the transverse diameter of the left portal vein should be reported to prevent a significant size mismatch.[18]

Variants of note include trifurcation of the portal vein, where the left portal vein and both the anterior and posterior branches of the right portal vein originate from the same point (without a recognizable right portal vein) (**Figure 24)**. This lack of a right main portal vein

may necessitate a change in surgical technique.[22] Another variant requiring two portal vein anastomoses in liver transplantation is where the right anterior portal vein drains into the left portal vein (at a distance from the bifurcation), and the right posterior portal vein drains into the main portal vein.[1] Clearly, if the left portal vein is resected at the bifurcation, then this variant right anterior portal vein (and therefore segments 4, 5 and 8 that it irrigates) will be placed at risk.[20]

In liver transplantation, the distance between any two potential venous openings introduced by an anatomical variant can be measured as the surgical options include a venoplasty (both draining into the same opening), the construction of two anastomoses, or the use of a Y-shaped vascular graft to allow the construction of a single anastomosis.[18] The angle of portal vein branching should also be considered preoperatively for the recipient. This is indicated by the distance between the left and right portal vein branches at the bifurcation – a smaller distance indicating a smaller angle. If the angle is too acute, the vein is at risk of encasement and vascular insufficiency by the liver regenerative process,[26] and may require vascular reconstruction.

IMAGING ANATOMY OF THE HEPATIC VEINS

Normal anatomy

Blood from the liver drains via the hepatic veins to the IVC, with the hepatic venous anatomy being extremely variable. The hepatic veins have very short extrahepatic lengths (up to 1.5 cm) and unite with the IVC at the level of T9. Unlike the hepatic arteries, bile ducts, and portal veins, the major hepatic veins are found intrahepatically within the intersegmental planes. A hepatic vein will drain blood from its adjacent segments. The right hepatic vein is the largest, draining the majority of the right liver via segments 6, 7 and parts of segments 5 and 8. The middle hepatic vein mainly drains the central liver via segments 4, and parts of 5 and 8. The left hepatic vein drains segments 2 and 3, as well as part of segment 4. The middle hepatic vein usually joins the left hepatic vein (60% of cases)[27] to form a common trunk draining into the IVC [18] (**Figure 25)**.

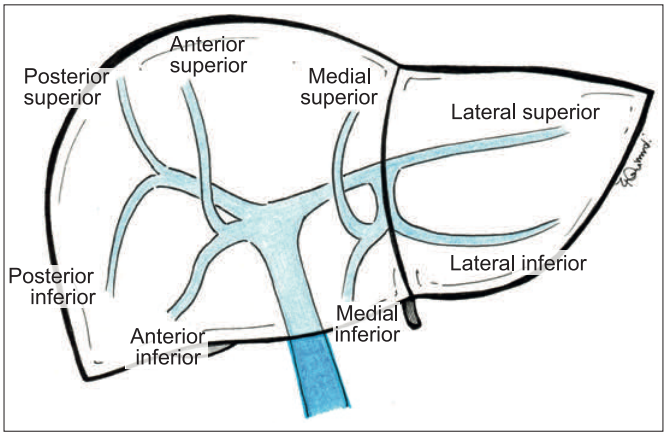


Figure 23. Diagrammatic representation of the portal venous anatomy of the liver.

Common vascular variants

Following transplantation or partial hepatectomy, graft or remnant liver regeneration is dependent upon good venous drainage, with venous congestion potentially leading to graft failure. Thus, accurate preoperative assessment of the

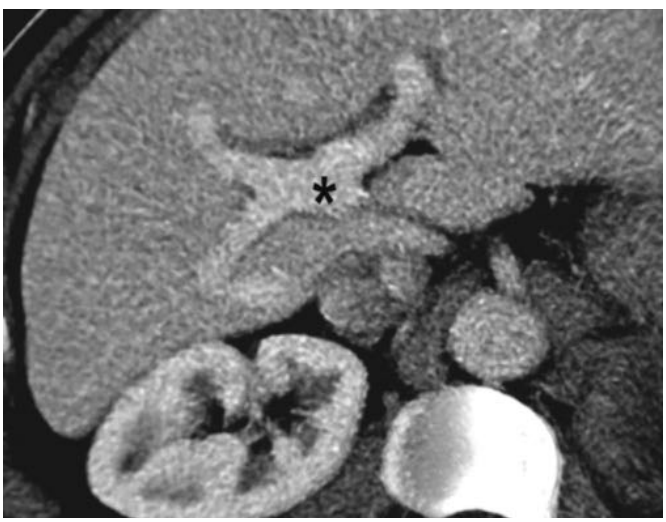


Figure 24. Trifurcation of the portal vein. The portal vein (asterisk) can be seen to divide into three branches, with absence of the right main portal vein.

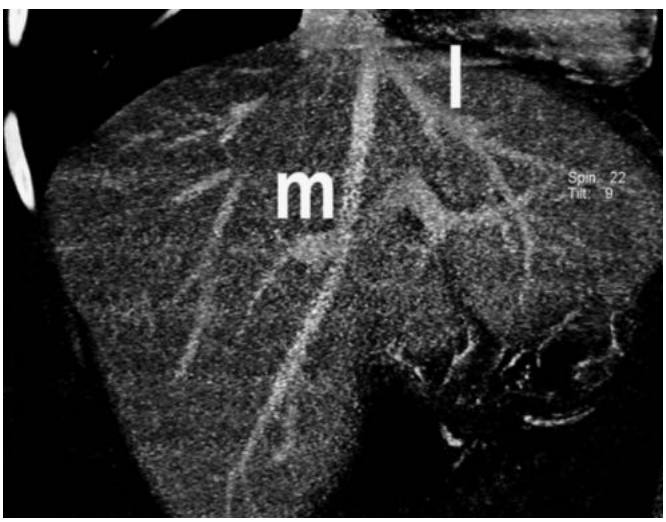


Figure 25. Coronal reconstruction of a computed tomography (CT) angiogram of the liver using a volume rendering technique (VRT). In this example, the middle hepatic vein (m) is seen joining the left hepatic vein (l).

hepatic venous anatomy is important, and the identification and re-implantation of accessory hepatic veins measuring more than 2 mm in diameter is often undertaken.

The surgical hepatectomy plane is usually about 1 cm to either side of the middle hepatic vein (MHV), and the middle hepatic vein anatomy can thus affect the hepatectomy plane and surgical approach. When removing the right liver, it may be necessary to transect significant branches of the MHV, as branches draining segments 5 and 8 may drain into the MVH, with 9% of the population having a branch draining segment 8 into the MHV.[18] Any transected branches will require re-anastomosis in the recipient in order to avoid congestion and potentially rejection.

An accessory RHV is commonly seen, with the most common hepatic venous variant being an accessory inferior RHV which usually drains segment 6 or 7 [22,26] and which has a reported incidence of 68%.[28,29] If an accessory vein is significant in size (> 3 mm), then care must be taken to avoid inadvertent damage with the associated risk of bleeding or ischemic graft malfunction. Significant accessory RHVs with a cross sectional diameter of > 5 mm should be re-implanted onto the recipient IVC to prevent the development of a congested graft and organ rejection.[13] Furthermore, the distance between the accessory drainage site and that of the main hepatic venous drainage point along the IVC is important to delineate. This distance has been found to be greater than 4 cm in 44% of patients,[30] and this is technically important in liver transplantation as it may be difficult to surgically implant both veins with a single partially occluding clamp when this distance is greater than 4 cm.[18]

Other anomalous venous drainage patterns to consider include drainage of segments 5 and 7 to the MHV, as well as early branching of the vein that drains segment 8 into the MHV.[26] Such early branching may require re-implantation of this segment 8 venous anatomy in order to prevent segment congestion and the associated complications. The segment 4 draining veins can be highly variable, and although they usually drain into the MHV, they can be multiple and small in caliber.[20]

THE BILIARY SYSTEM

IMAGING THE BILIARY SYSTEM

Ultrasound is usually employed as the first-line imaging test to assess the biliary tree. The gallbladder is well assessed using this technique, with a high diagnostic accuracy in determining the presence of gallstones, polyps, mass lesion or gallbladder wall thickening associated with cholecystitis. The normal common bile ducts measures less than 10 mm at the level of the porta hepatitis and normal intrahepatic ducts are usually not well seen on ultrasound. When dilated, these appear as tubular structures which parallel the course of the vascular liver supply and its branches (**Figure 26**).

Magnetic resonance cholangio-pancreaticography (MRCP) has largely replaced endoscopic retrograde cholangio-pancreaticography (ERCP) for the evaluation of the biliary tree and pancreatic duct. The technique is relatively quick to perform, is non-invasive, and can be used to identify the cause of biliary tree obstruction. The normal biliary tree anatomy is well demonstrated by MRCP and can be used to plan surgical treatment. However, MRCP can sometimes fail to demonstrate the intrahepatic ducts. Furthermore, it can be prone to artifact, and will not clearly demonstrate calcifications.[31]

CT cholangiography may be performed using an intravenous biliary contrast agent (e.g. Cholografin: iodipamide meglumine) after a 6 to 10 hour delay.[32,33] Yeh et al.[34] found that CT cholangiography was potentially better than MR cholangiography in the assessment of second order bile ducts. In another study, CT cholangiography was shown to be more accurate than MR cholangiography in the diagnosis of aberrant biliary anatomy prior to laparoscopic cholecystectomy.[35]

Using radionuclear techniques, the excretory function of the biliary system can be assessed. Iminodiacetic acid analogues (HIDA) are taken up by hepatocytes and then excreted into the biliary system. Liver activity is seen at 5-15 minutes following intravenous injection of radiopharmaceutical, with the cystic duct seen at 10-

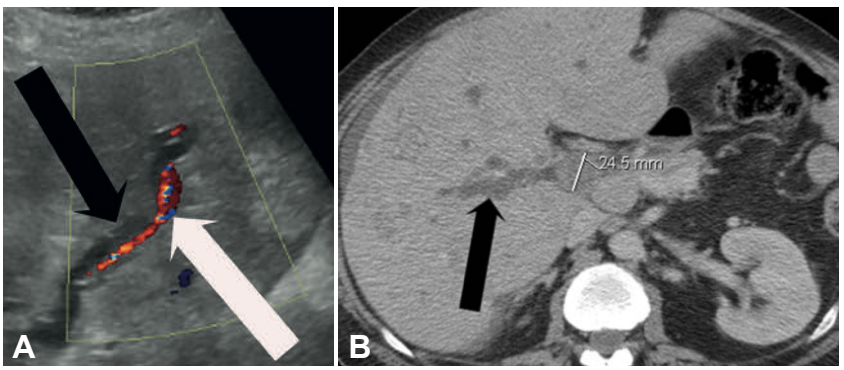


Figure 26. A) Transverse Doppler ultrasound view of the left liver demonstrating intrahepatic biliary duct dilatation. The dilated biliary duct (black arrow) is seen as an echo-poor tubular structure paralleling the course of a branch of the portal vein (white arrow). **B**) Axial CT obtained during the portovenous phase demonstrates the cause: an obstructing metastatic lymph node at thAZe porta hepatis (indicated by the measurement) associated with dilated biliary ducts (arrow).

30 minutes and the gallbladder at 20-60 minutes after tracer administration. In normal individuals, tracer activity should be seen to pass into the duodenum at 30 minutes following injection. Patients must fast beforehand to avoid a contracted gallbladder, and opiates have to be stopped as they contract the sphincter of Oddi (opiates can be intentionally given during the examination to increase biliary pressures, to encourage retrograde gallbladder filling). Non-visualization of the gallbladder under these conditions suggests a diagnosis of cholecystitis, with the absence of activity within the duodenum within 60 minutes suggesting biliary obstruction. However, acute pancreatitis and liver dysfunction can lead to a false positive result.

IMAGING ANATOMY OF THE BILIARY TREE

Normal anatomy

Bile initially drains from the hepatic lobules into bile duct tributaries, which together with the portal vein radicles and hepatic arterial branches form the portal triads within the liver parenchyma. Biliary segmentation is identical to liver segmentation defined by the vasculature, but in contrast to portal venous branches, which may demonstrate communication between segments, there is no communication between biliary branches. The right hepatic duct is usually formed from an anterior and posterior branch, which are further divided into superior and inferior branches. Therefore the four segments of the right liver are drained by the following: segment 5 by the right anterior inferior branch, segment 6 by the right posterior inferior branch, segment 7 by the right posterior superior branch, and finally segment 8 by the right anterior superior branch. The left hepatic duct is usually formed from medial and lateral branches, each of which is further supplied by inferior and superior branches. Therefore the left hepatic duct drains segments 2 (left lateral superior branch), 3 (left lateral inferior branch), and 4 (left medial superior and inferior branches) (**Figure 27)**. The caudate lobe usually drains into both left and right hepatic systems. Percutaneous radiological access to the biliary tree can be usually gained via segment 3 within the left liver, and segments 5 and 6 within the right liver.

At the porta hepatis, the left and right hepatic ducts unite to form the common hepatic duct, which travels within the free edge of the lesser omentum anterior to the portal vein and to the right of the hepatic artery. At a variable distance it is joined by the cystic duct, draining the gallbladder, and from this point on it is then termed the common bile duct or choledochal.

Common anatomical biliary variants

Postoperative biliary complications, which are observed in 15-40% of recipients and 4-13% of donors following surgery of liver transplantation surgery, are often the result of unknown anomalous biliary tract anatomy.[1] Preoperative MRCP thus plays a potentially important role in the preoperative assessment of patients. Although there are numerous variants, the most common involves the right posterior branch. This usually joins with the right anterior branch to form the right hepatic duct. However, variants include the right posterior branch draining directly into the right anterior branch or into the left hepatic duct before it joins with the right hepatic duct (**Figure 28A**). Alternatively, a triple confluence of the right anterior and posterior ducts, together with the left hepatic duct, can be seen.[36] Both the right posterior branch and left hepatic duct can drain directly into the common hepatic duct, and accessory right hepatic ducts draining into the common hepatic duct are known to occur. The cystic duct can also run parallel to the common hepatic duct for some distance within a common fibrous sheath. In this case, the common bile duct may be misinterpreted as the cystic duct, with resultant inadvertent ligation or transection of the extrahepatic bile duct (**Figure 28B**).[22]

IMAGING CONSIDERATIONS SPECIFIC TO SURGERY

LIVER TRANSPLANTATION

Improved morbidity and mortality associated with cadaveric liver transplantation has resulted in an overall shortage of available donor organs. This has resulted in the development of a number of new techniques, including living donor liver transplantation (LDLT), split liver transplantation, and auxiliary transplantation in order to expand the donor pool. In LDLT, the donor will only undergo a partial hepatectomy for donation. Split liver donation involves dividing

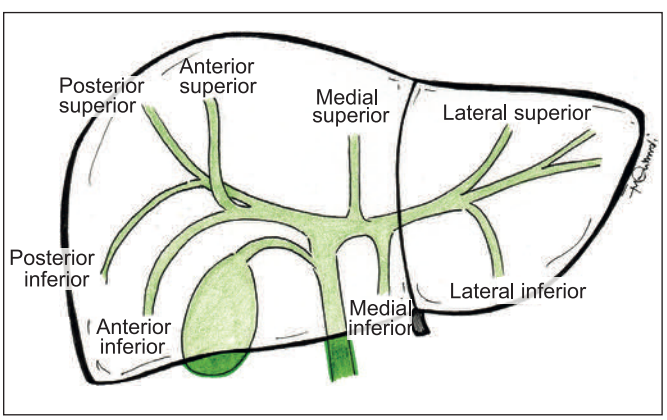


Figure 27. Diagrammatic representation of the normal biliary anatomy of the liver.

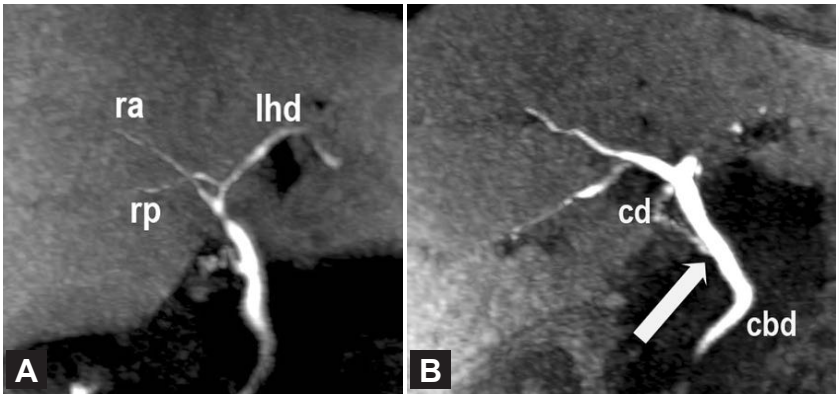


Figure 28. Aberrant liver bile duct anatomy. **A**) Coronal maximum intensity projection (MIP) reconstruction of a 3D T1 weighted fat saturated imaging dataset after Gd-EOB-DTPA contrast enhancement. Contrast fills the biliary system in the excretory phase of enhancement. The right posterior biliary duct (rp) can be seen to directly drain into the left hepatic duct (lhd). The right anterior hepatic duct (ra) is also indicated. **B**) Gd-EOB-DTPA contrast enhanced MRCP examination. Coronal T1-weighted reformat demonstrates a long cystic duct (cd) with a corresponding low insertion (arrow) onto the common bile duct (cbd).

a cadaveric liver such that the lateral segment of the left liver can be transplanted into a pediatric recipient, with the remaining liver tissue used for an adult recipient. Auxiliary transplantation can involve "piggy-backing" a graft alongside the native liver, for example if a patient has reversible liver failure (where the graft is used as a temporary measure) or if a patient has a non cirrhotic liver based inborn error of metabolism (where the graft replaces the deficient enzyme or protein).[37]

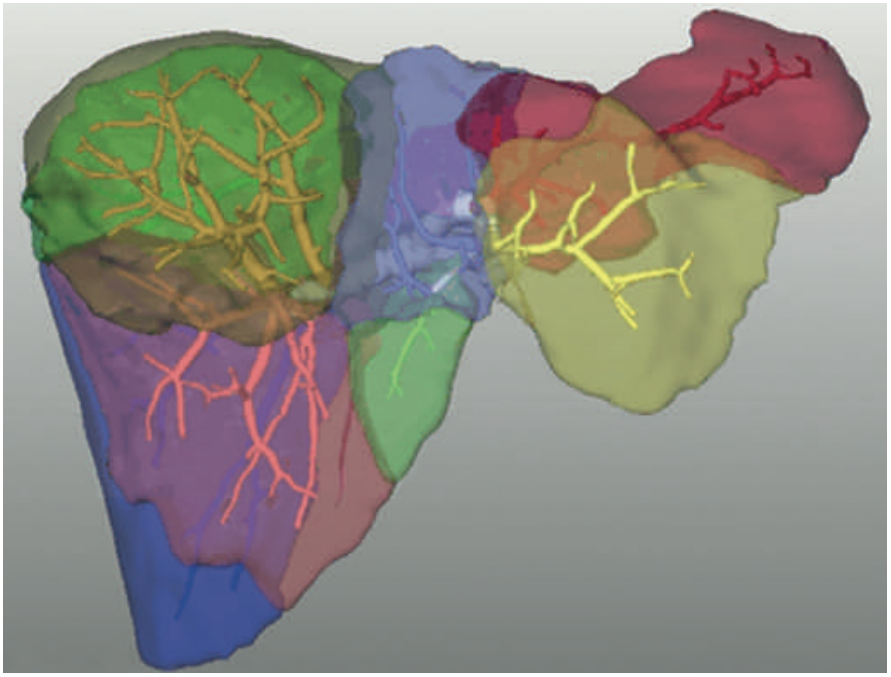
Clearly, the surgical approach for LDLT involves removal of a portion of liver in such a way that the vascular supply or hemostatic function of the remaining donor tissue is not compromised. For a pediatric recipient, it is usually the lateral segment of the left liver that is transplanted, and the transection plane is along the course of the falciform ligament. The lateral segment that is transplanted comprises segments 2 and 3 along with the left hepatic vein, portal vein, and bile duct. If the recipient is an adult, it is usually the right liver that is transplanted, since the lateral segment of left liver graft will fail to meet the metabolic requirements of an adult recipient. The hepatectomy plane is 1 cm to either side of the middle hepatic vein and parallel to the principal plane, and involves preservation of the hepatic artery to segment 4, the middle hepatic vein, as well as the left portal vein.[38] The transplanted segment is usually the entire right liver, along with the right hepatic vein, hepatic artery and bile duct. The gallbladder is also transplanted, although the middle hepatic artery and vein are left in situ in order to maintain the residual donor tissue.[20]

Donor safety is a primary concern with LDLT, and therefore the radiologist plays a role in excluding unsuitable donors for either anatomical or medical reasons. As extrahepatic collaterals that are present within a donor in situ liver are no longer present following transplantation, all vessels supplying a liver need to be identified postoperatively. Furthermore, graft vessels have to be of a sufficient length to prevent "kinking", particularly as there is a tendency for a transplant to migrate caudally over time. This will tend to be less of an issue on cadaveric transplants, as naturally longer vessel lengths can be harvested in this situation.

Liver volumes can vary quite significantly in relation to body weight, and therefore accurate preoperative evaluation of liver volume is essential. CT is usually used to assess the donor and recipient liver volumes, so as to ensure an appropriate match is made. The graft to recipient body weight ratio should be $\geq 0.8\%$.[39] If the donor liver is too large, then abdominal closure may prove difficult. If the graft volume is insufficient there is a risk of a "small for size" syndrome, whereby the graft may become dysfunctional not only due to its insufficient hemostatic capacity, but also due to the potential for injury due to relative excessive portal venous perfusion.[28] In order to permit normal metabolic function, the minimum graft volume required is 40% of the recipient's original liver mass. Similarly, the donors will need to retain a minimum of 35% of their original liver volume in order to remain metabolically viable.[29] Modern CT (as well as MRI) used in conjunction with good post-processing software is able to generate virtual 3D liver models that allow the assessment of both donor and recipient graft volumes (**Figure 29**).

PARTIAL LIVER RESECTION SURGERY

Preoperative imaging evaluation of the liver will determine the size, location and number of lesions involved, which will determine the treatment strategy. Preoperative vascular assessment will also aim to assess the relationship of a focal lesion (e.g. a primary tumor or metastasis) to the surrounding vasculature such that a sufficient tumor-free resection margin can be achieved. Furthermore, it is important not to damage the vasculature supplying the remaining liver segments, as well as ensuring that sufficient viable liver tissue remains. Consequently, any variant vascular anatomy may affect the surgical technique. For example, if there is a Michel's type II hepatic artery variant, then the surgical approach needs to be modified only if the lesion is within the right liver, whereas a type IV variant requires modification of the surgical technique whether the lesion is within the left or right liver.[26]



Portal Venous

Territory	Volume (in ml)	(relative) (% of total)
P1	13	(1.1%)
P2	108	(8.9%)
P3	119	(9.9%)
P4a	77	(6.4%)
P4b	33	(2.7%)
P5	197	(16.3%)
P6	138	(11.4%)
P7	144	(11.9%)
P8	377	(31.3%)
Total	1206	(100.0%)

Figure 29. Liver volume calculations. Segmentation based on portal venous territories using MEVIS® software (MeVIS Medical Solutions, Germany). Such information would be useful for planning liver surgery, especially in patients with previous hepatic surgery.

GALLBLADDER SURGERY

Congenital anomalies and anatomical biliary variants have the potential to lead to diagnostic confusion, as well as increasing the risk of bile duct injury (including leaks or strictures). This is a particular risk during laparoscopic cholecystectomy, where the fields of view are more limited. Aberrant or accessory biliary ducts may be inadvertently ligated during surgery, with an aberrant or accessory right hepatic biliary duct draining into the common hepatic or cystic duct a common finding.[40] A low insertion of the cystic duct into the distal common bile duct occurs in 9% of patients,[41] and if this is not recognized then the common bile duct may be mistaken for the cystic duct with the potential for ligation of the common bile duct. Furthermore, an unsuspected common bile duct stone may require an additional operation if it cannot be removed endoscopically at the time of initial surgery.

Imaging can also preoperatively alert the surgeon to a number of potential congenital malformations of the extrahepatic biliary tree. These can be classified according to the Todani classification, and include choledochal cysts (type I), bile duct diverticulum (type II), a choledochocele (type III), multiple dilatations of the intra and extrahepatic biliary tree (type IV), and finally Caroli's disease (type V) (**Figure 30)**.

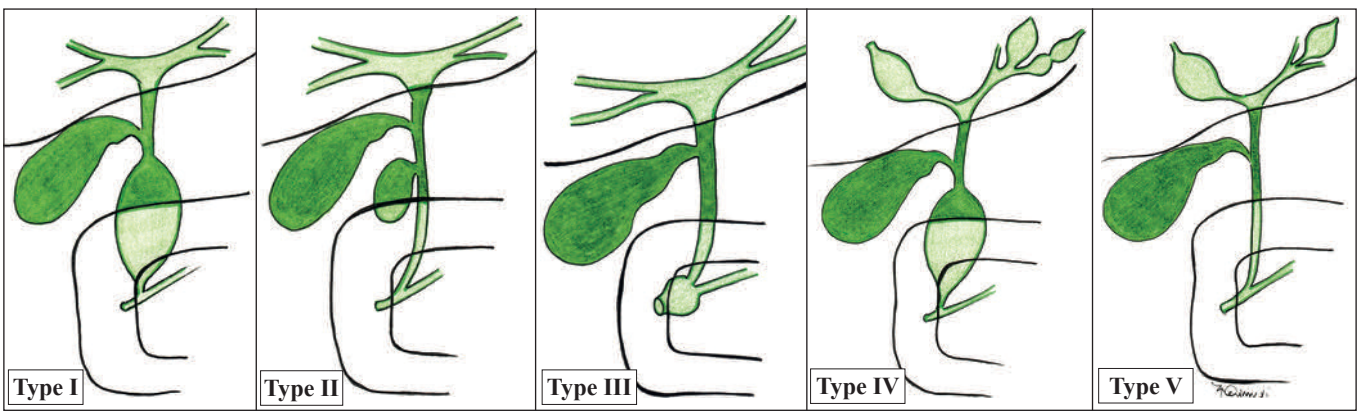


Figure 30. Biliary cystic disease classification. **Type I**: choldedochal cyst; **Type II**: bile duct diverticulae; **Type III**: choledochocele; **Type IV**: dilatations of the intra and extra hepatic biliary tree; **Type V**: dilatations of the intra hepatic biliary tree (Caroli's disease).

FINAL CONSIDERATIONS

Imaging is now an essential component of the preoperative assessment of many types of liver surgery. Imaging is used to define normal and variant anatomy in order to reduce the incidence of postoperative complications, which can result in significant morbidity and mortality. Imaging studies help in the characterization of disease but also provide assessment of the status of background hepatic parenchyma. Different imaging modalities have their own strengths and weaknesses and it is important for the surgeon to appreciate this, so that the best and most appropriate preoperative imaging can be utilized.

SUGGESTED READING

Erbay, N., Raptopoulos, V., Pomfret, E. A., Kamel, I. R. & Kruskal, J. B. Living donor liver transplantation in adults: vascular variants important in surgical planning for donors and recipients. *AJR Am. J. Roentgenol.* **181**, 109–114 (2003).

This retrospective study analyzed vascular variants of surgical importance in healthy patients (living liver donors). Vascular variants were identified in 65% of cases. Accessory right or left hepatic artery were the most common arterial variant and an accessory right inferior hepatic vein was the most frequent venous variant.

Sahani, D. *et al.* Evaluation of living liver transplant donors: method for precise anatomic definition by using a dedicated contrast-enhanced MR imaging protocol. *Radiographics* **24**, 957–967 (2004).

A very illustrative review comprising the complete radiological evaluation of the liver in living donors. The anatomy (vascular and biliary) and the detection of diffuse liver diseases by magnetic resonance imaging are discussed.

Kamel, I. R. *et al.* Impact of multidetector CT on donor selection and surgical planning before living adult right lobe liver transplantation. *AJR Am. J. Roentgenol.* **176**, 193–200 (2001).

An interesting study on liver living donors evaluating the impact of the computed tomography (CT) on the detection of vascular and/or biliary anatomical variants, and parenchymal diseases. Multidetector CT allowed detection of exclusion criteria in more than one third of potential donors.

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INVITED COMMENTS

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In the chapter of Radiological Anatomy of the Liver written by Lee Grant and coworkers, authors have nicely detailed the normal liver anatomy, the normal liver vasculature as well as the most common abnormal variants. As this book is devoted to liver surgery with a target audience mostly composed by surgeons, it might be of interest to describe the postoperative imaging aspects following liver resection.

Some imaging findings are common to all liver resections: presence of air or fluid collection may be depicted in the early postoperative course up to two months; hypoattenuating linear band adjacent to the liver resection is seen in 30–50% of the cases and corresponds to bile or blood accumulation, fibrous infiltration, focal steatosis, or devascularized parenchyma. This abnormality disappears over time; fat-density area related to epiploplasty can be seen next to the liver. Last, pleural effusion is noticed in 50–80% of the cases, in particular after right hepatectomy.[1,2]

The presence and degree of liver regeneration after liver resection is correlated with the amount of liver volume that has been resected. For instance liver regeneration is minimal after left liver lobe resection while it is major after right hepatectomy and extended right hepatectomy (**Figure 31A**). After right hepatectomy, the liver remnant at day 7 shows a mean increase in the volume of 64% from the future liver remnant. The most important factors that significantly alter liver regeneration are the presence of liver fibrosis or cirrhosis and disturbance of the outflow. Patients with harvesting of the middle hepatic vein have volume and segmental regeneration index significantly lower than in other patients, for both the caudate lobe and segment 4.[3]

Shape and location of the postoperative liver depend on the type of liver resection. Right hepatectomy involves the resection of segment 5, 6, 7 and 8 which approximately represents 65% of the total liver volume.[4] The right pedicles are ligated. The section plane courses parallel to the middle hepatic vein, which might be preserved. Extended right hepatectomy involves the resection of segments 4 to 8 and can include resection of the caudate lobe (segment 1). This resection is necessary to treat right-sided tumors that compromise segment 4. The umbilical fissure is opened, and all vascular and biliary branches to segments 4a and 4b are ligated. This resection represents approximately 80% of the total liver volume.[4] The outflow is maintained via the left hepatic vein. After right hepatectomy, the left hepatic lobe extends in epigastrium and becomes ovoid with round contours. The caudate lobe may increase in volume or not. The umbilical fissure is displaced to the right, whereas inferior vena cava is displaced posteriorly. Right colon and ileum may occupy the right hypocondrium. After extended right hepatectomy, findings are similar but the segment 4 is no longer visible (**Figure 31A**).[5]

Left hepatectomy involves the resection of segment 2, 3 and 4 which approximately represents 35% of the total liver volume.[4] The left pedicles are ligated. The section plane courses parallel to the middle hepatic vein, which might be preserved. Left lobectomy involves the resection of segment

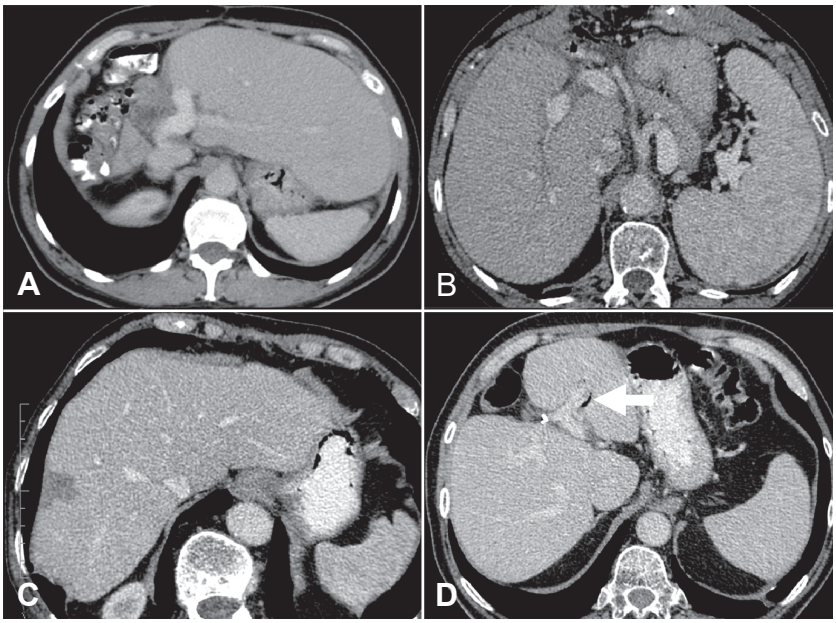


Figure 31. A) CT scan two years after a right trisectionectomy extended to segment 1 for hilar cholangiocarcinoma. Left lobe is increased occupying the left hypocondrium. **B**) CT scan three years after a left hepatectomy with middle hepatic vein resection for hepatocellular carcinoma. Right liver is hypertrophied with round contours. **C**) CT scan 10 days after a wedge resection for a colorectal liver metastases. An irregular hypodense area is seen in the periphery of the right liver. **D**) CT scan three years after resection of segments 4 and 5, associated to resection of the biliary confluence and hepatico-jejunal anastomosis. Note the presence of hyperdense images due to the presence of metallic clips and the presence of air in the biliary tree (arrow).

2 and 3 which approximately represents 20% of the total liver volume.[4] The section plane is the umbilical fissure. The left pedicles are ligated at the left side of the umbilical fissure while preserving the left branch of the portal vein. After left hepatectomy, right liver becomes hypertrophic extending below the costal skeleton and has round contours. (**Figure 31B**) The caudate lobe may enlarge or not. The portal vein is displaced to the left. The stomach and transverse colon are next to the right liver.[5] After left lobectomy, the left portal branch is the inner border of the liver. The left portal branch usually decreases in size over time. Morphologic changes of the remnant liver are minimal.[5]

The other surgical procedures are less common. The caudate lobe represents less than 5% of the total liver volume and is deeply located between the inferior vena cava, the hepatic hilum and the distal portion of the middle and left hepatic veins. This explains why isolated resection of the caudate lobe is rarely performed.[6] Right or left hepatectomy may be associated to resection of the caudate lobe. Right anterior hepatectomy involves the resection of segment 2, 3, 4, 5 and 8 which approximately represents 65% of the total liver volume.[4] The section plane courses parallel to the right hepatic vein, which has to be preserved. Central hepatectomy involves the resection of segment 4, 5 and 8 which approximately represents 50% of the total liver volume.[4] This resection might be indicated in central tumors that do not invade primary biliary confluence. The middle hepatic vein is removed. The drawback of this surgical procedure is to have two liver sections, which potentially increase the postoperative complications. Posterior sectorectomy involves the resection of segment 6 and 8 which approximately represents 35% of the total liver volume.[4] This resection is mainly performed when liver volume should be preserved as much as possible especially in patients with chronic liver disease.

After wedge-resection, a peripheral capsular retraction may be seen at the site of the resection (**Figure 31C**). Surgeons may use or not metallic clips (**Figure 31D**).[5] Also, after liver resection with associated biliodigestive anastomosis, air can be seen in the intrahepatic biliary tree (**Figure 31D**).

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3 Intraoperative Assessement of the Liver

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- *Intraoperative ultrasound (IOUS) is a fundamental tool used in modern hepatic surgery, which can precisely define the liver anatomy and accurately identify target lesions.*
- *IOUS is one of the key factors to spare hepatic parenchyma without compromising the oncological endpoints.*
- *IOUS should be performed by the first surgeon with the aim of gathering information that might impact the surgical strategy.*
- *IOUS is an important tool for staging malignancies, determining resectability, and planning the most adequate procedure.*
- *Contrast-enhanced IOUS (CEIOUS) is useful in the differential diagnosis of new lesions eventually detected with basic IOUS and can increase its overall sensitivity.*

This chapter focuses on the technique and applications of intraoperative ultrasound, an indispensable tool used in hepatic surgery. For more precise information concerning diagnosis by ultrasonography, we recommend the consulting specific textbooks (see references).[1–3] Comments on intraoperative cholangiography and bile leak tests are found at the end of the chapter.

INTRAOPERATIVE ULTRASOUND

INTRODUCTION

Intraoperative ultrasound (IOUS) is a fundamental tool in modern hepatic surgery. IOUS can precisely define the liver anatomy and accurately identify target surgical lesions. The relationship between lesions and intrahepatic landmarks can be easily identified with IOUS. Also, surgical margins can be assessed with real-time guidance, permitting safe oncological procedures.

Currently the focus of resectability for many hepatic malignancies has shifted from tumor characteristics (number and size) to the possibility of achieving a complete clearance of disease (intra- and extrahepatic). Along with the technical issues involved in achieving complete tumor clearance, the biological behavior of disease should be appropriate from an oncological standpoint.

Whenever possible, parenchyma-sparing strategies should be used to minimize surgical complications, mainly postoperative liver failure. IOUS is one of the key-factors to spare hepatic parenchyma without compromising oncological endpoints.[4] The use of IOUS has allowed for so-called "radical but conservative surgery". This approach has enabled a chance of cure for an increasing number of patients (mainly those with multiple colorectal liver metastases and those with hepatocellular carcinoma with associated cirrhosis), who until a few years ago were considered only as candidates for palliative care.[5]

Historically, liver surgery was associated with high

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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operative mortality rates. Nowadays, hepatic resections can be performed with very low mortality even if cirrhosis is present.[6-7] As favorable short and long-term outcomes have been consistently reported, the indications for hepatic resection have expanded. Reasons for this are multifactorial and include not only refinements in surgical techniques, with the use of IOUS, but also improvements in perioperative care.[8-11]

Since its introduction in the 1980s,[12-13] IOUS has changed the surgical approach to the liver and, more recently, new advancements have further enforced its role as a fundamental stronghold for the hepatic surgeon.[14-16]

Starting from the probe selection, this chapter describes techniques for liver examination and focal liver lesion characterization using IOUS.

SELECTION OF TOOLS FOR IOUS

Generally, high-frequency probes (7.5 to 10 MHz) are recommended when performing IOUS. They offer a higher spatial resolution than those that operate at lower frequencies (3.5 to 5 MHz). However, considering that the lower the frequency the deeper the area explored, it is the authors' choice to begin hepatic assessment with low-frequency probes. Low-frequency devices provide an overall anatomical assessment of the liver with the evaluation of deeper structures. Also, the superficial portions of the liver seen on IOUS are generally appreciable by palpation, and obtaining spatial resolution of the superficial portion of the liver with the use of high-frequency probes, is less important than the assessment of the deeper structures. Therefore, probes working at a wide range (3.5 to 10 MHz) of frequencies should be preferred.

The shape and size should be considered when selecting a probe. Ideally, it should be minimal in size to allow handling in narrow spaces, but at the same time it should be stable and large enough to provide the widest possible scanning area. In this sense, convex probes or linear probes with trapezoidal scanning represent an optimal balance between the need for minimal size and a wide scanning window. **Figure 1** shows the three main used probes for IOUS. Easy handling during IOUS-guided maneuvers (finger compression technique or demarcation of the area of transection, for example) should also be considered in the selection of a probe.[17]

With regard to ultrasound, contemporary machines should allow for potential additional information during liver exploration, such as color flow imaging analysis to determine blood liver inflow and outflow.

Recently, contrast enhanced intraoperative ultrasound (CEIOUS) has been used in liver surgery. This recent advancement in IOUS demands dedicated probes and equipment with specific software. Nowadays two contrast agents are available for CEIOUS. The first is sulfurhexafluoride (SonoVue®, Bracco Imaging, Milan, Italy), which consists of sulfur hexafluoride micro-bubbles stabilized by a phospholipid shell. It is a vascular contrast medium that can help in the characterization of focal liver lesions using the vascularization as the main criteria. The second contrast medium is perflubutane (Sonazoid®, Daiichi Sankyo, Japan). This is a liver-specific agent that accumulates in Kupffer cells, with properties similar to that seen in liver-specific contrast media used in magnetic resonance imaging. Its application in CEIOUS is progressively widening.[18-20]

In conclusion, with IOUS it is advisable to use probes featuring: i) a wide range of frequencies, ii) wide scanning windows, iii) small size, and iv) a suitable shape for optimal handling during surgical maneuvers.

LIVER EXPLORATION

Despite the advances in IOUS, surgical exploration should always start with the inspection and palpation of the liver, as well as the exploration of the entire peritoneal cavity. Hata et al.[21] recently demonstrated that visual inspection and palpation of the liver are complementary techniques and should not be avoided in favor of IOUS.

Once into the peritoneal cavity, IOUS can be facilitated by partial liver mobilization. The division of the round and falciform ligaments, as well as casual adhesions, will free the anterior-superior and inferior surfaces of the liver, allowing enough space to handle the probe for IOUS (**Figure 2**). Pulling on the round ligament for traction, the liver surface is widely exposed, and following the portal branches and the hepatic veins, the liver can be entirely studied without complete mobilization. This initial screening practice

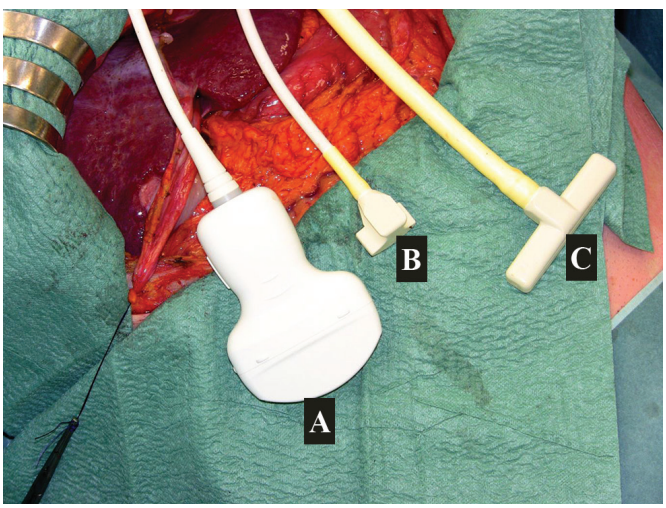


Figure 1. The three main probes used for intraoperative ultrasound (IOUS). **A**) 3.5 to 5 MHz standard convex probe, usually used for percutaneous ultrasound, but very useful even for IOUS; **B**) 7.5 to 10 MHz micro-convex probe, also called Makuuchi's probe, usually used for IOUS; **C**) 7.5 to 10 MHz T-shape probe, usually used for IOUS.

minimizes artifacts such as air, which can obscure the field of lesions. However, further detachment of the liver with section of the left and right triangular ligaments can facilitate IOUS assessment, and is especially useful during hepatic resection or for other purposes (IOUS-guided procedures).

The ultrasound equipment should be placed in front of the surgeon, providing a simultaneous view of the screen and of the operative field. The screen must be large enough to offer optimal visibility to the surgeon. The operating room lights should be lowered or even turned off, if necessary. The equipment's keyboard can be covered with a sterile drape and controlled by assistants. Since the information gathered during IOUS requires interpretation that might impact the surgical strategy, the surgeon - rather than the assistants or the radiologist - should perform the IOUS procedure.

ULTRASOUND LIVER ANATOMY

A detailed knowledge of the liver anatomy is obviously needed to perform IOUS. Usually, the assessment starts at the portal tree, which can be easily recognized. The portal vein branches are followed from their main bifurcation, which can be easily identified by positioning the probe transversally at the mid-portion of segment 4. As portal triads enter the liver, they are surrounded by Glisson's capsule. The presence of this thickened sheath appears as a dense hyperechogenic line encircling the portal triad (which includes portal vein branches, arteries, and bile ducts) (**Figure 3**).

In contrast, hepatic veins appear as echo-free tubular structures in the liver parenchyma. They have a very thin hyperechogenic wall and cardiac pulsation transmission may eventually be seen (**Figure 4**). Of note, the walls of hepatic veins can be thicker in a cirrhotic liver and their lumens thinner, owing to the stiffness of the diseased liver (**Figure 5**).

The portal vein, artery, and bile duct can be separately identified by carefully moving the probe above a Glissonean pedicle. The use of color flow modalities may help in the differentiation of the three elements.

Following the Glissonean pedicles and their relation to the hepatic veins, IOUS can precisely define hepatic sectors, segments, and subsegments, which are the basis of modern liver surgery.

Usually, the right anterior sectional pedicle and its segmental and subsegmental branches to segments 5 and 8

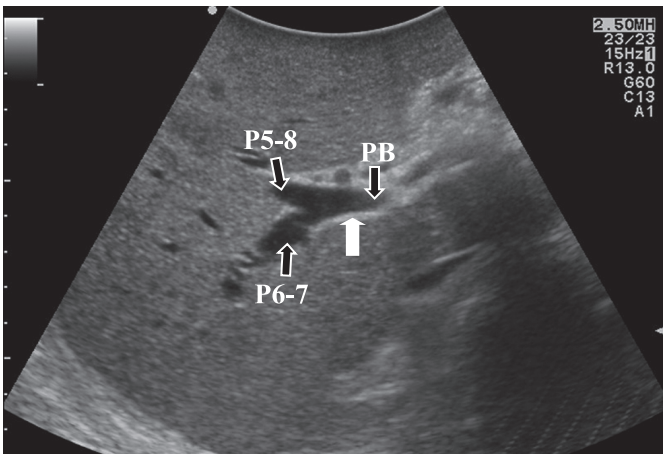


Figure 3. Intraoperative ultrasound appearance of the portal pedicle. The figure shows the main portal bifurcation (PB) and the right portal bifurcation (P5-8: portal branch to segments 5-8; P6-7: portal branch to segments 6-7). The white arrow shows the typical hyperechogenic layer around the pedicles, which characterizes these intrahepatic structures.

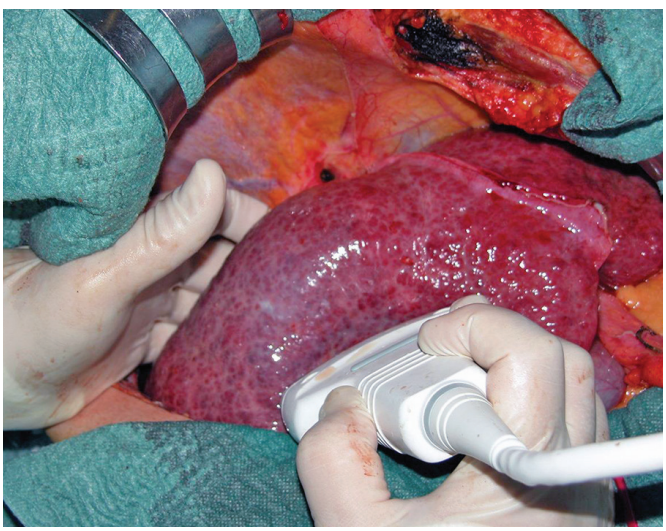


Figure 2. Preparation of the liver for intraoperative ultrasound. The figure shows the space around the liver required to properly perform IOUS.

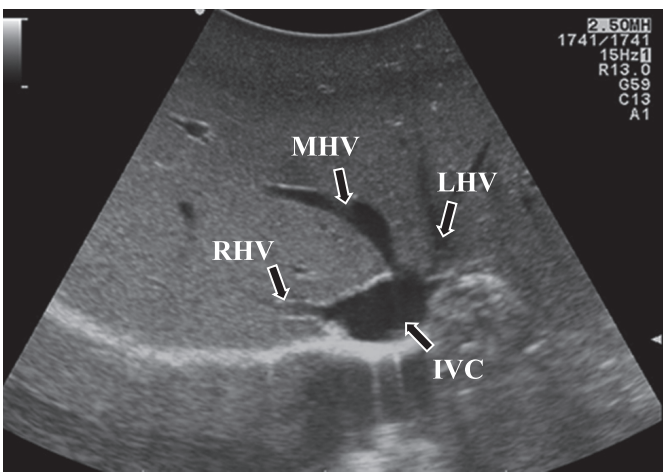


Figure 4. Intraoperative ultrasound appearance of the hepatic veins in normal liver. The figure shows the typical appearance of the hepatic veins at ir confluence into the inferior vena cava. RHV: right hepatic vein; MHV: middle hepatic vein; LHV: left hepatic vein; IVC: inferior vena cava.

are followed at first. The next is the right posterior sectional branch and its segmental vessels to segments 6 and 7. Then, the left portal branch and the segmental branches to segments 4 (inferior and superior), 3, and 2 are scanned. The tilting upward of the probe shows the confluence of the hepatic veins into the inferior vena cava allowing the study of the outflow. Finally the paracaval portion of segment 1 is explored, followed by a separate evaluation of the remaining caudate lobe.

In normal conditions, the bile ducts appear as thin echo-free zones in the Glissonean pedicle (**Figure 6**). When dilated, they appear as more evident echo-free zones with a tortuous path (**Figure 7**). Of note, the segmental and subsegmental anatomy of the bile ducts is probably the most difficult element to recognize using IOUS. The confluence of sectional and segmental ducts is closer to the hilum when compared with the portal branches. Because of this, it is possible to visualize more than one segmental bile duct on the same screen. Despite the difficulties, when performed by experts, IOUS can precisely define bile duct anatomy - not only in pathologic conditions, but also in the normal liver. This is very important, as anatomical biliary variations are not uncommon. For example, the confluence of the right posterior sectional bile duct into the left hepatic duct must be identified, especially when performing left hepatectomy, to avoid biliary injury.

Contrast enhanced cholangio-ultrasound can be performed to define unclear anatomy and assure proper biliary drainage of all the segments of the remnant liver. This can be done with the injection of a solution of saline and air in the bile duct. This simple method offers an adequate visualization of the main biliary branches (**Figure 8**).

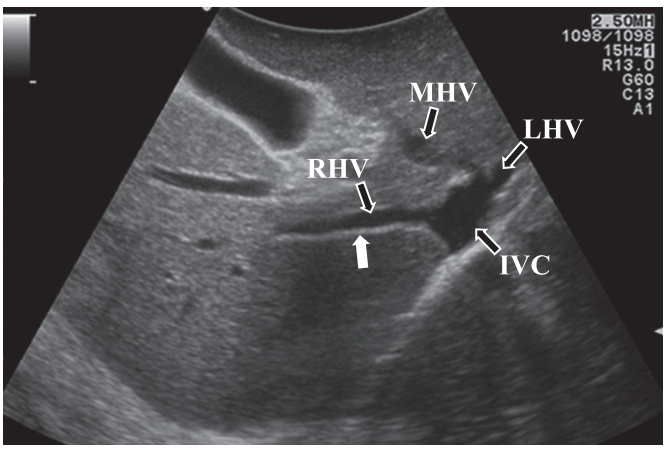


Figure 5. Intraoperative ultrasound appearance of hepatic veins in a cirrhotic liver. The figure shows the typical appearance of the hepatic veins at their confluence into the inferior vena cava in a cirrhotic liver. The white arrow shows the hyperechogenic thick wall of the RHV. RHV: right hepatic vein; MHV: middle hepatic vein; LHV: left hepatic vein; IVC: inferior vena cava.

STAGING AND PLANNING OF RESECTION OF LIVER MALIGNANCIES

IOUS is the most accurate method to identify liver tumors and can define their location with precision. Further, this method accurately outlines the relation of the lesions with vascular and biliary structures of interest, and is useful

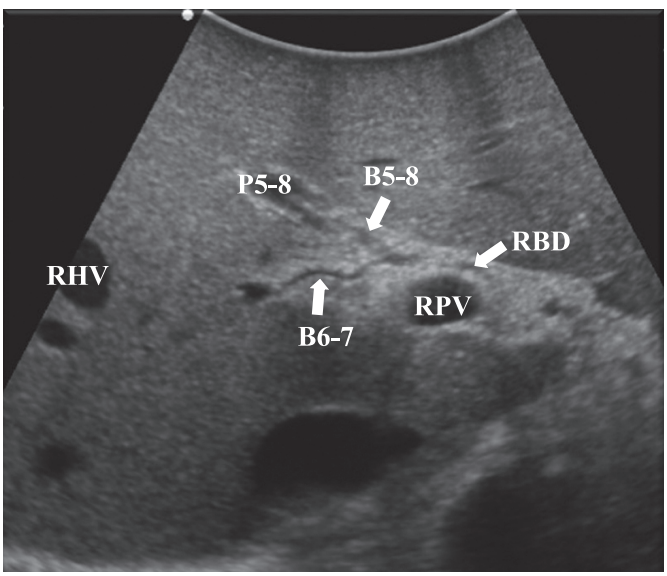


Figure 6. Intraoperative ultrasound appearance of the bile ducts. Normally the bile ducts (arrows) appear as thin echo-free zones in the Glissonean pedicle. B6-7: right posterior bile duct; B5-8: right anterior bile duct; P5-8: right anterior portal trunk; RBD: right bile duct; RPV: right portal vein; RHV: right hepatic vein.

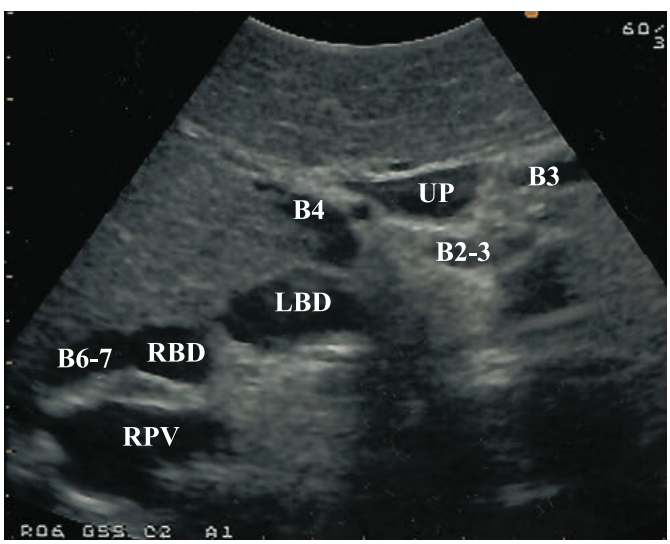


Figure 7. Intraoperative ultrasound appearance of the bile ducts. Once dilated, the bile ducts appear as more evident echo-free zones with a tortuous path. B6-7: right posterior biliary duct; RPV: right portal vein; RBD: right bile duct; LBD: left bile duct; B4: bile duct for segment 4; UP: umbilical portion; B3: bile duct for segment 3; B2-3: bile duct for segment 2-3.

in identifying vascular invasion. Thus, it is an important tool for staging malignancies, determining resectability, and planning the most appropriate procedure. The vast majority of IOUS studies are performed in the setting of malignancies, mainly hepatocellular carcinoma (HCC) and colorectal liver metastasis (CLM), which are frequently treated by liver resection.

Most HCCs occur in cirrhotic patients. The irregular surface of cirrhotic livers makes palpation an inaccurate method to detect small nodules. Thus, IOUS is an indispensable tool in identifying target lesions during liver resections in cirrhotic subjects. On the other hand, IOUS can overestimate the burden of disease as it can detect up to 30% more nodules than usual preoperative radiological examination. However, it should be noted that most of these "new lesions" are not malignant lesions, but mainly regenerative nodules (**Figure 9**).[22]

The patterns of new nodules detected during surgery for HCC can provide a clue to their origin. Takigawa et al.[23] reported that new nodules with mosaic pattern were malignant in 84% of the cases. Those hypoechogenic and hyperechogenic nodules proved to be malignant in 30% and 18%, respectively (**Figure 10**). To overcome this problem, CEIOUS can be used specifically to characterize new nodules found on regular IOUS. Indeed, CEIOUS increases the specificity rather than sensitivity for the diagnosis of HCC. Conversely, in patients with CLM, CEIOUS can increase the sensitivity of the staging. In other words, the use of CEIOUS helps in the finding of new CLM during operations, and is used for the differential diagnosis of new lesions eventually detected using IOUS during surgery for HCC.

Even with the use of modern preoperative imaging techniques, IOUS detects new CLM in up to a quarter of patients. New lesions are mainly detected in cases of multiple lesions, but do not necessarily demand changes in surgical strategies.[21,24–26] The relationship between liver metastasis and Glissonean pedicles is properly evaluated with IOUS. The presence of contact extension of more than one-third of the circumference of the pedicle, bile duct dilatation, tumor thrombus, or clear invasion of the vessel wall are considered contraindications for preserving the pedicle.[27] The contact of CLM with a hepatic vein should account for less than two-thirds of the circumference to preserve it. The presence of a tumor thrombus or invasion of the vessel wall are also contraindications for preserving the hepatic vein.[27]

CEIOUS for HCC

In cases of HCC, CEIOUS is useful in the differential diagnosis of new lesions eventually detected on IOUS.[28] As mentioned above, CEIOUS improves the specificity of regular IOUS, mainly in cirrhotic patients, who frequently have multiple hepatic nodules. The characterization of a malignant nodule can be based on the arterial phase of CEIOUS. Generally, only malignant nodules have a typical arterial phase. Indeed, the neo-angiogenesis of tumor nodules have been found to be one of the most specific criteria to differentiate HCC from regenerative or dysplastic nodules.[29] Since the arterial phase on CEIOUS only lasts for approximately 20-30 seconds, the presenc e

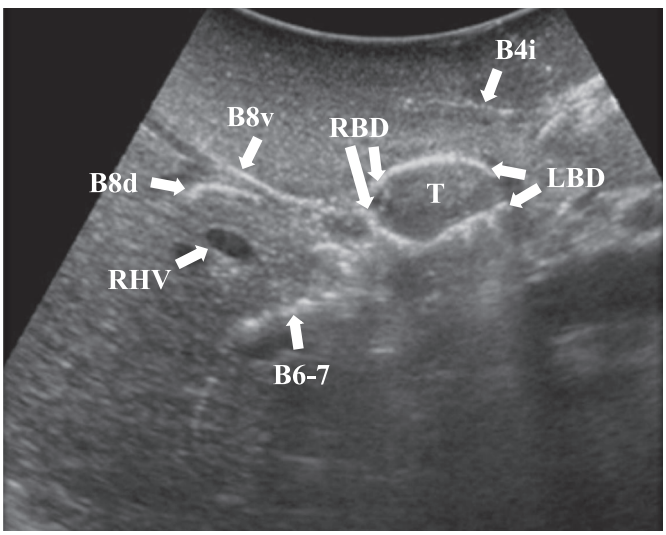


Figure 8. Contrast enhanced cholangio-ultrasound in a tumor of the biliary confluence. The biliary anatomy can be studied by injecting a solution of saline and air into the bile duct with the aim to contrast the ducts. B8d: bile duct for segment 8-dorsal; B8v: bile duct for segment 8-ventral; RHV: right hepatic vein; RBD: right bile duct; LBD: left bile duct; T: tumor; B4i: bile duct for segment 4-inferior; B6-7: right posterior biliary duct.

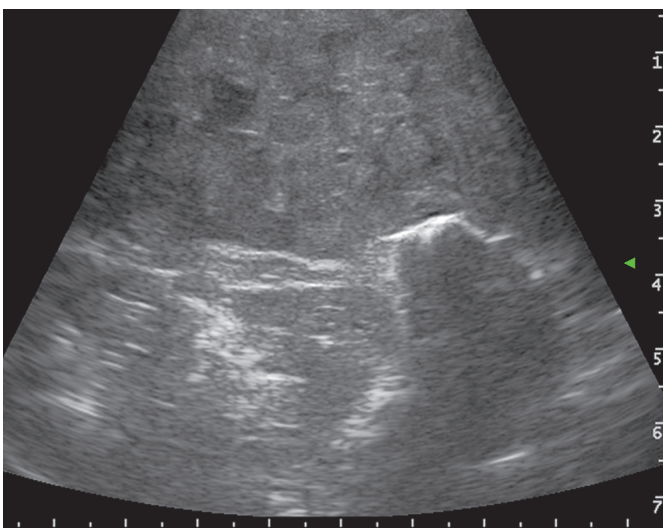


Figure 9. Intraoperative ultrasound (IOUS) appearance of a cirrhotic liver. Multiple nodules can be detected by IOUS, and the disease can be overestimated.

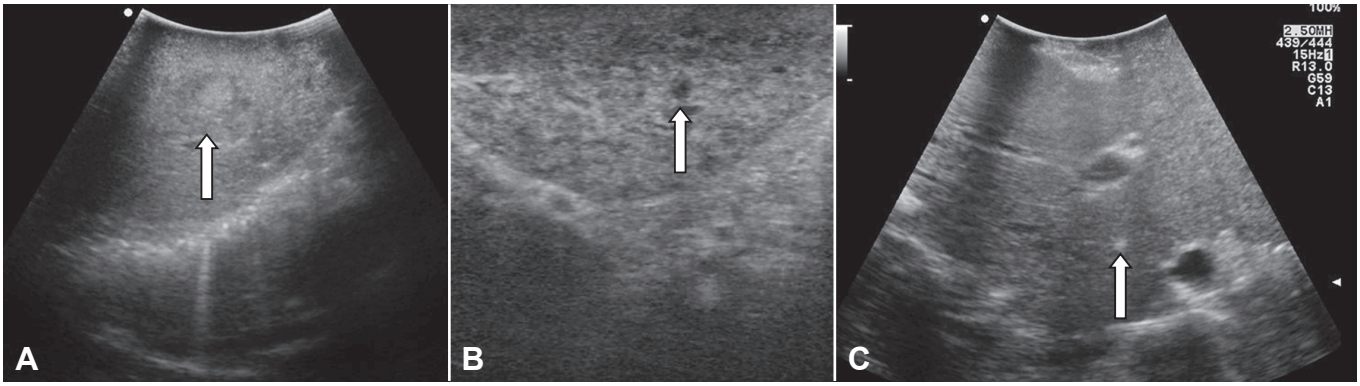


Figure 10. Intraoperative ultrasound appearance of the three commonest patterns of nodules in a cirrhotic liver. **A**) Typical nodule with a mosaic pattern; **B**) hypoechogenic nodule; **C**) hyperechogenic nodule.

of multiple nodules may require more than one contrast injection (**Figure 11**).

For HCC, a specificity of up to 95% has been reported with the use of percutaneous contrast-enhanced ultrasound.[30] CEIOUS is frequently used to characterize nodules up to 1 cm in diameter, since larger nodules are generally characterized by preoperative imaging technique. Unfortunately, even with CEIOUS, the specificity for such small nodules is definitely lower, and the criteria of vascularity may not be enough. For these reasons, a classification using the pattern of enhancement was introduced to help the surgeon during the operative decision-making **(Figure 12)**.[28] Overall accuracy using this classification was 80%. Notably, after a follow-up of 12 months, none of the lesions that presented the same enhancement of surrounding liver parenchyma during all phases of CEIOUS proved to be malignant.[28] This classification is particularly valuable for small lesions (less than 1 cm) for which the vascular criteria is somehow not sufficient. Interestingly, different enhancement patterns of HCC might be related, with differing prognoses.[31]

Changes with the use of the new liver-specific contrast agents may persist for several minutes after their injection. This property allowed for persistent visualization of hypoechogenic nodules (approximately 15 minutes following contrast administration), which proved to be malignant in two thirds of cases.[18] These findings, once confirmed in further studies, should offer proof that CEIOUS improves not only the specificity but also the sensitivity of IOUS for HCC diagnosis.[32]

IOUS is also useful in the presence of portal or hepatic vein thrombosis to distinguish between a tumor-associated thrombus (which is avascular) and a tumor thrombus (which has an arterial waveform on Doppler evaluation).[33]

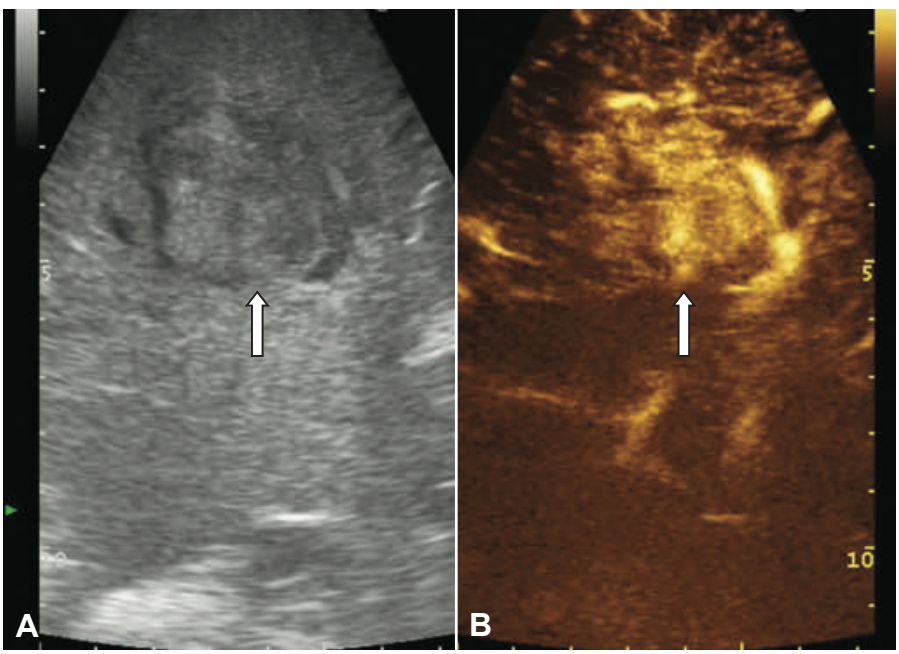


Figure 11. Contrast enhanced intraoperative ultrasound (CEIOUS) for hepatocarcinoma (HCC). **A**) Standard unenhanced IOUS of HCC; **B**) CEIOUS of HCC with a marked arterial phase typical of a malignant nodule.

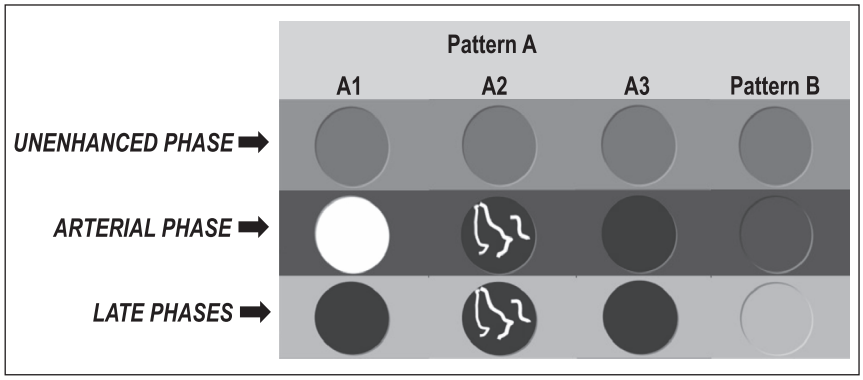


Figure 12. Schematic representation of different patterns of enhancement of hepatocellular carcinoma and liver parenchyma with contrast-enhanced ultrasound. Nodules pattern A1 present fully enhanced in arterial phase and unenhanced in late phase. Nodules pattern A2 present intranodular neovascularization in arterial phase, which remains evident in late phases. Nodules pattern A3 remain unenhanced in both arterial and late phases. Nodules pattern B are those with same enhancement of surrounding liver parenchyma in all phases. (Adapted from Torzilli et al.[28])

CEIOUS for CLM

The main target of CEIOUS during CLM surgery is to improve the sensitivity of IOUS. During the 1990s, approximately half of all patients who underwent surgery for CLM had their surgical strategy modified by IOUS findings.[34] Nowadays, improvements in preoperative workup have lowered this rate.[35] However, the adding of CEIOUS to IOUS can still change operative decision-making in up to 38% of patients with CLM.[36,37] Although the rate of changes in surgical procedures may vary considerably according to surgical policies used by different groups, there is no doubt that CEIOUS plays a clear role.

During CEIOUS, CLM remains unenhanced (hypoechogenic) compared with the surrounding liver parenchyma, two to five minutes after contrast injection (**Figure 13**). This feature provides an easier visualization of lesions, improving the sensitivity of regular IOUS (an increase of 9%, according to our data).[36] However, in the case of a steatotic (and consequently brighter) liver, the accuracy of IOUS decreases. Despite this, one study found that CEIOUS (using perflubutane) was able to detect half of disappearing metastases under chemotherapy, while IOUS detected only 12%.[19] Thus, following chemotherapy, CEIOUS is a useful tool to detect colorectal liver metastasis.[38–40] The best yield for CEIOUS on CLM seems to be in the setting of multiple tumors and in hypo- or iso-echogenic nodules on IOUS.

IOUS-GUIDED PROCEDURES

Beyond the detection of focal hepatic lesions and extent of tumors, IOUS is useful as a technical tool for liver resections. During an anatomical liver resection, IOUS is useful in identifying anatomical landmarks. Also, the strategy of liver resection may be guided by IOUS. This method offers proper definition of hepatic segmental boundaries, boundaries of the tumor itself and its relationships with biliary and vascular structures, and the presence of various anatomical variations (**Figure 14**). Therefore, IOUS-guided hepatic resection may allow for more conservative procedures, since the relationship between the tumor edge and the dissection plane can be followed in real time and modified whenever needed, and vascular occlusion or invasion is adequately evaluated.[5]

The IOUS-guided finger compression technique is a useful tool, especially for conservative resection of hepatocarcinoma. This method consists of compression of a portal pedicle between the ultrasound probe and the surgeon's fingertip. The most peripheral portal pedicle feeding the tumor can be identified and compressed proximally to the tumor to delimit the ischemic area (to be resected).[17,27,41]

Post-resectional control by IOUS may be performed on the remnant liver and also on the surgical specimen to ensure that the tumor was completely excised, and to evaluate the margins. IOUS of the specimen is facilitated by immersing it in saline solution.

Kokudo et al.[42] demonstrated the use of IOUS to safely perform the hanging maneuver. The most significant complication of this procedure, which consists of suspending the liver after passing a tape between the retrohepatic vena cava and the liver, is injury of the short hepatic veins. In this study, the use of IOUS enabled a safe dissection by identification of short hepatic veins draining directly to the retrohepatic vena cava.

EVALUATION OF VESSEL PATENCY

Vessel patency is easily verified using intraoperative Doppler ultrasound. This tool is crucial in liver transplantation for evaluation of vascular anastomosis, but is also useful to assure adequate vascular inflow and outflow of the remnant liver, especially after a major hepatectomy. Congestion of a hepatic segment can be evaluated by IOUS, since congestion induces reverse portal flow into the congested segment. If a segment to be preserved has a normal portal flow direction, it means that the outflow is adequate; however, if portal flow is reversed, a vein reconstruction or segment resection is necessary.[43] Color-Doppler IOUS is useful for this evaluation. Assessment of vascular and biliary extension of hilar cholangiocarcinoma can also be achieved

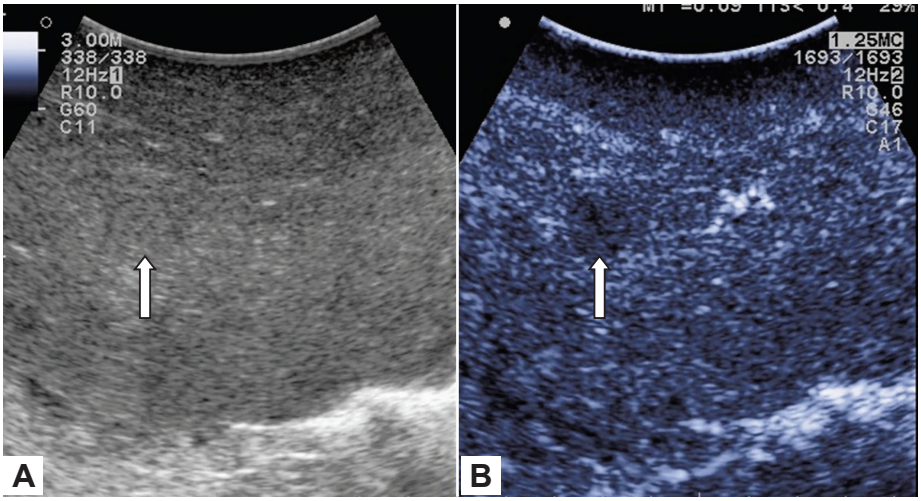


Figure 13. Contrast enhanced intraoperative ultrasound (CEIOUS) for colorectal liver metastasis (CLM). **A**) Standard unenhanced intraoperative ultrasound of CLM; **B**) CEIOUS of CLM with the typical black--hole effect.

through IOUS.

Permeability of intrahepatic bile ducts can be verified by injecting air through a transcystic catheter and simultaneous echography of hepatic parenchyma. The passage of air into intrahepatic bile ducts produce areas of hyperechogenicity.

INTRAOPERATIVE COLANGIOGRAPHY AND BILE LEAK TESTS

Intraoperative cholangiography is usually performed by injection of contrast agents into the biliary tree using the cystic duct after cholecystectomy. The use of classical cholangiography during liver surgery is especially important in clarifying biliary anatomy and its frequent variations, determining the level of a biliary obstruction, identifying possible iatrogenic biliary damage, checking the patency of a biliary anastomosis, and verifying the presence of intrahepatic stones, strictures or communications with cystic lesions. The combination of preoperative imaging, IOUS, and intraoperative cholangiography is useful to determine local extension of hilar tumors. The use of intraoperative cholangiography to detect bile leakage is considered controver- sial.

The rate of bile leakage after hepatic resection without biliary reconstruction has been reported to be anywhere from 4% to 20%,[44–49] and represents one of the most common complications leading to a prolonged hospital stay. Intraoperative tests to identify bile leakage include injection of a variety of products (saline solution, methylene blue, green indocyanine, fat solution) through the cystic duct after its canulation. However, detection and closure of bile leakage immediately after liver resection does not necessarily reduce the incidence of postoperative biliary

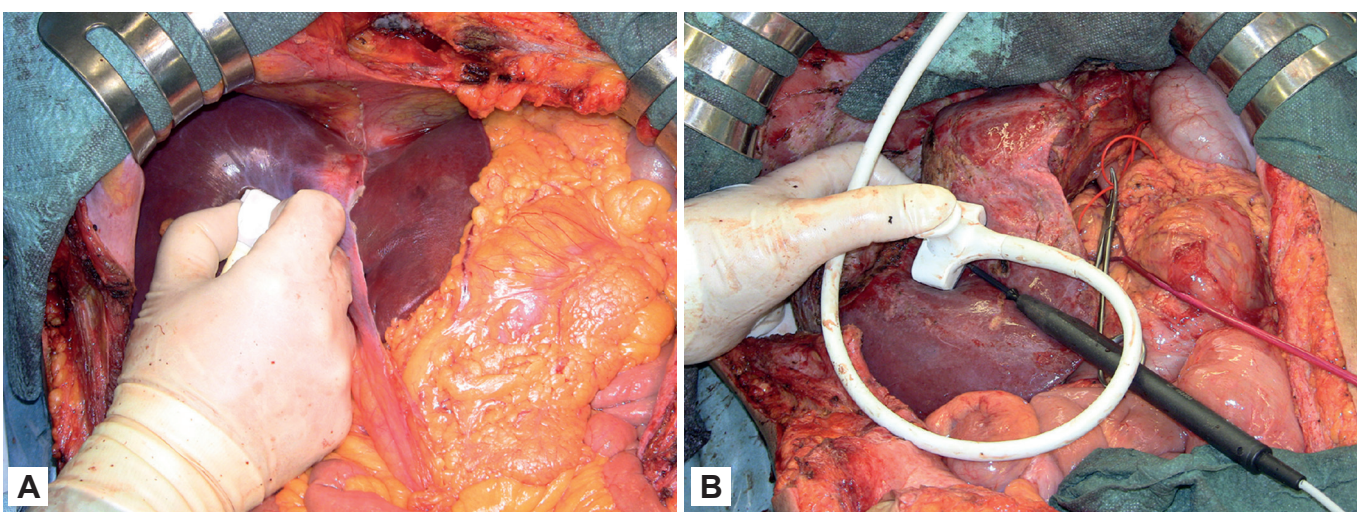


Figure 14. A typical operative field in liver surgery. **A**) Handling of the intraoperative micro-convex probe by the first surgeon; **B**) Handling of the intraoperative probe and the electrocautery for tailoring the area of resection.

leakage. In fact, some studies were not able to demonstrate significant reduction in the occurrence of this complication postoperatively, despite the use of tests with saline solution or intraoperative cholangiography.[49,50] On the other hand, some authors found a reduction of postoperative biliary fistulae with the use of biliary injection of methylene blue, indocyanine green, or fat solution.[50–53] A prospective study with 74 patients validated the so-called "white test" (biliary injection of a fat solution), and postoperative bile leakage was found in 23% of control group patients (no bile test) versus 5.3% of tested patients ($P < 0.01$).[54] Currently, there is no consensus concerning the use of intraoperative tests for preventing bile leakage.

FINAL CONSIDERATIONS

IOUS is the best method for staging liver disease in real time. More importantly, it is the best instrument for the surgeon to fully understand the liver anatomy and its relation to a tumor. The systematic use of IOUS allows for "radical but conservative" hepatectomies, with the aim of sparing liver parenchyma. Aside from extending surgical indications, and offering a chance of cure to an increasing proportion of patients, IOUS also minimizes operative risks. Thus, IOUS must become part of any modern hepatic surgeon's arsenal of tools and techniques.

SUGGESTED READING

Torzilli, G. *et al.* 'Radical but conservative' is the main goal for ultrasonography-guided liver resection: prospective validation of this approach. *J. Am. Coll. Surg.* **201**, 517–528 (2005).

The authors propose criteria for IOUS-guided hepatic resection.

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A prospective analysis reporting the results of IOUS-guided hepatectomy for advanced HCC in a single center.

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4 Underlying Liver Disorders in Hepatic Surgery

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- *The function and the volume of the residual liver should be assessed prior to a hepatectomy. Combinations of imaging and blood samples are currently used to assess liver function but no optimal screening for liver injury exists. Thus, pre-resection biopsy may be indicated in selected cases. Volumetry based on imaging is used to estimate residual liver volume and can be used for treatment decision. Volumetry before and after portal vein embolization (PVE) also reveals the regenerative potential, a marker of underlying liver injury.*
- *Cirrhosis, a common finding in patients with primary liver malignancies, limits the extent of resection. Preoperative chemotherapy may cause different types of liver injury associated with adverse outcome events after liver resection.*
- *Non-alcoholic fatty liver disease (NAFLD) is associated with the use of irinotecan-based chemotherapy and features of metabolic syndrome. Sinusoidal liver injury occurs in 19-50% after preoperative treatment with oxaliplatin-based chemotherapy, and is associated with increased postoperative morbidity. Bevacizumab has oncological benefits in the treatment of colorectal liver metastases when administered together with oxaliplatin, and protects against oxaliplatin-induced sinusoidal injury.*
- *Regarding the volume of the future liver remnant (FLR), the following are suggested: >40% in patients with cirrhosis; >30% in patients who receive more than three months of preoperative chemotherapy; >20% in the normal liver.*

INTRODUCTION

Owing to an increased number of patients being diagnosed with liver malignancy in parallel to improved outcomes following hepatic resection, the number of liver resections in patients with underlying liver disease has increased markedly over the past two decades. Today, most major centers report <5% mortality after hepatectomy, compared to the historically reported mortality of about 10%.[1–3] The reason for this improvement is multi-fold, and is correlated - among other factors - with a stringent selection and preparation of patients before surgery, as well as improved surgical techniques minimizing intraoperative and postoperative factors associated with morbidity and mortality. The selection process is three-sided: patient co-morbidity, extent and biology of the disease, and volume and function of the planned residual liver. One of the major steps forward in the era of modern hepatobiliary surgery has certainly been a better understanding of the liver regeneration process and how liver volumetry should be integrated into surgical strategy.[2] Also, it is important to bear in mind that the volume itself may not be the only key to safer hepatic resections and improved outcomes; the ability of the liver to regenerate following portal vein embolization is being increasingly described as an important factor associated with postoperative outcomes.[4,5] Both the volume threshold of the future liver remnant (FLR) for a safe resection and the regenerative capacity of the liver rely on the severity of the underlying liver disease.[6] The latter is a key component in the selection process before liver resection and should be detected preoperatively.

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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SPECTRUM OF LIVER INJURIES

The spectrum of liver injuries - and their surgical impact after liver resection - that hepatobiliary surgeons should understand and be aware of is wide, but may be dichotomized for the sake of clarity. Apart from cirrhosis (the ultimate stage of chronic liver disease that may develop in any patient chronically exposed to any kind of hepatotoxicity), hepatic parenchymal injury can be divided into two main categories: non-alcoholic fatty liver disease (NAFLD)[7] and sinusoidal injury.[8] **NAFLD** describes a large spectrum of liver lesions[7] unrelated to alcohol intake, but similar lesions may be found among alcohol abusers, ranging from mild steatosis to cirrhosis. NAFLD is being increasingly described as a new histological entity arising in patients with metabolic disorders related to insulin resistance[9] and more recently to patients receiving chemotherapy for colorectal liver metastases (CLM).[10–12] Steatosis is defined by an intracellular hepatocyte lipid accumulation and this is the hallmark of NAFLD. Steatohepatitis is defined by histologic evidence of an inflammatory component associated with steatosis.[7] Apart from patients with insulin resistance syndrome, NAFLD may be specifically observed in patients receiving irinotecan-based chemotherapy for CLM.[13] **Sinusoidal injury** is a variant of the sinusoidal obstruction syndrome initially described in patients undergoing myeloablative-conditioning therapy before hematopoietic stem cell transplantation.[14] Sinusoidal injury is now mainly associated with the preoperative use of oxaliplatin in patients with CLM, with prevalence ranging from 19% to 50%.[13,15–18] As with NAFLD, sinusoidal injury describes a large spectrum of lesions that can range from mild sinusoidal dilatation to complete sinusoidal obstruction with portal hypertension.[17] Liver injury presenting after chemotherapy, either NAFLD or sinusoidal injury, is often termed chemotherapy associated liver injury (CALI).

MOLECULAR BACKGROUND OF LIVER INJURIES

Both NAFLD and sinusoidal injury, though histologically distinct, have pathways that involve chemical damage by reactive oxygen species (ROS; **Figure 1**).[19] The initial event in the NAFLD sequence is likely to be a drug-related damage to the mitochondrial membrane that interferes with oxidation of fatty acids and ultimately leads to the accumulation of ROS within hepatocytes.[20,21] Fluoro-β-alanine, a fluorouracil metabolite, is also thought to impair metabolism in hepatocytes, thus prolonging their exposure to toxic substances.[22]

The pathophysiology of sinusoidal injury also involves the accumulation of ROS. Wang et al.[23] developed a rodent model of sinusoidal injury using exposure to pyrrolizidine alkaloids. Pyrrolizidine alkaloids deplete the sinusoidal endothelial cells' glutathione stores, leaving them susceptible to subsequent ROS injury. Pyrrolizidine alkaloids also decrease nitric oxide concentrations, resulting in the up regulation of matrix metalloproteinase activity, which can be prevented by pre-treatment with nitric oxide donors.[24]

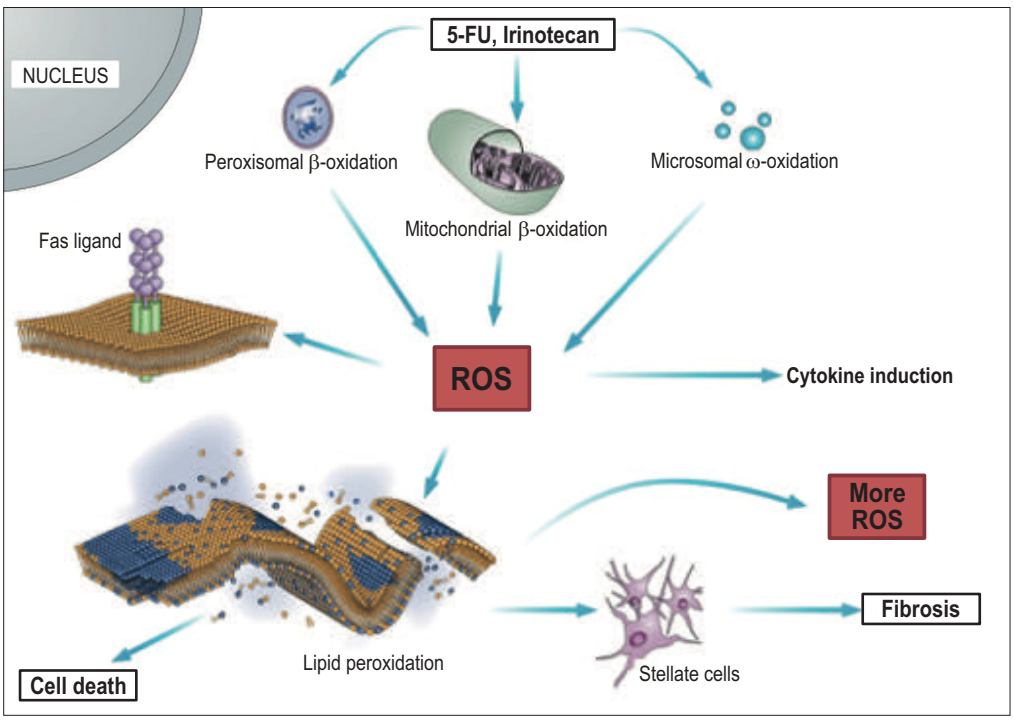


Figure 1. Cytotoxic drugs impair mitochondrial oxidation, leading to production of reactive oxygen species (ROS), Fas ligand death receptor expression, and cytokine induction. Lipid peroxidation results in cell death, stellate cell activation, and fibrosis. (Adapted from Chun et al.[19] with permission)

Damage induced by exposure to pyrrolizidine compounds can also be abrogated in a dose-dependent manner by pre-treating sinusoidal endothelial cells with exogenous glutathione or N-acetyl-L-cysteine in this model.[23] However, these preventive pharmacologic strategies have not yet been tested in humans.

SINUSOIDAL INJURIES

In the context of liver surgery, sinusoidal injuries are mostly related to the use of oxaliplatin, which is a potent platinum-derived cytotoxic agent used in advanced colorectal cancer. Sinusoidal injury caused by oxaliplatin was initially described by Rubbia Brandt et al.,[17] who studied pathologic changes of non-tumorous liver parenchyma in 157 patients who underwent resection of colorectal liver metastases with or without preoperative chemotherapy.[13,15–18]

At the cellular level, initial damage affects endothelial cells of the sinusoids leading to a rupture of the continuity of the sinusoidal wall. The sinusoidal wall disruption triggers a coagulation cascade and causes a deposit of coagulation factors, erythrocyte aggregates, and cytoplasmic fragments into the perisinusoidal space, ultimately leading to sinusoidal obstruction.[8] Histologically, the severity of sinusoidal injury can be graded semi-quantitatively using the scoring system developed by Rubbia-Brandt.[17] This system evaluates the proportion of centrilobular involvement relative to the entire lobular surface (**Figure 2**). A score of 0 indicates no sinusoidal dilatation; 1 indicates mild sinusoidal dilatation, characterized by centrilobular changes limited to one-third of the lobular surface; 2 indicates moderate sinusoidal dilatation, characterized by centrilobular changes extending to two-thirds of the lobular surface; and 3 indicates severe sinusoidal dilatation, characterized by evidence of complete lobular involvement.[17] The incidence of sinusoidal injury can range from 19% to 52% in patients who have received preoperative oxaliplatin-based chemotherapy.[13,15–18]

Several studies suggest that the presence of sinusoidal injuries related to the use of oxaliplatin-based chemotherapy can increase the risk of postoperative morbidity after resection of CLM.[16,18,25–27] In a series of 92 patients, Aloia et al.[25] reported that the most severe forms of vascular lesions induced by preoperative oxaliplatin were associated with an increase in blood transfusion requirement. More recently, two studies have shown that sinusoidal injury could increase the risk of hepatic dysfunction after major liver resection.[16,18] Indeed, Nakano et al.[16] reported that, in 36 patients who underwent major liver resection for CLM after oxaliplatin-based chemotherapy, those patients who had sinusoidal injuries had increased risk of postoperative complication (40% *vs.* 6% without sinusoidal injury, P = 0.026) and prolonged postoperative hospital stay (17 days *vs.* 10 days without sinusoidal injury, P = 0.006). In the Nakano et al.[16] study, multivariate analysis showed that female gender, ³6 cycles of preoperative chemotherapy, elevated transaminases (>36 UI/L), and a preoperative value of Indocyanine Green Retention at 15 min (ICG-R15) >10% were independently associated with the presence of sinusoidal injuries. Soubrane et al.[18] confirmed these findings in a later study reporting that high-grade sinusoidal injuries (grade 2-3) were associated with an increased risk of ascites and hepatic dysfunction in 51 patients undergoing major liver resection. Furthermore, in the Soubrane et al.[18] study, elevated aspartate aminotransferase (AST), a short interval between the end of chemotherapy and surgery, and a low platelet count were associated with high-grade sinusoidal injuries.

STEATOSIS AND STEATOHEPATITIS

There has been an increasing interest in NAFLD as indicated by the rising number of publications in the last decade. NAFLD is typically graded using the composite scoring system of Kleiner et al.[7] including the degree of steatosis (0-3 points), lobular inflammation (0-3 points), hepatocellular ballooning (0-2 points), and fibrosis (0-4 points). A score of 5 defines steatohepatitis. All degrees of NAFLD may be observed in patients with metabolic disorders featuring the metabolic syndrome [9] and in patients receiving chemotherapy before liver resection for CLM. Indeed, the use of chemotherapy may increase the risk of steatosis, which can be detected in 30-47% of patients receiving systemic chemotherapy.[10–12] Although no specific chemotherapy regimen has been formarlly related to its occurrence, steatosis is usually associated with the use of 5-fluorouracil and/or irinotecan.[13] Whether chemotherapy is directly hepatotoxic or aggravates pre-existing lesions is

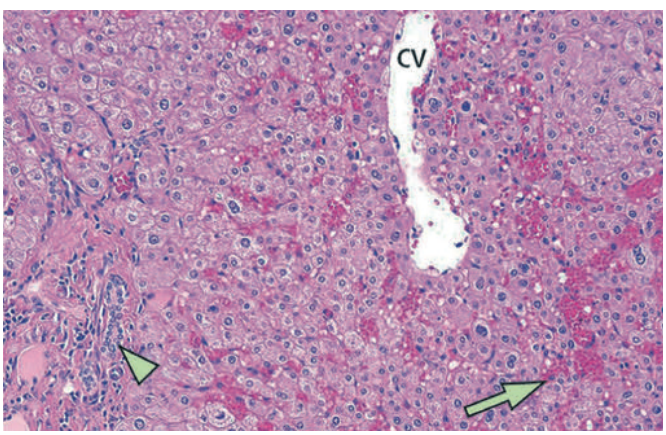


Figure 2. Severe sinusoidal injury with sinusoidal congestion and dilatation (arrow) in hepatic metabolic zones 1 (arrowhead), 2 and 3. CV = central vein. Stained with haematoxylin and eosin, magnification ×200. (Reproduced from Chun et al.[19] with permission)

still debated. Caution is particularly required when using irinotecan in patients with risk factors for NAFLD.[13] For example, elevated body mass index (BMI) and administration of irinotecan have shown to be synergetic factors for the development of chemotherapy-associated steatohepatitis.[12] In patients with a BMI ≥ 25 kg/m^2 who received irinotecan-based chemotherapy, the prevalence of NAFLD was up to 25%.[13]

The distinction between steatosis and steatohepatitis is particularly relevant when considering their influence on postoperative outcome after liver resection. The effect of steatosis on intraoperative and postoperative course after hepatectomy has long been debated, but there is now a widespread agreement that marked steatosis (>30%) does not increase postoperative mortality but is associated with increased postoperative morbidity and especially infectious complications.[10,28–30] In contrast, steatohepatitis appears to increase the risk of postoperative death related to liver failure after resection of CLM. In a series of 406 patients who underwent resection with (n = 248, 61.1%) or without (n = 158, 38.9%) preoperative chemotherapy, we reported that postoperative morbidity and mortality rates were correlated to pathologic features of the non-tumorous liver.[13] Upon pathologic review of the non-tumorous liver, 36 patients (8.9%) had steatosis, 34 (8.4%) had steatohepatitis, and 22 (5.4%) had sinusoidal dilatation. In this study, the risk of 90-day postoperative mortality was dramatically higher in patients with steatohepatitis compared to other patients (14.7% *vs.* 1.6%, respectively; P< 0.001). The presence of steatohepatitis was associated with the preoperative use of irinotecan compared with no chemotherapy, irrespective of BMI (20.2% *vs.* 4.4%, respectively; P< 0.001). The risk of steatohepatitis imposed by irinotecan was further increased in patients with increased BMI (BMI <25 kg/m^2, 12.1% *vs.* BMI ³25 kg/m^2, 24.6%; P= 0.01). In conclusion, irinotecan should be used with caution in patients with CLM eligible for curative resection, especially in case of increased BMI.

PREOPERATIVE DETECTION OF HEPATIC INJURIES

Owing to surgical implications, several studies have evaluated the usefulness of different tools to preoperatively detect the occurrence of different types of hepatic injury. Liver function tests can be elevated in case of hepatic injury, but none is specific for one type of injury.[15,16,18] For these reasons, Soubrane et al.[17] evaluated the usefulness of a composite score which includes platelet count and AST plasma level to predict high-grade sinusoidal injuries (grade 2-3).[31] Using Receiving Operator Curve (ROC) and multivariate analysis, AST to Platelet Ratio Index (APRI) scoring adequately predicted high-grade sinusoidal injury in 78 patients.[18,31] These results have yet to be externally validated. In patients with severe sinusoidal injuries, overt portal hypertension with thrombocytopenia and splenomegaly can be observed.[32] Spleen enlargement and other signs of portal hypertension (low platelet count, collateral venous circulation, and ascites) are therefore indirect signs of sinusoidal injuries that should be detected to guide treatment strategy.[32,33]

As for sinusoidal injury, the ability to preoperatively detect and quantify the severity of NAFLD is of major clinical interest. However, despite abnormal liver function tests suggestive of steatosis or steatohepatitis, the tests themselves are not conclusive regarding the presence of NAFLD.

Numerous imaging modalities have been evaluated to detect hepatic injuries. Aside from showing evidence of portal hypertension or spleen enlargement, no specific protocol of computed tomography (CT) or ultrasound (US) imaging of the liver have been shown to accurately predict the presence and the severity of sinusoidal injuries. Enhanced magnetic resonance imaging (MRI) using specific contrast agents (super paramagnetic iron oxide) has been reported with promising results, but the cost and the availability of this modality precludes its routine use.[34] Similarly, current imaging does not provide accurate predictive information regarding the presence and severity of NAFLD. Ultrasound is ineffective in differentiating hepatic steatosis from fibrosis. It is operator dependent, and therefore prone to inter-observer variations.[35] CT offers the advantage of being part of the preoperative work-up of most hepatic malignancies, and its performance in detecting steatosis has been evaluated. Unenhanced CT images more accurately estimate hepatic steatosis than do contrast-enhanced images. Unenhanced liver parenchyma with an attenuation value <40 Hounsfield units is indicative of >30% hepatic steatosis.[36] However, marked steatosis cannot be excluded on non-contrast-enhanced CT.[37] A preoperative biopsy alone on the non-tumorous liver probably has limited value, mainly because of the heterogeneous repartition of lesions and inter-observer variation in evaluation of the severity of lesions. Therefore, its routine use is not recommended. In patients suspected to have severe hepatic injury, laparoscopic exploration allows for assessment of the general aspect of the liver and can be further associated with intraoperative targeted liver biopsy. However, this approach is valuable only in a small subset of patients and is limited by its cost and its invasiveness.

As a consequence, there is no consensus as to approach for the preoperative diagnosis of hepatic injury. In patients receiving oxaliplatin-based chemotherapy, biologic changes including increase in AST plasma level, γ glutamyl transferase level, and drop in platelet count may suggest sinusoidal injury. In patients receiving an irinotecan-containing regimen, the preoperative diagnosis of NAFLD-associated lesions may be

suggestive of liver injury. In selected patients at high risk of sinusoidal injury or steatohepatitis, laparoscopic evaluation with liver biopsy may be the best diagnostic tool to exclude severe liver injury before further liver resection.

MINIMIZING THE RISK OF HEPATIC INJURIES AND THEIR CONSEQUENCES ON OUTCOMES OF LIVER RESECTION

Strategies to minimize hepatic injury have gained interest for patients receiving preoperative chemotherapy, as most attempts at preoperative diagnosis remain inconclusive.

The risk of complications associated with preoperative chemotherapy is related to the duration of treatment and the time interval between the cessation of chemotherapy and surgery, irrespective of the presence of hepatic injury. Karoui et al.[26] first reported that prolonged chemotherapy (> 6 cycles) was associated with an increase in the risk of postoperative complication after major hepatectomy. The relationship between a high number of cycles of preoperative chemotherapy and postoperative morbidity was also reported by Aloia et al.[25] In this study, preoperative chemotherapy did not increase the morbidity rate per se; however, it was associated with an increased risk of transfusion, whereas prolonged chemotherapy (> 12 cycles) was associated with an increase in the risk of re-operation and longer hospitalization. The effect of prolonged chemotherapy was recently confirmed in a multi-center study of 219 patients who received preoperative oxaliplatin-based chemotherapy, with or without bevacizumab. This study showed that prolonged chemotherapy of 9 cycles or more, compared to short-course chemotherapy, was associated with an increase in postoperative liver insufficiency, defined by serum bilirubin peak >7mg/dL (11% *vs.* 4%; P= 0.035). Furthermore, long duration of chemotherapy did not improve pathologic response (long duration *vs.* short duration, 55% *vs.* 57%, P= 0.74).[38] Furthermore, based on a study of patients who underwent extended right hepatectomy, Shindoh et al. determined that an estimated FLR of 30% or more is needed to avoid severe postoperative liver insufficiency in patients who have received more than three months of preoperative chemotherapy.[39]

The timing of surgery after completion of chemotherapy must be balanced between the risk of tumor progression and the risk of liver injury and postoperative complications. Welsh et al.[40] reported that an interval of four weeks or less between completion of chemotherapy and liver resection was a risk factor for the development of postoperative complications. Recently, a time interval of four weeks or less was identified as an independent risk factor for chemotherapy-related liver injury in patients who underwent liver resection for CLM after preoperative chemotherapy, which is in agreement with the Welsh et al. study. Subsequently, the influence of the time interval on the severity of hepatic injury supports current recommendations to wait five weeks between completion of chemotherapy and liver resection.

Other strategies to minimize liver injury have focused on the use of additional pharmacologic agents. Bevacizumab is a monoclonal antibody directed against the vascular endothelial growth factor receptor (VEGF-R). This biologic agent used in association with chemotherapy improves survival in patients with advanced colorectal cancer.[41] Several studies have shown that the addition of bevacizumab to preoperative chemotherapy is safe, provided a sufficient time interval between the completion of chemotherapy and liver resection (i.e. two half-lives = six weeks) has elapsed.[42–44] Ribero et al.[45] evaluated the influence of bevacizumab on pathologic response and hepatic injury in a series of 105 patients who underwent liver resection for CLM after preoperative chemotherapy. They found that preoperative bevacizumab with oxaliplatin was associated with improved pathologic response, assessed by the proportion of patients with < 25% viable tumor cells (45% with bevacizumab versus 23% without bevacizumab) and a lower incidence of sinusoidal injury (any grade: 27.4% with bevacizumab versus 53.5% without bevacizumab; moderate or severe: 8.1% with bevacizumab versus 27.9% without bevacizumab; both P< 0.01; **Figure 3**). The protective effect of bevacizumab against sinusoidal injury has been confirmed in two other studies.[43,46] Other pharmacologic agents such as anticoagulants like defibrotide, anti-MMP, replenishment of glutathione, aspirin, and monoHER may also have a protective effect against liver injury.[15,23,24,47–49] The beneficial effect of these different agents has yet to be confirmed in prospective studies.

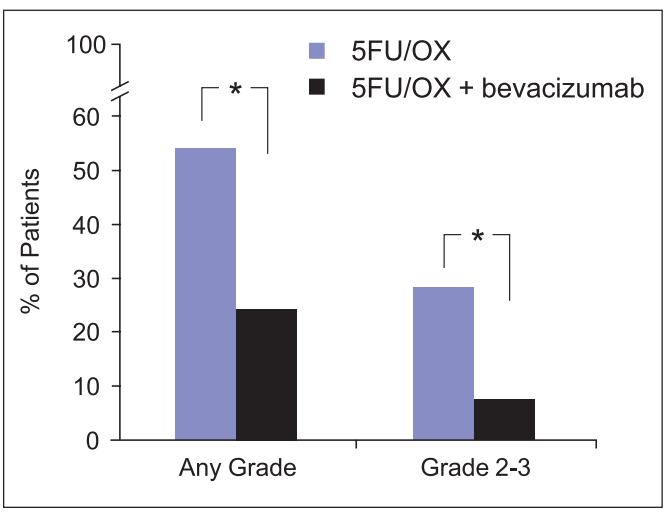


Figure 3. Frequency of sinusoidal dilatation (any grade, left; Grade 2-3, right) observed in non-tumor bearing liver versus type of preoperative chemotherapy regimen (5FU/OX = 5-fluorouracil and oxaliplatin). (Adapted from Ribero et al.[45] with permission)

PATIENT SELECTION IN THE SETTING OF SUSPICION OF HEPATIC INJURY

Evaluation of liver functional reserve (volume and function) is a key element in the preoperative evaluation of patients with possible hepatic injury.[50–53] The use of clinicopathological scores such as Child-Pugh and MELD (model for end-stage liver disease), as well as indocyanine green clearance have demonstrated limited value (especially in patients undergoing major liver resection and subsequently at higher risk of liver insufficiency) in this setting, as most patients will have normal liver function based on these parameters. Therefore, combinations of imaging, blood tests, and in selected cases laparoscopy and biopsy, are used to assess liver injury. In contrast, the future liver volume (FLR) is easier to assess and it has been well demonstrated that FLR is associated with outcomes. As a consequence, CT liver volumetry has gained importance in preoperative planning.[2] There are several methods of calculation for FLR volume, and no consensus has yet been reached on the formula that should be used. At the University of Texas M.D. Anderson Cancer Center, the standardized FLR (sFLR) is calculated as the ratio of the FLR to the estimated total liver volume (TLV). The estimated TLV is previously calculated using a formula that relies on the linear correlation between the TLV and body surface area (BSA): TLV (in cm^3) = -794.41 + 1,267.28 × BSA (in m^2). Based on the association between the FLR volume and the risk of postoperative liver failure, minimal FLR requirements for safe liver resection have been set: 20% sFLR or more in patients with normal liver,[2,5] and 40% sFLR or more in cirrhotic patients (**Figure 4**).[54,55] In patients with a small FLR, portal vein embolization (PVE) may be indicated to increase the volume and to evaluate the regenerative capacities of the liver. The degree of hypertrophy after PVE is also a reliable parameter to predict outcome after resection and a degree of hypertrophy of the FLR of less than 5% in patients with normal liver,[4] or less than 10% in cirrhotic patients, is associated with increased mortality after resection. As such, response to PVE directly allowing measure of regenerative potential may in fact be a more reliable factor of functional reserve of the liver and liver injury than current blood samples and imaging. At this point, there is no consensual cut-off value for the volume of FLR, nor for the degree of hypertrophy required in patients with hepatic injury. At the University of Texas M.D. Anderson Cancer Center, 30% sFLR is considered sufficient and a degree of hypertrophy of 5% is considered necessary after PVE to safely perform resection in patients with hepatic injury (**figure 5**).[19,56]

Patients with severe sinusoidal injuries can have an equivalent intrahepatic Budd-Chiari syndrome which naturally evolves toward portal hypertension.[32] Besides their potential role in the genesis of lesions, low platelets may also be directly involved in the pathophysiology of postoperative morbidity. Indeed, Lesurtel et al.[57] showed that platelets promote liver regeneration via a serotonin-mediated mechanism and that liver regeneration is impaired in a thrombocytopenic mice model, suggesting its role in the early phase post-hepatectomy.[58] We reported a series of six patients receiving oxaliplatin who developed non-cirrhotic overt portal hypertension. Thrombocytopenia was present in all cases, with a significant decrease between pre-chemotherapy and post-chemotherapy platelet count and associated with an increase in splenic volume between the beginning and the end of the chemotherapy. In patients with a significant drop in platelet count after chemotherapy, we proposed to selectively perform splenic artery embolization to restore normal platelet count before surgery. This policy has yet to be evaluated in a clinical study.

This chapter addresses general concerns regarding resection of the injured liver (NAFLD and sinusoidal

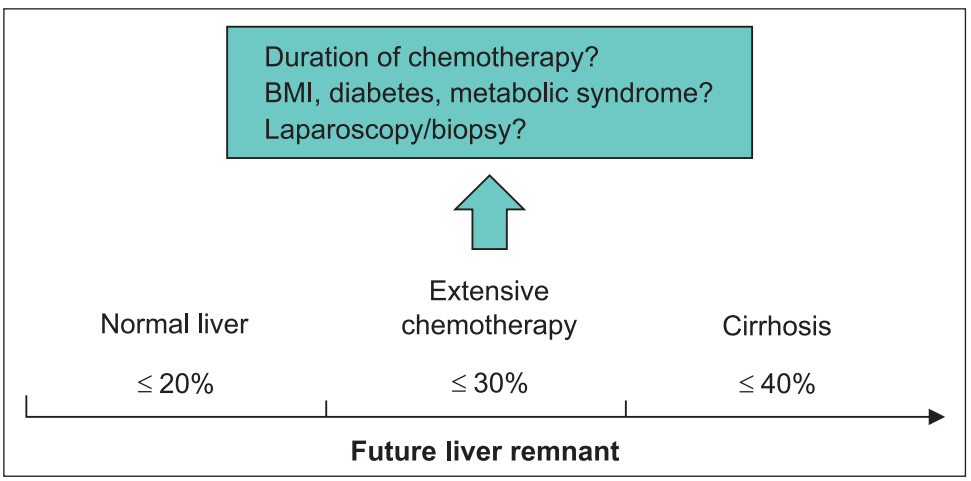


Figure 4. Indications for portal vein embolization. There is consensus that, in patients treated with aggressive preoperative chemotherapy, the remnant liver volume should be at least 30% of the total liver volume to avoid a high risk of complications following hepatic resection. BMI (body mass index). (Adapted from Zorzi D et al.[55], used with permission)

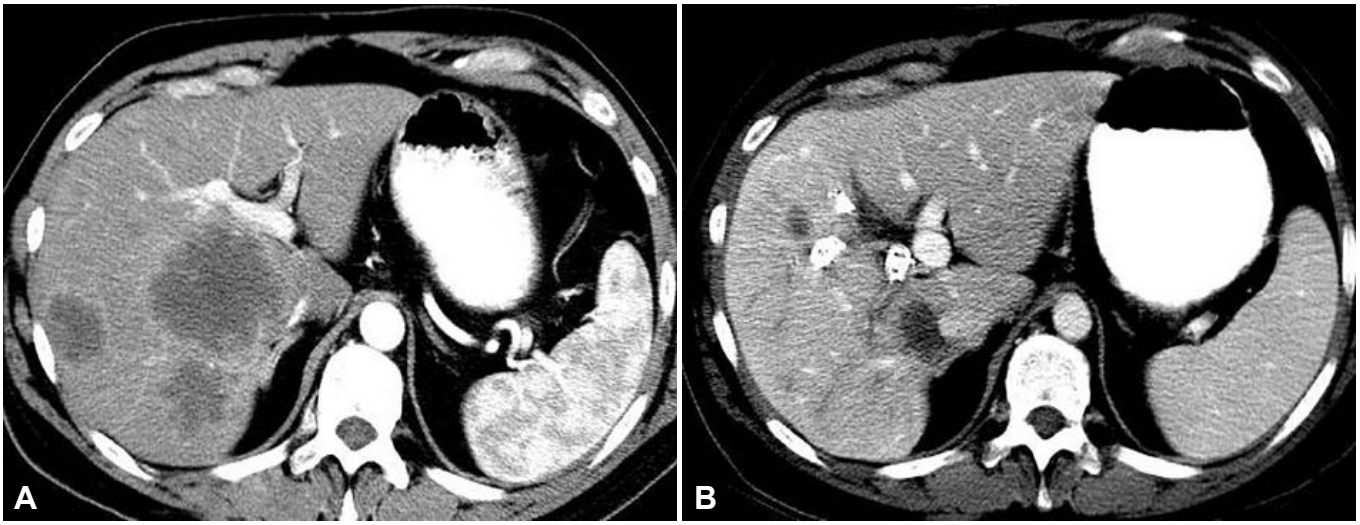


Figure 5. A patient with multiple, large metastases requiring extended right hepatectomy. **A**) The measured volume of the future liver remnant (segments 2 and 3, outlined in white) was 291 ml, and the standardized future liver remnant (sFLR) was calculated as 17% of the estimated total liver volume (TLV). To downsize metastases and induce hypertrophy of the FLR before hepatectomy, chemotherapy was administered followed by portal vein embolization. **B**) This led to an increase in volume of the FLR to 510 ml and sFLR to 30% of the estimated TLV allowing resection. (Reprinted from Chun et al.,[19] with permission)

injury) and the cirrhotic liver. In general, these concepts are applicable to all types of chronic liver disease potentially causing cirrhosis, such as chronic viral hepatitis, autoimmune hepatis, alcoholic hepatitis, biliary cirrhosis, sclerosing cholangitis, and hemochromatosis.

FINAL CONSIDERATIONS

In conclusion, with the expansion of the use of preoperative chemotherapy, hepatobiliary surgeons face an increasing number of patients with various types of hepatic injury. The choice of regimen and the monitoring of duration are key elements in the management of the hepatotoxicity of chemotherapy. We recommend short duration (four to six cycles) chemotherapy in patients with resectable metastases (**Figure 6**). In patients receiving prolonged use of chemotherapy, preoperative work-up should include assessment of liver volume and detection of overt signs of hepatic injury, including portal hypertension. The presence of liver injury in the remaining liver parenchyma sets cut-offs for FLR volume and subsequently indication for PVE: ≥40% FLR in cirrhotic patients, ≤30% in patients with a normal liver if they have received more than 6 cycles of chemotherapy, and ≤20% in patients with a normal liver.

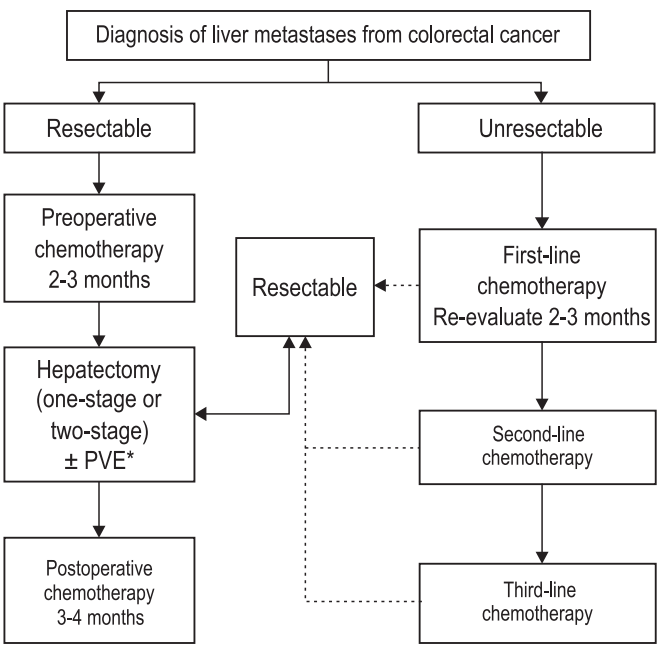


Figure 6. Recommendations for treatment of colorectal liver metastases. *PVE (Portal vein embolization) considered if future liver remnant less than or equal to 20% of healthy liver, less than or equal to 30% after extensive chemotherapy, or less than or equal to 40% in patients with cirrhosis. (Adapted from Kopetz and Vauthey,[56] with permission)

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Kishi, Y. *et al.* Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann. Surg.* **250**, 540–548 (2009).

A large series of extended right hepatectomies that defines a future liver remnant of more than 20% (before or after portal vein embolization) of the total liver volume as safe for surgery.

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5 Liver Function Assessment Before and After Hepatic Resection

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- *The main goals of liver function assessment before and after hepatic resection are ultimately prevention and early detection of postoperative liver failure (PLF).*
- *The minimal required volume of remnant liver parenchyma after resection is proportional to severity of parenchyma injury. Thus, both liver volumes and function tests should be assessed preoperatively.*
- *The estimate of remaining liver volume is usually enough to predict the risk of PLF in patients without underlying chronic liver disease. However, adequate evaluation of hepatic function in the presence of chronic underlying liver disease (i.e. cirrhosis, chronic hepatitis, chemotherapy associated liver injury, etc.) is complex. Most available tests evaluate only one or few of the multiple liver functions and rarely take into account regional variations of underlying disease severity.*
- *Clinical scores, such as the Child-Turcotte system and Model for End-Stage Liver Disease (MELD), combine several biochemical and clinical parameters and have variable ability to predict PLF. Indocyanine green retention test (a dynamic quantitative test) is among the most commonly used tests in the Orient, and it is incorporated in a commonly used algorithm in Japan. Molecular nuclear imaging techniques, such as 99mTC-labeled galactosyl human serum albumin (GSA) scintigraphy, have been used pre- and postoperatively to estimate functional hepatocyte volume. Associated CT images can provide functional evaluation of each hepatic region.*
- *Transient liver dysfunction is expected after partial hepatectomy, but severe liver function tests deterioration and/or delayed recovery should raise concern for PLF.*

INTRODUCTION

Rapid expansion of liver surgery in the latter half of the last century can be attributed in great part to advances in safety that have allowed extensive resections to be performed, even in patients with underlying parenchymal disease. Careful preoperative selection of patients through the use of various advanced imaging and functional studies, as well as careful postoperative monitoring, has allowed hepatobiliary surgeons to reduce operative mortality to less than 5% (**Table 1**).[1–5] Despite these gains, liver failure remains the leading cause of postoperative mortality. To minimize this complication, surgeons must have a solid understanding of the available methods to assess preoperative risk, an appreciation of the physiological impact of liver surgery, and knowledge of strategies to guide postoperative recovery.

The liver has multiple homeostatic functions, including the synthesis of proteins, fatty acids, and glycogen; production of clotting factors; degradation of senescent proteins; metabolization and detoxification of small molecules; and the processing and excretion of bile. Underlying cirrhosis, hepatitis, steatosis, and biliary stasis impair the capacity of the liver to perform these functions in many patients undergoing liver resection. These physiological functions are all altered postoperatively in proportion to the extent of functioning hepatic parenchyma resected. Through careful intraoperative and postmortem measurements, Stone et

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Table 1. Morbidity and mortality statistics from selected large single institutional series of open hepatectomies.

Author Country	Years	N	Mortality	Morbidity
Cescon Italy	1985-2007	1500	3.0%	22.5%
Huang China	1986-2005	2008	0.55%	14.4%
Belghiti France	1990-1997	747	4.4 %	22%
Jarnagin USA	1991-2001	1803	3.1%	45%
Imamura Japan	1994-2002	1056	0%	39%

al.[6] in 1969 showed that operative mortality was inversely proportional to the amount of remaining functional liver parenchyma (**Figure 1**). However, predicting postoperative liver failure must take into account not only the mass of liver parenchyma removed, but it must also account for the demands placed on the liver for regeneration and wound healing. This partially explains why even a non-extensive liver resection, such as a segmentectomy, which may be functionally insignificant in patients with normal livers, often leads to catastrophic and fatal liver failure in patients with advanced cirrhosis. Balancing the preservation of hepatic functional reserve with the need for adequate resection margins is therefore an important task facing a surgeon in preoperative planning.

PREOPERATIVE RISK STRATIFICATION

Numerous tests exist to measure liver function, volume, and functional volume. A partial list is presented in **Table 2**. Each test aims to capture the function of the liver by measuring a unique function of the liver, such as cytochrome p450 function or excretion of indocyanine green in bile. Though daunting in number the available tests of liver function pale in comparison to the myriad functions of the liver, which is why no one test can be perfect in identifying patients who will succumb of post-operative liver failure. No single test or scoring system has been proven to be clearly superior to all others, and most hepatic surgeons will use a variety of clinical, laboratory, and radiological parameters in deciding an individual patient's risk of undergoing hepatic surgery. It is therefore incumbent upon the hepatic surgeon to use good judgment along with an understanding of the strengths and shortcomings of available tests to determine which patients are at high risk for liver resection.

CLINICAL SCORING SYSTEMS

Child and Turcotte first proposed their clinical scoring system in 1964 to classify the severity of cirrhosis, in order to understand the natural history of portal hypertension and mortality of surgical porto-systemic shunting.[7] The Child-Turcotte system took into account the patient's bilirubin and albumin levels, as well as the severity of encephalopathy and ascites to classify the level of

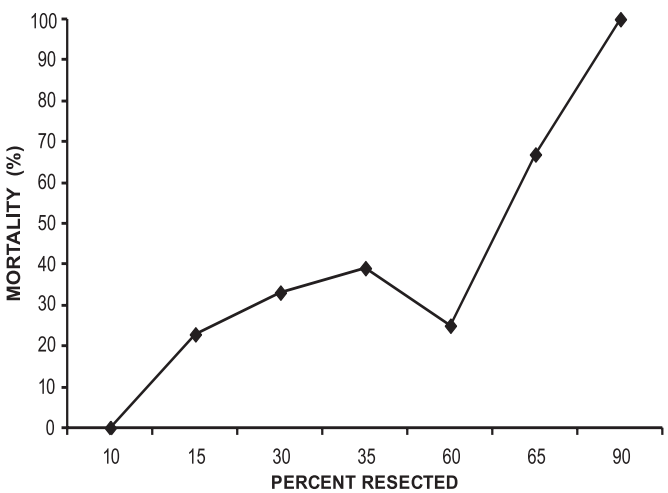


Figure 1. Relationship between percent of liver resected by weight and mortality. (Adapted from Stone et al.[6])

Table 2. Available tests to assess hepatic function.

Aminopyrine breath test
Amino acid clearance test
Arterial ketone body ratio
Beta-hydroxy butyrate/acetoacetate test
Bile acid tolerance test
Bromosulpthalein retention test
Caffeine clearance test
Galactose-elimination capacity
Hippurate ratio
Hepatic Imino-Diacetic Acid (HIDA) scan
ICG clearance rate
Monoethylglycinexylidide (MEGX)
Sulfur colloid
Trimethadione
99mTc-GSA
99mTc-mebrofenin

GSA: Galactosyl-human serum albumin.

cirrhosis as A, B, or C (**Table 3**). The widely used Pugh modification of Child's system added measurements of prothrombin time (or INR).[8] This system has since been adopted to determine general operative risk and candidacy for transplantation in patients with cirrhosis, though it has been supplanted by the MELD (Model of End-Stage Liver Disease) scoring system for the latter purpose. The ability of Child-Turcotte-Pugh (CTP) to predict postoperative mortality and liver failure after liver resection has been mixed. In one series of patients with hepatocellular carcinoma (HCC) undergoing liver resection, the rate of liver failure in CTP Class A patients was 7.6% vs. 38.5% in class B patients.[9] In general, CTP class B and C patients carry a high risk of postoperative liver failure and mortality, and in the proper setting should be considered for transplantation. However, even Class A patients have developed liver failure after comparatively small hepatic resections. The need to further refine "good" risk class A patients from "poor" risk class A patients requires the application of more sophisticated tests, though to date none has been shown to be clearly superior to CTP in predicting postoperative liver failure and mortality.

An alternative to Child-Turcotte-Pugh classification is MELD, a model first developed to predict 90-day mortality in patients after a transjugular intrahepatic porto-systemic shunt procedure. The original MELD model is a mathematical model based on the patient's creatinine, bilirubin, and INR (MELD= 9.57x Log_e[creatinine in mg/dL] +3.78x Log_e[Bilirubin in mg/dL] +11.2x Log_e [INR] + 0.643), and is therefore more cumbersome to calculate than the CPT system, though several online calculators exist to aid in this task (http://www.mayoclinic.org/meld/mayomodel6.html). The literature regarding MELD score is limited to patients with HCC and is somewhat mixed. In patients matched for portal hypertension, MELD score but not CTP classification (Class A and B) was predictive of postoperative liver failure on multivariate analysis in patients with HCC.[9] A MELD score of >9 has also been found to predict postoperative mortality in this patient population.[10,11] However, other reports of single institutional experiences have not found MELD to be predictive of postoperative mortality,[12] and a review of NSQIP (National Surgical Quality Improvement Program) data found CTP score to be a better predictor of postoperative mortality.[13] In general, a MELD score of <10 is associated with acceptable operative risk.

AMINO ACID CLEARANCE TEST

Developed to measure the protein synthesis capacity of the liver, the amino acid clearance test calculates the ratio of amino acids in peripheral circulation to the arterial concentration after processing by the liver. To achieve a controlled blood plasma level of amino acids, the patient undergoes an overnight fast followed by an 18-hour infusion of amino acids. Blood samples are obtained from the femoral artery and vein and used to calculate the central plasma clearance rate of amino acids (CPCR-AA). Interest in this test peaked when it was shown that CPCR-AA correlated with the rate of hepatic protein synthesis from liver biopsies obtained prior to liver resection and correlated to postoperative mortality in patients with early and advanced cirrhosis.[14,15] However, in a prospective study of patients undergoing liver resection for HCC, the amino acid clearance test failed to predict postoperative mortality when compared to indocyanine green retention (ICGR) at 15 minutes (ICGR-15).[16] Due to its invasiveness, time-consuming nature and non-superiority over other widely available tests, interest in this test has diminished, though recent advances to reduce the invasiveness of this test, such as the L [1-^{13}C] phenylalanine breath test may hold promise.[17]

HIPPURATE RATIO

The liver is responsible for metabolism of para-aminobenzoic acid (PABA) to para-acetamidohippuric acid (PAAHA) by phase II conjugation to glycine and acetyl-CoA to form the intermediary molecules para-acetamidobenzoic acid (PAABA) and para-aminohippuric acid (PAHA). The measurement of these metabolites by high pressure liquid chromatography 30 minutes after a 50 mg/kg oral load of PABA shows a positive correlation to ICGR-15 and postoperative liver failure.[18] Though easier to administer than other widely used quantitative liver function tests, the cutoff value for the hippurate ratio below which liver resection should be avoided has not been defined.

Table 3. Child-Turcotte-Pugh scoring system.

	Points		
	1	**2**	**3**
Ascites	None	Mild-Moderate	Tense
Encephalopathy	Absent	Mild or medically controlled	Severe or Refractory
Albumin (g/L)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dL)	<2	2-3	>3
INR	<1.7	1.7-2.3	>2.3

Class A <7 points, Class B=7-9, Class C >9. Encephalopathy is also graded as absent, grade I-II (confused/disoriented) and grade III-IV (somnolent/coma).

MONOETHYLGLYCINEXYLIDIDE (MEGX)

The liver is the site of metabolism for greater than 95% of lidocaine. Lidocaine is oxidized by the P450 pathway to monoethylglycinexylidide (MEGX), which can be measured by immunofluorescent techniques after a 1mg/kg IV load. A level of >50ng/mL is considered normal. Decreasing levels of MEGX correlate to higher CPT classification and can predict higher postoperative liver failure rates in cirrhotic patients with levels <25 ng/mL and non-cirrhotic patients with levels <32 ng/mL.[19–21] MEGX has found wide application in liver transplantation where it is used to predict patients at high risk for death while awaiting liver transplantation.[22] MEGX measurements can be affected by hepatic blood flow and by drugs that alter the cytochrome P450 system.[23]

AMINOPYRINE BREATH TEST

Aminopyrine is degraded by liver microsomes to yield formaldehyde, which is then partially converted to carbon dioxide. The detection of radioactive carbon dioxide after the intravenous injection of ^{14}C labeled aminopyrine can thus be used to measure liver function. Decreasing levels are correlated with increasing liver dysfunction[24] and increasing mortality in cirrhotic patients undergoing surgery.[25] Despite this, the aminopyrine breath test has not been noted to predict postoperative mortality in patients undergoing hepatectomy for HCC.[16,26] Since aminopyrine degradation relies on the cytochrome p450, it too is affected by drugs that alter this system.

GALACTOSE ELIMINATION CAPACITY TEST

The uptake of galactose and phosphorylation by hepatic galactokinase can be measured using intravenous injection of 0.5g/kg of 45% galactose. A rate of elimination >6mg/kg/min is considered normal, though patients with cirrhosis have lower baseline levels.[27] Galactose elimination capacity (GEC) is diminished after liver resection, reaching a nadir at two weeks post-surgery, and it returns to normal after regeneration.[28] In patients with underlying cirrhosis, a postoperative decrease in GEC has been observed in patients who develop liver failure.[27] In patients with HCC, an elimination rate of <4mg/kg/min has been associated with increasing morbidity and mortality.[29]

INDOCYANINE GREEN (ICG) RETENTION TEST

The most widely studied and applied test of liver function is the indocyanine green retention test (ICGR). Indocyanine green (ICG) is a synthetic dye that binds albumin and alpha-1 lipoproteins and is rapidly taken up by the liver and excreted in bile. The ability of the liver to clear ICG is affected by blood flow to the liver[30] as well as biliary obstruction,[31] and correlates to liver ATP consumption.[32]

A standard test involves the intravenous injection of 0.5mg/kg of ICG following an overnight fast. ICG levels can be measured at various times by venous sampling, though in practice the ICG retention value at 15 minutes (ICGR-15) is the most common measure reported. In non-cirrhotic livers, the ICGR-15 level is <10% and levels >14% in cirrhotic patients have been correlated with postoperative mortality and complications.[26] Other groups have confirmed the ability of ICG testing to predict postoperative mortality and complications.[33,34] Non-invasive measurements of ICG using pulsed spectrophotometry have been developed and show strong correlation with traditional methods.[35] Pulsed spectrophotometry can be used to calculate the ICG clearance rate constant (ICG-K). A postoperative ICG-K level of <0.86-0.90, which can be accurately estimated based on preoperative ICG-K and CT volume measurements, is predictive of postoperative mortality and liver failure.[36,37]

ICG retention is incorporated into the Makuuchi criteria (**Figure 2**), a commonly used algorithm in Japan.[38] In 1,053 consecutive liver resections, Imamura et al.[5] followed this algorithm in determining patient selection for hepatic resection and reported a 0% mortality rate and hepatic failure in only one patient, though the true hepatic failure rate may have been higher. Whether these results will be reproduced in the West remains to be seen.

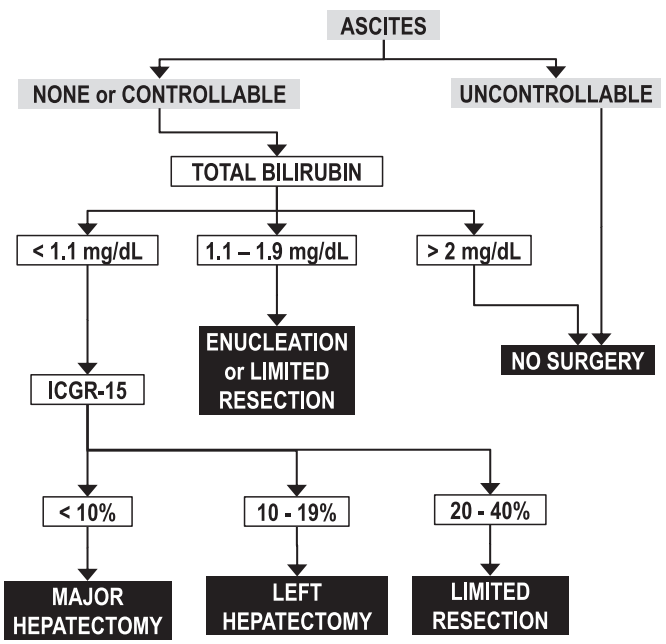


Figure 2. Makuuchi's criteria for hepatic resection. (Adapted from Makuuchi et al.[38])

LiMAx TEST

The maximum liver function capacity (LiMAx test) is based on the intravenous bolus injection of ^{13}C-labeled methacetin. Methacetin is metabolized into acetaminophen and $^{13}CO_2$, and then exhaled. The $^{13}CO_2/^{12}CO_2$ concentration ratio is continuously measured using a special device (FLIP, Humedics GmbH, Berlin, Germany).[39–41]

^{99m}Tc-GSA SCINTIGRAPHY

The asialoglycoprotein receptor (ASGPR), found in the membrane of hepatocytes, recognizes and removes harmful desialylated glycoproteins.[42] A radioactively labeled synthetic asialoglycoprotein, galactosyl human serum albumin (GSA), detected by gamma camera (planar scintigraphy) or by single-photon-emission computerized tomography (SPECT) can thus measure levels of ASGPR and estimate functional hepatocyte volume. Dynamic scintigraphy over the heart and liver is used to measure radioactivity after a bolus intravenous injection of ^{99m}Tc-GSA. Over time, a non-cirrhotic liver will see an increase in activity as the activity in the heart decreases. Various values can be derived from analysis of planar ^{99m}Tc-GSA.[43–46] The hepatic uptake ratio (the ratio of hepatic activity to the sum of hepatic and heart activity at 15 minutes – HH15) has been correlated to the ICGR-15 level as well as decreased postoperative complications.[43] The total hepatic ^{99m}Tc-GSA clearance and receptor concentration also correlates positively with ICGR-15 levels and can predict postoperative liver failure.[47,45] Since bilirubin does not bind to asialoglycoprotein receptors, this test is not influenced by hyperbilirubinemia. For the same reason, it is not useful to evaluate biliary obstruction, such as in hilar cholangiocarcinoma.[48]

Static SPECT ^{99m}Tc-GSA scintigraphy has the ability to measure segmental liver function and functional liver volume.[49,50] More recently, dynamic ^{99m}Tc-GSA scintigraphy has been used fused with 3D computed tomography images (Dynamic ^{99m}Tc-GSA SPECT/CT) to provide a visual estimation of function for all regions of the liver, particularly the future remnant liver.[51,52]

Another scintigraphic test using ^{99m}Tc labeled mebrofenin, which is an iminodiacetic acid analogue, with biliary excretion without metabolization, has been used for the assessment of liver function (hepatobiliary scintigraphy) similarly to ^{99m}Tc-GSA scintigraphy.[53,54]

GADOLINIUM ETHOXYBENZYL DIETHYLENE-TRIAMINE PENTAACETIC ACID (Gd-EOB-DTPA) MAGNETIC RESONANCE IMAGING (MRI)

Gd-EOB-DTPA is a contrast agent taken up by hepatocytes through the organic aminonic transport system and excreted into the bile, similarly to iminodiacetic acid analogues (e.g. mebrofenin). Gd-EOB-enhanced MRI is a recent imaging-based liver function test and represents an alternative to the scintigraphic methods for regional hepatic function assessment. The advantages of MRI-based imaging are that it does not rely on a radioactive tracer and Gd-EOB-DTPA MRI easily integrates into preoperative clinical workflow.[53,55]

COMPUTED TOMOGRAPHY (CT) VOLUMETRY

Though not a functional test, CT volumetry is widely used by surgeons to estimate the remnant liver volume after hepatic surgery. The mortality and complication rate after partial liver resection is significantly related to the number of segments removed (**Figure 3**).[4] Recent developments in computer-aided 3D modeling allow hepatic surgeons not only to plan the anatomic resection, but also to estimate the residual volume of liver after resection. There is a strong inter-operator correlation as well as a positive correlation to resected specimens.[56] The normal liver volume to body weight ratio is 20-27 cc/kg and is typically lower in patients with liver dysfunction, depending on the underlying cause of cirrhosis.[57] The recommended minimal functional residual liver volume following hepatectomy, particularly after extended resections, is estimated to be $\geq$ 25% in a normal liver, and $\geq$ 40% in a "compromised" liver observed in cirrhosis, steatosis, cholestasis, fibrosis, and previous chemotherapy.[58] In a survey of 100 liver centers, a minimum acceptable liver remnant after resection was 25% for healthy livers and 50% for dysfunctional livers, but the ranges of acceptability varied widely.[59]

Several formulae have been developed that use the patient's body weight and/or body surface area to calculate the absolute liver volume. The most popular for Japanese patients is the one proposed by Urata et al.[60,61], and the most popular for Western populations is by Vauthey et al.[62] The three-dimensional CT volume reconstructions

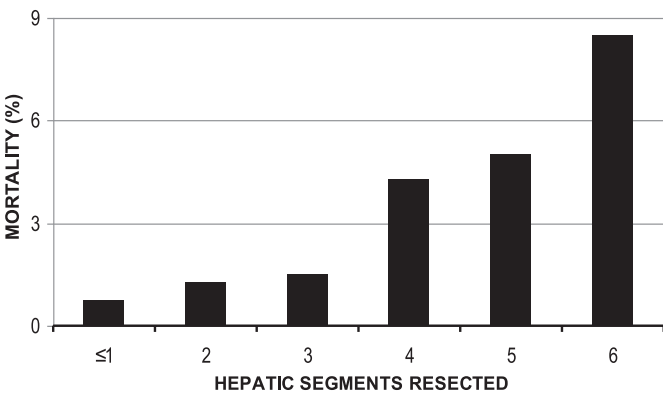


Figure 3. Perioperative mortality after partial hepatectomy increases with the number of segments resected (Adapted from Jarnagin et al.[4]).

are critical in deriving the functional residual liver volume. Liver volume can be calculated using the Urata formula [estimated liver mass (mL) = (706.2 x body surface area in m^2)+2.4], which was derived from CT imaging of the liver for 96 Japanese children and young adults. Autopsy studies of Western populations reveal that this formula underestimates the total liver volume for Western adults by an average of 323 cm^3. A multi-center collaborative study by Vauthey et al.[62] used CT volumetric measurements to generate a pooled sample regression equation for total liver volume (TLV): -794.41 + 1267.28 x BSA. When incorporating patient age, the formula for TLV was: -695.81 + 1279.38 x BSA- 2.26 x age.

Though remnant liver volume probably correlates well to remnant postoperative liver function in normal livers, the same cannot be said in cirrhotic livers, which are not homogenously dysfunctional. Some of the caveats of using these formulae for estimating TLV include the effects of other confounding variables on liver function, such as pre-existing liver disease (cirrhosis, fibrosis, steatosis), increased portal pressure from post-hepatectomy hypertrophy, and chemotherapy-associated liver injury (CALI). This is probably why remnant liver volume alone has failed to predict postoperative liver failure and mortality, especially when compared to functional studies such as hepatobiliary scintigraphy (99m-Tc-mebrofenin) and the ICG retention test.[63,64]

POSTOPERATIVE LIVER FAILURE

As outlined earlier, the development of liver failure is the most dreaded complication after liver resection both because it is the leading cause of early death and because it is difficult to manage, sometimes requiring immediate liver transplantation. The recognition of postoperative liver failure may be masked because it is often accompanied by multiple organ failure, making it sometimes difficult to distinguish from other syndromes such as sepsis. The identification of postoperative failure is made even more difficult by the lack of a consensus definition. This is complicated by the fact that all patients will exhibit some level of liver dysfunction postoperatively. In an effort to develop a simple and standardized method, Balzan et al.[65] have developed the "50-50 criteria" based on the analysis of postoperative enzymes and their normal recovery. The presence of hyperbilirubinemia (serum bilirubin > 3.0 mg/dL) and PT < 50% on postoperative day 5 was found to predict hospital mortality with a sensitivity of 69.6% and specificity of 98.5%.[65] Though easy to remember and apply, it should be remembered that the "50-50 criteria" is a predictive tool and not a definition of liver failure. Prolonged laboratory derangements (hyperbilirubinemia, coagulopathy) or clinical signs of portal hypertension (hepatic encephalopathy, significant ascites) should be cause for concern.

The natural course of recovery from partial liver resection is a transient rise in several laboratory measures of hepatocyte dysfunction with a rapid recovery of most parameters to baseline levels within days, as the remaining hepatocytes initially hypertrophy and eventually regenerate over a period of weeks. **Figure 4** shows the serum levels of serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), glucose, and prothrombin time after successful anatomic resections.[66] A similar pattern of rise is seen in patients undergoing non-anatomic resections though to a much lesser degree. An abnormally high elevation and/or delayed recovery should raise concern for liver dysfunction. Immediate postoperative thrombocytopenia (platelet count < 100,000/μL) has also been associated with higher peaks of transaminases, bilirubin, and prothrombin time, and is an independent predictor of delayed recovery of liver function and increased 90-day mortality.[67] Therefore, the routine measurement of serum transaminases, bilirubin, coagulation profile, serum chemistries, and blood count is a useful and standard practice.

Though not routinely used, the serum level of hyaluronic acid (HA) has been proposed as both a preoperative marker of hepatic fibrosis and sinusoidal endothelial damage, as well as a postoperative marker of poor hepatic regeneration. Hyaluronic acid levels of > 200 ng/mL seem to correlate with increased hepatic failure compared to levels of approximately 100 ng/mL in patients who did not develop this complication. Furthermore, postoperative hyaluronic acid levels significantly correlate to ICGR-15 and liver activity at 15 minutes by 99m-Tc-GSA.[68–70] However, HA levels in patients with obstructive jaundice are routinely low, and therefore it is not useful in this patient population.

Two of the previously discussed liver function tests, indocyanine green clearance and hepatic scintigraphy, are also used postoperatively to determine residual function and recovery. The measurement of ICG retention using pulse spectrophotometry is attractive because it is a non-invasive test and is a test already familiar to most hepatic surgeons. Postoperative ICG clearance as measured by ICG-K decreases significantly on postoperative day 1, and remains low through postoperative day 7 both in patients with normal livers and patients with cirrhotic livers.[37] In patients with normal liver function, low ICG clearance on postoperative day 1 is associated with increased risk of subsequently developing liver failure.[71] This observation also holds true in cirrhotic HCC patients undergoing liver resection, and it has been suggested that perioperative ICG monitoring with an effort to preserve a postoperative ICG-K > 0.09 leads to decreased postoperative liver

failure.[36]

Postoperative hepatic scintigraphy using 99m-Tc-mebrofenin has been shown to correlate with postoperative liver regeneration as measured by CT volume measurements.[64] 99m-Tc-GSA has also been used to follow patients with fulminant liver failure,[72] and increasing 99m-Tc-GSA uptake ratio at 15 minutes correlates with functional recovery after liver resection.[54] However, the utility of dynamic scintigraphy techniques in the peri-operative period has yet to be studied, and is not likely to be as convenient or available as real-time ICG measurements using pulsed spectrophotometry.

FINAL CONSIDERATIONS

The planning for liver resection must finely balance the need for complete resection with the need to preserve functional reserve. The hepatic surgeon must therefore assess patient risk based on the presence and severity of underlying hepatic injury. A patient with normal liver parenchyma can compensate with as little as 25% residual liver volume, but the wide variability of functional liver reserve in cirrhotic patients requires careful assessment by experienced hepatic surgeons. In addition to traditional scoring systems of underlying liver disorder such as Child-Turcotte-Pugh or MELD, a variety of functional tests are now available. Although not widely used in the West because of cost and logistical issues, ICG clearance tests and ^{99m}Tc-GSA are being widely applied in the East with impressive results. Also, Gd-EOB-enhanced MRI seems provide valuable information on hepatic function. Tests that allow global assessment of hepatic function are usually applied in combination with volumetric methods to estimate the postoperative liver function capacity. However, liver function can be inhomogeneously distributed in situations such as unilateral cholestasis, portal vein embolization, or chronic underlying liver disease. Scintigraphy and Gd-EOB-enhanced MRI are the only available tests able to estimate hepatic function of particular liver segments, and could provide a more precise knowledge of functioning of the remnant liver. In fact, no single test is clearly superior, so hepatic surgeons should understand the strengths and limitations of available modalities and apply them judiciously to guide preoperative patient selection.

Despite these advances, postoperative liver failure continues to be the primary cause of death after hepatectomy. Postoperative monitoring of clinical parameters, serum enzymes, platelet count, and chemistries, as well as an understanding of the normal pattern of these tests after successful resection, are crucial to the early recognition of liver failure. Further prognostic information can be gathered by application of ICG clearance and ^{99m}Tc-GSA. Unfortunately, with the exception of liver transplantation, the treatment of postoperative liver failure remains supportive. Prevention is therefore the best medicine.

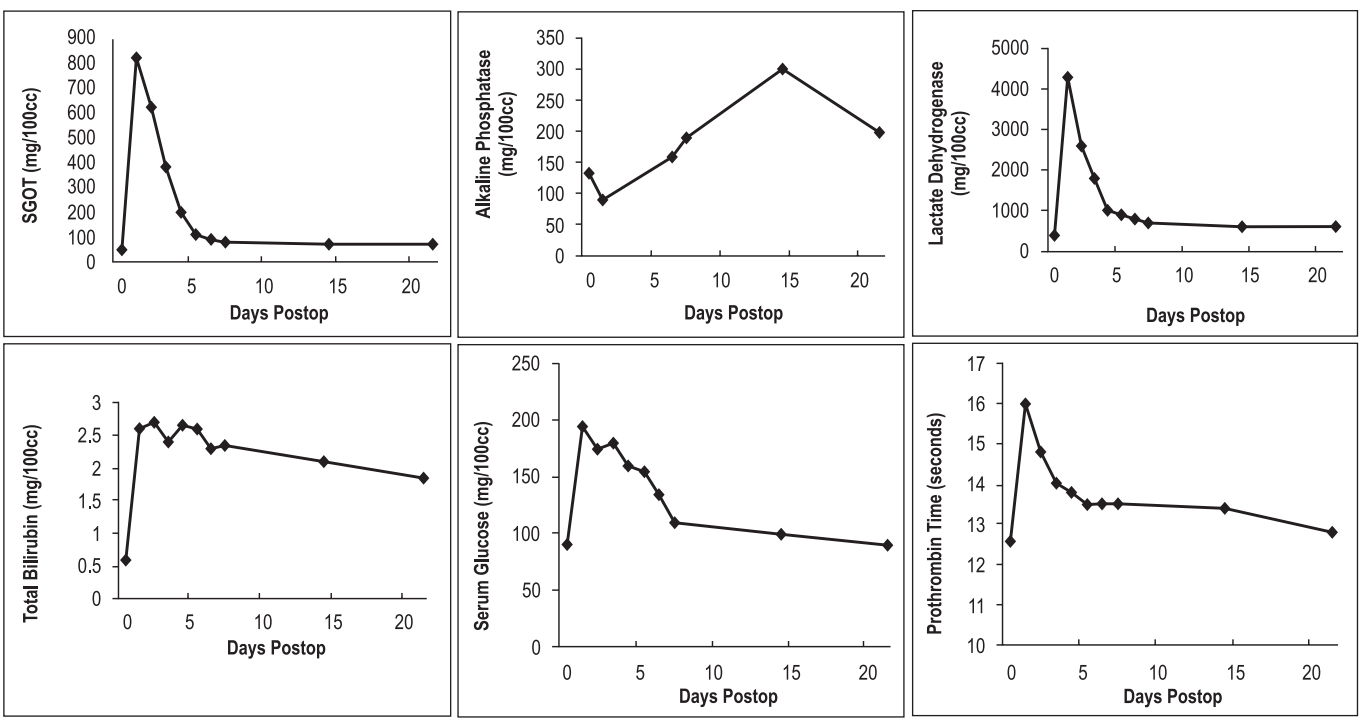


Figure 4. Postoperative levels of common serum chemistries after hepatic lobectomy. (Adapted from Pelton et al.[66])

SUGGESTED READING

Ohwada, S. *et al.* Perioperative real-time monitoring of indocyanine green clearance by pulse spectrophotometry predicts remnant liver functional reserve in resection of hepatocellular carcinoma. *Br. J. Surg.* **93**, 339–346 (2006).

The use of non-invasive measurement of indocyanine green clearance is evaluated in 75 patients before surgery, during intraoperative inflow occlusion, and after resection.

Mao, Y. *et al.* Using Dynamic 99mT c-GSA SPECT/CT fusion images for hepatectomy planning and postoperative liver failure prediction. *Ann. Surg. Oncol.* **22**, 1301–1307 (2015).

Interesting study evaluating the use of dynamic functional scintigraphy associated with computed tomography images to estimate the functional remnant liver after hepatectomy.

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6 Surgical Approach in Cirrhotic Patients

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- *The number of patients with cirrhosis requiring liver surgery is increasing, with hepatocellular carcinoma being the major indication. The mortality rate of cirrhotic patients is –two to three times higher than that of non-cirrhotic patients.*
- *Preoperative assessment and risk stratification are challenging. Attention should be paid to liver function, portal hypertension, and systemic conditions including nutritional status.*
- *Low central venous pressure, anterior approach, and vascular occlusion are useful strategies to reduce bleeding during hepatectomies on cirrhotic patients. Also, laparoscopic resections can minimize some postoperative complications, mainly ascites.*
- *Fresh frozen plasma and/or albumin, as well as diuretics, are useful in the management of postoperative ascites, which occurs in more than a third of patients. Postoperative liver failure is associated with very high mortality and should be early recognized for proper management.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the main indication for hepatectomy in the cirrhotic liver. The vast majority of HCC developed in patients with chronic liver disease (CLD) is related to hepatitis B or C viral infection, chronic alcoholic consumption, and metabolic syndrome. Rarely, other malignant tumors, such as cholangiocarcinoma and hepatic metastasis, develop in livers with chronic disease.[1–3] Some benign tumors, including regenerative nodule, hemangioma, and focal nodular hyperplasia (FNH) can also be found in the cirrhotic liver.[4–7] Although liver transplantation (LT) offers the best chance of cure in patients with early-stage HCC,[8] the persistence of graft shortage in many countries has led some authors, including our group, to advocate hepatic resection as the first-line treatment for HCC in cirrhotic patients with preserved liver function.[9–12] Liver resection in a cirrhotic patient is risky, with a two- or three-fold higher mortality rate as compared to patients with normal livers.[13] The higher risk for hepatic resection in patients with underlying CLD derives from increased perioperative bleeding and postoperative complications. In cirrhosis, postoperative hepatic failure occurs mainly due to the impaired regeneration ability of the liver. The reduced hepatic perfusion at baseline makes cirrhotic livers more susceptible to hypoxemia. This is a consequence of reduced portal flow (portal hypertension), reduced arterial flow (impaired autoregulation), systemic arteriovenous shunting, and reduced splanchnic inflow. Certain anesthetic agents may also have a detrimental effect on the hepatic perfusion with a reduction of hepatic blood flow up to 50%. Moreover, cirrhotic livers show an increased risk of ischemia-reperfusion injury and fibrosis, leading to regional ischemia that contributes to impaired growth and regeneration.[14]

Nowadays, major centers are reporting acceptable operative morbidity and mortality rates in patients with cirrhotic livers. This has been achieved by appropriate preoperative patient selection, adequate liver function

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assessment, understanding of the segmental liver anatomy with accurate imaging studies, and optimal operative and perioperative care.[15–18]

In this chapter, we describe general surgical aspects and risks of liver surgery in patients with cirrhosis.

PREOPERATIVE ASSESSMENT

The improvement in outcomes of liver resection in cirrhotic patients is primarily a result of adequate preoperative evaluation and patient selection.[19] Proper patient selection requires systematic and careful assessment of i) the patient's general medical fitness, ii) tumor extension and stage, iii) underlying liver function, and iv) volume of the anticipated future remnant liver (FRL) (**Table 1**).

Suitable balance between quality (degree of damage) and quantity (volume) of future remnant parenchyma is essential to prevent postoperative liver failure (PLF). The greater the parenchymal damage, the higher the need of remnant liver volume. Cirrhotic patients with a lesser degree of fibrosis can sustain more extensive resections than those with an advanced level of fibrosis. Parenchymal quality in liver cirrhosis is affected by steatosis, hepatitis, old age, liver atrophy, intraoperative ischemia, and preoperative chemotherapy. These associated factors lead to an even greater parenchymal quantity need. Preoperative identification of these confounding factors has made liver resection safer.

GENERAL STATUS OF PATIENTS

Cirrhotic patients are at higher risk of postoperative complications. Comorbid conditions like congestive heart failure, pulmonary disease, chronic renal failure, and diabetes increase the risk of mortality in cirrhotic patients undergoing hepatectomy.[15] Severe comorbid illnesses, such as congestive heart failure and chronic renal failure, are often considered as an absolute contraindication for major hepatectomy. The impact of diabetes mellitus on surgery in cirrhotic patients remains debatable.[20] However, with optimal perioperative control of blood glucose and postoperative care, equivalent morbidity and mortality after hepatectomy can be achieved in diabetic patients.[21]

TUMOR STATUS

The assessment of the tumor extent includes a triple phase (early vascular or arterial phase, portal phase, and delayed phase) helical computed tomography (CT) of the thorax and the abdomen. The liver is studied using thin slices acquired during the unenhanced phase and during the arterial, portal, and late (or equilibrium) phase after contrast administration. HCC appears as a hyperdense/vascular tumor during the early arterial phase and as a hypodense/vascular lesion in the later phases (early washout) (**Figure 1**). Magnetic resonance imaging (MRI) is the modality of choice if contrast agents are contraindicated, if there is a need of more precise lesion characterization, or to delineate the anatomical relationship between tumor and major vascular or biliary structures.

Table 1. Preoperative assessment of cirrhotic patients.

- patient general conditions
- tumor extension and stage
- underlying liver function
- volume of future remnant liver

The usual criteria for hepatic resection with regard to tumor status include absence of extrahepatic metastasis and tumor thrombus in a main portal vein or the inferior vena cava. Large tumor size alone should not be considered a contraindication for hepatic resection. Despite the technical difficulties encountered with large tumors, liver resection for large HCCs has been shown to be safe.[22–26] In a series of 300 patients who underwent partial hepatectomy for HCCs larger than 10 cm, the 30-day mortality rate was 5%.[23] Since cadaveric OLT and radiofrequency ablation (RFA) are contraindicated in these patients, surgical resection remains the treatment of choice for large HCCs.

HCCs with biliary tree involvement presenting as jaundice are usually a contraindication for resection in cirrhotic patients because these cholestatic individuals generally do not tolerate the extended liver resections often required. However, peripherally located tumors with biliary invasion should not be considered a contraindication if a curative resection is likely.[27–29] Some selected non-cirrhotic patients can benefit from major liver resection after biliary drainage. In all cases, bilioenteric anastomosis should be avoided. In general, multifocal disease is a contraindication to surgical resection, but if clearance or stabilization of the nodules in the remnant liver is achieved (by chemoembolization or local ablation, such as radiofrequency), surgical resection can be considered in patients with good liver function.[22,30–32]

Major portal or hepatic vein involvement represents a technical and oncological challenge in HCC (**Figure 2**). Although controversial, selected cases might benefit from hepatectomy associated to main portal vein thrombectomy and/or resection.[33] Involvement of hepatic veins or vena cava is associated with a high rate of pulmonary metastases.[34] However, it has been shown that in a selected group of patients with normal liver function and excellent general status, extensive liver resection with removal of the vascular thrombus can achieve favorable survival results.[33,35–37]

Tumor recurrence represents the major drawback

after curative liver resection and is the most common cause of treatment failure. Within five years of resection, recurrence in the liver remnant occurs in about 50–70% of cases.[38–40] The rate of repeated resection, ranging from 10 to 30%, depends on the underlying liver status, the pattern of recurrence, and the extent of first resection. Those series that included a high proportion of major hepatectomy as the initial procedure were associated with lower rates of repeated resections. Re-hepatectomy has been proven to be a safe and worthwhile procedure with a low mortality rate and an acceptable 5-year survival rate (20-57%).[41–44]

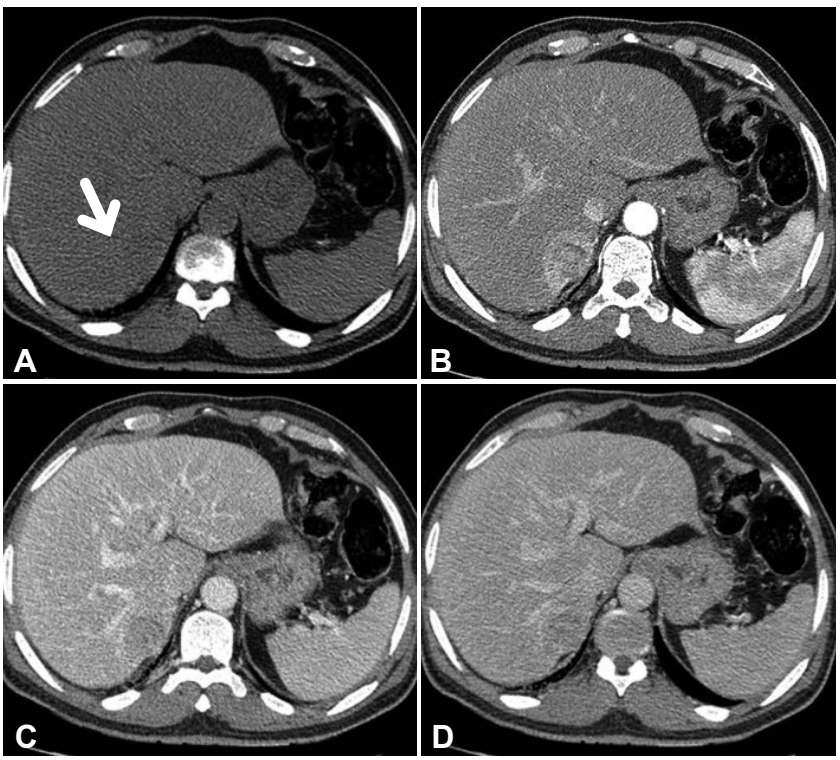


Figure 1. A Computed tomography (CT) scan in a man with hepatitis B related cirrhosis, elevated alpha fetoprotein level, and hepatocellular carcinoma. On CT scan without injection (**A**) we observe a slight hypodense area in segment 7 (white arrow) that became hyperdense on arterial phase after contrast injection (**B**), hypodense (wash out) on the portal (**C**), and very delayed (**D**) phases.

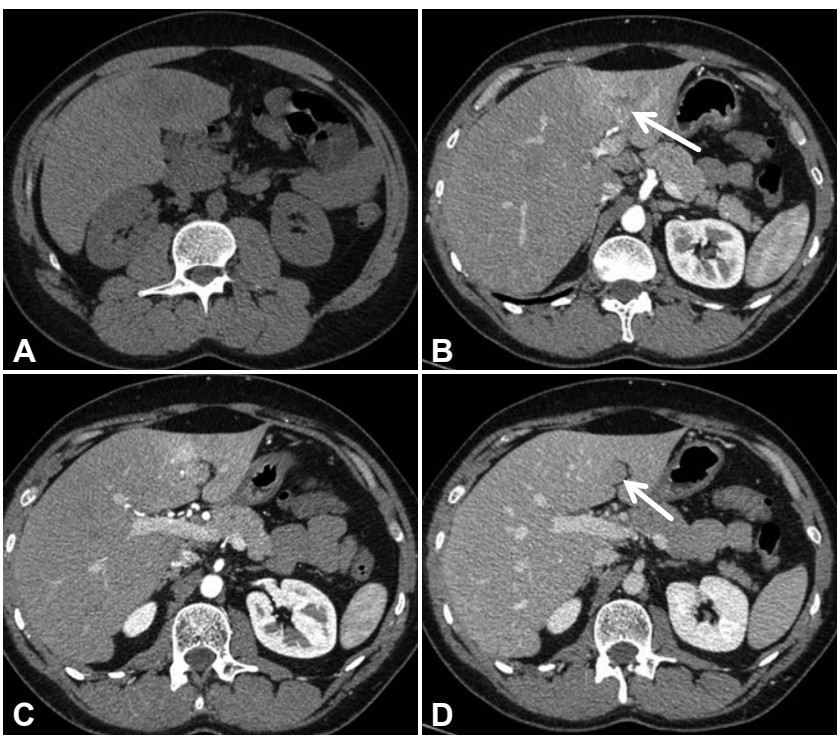


Figure 2. Hepatocellular carcinoma developed on hepatitis C related infection. On computed tomography (CT) scan without injection (**A**), we observe a hypodense mass in the left liver, which becomes hyperdense on arterial phase after contrast injection (**B** and **C**). We can also observe the tumor invasion of the left portal vein (**B** and **C**), which is dilated and containing contrast enhanced material (black arrow). Wash out (white arrow) on the delayed phase (**D**).

Spontaneous rupture of HCC occurs in 5 to 15% of patients, particularly with large superficial or protruding tumors. In patients with good liver function and single tumor, rupture of HCC should not be regarded as a contraindication to subsequent elective surgical treatment.

Extension to surrounding structures, such as the diaphragm or the stomach, does not represent a contraindication to a curative resection. These adhesions to the surrounding structures are often due to the inflammatory response to the tumor and are non-malignant. As preoperative imaging is not sensitive to detect spread to surrounding structures, surgical exploration is advisable in these patients.

For further details refer to **Chapter 13** (Hepatocellular Carcinoma) and **Chapter 30** (Liver Transplantation for Malignant and Benign Liver Tumors).

ASSESSMENT OF LIVER FUNCTION RESERVE

To avoid postoperative liver failure and mortality, careful assessment of the hepatic function reserve is a critical step in the selection of cirrhotic patients for hepatectomy.

Child-Pugh classification

Child-Pugh classification incorporates conventional liver function tests and signs of portal hypertension. It is easy and very accurate to assess surgical risk (**Table 2**). According to this classification, major resection can be safely performed only in Child A patients. Limited resection of small superficial tumors can be performed in Child B patients. Child C patients are not considered candidates for any kind of resection. However, this classification is not sufficient to predict the surgical risk. The risk of hepatic resection can be underestimated in some Child A cirrhotic patients with apparently normal liver function. Therefore, more sophisticated quantitative liver function tests or volumetric assessment are needed to predict the real operative risk.[45]

Indocyanine green test

Most Eastern centers use more sophisticated quantitative liver function tests, such as the indocyanine green (ICG) clearance test,[18] galactose elimination capacity,[46] and the lidocaine test,[47] to predict the risk of postoperative liver failure in patients with cirrhosis. In a multivariate analysis, the Hong-Kong Group showed that, among many liver function tests, ICG retention at 15 minutes (ICG-15min) greater than 20% was the best test in predicting hospital mortality after major hepatectomy for HCC.[48,49] Imamura et al.[50] proposed a decision tree based on combined parameters of Child Pugh classification (ascites and bilirubin) and the ICG retention test (**Figure 3**).[51] Based on this strategy, liver resection is contraindicated in patients with elevated serum bilirubin (>2 mg/dL) or ascites. In those with a serum bilirubin lower than 2 mg/dL, the extent of liver resections should be based on the ICG-15min. Major liver resection is proposed only in case of normal bilirubin and ICG-15min < 10%. Adopting this decision strategy, the authors reported only one postoperative death among the 685 patients who underwent liver resection for HCC.[50]

MELD score

The Model for End-stage Liver Disease (MELD), which uses only objective variables, is calculated from the INR (International Normalized Ratio), serum total bilirubin (mg/dL), and serum creatinine (mg/dL). This model was developed to predict survival in patients with complications of portal hypertension undergoing elective placement of transjugular intrahepatic portosystemic shunts (TIPS).[52] Later, the MELD score was validated as an accurate predictor of survival among different populations of patients with advanced liver disease.[53] The major use of the MELD score has been in the allocation of organs for patients awaiting liver transplantation.[54,55] Regarding liver resection in cirrhotic patients, MELD score was only evaluated in retrospective studies. Higher morbidity and mortality, and impaired long-term survival were observed in cirrhotic patients with MELD score >8 who underwent liver resections for HCC.[56,57]

Platelet count

A low platelet count (<$100x10^3$/μL) in a cirrhotic patient can be due to portal hypertension, active viral hepatitis, and/or

Table 2. Pugh's modification of Child's grading of cirrhosis.

Measurements	1 point	2 points	3 points
Bilirubin (μmol/L)	17-34	35-50	> 50
Prothrombin time - prolongation (s)	1-3	4-6	> 6
Albumin (g/L)	> 35	28-34	< 28
Ascites	none	mild	moderate to severe
Encephalopathy	none	grade 1 or 2	grade 3 or 4

Child's A : 5-6 points; B : 7-9 points; C : 10-15 points

liver insufficiency. These three factors increase the risk of morbidity and mortality, and thus contraindicate major liver resections in cirrhotic patients.[58] Also, thrombocytopenia has a direct and indirect negative effect on liver regeneration. It has been shown that preoperative platelet count less than $150x10^3/\mu L$ is associated with major complications, such as postoperative liver failure, and mortality after resection of HCC. This is independent of Child-Pugh classification, MELD score, and tumor burden.[59]

Transaminase level

Postoperative mortality is higher in patients with cirrhosis and active hepatitis.[60] A high serum transaminase level does not always correlate with hepatitis activity and may be due to intratumoral necrosis in a huge lesion. Despite this, increased morbidity and mortality rates have been reported in patients whose transaminases were elevated.[61,62] Patients with aspartate aminotransferase levels greater than 100 IU/L or alanine aminotransferase level more than twice the superior upper normal limit are poor candidates for major liver resection in the setting of cirrhosis. Thus, in patients with underlying chronic liver disease, cirrhosis should be ruled out by a liver biopsy when preoperative transaminase levels are elevated and a major hepatectomy is planned.[63]

Portal hypertension

Portal venous pressure greater than 10 mm/Hg is often associated with esophageal varices, splenomegaly, and thrombocytopenia (<100 000/μL). Undiagnosed and latent portal hypertension in a cirrhotic patient undergoing liver resection places the patient at risk of major complications, such as variceal bleeding, endotoxemia, and hepatic decompensation in the postoperative period. In a prospective study in Child-Pugh A cirrhotic patients, it has been shown that the hepatic venous pressure gradient, a surrogate measurement of portal venous pressure, was the only predictor of hepatic decompensation following liver resection.[64] Thus, all major centers of liver surgery contraindicate any liver resection in cirrhotic patients with esophageal varices. However, several authors have shown that portal hypertension is not an absolute contraindication to minor surgical resection in patients who had preserved liver function tests.[32,65] According to them, with an aggressive prophylactic preoperative treatment of portal hypertension and its consequences, including esophageal varices ligation or splenectomy (in case of thrombocytopenia), minor hepatic resections can be accomplished.[66] The development of venous collaterals in patients with elevated portal pressure can reduce the hepatic portal flow, and therefore impair the regenerative capacity of the remnant parenchyma after liver resection. Thus, we do not advocate major liver resection in cirrhotic patients with venous collaterals.

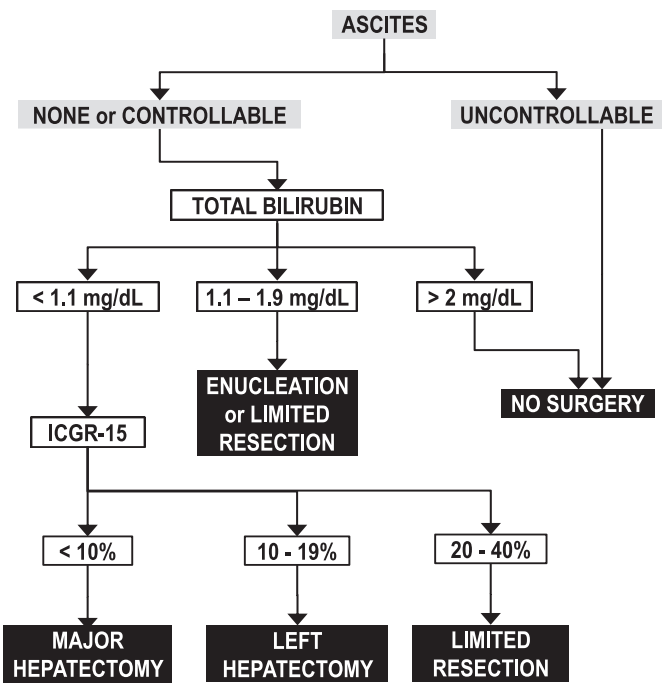


Figure 3. Japanese algorithm for resection in cirrhosis. ICGR: Indocyanine green retention value at 15 minutes. (Adapted from Makuuchi et al.[51], used with permission)

Liver atrophy

Liver atrophy is a major prognostic factor for hepatic resection, which should be considered before any resection - even in patients with preserved liver function tests. In our practice, we do not consider major hepatic resection in patients who have liver atrophy.

Degree of fibrosis

Among patients with CLD, the postoperative risk is higher in those with cirrhosis (METAVIR F4) than in those with extensive fibrosis (METAVIR F3). A preoperative liver biopsy in all candidates for major liver resection is useful for histological grading of fibrosis and risk stratification.[63] The underlying etiology of liver cirrhosis could be also an important predictor of surgical risk, since the extent of fibrosis is more severe in patients with hepatitis C than in patients with hepatitis B. Our tendency is to consider a major liver resection more favorably in patients with hepatitis B than in patients with other etiology of CLD, even if the remnant liver volume is similar. In patients with METAVIR F3 or F4 fibrosis requiring major hepatectomy, preoperative portal vein embolization should be performed to decrease morbidity.

Volume of the future remnant liver

A small future remnant liver (FRL) volume in cirrhotic patients is a contraindication for liver resection.[65] Although the safety limit of FRL volume in patients with CLD has

not been clearly established, it should be around 50% of the total functional liver volume. FRL volume cutoff is influenced by the severity of cirrhosis and the presence of associated inflammation or steatosis, which could impair the regeneration capacity of the diseased parenchyma.[49,67,68]

There is a general concern that preoperative PVE may be less effective in the cirrhotic liver compared with the normal liver because of impaired regenerative capacity.[69,70] However, preoperative PVE is effective in inducing hypertrophy of remnant liver and it is well tolerated. The degree of hypertrophy varies according to the degree of fibrosis and to the severity of cirrhosis.[63] Absence of the hypertrophy of the future liver remnant should be considered as an absolute contraindication for hepatic resection.[71,72] We have shown that preoperative sequential transarterial chemoembolization and portal embolization increases the hypertrophy of the FRL (**Figure 4**). Additionally, we have found a clear relationship between the rate of hypertrophy and postoperative risk after major hepatectomy in cirrhotic patients. After right hepatectomy for HCC, all the postoperative deaths and the majority of severe complications were experienced in F4 patients with <10% increase of FRL after PVE. Based on these observations, we propose that a minimum increase of 10% of the FRL in F3 or F4 patients is essential to safely perform a right hepatectomy.

For further details on underlying liver diseases and liver function assessment, please refer to **Chapter 4** (Underlying Liver Disorders in Hepatic Surgery) and **Chapter 5** (Liver Function Assessment Before and After Hepatic Resection), respectively.

OPERATIVE TECHNIQUES

The general techniques of liver resection are described in details in Section 4 (*Technical Aspects of Liver Resections*) of this textbook. This chapter focuses mainly on operative techniques specifically applied with cirrhotic patients.

INCISION

Bilateral subcostal incision is a frequently used incision for hepatic resection and it is adequate for most cases of hepatectomy. An upward midline extension to the subcostal incision or a J-shaped incision is useful to approach large tumors located in the upper segments of the right liver or in its posterior surface (segment 7). In such tumors, this approach, combined with a diaphragm incision, facilitates parenchymal transection;[72] however, it increases the rate of pleural effusion. A study from the Hong Kong Group showed that a thoraco-abdominal approach for right-sided hepatectomy did not increase the operative morbidity

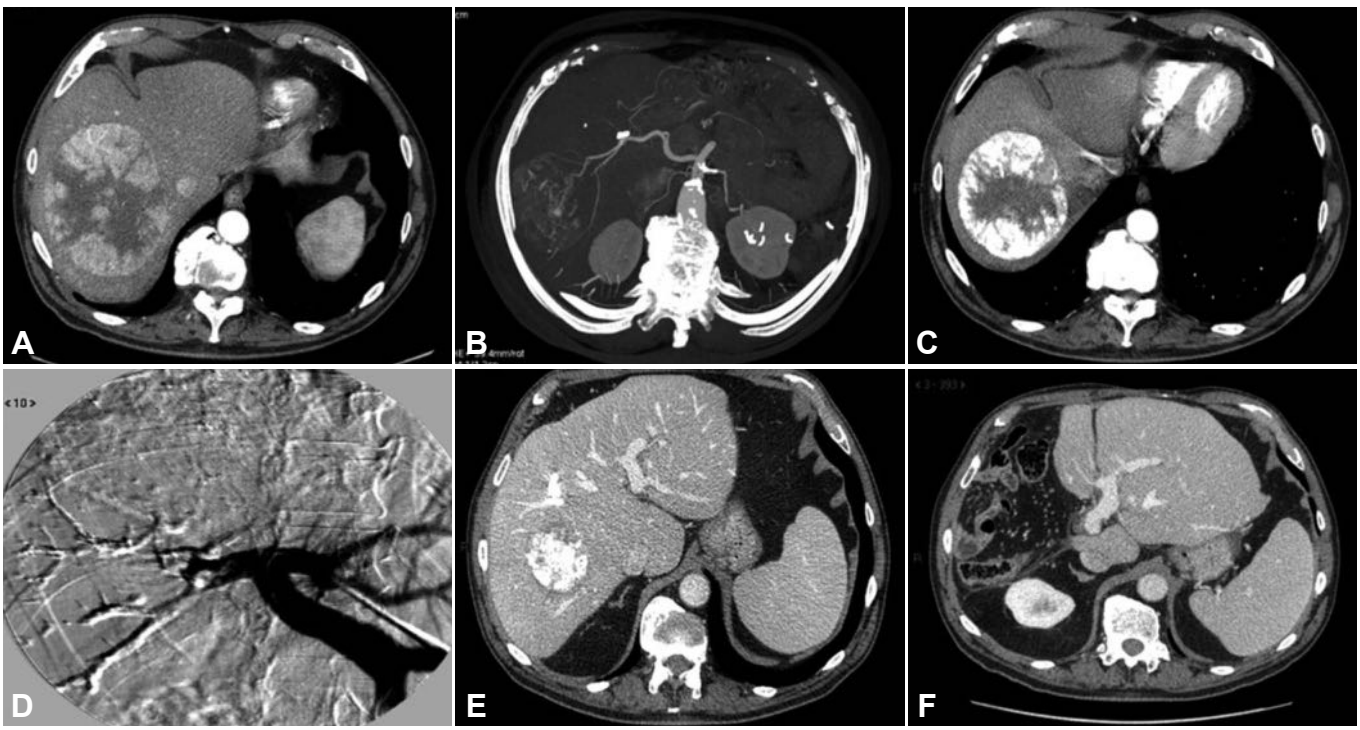


Figure 4. A 72-year-old male with a hepatocellular carcinoma developed on steatohepatitis treated by sequential preparation and resection. **A**) Computed tomography (CT) with a large hepatocellular carcinoma of the right liver. **B**) Initial treatment by intra-arterial chemoembolization. **C**) CT three weeks after chemoembolization with complete response. **D**) Right portal vein embolization. **E**) CT showing excellent hypertrophy of the remnant liver 4 weeks later. **F**) CT after right hepatectomy.

compared with an abdominal approach alone. Furthermore, the thoraco-abdominal approach may reduce blood loss and transfusion requirements.[73] For cirrhotic patients with HCC in the superior segments of the liver located underneath the right diaphragm, an exclusive trans-thoracic approach has been described, but this approach allows only limited resection with a high risk of positive margin.[74]

INTRAOPERATIVE ULTRASOUND (IOUS)

IOUS with color doppler is a valuable tool in hepatic resection, allowing localization of intrahepatic vessels, their relationship with tumors, and eventually detecting other nodules and tumor thrombus. Contrast-enhanced ultrasound examination done intraoperatively, using microbubble contrast agents such as SonoVue® (Bracco-Imaging, Milan, Italy), provides information about tumor vascularity, which is useful for nodule differentiation. IOUS also enables accurate marking of the transection line to ensure an adequate tumor-free margin. The use of IOUS optimizes the balance between oncological radicality and sparing of the largest amount of functioning liver parenchyma in the cirrhotic liver. Recently, systematic segmentectomy and subsegmentectomy by IOUS-guided finger compression was described.[75] This technique can be potentially applied in each segment of the liver as long as the thickness of the parenchyma and the anatomy of the liver are suitable. The IOUS-guided finger compression of the vascular pedicle feeding the tumor at the level closest to the tumor results in a demarcation area allowing oncological resection.

For further reading on oriented segmental resections and IOUS please refer to **Chapter 3** (Intraoperative Assessment of the Liver).

ANTERIOR APPROACH

When liver tumors are large, the use of conventional techniques usually requires forceful retraction and mobilization of the liver with possible disadvantages including compression of both right and left lobes and tumor dissemination. Liver mobilization in the cirrhotic liver is technically more demanding because of the firm texture of the fibrotic parenchyma. The collateral vessels formed secondary to portal hypertension may increase the risk of bleeding during liver mobilization. Prolonged forceful rotation of the liver increases the risk of avulsion injury of the hepatic veins and may twist the inflow and outflow vascular pedicles, resulting in ischemic damage to the remnant liver. Care should be taken to avoid prolonged rotation of the liver. The anterior approach attempts to diminish manipulation of the tumor-bearing liver through initial vascular inflow control, parenchymal transection until the anterior surface of the inferior vena cava is exposed, venous outflow control and finally mobilization of the right liver.[76] Once the devascularized tumorous liver is disconnected from the vena cava, it is intuitive that its mobilization is less hemorrhagic and that this "no-touch" liver resection could reduce possible systemic dissemination of cancer cells. The anterior vs. conventional approach in patients with HCCs of more than 5 cm was tested in a prospective randomized controlled study by the Hong Kong University Group. In this trial, operative blood loss of more than 2 liters was less frequent with the anterior approach (28.3% vs. 8.3%). Nonetheless, a superior overall survival (median 68.1 vs. 22.6 months) was reported.[76] The liver hanging maneuver (LHM), originally described by our group, involves the passage of a tape in the avascular retro-hepatic precaval space to suspend the liver during parenchymal transection facilitating the anterior approach by minimizing bleeding in the deeper parenchymal plane and guiding the direction of the parenchymal transection.[76] The traction of this tape allows a delimitation of the plan of parenchymal section which follows a hepatic vein. Application of the LHM has been further extended to the three Glisson's pedicles and hepatic veins facilitating the performance of right and left anatomic liver resections (**Figure 5**).[76] While more data based on long-term survival are forthcoming, there are several arguments leading to the recommendation of anterior approach in combination with hanging maneuver as the preferred operative approach for liver malignancy.

TECHNIQUE OF LIVER TRANSECTION

The main difficulty of hepatic resection in the cirrhotic liver lies in the control of bleeding during transection of the fibrotic parenchyma. Clamp crushing; the conventional method of liver transection, is still used in some centers. The Cavitron ultrasonic surgical aspirator (CUSA®), which reduces blood loss as compared with the clamp crushing technique, has become the standard technique of liver transection in the cirrhotic liver. Other techniques for liver transection include the Harmonic Scalpel™ (Ethicon Endo-Surgery, Cincinnati, OH) and multi-probe bipolar radiofrequency device (Habib 4X™; RITA Medical Systems Inc., Fremont, California). The latter procedure might allow surgeons to perform minor and major hepatectomies with minimal blood loss, a low blood transfusion requirement and reduced mortality and morbidity rates. However, this device is seldom used in tertiary reference centers, where more complex procedures are performed for treatment of HCC, because there are some concerns about the preservation of venous drainage of the remnant liver and the risk of postoperative bile leak and necrosis. The role of this technology probably is limited to segmental or wedge excision because of the potential risk of vascular and bile duct injuries when using this instrument near

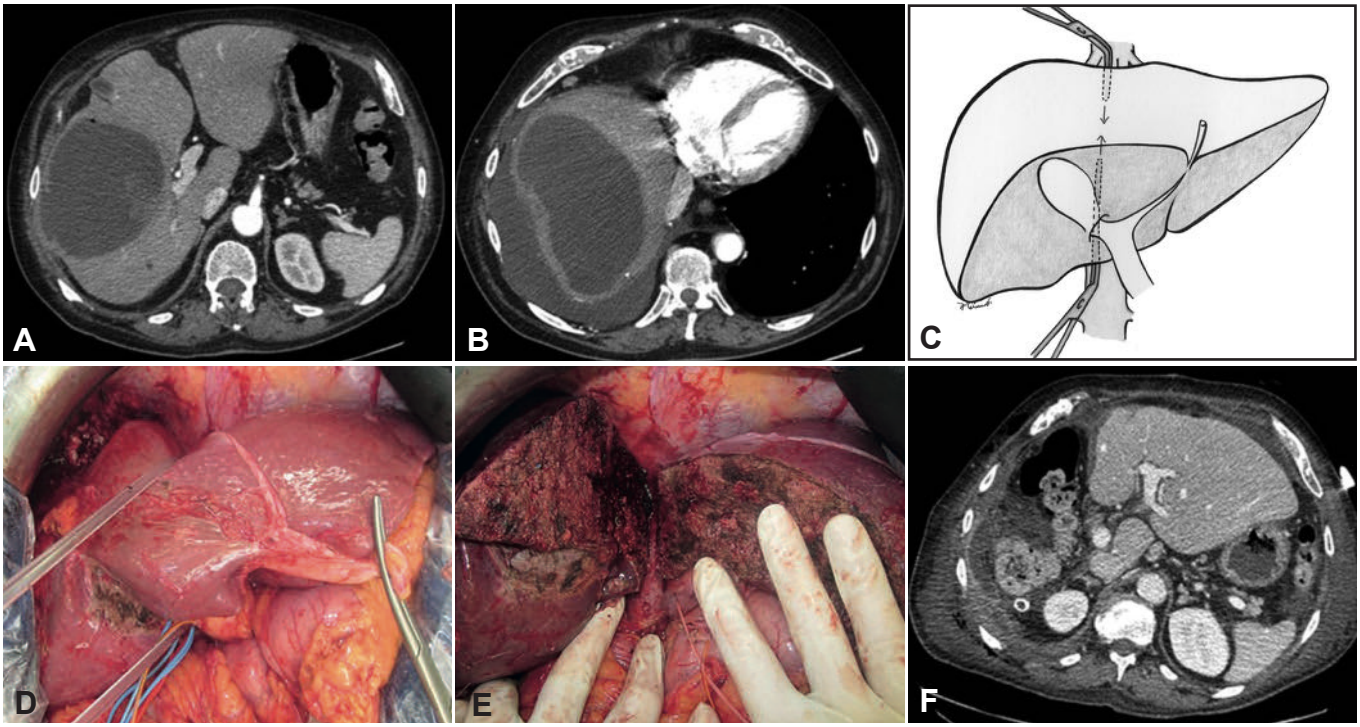


Figure 5. Ruptured hepatocellular carcinoma (HCC) after sequential preparation treated by right hepatectomy with the anterior approach and hanging maneuver. **A** and **B**) Computed tomography (CT) showing ruptured HCC. **C**) Schematic representation of the avascular space for the hanging maneuver on the right-anterior border of the vena cava. **D**) Surgical aspect with the liver-hanging maneuver. **E**) Surgical aspect after complete and safe transection of the liver parenchyma without any mobilization of the right liver. After transection, the devascularized specimen can be safely removed. **F**) Postoperative CT scan.

the liver hilum, and its inability to control bleeding from large venous branches. Saline-linked cautery (TissueLink Medical Inc, Dover, NH) uses a metal probe to deliver radiofrequency energy conducted through a slow infusion of saline. This procedure, which enlarges the transection margin, can be associated with ultrasonic dissection in a standardized fashion.

For further details on transection techniques refer to **Chapter 23** (Vascular Control and Parenchymal Transection Techniques).

ANATOMIC AND NON-ANATOMIC RESECTION

Metastatic spread along the intrahepatic segmental portal branches is the basis for anatomic liver resection of HCC, in other words, systematic removal of the hepatic segment fed by tumor-bearing portal tributaries, namely the entire functional unit. In cirrhotic patients, oncologic safety needs to be balanced with future remnant liver volume. Analysis of nationwide Japanese database including 72,144 patients, showed improved disease-free survival with anatomic resection as compared to non-anatomic resection, but no difference in overall survival was found.[77] When survival was stratified by tumor size, disease-free survival was significantly improved with an anatomic resection for HCC with a diameter of 2 to 5 cm. The low incidence of vascular invasion in HCC of less than 2 cm may explain the absence of a beneficial effect with anatomic resection and the equivalent efficacy of local ablative therapy. For HCC greater than 5 cm, the tumor is often associated with vascular invasion, satellite nodules, and other adverse pathological features, which probably offset the effects of the type and extent of hepatectomy.[76] A recent meta-regression analysis demonstrated survival benefit with anatomic resection, although these results are biased due to the greater tumor size and poorer hepatic function in patients submitted to non-anatomic resection. Thus, it remains unclear whether hepatectomy for hepatocellular carcinoma should be performed as an anatomic resection or a non-anatomic resection.[78]

USE OF VASCULAR STAPLERS

Staplers can be used in liver surgery for control of inflow and outflow vessels. The use of the vascular stapler helps to reduce blood loss, especially in situations in which a large tumor in the right or left lobe hinders exposure of the right or left hepatic vein or during control of the middle hepatic vein deep in the transection plane. A vascular stapler also can be used to divide the hepatic pedicle in right or left hepatectomy [79] with similar results to hilar dissection. The

use of a vascular stapler to divide the hepatic pedicle saves time from suturing, but care has to be exercised not to narrow the hepatic duct confluence, especially during a right or left extended hepatectomy.[80]

VASCULAR OCCLUSION

During liver resection, reducing blood loss and transfusion are essential, especially in cirrhotic patients who have a poor tolerance for hemodynamic instability and massive transfusion. A review of the literature concerning the relationship between blood loss and blood transfusion during liver surgery for malignant tumors and postoperative outcome has shown a significant and clinically relevant association between blood transfusion and postoperative mortality and morbidity, especially postoperative infectious complications.[81] In particular, blood transfusion may have an impact on tumor recurrence. Vascular clamping aiming to reduce intraoperative blood loss is counterbalanced by a poor tolerance of cirrhotic parenchyma to warm ischemia. Total vascular occlusion, even when associated with in situ cold perfusion of the liver, is contraindicated in patients with diseased liver.[82] Intermittent inflow occlusion with periods of 15 minutes of clamping and 5 minutes of unclamping was well tolerated up to 90 minutes in selected cirrhotic patients with good liver function.[83] In our center, we do not hesitate to use intermittent inflow clamping when resection is difficult or when there is a need to define adjacent vascular or biliary structures in the margin of resection. Overall, there is a tendency to perform hepatic resection without clamping. This tendency resulted from several factors including i) increased experience of the surgeons in liver resection; ii) the use of isolated infrahepatic inferior vena cava occlusion without any risk of ischemia on the liver parenchyma, and iii) the practice of low central venous pressure anesthesia. One of the most important factors related to intraoperative blood loss is pressure within the inferior vena cava.[84] As hepatic vein pressure directly reflects the caval pressure, the maintenance of a low central venous pressure is an effective technique to reduce back bleeding from the hepatic veins.

Further details on vascular occlusion techniques and perioperative bleeding are depicted on **Chapter 23** (Vascular Control and Parenchymal Transection Techniques) and **Chapter 9** (Morbidity and Mortality after Liver Surgery).

BILIARY INTEGRITY

Intraoperative biliary integrity can be confirmed by injection of diluted methylene blue solution through the cystic duct catheter and keeping a white gauge on the cut surface. In our experience, this method detects significant bile duct leaks from cut surface and is more effective than cholangiography.

HEMOSTATIC AGENTS

Topical hemostatic agents improve hemostasis on the resection surface of diseased parenchyma and particularly valuable in posterior segment resections. Hemostatic agents consist of those providing a matrix for endogenous coagulation. These are made of collagen, cellulose or gelatine (e.g. Gelfoam® or Surgicel®) and do not contain active components. The second group of agents contains active components, the fibrin sealants (Hemaseel®, TachoSil®), which mimic endogenous coagulation.

ABDOMINAL DRAINAGE

Many surgeons consider abdominal drainage due to the high risk of hemorrhage, bile leakage and ascites after hepatectomy in the cirrhotic liver. In a retrospective study, including 1,269 consecutive patients who underwent elective hepatectomy with drain insertion for malignant tumors showed that seven patients had postoperative bleeding (0.6%) and bile leakage was found in 111 (8.7%) patients.[85] They concluded that placement of drains was effective in a considerable proportion of patients undergoing hepatectomy, with regard to reducing the frequency of development of subphrenic fluid collections and biliary fistula. However, the use of drainage after liver resection remains controversial. A randomized controlled trial performed in the Hospital Clinic of Barcelona [86] showed that intra-abdominal closed drainage is advisable in cirrhotic patients undergoing liver resection for HCC, mainly if presenting preoperative portal hypertension. Another randomized controlled trial showed that the placement of the abdominal drain after hepatic resection in the cirrhotic liver was associated with increased wound complications, septic complications, and prolonged hospital stay.[31] The drain provides a route for ascending infection and results in loss of protein and electrolytes.

In our experience, drainage is not systematically performed but it is routinely done in patients at higher risk of biliary fistula (exposure of the biliary confluence, segment 8 resection) or in case of unsatisfactory hemostasis.

LAPAROSCOPIC RESECTION

Laparoscopic liver resection represents about 10-20% of all liver resection; usually performed in centers of excellence worldwide.[87–89] Major obstacles for laparoscopic liver resection include i) long learning curve, ii) difficulty in achieving wide resection margin and performing anatomic resections, and iii) technical difficulties in liver mobilization and parenchymal transection, with risk of massive bleeding. Anticipated advantages from laparoscopic liver resections are i) less aggressive approach (incision with less pain, fewer pulmonary complications, early recovery), and ii) less perito-

neal dissection (avoidance of collateral ligation, less bleeding, minimal ascites, decreased postoperative liver failure).[90]

These postulated factors could expand indications of liver resection in some Child B patients.[76] Moreover, less postoperative adhesions after laparoscopic liver resection compared to open liver resection facilitate subsequent salvage liver transplantation with decreased morbidity.[91] This laparoscopic approach is a tool to the treatment by radiofrequency ablation.[92]

Lesions located in posterior segment (7, 8, 4b or 1) are classically not good indications for pure laparoscopic approach but are more frequently reported with hand assisted [93,94] or laparoscopic assisted resection.[95] Laparoscopy also has limited role in lymph node dissection or peritoneal partial resection.

For further details refer to **Chapter 27** (Principles of Laparoscopic Liver Resections).

MORBIDITY AND MORTALITY

Improvements in patient selection and surgical technique have resulted in a remarkable decrease in perioperative mortality rates. In the 1980s, the mortality rate after liver resection in cirrhotic patients was typically 15% to 30%, and liver resections in cirrhotic patients were largely restricted to segmental or subsegmental resections.[96,97] Currently, the mortality rate is approximately 5% with some centers approaching close to zero mortality.[98,99] The Hong Kong Group showed that even extended right or left hepatectomy could be performed in cirrhotic patients. The morbidity and mortality rates in these patients were similar to those submitted to smaller resections.[100] Since the operative morbidity after hepatic resection in the cirrhotic liver remains high (30-40%), further efforts are required to reduce the operative morbidity. Cirrhotic patients who underwent a liver resection should be monitored in the intensive care unit in the immediate postoperative period.

Management aims to adequate oxygenation and perfusion in order to ensure optimal function and regeneration of the remnant liver.

PERIOPERATIVE CARE

Intravenous fluid

Although fluid restriction has been found to reduce the incidence of postoperative morbidity in some surgical patients,[101] optimal fluid substitution strategies remain controversial since fluid optimization increases tissue oxygen tension and microcirculatory perfusion.[102] It has been shown that excessive fluid restriction increase the level of hypovolemia, leading to reduce central venous oxygen saturation and thereby increase the incidence of postoperative complications.[102] Too strict fluid restriction should be applied cautiously in cirrhotic patients. Crystalloid solution (dextrose and saline) is used for maintenance of intravenous fluid. In some centers, fresh frozen plasma is used routinely for fluid replacement during and after the operation.[18] In our center, we use albumin instead of fresh frozen plasma, which can alter the assessment of postoperative function tests.

Antibiotics

There is a tendency to administrate prophylactic antibiotics because cirrhotic patients are immunocompromised. Perioperative antibiotic prophylaxis must be administered to prevent translocation of intestinal enterobacteria to the systemic circulation in patients with both healthy and diseased livers. In the cirrhotic patient the risk of infection is further aggravated by the prolonged operation length and the high frequency of postoperative ascites. Septic complications, especially wound infection, are the most common ones after hepatectomy for HCC.[103] There is no randomized trial suggesting the optimal regimen of antibiotics. In our experience, in non-complicated cases, only preventive antibiotics (Cephalosporin) are given perioperatively. However, in patients with suspected bile infection (such as those with biliary drainage and bilioenteric anastomosis), wide spectrum therapeutic antibiotics are given for five days and adapted according to the results of culture from bile collected before surgery (drain) or intraoperatively.

Thromboembolic events prophylaxis

Even in cirrhotic patients, thrombo-embolic complications can be observed related to an imbalanced state between the hypo- and hyper-coagulabitity factors**.** In all cases, patients with impaired liver function (low prothrombin time or platelet count) are less likely to undergo surgical resection**.** Routine prophylactic anticoagulation is performed as in non-cirrhotic patients, and includes subcutaneous low molecular weight heparin (LMWH) initiated a few hours before surgery (0.4ml and 0.6 ml, if body mass index >35 kg/m^2) and continued for four weeks.

POSTOPERATIVE COMPLICATIONS

In addition to complications associated with all major surgery, specific risks of liver resection in cirrhotic patients include ascites, right pleural effusion, subphrenic abscess, bleeding, biliary leak/fistula, portal thrombosis, and hepatic insufficiency.

Postoperative ascites

Postoperative ascites is a classical complication following liver resection in cirrhotic patients affecting more than

one third of cases. Significant ascites is poorly defined, but the presence of ascitic fluid drainage from thoracic and abdominal drains exceeding 10 mL/kg of preoperative body weight [104] or a daily output >500 mL after postoperative day 3, require specific management. Factors increasing the rate and amount of ascites include preexisting ascites before resection, presence of portal hypertension, low platelet count, major resection, pedicular clamping, lymph node dissection, and perioperative fluid (including blood transfusion) overload. Ascites after liver resection in cirrhotic patients has several potential deleterious consequences including abdominal pain, restriction of ventilation, development of pleural effusion, infection, impairment of renal function and abdominal leak. Ascites leakage through the abdominal incision can result in loss of electrolytes and protein, and also increases the risk of intra-abdominal infection. The management of ascites requires replacement of fluid lost and in some cases diuretic therapy. The beneficial effect of fresh frozen plasma transfusion during and after liver resection advocated by the group of Makuuchi [98] is not supported by other studies due to the risk of transmitting diseases, adverse effects such as transfusion-related acute lung injury, acute allergic and anaphylactic reactions, and high cost.[105] In several centers, including ours, fresh frozen plasma is replaced by albumin or other plasma expanders.

Postoperative Bleeding

The risk of postoperative bleeding is very low, typically around 1%.[13,18,105] There is no clear definition of posthepatectomy bleeding but according to our experience,[107] postoperative bleeding can be suspected or diagnosed if i) evidence of blood loss via abdominal drain of at least 100 ml, ii) deglobulisation (defined by a decreased hemoglobin level of at least 3 or 4 points from the baseline value) necessitating transfusion, iii) diagnosis of hematoma or active bleeding by imaging, and iv) hemodynamic instability with continuing requirement of blood transfusion. Bleeding should be suspected especially in patients in whom hemostasis was not optimal at the end of the intervention. Presence of bleeding during the first postoperative day is a life-threatening complication requiring reoperation with a 30% risk of mortality in cirrhotic patients. This high risk leads us to ensure a perfect hemostasis at the end of resection for any hepatectomy, but especially in cirrhotic patients.

Biliary fistula

Bile leakage after hepatic resection can cause septic complications, which leads to a high risk of mortality in cirrhotic patients. The rate of biliary leakage, which was found to be around 6% in a single center series of 605 liver resections for HCC, was associated with preoperative chemoembolization and central tumor location.[108]

Approximately one third of patients with biliary leakage develop an abdominal fluid collection, in spite of routine abdominal drainage. In these cases, percutaneous drainage is a valuable option.[85] The risk of abdominal collections lead some authors to advocate the use long-term drains.[109] In a prospective cohort study enrolling 58 patients who underwent liver resection for tumors, abdominal drains were kept in place for at least seven days postoperatively. Bilirubin level in drainage output was higher on the fifth postoperative day than on the third or the seventh postoperative days.[109] Therefore, the authors advocate evaluation of bile leakage between the fifth and seventh postoperative days and recommend the use of long-term drains.

Portal thrombosis

This life-threatening postoperative complication in cirrhotic patients is poorly described and can be induced by several factors including portal hypertension, previous PVE, and portal vein injury. While hepatic-related coagulation tests are altered by portal thrombosis the other liver function tests keep the usual postoperative kinetic. Therefore, cirrhotic patients should be regularly assessed by ultrasound during the first postoperative week, especially if there is no recovery of coagulation test or if the patient decreases its consciousness. The presence of portal thrombosis, assessed by CT scan, could lead to urgent re-operation and/or to efficient anticoagulation treatment.

Liver Failure

Patients with a cirrhotic liver have decreased liver function reserve and limited capacity of liver regeneration. As a result, major hepatectomy in the cirrhotic liver is associated with a significant risk of liver failure. Liver failure could occur primarily as a result of inadequate liver remnant, but more often it is precipitated by massive bleeding or septic complications. Despite improved safety of hepatectomy in recent years, postoperative liver failure still occurs in about 3% to 10% of patients after resection for HCC.[110,111] Liver failure is associated with a high mortality rate and is the most common cause of hospital mortality after hepatic resection in the cirrhotic liver.[13,112] Cirrhotic patients are also prone to gradual hepatic decompensation with long-term follow-up, especially after major hepatic resection for large HCC.[113] Although several clinical and biological factors such as ascites, encephalopathy, jaundice, prolonged prothrombin time, hyperbilirubinemia and hypoalbuminemia are markers of impaired liver function, there is neither standardized definition of postoperative liver failure (PLF) nor precise data on its correlation with postoperative mortality. The need for standardization of PLF is important. Prothrombin time (PT) and serum total bilirubin level (SB) are two biological indicators of liver function and used to calculate the Child-Pugh score (and also two of the three components of the MELD score). However, they are not readily usable

postoperatively, since there is a natural impairment of liver function tests during the first post resection days. We found that on postoperative day 5, the association of PT<50% and SB>50mml/L (the "50-50 criteria") was a simple, early, and accurate predictor of mortality (more than 50%) after hepatectomy.[114] Moreover, these biological criteria could be identified earlier than the clinical evidence of complications, allowing the performance of specific intervention for portal thrombosis, ascites, and pulmonary infection that might be difficult to diagnosis and result in late mortality.

SUGGESTED READING

Imamura, H. *et al.* One thousand fifty-six hepatectomies without mortality in 8 years. *Arch. Surg.* **138**, 1198–1206 (2003).

Retrospective cohort study to analyze postoperative morbidity and mortality in 1056 consecutive hepatectomies performed at a single medical center during 8 years. No operative mortality occurred. Major complications, as defined by postoperative radiologic or surgical intervention, occurred in 3% of patients with hepatocellular carcinoma, 8% with other liver malignancy, 28% with biliary malignancy, and 5% of living donor liver transplantation donors. Independent risk factors associated with major complications were operative blood loss of 1000 mL or greater for hepatocellular carcinoma and total bilirubin level of 1.0 mg/dL or greater (>or=17 micro mol/L) and operative time greater than 6 hours.

Torzilli, G. *et al.* Anatomical segmental and subsegmental resection of the liver for hepatocellular carcinoma: a new approach by means of ultrasound-guided vessel compression. *Ann. Surg.* **251**, 229–235 (2010).

Article describes a novel technique for the demarcation of the resection area by means of IOUS-guided finger compression to systematically accomplish anatomic segmental and subsegmental resections. This technique consisted in the demarcation of the resection area by IOUS-guided finger compression of the vascular pedicle feeding the tumor at the level closest to the tumor but oncologically suitable.

Agrawal, S. & Belghiti, J. Oncologic resection for malignant tumors of the liver. *Ann. Surg.* **253**, 656–665 (2011).

An evidence-based review to ascertain the operative strategy for oncologic resection of malignant tumors of the liver and an optimal postoperative outcome. Anterior approach to major hepatectomy is a "no-touch" technique that minimizes manipulation of the tumor-bearing liver. The operative strategy for resection of malignant tumors of the liver should address the key components of the extent of hepatectomy including anatomic resection and optimal pathologic margins, necessity for vascular resection, regional lymphadenectomy and measures to minimize blood loss and postoperative morbidity for maximal survival benefit.

Balzan, S. *et al.* The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann. Surg.* **242**, 824–828 (2005).

This article standardizes the definition of postoperative liver failure for prediction of early mortality after hepatectomy. Between 1998 and 2002, 775 elective liver resections, including 69% for malignancies and 60% major resections, were included in a prospective database. The lowest prothrombin time (PT) level was observed on postoperative day (POD) 1, while the peak of serum bilirubin (SB) was observed on POD 3 and return to preoperative values by POD 5. Postoperative mortality significantly increased in patients with PT <50% and SB >50 µmol/L. The conjunction of PT <50% and SB >50 µmol/L on POD 5 was a strong predictive factor of mortality.

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7 Portal Vein Embolization, Transarterial Chemoembolization and Local Ablation of Hepatic Tumors

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- *Portal vein occlusion, through portal vein embolization or portal vein ligation, is a strategy used to induce hypertrophy of the future remnant liver (FRL) before extended hepatic resections.*
- *The ordinary indications for portal vein occlusion are: i) FRL ≤20% of the total liver volume in healthy hepatic parenchyma, ii) FRL ≤30% of the total liver volume in patients submitted to systemic chemotherapy, and iii) FRL ≤40% of the total liver volume in the presence of chronic hepatic disease.*
- *Transarterial chemoembolization (TACE) is an effective palliative treatment for hepatocellular carcinoma (HCC) and the standard of care for unresectable HCCs. Randomized trials have shown long-term survival advantages with TACE when compared to best supportive care.*
- *TACE is an attractive palliative therapy for other tumors, such as intrahepatic cholangiocarcinoma and metastatic disease from a variety of primaries (ocular melanoma, colorectal cancer, breast cancer, neuroendocrine tumors, renal cell carcinoma, and abdominal sarcomas).*
- *Hepatic malignancies can be destroyed through chemical or thermal ablation. Radiofrequency ablation and ethanol injection, percutaneous or intraoperative, are the most commonly used methods of local ablation for hepatocellular carcinoma and liver metastases. Results are promising but inferior to liver resection or transplantation.*

INTRODUCTION

A variety of advances have allowed for the accomplishment of hepatic resections in patients who would otherwise not be suitable candidates for surgery. Less invasive techniques, applied to primary and secondary malignancies, have become the current treatment option in the management of many of these patients. Through portal vein occlusion, an increase in the volume of the functional remnant liver helps to avoid postoperative hepatic failure, the lead cause of mortality after liver resection. Transarterial chemoembolization is mainly used as a neoadjuvant or palliative treatment for hepatocellular carcinoma, but recent technologies have made this option also attractive to treat other hepatic malignancies. Local ablation technologies, such as chemical and thermal, are an excellent alternative for the management of liver tumors in patients without conditions to undergo surgery or as an adjunct in the treatment of multiple tumors. This chapter will discuss these modalities, including technical aspects, indications, limitations, and outcomes.

PORTAL VEIN EMBOLIZATION

INTRODUCTION

Surgical resection is the first-choice treatment for patients with malignant liver tumors (either primary or metastatic) because it offers the greatest chance of long-term survival. However, this therapeutic option cannot be offered to many patients because up to 45 % of liver tumors require

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an extended liver resection to provide adequate surgical margins.[1] In fact, only 20% of liver tumors are amenable to resection for this reason.[2]

The most common cause of death following hepatic resection is liver failure. The most important factor that predicts postoperative liver failure and subsequent mortality is the remaining volume of the functional remnant liver (FRL).[3] The perioperative mortality rate after hepatectomy has been reported to be between 3-7% in patients with a normal liver, but it increases up to 32% in those with cirrhotic livers.[4–6] Some techniques have been described to increase the remaining liver prior to resection and include: portal vein ligation, portal vein embolization, biliary occlusion, and arterial embolization of the segments to be resected.[1] The most effective of these techniques is portal vein embolization (PVE) because it induces consistent and reliable atrophy of the treated segment and hypertrophy of the FRL.

Portal vein embolization has become the standard of care in large medical centers for preoperative management of patients with small FRL following partial hepatectomy. This procedure was shown to improve the perioperative mortality rate of patients who would otherwise not qualify for surgical resection.[1]

HISTORICAL PERSPECTIVE

The demonstration of liver hypertrophy after portal vein ligation was first described in rabbits in 1920.[7] Later, in 1956, Bax et al.[8] described atrophy of a liver segment after occlusion of either the bile ducts or the portal vein. This principle was not applied to oncology until 1986, when Kinoshita et al.[9] described the use of PVE in conjunction with transarterial embolization for the treatment of hepatocellular carcinoma (HCC). He also suggested its use for hypertrophy of the remnant liver as a preparation for surgery.

Since then, many papers have described the use of portal vein occlusion as an adjunctive to partial hepatectomy in primary or metastatic liver tumors. Many techniques have been described, and most of these show good clinical results.[2,10] In addition, the indications, complications, and long-term results have been further delineated in the literature.[11–15]

ANATOMY

The portal vein is formed at the confluence of the superior mesenteric vein and the splenic vein, immediately posterior to the head of the pancreas in the retroperitoneum. It reaches the liver through the lesser omentum. At the porta hepatis, it divides into the right and left branches; the right and left portal veins then branch into their corresponding segments.

The anatomy of the portal vein at its bifurcation is varied; approximately 53% of bifurcations are intrahepatic and the remaining 47% are extrahepatic.[16] Ten to 20 percent of the population has variations of the traditional portal venous anatomy described above. The three main variants of portal venous anatomy are: main portal vein (MPV) trifurcation (10.8-12.4%), right posterior portal vein as the first branch of the MPV (4.7-9.2%), and right anterior portal vein as the first branch of the left portal vein (4.3%)[17,18] (**Figure 1**). However, the branch to segment 4 is consistently the first one of the left portal vein. Complete knowledge of these anatomic variants is essential for successful portal vein embolization and successful hepatic resection.

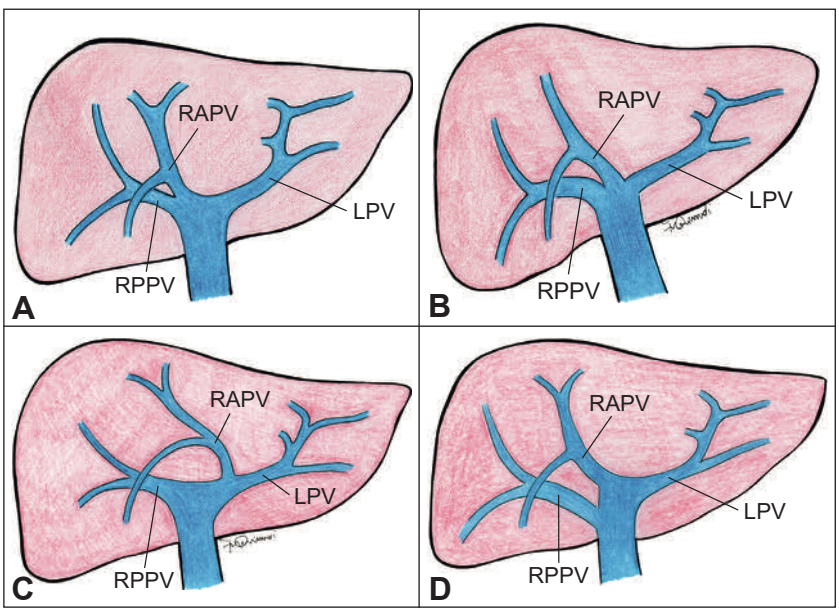


Figure 1. Most frequent portal vein variations. **A**) Usual pattern; **B**) Trifurcation of the main portal vein; **C**) Right posterior portal branch arising directly from the main portal vein; **D**) Right anterior portal branch arising from left portal vein.

CALCULATION OF FUNCTIONAL REMNANT LIVER (FRL) INDEX

The functional remnant liver (FRL) index is the most important predictor of postoperative mortality following liver resection. The calculation of the FRL index is extremely important in those patients being considered for a major hepatic resection.

The method of calculating the FRL index [FRL/total liver volume (TLV)] has not been standardized. In Japan and Europe, the convention has been to measure the actual total liver volume and measure the tumor volumes (considered as non-functional liver) based on computed tomography (CT) scanning. The FRL index would then be FRL/(total liver volume – tumor volume). This, however, can be inaccurate in cases of multiple tumors and does not take into account changes in volume as a consequence of arterial obstruction, biliary obstruction or chronic liver disease.[19]

A more accurate way of calculating FRL index has been proposed using a total estimated liver volume (TELV) based on the body weights or body surface area in health subjects. The most precise formula is: TELV (cm^3) = -794.41 + 1267.28 * body surface area (m^2).[20] The reason for the improved accuracy is because liver volume is altered with chronic disease and large tumors (and therefore TLV based on computed tomography (CT) volumes would be inaccurate).[21] A CT scan is usually performed before PVE and also 2-6 weeks following PVE to assess for hypertrophy of the remnant liver.

A minimum threshold for FRL index has not been delineated clearly in the literature. The generally accepted FRL/TELV ratio is 25% in otherwise normal livers and 31-40% in stable chronic liver disease or after chemotherapy.[22] A ratio below this threshold is generally considered an indication for PVE (**Figure 2**).

PHYSIOPATHOLOGY

A change in the dynamic state of the liver can dramatically change liver volumes; this is evidenced by hypertrophy of the non-embolized liver after portal vein occlusion (ligation or embolization) or partial hepatectomy. In the case of portal embolization, there is an immediate increase in hepatic arterial flow in the treated lobe from liver auto-regulation (also called "hepatic arterial buffer response").[23] A possible explanation for this increase in arterial blood flow is adenosine; following PVE, less adenosine is washed through the portal vein and therefore accumulates in the liver parenchyma. This increased adenosine causes hepatic arterial dilatation.[24,25] In addition, there is an increase in portal venous flow to the untreated lobe as the return from the mesenteric veins is virtually unchanged.

A similar process of increased blood flow and compensatory hypertrophy also occurs after partial resection. The blood flow differences are more pronounced after partial hepatectomy as compared to PVE, and this may contribute to quicker activation of factors responsible for hypertrophy **(Figure 3)**.[26,27]

The aforementioned hemodynamic changes accompanying PVE is only partly responsible for the hypertrophy of the untreated lobe. Numerous humoral mediators are also responsible for hepatic regeneration and are likely partially responsible for hypertrophy. These include cytokines (Interleucine-6 and Tumor Necrosis Factor-α);[28] growth factors, such as hepatocyte growth factors (HGF), transforming growth factor (TFG-α), and epidermal growth factor (EGF);[29–31] vasoregulatory factors (nitric oxide, prostaglandins I_2 and E_1);[32,33] and hormones (insulin and estrogen).[34,35]

Regenerative rates post-portal vein occlusion (embolization/ligation) peak in fewer than 14 days following the procedure.[18] Duncan et al.[36] showed that peak hepatocyte regeneration occurs seven days after portal vein embolization.

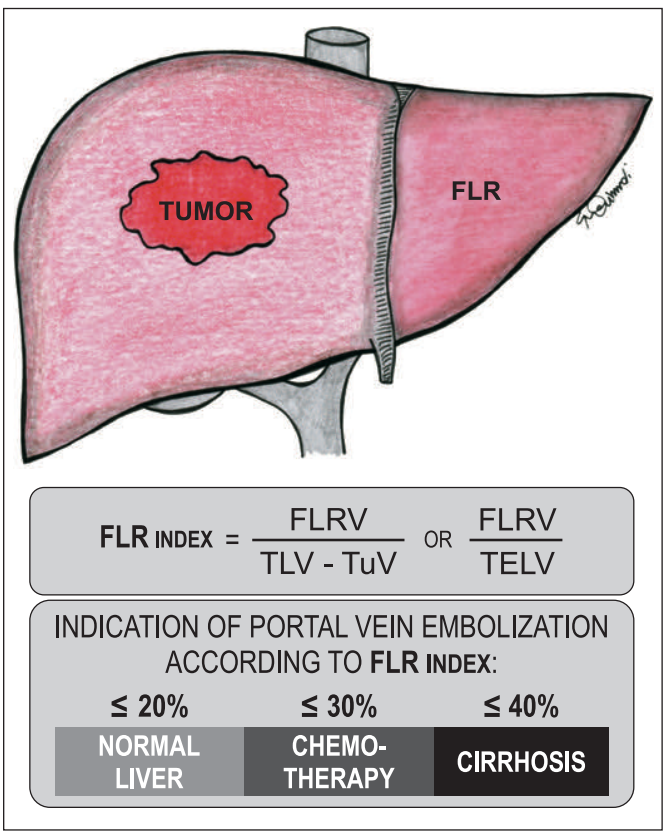


Figure 2. Calculation of Functional Liver Remnant (FLR) index and indications for portal vein embolization. FLR index can be calculated using the actual measured liver volume (by computed tomography volumetry) or using an estimated liver volume (calculated by a formula). The presence of underlying liver disease results in necessity of greater FLR index. TuV: tumor volume; FRLV: future remnant liver volume; TLV: total liver volume; TELV: total estimated liver volume.

Numerous clinical factors have also been shown to suppress regeneration and hypertrophy. These include biliary obstruction, hepatic congestion, diabetes, ethanol consumption, poor nutrition, male gender, old age, and chronic hepatic infection.[37] Biliary obstruction reduces the ability of the liver to hypertrophy following PVE or hepatic resection.[38,39] Possibilities for the mechanism of reduced proliferation include decreased portal flow and down-regulation of aforementioned humoral mediators.[37] Congestion of hepatic segments limits regeneration after hepatectomy. Diabetes also has a negative effect on regeneration. Insulin and Insulin-like Growth Factor (IGF) have been shown to increase after PVE and resection [40–42] and have been shown to contribute to regeneration. Clinical studies have shown a decrease in liver hypertrophy in diabetic patients.[13] Alterations in these humoral mediators have also been shown to be the cause for decreased regeneration in patients with chronic ethanol consumption, poor nutrition, male gender, old age, and infection.[43–50]

INDICATIONS

As described earlier, the ratio between the FRL and TELV is the most accurate predictor of how a patient will do after partial hepatectomy. A low ratio is a primary indication for performing a portal vein embolization. A thorough understanding of the resection volume (whether it will be a lobectomy or extended lobectomy, or a combined surgery such a hepatectomy and right colectomy) is necessary to determine the FRL threshold necessary for surgery. Another test to measure liver function is the indocyanine green clearance test (ICG).[51,52] In those patients with cirrhosis, an ICG retention rate at 15 minutes (ICG R15) is acceptable for resection if it is less than 10-20%.[52]

In a study of CT volumetrics in 102 patients, Abdalla et al.[53] showed that the left lateral liver contributes less than 20% of the total liver volume in about 75% of patients. Patients who need left segmentectomy therefore rarely will need PVE. On the other hand, 75% of patients who have an extended right hepatectomy will have an FRL index less than 20% (and would need PVE assuming no other reason for compensatory hypertrophy). In these patients, PVE would consist of embolizing the right lobe as well as the portal vein supplying segment 4. It is also unlikely for patients needing a trisegmentectomy (extended left hepatectomy) would need PVE.[54]

An FRL index of at least 25% is recommended in those with normal livers. In those patients with chemotherapy or chronic liver disease (which is considered stable), an FRL index of 40% is adequate for resection.[22] If the FRL index is below these thresholds, PVE is recommended.

Also described earlier, there are other factors, including biliary obstruction, alcohol use, male gender, poor nutrition, liver congestion, and diabetes, which can limit regeneration following resection. This can alter the FRL index threshold for PVE in patients with these clinical conditions.[43–50]

In summary, the indications for PVE include: i) hemihepatectomy for those patients with chronic diseases (see disease above); ii) extended hemihepatectomy for those patients with normal livers; and iii) FLR <40% in those patients with ICG R15 <10%, FLR <50% if ICG R15 is between 10 and 20%.[55]

CONTRAINDICATIONS

Those patients who are not candidates for resection because of distant metastatic disease are also not candidates for PVE. In the past, multiple tumors in both lobes of the liver had been a contraindication to resection and PVE. More recent reports have shown success in staged hepatectomy following PVE.[56]

There are not absolute contraindications for PVE; relative contraindications include: uncorrectable coagulopathy, portal vein thrombosis, tumor in the liver at the access site to the

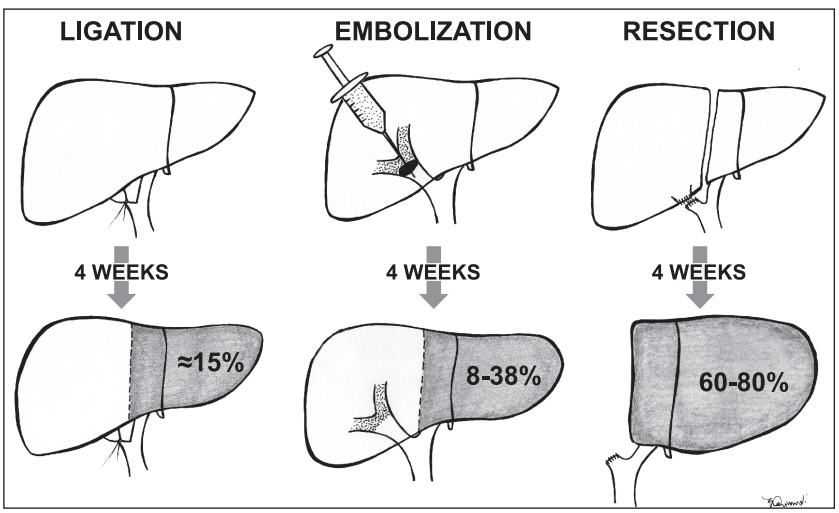


Figure 3. Expected hypertrophy rates with different methods of portal vein occlusion. Right portal vein ligation alone results in less contralateral liver hypertrophy than right portal vein embolization or right liver resection.

portal vein, portal hypertension, biliary obstruction (in this case biliary tract should be drained prior to PVE), and renal failure.[18] The inability to pass a catheter through a tumor-free liver can often be overcome by accessing the portal vein through the FRL.

CLINICAL CONSIDERATIONS

Pre-procedure

A cross-sectional imaging study should be performed, and FRL and FRL index should be calculated. Portal vein anatomy should be clearly delineated and anatomic variants should be identified (see Anatomy section). Distant metastatic disease should be ruled out before proceeding.

A history and physical exam should be performed in a pre-procedure clinic visit. At this time, serum chemistries, hematology and coagulation factors should be checked. Platelets should be greater than 50,000 and INR should be no more than 1.5. An increased bilirubin level should warrant further investigation; if there is evidence of obstruction, percutaneous or endoscopic drainage should be performed before PVE.[57]

Technique

The goal of portal vein embolization is to completely embolize the treated portal vein and minimize the chance of recanalization. Recanalization and subsequent development of portal collaterals have shown to decrease rates of regeneration.[58]

Three different techniques have been described for PVE: ipsilateral to the segments that are going to be resected, contralateral to the segments that are going to be resected, and intraoperative through the transileocolic vein. The most common approach to PVE used today is contralateral to segments to be resected (i.e., gaining percutaneous access in the liver remnant). This technique was first described by Kinoshita et al. in 1986.[9] With this method, a peripheral portal vein radical is accessed using ultrasound guidance and a vascular sheath is placed within the portal vein. The primary advantage to the contralateral approach (ipsilateral to FRL lobe) is that the treated lobe is easily accessible; however, the portal vein that will be preserved can be injured or embolized as part of the process. In a retrospective analysis of 188 patients with ipsilateral to FRL access, adverse events occurred in 24 patients (12.8%), including 12 clinical complications and 12 incidental imaging findings. Complications included thrombosis of the portal vein feeding the FRL (n=1); migration of emboli in the portal vein feeding the FRL, which necessitated angioplasty (n=2); hemoperitoneum (n=1); rupture of a metastases in the gallbladder (n=1); transitory hemobilia (n=1); and transient liver failure (n=6).[59] Some of these complications can be attributed to the contralateral approach, and the contralateral approach could be responsible for making the subsequent resection extremely difficult or impossible.

The ipsilateral approach (ipsilateral to embolization) was first described by Nagino et al.[60] in 1996. All 38 patients in this study had successful PVE through an ipsilateral approach. However, this technique used a large balloon catheter that is not available outside of Japan. The technique was modified by numerous groups in the US for use with standard catheters and vascular sheaths. The main advantage to this approach is that the FRL is not accessed during the procedure (and subsequent damage to the vasculature is not possible). Technically, this approach is more challenging because the portal veins that need to be embolized are at acute angles to the site of portal vein puncture. In addition, there is an increased theoretical risk of embolization material traveling to the FRL during the procedure, although this has not happened in a large series of patients (**Figure 4**).[61]

The transileocolic venous approach is an intraoperative technique that has primarily been used in Asia. Usually, it is used when an angiographic suite is not available or when there is a contraindication to percutaneous puncture. Obvious disadvantages include the need for general anesthesia and laparotomy. For these reasons, this technique is seldom used. In addition, the percutaneous route has shown increased hypertrophy of the FRL as compared to the transileocolic route (11.9% vs. 9.7%, P=0.00001).[2]

Embolization Material

Numerous embolic agents have been described in the literature, including but not limited to: cyanoacrylate and lipiodol, gelfoam and thrombin, particulates (polyvinyl alcohol - PVA), absolute alcohol, and coils. Similar rates of hypertrophy of the FRL have been reported with all of these agents.[62] It should be kept in mind that the goal of the procedure is a permanent portal vein occlusion.

The use of gelatin sponge as an embolic agent has been well described; however, there is a high rate of recanalization of the embolized portal vein segment two weeks after the procedure.[63,64] The addition of ethiodized oil to gelfoam particles decreases the incidence of portal vein recanalization.[65] The use of n-butyl cyanoacrylate (NBCA) has also been described with nearly complete embolization and minimal PV recanalization after four weeks.[59] However, non-target embolization has been described due to technical difficulties with the use of NBCA. In addition, NBCA induces strong peri-portal inflammation, making subsequent surgical resection difficult.[13]

In addition, the use of permanent particulate agents (Polyvinyl alcohol - PVA) has been described.[66] In a single center trial of 58 consecutive patients, there were no major complications with similar rates of hypertrophy as compared to the other agents described above.

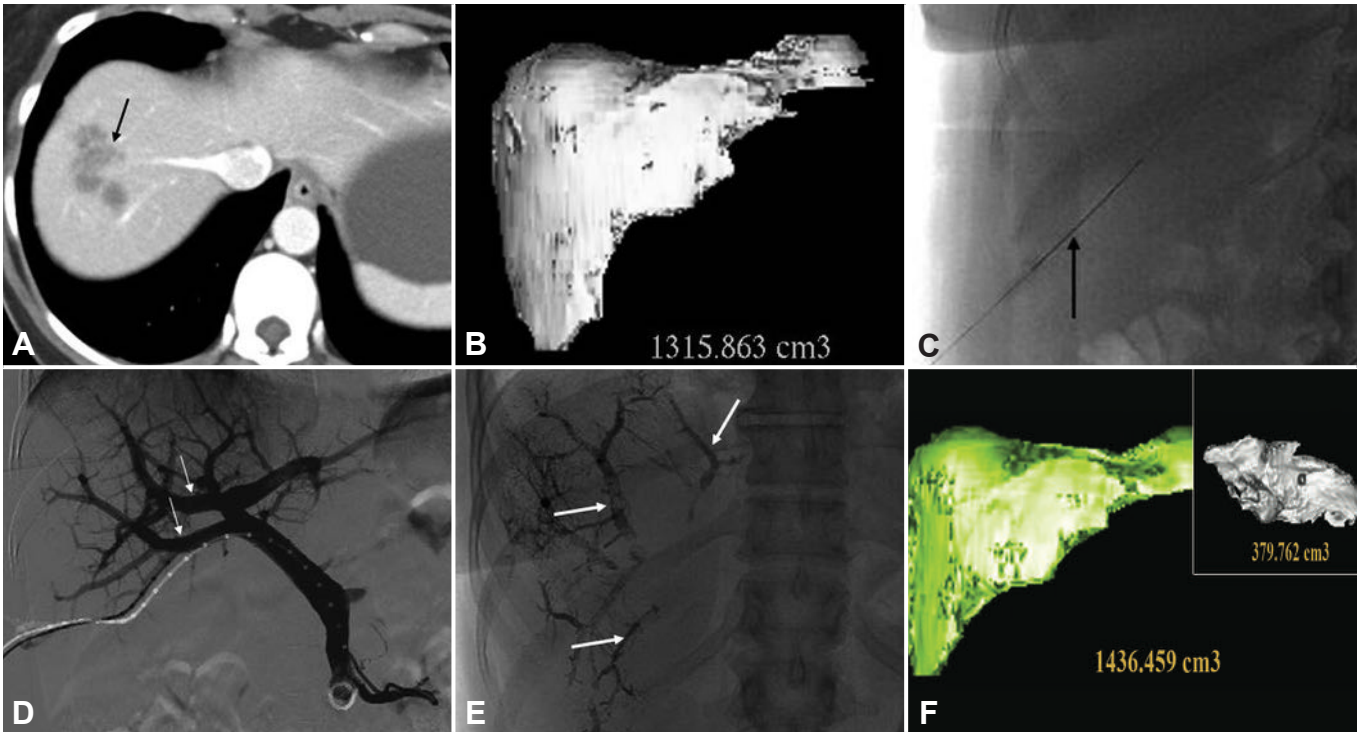


Figure 4. A) Portal venous phase computed tomography (CT) scan showing colorectal metastases in segments 7 and 8 of the liver (arrow). CT scan before right portal vein embolization. **B**) CT volumetrics pre-embolization. Total liver is showed in the figure, the left functional liver remnant (segments 1-4) was estimated to be 26% of total liver. **C**) Radioscopy showing access to right portal vein by percutaneous needle (arrow). **D**) Portal venogram after percutaneous access. The anterior and posterior right portal veins are highlighted with arrows. **E**) Status post ipsilateral portal glue injection (portal embolization). Cast of the right portal vein branches is shown (arrows). **F**) CT volumetrics of the liver and future liver remnant (FLR) post-embolization. The post-embolization FLR index was 32%. The patient had a successful resection about 6 weeks after portal embolization.

Changes in volume after PVE

Nagino et al.[50] examined 240 consecutive patients after PVE. In these patients, the FRL index increased from 33% ± 8% before PVE to 43% ± 8% after embolization. While there was an increase in the non-embolized lobe, the embolized area reduced its volume by 15% ±11%. A hypertrophy rate of 8- 38% of the FRL can be expected after four weeks of portal vein occlusion pending on the method and underlying chronic liver disease.[67–69]

Complications / Side effects directly related to PVE

The complication rate directly related to the PVE procedure is low. Technical complications can include subcapsular hematoma, hemoperitoneum, hemobilia, arteriovenous fistula and portal vein thrombosis.[59] One of the most serious technical complications is portal and mesenteric thrombosis. For one patient in Di Stefano et al.'s study, this complication caused acute gastrointestinal bleeding and encephalopathy with long-term duodenal stenosis secondary to ischemia.[59]

A fairly rare side effect of the procedure is post-embolization syndrome, which is characterized by low-grade fevers, abdominal pain, and/or nausea for three to 10 days following the procedure. Changes in liver function following PVE are not common and are typically transient. Transaminitis typically peaks one to three days after the procedure and resolves within 10 days of treatment.[70]

Surgical Results Following PVE

In a large meta-analysis performed by Abulkhir et al.[2], 1,088 patients were analyzed for their surgical results following PVE. Eighty-five percent (930) of these patients underwent subsequent laparotomies for attempted major hepatectomy. In 17% of these patients (158), resection was not possible; causes included intraoperative finding of disseminated peritoneal metastatic disease, tumor extension, portal node metastases, and tumor invasion of the vascular structures. The remaining patients (n=158) did not undergo a laparotomy because of inadequate hypertrophy of the functional remnant (n=18), severe progression of liver metastases (n=43), extrahepatic spread of tumor (n=35), patient refusal, and remission of disease from chemotherapy.

TRANSARTERIAL CHEMOEMBOLIZATION

INTRODUCTION

According to the most recent epidemiological data, the incidence of hepatocellular carcinoma (HCC) is rising worldwide.[71,72] There are a number of therapeutic options for patients with primary liver cancer. The two definitive therapies are either surgical resection or liver transplantation (see **Chapters 13** and **30**). However, surgical resection is often not possible because of multifocal tumors or poor hepatic reserve, and transplant donors significantly outnumber recipients. Transarterial chemoembolization (TACE) has been shown to improve survival in those patients that are unresectable.[73]

HISTORY

Yamada et al.[74,75] had first described the delivery of chemotherapy-soaked gelfoam pledgets within the hepatic arteries of those patients with HCC in the 1970s. The rationale for chemoembolization is as follows: normal liver tissue receives most (75-83%) of its blood supply from the portal vein, while liver tumors receive most (90-100%) of their blood supply from the hepatic artery.[76]

Lipiodol, an iodine ester derived from poppy seed oil, began to be used in the 1980s as part of the chemoembolization cocktail. Lipiodol (or ethiodol) is taken up by the liver (normal hepatocytes and tumor cells), but it not metabolized by tumors because of their lack of Kupffer cells. As a result, lipiodol can be seen in tumors months after treatment and can be used to monitor treatment areas after TACE. In addition, lipiodol has been shown to have an embolic effect, which serves to decrease blood flow and retain chemotherapeutic agents in the tumor.[77]

Although there are no data showing increased efficacy of one chemotherapeutic agent over another, the most common cocktail used in the procedure is a combination of cisplatin, doxorubicin, and mitomycin.[78,79] These agents have all shown to have good liver extraction and low systemic drug concentrations when administered into the hepatic artery. In addition, the intratumoral concentration of chemotherapeutic drugs is reported to be 10 times higher than if it was delivered through the hepatic artery as compared to the portal vein.[80] The most common dosages of the medications are as follows: 50 mg Doxorubicin (Adriamycin; Pharmacia-Upjohn, Kalamazoo, MI), 100 mg Cisplatin (Bristol Meyers Squibb, Princeton, NJ) and 10 mg Mitomycin-C (Bedford Laboratories, Bedford OH). This mixture is usually mixed in a 1:1 ratio with lipiodol.

Embolic agents are usually also employed during the chemoembolization procedure, whether as temporary agents (gelfoam slurry or pledgets) or as more permanent agents (polyvinyl alcohol - PVA, or other particulates). The way the embolic agent is administered is not standardized. Some prefer to mix with the chemotherapic agent, while others prefer to give the embolic agent after that, at the end of procedure. Some data suggest that a post-chemotherapy embolic agent helps to improve long-term arterial patency.[81] Long-term arterial patency is necessary for repeated chemoembolization, as its efficacy is related to the number of times it can be repeated.

TECHNIQUE

A thorough pre-procedure workup is necessary prior to performing chemoembolization. The diagnosis of HCC is made through either: i) tissue diagnosis or ii) imaging characteristics and elevated alpha-fetoprotein levels. A multiphase cross-sectional imaging study (either magnetic resonance imaging (MRI) or CT) should be obtained to determine: i) the size of tumor, ii) extrahepatic tumor spread, iii) possible variant arterial anatomy supplying the tumor, iv) biliary dilatation, and v) portal vein infiltration. Serum chemistries/hematology values also need to be ordered, including prothrombin time, international normalized ratio (INR), liver function tests, creatinine, and alpha-fetoprotein levels. Prior to the start of the procedure, intravenous fluids, prophylactic antibiotics (broad spectrum to cover gram negative and enteric germs), and antiemetics are administered.

Vascular access is typically obtained from one of the common femoral arteries in the groin. A vascular sheath is placed, and angiography of the superior mesenteric artery (SMA) is performed with delayed portal venous imaging. The purpose of visualizing this vessel is to identify any anomalous arterial supply to the liver parenchyma originating from the SMA, as well as to verify the patency of the portal vein. Next, the celiac artery is catheterized and arteriography is performed to identify any anomalous vessels and primary supply to the tumor. Potentially dangerous locations for chemotherapy administration are identified on this angiogram, including the left gastric artery, right gastric artery, cystic artery, and falciform artery. Many catheters can then be used for selective catheterization of the hepatic artery; usually this is accomplished with a 5 French reverse-curve catheter, such as a Cobra, Simmons, or Sos. Based on tumor burden, superselective catheterization is obtained with a microcatheter and microwire **(Figure 5).** On occasion, fluoroscopy is not sufficient to delineate the proper location of the microcatheter for embolization; in these cases, a CT scan can be obtained immediately following injection to verify optimal positioning (**Figure 6**).

As stated previously, the standard chemotherapy cocktail contains Adriamycin, Cisplatin, and Mitomycin. This cocktail

is mixed with lipiodol (see above for details) and administered through the microcatheter in a relatively superselective position. Although the lipiodol is embolic, further stasis is achieved after the administration of chemotherapy with another embolic agent; this agent can be gelfoam slurry, PVA particles, or gelatin microspheres. The most commonly used agents include gelfoam and PVA.[82] The primary reasons for the additional embolic agent are to help retain the chemotherapeutic agents within the tumor and to induce ischemic necrosis.

PALLIATION FOR HEPATOCELLULAR CARCINOMA

Transarterial chemoembolization is considered the standard of care for palliation of unresectable HCC (**Figure 6**). In two randomized controlled trials,[73,77] TACE has shown survival benefit as compared to best supportive care in a well-functioning patient population. In a paper published by Llovet et al.[73], the 1-year and 2-year survival rates for chemoembolization were 82% and 63% respectively, and for conservative management, 63% and 27% respectively (P=0.009). The trial had to be stopped early, after the ninth sequential inspection showed a survival benefit with TACE as compared to conservative management. The responses induced by chemoembolization were sustained for at least six months in 35% of cases. In addition, treated patients had a lesser chance of portal vein invasion as compared to those patients who had conservative management. All patients were Child-Pugh class A or B and Okuda stage I or II.

In a randomized control trial by Lo et al.[77], 40 patients were assigned to a chemoembolization group (using cisplatin, ethiodol, and gelfoam) and 40 patients were assigned to a control group (supportive management only). The 40 patients assigned to the experimental group received 192 courses of chemoembolization, a median of 4.5 per patient. The 1-, 2-, and 3-year survival rates were 57%, 31%, and 26% for the chemoembolization group, versus 32%, 11%, and 3% for the group who had conservative management, respectively (P=0.002). However, death from liver failure was more frequent in the experimental group that received chemoembolization.

5-year survival in most of the trials reported is low, but there is a subset of the treated population that survives over five years. In a study published by O'Suilleabhain et al.[83], there was an 8% survival rate (25 out of 320 patients) beyond five years. Three independent prognostic indicators were: unilobar tumors, alpha-fetoprotein levels below 1,000 ng/mL, and albumin concentration >35 g/L. Although there were numerous patient and tumor factors that predicted 5-year survival, even some patients with advanced tumors and portal vein invasion did survive longer than five years.



Figure 5. Schematic representation of transarterial chemoembolization (TACE). Access is obtained from femoral artery with a highly selective release of agents (chemotherapy, lipiodol, microspheres) into the arterial branches that nourish the tumor.

PALLIATION FOR OTHER LIVER TUMORS

TACE is not only utilized in the setting of hepatocellular carcinoma (HCC). It has also been used for palliation of cholangiocarcinoma.[84] In addition, TACE has been used for the palliation of a variety of metastatic tumors to the liver such as ocular melanoma,[85] neuroendocrine tumors,[86] colorectal carcinoma,[87] renal cell carcinoma,[88] some sarcomas,[89] and breast cancer.[90]

Cholangiocarcinoma is a rare hepatic malignancy, typically with a poor prognosis. The only curative option for cholangiocarcinoma is surgical resection. The prognosis is especially poor in those patients with unresectable disease (five to eight month survival), which usually comprises more than 70% of patients.[91] Systemic chemotherapy has shown no impact on survival as compared to supportive care.[92] Just like HCC, the majority of the blood supply to intrahepatic cholangiocarcinoma (ICC) is derived from the hepatic artery, making intra-arterial therapy attractive. However, given the rarity of the disease, it has been difficult to accrue significant data.[83] In a study by Burger et al.[93], 17 consecutive patients were treated with conventional TACE (doxorubicin, cisplatin, mitomycin C, ethiodol, and embosphere particles (Biosphere Medical, Rockland, MA)). These patients were relatively healthy (15 out of 17 patients were Child-Pugh A, and 14 had Eastern Cooperative Oncology Group (ECOG) status 1-2). The median survival in this group was 23 months. Two patients who were unresectable went on to resection after TACE. In another retrospective analysis by Herber et al.[94], 15 patients treated for intrahepatic cholangiocarcinoma with TACE (single agent Mitomycin C) had a median survival of

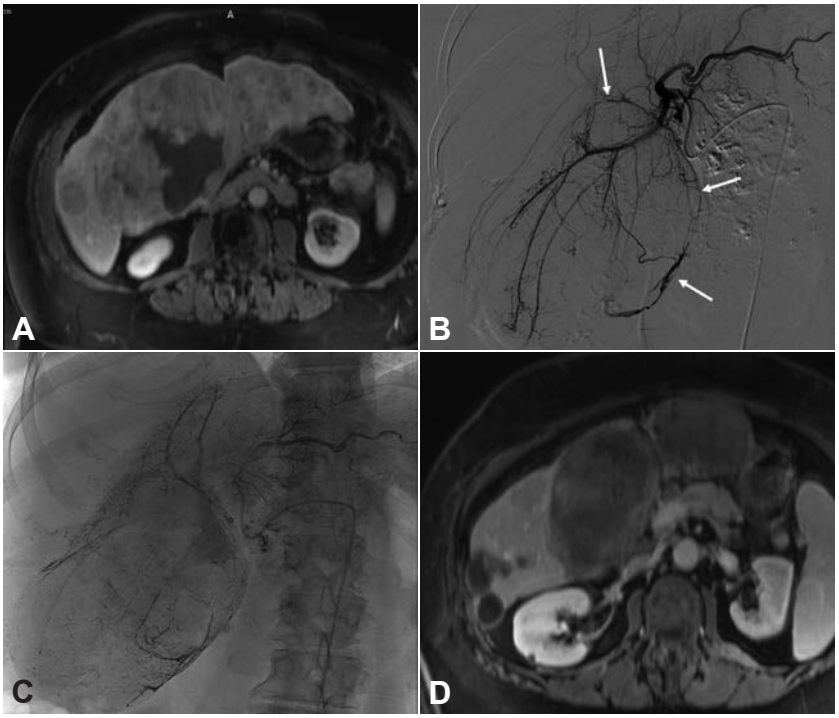


Figure 6. A) 58 year old woman, Child-Pugh class A, with multi-centric hepatocellular carcinoma. Figure shows early phase enhanced Magnetic Resonance Imaging (MRI) that reveals large left liver lesion. **B**) Left hepatic arteriogram of the same patient showing multiple irregular vessels outlining large mass (arrows). **C**) Status post-chemoembolization. Stain of tumor with lipiodol. **D**) Early phase of contrasted enhanced multiphasic Magnetic Resonance Imaging showing decreased enhancement of left sided liver masses (arrows).

16.3 months and 1-, 2-, and 3-year survival rates of 51%, 27%, and 27% respectively. In this study, the patients were generally healthy with good liver function (14 out of 15 were Child-Pugh A). Both of these studies showed improved survival in those patients with intrahepatic cholangiocarcinoma after receiving TACE therapy.

Ocular melanoma is the most common intraocular malignant tumor in adults.[95] Up to 50% of those patients diagnosed with ocular melanoma will subsequently develop systemic metastases within two to five years.[96] The metastatic disease tends to involve the liver; more than 70% of cases of metastatic ocular melanoma involve the liver, and the liver is generally the first site of metastases.[97] Once the melanoma metastasizes to the liver, the prognosis worsens, and survival is typically between two and nine months.[98,99] In a study by Sharma et al.[100] published in 2008, 20 patients with ocular melanoma were treated with Cisplatin, Doxorubicin, Mitomycin C, and Gelfoam. After TACE, 13 of 20 patients had stable disease, with an overall survival of nine months. In another study by Vogl et al.[101] published in 2007, 12 patients were treated with Mitomycin C, ethiodol, and microspheres. Three out of 12 had a partial response, and five out of 12 had stable disease. The overall survival in these patients was 21 months.

Colorectal cancer most commonly metastasizes to the liver, and liver metastasis is the leading cause of death in colorectal cancer patients. At the time of initial diagnosis, 20-50% of patients already have liver metastases.[102] Patients with colorectal liver metastases, receiving supportive care only, typically have a seven to eight month survival.[103] The only curative option for these patients is surgical resection; surgical resection allows for a median survival of 28-46 months, with 5-year survival rates of 24-40%.[104] In a study by Vogl et al.[87] published in 2009, 463 patients with unresectable colorectal hepatic metastases that were refractory to systemic chemotherapy were treated with TACE. By imaging characteristics, 68 patients (14.7%) had partial response, 223 patients (48.2%) had stable disease, and 172 patients (37.1%) had progressive disease. The 1-year and 2-year survival rates after chemoembolization were 62% and 28% respectively. Median survival from date of diagnosis of liver metastases and date of first chemoembolization was 38 months and 14 months respectively. In a study performed by Hong et al.[105], 36 patients were divided into two groups, those who received TACE therapy (n=21) and those who received Yttrium-90 radioembolization therapy (n=15). In these patients, the median survival times for the TACE and Yttrium-90 radioembolization groups were 7.7 months and 6.9 months respectively (from the start of therapy). The 1-, 2-, and 5-year survival rates for the chemoembolization group were 43%, 10%, and 0%, respectively. There were no significant survival benefits of TACE vs. radioembolization.

Metastatic neuroendocrine tumors represent approximately 10% of metastatic disease of the liver. Carcinoid and pancreatic islet cell have a predilection to metastasize to the liver, and those patients with liver metastases have a poorer prognosis and quality of life.[106] Surgical resection is curative, but it is only possible in less than 10% of patients.[107–109] In a study performed by Gupta et al.[110] published in 2005, 69 patients with carcinoid

metastases to the liver and 54 patients with pancreatic islet cell metastases to the liver underwent treatment with either hepatic arterial embolization (HAE) or chemoembolization (TACE). They found that patients with carcinoid tumors had better outcomes than those with islet cell carcinomas in terms of response rate (66.7% vs. 35.2%, P=0.001), progression-free survival (22.7 months vs. 16.1 months, P=0.046), and overall survival (33.8 months vs. 23.2 months, P=0.012). Patients treated with TACE had a trend towards higher overall survival and improved response in islet cell tumors but not carcinoid tumors, but this difference was not statistically significant. Touzios et al.[111] reported a median and 5-year survival of 50 months and 50% respectively, performing TACE with cisplatin, doxorubicin, and mitomycin C for metastatic neuroendocrine tumors. Ruutiainen et al.[112] performed TACE with cisplatin, doxorubicin, mitomycin, iodized oil, and PVA. The 1-, 3-, and 5-year survival rates were 86%, 67%, and 50% respectively. Most recently, Vogl et al.[86] compared two separate chemoembolization protocols, one with mitomycin C alone and the other with mitomycin C and gemcitabine. Their results showed that the combined mitomycin C and gemcitabine had significantly better 5-year and overall survival as compared to the mitomycin C alone (5-year survival: 47% vs. 11%; overall survival 57.1 months vs. 38.7 months).

Renal cell carcinoma is rarely metastatic to the liver. However, its metastases are extremely vascular, making it an ideal candidate for intra-arterial loco-regional therapy. In a study by Nabil et al.[88] published in 2008, 22 patients were treated with TACE (either mitomycin C alone or mitomycin C with gemcitabine). Imaging showed a partial response in 13.7%, stable disease in 59%, and progression in 27.3%. Median survival times from diagnosis and from TACE were 68.6 months and 8.2 months respectively. One- and 2-year survival was 31% and 6% respectively. Although these survival results are worse than those achieved with surgery, the patients treated in this study had significantly more advanced disease as compared to those with surgical resection.

Even patients with early **breast carcinoma** will experience distant metastases.[113] The 5-year survival rate in these patients with stage IV disease is 10-18%. Among these patients, 3-12% will have metastases limited to the liver.[114] In a study performed by Giroux et al.[90], eight patients with metastatic breast cancer were treated with TACE. On imaging, five patients had a partial response, one had stable disease, and two had disease progression. All patients died within 13 months after receiving the treatment, with a mean of 49 months from primary diagnosis.

Approximately 64-70% of **abdominal sarcomas** metastasize to the liver.[115,116] Once the sarcoma metastasizes to the liver, the median survival is 14 months for those patients who receive supportive care only.[115] In a study published by Rajan et al.[89], 16 patients with a variety of gastrointestinal sarcomas were treated. Post-procedure imaging showed two patients had a partial response, 11 patients had stable disease, and three had progression. Survival from diagnosis was 81% at one year, 54% at two years, and 40% at three years. Median survival was 20 months.

TACE AS A NEOADJUVANT TO SURGERY FOR HCC

In addition to its palliative indications, TACE can also be used as a neoadjuvant therapy before surgery.[117–120] A study by Zhang et al.[118] included a retrospective analysis of 120 patients who had a hepatectomy for HCC, with patients stratified into three groups: TACE more than two times before surgery, TACE once before surgery, and no TACE. The 5-year disease-free survival rates in the TACE≥two times, TACE once, and no TACE groups were 51%, 35.5%, and 21.4% respectively, and the mean disease-free survival times of the same groups were 66.4, 22.5, and 12.5 months respectively. Slightly different results were obtained by Lu et al.[120] In an analysis of 120 patients who had a hepatectomy for HCC (44 of which had TACE, 76 of which did not), there was no survival advantage between the TACE and non-TACE groups. However, if tumor size was used to stratify patients with tumors larger than 8 cm, the TACE group had 1-, 2-, and 5-year cumulative survival rates of 90%, 53%, and 42%, while the non-TACE group had 1-, 2-, and 5-year cumulative survival rates of 72%, 33%, and 11% (P=0.01).

These results were contradicted by an article published by Choi et al.[119] In this retrospective study, a total of 273 patients had a curative resection for HCC, out of which 120 patients underwent preoperative TACE. Disease-free survival and recurrence patterns were analyzed in multiple groups, including: TACE vs. non-TACE, initial tumor size (<3 cm, 2-5 cm, >5 cm), pathologic tumor stage (stage I-II, stage III-IVa), and imaging results after TACE (complete necrosis, incomplete necrosis, and non-TACE). In all of these groups, preoperative TACE neither reduced the recurrence incidence nor improved the recurrence pattern after resection. None of the aforementioned subgroups gained a therapeutic benefit from preoperative TACE.

TACE AS A BRIDGE TO LIVER TRANSPLANT IN HCC

Orthotopic liver transplant (OLT) has been shown to be the best treatment for early-stage HCC.[121] As such, TACE also has utility as a bridge to transplant. TACE is used as an adjunct prior to transplant for three reasons: i) to bring the patient into transplant criteria (downstaging the tumor into Milan or extended transplant criteria), ii) to control

disease while the patient awaits transplant (the number of donated livers are far exceeded by the number of transplant candidates), and iii) to ascertain the biological activity of the tumor before transplant.[122]

In a study published by Graziadei et al.[123], 48 patients with HCC were included for analysis. All patients received TACE (mean of 2.5 ± 1.6 sessions). Forty-one of the patients received a transplant, and seven were still on the waiting list. The 1-, 3-, and 5-year survival rates after OLT were 98%, 98%, and 93% respectively. Tumor recurrence only occurred in one patient. Fifteen patients (out of 48) that had advanced disease were successfully downstaged into transplant criteria. However, in these patients, the survival data was significantly worse compared to the group with early-stage HCC.

Lesurtel et al.[122] published an evidence-based analysis of TACE as a neoadjuvant therapy for OLT for HCC. In their analysis, they found that although TACE does not increase the risk of postoperative transplant complications (grade C), there is no evidence (grade C recommendation) that preoperative TACE improves long-term post-transplant survival, expands transplant criteria, or decreases drop-out rates on the waiting list. They suggest that more randomized controlled trials (RCT) are necessary for further elucidation of the role of preoperative TACE on liver transplantation.

A study by Otto et al.[124] further analyzed the role of TACE as a biological selection criteria for patients with HCC who are candidates for liver transplantation. In this study, 96 patients underwent TACE, and 62 of them were outside Milan transplant criteria. The patients within criteria were immediately listed for transplant, and the others were listed when they were downstaged into Milan criteria. Fifty patients were eventually transplanted. The overall 5-year survival of the patients undergoing transplant was 80.9%. Tumor recurrence was significantly higher in those patients who had tumor progression after initial response after TACE. The authors concluded that sustained response to TACE is a better selection criterion for OLT compared to the current criteria (tumor size and number).

SYMPTOMATIC INDICATIONS TO TACE

Spontaneous rupture is a potentially fatal consequence/presentation of HCC. A number of studies have reported 30-day mortality rates after HCC rupture ranging from 30-70%.[125,126] The incidence of spontaneous rupture is considerably higher in the Far East (12.4% in Thailand and 14.5% in Hong Kong)[125,126] compared to Western countries (3% in Great Britain).[127] Although hepatic resection is considered a very good treatment modality for ruptured HCC, many patients do not qualify for resection. In a study performed by Hirai et al.[128], they reviewed 47 cases of spontaneous rupture of HCC causing hemorrhage into the peritoneum. Thirty-three of these patients received supportive care, and the mean survival time of this cohort was 13 days. Fourteen of these patients underwent emergency transcatheter arterial embolization, and the mean survival time was 98.5 days. Similar results were obtained by Kirikoshi et al.[129] This was a multicenter study in which a retrospective analysis was performed in 48 cirrhotic patients, 32 of which received conservative treatment while 16 patients received transarterial embolization (TAE). The patients who did not receive TAE were typically worse clinically than those patients that did receive TAE (Child-Pugh score of 9.2 ± 1.8 for conservative management, 7.6 ± 2.0 for TAE, P = 0.0074). However, the results were striking: the median survival time in the control group was 13.1 days, and the seven-, 14- and 30-day survival rates were 59.4%, 37.5%, and 6.3% respectively, while the median survival time in the TAE group was 244.8 days and the 1-, 3-, 12-, and 24-month survival rates were 87.5%, 56.3%, 23.4%, and 15.6% respectively. The performance of TAE alone was a significant independent factor influencing overall long-term survival.

CONTRAINDICATIONS TO TACE

Although there are no absolute contraindications to the TACE procedure, relative contraindications can be identified based on the exclusion criteria in most clinical trials: advanced liver disease (Child-Pugh classification C or above), active gastrointestinal bleeding, biliary obstruction, encephalopathy, refractory ascites, vascular invasion or portal vein invasion from tumor, extrahepatic metastases, portosystemic shunts, contraindication to arterial intervention (INR >1.8, platelets <50,000 per mcL, creatinine >1.5 mg/dL), and poor performance status (ECOG>2).

In the case of biliary obstruction, care must be taken to avoid biliary necrosis of the obstructed segments, which could result in abscess formation. In a study by Kim et al.[130], the authors recommend a reduction in the amounts of oil/gelatin sponge particles to reduce the amounts of biliary complications after TACE (bilomas and focal biliary strictures). If there is a reversible cause for the biliary obstruction, a percutaneous biliary tube should be inserted prior to TACE. In addition, prior biliary reconstructive surgery has been identified as an independent risk factor for the formation of abscesses after TACE.[131,132]

With regard to portal vein thrombosis, numerous studies have shown that TACE is safe in these patients. In a study by Pentecost et al.[133], nine patients with portal vein thrombosis underwent transarterial chemoembolization. Among these, eight patients responded to treatment. No patient developed hepatic infarction or insufficiency as a consequence of the procedure. A larger study was performed by Georgiades et al.[134], in which 32 consecutive patients with portal vein

thrombosis were treated with TACE. In these patients, the median overall survival was 9.5 months. The 30-day mortality rate was zero and there was no TACE-related hepatic infarction or acute liver failure. The 6-, 9-, 12-, and 18-month survival rates were 60%, 47%, 25%, and 12.5%, respectively. The authors concluded that portal venous thrombosis should not be considered a contraindication to TACE.

Kothary et al.[135] performed a study in which 52 patients underwent high-risk procedures. All patients had an elevated serum bilirubin value, 76.9% of patients had serum albumin levels below 3.5 mg/dL, and 25% of the patients had portal vein invasion. More than 50% had a Child-Pugh score of nine points or greater. Although patients with multifocal disease and lobar invasion had significantly higher mortality rates, the 1- and 2-year survival rates were 67.9% and 37.7% respectively. The authors concluded that high-risk patients did not have a higher rate of mortality as a consequence of the procedure.

COMPLICATIONS OF TACE

The most common complication following TACE is post-embolization syndrome (PES), which occurs in approximately 2-7% of patients.[136] Symptoms of PES include abdominal pain, nausea, vomiting, and mild fever. In a study performed by Leung et al.[136], two factors associated with an increased risk of PES were the embolization of the cystic artery, and the total chemoembolization dose administered. They also found that previous embolization was associated with a decreased risk of PES. Patel et al.[137] performed a study where they showed that no patient factors (age, lab values) were associated with a higher risk of PES. The treatment of PES is supportive care only.

The most important and serious complication of TACE is hepatic insufficiency/failure. Chan et al.[138] found that acute hepatic decompensation occurred in 20% of all patients treated with TACE, with 3% being irreversible. Patient factors associated with a higher rate of hepatic decompensation included: dose of cisplatin used, baseline bilirubin level, baseline prothrombin time, baseline aminotransferase (AST) level, and stage of cirrhosis.

Rarer (but equally as serious) complications of TACE include cerebral lipiodol embolism and pulmonary embolism/infarction. The former (cerebral lipiodol embolism) is caused by an arteriovenous shunt in the liver with either an intra-cardiac shunt or pulmonary shunt. Five total cases of cerebral lipiodol embolism have been reported in the literature.[139] Pulmonary embolisms/infarctions can occur from an arteriovenous shunt occurring in the liver. A study by Chung et al.[140] showed that the incidence of pulmonary complications increases as the dose of lipiodol increases.

DRUG ELUTING BEADS

The use of drug-eluting microspheres signaled a new frontier in interventional oncology. This agent, which incorporates the chemotherapeutic agent on a microsphere, has a dual function: the capability to slowly release chemotherapy in a controlled fashion over time and to embolize the treated artery. There are two types of drug eluting microspheres: DC bead™ microspheres (Biocompatibles, UK) and Quadrasphere™ microspheres (Biosphere Medical Inc., USA). Much more data has been gathered regarding DC beads compared to Quadrasphere; as a result, only DC beads will be discussed here. DC beads are derivatives of polyvinyl hydrogel and received CE mark approval in 2003 for malignant hypervascular tumors. DC beads are most commonly loaded with doxorubicin and are typically used for the treatment of hepatocellular carcinoma (HCC), cholangiocarcinoma, and neuroendocrine metastases. The beads can also be loaded with irinotecan; this agent is used for treatment of colorectal metastases to the liver.

Current Evidence. The pharmacokinetics profile of drug-eluting bead TACE (DEB-TACE) is significantly different compared to that of conventional TACE. Peak drug concentration occurs in both treatments within five minutes following injection, but it is significantly lower in the DEB-TACE group (78.97 ± 38.4 ng/mL vs. 895.66 ± 653.1 ng/mL, P=0.001).[141] In addition, the variability of the maximum concentration of doxorubicin is considerably higher in the conventional TACE group compared to the DEB-TACE group. In addition, the total systemic dose of doxorubicin with conventional TACE is also significantly higher compared to DEB-TACE. This improved pharmacokinetic profile of DEB-TACE allows more selective dose delivery to the tumor and a reduction of systemic toxicity.[141]

One of the first studies to ascertain the effectiveness and safety of DC beads for unresectable HCC was performed by Malagari et al.[142] In this open-label study of 62 patients with unresectable HCC, mean tumor diameter was 5.6 cm and all patients were either Okuda stage I or II. Based on imaging, after nine months of treatment, a complete response was seen in 12.2% of patients, partial response in 80.7%, progression of disease in 6.8%, and stable disease in 12.2%. Alpha-fetoprotein levels showed a mean decrease of 1,123 ng/mL after the first session. Severe post-procedure complications were seen in two patients: one had cholecystitis and one had a liver abscess. Similar results were obtained in a study performed by Reyes et al.[143] In this study, 20 patients underwent DEB-TACE. On one-month imaging, according to European Association for the Study of Liver (EASL) criteria, 12 patients had objective tumor response and eight had stable disease. No patients had a progression of disease during treatment. Overall survival rates at one and

two years were 65% and 55% respectively. Median overall survival was 26 months.

In a prospective randomized trial comparing DEB-TACE to bland embolization,[144] 41 patients were assigned to the DEB-TACE group, and 43 patients were assigned to the bland embolization group. Tumor response was evaluated using the EASL criteria and alpha-fetoprotein levels. The results showed that the recurrence rate was higher at nine months with the bland embolization group compared to the DEB-TACE group. There was also a longer time to progression (TTP) for the DEB-TACE group (42.4 ± 9.5 weeks vs. 36.2 ± 9.0 weeks, P=0.008).

The Precision V trial[145] is the only prospective randomized trial comparing DEB-TACE and conventional chemoembolization (administration of doxorubicin-oil emulsion followed by conventional TACE). In this study, there were 212 total patients, 102 in the DEB-TACE group and 110 in the conventional TACE group. All patients were Child-Pugh A or B and unresectable; they were randomized according to Child-Pugh status, performance status, extent of disease, and prior treatment. The primary endpoint was EASL criteria six months after treatment. There was a trend towards improved EASL criteria in the DEB-TACE group, although this was not significant (DEB-TACE vs. TACE complete response 27% vs. 22%, objective response 52% vs. 44%, disease control 63% vs. 52%, respectively, P=0.11). A more specific subgroup analysis (Child-Pugh B, ECOG 1, bilobar disease) showed a significant increase in objective response in the DEB-TACE group vs. TACE (P=0.038). Equally as important, the DEB-TACE group had reduced amounts of serious liver toxicity (P<0.001) and a significantly lower rate of doxorubicin-related side effects (P=0.0001). The authors concluded that DEB-TACE is a safe procedure, with a better side effect profile than conventional TACE, and that it is beneficial to patients with more advanced disease.

Many smaller trials have described the use of drug-eluting beads for metastatic liver disease, including primaries from colorectal cancer, neuroendocrine tumors, and cholangiocarcinoma. There have been a few promising trials describing the use of irinotecan-eluting beads for metastatic colorectal carcinoma.[146]

In one study, 55 patients with metastatic colorectal cancer refractory to multiple lines of systemic chemotherapy underwent 99 treatments with irinotecan drug-eluting beads. Response rates were 66% and 75% after six months and 12 months respectively. The median disease-free and overall survival from the time of first treatment was 247 days and 343 days respectively.[147] A small trial with 11 patients was performed by Aliberti et al.[148] describing preliminary results from treating intrahepatic cholangiocarcinoma with DEB-TACE. They reported a median survival of 13 months and 100% RECIST response from DC bead treatment.

TACE IN COMBINATION WITH OTHER THERAPIES

TACE combined with other interventional treatments

TACE combined with other minimally invasive therapies (i.e., thermal ablation or percutaneous ethanol ablation) has shown better efficacy than either therapy alone.

TACE and radiofrequency ablation (RFA) together should increase the efficacy of either treatment alone because the TACE (before the RFA) would reduce blood flow to the tumor, allowing an increased RFA burn by reducing heat loss. Numerous articles have been published comparing the use of TACE and RFA together rather than either treatment alone. A recent study published by Kagawa et al.[149] compared results from TACE-RFA versus surgery. Surgery, as discussed elsewhere, is considered the best therapeutic option for HCC, but can often not be performed secondary to tumor or patient factors. In this study, 62 patients received TACE-RFA, while 55 patients received surgical resection. The probability of survival at 1, 3, and 5 years was 100%, 94.8%, and 64.6% for the TACE-RFA group, and 92.5%, 82.7%, and 76.9% for the surgical resection group (P=0.788). In a randomized controlled trial,[150] 37 patients with hepatocellular carcinoma were randomized to two groups: a TACE-RFA group and an RFA group. The ablated size of the lesions were significantly greater in the TACE-RFA group vs. RFA alone (mean diameter with RFA was 50 ± 8.0 mm vs. 58 ± 13.2 mm for the TACE-RFA group, P=0.012), and the rate of tumor progression was greater for the RFA group alone (local tumor progression after three years of RFA was 39% vs. 6% for TACE-RFA, P=0.012). However, the 3-year survival for both groups was not significantly different (80% for RFA and 93% for TACE-RFA, P=0.369). These two studies and others show that TACE-RFA has promise to be more efficacious than RFA alone and possibly as efficacious as surgical resection.

Similarly positive results have been reported with combined percutaneous ethanol injection (PEI) and TACE. In a study by Lubienski et al.[151], a total of 50 patients (Child-Pugh A/B) underwent a TACE procedure; 22 underwent combined repeat TACE and PEI, while 28 received repeat TACE. The 6-, 12-, 24-, and 36-month survival rates for TACE monotherapy were 61%, 21%, 4%, and 4% respectively, while for combined TACE-PEI the rates were 77%, 55%, 39%, and 22% respectively (P=0.002). A recent meta-analysis performed by Wang et al.[152] identified seven randomized trials comparing TACE-PEI and TACE alone, with a total of 623 patients. The 6-month, 1-, 2-, and 3-year survival rates were significantly better for the TACE-PEI group vs. TACE alone. In addition, there were fewer adverse effects in the combined TACE-PEI group vs. TACE alone. Overall, the results of this meta-analysis and the results of others showed better results are obtained combining TACE

and PEI vs. TACE alone.

Based on the fact that HCC can metastasize through portal vein dissemination, a recent paper used portal vein embolization to prevent intrahepatic metastases to the non-embolized liver in patients with unresectable tumors followed by TACE. The use of PVE plus TACE resulted in a longer overall survival than TACE alone (1-, 3- and 5-year overall survival rates were 88.2%, 38.2%, and 38.2% in the PVE plus TACE group, and 68.1%, 22.7%, and 8.5% in the TACE alone group, respectively, $P<0.05$).[153]

TACE combined with systemic therapies

There have been some early positive results when combining TACE with some new systemic therapies. One of these agents, bevacizumab (Avastin®, Genentech/Roche, San Francisco CA, USA) is a human monoclonal antibody that binds to vascular endothelial growth factor A (VEGF-A). VEGF-A is a cytokine that stimulates angiogenesis. The Food and Drug Administration (FDA) has approved it for metastatic disease, including primaries from colon cancer, non-small cell lung cancer, and breast cancer. In a recent pilot study by Britten et al.[154], bevacizumab combined with TACE showed prolonged disease control and good tolerance. There are numerous ongoing trials evaluating the efficacy and safety of bevacizumab for primary and metastatic liver cancer. Sorafenib (Nexavar®, Bayer pharmaceuticals, USA), is a small molecule inhibitor of several tyrosine protein kinases that is approved for unresectable, advanced renal cell carcinoma and hepatocellular carcinoma. Numerous phase II trials are currently being performed to evaluate the efficacy of Sorafenib and TACE.

HEPATIC ABLATION

INTRODUCTION

The two main treatment strategies for primary and metastatic disease of the liver are surgical resection and transplantation. The results of resection and transplantation are overwhelmingly positive in terms of survival. However, in the case of transplantation, many patients are outside criteria prior to presenting for transplantation. Even if these patients are within transplant criteria, they often have to wait for a long time for a transplant, during which significant disease progression can occur. In the case of surgical resection, patient factors often preclude them from receiving these procedures.

Ablation has become a viable option for patients who are not surgical candidates because of good long-term survival data and minimal complications.[155–157] The goals of ablation are to kill the targeted tumor cells and also to limit damage to the normal surrounding parenchyma. Although the original intent of ablation was as an alternative to surgery, ablation can also serve as an adjunct to surgery. In addition, since ablation is minimally invasive compared to surgical resection, recovery time is shorter and cost is considerably less. Three different types of ablation will be discussed here: chemical ablation (including percutaneous ethanol injection and percutaneous acetic acid injection), thermal ablation (radio-frequency ablation, microwave ablation, and cryoablation), and experimental ablative techniques (irreversible electroporation) (**Table 1**).

CHEMICAL ABLATION

The injection of percutaneous chemicals into small liver tumors has been well studied in Japan. It is cheap, well tolerated, simple to perform, and can be performed under conscious sedation. In addition, as compared to thermal ablation (discussed later), there is no heat-sink that limits ablation. Complications are relatively rare (<2%), the most significant being tumor seeding.[158] Other reported complications include portal venous thrombosis, cholangitis, and intraperitoneal dissemination of tumor.[159,160]

Percutaneous injection tends to work well in the liver because tumors are soft in comparison to the surrounding fibrotic (cirrhotic) liver.[161] On the other hand, percutaneous ethanol injection (PEI) has not gained more popularity because it needs to be repeated many times; PEI usually only induces approximately 70% necrosis of the treated tumor because of internal septations within the tumor,[162] vascular washout, and the needle not being centrally located within the tumor.

Some of these limitations can be overcome with percutaneous acetic acid injection (PAI). It is equally as cheap as ethanol, but because of lower pH, it can disrupt internal septations and surrounding capsules, and as a result requires fewer treatments.[163,164] In a study performed by Ohnishi et al.[163], patients were randomized to two groups: percutaneous ethanol ablation (PEI) and percutaneous acetic acid injection (PAI). The percutaneous acetic acid group had fewer recurrences ($P=0.012$) and longer cancer-free survival ($P=0.017$). These differences were also likely related to the lower pH of acetic acid (as compared to ethanol).

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) causes tumor cell death by heating the tissue beyond what is tolerable by the tissue. The heat causes thermal coagulative necrosis in the tissue. The tumor tissue can easily tolerate temperatures up to 40 degrees Celsius; however, at a temperature above 46 degrees, irreversible cellular damage occurs.[165] The temperature should not exceed 100 degrees Celsius, as at these temperatures

there is tissue vaporization, which causes complete energy impedance. The important factors that mediate tissue temperature can be summarized by the following equation: tissue temperature = (total energy deposited x local tissue interactions – heat loss).[166]

There have been many methods developed (mostly by the industry) to increase the energy deposited within tumors. Some of these include: multiple RF applicators at once (this produces more coagulative necrosis compared to sequential applicators), multi-tine applicators (expandable electrodes, increasing ablated volume), bipolar electrodes (this increases the total amount of heat that can be deposited into the tumors), internally cooled electrodes (to reduce overheating and allowing for increased heat deposition), and pulsed radiofrequency application (to allow increased energy deposition). In the few comparison studies between the commercial devices, there have been no significant differences in complication rates, local progression, or survival in small HCC.[167,168]

As discussed earlier, the temperature achieved in the target tissue is also largely affected by intrinsic tissue factors. The target tissue is obviously a key component, but also the background tissue is important as well. This point is well illustrated by the different times to successfully ablate metastatic disease in the liver (normal surrounding liver) as compared to primary liver cancer (cirrhotic, fibrotic surrounding liver). Altering the environment around the electrode can also alter energy deposition. The administration of saline before or during ablation can significantly increase coagulative necrosis.[169] A negative factor for effective tumor ablation is the presence of a heat sink adjacent to the tumor (heat loss in the above mentioned equation). Adjacent vessels can provide this heat sink and thus limit effective tumor ablation. This effect is especially evident if the adjacent vessel is greater than 3 mm.[170] The opposite is also true; the occlusion of these vessels causes increased areas of ablation.[171]

Some of the advantages of RFA include: few total procedures, abundance of clinical data (long track record), wide availability, reproducibility, good safety profile, and small electrode size.

Limitations of RFA also exist. During ablation, the probes get extremely hot and can char the tissue immediately adjacent to the tumor. This results in dramatic increases in tissue impedance, which limits ablation volume. Tumor impedance is also very high in certain tissues, such as lung and bone. This also limits ablation size. As discussed previously, heat sink can also limit tumor ablation. In addition, current can only go from one point to another, and as a result only one probe can be activated at once. As a result, in larger

Table 1. Comparison of main percutaneous ablation techniques.

ABLATION TYPE	POSITIVES	NEGATIVES
Percutaneous ethanol ablation (PEI)	Cheap Well tolerated Minimal pain No heat sink limitation Well studied	Incomplete treatment – multiple sessions necessary
Percutaneous Acetic Acid Injection (PAI)	Cheap Well tolerated Minimal pain No heat sink limitation More tumor penetration, less retreatment (vs. PEI)	Incomplete treatment – multiple sessions necessary
Radiofrequency ablation (RFA)	Smaller needles (compared to other thermal ablation) Reproducible results Well studied	Susceptible to heat-sink Less effective ablation in large lesions Less effective ablation in lesions in lung, bone where tissue impedance is high Only 1 probe can be activated at once; long procedure times
Microwave ablation	Larger ablation zones as compared to RFA Less heat-sink as compared to RFA Less impact of adjacent tissues (good results with bone/lung) Multiple probes can be activated simultaneously in large lesions	Larger diameter probes Less studied as compared to RFA
Cryoablation	Can monitor ablation zone in real-time Possibly fewer complications compared to RFA Iceball fracture	Cryo-shock

lesions involving multiple probes, procedure times can be extended significantly (**Figure 7**).

Current evidence for the treatment of HCC

As stated previously, the majority of clinical data with regard to ablation focuses on RFA. There are a number of studies with five-year survival data.[157,172,173] In a study by Lencioni et al.[172], 187 patients with Child A/B cirrhosis, with tumors in the range of 1.5 cm to 5.0 cm (mean 2.8 cm), were treated with RFA. Complete ablation occurred in 90% of patients, with 3- and 5-year survival rates of 71% and 48%, respectively. A study by Livraghi et al.[157] with only Child-Pugh A patients, all with tumor sizes smaller than 2 cm, showed three- and five-year survival rates of 76% and 55%. Finally, in a study by Tateishi et al.[173], 319 patients were treated with RFA or combination RFA/TACE. These patients were mostly Child A/B, with a mean tumor size of 2.6 cm (range 0.8-9.7 cm). Complete ablation occurred in 93% of patients, with three- and five-year survival rates of 78% and 54%, respectively. The rates of complications in these studies were less than 5%.

Current evidence for the treatment of colorectal metastases

Historically, the median survival time of metastatic colorectal cancer of the liver with no treatment is five months, with virtually zero chance of surviving five years. A large number of studies have shown that long-term survival is achievable in 40% of patients with metastatic colorectal cancer after surgical resection.[174] Unfortunately, the vast majority of metastatic patients cannot be resected.

Either as the sole treatment or as an adjunct to achieve complete hepatic clearance when multiple lesions are present, RFA has emerged as an alternative to liver resection in patients with colorectal metastases. Most of the data regarding the efficacy of RFA in this scenario comes from single-arm studies, retrospective or prospective. There is a wide variability in five-year survival (14-55%) and local recurrence rate (3.6-60%) among studies. This has been attributed to tumor biology, technique, and patient selection.[175]

The only randomized trial published to date on the possible benefits of RFA in patients with non-resectable colorectal liver metastases randomized 119 patients for systemic treatment or systemic treatment plus RFA (± resection). The primary endpoint, 30-month overall survival, was no different between groups (61.7% vs. 57.6% for RFA and systemic treatment groups, respectively).[176]

The ultimate role and efficacy of RFA in the setting of colorectal liver metastases remains to be determined.[176]

MICROWAVE ABLATION

Microwave ablation causes tissue destruction by the application of an electromagnetic field, which causes water molecules of the target tissue to oscillate at very high frequencies. The continuous re-alignment of these molecules causes an increase in their kinetic energies and temperatures. At temperatures above 46 degrees Celsius, there is cell death due to coagulative necrosis.[165] Applied electromagnetic fields are typically greater than 900 MHz.[177–179] Compared to other thermal ablative technologies, microwave ablation consistently achieves higher tumoral temperatures, larger ablation volumes, faster ablation times, and optimal heating of cystic masses.[180,181]

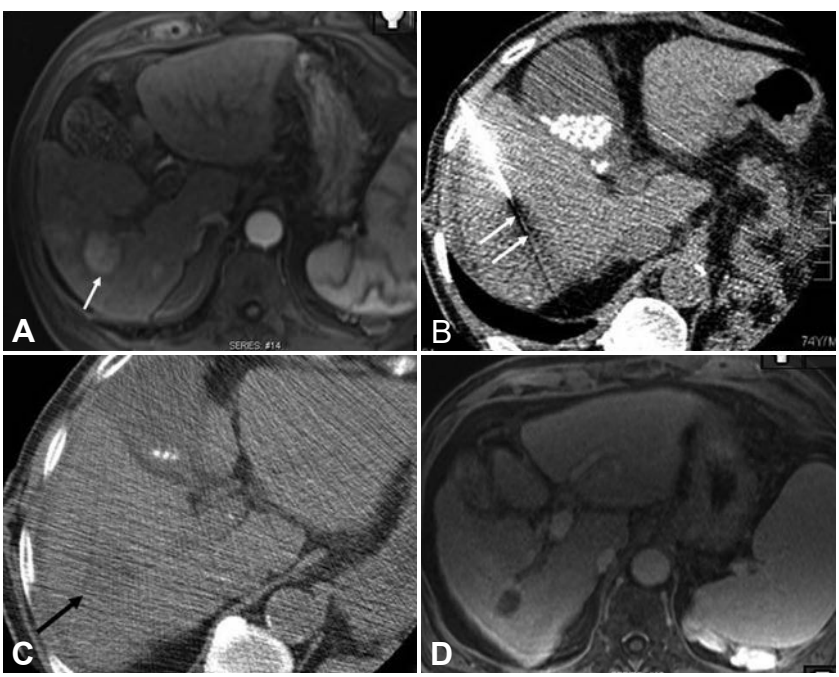


Figure 7. A) Early phase of contrast enhanced Magnetic Resonance Imaging (MRI) showing a single hepatocellular carcinoma of 2.8cm (arrow) in the segment 6 of the liver in a 74 year old male. **B**) Computed tomography (CT) scan of the same patient showing Radiofrequency Frequency Ablation (RFA) probe within the lesion (arrows). **C**) CT scan immediately following RFA showing the lesion with low density (arrow). **D**) Early phase contrast enhanced MRI showing minimal contrast enhancement in the lesion after RFA treatment.

This form of tissue heating significantly differs from that produced by RFA. RFA creates heat immediately adjacent to the electrode when electrical current passes through the tissue. For this reason, RFA notoriously gives a suboptimal zone of necrosis in certain types of tissue where there is high baseline impedance, such as bone and lung.[182–184] Microwave ablation, in comparison, readily ablates tissue regardless of impedance or low electrical conductivity.

There are some limitations with microwave ablation. There is significant shaft heating caused by reflective power; as a result, the shaft of the antennas are equipped with a cooling system, which makes them much larger in diameter compared to RFA probes. The only FDA-approved microwave system (Valley Lab/Covidien®, Boulder, Colorado) has a 13-gauge shaft. Newer products with much smaller shafts are currently being used in Japan. In addition, there is a relative paucity of clinical data with microwave ablation compared to RFA.

Current evidence for the treatment of HCC

Far fewer trials exist with microwave ablation for HCC than with RFA. Three published studies have long-term survival data from microwave ablation.[179,185,186] In a study by Dong et al.[185], most patients were Child A/B, with a mean tumor size of 4.1 cm. Three and five-year survival rates were 66% and 57% respectively, with a local recurrence rate of 7%. Liang et al.[186] had very similar results; mean tumor size was 3.8 cm, and three- and five-year survival rates were 72% and 51%, with a local recurrence rate of 6%. It should be noted, however, that these results were from older microwave probes, and newer probes should yield better results.

CRYOABLATION

Cryoablation, as the name suggests, causes cell death by freezing tissue. This technique was first described by Dr. James Arnott in the 19th century, who used cryoablation for treatment of breast, cervical, and skin cancers.[187] More recently, cryotherapy has been used for therapy of liver, lung, kidney, prostate, and breast malignancies.[188]

Cryoablation freezes tissue by rapidly cooling and removing heat from adjacent tumor tissue by conduction. The probes are rapidly cooled by utilizing the Joule-Thompson effect, which states that a gas will rapidly cool if allowed to expand rapidly (provided other parameters are held constant). Argon is the gas responsible for cooling in the cryoprobe system. When the cryoprobe is activated (within the tumor), the argon is forced through a narrowing and then allowed to expand rapidly. This causes sudden cooling, which is transferred to the walls of the cryoprobe and ultimately into the tissue.

Cryotherapy is effective in causing cellular damage and necrosis by indirect and direct means. It changes the osmolarity of the cells and also disrupts cellular membranes through the formation of extra and intra-cellular ice formation. It also induces delayed apoptosis by cold-induced vascular injury.[189–191]

One of the main advantages of cryotherapy over other forms of thermal ablation is the ability to identify the treatment zone in real time. During the transition between liquid and solid, an ice ball forms in the treated area. This can be easily seen on CT scan or ultrasound. In addition, cryotherapy typically tends to be less painful compared to other thermoablation because of the anesthetic effect of the ice. Further, in renal cell carcinoma, there tend to be fewer complications with cryotherapy compared to RFA.[192] Similar results have not yet been seen in hepatic ablation.

One of the most important disadvantages of cryotherapy as compared to other ablations is a syndrome called "cryoshock". This can involve hypotension, respiratory compromise, multi-organ failure, and disseminated intravascular congestion (DIC). It is typically seen after treating large liver tumors and is likely a consequence of the release of inflammatory cytokines.[193,194] Another significant potential complication from cryotherapy is ice ball/parenchyma fracture during probe manipulation.[195] This is a consequence of treated tissues being more brittle compared to untreated tissues.

FUTURE TECHNIQUES

Three emerging ablation technologies are currently in pre-clinical and/or phase I studies: laser-interstitial thermotherapy (LITT), high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE).

Laser interstitial thermotherapy (LITT) involves inserting a probe that contains high-intensity laser fibers into a tumor, which subsequently heats up the tumor. In some small series, there have been good results for small hepatocellular carcinoma and liver metastases.[196–198] Some trials have shown success with combined TACE and LITT for large hepatocellular carcinoma. In a study by Pacella et al.[199], LITT was performed before TACE in 30 large HCCs (3.5-9.6 cm in diameter). Complete response was achieved in 27 out of 30 patients (90%). These trials are mainly from Europe; one of the reasons this technology has not expanded is because the current devices are quite cumbersome.

High-frequency ultrasound ablation is an especially attractive mode of therapy because it is completely non-invasive. By focusing ultrasound beams, HIFU can cause coagulative necrosis at a precise location. This technology was applied to the treatment of large HCCs by Wu et al.[200] In a recent article by Zhang et al.[201], 39 patients with HCCs ranging from 1.5 to 22 cm were treated with HIFU. Forty-two total lesions were treated, and 21 were completely ablated after one-treatment sessions. The rest of the lesions were ablated by more than 50% of lesion volume. There were

no direct complications of the procedure. Although in its infancy, these results show that HIFU is a promising therapy for the treatment of hepatocellular carcinoma.

Irreversible electroporation (IRE) is an experimental ablation technique that utilizes the potential differences across cell membranes. The application of an electric field across the membrane has been shown to disrupt cell membranes and create small nanopores that allow molecules to pass in and out of cells.[202–205] If the voltage applied is high enough, these nanopores become permanent and can cause cell death. In animal models, this ablation technique has shown great promise, as there is sparing of connective tissue and major blood vessels and complete ablation of targeted areas after five minutes of ablation.[206] In a pre-clinical model published recently by Lee et al.[207], 16 pigs underwent ultrasound-guided IRE of the liver. No complications were seen, and ablation was achieved in 6.9 minutes. There was no damage caused to the bile ducts or vessels within the treated areas. They concluded that IRE is a fast, safe, and potent ablative method.

COMPARISON OF RFA AND CHEMICAL ABLATION: CLINICAL RESULTS

In three comparison trials between RFA and PEI, the recurrence-free survival rates were superior in RFA compared to PEI. In a randomized controlled trial by Lencioni et al.[208], 102 patients with HCC with lesions less than 5 cm were randomized to RFA or PEI. One- and two-year recurrence-free survival rates were 98% and 96% for RFA, and 83% and 62% for PEI (P=0.02). In a similar study by Livraghi et al.[209], 86 patients were randomized to RFA or PEI. Complete necrosis rates were higher (90% vs. 80%) for RFA compared to PEI, and there were fewer treatment sessions for RFA compared to PEI (4.8 vs. 1.2 sessions, respectively). A randomized controlled trial comparing RFA, PEI, and PAI also showed similar results.[210] In this study, 187 patients were randomized to a RFA, PEI, or PAI group. The local recurrence rates, overall survival, and cancer-free survival rates were favorable for RFA over PAI or PEI.

The superiority of RFA versus PAI or PEI has been further validated by two recent meta-analyses.[211,212] In a meta-analysis by Germani et al.[211], eight studies were included for comparison. This analysis showed that PAI was not superior to PEI for survival and recurrence (P=0.18), but it did require fewer treatment sessions. RFA was superior to the other modalities in terms of survival (P=0.001), complete necrosis of tumor, and recurrence. In a meta-analysis by Bouza et al.[212], six studies were eligible for comparison. The survival rate at one, two, and three years was significantly longer with RFA compared to PEI. RFA also had significantly lower rates of local recurrence. However, the rate of adverse events was higher in the RFA group compared to the chemical ablation group.

COMPARISON OF RFA AND MICROWAVE ABLATION: CLINICAL RESULTS

There is limited data comparing these two ablation methods. The only randomized controlled trial to date was performed by Shibata et al. in 2002.[177] In this study, 72 patients were randomly assigned to either RFA or microwave ablation. Although survival data was not obtained for this study, the total number of ablations needed per nodule was lower for the RFA group (P<0.001). Otherwise, the two therapies had equivalent therapeutic effects, complication rates, and rates of residual foci of untreated disease.

Another study comparing the two therapies was performed by Ohmoto et al.[213] In this unmatched study, 34 patients were assigned to RFA and 49 patients were assigned to microwave therapy. The results of the study were markedly in favor of RFA: fewer treatment sessions necessary (P<0.001), smaller necrotic area (P<0.001), lower local recurrence rate (P=0.031), lower pain/complication rate, and a higher survival rate (P=0.018).

A similar retrospective unmatched study was performed by Lu et al.[214], in which 49 patients underwent microwave therapy and 53 patients had RFA. Results showed no difference in major complication rates (8.2% vs. 5.7%, P=0.71) or cumulate survival rates (four-year survival 36.8% vs. 24.2% respectively, P=0.12).

Given these conflicting results, a prospective randomized controlled study is necessary to further delineate the differences between these two therapies.

PERCUTANEOUS ABLATION VERSUS SURGICAL RESECTION

There have been two published randomized controlled trials comparing the accepted standard therapy (surgical resection) and percutaneous RFA.[156,215]

In a study by Chen et al.[156], 180 patients with solitary ≤5 cm HCCs were randomized to either surgery or percutaneous ablation. Complications after surgery were more frequent and more severe after surgery compared to percutaneous ablation. The one-, two-, three-, and four-year overall survival rates were 95.8%, 82.1%, 71.4%, and 67.9% for ablation and 93.3%, 82.3%, 73.4%, and 64.0% for surgery. There was no statistically significant difference between the two groups.

In a study by Lu et al.[215], 105 patients were randomized into surgical resection or percutaneous ablation (microwave or RFA) groups. As with the previous study, the percutaneous ablation group required less treatment time, had less necessity for blood transfusion, and had briefer hospital stays. The 1-, 2-, 3-year overall survival rates for the surgery group were 91.3%, 86.4%, and 86.4%, and were 93.5%, 87.1%, and 87.1% for the ablation group.

A recent meta-analysis concluded that surgical resection is more effective than percutaneous RFA.[216] This meta-analysis included one randomized controlled trial and nine non-randomized controlled trials, with a total of 1,411 patients: 744 treated with RFA and 667 treated with resection. The three- and five-year overall survival rates were greater for the patients who received surgical resection compared to percutaneous RFA. In addition, the intrahepatic recurrence rate was higher for the RFA group compared to the surgical group. This meta-analysis was limited, however, by the low level of evidence (only one randomized controlled trial and nine non-randomized controlled trials). Clearly, there is a need for more data to help elucidate the role of RFA compared to surgery in the case of small HCCs.

SUGGESTED READING

Abulkhir, A. *et al.* Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann. Surg.* **247**, 49–57 (2008).

This was a meta-analysis performed in 2008. A total of 37 publications met the criteria for analysis, and a total of 1,088 patients were included. The overall morbidity rate (0% mortality rate) was 2.2%. Four weeks after PVE, 85% underwent the planned resection. Fifteen percent of the patients (158) were not resected for the following reasons: inadequate hypertrophy of the remnant liver (n=18), progression of liver metastases (n=43), extrahepatic spread (n=35), refusal (n=1), poor general health (n=1), change of treatment to chemotherapy (n=24), complete disease remission (n=1), and incomplete scanning (n=8). Two different techniques were used for PVE: percutaneous and transileocolic (in the operating room). There was a significantly higher amount of hypertrophy in the percutaneous group versus the transileocolic group (P=0.00001). In terms of complications, the two most common minor complications were abdominal discomfort (n=209) and fever (n=250). Major complications were rare; they included liver abscess (n=3), cholangitis (n=2), portal vein thrombosis (n=2), subcapsular hematoma (n=2), portal hypertension (n=1), and septic necrosis (n=1).

Llovet, J. M. *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* **359**, 1734–1739 (2002).

This was a prospective randomized controlled trial that included patients with hepatocellular carcinoma that were unresectable. They were either Child-Pugh class A or B and Okuda stage I or II. Patients were randomly assigned to three groups: repeated arterial embolization, chemoembolization, and conservative treatment. A total of 903 patients were assessed, and 112 were included in the study. The trial was stopped when chemoembolization repeatedly showed a survival benefit as compared to conservative management. One- and two-year survival across the three groups were as follows: 75% and 50% for embolization, 82% and 63% for chemoembolization, and 63 and 27% for the control group (chemembolization vs. control, P=0.009). Treatment allocation was the only variable independently related to survival (odds ratio 0.45, P=0.02). This was one of the landmark trials that established chemoembolization as the treatment of choice for unresectable hepatocellular carcinoma.

Lammer, J. *et al.* Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc. Interv. Radiol.* **33**, 41–52 (2010).

This was a prospective randomized study comparing conventional TACE (doxorubicin – lopiodol followed by gelfoam) and drug eluting beads (DC Bead). Two hundred twelve patients were randomized to both groups. They were randomized based on Child-Pugh status, performance status, disease burden, and prior treatment. The primary endpoint was MRI (EASL) response after six months. There was a trend to improved complete response, objective response, and disease control with drug eluting beads as compared to conventional TACE, but these statistics were not significant. However, in more sick patients (Child-Pugh B, ECOG 1, recurrent disease), DC beads showed an increase in objective response (P=0.038) compared to TACE. In addition, DC beads showed better side effect profile as compared to TACE (significantly less liver toxicity, doxorubicin-related side-effects). Although these results appear promising for the continued use of DC beads, there needs to be survival data comparing both treatments before the standard of care changes.

Chen, M. S. *et al.* A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann. Surg.* **243**, 321–328 (2006).

This was a prospective randomized trial comparing hepatectomy and local ablation for solitary HCC less than 5 cm. 180 patients were randomized to one of two groups, radio-frequency ablation and surgery. The one-, two-, three-, and four-year survival rates after ablative therapy were 95.8%, 82.1%, 71.4%, and 67.9%, while after surgery they were 93.3%, 82.3%, 73.4%, and 64.0%, respectively. These were not significant. In addition, there was one mortality (1.1%) in the surgical resection group as a consequence of the procedure, while there was no procedure-related mortality in the RFA group.

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INVITED COMMENTS

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We have no criticism to offer on the excellent work presented by N Baghat and JF Geschwind, only additional information to give:

Concerning Portal Vein Embolization (PVE)

Technical aspects

Right PVE performed by interventional radiology is more efficient than surgical right portal vein ligation to induce hypertrophy of the future remnant liver (FRL) (see **Figure 3**). Several teams perform the right portal vein ligation when resecting the primary tumor in the context of liver metastasis. A problem of this approach is the secondary opening of intraparenchymatous shunts resulting in repermeation of the distal branches of the right portal vein and a relative failure of the contra-lateral hypertrophy. Sealing off the arborescence of the portal tree with glue prevents this phenomenon. Several studies have confirmed that radiological PVE was more efficient than surgical portal ligation in terms of hypertrophy of the FRL.[1–6]

Techniques other than embolization of the right portal vein branch (associated or not with embolization of segment 4 branches)[7] are possible but less frequent. Indeed, they are useful, for example, in cases when hypertrophy of segments 6 and 7 is required. In this situation, embolization of the left portal vein plus of the portal branches to segments 5 and 8 is performed. Similarly, to selectively hypertrophy segments 5, 8 and 1, the portal branches to all other segments are embolized.[8]

Quantitative and qualitative assessment of the liver

The goal of elective PVE is to increase the FRL, and it is measured by a quantitative (volumetric) assessment of the FRL. However, it is important to emphasize, as well done by the authors, that a qualitative assessment of the liver function is also required. A high volume of poor functional parenchyma will result in postoperative liver failure. Besides the traditional chronic liver diseases (mainly chronic viral hepatitis and cirrhosis), liver function impairment can result from chemotherapy. Chemotherapy associated liver injury (CALI) has been more frequent due to the more numerous lines of chemotherapy used and their longer duration. Sinusoidal obstruction syndrome (SOS) associated with oxaliplatin, and steatohepatitis associated with irinotecan, have become more frequent. One simple tool to improve the functional assessment of liver parenchyma is the measure of indocyanine green (ICG) clearance, the normal value being less than 11% of retention after 15 minutes.

We extensively use intra-arterial chemotherapy with oxaliplatin [9,10] because of the high rate of response associate to this method, consequently we frequently observed a progressive increase of ICG retention, reaching values higher than 40% at the 15th minute. Unresectable patients that become resectable under intra-arterial chemotherapy are usually initially non-operable due to the risk of liver failure. Two to four months after stopping intra-arterial chemotherapy ICG clearance tends to return to normal values and resection become possible.

In fact, there is a similar phenomenon with PE. If it is performed on a damaged liver (cirrhotic or with SOS), failure of hypertrophy of the FRL is frequent. This failure is associated with an impaired ICG clearance test. A high value of ICG retention (greater than 20%) should be considered a transitory contra-indication to perform a PE, since parenchymal hypertrophy is impaired. In this case, chemotherapy should be stopped and PE postponed until ICG clearance normalized.

Another point that should be underlined is that hypertrophy following EP continues with time, and over a long period.[11,12]

Concerning radiofrequency ablations (RFA)

Authors have given the essential of information concerning RFA.

Some points can be underlined:

First. Despite destruction of a tumor is efficient when its diameter is lower than 30 mm, the rate of recurrence is more than 33% when its diameter is higher. So, we use the following approach for RFA: "green light" for lesions of less 25 mm, "yellow light" for lesions between 25 and 30 mm, and "red light" for those with more than 30 mm in diameter.

Second. Intraoperative use of RFA in complement to hepatectomy is very useful, since resection of multiple bilateral metastases has become frequent. In such cases it advisable, despite time-consuming, to assess preoperatively the volume of the liver to be resected and also the volume of the liver metastases that will be destroyed with RFA (plus a security margin of 5 mm), in order to precisely predict the FRL.

Third. RFA cannot be used close to a main biliary branch because it induces necrosis and further stenosis, due to the heating effect. This complication can be prevented by cooling the biliary branch with cool saline irrigation through a catheter inserted in the common bile duct.[13]

Fourth. When a liver metastasis or a part of a liver metastasis is situated on the "ideal" plane of transection, it is possible firstly ablate the lesion (or the area on the transection plane) with radiofrequency, and after perform the transection passing through the treated area. This is called trans-RFA hepatectomy.[14] This approach is also useful when the future margins risk being involved. In this case the area of the future margin is treated with RFA before transection.

Concerning potential future techniques

The development of **stereotaxic radiotherapy** allows for more radiation in a more precise volume than classical radiotherapy.

It may be useful to treat patients with poor general status and that are not candidate to surgery. Also, it could be useful to treat lesions that are neither resectable with surgery nor treatable with RFA. For example, the liver metastases located on the upper part of the liver, between two hepatic veins that must be preserved, and with other concomitant liver metastases that are resectable. In this situation, stereotaxic radiotherapy could be used to treat the problematic lesion, and the others would be resected. The preliminary data seems to indicate that a curative treatment of the liver metastases can be obtained in 40-60% of cases, but in less than 20% for the treatment of hepatocellular carcinoma. Similarly to the impact of the volume on RFA results, large lesions result in poorer outcomes.

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8 Anesthesia and Pain Control in Liver Surgery

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- *Anesthetic management plays a key role in the reduction of perioperative causes of mortality in liver surgery, such as bleeding and liver failure.*
- *Intraoperative reduction of the hepatic blood flow can result from changes in blood volume status and also from mechanical or pharmacological effects, and can lead to liver dysfunction.*
- *Central venous pressure lower than 5mmHg reduces blood loss during hepatic parenchymal transection.*
- *Inhalational anesthetics such as sevoflurane, desflurane, and isoflurane can maintain or even increase total hepatic blood flow; meanwhile, intravenous anesthetics have a modest impact on that.*
- *Intraoperative fluid management should not be guided exclusively by central venous pressure, and the use of colloids (such as 5% albumin) as a maintenance and replacement solution reduces extravascular translocation of fluids.*
- *Pharmacological preconditioning, mainly with the use of inhaled anesthetics, has been used to prevent ischemia-reperfusion syndrome, although its pathophysiology is not entirely understood.*

INTRODUCTION

Improvements in surgical techniques (including new technology and better understanding of anatomy, among other factors) have reduced surgical risk in hepatic resections, and the limits for liver resections have been extended.[1–6] Despite the marked reduction in the risk of blood loss and hemodynamic changes during hepatectomy, the main causes of perioperative death are bleeding and liver failure. Anesthetic care plays an important role in the reduction of perioperative morbidity and mortality.

Intraoperative blood loss is still a threatening complication during liver resection, despite the terrific reduction of this problem over the last few decades. Methods to minimize intraoperative bleeding depend on surgical techniques, and largely anesthetic management. Besides vascular clamping techniques, acute normovolemic hemodilution and low central venous pressure anesthesia have been considered crucial concerns for major hepatectomies and involve anesthetic tools. Additionally, air embolism diagnosis depends on the anesthesiologist's attention. Moreover, surgical and anesthesiological teams should act together to avoid (or minimize) the consequences of ischemia-reperfusion syndrome. Hemodynamic changes during major liver resections are not uncommon and depend on a variety of conditions such as blood loss, vascular clamping or compression, and pharmacological effects of anesthetic drugs, among others.

Thus, hepatic surgery has developed in an associative cooperation between surgical and anesthesiological teams. Surgical and anesthetic strategies should be planned together. This chapter provides an introduction to the main topics related to anesthetic approach to liver surgery.

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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HEPATIC BLOOD FLOW AND FUNCTIONS

The liver of an adult weighs roughly 1,500 to 1,700 grams, and receives approximately 25% of cardiac output (approximately 800 to 1,200 mL/min). Hepatic blood inflow occurs by the portal vein (75%) and the hepatic artery (25%). The arterial system is high pressure and high resistance (mean pressure similar to the aorta), while the portal vein system is low pressure and low resistance (mean pressure between 5 and 12 mmHg). The arterial blood delivers 40-50% of the total hepatic oxygen supply, and the portal vein 50-60% of that. The arterial flow experiences variations according to alterations in the portal flow (the called hepatic arterial buffer response), but the inverse does not occur (i.e., modifications in the arterial flow do not result in compensatory portal flow changes).[7,8] Temporary occlusion of the portal vein may increase arterial flow by about 30%.[7] Indeed, the increase in hepatic arterial blood flow is capable of buffering 25-60% of the decreased portal flow.[9,10] Extended liver resections induce a significant increase in the portal flow of the remnant liver (portal flow can double after resection of 60% of the liver) due to the incapacity of auto-regulation of the portal flow.[11,12] This change can result in arterial spasm (with consequences from mild cholestasis to liver failure) and portal hyperperfusion injury (represented by the so-called "small-for-size" syndrome).[13–16] Similar effects occur in the context of living liver donor transplantation with a small graft.[17,18] High portal pressure building up in the context of portal hyperperfusion shuts down the flow through the hepatic arterioles and the liver becomes de-arterialized, worsening the consequences of small-for-size syndrome.[19] Splenic artery ligation (or embolization) or portocaval (or mesocaval) shunts may lead to reduction of the portal flow, and they have been suggested as a means of minimizing the impact of small-for-size syndrome.[11,20] Pharmacological interventions to enhance hepatic arterial flow have also been tested, and include hepatic arterial infusion of adenosine, or portal vein infusion of prostaglandin E or proteolytic enzyme inhibitors.[21–23]

The liver plays a substantial role as blood volume reservoir. The liver holds approximately 500 ml of blood, or 10-15% of the total blood volume.[24] Part of this volume can be expelled following a sympathetic stimulation (by central nervous system control of the hepatic blood flow by way of the thoracic sympathetic fibers), providing additional circulatory blood if needed.

The liver is responsible for complex functions in biosynthesis, metabolism, and clearance. Important functions of the liver include synthesis of proteins involved in clotting (such as production of factors II, V, VII, IX, X, and XII), oxygen transport and immune system function, glucose homeostasis, fatty acid β-oxidation, production and excretion of bilirubin, and excretion of drugs.

Intraoperative reduction of the hepatic blood flow during a hepatectomy can result not only from changes in blood volume status, but also from mechanical or pharmacological effects, such as the use of volatile anesthetic agents (such as sevoflurane and desflurane), mechanical ventilation, positive end-expiratory pressure, hypercarbia, and vascular clamping or compression during liver mobilization. Reduction of the hepatic blood flow should be avoided, since it can result in parenchymal necrosis and liver dysfunction.

In liver disease, drug metabolism and clearance depend on the volume of distribution, liver blood flow, and hepatic microsomal activity (P450 cytochrome system). Thus, different liver disease states are related to diverse changes in drug biotransformation. Drugs frequently used in anesthetic practice (such as opioids, lidocaine, benzodiazepines, non-depolarizing muscle relaxants, and thiopental) have their half-lives increased and/or experience a cumulative effect. Monitoring of drug effects and/or titrating the drug should be considered during anesthesia of patients with liver disease.

Hemostatic changes in patients with liver disease are associated with reduction in the production of all coagulation factors (except factor VIII, produced by the endothelium), thrombocytopenia (secondary to splenomegaly due to portal hypertension), and platelet dysfunction, as well as abnormalities of fibrinogen, among other alterations. These changes lead to an increased risk of perioperative bleeding. Coagulopathy is more severe in more advanced liver disease. A prolonged International Normalized Ratio (INR), reduced levels of factors V and VII, and low counts of platelets are common findings in acute liver failure. On the other hand, a state of hypercoagulability can occur, especially in patients with cholestatic liver disease, due to an elevation of von Willenbrand Factor (vWF) and heparin cofactor II, and a decreasing of vWF cleaving protease (ADAMTS-13), plasminogen, and some anticoagulants such as protein C and S and α2 macroglobulin.

CHRONIC LIVER DISEASES

Chronic liver diseases include viral hepatitis (B and C), autoimmune hepatitis, non-alcoholic steatohepatitis (NASH), cirrhosis from any etiology, metabolic diseases (such as hemochromatosis and Wilson's disease), and cholestatic diseases (including primary biliary cirrhosis and primary sclerosing cholangitis). Patients undergoing chemotherapy can present sinusoidal injury (with oxaliplatin-based chemotherapy) and peliosis (with irinotecan-based chemotherapy). The main systemic effects of end-stage liver diseases are shown in **Table 1**.[25]

Cirrhosis may result in portal hypertension, ascites, and hepatocellular insufficiency. Portal hypertension (PH) starts

with splanchnic vasodilation (due to nitric oxide increase – shear stress), reduction of the peripheral vascular resistance and of the mean arterial pressure, and increase in the plasmatic volume, splanchnic blood flow, and cardiac output (these findings determinate the hyperdynamic status seen in cirrhotic patients).[26] PH is responsible for splenomegaly (and hypersplenism), thrombocytopenia, ascites, and esophageal varices. These findings usually occur when portal pressure is more than 20 mmHg (normal portal pressure is 5-12 mmHg). Ascites results from multiple factors, including decreased production of albumin, portal hypertension, and renal retention of sodium and water. Secondary hyperaldosteronism may manifest as hypokalemic metabolic alkalosis. Inadequate synthesis of coagulation factors produces coagulopathy. Hypersplenism worsens thrombocytopenia due to bone marrow suppression. Encephalopathy involves the activation of GABA receptors.

Cirrhotic patients usually have a hyperdynamic circulation due to a decreasing of systemic vascular resistance (SVR) and a compensatory increasing of cardiac output to maintain an adequate tissue perfusion. Other alterations may also include cirrhotic cardiomyopathy and pulmonary vascular abnormalities.[26]

Hepatorenal syndrome, hepatopulmonary syndrome, portopulmonary hypertension, and encephalopathy are conditions associated with severe cirrhosis. They are classically considered contraindications for partial liver resection, but can be present in recipients of liver transplantation (see below the topic of anesthesia in liver transplantation).

Hepatorenal syndrome (incidence of 20% in cirrhotic patients with ascites) occurs due to an unbalance among vasoconstrictor mechanisms (such as renin-angiotensin, antidiuretic hormone, and endothelin) and vasodilator mechanisms (such as prostaglandins and nitric oxide), resulting in chronic renal vasoconstriction and function deterioration. Diagnostic criteria include the association of liver failure and renal failure without other possible causes of renal failure (such as shock, sepsis, and diuretics, among others) and persistence of renal failure after correction of hypovolemia. The definitive treatment is liver transplantation.[27–29]

Hepatopulmonary syndrome (incidence of 4-17% in cirrhotic patients) is characterized by a clinical triad consisting of: i) hepatic disease and/or portal hypertension, ii) intrapulmonary vascular dilatations, and iii) abnormal arterial oxygenation (partial oxygen pressure <70 mmHg or an alveolar-arterial oxygen gradient >20 mmHg). The alveolar-arterial oxygen gradient seems to be the best parameter to assess abnormalities of arterial oxygenation. Liver transplantation is the main therapeutic option, with encouraging results.[30–33]

Portopulmonary hypertension (incidence of 5-10% among Child C cirrhotic patients) is defined by the association of cirrhosis, increased pulmonary arterial pressure and pulmonary vascular resistance. Most patients are asymptomatic and clinical manifestations of right cardiac failure appear during the evolution of the disease. Contrary to hepatopulmonary syndrome, liver transplantation does not cure portopulmonary hypertension. In fact, severe arterial pulmonary hypertension (present in portopulmonary hypertension) can represent a contraindication to liver transplantation because

Table 1. Main effects of chronic hepatic diseases.

System	Clinical manifestation	Causes
Cardiovascular	▪ Hyperdynamic circulation ▪ Portopulmonary hypertension	▪ High cardiac output (and cardiac index) ▪ Low systemic vascular resistance ▪ Arteriolar vasodilatation ▪ Cirrhotic cardiomyopathy ▪ Autonomic neuropathy
Respiratory	▪ Hypoxia	▪ Restrictive pattern (ascites) ▪ Pleural effusion ▪ Hepatopulmonary syndrome ▪ Portopulmonary hypertension
Hematologic	▪ Coagulopathy ▪ Anemia	▪ Defective synthesis of factors II, V, VII and X ▪ Thrombocytopenia (hypersplenism and/or marrow depression) ▪ Platelet dysfunction ▪ Disseminated intravascular coagulation and/or hyperfibrinolysis
Renal system, electrolyte and metabolic disorders	▪ Renal failure ▪ Hyponatremia ▪ Hypomagnesemia ▪ Hyperkalemia ▪ Hypokalemia, and/or metabolic acidosis and hypoglycemia	▪ Hepatorenal syndrome ▪ Acute tubular necrosis from sepsis ▪ Renal impairment drug (Tacrolimus/cyclosporine) related

of the poor prognosis.[30,34–36]

Encephalopathy can result from the effect of neurotoxic substances (such as ammonia) in the setting of acute liver failure (type I), portosystemic shunts (type II), or cirrhosis (type III).[37,38] Overt encephalopathy occurs in 30-45% of cirrhotic patients and the primary treatment is liver transplantation.[39]

PREOPERATIVE ASSESSMENT

Patients with no underlying liver disease tolerate resection of up to 75% of hepatic parenchyma with low rates of postoperative liver failure and mortality. Otherwise healthy patients submitted to no complex hepatectomy are assessed following routine preoperative protocols. However, patients presenting for extensive liver resection and/or those with significant comorbidities need additional assessment. Mainly hemodynamic, respiratory, and hepatic functional status should be evaluated. Patients with known cardiac diseases and those undergoing extensive hepatectomies or with predictable need for hepatic vascular exclusion or major vascular clamping should have additional cardiac tests. Stress echocardiography evaluates the contractile cardiac reserve, blood flow through the cardiac chambers and the pulmonary circulation, guiding the anesthetic management and even surgical strategy. Inadequate respiratory function should be suspected if a low saturation is measured on pulse oximetry, which provides an estimate of arterial pO_2 and could guide additional respiratory tests and perioperative adjustments. Routine liver function tests in patients with no risk factors for chronic liver disease preclude additional tests for most liver resections. Asymptomatic elevations in preoperative serum transaminase levels up to two times normal values have a minimal impact on perioperative outcomes. However, patients with acute hepatitis should not undergo elective liver resection. Obstructive jaundice is also a risk factor for morbidity and mortality. Global mortality rates for hepatectomy in patients with no underlying liver disease are less than 2-3%. Mortality rates can reach 6% for major hepatectomy and up to 15% for liver resections for hilar cholangiocarcinoma.[40] Postoperative morbidity has reached up to 40% in large series of hepatectomies. Most frequent postoperative complications include respiratory complications (such as atelectasis, pleural effusion, and pulmonary infection), biliary complications (mainly leakage), bleeding, ascites, and liver failure, among others. Many predictors of postoperative complications have been identified, including preoperative American Society of Anesthesiologists (ASA) classification, presence of steatosis, extent of liver resection, simultaneous extrahepatic resection, and perioperative blood loss and transfusion.[1,40]

Patients with underlying chronic liver disease, especially cirrhosis, are at increased risk for morbidity and mortality and need specific preoperative anesthetic assessment. As cited above, general anesthesia reduces cardiac output, induces splanchnic vasodilatation, and causes a reduction in hepatic blood flow. Thus, cirrhosis represents an additional risk, especially in hepatic surgery. Anesthesia in patients with end-stage liver disease should be designed to maximize hepatic perfusion and hepatic oxygen delivery, and to prevent and treat the cirrhosis associated complications, such as coagulopathy, portal hypertension, and encephalopathy.

The severity of hepatic dysfunction can be evaluated by a variety of methods, such as Child-Pugh score (**Table 2**) and the Model for End-Stage Liver Disease (MELD) score (**Figure 1**), both scoring systems that have been reliably correlated with postoperative mortality rate in cirrhotic patients undergoing liver surgery. Other criteria, such as portal hypertension, have been evaluated as risk predictors in cirrhotic patients. This issue is also discussed in **Chapter 5** (Liver Function Assessment Before and After Hepatic Resection) and **Chapter 6** (Surgical Approach to Patients with Cirrhosis). Cirrhosis may result in specific organ dysfunction, such as respiratory, renal, or circulatory dysfunction. Arterial blood-gas measurements and Doppler echocardiography are useful to recognize pulmonary hypertension. Abnormal preoperative serum creatinine concentration demands additional renal function studies.

Child-Pugh score (**Table 2**), initially designed to stratify

Table 2. Child-Pugh score.

Parameter	score		
	1	2	3
Ascites	None	Mild	Moderate or severe
Encephalopathy (grade)	None	1-2	3-4
Bilirubin (µmol/L)	<35	35-50	>50
INR	<1.8	1.8-2.3	>2.3
Albumin (g/L)	>35	28-35	<35

The sum of the five scores is used to assign a "Child-Pugh grade" of A (5-6 points), B (7-9 points) or C (10-15 points). INR: International Normalized Ratio.

risk of surgical treatment of portal hypertension, is classically used as a predictor of mortality after abdominal surgery in cirrhotic patients. A study before the development of laparoscopic surgery demonstrated an increase in mortality rates after abdominal surgery, from 10% in Child A to 31% in Child B, to 76% in Child C cirrhosis.[41] The Child-Pugh score has also been demonstrated to be a useful tool to stratify operative risk in liver resections in cirrhotic patients. Extent of hepatic resection in a cirrhotic patient is generally delimited by Child-Pugh classification: Child A patients may tolerate resections of up to 60% of hepatic parenchyma (such as a right hepatectomy), Child B patients tolerate only segmentectomies, and Child C patients tolerate only tumor enucleation.

The MELD score is calculated based upon serum creatinine, total bilirubin, and prothrombin time levels (**Figure 1**). It was originally designed to estimate long-term survival in cirrhosis. In patients with cirrhosis, the preoperative MELD score has been identified as a risk factor for morbidity and mortality after liver resection. Delis et al.[42] reported a nil mortality rate in patients with MELD ≤9 versus a 15.3% mortality for MELD >9 (P<0.001). Another recent study in cirrhotic patients stratified the risk of irreversible postoperative liver failure according to MELD score (MELD scores <9, 9-10, and >10 were associated with 0.4%, 3.8%, and 20.3% irreversible postoperative liver failure, respectively). Additionally, preoperative serum sodium level ≥140 mEq/L identified low-risk patients.[43] On the other hand, Schroeder et al.[44] found that Child-Turcott-Pugh (CTP) score and physical scores of the American Society of Anesthesiologists (ASA) were superior to MELD in predicting outcomes after elective liver resections. MELD score seems to be an accurate predictor of early outcomes after hepatectomy in cirrhotic patients, but not in patients without cirrhosis.[45,46]

Another sign of chronic liver disease, the presence of portal hypertension, was once considered a contraindication for liver resection. However, recent studies suggest that in Child A patients, the presence of portal hypertension does not increase the risk of mortality, but does increase the risk of morbidity.[47] In comparing patients with same MELD score, the presence of portal hypertension showed no effect on the mortality, in a retrospective study.[48] A recent study in patients with Child A cirrhosis demonstrated that severe clinically significant portal hypertension (and also a preoperative neutrophil:lymphocyte ratio (NLR) ≥2.8) was an independent risk factor for liver failure after hepatic resection.[49]

Acute hepatitis and other manifestations of end-stage liver disease, such as encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome, and portopulmonary hypertension, are also well-established contraindications for partial hepatectomy. They should be treated accordingly, if possible, before hepatectomy, but in most cases the definitive treatment is liver transplantation.

MELD SCORE

3.78 x $\log_e$ **serum bilirubin** (mg/dL) +
11.2 x $\log_e$ **INR** +
9.57 x $\log_e$ **serum creatinine** (mg/dL) +
6.43

NOTES:
- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than 1 is given a value of 1

Figure 1. Formula to calculate MELD (Model for End-Stage Liver Disease).

LOW CENTRAL VENOUS PRESSURE (CVP)

Many studies have demonstrated that a low CVP (below 5 mmHg) reduces blood loss during hepatic parenchymal transection,[50–52] and the anesthesiologist team plays a crucial role. The intravenous fluids administration (pre- and intraoperatively until the end of hepatic resection and hemostasis) should be limited to keep systolic blood pressure over 90 mmHg and a diuresis of at least 0.5 mL/kg/h.[53–55] Active dehydration can be obtained with diuretics such as furosemide or manitol. Vasoactive agents, such as intravenous nitroglycerin, and intravenous morphine are also used to reduces CVP in case of fluid restriction is ineffective.[56] Intravenous fluid administration (using crystalloid or colloid) is used to increase the intravascular volume and CVP just after the parenchymal cross section.

Despite its clear benefits during liver resection, a low CVP carries some disadvantages that are inadequate organ perfusion, insufficient volume reserve in case of bleeding, and possible increased risk of air embolism. The latter increases in cases of resection of tumors close to major hepatic veins. It is worth noting that when a liver resection is performed using total vascular exclusion, a low CVP is not required. On the contrary, a volume expansion to a CVP of more than 14 mmHg is usually necessary for cross-clamping of the inferior vena cava while maintaining adequate circulation and blood pressure.[57]

Air embolism with clinical expression is very uncommon on hepatic surgery,[58] although intracardiac air bubbles are frequently identified during hepatic parenchymal transection when transesophageal echocardiography is used. Intraoperative signs of air embolism include: i) decrease in end-tidal carbon dioxide, and decrease in both arterial oxygen

saturation (SaO_2) and tension (PO_2), along with hypercapnia; ii) tachyarrhythmias; iii) electromechanical dissociation; iv) pulseless electrical activity; v) ST-T changes; and vi) sudden hypotension. Massive air embolism can result in death of the patient.

The consequences of air embolism can be minimized by placing the patient in a 15 degree Trendelenburg position and with the use of 1.0 fraction of inspired O_2 (FiO_2). Also, the use of hepatic vascular exclusion can be used in patients with high risk for air embolism.[59] The presence of a patent oval foramen (10% to 25% of patients) presents the risk of embolism into the systemic circulation with more severe consequences, such as cerebral or cardiac ischemia. Similar processes may occur in the presence of hepatopulmonary syndrome due to intrapulmonary shunts.

HEMODYNAMIC CHANGES

Some intraoperative events may compromise hemodynamics during elective liver resection, such as intraoperative bleeding, liver vessel occlusion, air embolism, and surgical liver mobilization.

The risk of intraoperative bleeding during liver resections has decreased over time. Recent series report a low percentage of – or even no – blood transfusion. Intraoperative bleeding is anticipated in situations such as repeat surgery, combined organ resection, large tumors, vascular reconstruction, and increased portal pressure. Patients with cirrhosis but no ascites, no hepatocellular insufficiency, no acute alcoholic hepatitis, and a normal coagulation have a prognosis similar to that of patients with no underlying chronic liver disease.[60–62]

During surgical liver mobilization it is possible that the inferior vena cava or portal vein may be compressed or twisted. This occurrence should be suspected when a combined reduction of the systemic arterial pressure and expired PCO_2 occurs. Surgeons should be advised of these findings to, if possible, replace the liver to the anatomical position.

Vascular clamping. Vascular clamping is largely used in major liver resections and is partially responsible for the reduction of intraoperative bleeding. The existence of numerous portosystemic anastomoses (between the splanchnic system and the superior and inferior vena cava system) explains the few variations in the splanchnic venous resistance and cardiac preload during portal clamping.

Vascular control techniques include inflow vascular clamping (total or selective, continuous or intermittent), and inflow plus outflow vascular clamping (total or selective vascular exclusion) (**Figure 2**).

Total inflow vascular occlusion (**Pringle maneuver**) reduces cardiac output by 10- 20%, due to a reduction in the venous return. The decrease in the preload is also responsible for reduced central venous pressure and backflow hepatic bleeding. On the other hand, the Pringle maneuver leads to increase of the systemic vascular resistance (by up to 40%) and mean arterial pressure (10-30%), due to a sympathetic activation by baroreceptors in the hepatic pedicle.[63,64] The blockage of the autonomic nervous plexus on the hepatic pedicle by lidocaine infiltration prevents the arterial pressure from increasing.[65] These hemodynamic changes quickly return to baseline values following unclamping.

A normal liver tolerates continuous ischemia by inflow occlusion for up to 60 minutes (30 minutes when cirrhosis is present). Reperfusion delivers mediators responsible for the ischemia-reperfusion injury. Intermittent pedicular clamping minimizes this syndrome and allows longer and yet undetermined cumulative periods of clamping.

Total Vascular Exclusion (TVE) of the liver results in important hemodynamic changes. Complete clamping

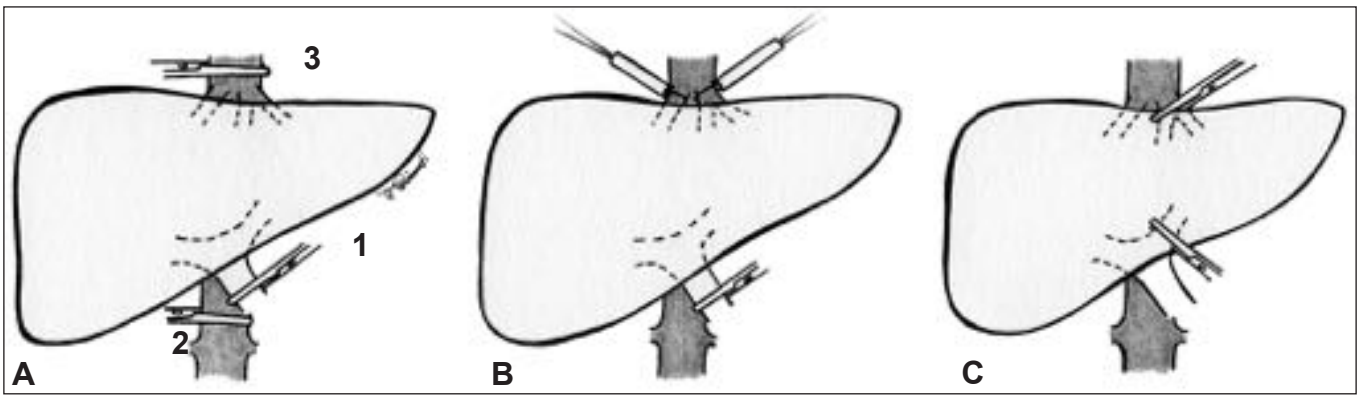


Figure 2. Schematic representation of vascular clamping techniques in liver surgery. **A**) Clamping of hepatic pedicle (1), infrahepatic vena cava (2), and suprahepatic vena cava (3) is used for classical total vascular exclusion of the liver. Clamping of only (1) represents Pringle Maneuver. Clamping of only (1) and (2) can be used to occlude inflow and reduce central venous pressure and backflow. **B**) Total vascular exclusion of the liver without vena cava occlusion. This technique demands ligature of all direct branches to retrohepatic vena cava. **C**) Unilateral vascular exclusion, allowing continuous inflow and outflow on the opposite side.

of the inferior vena cava and portal vein leads to a 40-60% reduction of venous return and cardiac output.[66,67] Despite a compensatory 80% increase in systemic vascular resistance and a 50% increase in heart rate, the cardiac index is reduced by half.[55,68,69] Intravenous fluids infusion can be used before hepatic TVE to prevent abrupt decrease in cardiac output. Colloids are preferred because they additionally improve splanchnic circulation and reduce bowel edema. Vasoactive drugs (vasopressin or norepinephrine) can be used if volume loading is inadequate to maintain acceptable blood pressure. If the mean arterial pressure and/or the cardiac debit decrease more than 50% even after three to five minutes of TVE, the TVE is interrupted. Hemodynamic intolerance, despite volemic load and vasoactive drugs, is observed in 5-20% of patients.[67,70] Venovenous bypass can be used in these cases (**Figures 3** and **4**). Declamping after TVE is generally well tolerated, with rapid normalization of hemodynamics parameters. Acute volemic overload with pulmonary edema can occur with declamping if large endovenous volumes are needed for an adequate tolerance to TVE of the liver.

Hepatic selective vascular exclusion, i.e., inflow and outflow occlusion of one hemiliver (or individual sectors) without caval clamping, has similar hemodynamic effects to the Pringle maneuver and it is well tolerated in most cases.

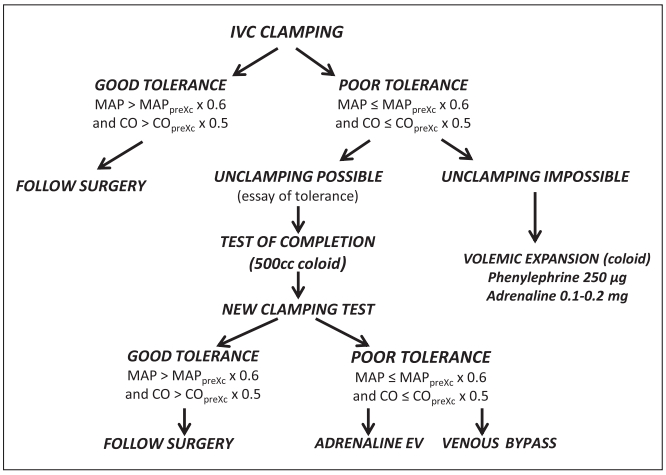


Figure 3. Approach according to hemodynamic tolerance of total vascular exclusion of the liver. IVC: inferior vena cava; MAP: mean arterial pressure; CO: cardiac output; preXc: before IVC clamping. (Adapted from Dilly et al.[69])

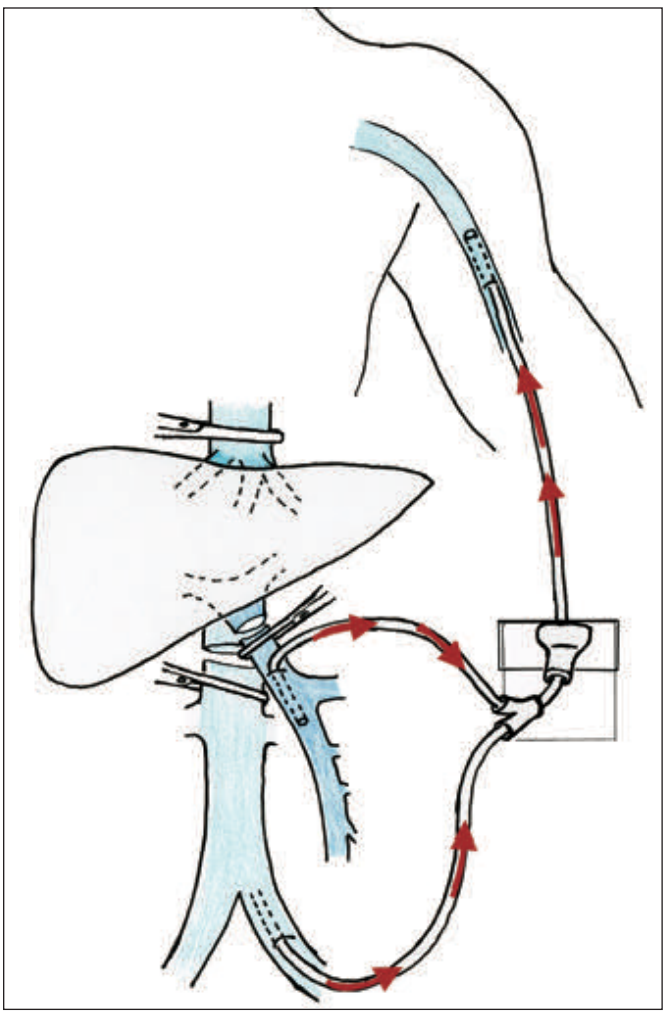


Figure 4. Schematic representation of venous bypass during total vascular exclusion of the liver. The blood from the inferior vena cava and portal vein is directed to superior vena cava.

HEPATIC BLOOD FLOW

Total hepatic blood flow tends to reduce during liver surgery (**Table 3**). During controlled ventilation, portal flow decreases because of an increase in splanchnic vascular resistance with hypocarbia. Positive end-expiratory pressure decreases blood flow, probably by increasing hepatic venous pressure and by a vasoconstrictive response in the preportal vasculature. Most inhalational anesthetics (such as halothane and enflurane) induce additional decrease of hepatic blood flow, but others (such as sevoflurane, desflurane and isoflurane) can maintain or even increase total hepatic blood flow.[71] Halothane induces the most profound reductions in hepatic blood flow and hepatic oxygen delivery.[71] Intravenous anesthetics have a modest impact on hepatic blood flow. Induction agents (such as etomidate and thiopental) decrease hepatic blood flow, either from increased hepatic arterial vascular resistance or from reduced cardiac output and/or blood pressure.[72] On the other hand, ketamine has little impact on hepatic blood flow, and propofol increases hepatic arterial and portal flow by a possible vasodilator effect.[73–75] Epidural anesthesia results in a 25% to 35% decrease in the hepatic blood flow, despite a constant cardiac output.[76] Treatment with norepinephrine to compensate systemic hypotension aggravates the decrease on hepatic blood flow.[77] Combined epidural and general anesthesia is suggested as a useful strategy to keep a low

central venous pressure during liver resection. Epidural anesthesia promotes redistribution of blood flow, decreasing venous return and portal venous pressure, and consequently the hepatic congestion.[78] Also, combined inhalatory and intravenous anesthesia is a useful strategy to minimize the need inhalation drugs.

Techniques to reduce blood loss during hepatectomy, such as the Pringle maneuver, total hepatic vascular exclusion and low PVC are worth while to diminish perioperative blood transfusion and morbidity, but the also have some risks. Studies have shown that low CVP can reduce blood loss and transfusion but also is associated with higher rates of perioperative renal failure.[64]

Fluid management should not be guided by CVP values since this method is not able to estimate volemic status, nor responsiveness to fluid tests.

ANESTHETIC MANAGEMENT

Liver resections are performed under general anesthesia with endotracheal intubation and controlled ventilation. Rapid sequence induction is used in patients with ascites or other risk factors for regurgitation. Maintenance of anesthesia is mainly by volatile halogenated combined with intravenous agents. Volatile anesthetics with low hepatic metabolism, such as isoflurane and sevoflurane, have low effect on hepatic blood flow and can be safely used. These drugs are also used to induce pharmacological hepatic preconditioning before continuous vascular clamping. However, postoperative hepatitis was associated in various degrees with inhalators anesthetics, mainly with halotane.

Chronic liver disease may impair the clearance, prolong the half-life, and potentiate the clinical effects of several drugs. Dosage and administration of these drugs should be adjusted accordingly in patients with liver dysfunction. Opioids, such as morphine and meperidine, have significantly reduced metabolism and prolonged half-life (almost doubled) in patients with cirrhosis. Alfentanil, but not fentanyl nor remifentanil, has the half-life prolonged in cirrhotic patients.[79–82] Thiopental, despite a small hepatic extraction ratio, has elimination half-life unchanged in cirrhosis due to its large volume of distribution, similarly to etomidate.[83] Propofol elimination is unchanged with chronic liver disease, but the mean clinical recovery times may be longer after discontinuation of infusions.[84] On the other hand, the half-life of midazolam is prolonged due to reduced clearance and reduced protein binding with cirrhosis, resulting in a prolonged duration of action and an enhanced sedative effect.[85] Steroidal muscle relaxants, such as vecuronium, mivacurium, and rocuronium, have prolonged half-lives (and consequently prolonged neuromuscular blockade) due to decreased clearance in patients with hepatic dysfunction.[86,87] Atracurium and cisatracurium have metabolism independent of hepatic function (Hofmann elimination) and can be used without modification of doses in cirrhotic patients.[88,89]

Effects of mechanical ventilation can have an impact on

Table 3. Factors affecting hepatic blood flow during anesthesia.

Hepatic blood flow	Factor	Mechanism involved
Decrease	Halothane and enflurane	Hepatic arterial constriction, increase hepatic vascular resistance (respectively)
	Thiopental and etomidate	Arterial blood flow and cardiac output reduction
	Regional anesthesia (spinal and epidural)	Systemic hypotension
	Mechanical controlled ventilation	Reduction of preload and cardiac output
	PEEP	Reduction of sympathetic tonus
	Hypoxia	Sympathetic activation
	Hypocapnia	Direct effects
	Alkalosis	Direct effects
Increase	Dopamine (renal dose)	Direct effects
	Propofol	Splanchnic vasodilatation
	Isoflurane	Increase in microvascular blood velocity
	Hypercapnia	Direct effects
	Acidosis	Direct effects
No significant effect	Ketamine	
	Sevoflurane and desflurane	

hepatic blood flow. Controlled positive pressure ventilation and positive end-expiratory pressure may reduce venous return and cardiac output, with compromise of the hepatic blood flow. Also, hyperventilation with hypocarbia reduces hepatic blood flow.

Intraoperative fluid management. The use of colloids (such as 5% albumin), rather than crystalloids, as a maintenance and replacement solution reduces extravascular translocation of fluids. Crystalloids should be limited to a minimum. Fresh-frozen plasma is used as maintenance fluid in patients requiring coagulopathy correction. Red blood cells are usually transfused if the hematocrit falls below 25%. In cirrhotic patients, the judicious use of vasopressin (2-5 U/hour) combined or not with norepinephrine restores peripheral vascular resistance and systemic blood pressure.[57] Any intraoperative decrease in systemic arterial pressure should be rapidly treated to preserve liver blood flow and, therefore, minimize postoperative liver impairment, especially in cirrhotic patients. On the other hand, infused fluids should be restricted until parenchyma sectioning is completed, to keep a low central venous pressure.[50]

Monitoring. Invasive hemodynamic monitoring (such as measure of CVP, continuous invasive arterial pressure, pulmonary artery catheterization, intraoperative echocardiogram) depends on the complexity of hepatic resection and patient's health status. Minor resections can be safely performed with no invasive hemodynamic monitoring. On the other hand, complex resections with TVE and/or veno-venous bypass might benefit from more invasive monitoring.

Other parameters such as urinary output, core temperature, electrolytes and, if available, coagulogram must be monitored

STRATEGIES TO PREVENT HETEROLOGOUS BLOOD TRANSFUSION

Blood loss is a major concern in hepatic surgery and transfusion of red blood cells is required in about 25-30% of patients.[90] It is the main intraoperative complication during hepatic resections. Intraoperative blood loss and perioperative blood transfusion are associated with a higher rate of postoperative morbidity and recurrence, and poorer long-term survival in patients with malignancies. Heterologous blood transfusion can raise the risk of nosocomial infections and lead to Transfusion Related Acute Lung Injury (TRALI).

Besides low central venous pressure and vessel occlusion techniques, other methods are useful to minimize blood loss and allogenic blood transfusion, such as intraoperative blood salvage, preoperative autologous blood donation, and intraoperative isovolemic hemodilution. The use of antifibrinolytic agents such as aprotinin, aminocaproic acid, and tranexamic acid is still controversial.[91] Conditions like hypothermia, acidosis, and hypocalcemia can disturb hemostasis and should be prevented and treated. Risk of red blood cell transfusion and auto donation, use of erythropoietin, and blood-saving devices and others ways to reduce perioperative blood transfusions are discussed in **Chapter 9** (Morbidity and Mortality after Liver Surgery).

ISCHEMIA-REPERFUSION SYNDROME

The reperfusion of the liver after a long period of ischemia (such as by vascular clamping) induces a diversity of hepatic lesions called ischemia-reperfusion (IR) syndrome, but its pathophysiology is not entirely understood yet. Cirrhotic and steatotic livers seem to be particularly susceptible to this injury.[92,93]

Several interventions have been developed to minimize IR injury. Ischemic preconditioning consists of a short period of ischemia followed by a short period of reperfusion, prior to a prolonged ischemia and reperfusion.[92,94] This strategy demonstrated no advantage compared to intermittent clamping.[95,96] The pharmacological preconditioning, mainly with the use of inhaled anesthetics, has also been used with the same goal.[97]

POSTOPERATIVE ANALGESIA

Postoperative pain management in patients with liver cirrhosis is challenging and is often inadequate due to the lack of therapeutic efficacy or the high incidence of adverse effects.[98] Severe complications from analgesia in cirrhotic patients include hepatic encephalopathy, hepatorenal syndrome, and gastrointestinal bleeding. Analgesics should be started with the minimum effective dose and should be titrated slowly with avoidance of polypharmacy. Adverse effects must be monitored, especially sedation and constipation. The first-line drug to mild pain is paracetamol, which is safe at doses of 2-3g/day. Tramadol is a safe option for moderate to severe pain. Non-steroidal anti-inflammatory (NSAI) agents are contraindicated because they can cause acute renal failure and/or gastrointestinal bleeding. Opioids should be used with caution to prevent encephalopathy. The opioids with the best safety profile are fentanyl and hydromorphone, with methadone as an alternative.[98,99] Patient-controlled analgesia (PCA) with morphine (1 mg with 7 min of refractory period) and paracetamol is often used.

Regional analgesia. Thoracic epidural analgesia (with bupivacaine or ropivacaine, combined or not with morphine) provides excellent analgesia for liver resections and reduces the need for systemic opioids. Placement of

epidural catheter represents a low-risk procedure; however, coagulation disturbances (due to cirrhosis or anticoagulant drug administration) are contraindications to insertion and removal of epidural catheters. Thus, patients with preoperative severe coagulation disturbances and those with probable prolonged postoperative coagulopathy secondary to the surgical procedure (including factors such as amount of remnant liver, perioperative blood loss, liver ischemia, and hemodilution) and the presence of underlying liver disease should not receive epidural catheters.

STEROID ADMINISTRATION

Some studies have demonstrated that preoperative steroid administration can reduce surgical stress and has a positive impact on liver function after liver resection.[100] Methylprednisolone (30 mg/kg or 500 mg preoperatively) or hydrocortisone (500 mg preoperatively, followed by 300 mg, 200 mg, and 100 mg on postoperative days 1, 2, and 3, respectively) can be used intravenously in cirrhotic or non-cirrhotic patients undergoing liver resection.[101–103]

In a review article, steroids significantly reduced post-operative blood levels of bilirubin, as well as inflammatory markers such as interleucine-6 and C-reactive protein. There was no evidence supporting a risk difference in infectious complications and wound healing between study groups. In conclusion, perioperative steroids seem to have a favorable impact on postoperative outcomes after liver resection.[104]

ANTIBIOTICS

Perioperative antibiotic prophylaxis is warranted, even in case of resection of non-complicated tumors, because of the long operating times, large remnant dead spaces, and areas of devitalized tissue. However, postoperative routine antibiotic administration has been shown to be unnecessary following liver resection.[105–107]

Bacterial translocation from the gut to the systemic circulation is the main responsible for peritoneum inoculation following major liver resection.[106] Thus, intravenous cefazoline (2g before induction of general anesthesia with 1g every 4h throughout surgery) is recommended.

Biliary obstruction, even when not associated with clinical infection, should be considered as a potential source of sepsis and it requires antibiotic therapy In this case, piperacillin (with or without tazobactam) combined with an aminoglycoside or with a fluoroquinolone are adequate choices.[3,105] Further antibiotic administration depends on the results of bacteriological examination of intraoperative bile samples.

Cirrhotic patients with ascites are likely to have translocation of intestinal enterobacteria to the systemic circulation. A 24h prophylaxis by a third generation cephalosporin or fluoroquinolone is warranted in these cases.[2,108]

FAST-TRACK LIVER SURGERY

Fast-track surgery (FTS), or enhanced recovery after surgery (ERAS), combines several techniques applied pre-, intra-, and postoperatively, with the goal of accelerating recovery. Fast-track programs include the selective use of drains, strict control of fluids, use of regional anesthesia, early removing of nasogastric tube (at the end of the surgery) and urinary tubes, early oral intake and deambulation (6-8 h after the surgery if no contraindication), and opioid-sparing analgesia (multimodal analgesia). These measures can be used collaboratively to reduce complications and the length of hospital stay in digestive, orthopedic, and cardiovascular surgery.[109–112] In liver surgery (including liver transplantation), fast-track or ERAS programs have been used with satisfactory results, causing in reduction of length of hospital stay without compromising morbidity, mortality, or readmission rates.[113–120] Both anesthesiological and surgical teams should be habituated to these protocols, since their application requires combined strategies and must be planned even prior to hospitalization.

ANESTHESIA FOR LIVER TRANSPLANTATION

PREOPERATIVE ASSESSMENT

Most liver transplantations are performed in the context of chronic liver failure. Prognosis in cirrhotic patients can be estimated using scores such as Child-Turcotte-Pugh and Revised Model for End-Stage Liver Disease (MELD). However, anesthetic perioperative management must take in account not only the liver function but also the usual associate comorbidities.

Disorders that are usually contraindications for partial hepatectomy are common in liver transplant recipients. **Cardiac diseases** comprise coronary artery disease (present in up to 25% of liver transplant recipients[121]) and cirrhotic cardiomyopathy. Cirrhotic cardiomyopathy is characterized by abnormal cardiovascular response to stress and it is present in up to half of patients undergoing liver transplant. Systolic and diastolic dysfunction, prolonged QT, and electrical and mechanical dyssynchrony are present. Despite a normal or increased myocardial contractility at rest, these patients have inotropic and chronotropic incompetence.[122] **Pulmonary disorders** include hepatopulmonary

syndrome (8-24% of end-stage cirrhotic patients) and portopulmonary hypertension (2-10% of end-stage cirrhotic patients). Hepatopulmonary syndrome is characterized by pulmonary vascular dilatation and a decreased systemic arterial oxygenation (PaO_2 <80 mmHg or alveolar arterial gradient >15 mmHg) in association with chronic liver disease. Portopulmonary hypertension is characterized by increased mean pulmonary artery pressure (>25 mmHg) and pulmonary vascular resistance (>240 dyne/s/cm^{-5}), and normal or decreased pulmonary artery wedge pressure (<15 mmHg). The most serious **renal disorder** is hepatorenal syndrome (18-40% of end-stage cirrhotic patients), defined as increased serum creatinine (>1.5 mg/dL) without other possible causes of renal failure.[123]

INTRAOPERATIVE MANAGEMENT

Liver failure is responsible for a decrease in metabolism and protein binding of drugs. The sensitivity of the microsomal enzyme induction accelerate the biotransformation (inhalational anesthetic agents and barbiturates) and the impairment of hepatic blood flow leads to a decreasing in the biotransformation with longer half-lives for some drugs (such as meperidine, lidocaine, diazepam, and thiopenthal).

Induction of anesthesia may be performed using thiopental, ketamine or midazolam, with minimal effects on hemodynamics. Succinylcholine should be avoided in cases of renal dysfunction with increase potassium levels. Muscle relaxants can be used safely. Atracurium has organ-independent elimination, and the duration of action of vecuronium and rocuronium can be used for the assessment of allograft function.[124,125]

Surgery in the recipient is divided in three phases: pre-anhepatic (or hepatectomy) phase, anhepatic phase, and neohepatic phase (**Table 4**). The main risk during **hepatectomy phase** is blood loss, and a low central venous pressure is helpful to minimize blood transfusion. During **anhepatic phase** preload can be severely restricted if venous clamping is necessary and a hyperfibrinolytic state may occur (due to increased tissue plasminogen activator without plasminogen activator inhibitor and alpha 2 antiplasmin) along with the preexisting coagulopathy. The **neohepatic phase** is characterized by organ reperfusion and coagulopathy (hyperfibrinolysis, dilutional coagulopathy, platelet dysfunction, hypothermia, and hypocalcaemia). The thromboelastography can be very useful, mainly during the anhepatic and neohepatic phases, allowing the accurate diagnosis of the coagulopathy and its adequate correction.

Ischemia-reperfusion injury results from a microcirculatory failure and production of reactive oxygen species, and it is associated with primary graft dysfunction. Ischemic and/or pharmacological preconditioning and antioxidants drugs have been tested to minimize the effects of ischemia-reperfusion syndrome. Particularities of anesthetic

Table 4. Anesthesia guidelines for liver transplantation at the University of Wisconsin.

Surgical phase	Anesthetic goals and procedures
Preanhepatic phase	- Anesthesia induction and invasive monitors - Antibiotic and baseline labs (including TEG) - **CVP <5 cmH_2O** (restrictive IV fluid – phlebotomy if Hgb>10g/dL) - BP > 60 mmHg (Norepinephrine or vasopressin) - CO >5 L/min (Dopamine or epinephrine) - Hgb>7 g/dL, platelets > 40,000/µL, MA on TEG > 45 mm, fibrinogen > 100 mg/dL - Mannitol 0.5 g/kg IV over 1h, prior to anticipated clamping - Just before clamping: - IV heparin 3,000 to 5,000 U, if TEG is normal of hypercoagulable; - Increase CVP to 10 cmH_2O with IV fluids; - 25% albumin in severe hypoalbuminemia
Anhepatic phase	- **CVP around 5 cmH_2O** (IV fluids) - Hb>7 g/dL - BP > 60 mmHg and CO > 5 L/min (Norepinephrine or vasopressin) - Correction of base deficit (Bicarbonate infusion) and hypocalcemia (IV calcium chloride)
Neohepatic phase	- BP > 60 mmHg (Vasopressin in bolus when systemic vascular resistance decline) - Heart rate > 60/min (Epinephrine in bolus) - **CVP 5-10 cmH_2O** (euvolemia) - BP > 60 mmHg (Norepinephrine or vasopressin) - CO >5 L/min (Dopamine or epinephrine) - Hgb > 7g/dl, platelets > 40,000/µL, fibrinogen > 100 mg/dl - Correction of coagulopathy: protamine, platelet transfusion, and ε aminocaproic acid according to TEG variations

TEG: Thromboelastogram; CVP: Central Venous Pressure; Hgb: serum hemoglobin; BP: Blood Pressure; CO: Cardiac Output; MA: Maximal Amplitude. (Modified from Hannaman and Hevesi [125])

management according to each surgical phase in the liver transplant recipient are described in **Table 4** (modified from Hannaman and Hevesi[126]).

LIVING LIVER DONORS

Adult-to-adult living donor liver transplantation (LDLT) has been used to minimize the scarcity of organs. The volume of liver to be resected from the donor must be enough to supply the needs of receptor; however, the donor remnant liver must also have adequate volume and function for the safety of the donor. This balance is frequently difficult, and donor safety must be the priority. Adequate volumetric and functional hepatic evaluation is crucial, but appropriate surgical and anesthetic techniques are crucial to optimize postoperative donor liver function. Besides a sufficient hepatic volume with adequate blood inflow, blood outflow, and biliary drainage, parenchymal injury should be avoided.

Despite efforts to avoid perioperative complications in liver donors, a significant number die. Control of postoperative pain is more difficult in donor patients, probably due to a neuroplasticity effect, along with various psychological factors, resulting in an exaggerated pain perception. Caution should be taken with the use of epidural analgesia since postoperative coagulation is unpredictable.

ANESTHESIA FOR ENDOCRINE TUMORS

Surgery for carcinoid tumors exposes a risk of carcinoid crisis. Efforts during the perioperative period are to avoid blood pressure variation and inadequate analgesia. An optimal analgesia with regional anesthesia avoids stressors such as pain, which could launch a carcinoid crisis. However, the potential hypotension and need of vasoconstrictors could lead to an exaggerated response. Intravenous or inhalation techniques for general anesthesia are used, in both the goal is maintain stability with adequate depth of anesthesia and analgesia. Drugs with potential for histamine release, such as morphine and atracurium, should be avoided.

Octreotide (in a dose of 300 mcg subcutaneously) before surgical resection of endocrine tumors, especially in patients with a history of carcinoid syndrome, may prevent a carcinoid crisis. Octreotide can also be used during a carcinoid crisis, in addition to plasma infusion, to restore hemodynamic instability, because usual fluid resuscitation is not efficient in this condition and the use of calcium or catecholamine can aggravate the clinical condition.

LAPAROSCOPIC LIVER RESECTION

Recent studies have demonstrated that laparoscopic liver resections (minor and major hepatectomies) are safe and have some advantages in selected patients. However, the use of laparoscopic access is associated with a high incidence of gas embolism during liver resections. The combination of low CVP, high pneumoperitoneal pressure, and opening of hepatic venous branches during parenchymal transection might favor gas embolism. However, a recent study comparing laparoscopic liver resections with different CVP/intra-abdominal pressure gradients demonstrated a similar incidence of gas embolism among groups.[127] Also, the definition of clinically significant air embolism is not clearly defined. The passage of air bubbles through cardiac chambers during hepatectomy is commonly identified by intraoperative echocardiography, but few of these patients exhibit clinical signs of severe gas embolism. More studies are necessary to elucidate the true frequency of clinical gas embolism and the effect of pneumoperitoneal and central venous pressures.[128]

SUGGESTED READING

Eipel, C., Abshagen, K. & Vollmar, B. Regulation of hepatic blood flow: The hepatic arterial buffer response revisited. *World J. Gastroenterol.* **16**, 6046-6057 (2010).

This paper reviews the relevance of a hepatic blood flow regulatory mechanism called the buffer system.

Koch, D. G. & Fallon, M. B. Hepatopulmonary syndrome. *Clin. Liver Dis.* **18**, 407–420 (2014).

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9 Morbidity and Mortality After Liver Surgery

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- *The historical high morbidity and mortality rates associated with liver resections has decreased significantly over time. The pattern of complications has also changed. Massive intraoperative blood loss has become very rare, but other complications such as bile leak remain high.*
- *Modern methods to prevent blood loss, especially allogeneic blood transfusion, include the use of intraoperative low central venous pressure, various methods of vascular clamping, intraoperative blood salvage, preoperative autologous donation, acute intraoperative normovolemic hemodilution, and efficient modalities of parenchymal transection.*
- *Postoperative liver failure is one of the most serious complications after a hepatectomy. Although uncommon, it is associated with high mortality. Knowledge of risk factors is crucial because prevention is the best approach to avoid mortality. However, early identification of liver failure allows for some effective measures.*
- *Bile leak is the most common biliary complication after liver resections. Most resolve with conservative approaches, and the need for surgical approach is associated with higher mortality rates. Proper intraoperative detection and closure of bile leaks is essential to prevent postoperative biliary fistula.*

INTRODUCTION

MORTALITY AFTER HEPATECTOMY

There has been a marked improvement in the safety of liver resections in recent decades. Mortality rates after liver resections have reduced from 13-30% in the 1970s to less than 5%, and even no mortality, at present.[1–3] A recently published series of 4,152 liver resections at Memorial Sloan Kettering reported a 90-day mortality rate that decreased from 5% before 1999 (1993 to 1999), to 2.3% between 2000 and 2006, and to 1.6% after 2007 (2007 to 2012).[3]

However, some important points should be considered when evaluating the risk of a hepatectomy. First, until recently, most studies on liver resections have considered operative mortality to be death occurring during hospital stay (in-hospital mortality) or up to 30 days after surgery. This definition is useful in conditions of high mortality, such as the case of hepatectomies until the 1980s. Nonetheless, deaths related to surgery may occur later depending on several factors, such as those related to hepatic regeneration. Thus, the 90-day mortality rate has been suggested to evaluate risk with liver surgery.[4,5] Mayo et al.,[5] using a linked SEER (Surveillance, Epidemiology and End Results)-Medicare database, demonstrated that the rate of 90-day mortality was almost twice that of 30-day mortality (10.1% vs. 5.7% for the whole group). After resection of HCC and CRLM, 30-day and 90-day mortality rates were 9.7% vs. 15% and 4.3% vs. 8.4%, respectively.

Second, most reports on mortality following liver

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resections have come from single high-volume institutions that are experts in hepatobiliary surgery. Modern large single-institution series report mortality rates of 0-1.3%.[2] Population-based analyses using administrative data usually identify higher mortality rates.[6] In a literature review, van den Broek et al.[7] reported a mean operative mortality rate of 1% after liver resections; however, a large computer-based study in the United States including 2,313 open hepatectomies found a 30-day mortality rate of 2.5%.[8] In another large study using a computer database of all liver resections in France, Farges et al.[4] reported a 90-day mortality rate of 5.8%.

Third, the characteristics of patients undergoing liver resection is variable across published series. There has been an increase in the proportion of liver resections for malignancies, mainly colorectal liver metastases, hepatocellular carcinoma, and biliary tumors. Such patients are more likely to demonstrate pathological changes in the underlying parenchyma, such as fibrosis, steatosis, and chemotherapy-associated liver injury.[9–12] Dokmak et al.[12] reported a six-fold higher risk for mortality in patients operated on for malignant disease (0.7% vs. 4.5% for benign vs. malignant diseases, respectively).

Thus, mortality after liver resections is related, among several other factors, to the definition of surgical mortality and patient features. Despite a clear reduction in risk, mortality remains significant after hepatectomy, at least in part as a result of an increasing proportion of major resections in patients with malignancy.[12]

MORBIDITY AFTER HEPATECTOMY

Despite a clear reduction in mortality after hepatectomy, morbidity remains frequent and complications still occur in 20-45% of patients in large series of hepatectomies.[3,7,13–22] This high morbidity despite the advances in liver surgery could be at least partially explained by the increasing complexity of procedures. Indeed, complications leading to death have shifted from bleeding, in the early days of hepatectomies, to liver failure, in the present. The risk of complications after a hepatectomy is mainly dependent on factors concerning the patient (such as comorbidities), the surgery (such as extent of resection and blood loss), and the liver parenchyma status (such as the presence of cirrhosis).

Nil morbidity was reported in some series of laparoscopic liver resections in strictly selected patients. However, even in healthy patients with normal livers (in the case of living liver donors), hepatectomy has been associated with relatively high rates of morbidity.

Standard definition and adequate stratification of severity of postoperative complications are essential to compare efficacy of different techniques and measures, especially among diverse institutions worldwide.

The general system for assessment of severity of morbidity proposed by Clavien et al.[23] (Clavien-Dindo classification) focuses on therapeutic consequences of morbidity, and it is appropriate for liver resections. Complications are scaled according their severity, from grade I to V. Grade I and II refer to minor complications, grade III and IV major complications, and grade V fatal complications (**Table 1)**. While Clavien-Dindo classification is probably the best system available for stratification of severity of complications, it does not take into account particularities of complications. Thus, it is very useful as a means of evaluating and comparing global results, but it lacks specificity to evaluate the efficacy of some measures, for example. The International Study Group of Liver Surgery (ISGLS) has attempted to standardize definition and grading of the most common specific postoperative complications for liver resections, as discussed below in specific topics in this chapter. The main surgery-specific complications after liver resections include postoperative liver failure, bile leak hemorrhage, and surgical site infection.

Complications after liver resection can lead to fatal early outcomes, especially when postoperative liver failure and/or sepsis occur. However, beyond this obviously early consequence, perioperative complications may result in longer hospital stays, increasing costs, and higher recurrence rates in oncological patients.

Table 1. ISGLS definition and grading of post-hepatectomy hemorrhage.

DEFINITION
1- Drop in hemoglobin > 3g/dL after establishing a postoperative baseline
2- Any postoperative transfusion for a failing hemoglobin and/or the need for any reintervention (embolization or re-laparotomy) to stop bleeding
3- Evidence of bleeding, such as blood loss via drains or active hemorrhage by imaging.
GRADING
Grade A- Bleeding requiring transfusion of up 2 units PRCBs
Grade B- Bleeding requiring transfusion of > 2 units PRBCs but without invasive intervention
Grade C- Bleeding requiring immediate postoperative transfusion secondary to intraoperative blood loss

ISGLS: International Study Group of Liver Surgery, PRBCs: packed red blood cells. (From Rahbari et al.[146])

RISK FACTORS ON LIVER RESECTIONS

Well-established risk factors in liver resections include those related to the patient (such as presence of comorbidities, malignancy, and obesity), to surgery (such as extent of resection, intraoperative bleeding, and simultaneous extrahepatic procedures), and to liver parenchyma status (such as cirrhosis, steatosis, chemotherapy-associated liver injury, and cholestasis).[24–26]

The presence of **underlying chronic liver disease**, especially cirrhosis, has been clearly identified as a risk factor in liver resection.

Cirrhosis is the most obvious underlying liver disease that increases the risk of a hepatectomy. The limited capacity of liver regeneration, the smaller functional reserve of the remnant liver, and the increased risk of perioperative blood loss are all responsible for an increased risk of postoperative liver failure in cirrhotic patients. Estimating surgical risk in patients with cirrhosis is challenging, and depends on the degree of hepatic dysfunction, the extent of liver resection, and the presence of comorbidities. Most liver resections in patients with cirrhosis are performed to treat hepatocellular carcinoma, and morbidity rates are 26-56%.[27–29] Mortality rates after major and minor hepatectomies in selected patients with cirrhosis are up to 25% and 3%, respectively.[18,30,31] In fact, postoperative outcomes in cirrhotic patients are markedly influenced by the severity of the underlying liver disease and the extent of liver resection being considered.[32–34]

Thus, cirrhosis requires an individualized preoperative assessment, as discussed in detail in **Chapter 5** (Liver Function Assessment Before and After Hepatic Resection) and **Chapter 6** (Surgical Approach to the Patient with Cirrhosis). In summary, several methods for liver function assessment before liver resection have been used. Risk stratification based on Child-Pugh (**Table 1)** and MELD (model for end-stage liver disease) (**Table 2**) scores have been used to estimate risk and select cirrhotic patients for surgery, leading to lower mortality rates. Despite conflicting reports, a MELD score greater than 8 has been accepted as a high risk factor.[35] Child-Pugh score A patients usually tolerate a major hepatectomy; however, patients with B and C scores have an increased risk and should undergo only minor hepatectomies or tumor enucleation, respectively.[35,36] The presence of portal hypertension has been discussed as a risk factor for hepatectomy in cirrhotic patients, but it has not been found as an independent predictive risk factor.

Table 2. Score of severity for postoperative liver failure.

Points	0	1	2
Total serum bilirubin (μmol/L)	≤ 20	21-60	> 60
Prothrombin time (seconds above normal)	< 4	4-6	> 6
Serum lactate (mmol/L)	≤ 1.5	1.6-3.5	>3.5
Encephalopathy severity grade	None	1 and 2	3 and 4

PLF: none (0 points), mild (1-2 points), moderate (3-4 points), severe (>4 points). (Adapted from Schindl et al.[127])

Chemotherapy-associated liver injuries, such as sinusoidal dilatation and steatohepatitis, occur mainly in oxaliplatin-based and irinotecan-based chemotherapy, respectively.[37] These hepatic injuries and steatosis have been associated with worse surgical mortality rates and postoperative liver failure after hepatectomy, mainly for colorectal liver metastases (see **Chapter 4** – Underlying Liver Disorders in Hepatic Surgery).[11,38–40]

Extensive liver resections, and more precisely small remnant liver, are associated with higher operative risk. The minimum safe volume of remnant liver is 25% of the total functional liver volume in patients with an otherwise normal liver. However, when underlying chronic liver disease is present, this cutoff should be higher, such as 40% in the case of chemotherapy-associated injury or cirrhosis.[41] The precise determination of the minimum safe future remnant liver is challenging when underlying chronic liver disease is present, because hepatocyte function varies according to the degree of parenchymal injury. Thus, a variety of liver function tests have been investigated to estimate parenchymal liver function. One of the most widely described is the indocyanine green retention at 15 min test (ICGR-15). Patients with a retention of less than 10% of indocyanine green at 15 minutes after infusion (ICGR-15<10%) could undergo extensive hepatic resection, while patients with ICGR-15≥30% should undergo only limited non-anatomical resections.[42] Other function tests include the LiMAx test (which measures cytochrome P450 activity by the ratio of exhaled $^{13}CO_2$:$^{12}CO_2$) and hepatobiliary scintigraphy (using measures of uptake and excretion of ^{99m}Tc-mebrofenin).[43]

Dynamic magnetic resonance imaging (MRI) techniques are promising methods to evaluate parenchymal function in different regions of the liver. Methods taking into account intrahepatic regional differences of liver function could help the technical planning of hepatectomies.[44]

BLOOD LOSS AND BLOOD TRANSFUSION

INTRODUCTION

Bleeding was the most feared complication of a hepatectomy in the 1970s, when it was responsible for one third of operative deaths. Before 1990, transfusion requirement during liver resection was roughly 90%. Currently, although major hemorrhagic complications have become uncommon, transfusion requirement is present in 5-49% of hepatectomies. Given the probable association of blood transfusion with

adverse outcomes, blood loss and blood transfusion remain a crucial topic concerning operative morbidity.[1,14–16,22,45–47]

Both blood loss and allogeneic blood transfusion have deleterious effects. Allogeneic blood transfusion has a potential immunosuppressive effect,[48,49] with reduction of the activity of natural killer cells and of T lymphocyte blastogenesis, and increase of the activity of suppressor T lymphocyte. These changes could result in diminished resistance to infections[47,50] and easier proliferation of malignant cells.[51] In fact, studies have found a relevant association between transfusion and postoperative morbidity, specifically infectious complications, and also with tumor recurrence and long-term mortality.[52,53] Allogeneic blood transfusion has also been associated with acute lung injury, perioperative myocardial infarction, postoperative low-output cardiac failure, and increased operative mortality.[14,16,46,50,54–56]

Post-hepatectomy bleeding occurs at a rate of 0.6% to 8%. Definitions of postoperative hemorrhage and its severity are challenging to establish. A standard definition and grading system of postoperative hemorrhage was proposed by the International Study Group of Liver Surgery (ISGLS), as shown in **Table 1**.[57–59] This definition was validated in a large sample (835 patients) that found mortality rates of 0%, 17%, and 50% for grades A, B, and C hemorrhage, respectively.[57]

Risk factors for bleeding and blood transfusion include factors related both to the tumor (in cases of malignancy) and to the patient. A well-known risk for hemorrhage is cirrhosis, which is present in most patients undergoing hepatectomy for hepatocellular carcinoma. Among these patients, low prothrombin activity (<70%), centrally located tumors, involvement of hepatic veins, obesity (body mass index >23 kg/m^2), and major resection were identified as risk factors for severe blood loss (more than 1,500 mL).[60] Avoiding blood transfusion, notwithstanding blood loss, could be helpful. However, indications for blood transfusion are quite variable in the literature. Cunningham et al.[61] used a decrease in hematocrit to 24% in patients without antecedent cardiac disease and a decrease to 29% in patients with cardiac disease as criteria for blood transfusion in liver resection. Other indications were a total volume blood loss of more than 20% and/or hemodynamic instability, hemoglobin less than 8 g/dL, or symptomatic patients with hemoglobin of 8 to 9 g/dL.[47]

BLOOD TRANSFUSION AND MALIGNANCIES

Despite the association of blood loss and blood requirement with poorer oncological outcomes, this topic remains controversial.[62–65]

Concerning hepatic malignancies, most studies cover **hepatocellular carcinoma** resection, since this type of tumor occurs almost exclusively in patients with chronic underlying liver disease – mainly cirrhosis, a well-known risk factor for perioperative bleeding. In this setting, perioperative blood loss and blood transfusion have been associated with poor overall and disease-free survival rates.[66–71] The deleterious effect of blood transfusion on long-term survival has been demonstrated for both advanced HCC (tumors larger than 10 cm in diameter)[72] and early HCC.[73,74] Katz et al.[70] showed a significant inverse correlation between estimated blood loss and disease-specific survival. In fact, in this study, blood loss was the only significant factor associated with worse disease-free survival. In a French study[75] including 209 consecutive patients undergoing liver resection for HCC, blood loss was also an independent risk factor for tumor recurrence and short overall survival.

Concerning liver resections for **colorectal liver metastases**, few studies have focused on the oncological effects of blood transfusion, and the results are less consistent. In a study of more than 1,300 patients treated for colorectal liver metastases, Kooby et al.[50] observed an association between blood transfusion and postoperative complications, in a dose-related effect. However, it was not a significant predictor of long-term survival. On the other hand, Stephenson et al.[76] in a series of 55 patients found a higher rate of recurrence after resection of hepatic colorectal metastases in patients that needed blood transfusion. It is worth noting that postoperative infectious complications, which also suffer the influence of immunosuppressive effects of blood transfusion, were associated with poor long-term outcomes. Farid et al.[47] evaluated outcomes of 705 liver resections for colorectal liver metastases, and found a poorer overall and disease-free five-year survival when complications were present (24% vs. 37% and 13% vs. 26%, respectively). In this study, blood transfusion and postoperative sepsis were independent factors associated with long-term survival. There is no convincing support nowadays for the deleterious effect of blood transfusion on recurrence or long-term survival after resection of colorectal liver metastases, but postoperative morbidity (comprising hemorrhage) has been associated with poor oncological outcomes.[47,77,78]

There are few studies evaluating the effect of perioperative blood transfusion or blood loss in patients undergoing liver resection for **cholangiocarcinoma**. Nagino et al.[79] observed a higher incidence of complications when allogeneic blood transfusion was required in a series of 100 hepatic resections for hilar cholangiocarcinoma. Recently, Ercolani et al.[80] identified that patients operated on for intrahepatic cholangiocarcinoma had a better prognosis when no blood transfusion was necessary.

It is still debatable whether blood loss and blood transfusion are responsible themselves for poorer outcomes. Other factors could be responsible for impairment of the immune system in patients with large-scale blood loss, such as intraoperative hypotension, duration of anesthesia, stage of malignancy, and degree of liver dysfunction, among others.

Major surgery per se has an immunosuppressive effect, and blood transfusion could reflect a more extensive procedure, resulting in greater need for blood transfusion.[81]

MINIMIZING BLOOD LOSS AND ALLOGENEIC BLOOD REQUIREMENT

Prevention of bleeding and blood transfusion includes an adequate preoperative evaluation. A careful drug history is taken, and drugs such as aspirin, clopidrogrel, or warfarin should be stopped before surgery. Coagulation abnormalities should also be corrected before hepatectomy, especially in jaundiced or cirrhotic patients.

The use of antifibrinolytic agents, such as inhibitors of plasmin (aprotinin and nafamostat mesylate) and inhibitors of plasminogen (tranexamic acid and epsilon-aminocaproic acid), and procoagulant agents (recombinant factor VIIa), have been evaluated in liver resections with conflicting results.[82–84]

Similarly, the use of topical sealants over the cross-section area remains a controversial topic. They stimulate hemostasis by mimicking coagulation (i.e., fibrin sealants), providing a matrix for endogenous coagulation (i.e., collagen, felatin, cellulose sponges), or both.[85] There is no consensus as to whether these agents should be routinely used to prevent blood transfusion.

Other strategies with the goal of avoiding allogeneic blood transfusion and its consequences include techniques to minimize blood loss during surgery (such as the use of **low central venous pressure** and **vascular clamping**) and techniques of autologous donation (such as **intraoperative autotransfusion**, **acute normovolemic hemodilution**, and **preoperative autodonation**).

Low central venous pressure

Central venous pressure (CVP) is an indirect measure of pressure into the hepatic veins and a low CVP (<5 cmH_2O) is a useful method to avoid backflow bleeding from hepatic veins during liver transection. [86–91]

Several approaches enable reaching and maintaining a low CVP during surgery. Crystalloid and colloid restriction and the use of diuretics (furosemide) helps maintain patients in a hypovolemic state. If necessary (arterial hypotension), intravenous dopamine is associated with maintaining systolic blood pressure above 90 mmHg.[90,91] Reduced mechanical ventilation tidal volume and administration of a sufficient amount of muscle relaxant work together to reduce the CVP. Extradural blockade and systemic nitroglycerine infusion can also be used.[90] Intraoperatively, partial or total clamping of the infrahepatic vena cava can be used for this purpose.[92–94] Another measure is placing the patient in the Trendelenburg position (15° head-down).[87]

Despite the well-established reduction of blood loss, low CVP carries a potential higher risk for complications such as air embolism, systemic tissue hypoperfusion, and renal failure,[87,95] and should be used carefully in patients with underlying chronic liver disease, such as cirrhosis.

Vascular clamping

Vascular clamping is an effective way to minimize blood loss and avoid transfusion during liver transection. This topic is discussed in more detail in **Chapter 23** (Vascular Control and Parenchymal Transection Techniques). Since the first description of pedicular clamping by Pringle in 1908,[96] different modalities of vascular occlusion have been developed. The main strategies comprise inflow vascular occlusion and total vascular occlusion. Inflow occlusion can be total or selective (hemihepatic or segmental), continuous or intermittent, and associated or not with outflow occlusion (such as in the case of hepatic vascular exclusion). Clamping of the infrahepatic vena cava (partial or complete) can be used alone or in combination with inflow clamping to reduce bleeding during hepatic transection by reducing CVP.[97–101]

The benefit of vascular occlusion in reduction of blood loss seems clear. However, prolonged hepatic ischemia can be responsible for major complications, such as postoperative liver failure and ischemia-reperfusion syndrome. To avoid these complications, beyond the use of intermittent clamping (whenever possible), hypothermia or preconditioning can be combined with some techniques of vascular clamping to minimize parenchymal injury by the prolonged ischemia.[102]

Intraoperative blood salvage

Intraoperative blood salvage and autotransfusion consist of recovering blood lost during surgery and re-infusing it, generally just after the period that is more susceptible to bleeding.

Various medical devices have been developed to collect blood lost during surgery and re-infuse it by a venous access. The lost blood is collected, heparinized saline solution is added, and the blood is then passed through a filter and collected in a reservoir. Red blood cells are separated by centrifugation and then washed and filtered across a semi-permeable membrane, which removes components such as free hemoglobin, plasma, platelets, white blood cells, and heparin. The salvaged blood cells are re-infused up to six hours after.

The use of intraoperative blood salvage in oncological surgery is controversial because tumor cells are identified in the blood collected before reinfusion, representing a potential risk of disseminating metastasis. However, despite the identification of malignant cells in the collected blood, there is no clinical evidence of increased recurrence rate or poorer long-term survival with the use of blood salvage in oncological patients. The use of "cell processors", which wash and save red blood cells, and the use of hemofiltration (or ultrafiltration) seem to reduce the risk of reinfusion of

malignant cells. Nevertheless, no guidelines are available concerning the use of blood salvage devices during surgery for liver cancer.[103]

Preoperative autologous blood donation

Preoperative autologous transfusion consists of withdrawing blood from the patient for a period of days or weeks before the surgery and re-infusing the collected blood during surgery or after that, if necessary.

The main goal of this procedure is avoid the potential risks of allogeneic transfusion. Moreover, an additional benefit of autologous blood donation would be the stimulation of erythropoiesis mediated by an increase in the endogenous erythropoietin level, resulting in an accelerated rate of recovery of hemoglobin after surgery. A similar effect is observed in acute normovolemic hemodilution, as described below.

Patients can donate up to one unit (approximately 450 mL) twice weekly, until 72 hours before surgery. Autologous blood transfusion can be accompanied by the use of recombinant human erythropoietin to minimize preoperative decreases in hematocrit due to blood donation.

Shinozuka et al.[104] reported a reduction in the necessity of homologous blood transfusion with preoperative autologous donation combined with the administration of recombinant human erythropoietin in patients undergoing liver resections. Chan et al.[105] demonstrated that preoperative autologous blood donation in patients with hepatic malignancies did not alter the rate of tumor recurrence or disease-free survival. Some studies examining the use of preoperative autologous blood donation actually resulted in improved prognosis in patients undergoing hepatectomy for hepatocellular carcinoma.[106,107] Autologous blood donation in the context of donor hepatectomy for living donor liver transplantation did not result in any benefits in a study by Jawan et al.[108] In fact, blood transfusion was not needed in the entire group of 84 patients, whether they preoperatively donated blood or not.

The main disadvantage of this method is that autologous donation is more expensive than allogeneic transfusion.

Acute intraoperative normovolemic hemodilution

The goal of acute normovolemic hemodilution (ANH) is to avoid allogeneic blood transfusion. The procedure involves the removal and storage of a calculated volume of autologous blood immediately before the surgery, and simultaneous replacement with crystalloid or colloid fluids. The collected blood is re-infused during surgery after the period of blood loss.

Physiological consequences of acute normovolemic hemodilution include reduction of viscosity of blood (with improvement of microcirculation, reduction of left cardiac afterload and increased cardiac output), peripheral vasodilatation (with reduced peripheral vascular resistance), increasing of central venous and pulmonary capillary wedge pressures (due to increased venous return), and right deviation of the hemoglobin dissociation curve (with better oxygen delivery in the periphery). The main concern in the use of acute normovolemic hemodilution is finding the point of critical oxygen delivery in specific organs. During this procedure, it is crucial to maintain an adequate cardiac output and normal tissue perfusion. The main contraindications for ANH are the presence of cardiac disease, baseline hemoglobin of less than 9 g/dL, and clotting disorders.[109]

The maximum volume to be withdrawn is determined according to estimation of initial blood volume (around 65-70 ml/kg for young adults) and initial and target hemoglobin. Thus, the acceptable volume of blood to be collected could be determined by the formula: $V = EBV \times (H_i - H_f)/H_{av}$, where V is the volume of blood to be withdrawn (in mL), EBV is the estimated blood volume of the patient (in mL), H_i is the initial hematocrit before the procedure, H_f is the target final hematocrit after hemodilution, and H_{av} is the average of the H_i and H_f. Hemodilution can be classified as mild (target hematocrit more than 30%), moderate (target hematocrit 20-30%) or severe (target hematocrit less than 20%).[54]

Usually, the first 450-500 mL of blood can be withdrawn without the need for fluid replacement. After that, blood is replaced with fluid in the ratio of 1 mL of blood: 3 mL of lactate ringer or normal saline. Optionally, 6% hydroxyethel starch or 5% albumin may be used in a 1:1 ratio. Between 2-4 units (approximately 400-500 mL each) of blood can typically be safely removed in most cases. The bags of blood should be kept in the operating theatre. Blood may be kept at room temperature for up to four hours, or at a temperature of 6°C for a longer period of time.

Method of transection

Several modalities and devices have been tested to reduce bleeding from the parenchymal cross section during liver transection. The use of vascular staplers enables simultaneous transection of hepatic parenchyma and vessels. Reddy et al.[110] found a significant reduction in intraoperative blood loss and transfusion requirements using vascular stapling devices. However, other studies have been unable to demonstrate similar results. Also, results comparing the use of radiofrequency, harmonic scalpel, water jet, and ultrasonic devices have been conflicting. Most have been unable to demonstrate superiority of any one technique, and no technique has proven to be preferable to the clamp-crush method to reduce blood loss during hepatectomy.[111–115] Another attempt to reduce cross section bleeding has been through the use of hemostatic topical agents, such as collagens, fibrins, and cyanoacrylate agents; however, there is no evidence that topical agents yield a significant difference in operative blood loss or transfusion requirement.[116–120]

MANAGEMENT OF POST-HEPATECTOMY BLEEDING

Hemorrhage after liver resection usually originates from the liver surface or the diaphragm and occurs within the first 48 hours.[121] Drainage of blood by abdominal drains and/or hemodynamic disturbances (hypotension and/or tachycardia) are indicative of hemorrhage. Loss of blood through abdominal drain does not exclude bleeding, since clots can prevent adequate drainage. Conservative management includes correction of an eventual coagulopathy and blood transfusion. Re-laparotomy is required in 1-8% of cases of postoperative hemorrhage and carries a high mortality rate (17% to 83%). Criteria for laparotomy are variable, but blood loss exceeding 1 L, ongoing need for transfusion, hemoglobin decreasing by 3-4 points requiring transfusion, and hemodynamic instability are reasonable indications.[58,59,121–123]

POSTOPERATIVE LIVER FAILURE

DEFINITION AND PATHOPHYSIOLOGY

After liver resection, there is an expected and limited deterioration of liver function. The ability of the remnant liver to regenerate leads to rapid restoration of liver volume and function, as can be demonstrated by liver function tests and volumetric measurements after major hepatectomy. Severe dysfunction leading to acute liver failure is uncommon, but it is among the most serious complications after hepatectomy because it is associated with a high morbidity and mortality (60% to 100% of all deaths after hepatectomy). Nevertheless, attempts to precisely define this condition are recent and the definition varies among groups, resulting in a widely variable incidence (0-32%) and making comparison of rates challenging.[6,14,17,19,124–131]

The precise pathophysiology of postoperative liver failure (PLF) remains poorly understood, but it occurs when the regenerative capacity of the remnant liver parenchyma is not able to surmount the increased postoperative metabolic demand and preserve or recover an adequate hepatic function. Thus, the **volume** and the **quality of the remnant liver** are some obvious predictors of PLF, relying on the extension of hepatic resection and the presence of underlying chronic liver disease, respectively. Small remnant liver volume may not have enough hepatocytes for adequate minimal liver functions. A damaged remnant liver parenchyma ha a reduced functional and regenerative ability. Cirrhosis, steatosis, and chemotherapy associated liver injury (CALI) are conditions associated with increased risk of mortality after liver resections (most of them for PLF). Indeed, the more the remnant liver parenchyma is injured, the greater the remnant volume that is needed, as discussed in other chapters of this textbook.

Other associated risk factors for PLF include hepatic parenchymal **congestion** (inadequate outflow), prolonged parenchymal **ischemia** (due to vascular clamping, hypotension, and anesthetic drugs, among others), and **ischemia-reperfusion injury** (mainly depending on duration of vascular clamping). A small remnant liver must have an adequate blood inflow and outflow, and biliary drainage. On the other hand, **hyperperfusion** (excessive portal flow to a small volume of hepatic parenchyma) is harmful because it leads to sinusoidal dilatation, hemorrhagic infiltration, centrilobar necrosis and prolonged cholestasis, and further impaired liver function (the so-called "small-for-size" syndrome).[132–134]

Sepsis has also a detrimental effect on liver function and hepatic regeneration; **blood transfusion** increases the risk of sepsis and postoperative liver failure. Occasionally, PLF occurs due to portal or hepatic vein obstruction (thrombosis, torsion, or surgical injury).

Postoperative liver failure leads to an unexpected kinetic of postoperative liver tests. After uncomplicated liver resection, serum bilirubin and INR – well-known measures of hepatic function – should tend to return to normal levels on postoperative day 5, as illustrated in **Figure 1**. Most proposed definitions of PLF in the literature are based on abnormalities of these tests, using various cut-off values at different postoperative time points.

Therefore, the consensus of the International Study Group of Liver Surgery (ISGLS) defines PFL as a "postoperative acquired deterioration in the ability of the liver to maintain its synthetic, excretory and detoxifying functions, which is characterized by an increased international

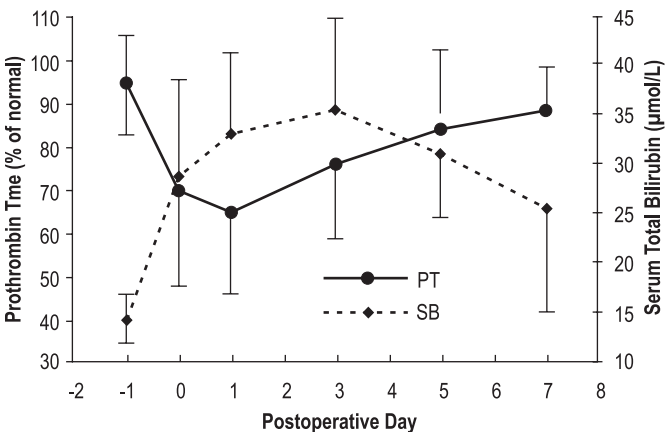


Figure 1. Natural history of two liver function tests (prothrombin time and bilirubin) after liver resection on survival patients. Serum bilirubin tends to return to preoperative levels on postoperative day 5, and prothrombin time usually reaches normal values quickly soon, on postoperative day 3. (Adapted from Balzan et al.[129])

normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5." Attention should be paid to patients with abnormal preoperative liver function tests and those that receive clotting factors, such as fresh frozen plasma (FFP), and/or present postoperative biliary obstruction, both being conditions that affect the expected levels of the evaluated postoperative liver function tests. However, no specific cut-off for these tests is defined and therefore any concomitant abnormality of INR and serum bilirubin is defined as PLF.

The presence of the "50-50" criteria,[129] a combination of prothrombin time index <50% (corresponding usually to a INR>1.7) and serum bilirubin >50 μmol/L (i.e., 2.9 mg/dL), on postoperative day (POD) 5 has been identified as a strong predictor of postoperative mortality and it has been frequently used as definition of PLF. In fact, the presence of the "50-50" criteria on POD 5 is associated with a mortality rate of 59%, as opposed to 1.2% if these criteria are not met. A study by Mullen et al.[13] found that a peak serum bilirubin concentration >7 mg/dL predicted liver-related death in non-cirrhotic patients after major hepatectomy, and this definition has also been used as a means of identifying PLF in non-cirrhotic patients.

The three definitions noted above represent those that are used most worldwide, and were recently compared in a large cohort study.[135] As expected, the ISGLS definition showed the highest sensitivity among the three. However, it was the least relevant in predicting mortality and morbidity (lower specificity and positive predictive value). The positive predictive value for mortality using the ISGLS criteria on POD 5 was only 18.3%, lower than the 47.1% and 40% obtained with the 50-50 and Mullen criteria, respectively. The incidence of PLF in this cohort was 11.6% using the ISGLS definition on POD 10 (and 9% on POD 5), 6.5% using the Mullen criteria, and 3.5% using the 50-50 criteria.

PLF has also been stratified according its severity. Schindl et al.[127] used four parameters (serum bilirubin, prothrombin time, serum lactate, and grade of encephalopathy) in a score to classify PLF into four grades of severity, as shown in **Table 2**. The ISGLS consensus classifies PLF according to its severity into three groups (**Table 3**): **Grade A** does not present specific symptoms, only a deterioration on routine laboratory liver function tests; **Grade B** includes patients that need non-invasive treatments but commonly require

Table 3. Criteria for grading of posthepatectomy liver failure.

	Criteria for **Grade A**	Criteria for **Grade B**	Criteria for **Grade C**
Specific treatment	Not required	- Fresh-frozen plasma - Albumin - Daily diuretics - Noninvasive ventilation - Transfer to intermediate/ intensive care unit	- Transfer to intensive care unit - Circulatory support - Need for glucose infusion - Hemodialysis - Intubation and mechanical ventilation - Extracorporeal liver support - Rescue hepatectomy/liver transplantation
Hepatic function	- Adequate coagulation (INR<1.5) - No neurological symptoms	- Inadequate coagulation (INR ≥1.5 and <2.0 - Beginning of neurologic symptoms	- Inadequate coagulation (INR≥2.0) - Severe neurologic symptoms
Renal function	- Adequate urine output (>0.5 mL/Kg/h) - BUN<150 mg/dL - No symptoms of uremia	- Inadequate urine output (≤0.5mL/Kg/h) - BUN<150 mg/dL - No symptoms of uremia	- Renal dysfunction not manageable with diuretics - BUN≥150 mg/dL
Pulmonary function	- Arterial oxygen saturation >90% - May have oxygen supply via nasal cannula or oxygen mask	- Arterial oxygen saturation <90% despite oxygen supply via nasal cannula or oxygen mask	- Severe refractory hypoxemia (arterial oxygen saturation ≤85% with high fraction of inspired oxygen)
Additional evaluation	Not required	- Abdominal ultrasonography/CT - Chest radiography - Sputum, blood, urine cultures - Brain CT	- Abdominal ultrasonography/CT - Chest radiography/CT - Sputum, blood, urine cultures - Brain CT - ICP monitoring device

The patient's posthepatectomy liver failure is graded by the worst idenfied criteria.
BUN: blood urea nitrogen; CT: computed tomography; ICP: intracranial pressure. (Adapted from Rahbari et al.[136])

additional diagnostic evaluation; and **Grade C** patients require invasive methods for management, and present symptoms such as ascites, hemodynamic instability, respiratory failure, and encephalopathy. Rahbari et al.[136] evaluated the clinical applicability of the ISGLS definition and grading in 835 patients, and found an incidence of 1%, 8%, and 2%, and mortality rate of 0%, 12%, and 54%, for PLF Grades A, B, and C, respectively.

RISK FACTORS

Clinical factors associated with the above-mentioned pathophysiological mechanisms and predictive of increased risk of PLF can be grouped as patient-related, surgery-related, and postoperative causes. These factors are summarized in **Table 4**.[137]

Underlying chronic liver disease increases the risk of PLF. Parenchymal injury from any etiology represents a potential risk factor for postoperative liver dysfunction. Hepatocyte damage leads to variable degrees of hepatic dysfunction, and preoperative evaluation is challenging. Chemotherapy-associated liver injury (CALI), such as that due to irinotecan and oxaliplatin, and cirrhosis of any etiology, are well-established risk factors for PLF. Moderate steatosis represents a risk factor for PLF.[138]

Diabetes, malnutrition, renal insufficiency, obesity, active viral hepatitis, and advanced age have also been reported as risk factors for PLF, likely associated with alterations in liver metabolism, immune dysfunction, and hepatic steatosis.[2,8,130,139–143] Surgery-related risk factors for PLF are mainly associated with a small remnant liver, ischemia, and bleeding.[144,145] In a group of non-cirrhotic patients, Schindl et al.[127] found an incidence of severe PLF of 0%, 9%, and 30% after minor resection, standard major resection, and extended major resection, respectively.

Large volume of estimated blood loss, intraoperative transfusion requirement, and need for vascular resection are associated with PLF.[121,129,146–149] Excessive blood loss might induce bacterial translocation and systemic inflammation, and blood transfusions exert an immunosuppressive effect. Thus, blood loss of more than 1000-1250 mL represents a risk factor for infection and PLF.[2,17,50,150,151] Postoperatively, hemorrhage and infection seem to increase the risk of PLF.[2,142]

Table 4. Risk factors for postoperative liver failure.

Patient related	-Diabetes mellitus -Obesity -CASH -Hepatitis B, C -Malnutrition -Renal insufficiency -Hyperbilirubinemia -Thrombocytopenia -Lung disease -Cirrhosis -Age >65 years
Surgery related	-EBL >1,200 mL -Intraoperative transfusions -Need for vascular resection -Major hepatectomy -Skeletonization of hepatoduodenal ligament -Future remnant liver <25%
Postoperative management	-Postoperative hemorrhage -Intra-abdominal infection

EBL: estimated blood loss; CASH: chemotherapy-associated steatohepatitis. (Adapted from Kauffmann and Fong[137])

PREVENTION

Prevention and/or treatment of the causes of PLF should minimize its incidence. First, careful selection of patients and procedures can help prevent insufficient residual functional liver parenchyma. It is crucial to planned hepatic resection to enable sufficient remnant liver volume, which has a correlation with the quality of remnant liver parenchyma.

The safe volume of remnant liver has been widely investigated, and this topic is discussed in detail in other chapters of this textbook. In brief, it has been established that a remnant liver volume of 20-25% of the total functional liver volume (excluding tumor volume) or a remnant liver volume-to-body weight ratio (RLV-BWR) of more than 0.5% of the body weight in an otherwise healthy liver is sufficient.[144,145] When a chronic underlying liver disease such as hepatitis or chemotherapy-associated liver injury is present, this limit should be 30-40%; if cirrhosis is present, a RLV-BWR of more than 1.4% should be reached in Child A patients.[152] Child B and C patients tolerate only minor or no resection, respectively.[17,153,154]

Aside from the preoperative estimation of remnant liver volume by radiological methods, other techniques have been evaluated to estimate hepatic function, mainly in cirrhotic patients. Some of these techniques are discussed in **Chapter 5** (Liver Function Assessment Before and After Hepatic Resection).

Patients preoperatively identified as being at high risk for PLF due to an insufficient future remnant liver could benefit from techniques to increase the remnant parenchyma, such as by portal vein embolization (PVE). Preoperative PVE of the hepatic segments to be resected induces a hypertrophy of the remnant segments and prevents an acute increase of the portal vein pressure at the time of resection. A degree of hypertrophy of more than 5% after three to four weeks of PVE is associated with improved outcomes after liver resection.[155–158] This topic is described in more detail in **Chapter 7** (Portal Vein Embolization, Transarterial Chemoembolization

and Local Ablation of Hepatic Tumors).

If the remnant liver is small, with a risk of small-for-size syndrome (usually less than 0.6% of body weight for major resections and less than 0.8% for partial liver transplantation), portal pressure can be reduced by ligature of the splenic artery.

Ischemia-reperfusion injury following prolonged vascular occlusion can be prevented by liver preconditioning (ischemic or pharmacological).[159–162] Ischemic preconditioning is the most used method and consists of a brief period of hepatic ischemia, usually 10 minutes, followed by a period of reperfusion before a prolonged period of vascular clamping.[163]

Intraoperative strategies to minimize blood loss include use of low central venous pressure, vascular clamping (preferably intermittent to avoid prolonged periods of hepatic ischemia), and hemostatic agents and surgical devices. Avoiding blood loss and blood transfusion should reduce the risk of postoperative liver failure.

Finally, venous drainage of the remnant liver should be optimized. Hepatic congestion could lead to bleeding in the cut surface, liver dysfunction, and impaired capacity of regeneration of the congested segments.[164] Adequate knowledge of the venous system anatomy, venous reconstruction when necessary, and fixation of the remnant liver in its anatomical position are measures to prevent congestion and liver failure.[165]

MANAGEMENT

Early detection of PLF is crucial to its management. Monitoring liver function by routine biochemical liver function tests is essential to recognize and predict PLF, as proposed with the ISGLS criteria and the 50-50 criteria. Severe PLF can lead to multiple organ failure and death. Clinical manifestations include potentially lethal renal failure due to relative hypovolemia and severe renal vasoconstriction leading to acute tubular necrosis, hepatic encephalopathy (from asterixis up to coma), ventilatory dysfunction due to arterio-venous shunt, hyperbilirubinemia, coagulopathy, and postoperative systemic inflammatory response syndrome. Reduced peripheral vascular resistance can lead to hemodynamic instability. Renal failure contributes to azotemia, ascites, and hepatic encephalopathy. Also, PLF increases susceptibility to serial complications, mainly infectious. Sepsis can occur secondary to PLF or aggravate it.[166–168]

Supportive therapy for system failures may require mechanical ventilation, vasopressor therapy, fresh frozen plasma, blood transfusion, artificial nutrition, and substitutive renal therapy.

Reversible causes of PLF should be promptly identified and treated. Vascular disorders – such as portal, arterial, or hepatic thrombosis – are usually recognized by Doppler ultrasound. Management of portal vein thrombosis and/or venous outflow obstruction is somewhat controversial. Surgical and endovascular approach are possible. Postoperative small-for-size syndrome may be managed by percutaneous splenic artery embolization or with the use of β-blockers or analogues of somatostatin.

Systematic use of antibiotic therapy should be initiated early, since sepsis is a common event leading to death in the context of PLF.[169,170] Cultures for bacteria and fungi should be performed frequently to guide treatment.

Optimal and early therapy for PLF may control metabolic requirements and restore homeostasis and the capacity of the liver to regenerate. If conservative management fails, liver transplantation may be proposed if there is no contraindication.[171] Most patients submitted to liver resection for secondary liver metastases are not good candidates for liver transplantation; however, those undergoing resection of primary tumors with favorable tumor characteristics could be eligible for emergency liver transplantation.[171,172]

Extracorporeal liver support devices (such as MARS® [molecular adsorbent recirculating system] and Prometheus®) using albumin-linked hemodialysis systems, and bioartificial liver-supporting systems using xenogeneic or human hepatocytes, have been tested for acute liver failure.[173,174] These systems lead to biochemical improvements but poor clinical outcomes. They could be used as a bridge for liver transplantation.

Chronic hepatic liver failure is rare, but can occur in cirrhotic patients with very limited ability for hepatic regeneration.

BILE LEAK

DEFINITIONS AND CLASSIFICATION

Bile leak is the most common biliary complication after a hepatectomy, occurring in 0.4% to 33% of cases.[7,17,175–187] Despite a decrease in mortality and other complications after hepatectomy, incidence of bile leak remains an important concern. In fact, a recent study including 2,628 liver resections even demonstrated a rising incidence of bile leak: from 3.7% in the early period of the study to 5.9% in the later period.[184]

The variability in the reported rate of bile leak after hepatectomy may partly be due to differences in definitions. The International Study Group for Liver Surgery (ISGLS) has proposed a standardized definition and grading system for bile leakage as outlined in **Table 5**.[188]

A recent study to validate these concepts included close to 1,000 patients, most undergoing liver resection for colorectal liver metastases, and identified an incidence of bile leak of 7.3%.[176] Most frequently, Grade A (3.3%) and Grade B (3.4%) bile leakage were found. Incidence of Grade C was 0.6%.

Bile leakage can also be classified according to its origin. Nagano et al.[181] classified postoperative bile leaks as i) type A, minor leaks from small bile radicles on the surface of the liver; ii) type B, leaks from inadequate closure of the major bile duct branches on the liver's surface; iii) type C, injury to the main duct commonly near the hilum; and iv) type D, leakage due to a transected duct disconnected from the main duct. Others[187] have classified bile leak as peripheral, i.e. that originating from the cut surface of the liver, and central, i.e. that from the extrahepatic bile ducts.

Bile leak can be graded according to the Clavien score for postoperative complications.[189] ISGLS grading of severity correlates with Clavien score.[176]

Bile leaks following liver resections result in increased morbidity (especially intraperitoneal septic complications and liver failure), prolonged intensive care and hospital stay, increased healthcare costs, and increased mortality rates.[22,175,177,190–195]

MANAGEMENT

While many patients with postoperative bile leak do not need any specific treatment, a large proportion require some form of intervention, from conservative procedures to re-laparotomy.

Several studies with large series of liver resections have reported spontaneous bile leaks healing in most patients.[181,185,186] Bile leaks originating from the cut surface of the liver are more prone to close spontaneously than central bile leaks.[181] A drain output of greater than 100 mL/day was identified as a factor for failure of conservative management in a multivariate analysis.[185] The initial management of bile leaks in patients with a preexisting drain is conservative, including prolonged drainage and antibiotics if persistent fever is present. In the initial report of ISGLS about bile leaks, nearly half were Grade A and no additional radiological, endoscopic, or surgical intervention was necessary. This was confirmed in a large multicenter study including almost 1,000 patients, where 45% of bile leaks were Grade A.

Patients without a well-functioning drain can develop intraperitoneal collections and sepsis. Percutaneous drains are usually placed by interventional radiology to treat these complications.

If bile leak is persistent despite adequate drainage, additional biliary drainage is useful to reduce intrabiliary pressure and bile flow out through the injured bile duct, leading to closure of the fistula. Drainage of the biliary tree is usually obtained using endoscopic retrograde cholangiography (ERC), sphincterotomy or stent placement, or percutaneous transhepatic drainage (PTD). After a hepatectomy with preservation of the common bile duct, ERC with stenting, nasobiliary drainage, or sphincterotomy is usually effective to resolve persistent bile leaks. When a hepaticojejunostomy is present (typically after associated bile duct resection), PTD is the best modality of biliary drainage.[196]

More aggressive treatment by laparotomy is reserved for failure of conservative endoscopic or radiological management, and is associated with a high mortality rate.[190] Failure of non-surgical management includes persistent bile leak, biliary peritonitis, and sepsis. Surgical drainage of a bilioma or a bile leak is the most frequent procedure, but in some cases bilioenteric anastomosis or even re-hepatectomy is needed. The frequent presence of adhesions and sepsis makes these procedures more difficult.

A special condition is bile leakage originating from an excluded segment, i.e. a bile duct disconnected from main biliary tree. A typical cause is aberrant biliary anatomy or a non-anatomical resection. Bile leak from a disconnected duct results in persistent bile drainage or recurrent intra-abdominal collection and sepsis. ERC or percutaneous cholangiography usually do not demonstrate any bile leakage; only a fistulogram or percutaneous cholangiography of the involved segmental duct are able to identify the location of the bile leak and the excluded segment. In this setting, endoscopic or percutaneous biliary drainage has no effect. Definitive treatment often requires a bilioenteric anastomosis with the bile duct disconnected, or a resection of the respective hepatic segment.[197–199]

Table 5. ISGLS definition and grading of post-hepatectomy bile leak.

DEFINITION
Bile leak is defined as fluid with an elevated bilirubin level (≥ three times the serum bilirubin level) in the abdominal drain or intra-abdominal fluid on or after postoperative day three or the need for radiological intervention drainage owing to biliary collections or re-laparotomy due to biliary peritonitis.
GRADING
Grade A- Bile leak requiring no or little change in patients' clinical management
Grade B- Bile leak requiring a change in patients' clinical management (such as additional diagnostic or interventional procedures) but manageable without a re-laparotomy. OR: a Grade A bile leak lasting for > 1 week.
Grade C- Bile leak requiring re-laparotomy

ISGLS: International Study Group of Liver Surgery. (Adapted From Koch et al.[188]).

RISK FACTORS

Despite the heterogeneity of definitions for bile leakage, some risk factors are well established in the literature.

Hepaticojejunostomy has been identified as a risk factor for bile leaks (rates from 13.6% to 21% when a hepaticojeunostomy is associated, versus rates from 3.2% to 4.6% in hepatectomy only).[187,200] In fact, complex liver resections have been associated with a higher incidence of postoperative bile leakage.[177] A recent study including more than 2,600 hepatic resections between 1997 and 2011 identified the following independent predictors of bile leak: i) bile duct resection, ii) extended hepatectomy, iii) repeat hepatectomy, iv) en bloc diaphragmatic resection, and v) intraoperative transfusion. The authors report an increase in the incidence of bile leakage in more recent years (from 3.7% to 5.9%), associated with the more frequent performing of complex hepatectomies.[184]

Other studies have identified specific risk factors for bile leakage after hepatectomy, including central bisectionectomy, repeat hepatectomy, a large cut surface area ($\geq$57.5 cm^2), intraoperative blood loss $\geq$775ml,[183] exposure of the major Glisson's sheath,[175,181] resections including segment 4, peripheral cholangiocarcinoma,[179] and long operative time.[201] Most of these factors characterize complex liver resections.

Some procedures, such as surgery for hydatic cysts or polycystic liver disease, are associated with high rates of postoperative bile leakage.[202–204] Biliary strictures previous to hepatectomy can also be responsible for postoperative bile leakage, and can originate from previous surgery, tumor ablative techniques (such as radiofrequency), or intra-arterial chemoembolization. Sadamori et al.[182] suggest latent strictures as the main cause of bile leakage requiring endoscopic or percutaneous treatment after liver resection for hepatocellular carcinoma.

PREVENTION

Despite the use of several strategies reported to prevent bile leak, or to detect and repair it intraoperatively, incidence of postoperative bile leak is still substantial. This is due, at least partially, to greater complexity of liver resections, as described in the section above. However, some points should be kept in mind to avoid this potentially fatal complication.

When a hepatectomy carrying a high risk of postoperative bile leakage (such as major hepatectomies, resections including segment 4 or with major Glisson's sheath exposition, or re-hepatectomy) is contemplated, preoperative assessment of the biliary anatomy should be considered to avoid intraoperative injury of hepatic ducts.[190,201]

Adequate intraoperative identification and closure of small and large bile ducts on the cut surface is crucial to avoid postoperative fistula.

A recent meta-analysis demonstrated a decreased risk of bile leak using a vessel-sealing system when compared with the clamp-crush method.[205] However, published studies are limited and have significant heterogeneity. Thus, considering the scarcity of randomized controlled trials, it is not possible to declare the superiority of one technique among the various techniques for parenchymal cross section.

Besides parenchymal transection, intraoperative detection and repair of bile leak seems to prevent postoperative fistula. There are many reports of reduction of bile leak after introduction of intraoperative detection tests.[175,187,206]

Various methods to identify bile leaks after parenchymal transection can be applied, and any detected bile leak point should be sutured. An easy method is the application of white gauze on the transection surface and verification of bile-tainted areas. The "white test" is a largely used tool with promising results in intraoperative detection and prevention of postoperative bile leak. A fatty emulsion is injected (usually in the cystic duct) and any extravasation detected is adequately sutured. The advantage of this tool is that the test can be repeated without contamination of the resection surface, because the fatty emulsion can easily be washed away with saline without leaving any color behind.[207–211] A prospective study including 137 patients validated the white test and found a postoperative bile leakage rate of 23% in the control group versus only 5.3% of tested patients ($P<0.01$).[208]

Other methods include the injection of solutions or air (air leak test) into the main biliary tract, usually by a catheter inserted through the cystic duct. Recent studies have demonstrated an increase in intraoperative detection of bile leaks and reduction of postoperative bile leak.[212] While the only randomized trial that assessed the efficacy of bile leak testing using saline[195] found a similar incidence of bile leaks in both the test group and the control group (6% vs. 4%, respectively) after liver resections, another series demonstrated a reduction of postoperative bile leaks. Zimmitti et al.[212] reported a rate of postoperative bile leak of only 1.9% when the air leak test was used, against a rate of 10.8% when the test was not performed. The test allowed for identification of uncontrolled bile ducts in 62.1% of patients. Yamashita et al.[175] reported no bile leaks in 102 consecutive liver resections after they started using intraoperative testing with transcystic saline injection. Before using the test, the rate of postoperative bile leak was 4.5% in 679 hepatectomies. Lam et al.[213] evaluated a test with injection of methylene blue and found a reduction in the incidence of postoperative biliary fistulae. Other recent studies[206,214] have reported a reduction of postoperative bile leaks with the use of a leak test with indocyanine green (ICG) fluorescent cholangiography. Kaibori et al.[206] identified postoperative bile leaks in 10% of the control group (conventional ICG test group) versus no bile leaks when ICG with PDE was used ($P<0.05$). Similarly, Near Infrared Imaging (NIR) has also

been used for intraoperative identification of bile leaks;[215] however, these recent techniques require equipment that is not widely available.

There is actually no consensus concerning the use of intraoperative tests for preventing bile leakage, but evidence suggests that classical cholangiography and injection of methylene blue are not useful for this purpose. Also, most studies are with a small number of patients and in single institutions without external validation.

The value of fibrin glue or other topical sealant application to reduce bile leakages has not yet been properly appraised.[216] Despite some studies suggesting a beneficial effect,[179,217] two randomized trials including 300 and 310 patients found similar incidence of postoperative bile leaks with the use of fibrin sealant and in controls (10% vs. 11% and 14% vs. 14%).[119,218]

The use of omental wrapping after hepatic resection is supposed to reduce the incidence of bile leakage; however, a recent retrospective study showed no differences with this technique.[219]

OTHER COMPLICATIONS

SURGICAL SITE INFECTION AND SEPSIS

Surgical site infection (SSI) is the most common nosocomial infection in surgical patients, accounting for 38% of all such infections. SSI after liver resection occurs in 3% to 21% of cases[3,182,220–224] and is associated with increased postoperative liver failure and mortality.[220]

The main risk factors associated with this complication are postoperative bile leak, preoperative biliary drainage, the presence of infected bile, repeat hepatectomy, inadequate postoperative glycemic control, obesity, excessive blood loss, major hepatectomy, and the presence of multiple comorbidities.[182,222–226]

A large study using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database and including 2,332 patients found pre-operative open wound, hypernatremia, hypoalbuminemia, elevated serum bilirubin, dialysis, and longer operative time as predictors of SSI.[221]

Three recent studies[182,220,222] evaluating SSI after HCC resection identified bile leak as a risk factor for organ/space SSI, which is more frequent than wound SSI. Incidence of SSI varied from 14% to 21%, and in one study it was associated with increased mortality (11% vs. 0.7%). Beyond bile leak, other risk factors for SSI were blood loss, prolonged surgery, and re-hepatectomy.

A Japanese study[226] suggested the presence of positive bile culture as a risk factor for SSI. They found bile culture positives in 83%, 8%, and 10% of patients operated on for hepatolithiasis, HCC, and colorectal liver metastasis, respectively.

Thus, avoiding postoperative bile leakage and reducing blood loss are potential strategies to reduce infectious complications after liver resections. Rigorous postoperative glycemic control is essential, and early recognition of postoperative infection as well as prompt administration of broad-spectrum antibiotics is crucial. Delayed antibiotic therapy was associated with increased infectious mortality in one study.[223] However, there is no evidence that routine use of postoperative systemic antibiotics reduces postoperative infective complications.[227] Also, the use of routine drainage after liver resection is considered controversial.[228–230] Usually, routine drainage is not recommended in patients with chronic underlying liver disease, and is recommended for patients with high risk of postoperative bile leak (such as in the case of hepaticojejunostomy). For the other patients, there is no strong evidence of advantages using routine drainage.

The evidence that disruption of gut barrier function and intestinal bacterial overgrowth can promote bacterial translocation and infectious complications[231,232] has led to the use of early enteral nutrition and symbiotic treatment as promising approaches. Symbiotic treatment is a combination of prebiotics (non-digestive food that alters the growth and activity of colonic flora) and probiotics (viable bacteria that improve the intestinal microbial balance) that reduces the rate of infectious complications after hepatobiliary surgery.[233,234]

Postoperative sepsis and liver failure are serious complications after liver resection that present a potent combined effect. Postoperative liver failure leads to a global suppression of the immune system. The reduced ability of Kupffer cells to eliminate pro-inflammatory mediators, bacteria, and bacterial products leads to an amplified inflammatory response. In another sense, the sepsis per se aggravates the liver dysfunction.[235]

Transitory liver dysfunction after major hepatic resection challenges the diagnosis of sepsis, since the typical picture of fever and leukocytosis may not be present and hyperbilirubinemia and encephalopathy may be due to the liver failure.[236]

Diabetes mellitus represents a higher risk of sepsis after hepatectomy for hepatocellular carcinoma.[237]

In most cases digestive bacteria are involved, but other aerobic and anaerobic bacteria and fungi may be at the origin of sepsis. Polymicrobial infection occurs predominantly when preoperative biliary drainage, prolonged sepsis, and previous use of antibiotic therapy is present.[223]

RESPIRATORY COMPLICATIONS

Incidence of respiratory complications after upper abdomen surgery varies between 7.5% and 80%, depending on the

definition applied.[238–240] After liver resection, pneumonia and pleural effusion are common complications, occurring in approximately 1.9-13% and 5-40%, respectively.[2,3,14] Pulmonary embolism is a less common complication (incidence less than 3%), although rates of up to 10% have been reported after living-liver donation.[3,241]

Diabetes and blood transfusion have been identified as independent risk factors for pneumonia after hepatectomy. Also, prolonged operative time and the use of nasogastric decompression are related to respiratory infection. Transverse subcostal bilateral incision, right liver resections, neoadjuvant chemotherapy, and prolonged surgery are associated with increased risk of pleural effusion. Chemotherapy-associated liver injury has been associated with increased postoperative morbidity.[240] Major resection of a non-cirrhotic liver has been identified as a risk factor for pulmonary embolism. Thrombosis of the hepatic veins is a potential source of pulmonary embolisms.[242,243] It is worth noting that a prolonged prothrombin time is not a protective factor, and thromboembolic prophylaxis should be used even in patients with a prothrombin time less than 50%.

Measures that possibly prevent respiratory complications include strict intraoperative glycemic control, periodic intraoperative reinjection of antibiotics, minimizing blood loss, use of thromboembolic prophylaxis with low-molecular-weight heparin, optimization of postoperative pain control, and use of postoperative noninvasive continuous positive airway pressure. Also, avoiding bi-subcostal incision and the use of nasogastric tubes should be helpful.[240]

RENAL FAILURE

Acute renal failure after large hepatectomies is the most serious postoperative renal complication. Its incidence may reach 15%, and some known risk factors are cardiovascular disease, elevated alanine aminotransferase (ALT), underlying renal disease, and diabetes mellitus.[237,244] The use of low central venous pressure (CVP) does not seem to increase the risk of renal failure. In fact, the incidence of renal failure attributable to a low CVP approach has not been demonstrated.[87] The precise mechanism of liver failure after hepatectomy is unknown. Acute tubular necrosis and hepatorenal syndrome may be responsible for postoperative renal dysfunction.

Hepatorenal syndrome occurs mainly in patients with cirrhosis, and it is characterized by oliguria and a low urine sodium concentration. Perioperative intravascular volume depletion can lead to renal ischemia and precipitate hepatorenal syndrome.

Rehydration and diuretics are usually sufficient to revert mild acute renal failure. Mannitol and hemodialysis can be necessary if severe renal dysfunction occurs.

PORTAL VEIN THROMBOSIS

Portal vein thrombosis (PVT) after liver resection is rarely reported, and most of the literature on postoperative PVT is on liver transplantation, where vascular complications are more frequent. However, the increasing extent of liver resections, mainly with associated vascular clamping, resection and reconstruction, has made this complication more frequent. Yoshiya et al. reported an incidence of 9.1% of PVT after hepatectomy, but most cases were peripheral (63%).[245]

Clinical manifestations of PVT after liver resection are variable. Abdominal pain, nausea, vomiting, anorexia, weight loss, diarrhea, and abdominal distention can be related to bowel congestion or ischemia and ascites. Esophageal varices, splenomegaly, hemorrhage, and cavernous transformation may be present due to the development of portal hypertension and collateral circulation. PVT may remain unrecognized due to the lack of specific symptoms.

Diagnosis is usually made by contrast-enhanced computed tomography (CT), which offers higher accuracy than color Doppler ultrasonography.

Risk factors are based on Virchow's triad (venous stasis, hypercoagulable state, and endothelial injury). Thus, portal vein reconstruction, prolonged Pringle maneuver, small remnant liver volume (probably due to increase in von Willebrand factor/ADAMTS13 ration), and cirrhosis probably increase the risk of PVT.[246]

PVT results in delayed recovery of liver function and delayed liver regeneration.[245] Complete portal vein occlusion and extension of PVT to superior mesenteric vein may result in mesenteric ischemia, sepsis, and death.

Although spontaneous resolution of PVT is not uncommon, anticoagulation therapy should be initiated immediately after diagnosis, if no contraindication is present, in order to limit the propagation of thrombus. If re-canalization does not occur with systemic anticoagulation, site-directed thrombolytics can be used, resulting in high rates of recanalization and low incidence of re-thrombosis. Surgery is required in cases of bowel ischemia.[247]

ASCITES

Ascites is one of the most common complications after resection of hepatic hepatocellular carcinoma, especially due to the presence of cirrhosis. Rates of postoperative ascites vary from 5% to 56%[28–30,248] and can lead to liver failure, early recurrence of hepatocellular carcinoma, and death.[249,250]

Definition of postoperative ascites is variable, but the most accepted is drainage of more than 10 mL/Kg/day. Many factors associated with a high risk of postoperative ascites include: impaired liver function, portal hypertension, small remnant liver, substantial blood loss, and blood

transfusion.[251–253] Cirrhotic patients with preoperative renal dysfunction that undergo liver resection for hepatocellular carcinoma are at risk of massive postoperative ascites and pleural effusion.[252]

Measures such as those to minimizing bleeding and transfusion during liver resection seem to reduce the occurrence of postoperative ascites.

Management of postoperative ascites includes the use of diuretic agents, which is sufficient in most cases. Albumin or fresh frozen plasma can also be used to maintain circulating plasma volume and osmolality. However, even liver transplantation may be necessary in cases of intractable ascites.

A special group of patients at risk for ascites is that undergoing liver resections for polycystic disease, in which ascites can occur in up to 42%. [254] Extensive resection with remnant liver volume less than 30% and the presence of fibrosis are associated with persistent and massive ascites.

SUGGESTED READING

Clavien, P. A. *et al.* The Clavien-Dindo classification of surgical complications: five-year experience. *Ann. Surg.* **250**, 187–196 (2009).

This large study consolidates the applicability of the morbidity classification proposed by the authors. Clinical scenarios were evaluated by different centers worldwide and a high degree of agreement was observed.

Stockmann, M. *et al.* The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery. *HPB (Oxford).* **12**, 139–146 (2010).

This study correlates the LiMAx test with perioperative liver function and a decision tree algorithm is proposed based on this test.

Rahbari, N. N. *et al.* Post-hepatectomy haemorrhage: A definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB* **13**, 528–535 (2011).

Proposal of a standardized definition and grading for post-hepatectomy hemorrhage, aiming for valid comparison among different studies and centers.

Balzan, S. *et al.* The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann. Surg.* **242**, 824–828 (2005).

This large cohort outlines an accurate and easily applicable definition for postoperative liver failure, based on postoperative bilirubin and prothrombin time. The proposed definition has been largerly used worldwide.

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10 Colorectal Liver Metastases

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- *The liver is the most common site of metastases from colorectal cancer, and complete resection of colorectal liver metastases (CLM) is the only potentially curative treatment.*
- *Resection of CLM is associated with low operative mortality and long-term survival has improved, with 5-year survival rates exceeding 50%.*
- *Besides a potential effect on survival, preoperative chemotherapy can increase the resection rate and improve patient selection. Despite no clear benefits for initially resectable CLM, neoadjuvant chemotherapy has a crucial role in initially unresectable disease.*
- *Surgical strategies, such as preoperative portal vein embolization, two-stage hepatectomy and resection combined with ablation, have enabled surgical resection of multiple bilateral CLM.*
- *Selected patients with extrahepatic disease, mainly lung metastases, have been considered for curative resection with substantial increases in overall survival.*
- *Synchronous CLM can be resected after, simultaneously with, or before resection of the primary cancer, according mainly to location, symptoms, and extent of colorectal cancer and hepatic metastases. Simultaneous resection should be avoided if major resections are required for both primary and hepatic diseases.*
- *Surgery for hepatic recurrence of CLM results in similar overall survival to that associated with first hepatic resection, and curative surgery should be considered for each relapse.*

INTRODUCTION

Colorectal cancer is among one of the most common malignancies worldwide, with over 1.2 million new cancer cases and more than 600,000 deaths per year.[1] Among those patients with advanced disease, more than 50% will develop hepatic metastases (nearly 1/3 synchronous and 2/3 metachronous) and many will have disease apparently confined to the liver, the most common site of metastases from colorectal cancer.

Resection of all evident metastases offers the only potential for definitive cure, with reported 5-year survival rates exceeding 50%, compared to a typically poor prognosis for those not undergoing resection.[2,3] While in earlier years only patients with very limited liver metastases were considered for surgical therapy, the number of patients thought to be eligible for surgical therapy has increased based on encouraging results in patients with more extensive disease. In spite of this increasingly aggressive approach, only about 30% of patients with liver-only metastases can be considered surgical candidates.[4–6]

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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Improved systemic chemotherapeutic regimens including oxaliplatin and irinotecan have improved survival and response rates.

The addition of biological therapies such as bevacizumab, cetuximab, panitumumab, aflibercept, and regorafinib have further improved the efficacy of combined-modality therapies for advanced colorectal cancer.[7] Also, strategies including preoperative hepatic preconditioning, staged liver resections, and resection combined with tumor ablation have expanded the ability to safely treat patients with more extensive disease.[8,9]

Multidisciplinary team evaluation is necessary in the management of metastatic colorectal liver patients. A periodical re-appraisal with the hepatic surgeon should be done even in initially non-resectable cases.

This chapter reviews advances in the surgical treatment of colorectal liver metastases (CLM).

LIVER RESECTION FOR COLORECTAL METASTASES

DEFINING RESECTABILITY

The decision to pursue surgical resection should be made based on the ability of the surgeon to locally treat all disease with negative pathological surgical margins, as well as the absence of any extrahepatic disease.

In the past, only patients with very limited disease were considered to be candidates for liver resection, often excluding patients with more than three or bilateral metastases.[5] However, more recent studies have shown that high survival rates can be achieved even in patients with more extensive disease, and a high tumor number or the proximity of major vessels are no longer contraindications for surgical resection, as long as complete eradication of gross disease can be obtained.[6]

The role of surgical margins has evolved over the years, and a predicted margin of less than 1 cm is no longer a contraindication to resection. The width of a negative surgical margin (≥1 mm) does not seem to affect survival, recurrence risk, or site of recurrence.[10–12] A large retrospective series including more than 2,000 CLM resections found similar overall survival (OS) for surgical margins of more than 1 mm and of more than 10 mm (**Figure 1**), better than for positive margins.[13] Also negative margins of less than 1 mm resulted in better OS than positive margins.[13] However, in the era of modern chemotherapy regimens, even R1 procedures performed by necessity in subjects initially deemed unresectable or marginally resectable might be beneficial in a selected group of patients, mainly those with optimal response to chemotherapy.[14–20] In fact, positive

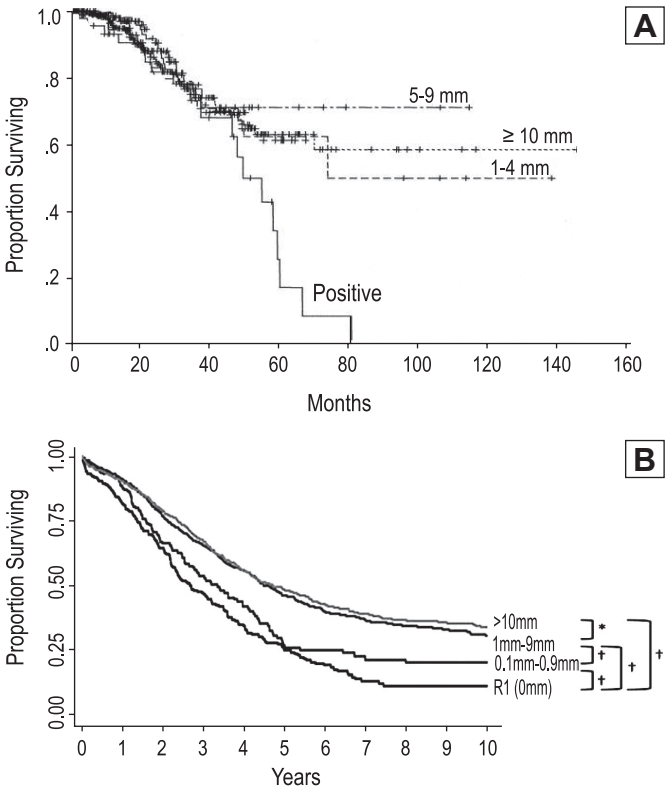


Figure 1. Survival stratified by margin status. Two major series evaluating the influence of surgical margin status on overall survival following colorectal liver metastases resection. **A**) No significant difference in survival in patients with a negative surgical margin, regardless of the width of the margin. Adapted from Pawlik et al.[12] **B**) No significant difference in survival in patients with a negative surgical margin of more than 1 mm. * P not significant; † P< 0.05. (Adapted from Sadot et al.[13])

margins may be a surrogate indicator of the biology of tumor rather than an independent predictor of survival, as demonstrated by multivariate analysis in some recent studies.[15,17] Nonetheless, the need of extensive procedures, such as vascular and/or contiguous organs resections, should not preclude patients from a potentially curative surgery (R0 resection) when feasible.

Standard requirements for the resection of hepatic colorectal metastases comprise the excision of all lesions (combined or not with ablation techniques) with sufficient functional remnant liver parenchyma. Sufficient remnant liver volume with adequate i) blood inflow, ii) blood outflow, and iii) biliary drainage is necessary. The remnant liver volume depends on the parenchymal features. Patients with diseased parenchyma require a larger remnant volume. Thus, cirrhosis, steatosis, and chemotherapy-associated liver injury (CALI) must be considered to accomplish a safe resection **(Table 1)**. Further information can be found in **Chapter 4** (Underlying Liver Disorders in Hepatic Surgery) and **Chapter 22** (General Technical Aspects of Liver Resections) of this textbook.

Such changes have led to the development of new strategies to achieve complete CLM resection. Frequently used strategies aim to increase the proportion of liver parenchyma free of metastases through portal flow modulation (embolization or ligation), or to reduce the burden of metastatic disease (chemotherapy). Local ablative technologies (including radiofrequency and microwave) can be associated in the clearance of the remnant hepatic parenchyma. Portal vein embolization and ablative technologies, including technical issues, are detailed in **Chapter 7** (Portal Vein Embolization, Transarterial Chemoembolization, and Local Ablation of Hepatic Tumors). Technical aspects of liver resections are outlined in chapters in **Section 4** (Technical Aspects of Liver Resections).

Concerning anatomical and non-anatomical resections, no oncological benefit has been proven for one over another. However, a potential advantage of a non-anatomical resection is the sparing of liver parenchyma, probably making patients more suitable to repeat hepatectomies in case of liver recurrence.

The paradigm towards complete resection of all disease has also shifted towards the management of patients with liver metastases and concomitant extrahepatic metastases. Recent studies have shown that long-term survival can be obtained in patients with concomitant lung metastases or even periportal lymph node metastases, although prognosis is generally poorer. However, the presence of aortocaval lymph node metastases or multiple extrahepatic metastatic sites portends a poor prognosis, and surgical resection should generally not be performed in these patients.[21,22]

PREOPERATIVE STAGING OF PATIENTS WITH COLORECTAL LIVER METASTASES

In order to assess the extent of tumor burden, every patient that presents with potentially resectable liver metastases should be subject to careful preoperative evaluation.

To perform *a la carte* procedures, avoiding futile and/or extensive resections, accurate information concerning both intra- and extrahepatic disease must be obtained. Improved preoperative assessment, including positron emission tomography (PET) imaging, has been responsible for a decrease in the rate of non-therapeutic laparotomies over the years.[23]

Table 1. Current Criteria Defining Resectability for Surgical Resection of Colorectal Liver Metastases.

Criteria
1. Macroscopic and microscopic (R0) treatment of the disease is feasible with either resection alone or resection combined with local ablation.
2. Sufficient remnant liver volume (staged procedures should be considered). 2a. 20% if normal liver 2b. 30% if chemotherapy-associated liver injury 2c. 40% if cirrhosis
3. Vascular inflow, outflow, and biliary drainage can be preserved.

Hepatic assessment

Contrast-enhanced high quality cross-sectional imaging is routinely used to evaluate intrahepatic metastases. The role of cross-sectional imaging is to define the number, location, distribution, and relation of hepatic tumors to vascular and biliary structures.[24] This information is useful to determine resectability and to plan the best surgical approach. In addition, radiologists reviewing images should be familiar with the amount of previous chemotherapy. Changes such as sinusoidal congestion and fatty replacement are frequent in patients undergoing preoperative chemotherapy and can lead to alterations in the appearance of the liver, resulting in false positive and negative studies.

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most frequently used cross-sectional methods. CT is the most often used, but emerging data suggests that MRI have a greater sensitivity.[25,26]

Triphasic contrast-enhanced CT scan has a sensitivity of 80-90% to identify liver metastases.[27–29] However, CT

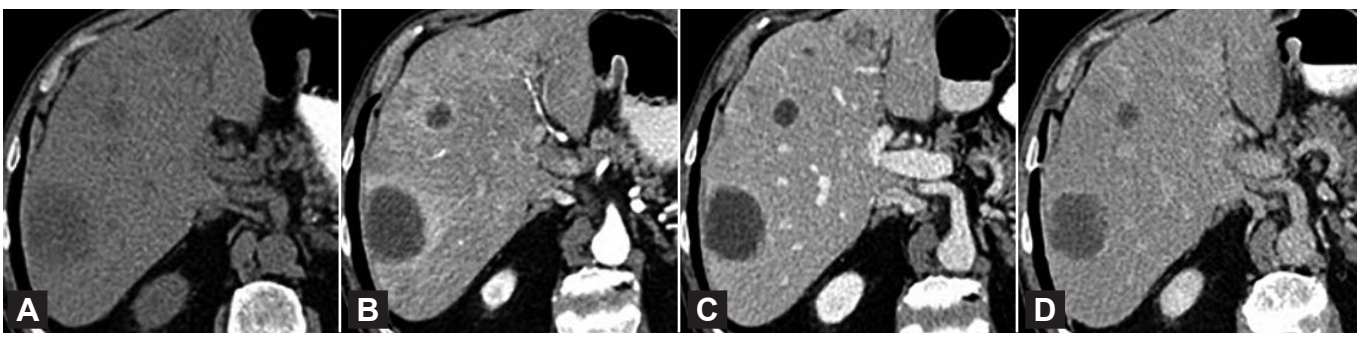


Figure 2. Colorectal liver metastases (CLM) aspect on dynamic computed tomography (CT). Lesions are poorly visualized on unenhanced CT (**A**) and demonstrate less enhancement than surrounding parenchyma on arterial (**B**), portal (**C**), and venous (**D**) phases. (*Courtesy of Dr Gustavo F Luersen, Department of Radiology, Hospital Moinhos de Vento, Brazil*)

lacks the sensitivity and ability to characterize lesions of less than 1 cm. The arterial phase is useful to define arterial anatomy and identify co-existing benign lesions. Colorectal metastases are best identified on the CT portal phase, when they usually appear as hypodense lesions (**Figure 2**). Nonetheless, CT scan is the preferred method to perform volumetric assessment.

Contrast-enhanced MRI has an accuracy of 80-90% to assess the extent of liver disease.[30–32] Compared to CT scan, MRI has the ability to potentially differentiate indeterminate lesions.[33,34] It also has a greater sensitivity for the detection of sub-centimeter hepatic tumors, especially when using liver-specific contrast agents (such as Gd-EOB-DTPA, Primovist® in Europe, and Eovist® in the USA) and/or diffusion-weighted imaging (DWI).[35–40] Like CT, detailed anatomy and volumetric data can be obtained, but without ionizing radiation exposure. Furthermore, MRI has a notable capacity to detect focal lesions in patients with hepatic steatosis. This ability makes it a particularly useful method for patients submitted to previous chemotherapy (CALI), as well as for those who are obese and/or diabetic.

Despite the potential benefits of MRI over CT, the latter is the cross-section imaging modality most frequently used for intrahepatic assessment, mostly due to its lower cost and broader availability. Moreover, the actual superiority of MRI over conventional multi-detector CT imaging in the management of these patients is still controversial, and most centers will use MRI scans selectively. A recent study with modern imaging modalities suggests that thoraco-abdominal CT provides adequate baseline evaluation, while MRI is the most rational approach to the subset of patients that will need staging and re-staging after neoadjuvant chemotherapy.[41]

The exact role of PET imaging in the assessment of intrahepatic disease remains controversial, since its sensitivity remains poorer than other imaging methods.[41–43] Importantly, it is preferable to obtain PET imaging prior to any preoperative chemotherapy since this decreases the sensitivity of F-fluorodoxyglucose (FDG) PET. Inflammatory tissues have increased FDG uptake and may result in false positive findings.

Extrahepatic assessment

A tailored work-up, according to the chance of additional metastatic disease being found and potentially change the patient management, should be performed.

Chest CT is usually indicated on preoperative assessment of colorectal cancer; however, preoperative CT scan detects sub-centimeter or indeterminate pulmonary nodules in approximately one third of patients submitted to CLM resection. Of these nodules, nearly one quarter are ultimately proven to be metastases, but they do not impact 3-year disease-specific survival after CLM resection. Thus, indeterminate or sub-centimeter pulmonary nodules seen on CT scans should not be considered a contraindication for liver resection.[44–48]

Assessment of pulmonary and other extrahepatic metastatic sites can be done by additional whole-body imaging modalities such as PET-CT and DWI MRI.

Positron emission tomography with 18-fluorodeoxyglucose (FDG PET) more recently has been introduced in the preoperative evaluation of patients with hepatic colorectal metastases. While cross-sectional imaging relies on anatomical and vascular changes in the liver parenchyma as a result of tumor growth, FDG PET imaging visualizes the increased uptake of glucose in tumor cells and is thus a form of functional imaging. When combined with CT imaging (PET-CT), FDG PET can provide an even more accurate depiction of disease spread.[49] Several studies have shown that PET imaging detects occult sites of extrahepatic disease in up to one third of patients, significantly altering clinical management in the majority of these cases.[42,43] Response to chemotherapy can be evaluated by a decrease in the standard uptake values (SUV) on PET. However, changes in SUV can lead to a decrease in the sensitivity of FDG PET. This stresses the importance of performing PET imaging before starting chemotherapy.

Diffusion-weighted MRI (DWI) is a rapidly evolving functional imaging modality for whole-body evaluation. DWI derives its image contrast from differences in the motion of water molecules between tissues. Recent comparisons with PET indicate a similar diagnostic ability of whole-body DWI (WB-DWI) in the work-up of oncological patients.[50,51] In the near future, WB-DWI will probably be performed before a PET-CT is done. WB-DWI is free of ionizing radiation and of contrast media, making it a suitable tool to optimize medical imaging workflow in metastatic patients.

In summary, often more than one imaging modality is required to gather the preoperative information needed. While CT, PET, and MRI have a comparable sensitivity for detection of large liver metastases, MRI excels at detection of sub-centimeter liver metastases and re-staging after chemotherapy. PET scan can alter clinical management in up to a third of patients, mostly due to the detection of occult sites of extrahepatic disease.

Further details on radiology of the liver can be found in **Chapter 2** (Radiological Anatomy of the Liver).

INTRAOPERATIVE ASSESSMENT AND INTRAOPERATIVE ULTRASOUND

Before liver resection is begun, a careful intraoperative assessment of the liver and abdominal cavity should be performed to evaluate the extent of intrahepatic disease and potential presence of unexpected extrahepatic intra-abdominal disease. To prevent patients from undergoing a non-therapeutic laparotomy, some have advocated a

laparoscopic assessment prior to open surgery, including intraoperative ultrasound.[52] However, with increasing accuracy of preoperative staging modalities, the rate of non-therapeutic laparotomies has dramatically decreased over recent years and is currently as low as 4.7%. Therefore, the yield of routine staging laparoscopy is considered to be low.[23]

Intraoperative ultrasound (IOUS) is an important addition to the operative evaluation of patients undergoing planned liver surgery. Not only does it provide valuable information to aid the surgeon in the planning and executing the hepatectomy, IOUS can also detect additional intrahepatic metastases as small as 3-4 mm in size. Studies have found that, even in the era of modern high quality preoperative imaging, IOUS has detected additional metastases in 1.4-10% of patients and can change the surgical strategy.[33,53–56] IOUS should always be performed using a dedicated intraoperative probe and experienced operator. Additional liver metastases are more likely to be detected in patients with multiple and hypoechoic tumors.[33,55] Moreover, the use of contrast-enhanced intraoperative ultrasonography (CE-IOUS) for patients with colorectal metastases seems to improve the sensitivity of intraoperative ultrasonography.[57] CE-IOUS may be helpful in identifying disappearing liver metastases from colorectal carcinoma after chemotherapy.[58]

Detailed techniques of IOUS can be found in **Chapter 3** (Intraoperative Assessment of the Liver).

OUTCOMES OF LIVER RESECTION FOR COLORECTAL METASTASES

Perioperative outcomes

The perioperative mortality of liver resection for colorectal metastases has decreased in recent decades, currently 1% or less in most high-volume centers (**Table 2**).[59] Complication rates remain similarly low, even following major resections. In a randomized controlled trial comparing outcomes following preoperative chemotherapy, overall mortality and morbidity was 1% and 20%, respectively.[60] One of the most important factors having an impact on the risk of adverse postoperative outcome is the presence of associated comorbidity. In one study, Breitenstein et al.[61] found that the presence of multiple comorbidities was associated with a 1.5 times increased risk of major postoperative complications. Selecting the appropriate patient for surgical therapy is important in order to minimize perioperative risk. In addition, the potential for adverse outcome and the complexity of these operations justifies the recommendation that major liver resection be performed at major centers and by experienced surgeons.[62]

Further information on evaluation of risk factors and complications after liver resection can be found in **Chapter 9** *(*Morbidity and Mortality after Liver Surgery*)*.

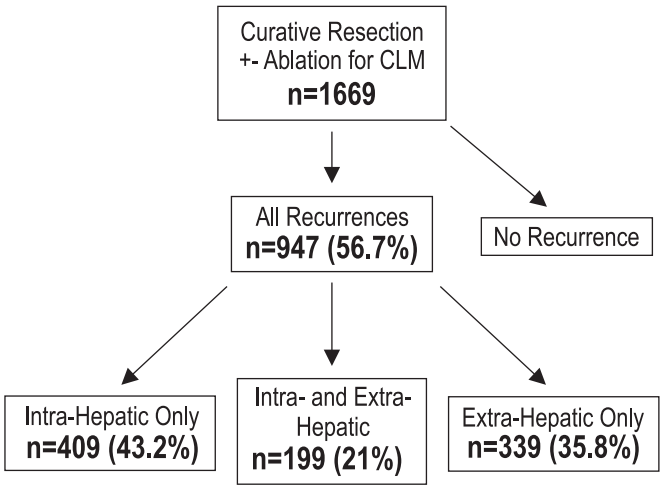


Figure 3. First site of recurrence after 1,669 curative intent surgeries for CLM with a median follow-up of 30 months. 608 (64.2%) patients presented with intrahepatic disease as a component of the first pattern of recurrence, while 409 had only intrahepatic disease. CLM: Colorectal Liver Metastases. (Adapted from de Jong et al.[72])

Long-term outcomes

With increasing safety, improved imaging, and more active chemotherapy, long-term outcomes of patients undergoing resection of liver metastases has markedly improved over the years, with a median survival of up to 46 months and corresponding 5-year survival rates exceeding 50% **(Table 2)**. The actual 10-year survival rate after resection of CLM is 17-36%.[63–70] Nathan et al.,[71] using a model of conditional survival, determined that the probability of surviving an additional five years, given that the patient had already survived three or five years after liver resection, is 40% and 50%, respectively. Considering that prolonged survival can be achieved in palliative settings with modern systemic

Table 2. Studies investigating long-term and short-term outcomes after curative intent liver resection for colorectal liver metastases.

Author and year of publication	Number of patients included	Mortality	Morbidity	5-year disease-free survival	5-year overall survival
Nordlinger, 1992	1568	2%	23%	15%	28%
Fong, 1999	1001	3%	31%	Not reported	37%
Malik, 2007	700	3%	29.5%	31%	45%
De Jong, 2009	1669	Not reported	Not reported	30%	47%

chemotherapy, cure should be considered after a 5-year disease-free survival or a 10-year overall survival.

In spite of these encouraging results, approximately two thirds of patients will still develop recurrent disease after liver resection. In a large cohort of 1,669 liver resections for CLM,[72,73] recurrence was observed in 947 cases (57%) after a median follow-up of 30 months, most of them intrahepatic only. Patterns of recurrence are depicted in **Figure 3**. Of the 947 patients who experienced recurrence, 197 patients (21%) underwent repeat curative intent surgery. Extrahepatic sites of recurrence included the lung, lymph nodes, peritoneum, bone, brain, adrenal, and ovary. Another study, based on 6,025 patients from the LiverMetSurvey registry, reported a recurrence rate of 45.4% after liver resection. Recurrence occurred within six months after hepatectomy in a quarter of cases and was mainly hepatic. Outcomes were poorer in early recurrence compared to late recurrence; however, re-hepatectomy was able to restore better survival, in both early and late relapse.[74]

Several clinical risk scores have been introduced in an attempt to stratify patients by their risk of recurrence and death prior to surgical intervention. In 1999, the Memorial Sloan Kettering Cancer Center group published their *clinical risk score* based on a retrospective review of 1,001 patients.[75] Five clinical variables were used to stratify patients: i) largest tumor size >5 cm, ii) more than one hepatic tumor, iii) disease free interval <12 months, iv) node-positive primary, and v) carcinoembryonic antigen (CEA) > 200 ng/ml). The greater the number of factors, the worse the prognosis. Similarly, Nordlinger et al. proposed a slightly different scoring system, which also incorporated surgical margin status and primary tumor stage.[76] While these and other risk scores offer some guidance to the clinician, and may help in the selection of patients for perioperative management, long-term survival can be achieved even among those with poor prognostic factors, and therefore should not be used to exclude patients from being offered surgical treatment. In addition, these risk scores do not incorporate more direct measures of tumor biology, such as the preoperative chemotherapy response or other biomarkers that may be more powerful predictors of long-term outcome.[77–79]

COMBINING CHEMOTHERAPY WITH HEPATIC SURGERY

NEOADJUVANT AND ADJUVANT CHEMOTHERAPY IN INITIALLY RESECTABLE PATIENTS

Currently, first-line chemotherapeutic regimens for advanced colorectal cancer usually include 5-fluorouracil and leucovorin or capecitabine in combination with either irinotecan (FOLFIRI or XELIRI) or oxaliplatin (FOLFOX or XELOX). Response rates of approximately 40% are seen, with median survival rates in unresectable patients of approximately 20 months. While the benefit of adjuvant chemotherapy in patients with stage III colon cancer is evident, the role and optimal sequencing of chemotherapy in patients with resectable stage IV disease is less clear.

Chemotherapy can be either administered preoperatively as a neoadjuvant regimen, postoperatively as an adjuvant treatment, or pre- and postoperatively as a split regimen. In this scenario, the goal for the administration of chemotherapy is to eradicate micrometastatic disease and prevent early recurrence, and thus prolong survival. However, level 1 evidence to support this strategy is not abundant, and no data is available to compare the efficacy of preoperative versus postoperative chemotherapy. A randomized controlled trial from France (EORTC 40983) investigating the impact of perioperative FOLFOX on long-term outcome in patients with resectable liver metastases showed an improved 3-year recurrence-free survival in the surgery plus chemotherapy group, when compared to the surgery-only group (42% vs. 33%, respectively), although no benefit in overall survival was shown in this trial.[60,80] Another trial investigating the added value of adjuvant 5-fluorouracil and folinic acid showed an increase in 5-year disease-free survival in the chemotherapy group (33.5% vs. 26.7%), although no significant difference in overall survival was detected and the trial was widely criticized for using a relatively inferior chemotherapeutic regimen.[81] On the other hand, the addition of cetuximab to standard chemotherapy (oxaliplatin or irinotecan based) for patients with KRAS exon 2 wild-type tumor genotype with resectable colorectal liver metastases was evaluated in the New EPOC. This randomized trial failed to find benefits for progression-free survival with the addition of cetuximab; in fact, progression-free survival was shorter with this association (14.1 months vs. 20.5 months, p=0.03).[82]

While the precise value of neoadjuvant chemotherapy with regard to overall survival might not be clear, the application of preoperative chemotherapy may be associated with other benefits in terms of increased resection rates and improved preoperative patient selection. First, occult lesions might become apparent while on chemotherapy, thus allowing for timely alteration of patient management and preventing futile surgical intervention. In addition, progression of tumor growth while on chemotherapy is a powerful predictor of worse prognosis. A French study showed that radiologic tumor progression of multiple metastases while on chemotherapy was associated with poor outcome, reporting a 5-year survival of only 8%.[83] In addition, a major or even complete pathological response to preoperative chemotherapy seems to be an extremely powerful predictor of good survival.[79,84,85] However, predicting the pathological response based on

post-chemotherapy imaging can be challenging, and many studies have shown vast discrepancies between the observed radiological response and the actual pathological response.

Despite these potential advantages, preoperative chemotherapy has also been associated with several potential disadvantages. First, patients might have disease progression to a point that their disease becomes unresectable. In addition, perioperative chemotherapy has been associated with increased complication rates. In the EORTC 40983 trial, surgical morbidity increased from 16% to 25% when preoperative chemotherapy was administered, compared to surgery alone. Other studies have also described an association between preoperative chemotherapy and postoperative morbidity, most likely mediated by chemotherapy-associated liver injury (CALI), further defined as chemotherapy-associated steatosis or steatohepatitis and sinusoidal obstructive syndrome.[86–88] For further details on the effects of chemotherapy on liver surgery, please refer to **Chapter 4** (Underlying Liver Disorders in Hepatic Surgery). For these reasons, it is generally recommended that no more than six cycles (three months) of preoperative chemotherapy should be administered in patients with resectable disease, since little oncological benefit is to be expected when chemotherapy is continued beyond this point, but the risk of liver injury and associated morbidity will continue to increase.[89]

CONVERTING UNRESECTABLE TO RESECTABLE DISEASE

High response rates with active cytotoxic chemotherapy regimens have afforded the opportunity to downsize patients initially considered unresectable. The addition of biological agents, such as those directed to vascular endothelial growth factor (bevacizumab, aflibercept, or regorafenib) or epidermal growth factor receptor (cetuximab or panitumumab) have further increased response rates and overall survival, even in patients with disease refractory to conventional first line chemotherapy. Folprecht et al.[90] reported that up to 30% of patients with initially unresectable disease and non-mutated KRAS became surgical candidates after first line cetuximab combined with either FOLFOX or FOLFIRI. Recently, in a multi-institutional trial from Japan including initially unresectable patients receiving upfront FOLFOX plus cetuximab or bevacizumab (and switch to FOLFIRI if still unresectable after six cycles), R0 resection was reached in 47% of cases (50% and 42% in the wild and mutant KRAS group, respectively, P=0.36).[91]

The goal of tumor downsizing is to be able to remove the gross residual disease from all original sites. Liver metastases located near major vascular pedicles that need to be salvaged are ideal candidates (**Figure 4**). In such cases, patients with unresectable liver metastases who would have a poor prognosis without surgery can be offered salvage resection of initially unresectable disease. In a study by Adam et al.[7] investigating the outcome of patients who underwent liver resection of initially unresectable disease, they found the overall 5-year survival was 33%, which compared favorably to those who were initially resectable (**Figure 5**). Patients that become more rapidly resectable (fast responders) seem to present better outcomes than those who need long treatment (slow responders).[92]



Figure 4. A) CT images of a patient with initially unresectable disease (left lesion abutting left portal pedicle); **B**) converted into resectable disease following preoperative chemotherapy. Following chemotherapy this patient was resected with a two-staged approach.

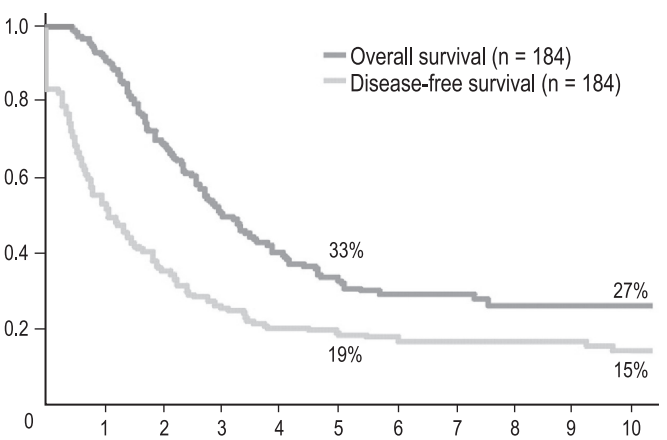


Figure 5. Overall and disease-free survival after surgery of initially unresectable metastases that underwent downsizing chemotherapy. (Adapted from Adam et al.[7])

DISAPPEARING METASTASES FOLLOWING CHEMOTHERAPY

An additional potential disadvantage of preoperative chemotherapy is related to the impact of chemotherapy on the accuracy of preoperative imaging. For example, chemotherapy-associated steatosis can significantly affect the sensitivity of preoperative CT scanning in the detection of colorectal metastases. Moreover, small liver metastases can shrink and disappear while on chemotherapy, further complicating the management of these patients (**Figure 6**). Benoist et al.[93] found that while these lesions might become completely invisible on post-chemotherapy CTscans, viable tumor cells are present in over 80% of these disappearing metastases. Other studies confirmed this discrepancy. Another study by van Vledder et al.[94] showed that viable tumor cells were present in approximately half of all disappearing lesions. In this study, disappearing metastases were common in patients undergoing preoperative chemotherapy, with approximately 25% of patients having at least one lesion disappear. Patients with multiple and small lesions were more likely to have lesions disappear. Importantly, when carefully assessed intraoperatively, approximately 50% of these lesions were detected with IOUS. Moreover, overall survival was not significantly affected if some of these disappearing liver metastases were left surgically untreated, possibly due to the opportunity of these patients to undergo repeat surgical intervention when a recurrence in these untreated lesions was observed during follow-up. In general, it is recommended to completely resect or ablate all known disease sites prior to chemotherapy, to prevent early recurrence and the need for re-operation. In selected cases, small metastases likely to disappear in the future remnant liver after preoperative chemotherapy may be marked with coils before chemotherapy.[95]

EXPANDING THE ROLE OF SURGICAL THERAPY FOR COLORECTAL LIVER METASTASES

MULTIPLE BILATERAL DISEASE

The resectability of multiple hepatic metastases that are not likely to be resected by wedge resections could be increased by using surgical options such as portal vein embolization, two-stage hepatectomy, and resection combined with ablation.[9]

Portal Vein Embolization

Portal vein embolization (PVE) is a well-established strategy to optimize the volume and function of the future remnant liver (FRL) before hepatectomy, reducing the risk of postoperative liver failure. More commonly, preoperative right portal vein embolization (with or without segment 4 portal branch embolization) is performed three to six weeks before right trisectionectomy in patients with FRL less than 30% of total liver volume in patients with CLM (**Figure 7**). Liver metastases (in both embolized and non-embolized lobes) usually have an increased growth rate following PVE and contralateral lesions can developed; however, the impact on recurrence and on overall survival after liver resection is not clear.[96–101] Chemotherapy before PVE or between PVE and hepatectomy seems to reduce tumor progression, improve long-term survival, and does not impede liver hypertrophy.[102–104] About one third of patients requiring preoperative PVE do not reach resection due to disease progression. For further details on PVE, please refer to **Chapter 7** (Portal Vein Embolization, Transarterial Chemoembolization, and Local Ablation of Hepatic Tumors).

Two-Stage Hepatectomy

Another approach in patients with bilateral metastases is a two-stage approach, in which partial resection is performed in the first stage, followed by a second resection after hypertrophy to complete the disease resection (**Figure 8**). Using this

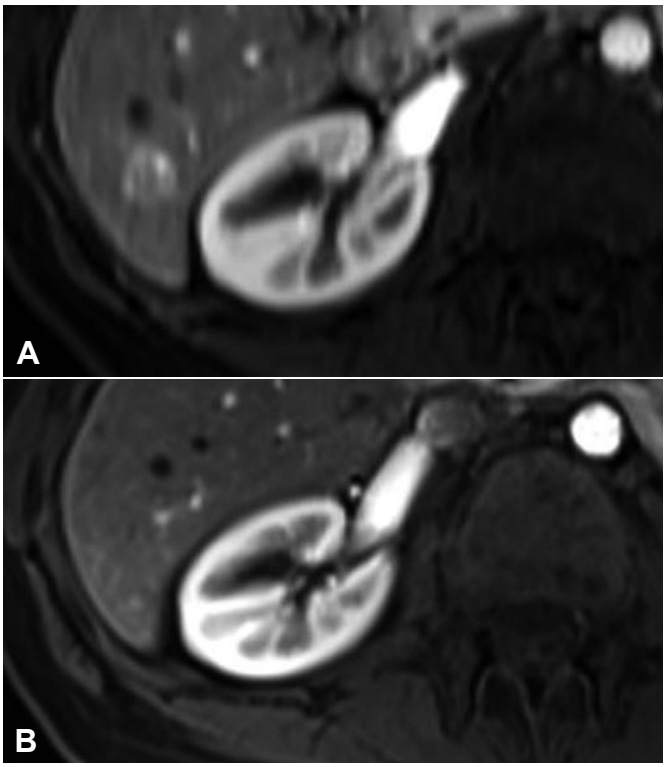


Figure 6. Missing colorectal liver metastases (CLM). **A**) T1-weighted magnetic resonance imaging (MRI) showing a CLM on segment 6 (arrow). **B**) After two months of oxaliplatin-based chemotherapy, the lesion is no longer visible. (*Courtesy of Dr Gustavo F Luersen, Department of Radiology, Hospital Moinhos de Vento, Brazil*)

technique, one hemiliver is cleared of all macroscopic disease during a first operation by either resection or ablation. Most commonly, the minor resection is performed first (usually resection of all metastases from the FRL) followed by the major contralateral resection, in order to avoid gross disease present in the hypertrophying liver. In some cases, the first operation can be combined with portal vein ligation (or postoperative PVE) of the contralateral liver that will be resected later (**Figure 9**).[105] Several studies haveshown that approximately two thirds of patients will be able to complete both stages of the resection without disease progression, and that prognosis of those patients is comparable to one-stage resections.[106]

The associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure is an alternative to PVE for increasing the FRL, in which right portal vein ligation and in situ splitting of the liver parenchyma is performed during the first stage, and after one to two weeks resection is completed. This procedure can be used after ineffective PVE. ALPPS presents high rates of morbidity and mortality, and future studies are required to clarify the benefits of this approach.[107,108]

In general, two-stage procedures allow selection of patients with favorable biology.

Resection Combined with Ablation

In some cases of unresectable disease, surgical resection can be combined with local ablative therapies to achieve complete local therapy of liver metastases. While a wide variety of ablative methods are available, radiofrequency ablation (RFA) is the most commonly used ablation method. More recently, microwave tumor ablation is gaining in popularity. In both approaches, direct tissue heating at the tumor site results in tissue denaturation and cell death. As with resection alone, a curative-intent strategy that utilizes RFA requires the goal of complete ablation in order to achieve durable local control at the site. A preponderance of evidence is emerging that RFA is most successful in small tumors (<3 cm) and those located away from major vascular structures.[109] Yet, it is often such situations in which the disease cannot be resected. Local recurrence rates after ablation vary significantly in reported series, ranging from 4% to 40%. A systematic review and meta-analysis investigating factors associated with local recurrence after RFA found an overall local recurrence rate of 14.7% for colorectal liver metastases treated with RFA.[110]

Outcomes regarding overall and disease-free survival following ablation, with or without resection, are difficult to compare to resection alone given the significant differences in patient selection and other biases. Indeed, de Jong et al. found that, although long-term survival was lower in patients undergoing ablation versus resection (**Figure 10**), oncological characteristics were significantly different, clearly impacting the ability to compare groups in any cohort study.[8,111]

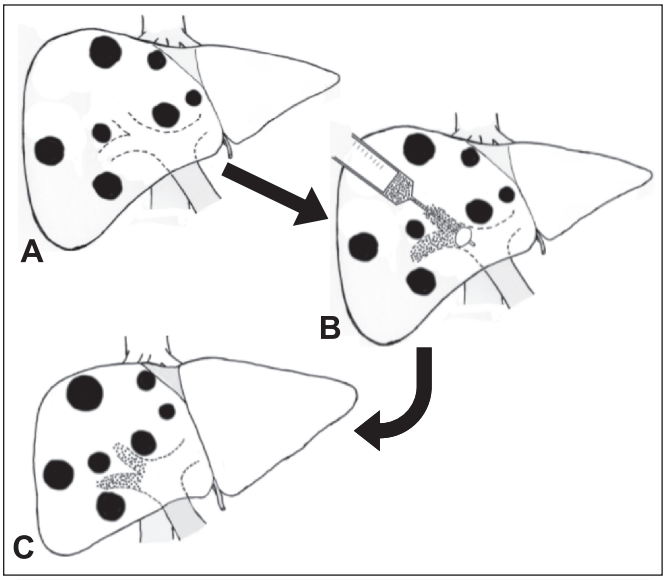


Figure 7. Portal vein embolization. **A**) Schematic representation of multiple colorectal liver metastases and a small future remnant liver (left lobe). **B**) Percutaneous right portal vein embolization (with or without segment 4 portal branch embolization) is performed. **C**) Future remnant liver hypertrophy usually occurs 4-6 weeks after portal embolization and right trisectionectomy is possible.

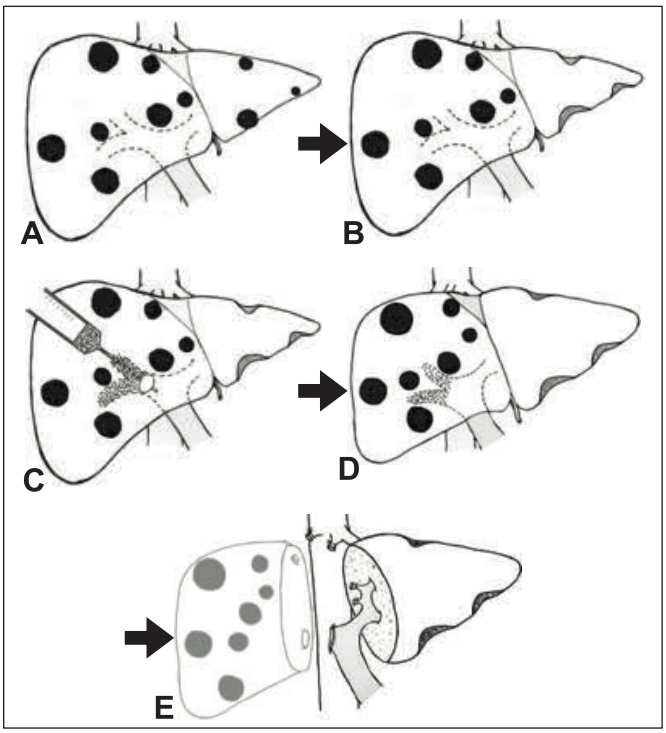


Figure 8. MSchematic representation of two-stage hepatectomy. **A**) Multiple bilateral colorectal liver metastases; **B**) enucleation of CLM of segments 2 and 3 (occasionally, deep located lesions may be ablated); **C**) Right portal vein embolization (with or without segment 4 portal branches embolization) or right portal vein ligation; **D**) Hypertrophy of non-embolized segments (future remnant liver); and E) Extended hepatectomy, usually 4-6 weeks after portal vein occlusion.

HEPATIC RESECTION AND EXTRAHEPATIC DISEASE

Extrahepatic disease commonly includes portal lymph node metastases, peritoneal metastases, and lung metastases, but other sites can be involved. Until recently, the simultaneous presence of hepatic and extrahepatic disease was considered an absolute contraindication to resection due to poor survival. However, recent studies have reported 5-year overall survival rates of up to 42% for selected patients with extrahepatic disease undergoing R0 resection.[21,112–114] These results suggest that surgery could have a role in highly selected patients with limited extrahepatic disease, i.e. with a single extrahepatic site and/or few metastases. Despite acceptable long-term results, recurrence occurs in the vast majority of these patients and this approach should not be considered curative. A recent review suggested that extrahepatic tumors limited to the lung and associated with little extension of hepatic disease (fewer than three lesions) resulted in the best outcomes in the setting of extrahepatic disease.[114] In fact, isolated lung metastasis was the only significant predictor of survival in the evaluation of a prognostic model for concomitant extrahepatic disease.[115]

Lymph node metastases

Microscopic lymph node involvement is present in approximately 15% of patients with liver metastases. It is associated with poor prognosis and generally represents a contraindication to liver resection.[116] However, some challenging points should be considered. First, prediction of metastatic lymph nodes in the hepatic pedicle can be difficult, preoperatively or even intraoperatively. Second, complete hepatic pedicle lymphadenectomy can result in long-term survival if nodal involvement is limited to the hepatic pedicle. However, it is unclear if these results can be extrapolated to patients with grossly enlarged nodes. Thus, hepatic pedicle nodal involvement may not be an absolute contraindication to surgery in selected cases. But there is no evidence that routine portal lymphadenectomy improves oncological outcomes.[117,118] On the other hand, celiac and/or para-aortic nodal involvement is rarely associated with long-term survival.[119–121]

Lung metastases

Retrospective data suggest that simultaneous resection of limited pulmonary and hepatic metastases in selected patients results in long-term survival.[122] Recurrence is frequent in this group of patients, but re-resection allows for adequate overall long-term survival.[123–128] Synchronous hepatic and pulmonary resection can be safely performed, especially if no extended resections are needed. Staged approach could be preferred if liver or lung surgery is likely to be complex, and in this situation the more severely involved organ is treated first. Thus, the presence of pulmonary metastases should not preclude hepatic resection in selected cases if lung disease can be resected or ablated.[129,130]

Peritoneal metastases

Peritoneal metastases is often observed in patients with advanced stage primary tumors. Limited peritoneal disease alone (without other metastatic sites) treated by

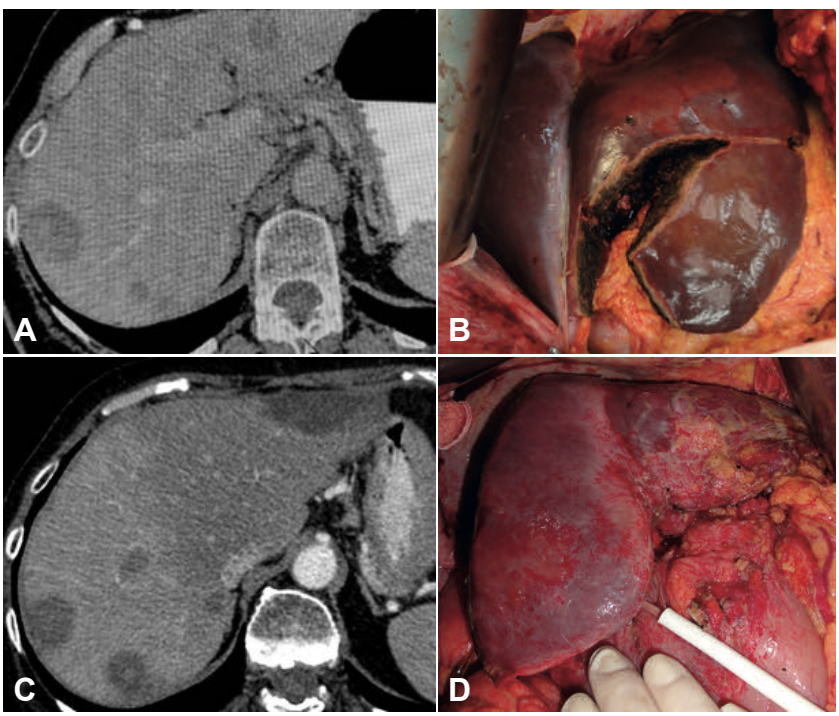


Figure 9. Two-stage hepatectomy for bilateral colorectal liver metastases (CLM). **A**) Preoperative computed tomography (CT) in a patient with multiple CLM in right hemiliver and two lesions in segment 3 (bigger lesion showed). **B**) Intraoperative view during first stage (segmentectomy 3 and right portal vein ligation). **C**) CT 6 weeks after the first stage. Note the hypertrophy of the left liver, arterialization of the right hemiliver (higher density than left hemiliver during arterial phase) and the area of resection of segment 3 (arrow). **D**) Intraoperative view after the second stage (right hepatectomy).

cytoreduction and intraperitoneal chemotherapy has resulted in favorable long-term survival, similar to patients with liver-only metastases undergoing R0 resection. The presence of concomitant but limited extent peritoneal and hepatic disease should not be an absolute contraindication to radical synchronous surgery in selected patients, since 3-year survival rates can reach 55%.[131–133]

In summary, the site of extrahepatic disease, the number of tumors, the ability to undertake a complete resection, responsiveness of disease to chemotherapy, and favorable tumor biology might guide a careful selection of patients that can benefit from radical surgery.

MANAGEMENT OF SYNCHRONOUS LIVER METASTASES AND PRIMARY TUMOR

Synchronous CLM are thought to have less favorable cancer biology and are associated with poorer long-term outcomes.[134] Particular consideration should be given to the patient with synchronous resectable liver metastases and a primary tumor that is still in place, as the options regarding management can be many. Current treatment strategies include various sequences and timing for therapeutic modalities. As with metachronous metastases, the management goals remain the same – complete resection of all macroscopic metastatic disease and integration of systemic therapy, as well as resection of the primary tumor.

Colorectal-first approach. In the past, patients with synchronous metastases traditionally underwent a resection of their primary tumor first, followed by a period to recuperate and potentially undergo systemic chemotherapy, followed by a subsequent staging and liver resection to address their metastases three to six months after colorectal resection. More recently, systemic chemotherapy has often been employed first in order to define the biology before embarking on surgical therapy, particularly in the asymptomatic patient. The main disadvantage of this strategy is the progression of CLM beyond resectability during the primary tumor resection, especially in case of postoperative complications after colorectal surgery. In fact, only a minority of patients with synchronous disease complete the planned treatment using a colorectal-first approach.[135]

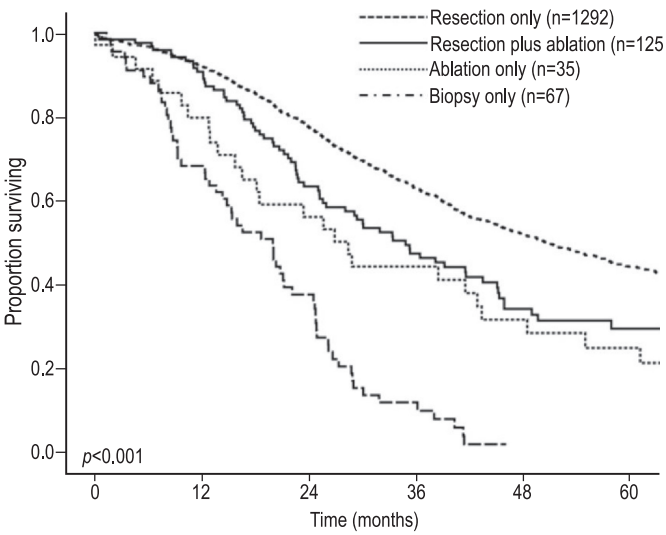


Figure 10. Kaplan Meyer curve showing overall survival in patients undergoing resection only, resection combined with ablation, or ablation only. (Adapted from de Jong et al.[8])

Simultaneous resection. Combined liver and bowel resection, with or without preoperative chemotherapy (or chemoradiation for rectal primary) has been shown to be safe in many cases.[136–141] Perioperative morbidity and mortality rates are similar when a bowel resection is associated with a minor hepatectomy.[139,142,143] In general, it is acceptable to perform a major colorectal procedure and a minor hepatic resection and vice-versa. However, simultaneous major colorectal and major hepatic resections should be avoided or limited to experienced centers.[144] During simultaneous resection, the liver is usually approached first to avoid congestion with increased risk for the digestive anastomosis. Data regarding oncological outcomes after simultaneous versus staged resections for stage IV colorectal cancer are more limited. Despite this, possible equivalent overall and disease-free survival rates, regardless of timing of resection, have been suggested.[145]

Liver-first (or chemotherapy-first) approach. A reversed or liver-first staged approach can be taken.[146] The liver-first approach comprises initial preoperative chemotherapy followed by liver resection and subsequent colorectal resection, with chemotherapy or chemo-radiation between surgeries. The rationale for the liver-first approach is to provide early systemic treatment for patients with stage IV colorectal cancer and to prevent progression of the liver disease while surgery of the primary tumor is undertaken.[146–148] As complications of digestive surgery can delay systemic treatment and enable progression of hepatic tumors, this strategy is particularly useful if digestive anastomosis is risky in patients with extensive liver disease (potentially resectable or initially unresectable). Also, preoperative chemotherapy may reduce the size of CLM, allowing for more conservative liver surgery or resection of initially unresectable disease. Thus, patients with unresectable or marginally resectable synchronous CLM and asymptomatic primary tumors could be initially treated by first-line chemotherapy, followed by liver resection if technically possible. Also, in some symptomatic patients, the primary tumor can be left *in situ* and managed endoscopically (i.e. by stent) or with a diverting ostomy to allow early initiation of systemic chemotherapy. Long-term survival outcomes with this approach are variable.[148,149]

Up-front hepatectomy. Patients with resectable synchronous CLM may undergo liver resection prior to chemotherapy. This strategy has the potential advantage of avoiding the risks related to chemotherapy-associated liver injury and the challenging management of missing liver metastases. Moreover, the oncological benefits for initially resectable CLM are not clear.[80,150–153] On the other hand, neoadjuvant chemotherapy would allow for proper selection of patients, avoiding unnecessary surgery in chemoresistant disease. Such a strategy may be particularly useful in patients with resectable liver metastases and an asymptomatic primary rectal tumor, especially when chemoradiation therapy is being considered prior to proctectomy.

Although no well-defined guidelines are present regarding the optimal management of patients with synchronous disease, any one of the aforementioned strategies can be considered, based on multidisciplinary evaluation.[154] Individual treatment should consider multiple factors, including the presence of symptoms, location of primary tumor and liver metastases, extent of tumor (both primary and metastatic), dominant disease (colorectal or liver), patient performance status, and underlying comorbidities.

In summary, the general directions for the approach of synchronous CLM include: colorectal-first or simultaneous resection for patients with symptomatic primary tumor; chemotherapy-first for initially unresectable or marginally resectable CLM, followed by liver resection if feasible; and up-front hepatectomy or neoadjuvant chemotherapy for patients with initially resectable CLM.

REPEAT LIVER RESECTION

Among the two-thirds of patients who will develop recurrence following apparently complete resection of colorectal liver metastases, approximately 50% will develop isolated recurrences again within the liver.[72,73] For these patients, repeat resection can be considered. As with the evaluation for initial resection, defining resectability should be based on the ability to achieve complete removal of macroscopic disease with preservation of sufficient functional liver parenchyma. If these criteria are followed, repeat hepatectomy (second, third, fourth) is associated with comparable perioperative outcomes to that after primary liver surgery.[155] Several studies have shown that long-term outcomes and patterns of recurrence of repeat resection are comparable to initial resection (**Figure 11**)[53, 156] Clearly, patients offered repeat resection are typically those with favorable biology and few comorbid conditions. In such cases, major resection is performed less commonly and tumor ablation is performed more frequently. The favorable outcomes following repeat surgical therapy support the need to consider a local strategy in patients with recurrent colorectal liver metastases (**Figure 12**).[157,158]

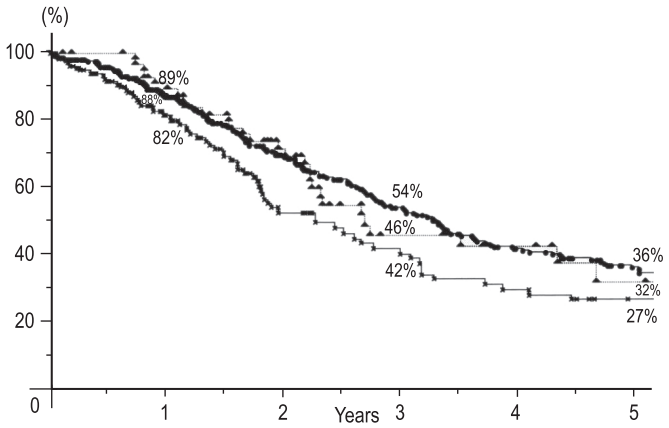


Figure 11. MCumulative survival after the last hepatectomy in patients with only 1 (–•–), only 2 (–×–), or 3 (–▲–) hepatectomies. (Adapted from Adam et al.[156])

LAPAROSCOPIC APPROACH

Laparoscopic hepatectomy has been increasingly performed in specialized centers. Laparoscopic approach for CLM seems to result in short-term benefits regarding surgical blood loss and operative transfusion rate, hospitalization time, and surgical morbidity.[159–163] Regarding oncological outcomes, laparoscopic resection provides similar benefits to open surgery, with 5-year overall survival rates of 36-

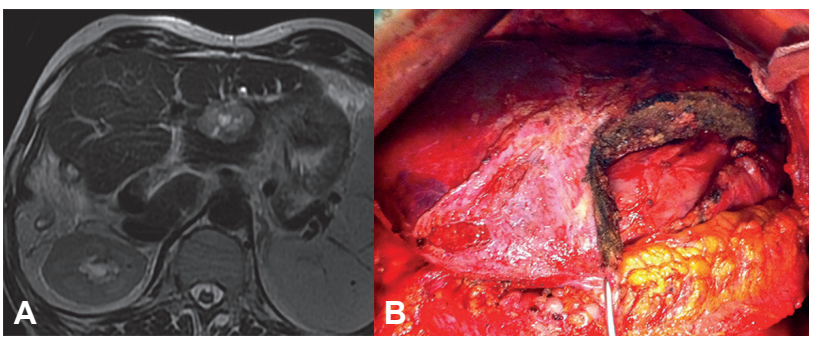


Figure 12. Second hepatectomy for hepatic recurrence 5 years after right hepatectomy for colorectal liver metastases. **A**) T2-weighted magnetic resonance imaging reveals lesion on segment 3 (arrow) in the remnant liver; **B**) Intraoperative aspect of the second hepatectomy (segmentectomy 3). Patient is alive and free of recurrence 3 years after re-hepatectomy.

64%.[162–168] Laparoscopic simultaneous resection of the primary tumor and liver metastases is also an option in selected cases.[169,170] Technical and oncological aspects of laparoscopic liver resections are discussed in **Chapter 27** (Principles of Laparoscopic Liver Resections).

FINAL CONSIDERATIONS

Surgical therapy for colorectal liver metastases has been shown to be increasingly effective. Preoperative staging and intraoperative assessment are important to achieve safe and complete resection of all sites of disease. Current methods for increasing the ability to offer liver resection include preoperative chemotherapy, staged resection, and ablative strategies. In the future, one can anticipate an increasing use of local therapies of colorectal metastases, particularly as systemic chemotherapy improves. The use of minimally invasive approaches, including laparoscopic and robotic resection, will likely increase, in addition to other non-resectional techniques.

SUGGESTED READING

Choti, M. a. *et al.* Trends in Long-Term Survival Following Liver Resection for Hepatic Colorectal Metastases. *Ann. Surg.* **235**, 759–766 (2002).

A large single-center study in hepatic resection for colorectal liver metastases showing a recent improvement in overall survival. Predictors of long-term survival are identified.

Wicherts, D. a *et al.* Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. *Ann. Surg.* **248**, 994–1005 (2008).

This large series of two-stage hepatectomy demonstrates the feasibility and usefulness of this technique for selected patients with extensive bilobar colorectal liver metastases. Overall five-year survival was 42% for 41 patients that completed a second hepatectomy (69% of patients planned for a two-stage procedure).

Pawlik, T. M. *et al.* Effect of Surgical Margin Status on Survival and Site of Recurrence After Hepatic Resection for Colorectal Metastases. *Ann. Surg.* **241**, 715–724 (2005).

This paper evaluates the effect of margin status on long-term survival and recurrence after resection of colorectal liver metastases. This large series shows that a margin of 1 mm to 4 mm results in similar margin recurrence to wider margins.

Nathan, H. *et al.* Conditional survival after surgical resection of colorectal liver metastasis: an international multi-institutional analysis of 949 patients. *J. Am. Coll. Surg.* **210**, 755–64 (2010).

Multi-institutional study including almost 1,000 patients that underwent colorectal liver mestastasis resection. Prognostic scoring systems are evaluated and another method of prognostic information (conditional survival) is proposed to estimate the survival after hepatectomy for colorectal liver metastases.

de Jong, M. C. *et al.* Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann. Surg.* **250**, 440–8 (2009).

This large multi-institutional series found recurrence after resection of colorectal liver metastases in more than half of patients. Most recurrences were intrahepatic only, allowing for repeated resection in selected patients, with similar recurrence-free survival.

Pulitanò, C. *et al.* Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. *Ann. Surg. Oncol.* **18**, 1380–8 (2011).

A large multi-institutional study including 171 patients that underwent resection of colorectal liver metastases and extrahepatic disease.

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11 Neuroendocrine Liver Metastases

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- *Neuroendocrine liver metastases (NELMs) occur in 50-95% of endocrine tumors and represent the main cause of death. Management of NELMs is challenging and should take into account factors such as the tumor biological behavior, the presence of symptoms, and the age and performance status of the patient.*
- *Different therapeutic options (such as partial hepatectomy, liver transplantation, non-surgical liver directed therapies, and systemic treatments) can be used alone or in combination.*
- *Surgical resection remains the gold standard and the only potentially curative treatment for NELMs. Despite high recurrence rates, partial hepatectomy is performed with curative intent (in a minority of patients due to the high frequency of multiple and bilateral metastases) or for control of symptoms. Partial hepatectomy is usually indicated in patients with no extrahepatic disease when at least 90% of tumor burden can be resected.*
- *The role of liver transplantation (LT) for NELMs remains unclear and established selection criteria are lacking. Reasons to support LT are the usual indolent tumor behavior, tendency to metastatize to the liver, reduced possibilities for curative intention partial hepatectomy, and high recurrence rates after partial hepatectomy. Liver transplant should be considered in carefully selected patients with unresectable NELMs confined to the liver.*

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of cancers that can arise from neuroendocrine cells and their precursors located throughout the body. They most commonly arise in the lungs and bronchi, small intestine, appendix, rectum, and pancreas. The natural history of NETs is quite variable, most often presenting an indolent biologic behavior. The ability to secrete peptides is a characteristic of NETs and can result in typical hormonal syndromes. Also, a small group of patients with NETs are affected by Multiple Endocrine Neoplasia type 1 (MEN1), which includes carcinoid tumors, pancreatic islet cell tumors, paragangliomas, pheochromocytomas and medullary thyroid carcinoma.

NETs are usually classified according to histologic features in well-differentiated (usually originated from the gastro-intestinal tract, lung, kidneys, and ovaries) and poorly-differentiated tumors. The first group usually presents with slow progression and better prognosis, in contrast with the second group, which is more aggressive and has a behavior similar to pulmonary small cell carcinoma. Well-differentiated gastroenteropancreatic NETs are classified by the World Health Organization (WHO) as low-grade (G1) or intermediate-grade (G2), based on proliferative rate as assessed by mitotic count and/or Ki67 proliferation index (≤2% for G1 and 3-20% for G2 tumors). Poorly-differentiated NETs (also called neuroendocrine carcinoma) are classified as high-grade (G3, Ki67 index >20%), with rare exceptions (**Table 1**).[1] Prognosis in low- or intermediate-

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grade histology depends on diverse factors, such as the location of the primary tumor, and results of different therapies are difficult to compare.

Despite the characteristic indolent course of NETs, about 40% of patients develop metastases during the course of their disease. Indeed, most NETs (40-80%) present metastases when diagnosed, the liver being the most common site of metastases.[2] Small bowel NETs develop hepatic metastases in 50-75% of cases.[3–5]

Neuroendocrine liver metastases (NELMs) are present at the time of diagnosis in 40-93% of cases and represent one of the most important factors in poor prognosis.[6–9] Indeed, the 5-year survival of patients with NELMs receiving supportive care alone is 0-40%.[7,10–14] Surgical resection of NELMs has provided the best long-term outcomes; however, complete tumor resection is possible in only a minority of patients (approximately 10% of cases), due to the presence of multiple bilateral liver metastases. Less common sites of metastases from NETs are bones (12-20%) and lungs (8-10%).[9,11,15–17]

Patients with metastatic disease may present symptoms due to tumor hypersecretion of hormones rather than due to tumor bulk. Hormonal syndromes occur in approximately 10-30% of metastatic NETs, and hormonal secretions originate either from the primary tumor or from the metastasis; for example, carcinoid syndrome can develop from vasoactive substances produced by liver metastases in a neuroendocrine tumor of the midgut. The standard treatment for NETs is the surgical resection of the primary tumor, irrespective of the presence of liver metastases or clinical symptoms (**Figure 1**).[9] Resection of primary midgut NETs prevents eventual bowel obstruction or ischemia.[18] Some authors advocate tumor resection if 90% of tumor burden is resected.[19] The therapeutic approach for metastatic disease from NETs is more controversial than the management of the primary site.



Figure 1. Computed tomography of a patient with pancreatic neuroendocrine tumor and liver metatases.

SURGICAL TREATMENT

Liver metastases are the main cause of death in patients with NETs. The best management of neuroendocrine liver metastases (NELMs) is a challenging task, and should take into account factors such as the biological behavior of the tumor, the presence of symptoms, and the age and performance status of the patient. The heterogeneity of primaries and the usual indolent tumor growth make it difficult to evaluate the exact role of treatment options for NELMs. Treatment of NELMs can be palliative, aiming for reduction of symptoms, or focus on increasing patient survival.

The different available therapeutic options for NELMs can be divided as follows: i) surgical resection (partial hepatectomy, total hepatectomy followed by liver transplantation); ii) non-surgical liver directed therapies (local ablation, arterial embolization); and iii) systemic therapies (systemic chemotherapy, somatostatin analogues, peptide receptor radionuclide therapy). These therapies can be used alone or in combination.

SURGICAL RESECTION

Results

Surgical resection, whenever possible, remains the best approach for patients with NELMs, despite the high recurrence rate after resection.[7–9,20–27] Studies comparing surgical resection of NELMs with conservative treatments showed increased long-term survival and symptom control with hepatic resection. Thus, hepatectomy is the only potentially curative therapy and remains the gold standard

Table 1. World Health Organization (WHO) grading system for neuroendocrine tumors.

	Grade 1 (G1)	Grade 2 (G2)	Grade 3 (G3)
Ki-67 index	< 3%	3-20%	> 20%
Mitotic count	< 2/10 HPF	2-20/10 HPF	> 20/10 HPF
Differentiation	Well-differentiated	Well-differentiated	Poorly-differentiated

HPF: high power field

of care for NELMs, despite the lack of prospective studies (**Figure 2**).

Surgical resection of NELMs comprises i) resection with curative intent (achieved in 10-54% of patients), and ii) cytoreductive surgery to control local and systemic effects or to increase overall survival. Surgery is usually only feasible when the removal of 90-100% of tumor burden is amenable.[11,28] However, selection of patients for aggressive surgical resection is still ill-defined.

Overall, liver resection can achieve symptom relief in most patients, with 5-year overall survival at 47-92% and 10-year overall survival at nearly 50%.[9,25,27,29–32] However, hepatic recurrence is common after hepatectomy. Even after complete resection with curative intent, the 5-year disease-free survival rate is only 16-45%.[9,14,33] The 5-year overall survival rate after palliative resection is 26-63%.[7,25]

Some studies have attempted to identify prognostic factors for NELMs and select patients that will benefit from liver resection. Recently, Watzka et al.[34], in a retrospective analysis of 204 patients with NELMs, found that surgical resection of NELMs could reduce or control endocrine-related symptoms and improve survival in selected patients with a Ki-67 index less than 20%. The 10-year survival after R0, R1, and R2 resection was 90%, 53%, and 51%, respectively. However, most patients (54%) in this series could not undergo resection and had a poorer 10-year survival (19%).

Another study examined outcomes associated with the morphological characteristics of liver metastases.[33] Hepatic lesions were classified as i) type I (single metastasis, any size), ii) type II (isolated metastatic bulk with accompanying smaller deposits, both lobes involved), and iii) type III (disseminated spread, both lobes involved, little normal liver parenchyma). All patients with type I lesions underwent curative resections with better long-term survival. Type I metastases would be more suitable for curative hepatectomy, type II would benefit from cytoreductive resection in addition to adjunctive therapies, and type III might benefit from liver transplantation.[33]

The presence of extrahepatic disease at the moment of liver resection, nonfunctional hormonal status, and synchronous disease were independent significant factors contributing to worse survival rates in a large multi-institutional study by Mayo et al.[26] The most common sites of extrahepatic disease in this study were the lung and peritoneum. The benefit of surgical resection in nonfunctional NELMs is somewhat controversial, although some authors have reported improved survival with cytoreductive surgery in this situation.[9,16,35] Another report from the cited multi-institutional cohort included an analysis of a matched subset of patients with high-volume liver burden (>25% liver involvement), and found that symptomatic patients benefited the most from surgical resection while asymptomatic patients did not derive a comparative benefit from surgery versus intra-arterial therapy.[11] Thus, surgical resection in patients with asymptomatic nonfunctional NELMs seems to be reasonable in cases of low-volume disease (**Figure 2**); however, in cases of high-volume disease and high surgical risk, other therapeutic options could be considered, as discussed later in this chapter.[27]

The high rate of intrahepatic recurrence may be related to an underestimation of the extent of the disease with preoperative cross-sectional imaging. A study with pathologic examination (including thin serial slices) of the surgical specimen found that less than half of hepatic metastases were detected preoperatively. Most lesions found only with pathologic study were less than 2 mm, and the accuracy of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging was 24%, 38%, and 49%, respectively.[36]

Despite high recurrence rates, overall survival is quite favorable after liver resection, probably due to the low proliferative rate of NETs. Treatment approach for recurrence should be similar to that for initial liver metastases. Whenever possible, repeat hepatectomy (second, third, or fourth hepatectomies) for recurrence results in an overall 5-year survival rate of more than 60%.[26,31]

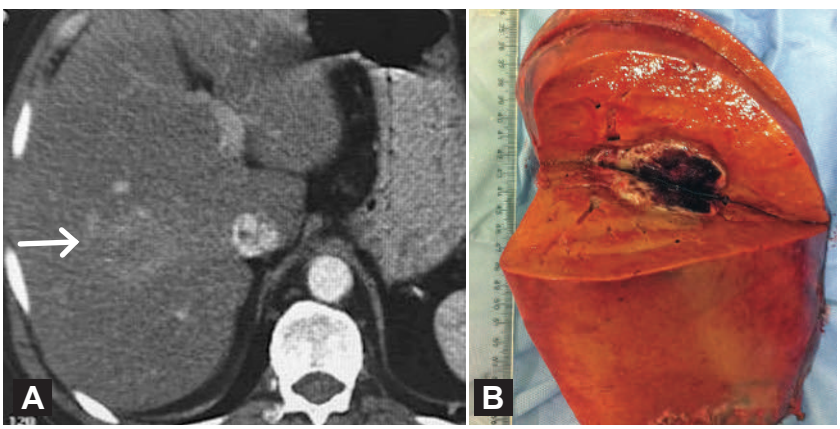


Figure 2. Metachronous hepatic metastasis from small bowel neuroendocrine tumor. **A**) Computed tomography shows a lesion centrally located in the right hemi-liver. **B**) Surgical specimen of a right hepatectomy showing the tumor macroscopic aspect.

Associated procedures

Hepatic embolization (intra-arterial embolization or chemoembolization) has been used together with surgery and without. However, surgical resection should be preferred whenever possible, since studies comparing these modalities of treatment have shown 5-year overall survival rates after ablation of only 35-40%, compared to 70-78% after surgery.[24,37]

Further, local ablation (mainly by radiofrequency or microwave ablation) associated with hepatic resection can increase the number of candidates for cytoreductive surgery, since the majority of patients with NELMs have bilobar disease. Radiofrequency ablation has been reported in the treatment of unresectable NELMs with a 5-year survival rate of 48%.[38,39] The combination of local ablation and surgical resection can lead to more complete cytoreduction and more conservative surgery in cases of lesions deep in the parenchyma. A large study evaluating adjunctive ablation found overall 5-year and 10-year survival rates of 80% and 59%, respectively.[40]

Technical aspects

Since the majority of patients with NELMs present with bilateral disease, surgical resection frequently involves nonanatomic resections, with most patients undergoing multiple wedge resections.[26,31] Other surgical approaches to accomplish adequate cytoreductive surgery include the use of preoperative portal vein embolization, staged procedures, and adjunctive local ablation. Most NELMs occur in non-cirrhotic livers, and a functional remnant liver volume of 20% from total liver volume is usually acceptable. Patients with chronic underlying liver disease (cirrhosis, hepatitis, non-alcoholic steatohepatitis) require higher hepatic remnant liver volume. Portal vein embolization (generally right portal vein embolization) leads to hypertrophy of the non-embolized hepatic segments. Staged hepatectomy consists mostly of a first procedure including tumor clearance of the left lobe plus right portal vein ligation, followed by a right lobectomy after left lobe hypertrophy. Adjunctive local ablation is most commonly by radiofrequency ablation lesions deeply located in the hepatic parenchyma, in addition to multiple wedge resections or to a major contra-lateral hepatectomy. Adjunctive local thermal ablation includes radiofrequency ablation and microwave ablation and can be performed preoperatively (percutaneously or by laparoscopy) or intraoperatively.

Conclusions

In summary, cytoreductive surgical resection of symptomatic NELM, in combination or not with adjunctive embolization or ablation, is indicated when at least 90% of the tumor burden is resected or destructed. This approach results in excellent symptom control and overall survival, despite hepatic recurrence being the rule. In asymptomatic patients with nonfunctional high-volume NELMs, surgical resection is more controversial. Practical clinical guidelines may result from ongoing studies on effectiveness of liver resection versus non-surgical treatment of NELMs. Future studies should provide additional directions on usefulness of neoadjuvant and adjuvant therapies, role of liver transplantation, and importance of primary tumor resection in the presence of unresectable NELMs.[41,42]

LIVER TRANSPLANTATION

The precise role of total hepatectomy and orthotopic liver transplantation (OLT) in the treatment of patients with NELMs remains unclear. The lack of established criteria for OLT for NELMs reflects the scarcity of large series of OLT for the treatment of NELMs, the variety of available therapeutic options, and the heterogeneity of patients (with potentially different tumor biological behavior). Usually, OLT is considered for unresectable NELMs.

The relatively indolent course of NETs and the propensity to metastasize exclusively to the liver, associated with the feasibility of hepatectomy in a minority of cases and the very high hepatic recurrence rate, are theoretical reasons to support liver transplantation for NELMs. However, overall 5-year survival after OLT for NELMs is quite variable (from 33% to 90%), and tumor recurrence occurs in most patients within a 5-year follow-up, contesting the curative role of liver transplantation.[43–56]

Specific inclusion criteria for OLT were proposed by Mazzaferro et al.[57] in a study including patients with low-grade NETs leading to excellent survival with low recurrence rates. The overall and disease-free 5-year survival in this series was 90% and 77%, respectively. The proposed criteria comprises: i) age less than 55 years, ii) low-grade tumor on histology, iii) primary tumor drained by the portal system (pancreas and midgut) and removed with a curative resection before transplantation, iv) no other extrahepatic spread, v) metastatic liver involvement of no more than 50%, and vi) stable disease for at least six months. This criterion was based on a limited number of patients. Another report on OLT for NELMs, which included patients with higher proliferation tumors, larger liver tumor involvement, and older patients, found a similar overall 5-year survival rate of 90%.[51]

However, a review of the European Liver Transplant Registry (ELTR), which included 213 patients who underwent OLT for NELMs, found overall and disease-free survival rates at five years after transplant of only 52% and 31%, respectively.[52] The 90-day postoperative mortality rate was 10%, and predictors of poor long-term outcomes were concomitant major procedures (in addition to OLT), poor tumor differentiation, and large hepatic involvement. Similar results were reported in a United Network of Organ Sharing (UNOS) database study, where overall and disease-free 5-year

survival rates after OLT for NELMs were 49% and 32%, respectively.[55] In this series, patients with longer wait-times for OLT had better long-term outcomes, suggesting that disease stability should be confirmed before considering OLT. Patients who waited more than two months had a 5-year survival rate of 63%, versus 36% for those who waited for a shorter period of time.

The site of the primary tumor was also implicated in outcomes after OLT, with NELMs from pancreatic primaries having poorer outcomes than those from gastrointestinal NETs.[47,48,52,54,58,59]

The worldwide scarcity of liver donors calls for an appropriate selection of patients, in order to allocate grafts for patients who would benefit the most from OLT. Thus, the European Neuroendocrine Tumor Society (ENETS), using the established guidelines for the management of patients with NELMs, have proposed the following minimal requirements for consideration of OLT: less than 10% operative mortality, exclusion of extrahepatic metastasis (accomplished by an extensive work-up), primary tumor removed prior to transplantation (at least six months prior), favorable histology (well-differentiated G1 or G2 tumors, Ki67 proliferation rate preferably less than 10%), stable disease for at least six months before liver transplantation, and liver involvement of less than 50% of the organ (and less than 75% for patients with refractory hormonal symptoms). This consensus considers liver transplantation a palliative treatment for patients with life-threatening hormonal disturbances refractory to medical therapy, or patients with nonfunctional diffuse unresectable liver metastasis. Liver transplantation with intent to cure is considered an exception.[43]

In view of the scarcity of cadaveric liver donors, some authors have advocated for the use of living donors in highly selected cases and in emergency situations. This approach is not a well-established indication for OLT, and there have been few cases reported.[60]

In summary, OLT should be considered in carefully selected patients with unresectable neuroendocrine liver metastases restricted to the liver (**Figure 3**). However, prospective studies are needed for appropriate patient selection.

NON-SURGICAL LIVER-DIRECTED THERAPIES

ABLATIVE TECHNIQUES

Ablative methods mainly comprise radiofrequency ablation (RFA), microwave ablation (MWA), and cryotherapy.[61,62] There is no available data comparing these methods for NELMs. Local ablation has been used in different settings of NELMs, as primary therapy or as an adjunctive procedure, and by different access (percutaneously, by laparoscopy, or during laparotomy). Globally, local ablation usually has lower morbidity rates than surgical resection or even intra-arterial embolization. However, destruction of lesions greater than 3 cm is less efficacious, and generally local ablation is limited to lesions up to 5 cm.[63]

Ablation as primary therapy for NELMs should follow the same selection criteria for surgical cytoreduction, i.e. a reduction of at least 90% of tumor burden should be achieved. The best scenario would be small liver metastases in patients who do not qualify for surgery. One study reported a 5-year survival rate of 48% after RFA of unresectable NELMs.[39] The use of ablation instead of surgical resection in patients suitable for surgery is controversial, and surgery probably leads to better long-term outcomes. Comparative studies including ablation and surgical resection were favorable to surgery.[24,64]

Ablation can also be used as primary therapy for recurrence of NELMs after surgical resection.[65] However, studies comparing ablation and re-hepatectomy or other non-surgical therapies are lacking.

Local ablation as an adjunctive procedure to complement surgical resection is very promising. Since most NELMs are bilateral, proper cytoreductive surgery (reduction of at least 90% of tumor burden) is frequently unattainable due to a future remnant liver that is too small. The association of surgical resection (usually a major hepatectomy) with ablation of contra-lateral lesions allows for proper cytoreduction in a subset of patients initially deemed unresectable, increasing the number of prospective candidates for cytoreductive surgery.[40] Local ablation can also allow for a more complete

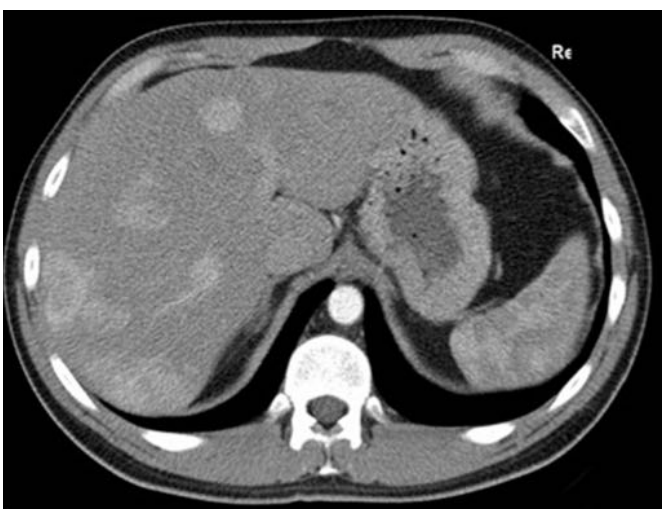


Figure 3. Computed tomography showing multiple hepatic hypervascular neuroendocrine metastases. No extrahepatic disease was detected and the treatment choice was liver transplantation.

cytoreduction in surgical patients. Taner et al.[40] reported 5-year and 10-year overall survival rates of 80% and 59%, respectively, in a series of 90 patients that underwent hepatic resection and adjunctive intraoperative RFA. These results are similar to those from some large series of surgical resection alone for NELMs.[9,26] Although the disease-free 5-year survival rate was only 16%, results of combined surgical and RFA procedures are better than those from other non-surgical therapies. This approach has been used for the treatment of other tumors, such as colorectal liver metastases.

Complications with local ablation are uncommon and include thermal injury to bile ducts (with subsequent stricturing) or adjacent organs, and local abscesses. Local recurrence after NELM ablation (4-11%) is probably due to incomplete tumor obliteration.

INTRA-ARTERIAL LIVER-DIRECTED THERAPIES

NELMs are highly vascular and mostly dependent on arterial blood for their oxygenation (80-90% of blood supply from the hepatic artery). Thus, occlusion of the arterial supply can lead to ischemia and necrosis. Selective arterial occlusion is performed alone or in combination with chemotherapeutic agents (chemoembolization), with drug eluting beads, or with radiotherapeutic agents (**Figure 4**).

All of these methods are options for symptom and locoregional tumor control in unresectable disseminated NELMs. They are used alone or in combination with systemic therapies, and they can allow for symptom control and decreases in somatostatin analog use, and can even prolong survival. Results using the different modalities of intra-arterial therapies for NELMs are similar, thus all of them have been considered reasonable options for palliative treatment in patients who are not candidates for surgical resection.[37,66,67]

Transarterial embolization (TAE) and Transarterial chemoembolization (TACE)

Hepatic artery embolization involves administering an embolic agent into the hepatic artery that is supplying the tumors, with the goal of inducing tumor ischemia. TACE combines temporary intra-arterial embolization (obtained through the use of a variety of embolic agents, such as ethiodized oil or lipiodol) with loading of chemotherapeutic agents (such as doxorubicin, cisplatin, gemcitabine, streptozocin, mitomycin C, or 5-fluorouracil). In addition to the ischemia, the reduction of blood flow by the embolic agents leads to a reduced washout of the chemotherapeutic agents, prolonging their local action.[68] TACE is usually performed sequentially, with a variable number of cycles. In a retrospective series with 123 patients with multifocal NELMs treated with TACE, the overall 5-year and 10-year survival rates were 36% and 20%, respectively.[69] There is no consensus regarding technique, embolizing agents, or chemotherapeutic agents in TACE. Furthermore, studies (including a small randomized trial) have shown similar results with TAE and TACE for NELMs, suggesting supremacy of the embolic effect over the chemotherapeutic one.[66,70–73]

Drug eluting bead transarterial chemoembolization (DEB-TACE) consists of intra-aterially loading large beads with cytotoxic drugs that are gradually released over a period of time, allowing for a longer intratumoral exposure with less systemic exposure and toxicity than conventional TACE.

Adverse effects after arterial embolization include pain, nausea, fatigue, fever, and liver enzyme elevation. Relative contraindications for arterial embolization include occlusion of the portal vein (due to the risk of parenchymal hepatic necrosis), severe liver dysfunction, and presence of bileodigestive anastomosis (due to the risk of cholangitis).[74] Intra-arterial embolization for NELMs is not contraindicated in the presence of extrahepatic disease, especially if the goal is symptom control.[75] Prophylaxis of carcinoid crisis (such as with octreotide) should be implanted before TAE in patients with carcinoid syndrome.[76]

Transarterial radioembolization (TARE)

Liver tumor radioembolization involves delivery of yttrium-90 (Y90) labeled microspheres through the hepatic artery. These microspheres are preferentially implanted within liver tumors (due to particularities of tumor arterial supply) with selective



Figure 4. Hepatic arteriography. Multiple neuroendocrine liver metastases are shown. The patient underwent chemoembolization with irinotecan.

radiation of tumors, while limiting the dose to normal liver parenchyma.[77,78]

Radioembolization, alone or in combination with systemic therapies, has been used for symptom and locoregional tumor control in unresectable disseminated NELMs. Its use can allow for symptom control and decreases in somatostatin analog use, and can even prolong survival. Effectiveness of TARE is comparable to that of TACE, with the advantage of typically requiring a single treatment, while TACE is usually applied multiple times.[79,80] Also, adverse effects after TARE typically have low severity.[81,82]

More recently, intra-arterial delivery of somatostatin analogs labeled with therapeutic radioactive agents (yttrium-90, indium-111, and lutetium-177) has been used for NELM. Tumor response was observed in 16-53% of cases.[83,84]

SYSTEMIC THERAPY

Systemic therapies for NELMs include cytotoxic systemic drugs, somatostatin analogues, and other agents.

CYTOTOXIC CHEMOTHERAPY

Cytotoxic systemic therapy is ineffective for low-grade and intermediate-grade NETs. However, for poorly differentiated tumors with a high proliferative index (Ki67 >20%), cytotoxic chemotherapy can induce an initial response, although it is not durable and progression is common. The overall response rate to chemotherapy varies from 25% to 78%, and overall survival can be improved in 12-24 months compared to patients without treatment.[85–94] Various drugs have been used in the treatment of NETs, including streptozocin, dacarbazine, 5-Fluorouracil (5-FU), doxorubicin, paclitaxel, gemcitabine, temozolomide, and topotecan, with similar results when used as monotherapy.[85,88,89,92–94]

Numerous agents has been tested for low-grade and intermediate-grade tumors, albeit with low response rates. Temozolomide is an orally bioavailable drug that has been used, alone or in combination with other agents, due to its low toxicity. Streptozocin-based therapy, alone or in combination with other drugs, is one of the most used for aggressive high-grade tumors. The combination of two drugs has shown a higher response rate and improved overall survival when compared to a single agent.[91,95,96]

SOMATOSTATIN ANALOGUES

Somatostatin receptors are expressed in approximately 70% of NETs. Somatostatin analogues bind to the somatostatin receptors and consequently limit hormonal release, being used for symptom relief. Patients treated with octreotide show a clinical improvement of 85% and a biochemical recovery of 70% during the first weeks of treatment.[97] Additionally, an anti-proliferative effect was demonstrated in patients with metastatic NETs and somatostatin analogues could be an option for inoperable metastatic carcinoid tumors, even without symptomatic disease.[98–100] Octreotide is also useful to prevent carcinoid crisis after certain therapies, such as intra-arterial therapies. Somatostatin analogues can be used safely in patients that have undergone liver resection.[101] Somatostatin analogues are useful agents for the treatment of metastatic NETs that produce symptoms.[98]

Somatostatin analogues have also been used with a radioligand (such as beta-emitting Yttrium-90 or Lutetium-177) to treat NET-expressing somatostatin receptors (peptide receptor radionuclide therapy). The combination is administered in the systemic circulation and internalized into the target cells, and the radiotoxicity affects the deoxyribonucleic acid (**Figures 5 and 6**). However, these agents can produce adverse effects such bone marrow toxicity, nephrotoxicity, myelodysplastic syndrome, liver dysfunction, and gastrointestinal disturbances.[102–104] Also, patients with a positive metaiodobenzylguanidine (MIBG) uptake can be treated with 131 I-MIBG therapy.[105,106] Other treatments with targeted pathways include sunitinib, bevacizumab (based on the vascular endothelial growth factor (VEGF) expression on NETs), and everolimus (inhibitor of mammalian target of rapamycin).[107]

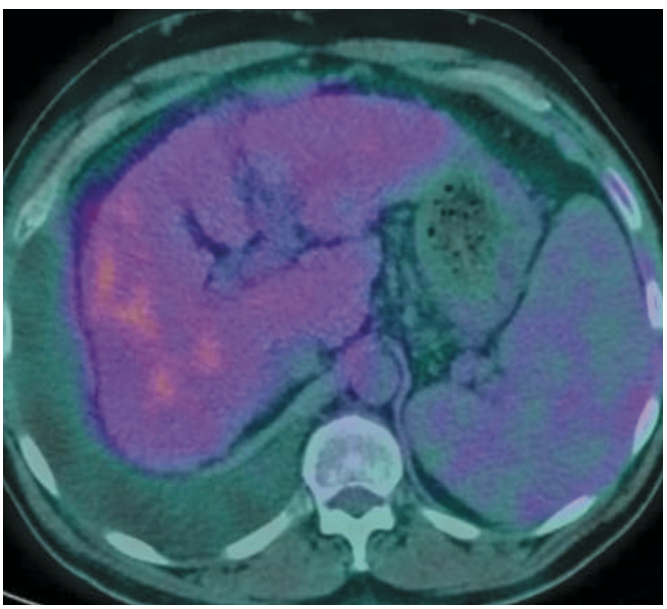


Figure 5. Positron emission tomography–computed tomography (PET-CT) of a patient with bronchogenic neuroendocrine tumor liver metastases prior to liver transplantation.

OTHER AGENTS

Interferon alpha is an alternative for patients with no response to somatostatin analogues, with some symptomatic response but no clear survival benefit. [86,87]

PREVENTION AND MANAGEMENT OF CARCINOID CRISIS

Carcinoid crisis is a life-threatening form of carcinoid syndrome that can be produced by tumor manipulation (during surgery procedures, biopsy, or patient palpation) or by anesthesia. It can be also seen after chemotherapy, hepatic arterial embolization, or radionuclide therapy. Carcinoid crisis develops when a large amount of biologically active compounds from the tumor are released in systemic circulation. It produces hemodynamic instability and symptoms such as flushing, diarrhea, tachycardia, arrhythmias, bronchospasm, and altered mental status.[108]

Octreotide before surgical procedures (in a dose of 300 mcg subcutaneously) specifically, in patients with a history of carcinoid syndrome, can prevent carcinoid crisis. Octreotide can also be used during a carcinoid crisis, in addition to plasma infusion, to restore hemodynamic instability, because typical fluid resuscitation is not efficient in this condition and the use of calcium or catecholamine can aggravate the clinical condition.

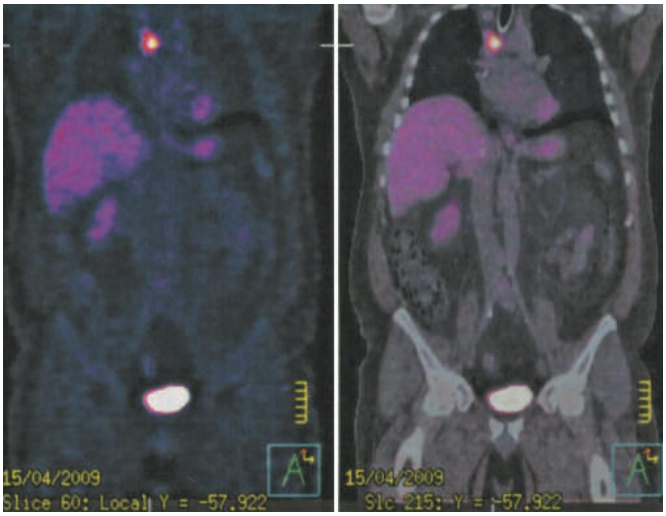


Figure 6. Positron emission tomography–computed tomography (PET-CT) demonstrating thoracic disease after liver transplant for neuroendocrine liver metastases. This patient was treated with 177Lu-[DOTA0, Tyr3] octreotate (DOTATATE) with satisfactory results.

SUGGESTED READING

Watzka, F. M. *et al.* Surgical therapy of neuroendocrine neoplasm with hepatic metastasis: patient selection and prognosis. *Langenbecks. Arch. Surg.* **400**, 349-358 (2015).

A retrospective single-center study with suggestions to improve patient selection for surgical resection of neuroendocrine liver metastases (NELMs). The authors propose that surgical resection of NELMs reduces symptoms and improves the survival in selected patients with a Ki-67 index less than 20%.

Mayo, S. C. *et al.* Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann. Surg. Oncol.* **17**, 3129–3136 (2010).

This multicenter international study demonstrates the efficacy of surgical resection of neuroendocrine liver metastases using a sample of 339 patients from eight hepatobiliary centers. On the multivariate analyses, they found that synchronous disease, nonfunctional tumors, and extrahepatic disease were independent factors for worse survival rates.

Mazzaferro, V., Pulvirenti, A. & Coppa, J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J. Hepatol.* **47**, 460–466 (2007).

A proposal of criterion for selection for liver transplantation in patients with neuroendocrine liver metastases (NELMs), based o n cumulative experiences on multicentric and institutional bases. Liver transplant for NELMs should be restricted to: age less than 55 years, low-grade tumor on histology, primary tumor drained by the portal system (pancreas and midgut), primary tumor treated with curative resection before transplantation, no extrahepatic disease, less than 50% metastatic liver involvement, and stable disease for at least six months. Exclusion criteria are also defined.

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12 Non-Colorectal Non-Neuroendocrine Liver Metastases

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- *The dogma "there is no role for the surgical treatment of liver metastases from non-colorectal non-neuroendocrine tumors" is no longer valid.*
- *There are no guidelines for the management of non-colorectal non-neuroendocrine liver metastases and the complex decision management should be done by a multidisciplinary tumor board.*
- *The variety of clinical situations, like individual tumor site and histology, patient age, disease-free interval between treatment of the primary tumor and diagnosis of the metastases, intrahepatic tumor burden, response to chemotherapy, and the presence of extrahepatic disease should be considered in the surgical management of non-colorectal non-neuroendocrine liver metastases.*
- *In general, liver resection of non-colorectal non-neuroendocrine liver metastases should be considered in patients with well-controlled disease or responding to chemotherapy.*
- *Hepatic resection of non-colorectal non-neuroendocrine liver metastases is a safe, feasible, and effective treatment.*
- *Selected patients with non-colorectal non-neuroendocrine liver metastases can have similar survival to their colorectal cancer counterparts.*

INTRODUCTION

The liver is one of the most common sites for metastatic spread of tumors, particularly for those originating in the gastrointestinal tract. Autopsy studies have shown that, in patients who die of malignant disease, hepatic metastases are found in up to 36% of cases, with the most frequent primaries being colon and rectum, lung, pancreas, breast, stomach, and unknown origin.[1] Almost half of all patients who die of cancer of the stomach, pancreas, or breast are found to have liver metastases.[2] Approximately 40% of patients with endometrial tumors develop liver metastases.[2] Less commonly, hepatic metastases can occur from soft tissue sarcomas, particularly visceral leiomyosarcomas.[3]

The prognosis of these untreated hepatic metastases is generally poor, with the majority of patients succumbing to their disease within 12 months of the time of diagnosis.[4,5]

While the evolution, treatment, and outcome of liver metastases from colorectal and neuroendocrine tumors has been extensively studied during the last decade, this is not the case for metastatic disease originating from non-colorectal non-neuroendocrine tumors. As more patients are detected at an earlier stage of their disease due to improvements in imaging techniques and screening, more attention should be paid to such patients, since long-term survival can be achieved with aggressive oncological and surgical therapies.

This chapter will discuss etiology, presentation, relevant investigations, and management options, with a particular emphasis on surgical resection in patients with non-colorectal non-neuroendocrine liver metastases (NCNNLM).

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PATHOPHYSIOLOGY OF HEPATIC METASTASES

The mechanisms for the development of liver metastases differ based on the location of the primary tumor site. In patients with primary tumors of the gastrointestinal tract, the most likely mode of spread to the liver is through portal venous drainage or via direct intra-abdominal lymphatic channels. In contrast, other liver metastases originate from tumors outside of the intra-abdominal cavity; typically, these metastases reach the liver via the systemic circulation, implying that extrahepatic sites may have an equal probability of being involved.[6]

In the metastatic spread, less than 0.1% of circulating tumor cells survive the mechanical trauma and host defense mechanisms, and those that do develop into metastases are a selected subpopulation.[7] This subpopulation is more homogenous compared to the primary tumor, since they are a clonal expansion of a few highly metastatic cells that have arrested in the capillary beds of the liver.[8] The process of invasion and metastases of a malignant cell involves a series of linked, sequential steps necessitating detachment from the primary tumor, invasion of the extracellular matrix and subsequent reattachment and independent growth in the new environment.[9] This involves a large number of factors, such as adhesion molecules, proteases (matrix metalloproteinases), growth factors, and angiogenic factors. Adhesion molecules such as E-cadherin have been shown to play an important role in tumor cell invasion,[10] as well as integrins, which are receptors for extracellular matrix proteins. The complex interactions of tumor cells with the lining endothelial and lymphatic cells are, in part, what determines this final organ distribution.[11] The complete explanation as to why a cancer cell leaves the circulation at a specific organ is not known, but it is thought to involve a homing receptor on the cancer cell and an addressing endothelial cell.[12] In several experimental tumor models of liver metastases, it has been shown that metastatic cells first come in contact with and implant in the portal endothelium, within a limited portion of the sinusoid.[13] From here, tumor cells may break off into a portal radical and reseed close to the initial lesion or may spread by periportal lymphatic pathways. Such satellite formation close to a large liver metastasis is common with secondary tumors of the liver.

The right lobe of the liver is involved with metastases more frequently than the left lobe, although the reasons for this remain unclear there is no gross difference of either arterial or portal venous blood received by each lobe.[14] It may be that this reflects the fact that the right lobe is usually larger than the left lobe, but it may also be a consequence of portal vein streaming, resulting in tumor emboli preferentially entering the right portal vein branches, whereas multiple deposits throughout the liver are commonly seen in patients with breast, esophageal, gastric, and pancreatic cancer, indicating a more widespread metastatic process.[2,15] Although there are no lymphatic channels draining directly to the liver from the gastrointestinal tract, a metastatic deposit may arise by sequential lymphatic spread from draining lymph nodes. Tumor cells that invade lymphatic may also spread hematogenously via venolymphatic communications or directly via the thoracic duct.[16] Certainly, liver metastases develop in the absence of lymph node involvement, and presumably this occurs via the hematogenic route. Some large metastases do not demonstrate spread to local periportal lymph nodes, even in the presence of extensive disease within the liver.[17]

EPIDEMIOLOGY OF NCNNLM

GASTROINTESTINAL PRIMARY TUMORS

Synchronous liver metastases from esophageal cancer occur in 23% to 47% of patients, usually with advanced primaries, and often are multiple and bilobar.[18] In the setting of metastatic disease, after the lymph nodes, the liver is the second most common site of spread (35%), and the lungs the third most common (20%). Recurrent disease following esophagectomy presents essentially with metachronous liver metastases (often multiple).[19,20]

The reported incidence of metastatic spread to the liver from gastric cancer at presentation ranges from 13% to 37%. A French study reported 30% of metastatic disease at initial presentation, with the majority of cases being liver metastases.[21] After gastrectomy, the recurrence ranges from 40% to 65%, with 54% being locoregional and 37% liver metastases.[22,23] Similarly, 30% to 38% of small bowel tumors are metastatic at initial presentation, with the majority of cases being liver metastases (59%).[24,25]

BILIARY AND PANCREATIC TUMORS

The vast majority of patients with biliary cancers (72%) will present with either lymph node (46%) or liver metastases (24%) at the time of diagnosis. Autopsy studies have shown that 73% of patients who die of pancreatic cancer have liver metastases.[5]

BREAST TUMORS

After the bones and lungs, the liver is the third site of metastatic spread from primary breast cancer, accounting for 12% to 15% of cases. Liver-only metastases are encountered in only 5% of cases;[26] however, with advanced disease, the rate of liver metastases increases to more than 50%.[27]

REPRODUCTIVE SYSTEM TUMORS

Typically, liver metastases from endometrial uterine cancer occur with concomitant extrahepatic disease. Metastatic spread to the liver occurs in approximately 40% of cases.[28] Similarly, liver metastases from epithelial ovarian cancer usually occur in the setting of concomitant diffuse metastatic liver disease and extrahepatic dissemination.[29]

UROLOGIC TUMORS

The hematogenic spread of prostate cancer occurs in 35% of patients. 90% of the metastases involve bony sites, 46% lungs, and 25% liver.[30]

Urinary bladder cancer principally spreads into lymph nodes, followed by multiple visceral dissemination (lungs, bones, and liver). The liver metastases occur in 37% of patients.[31] According to frequency, the lungs are the most common site of metastases from renal cancer (75%), followed by the liver (28%) and bones (28%).[32]

The main routes of dissemination of testicular cancer involve the lymphatic (lomboaortic lymph nodes) and hematogenic route (lungs, and much less commonly to liver metastases, accounting only for 8% of cases).[33]

At initial presentation, only 22% to 40% of patients with adrenal cancer have metastatic disease.[34] At autopsy, in the setting of metastatic dissemination, in 50% to 65% of cases the liver is involved.[35]

SARCOMA AND GASTROINTESTINAL STROMAL TUMORS (GIST)

The reported incidence of liver metastases from sarcoma varies according to the primary site. Extremity primaries have an incidence of 1% for liver metastases, 14% for retroperitoneal metastases (mainly leiomyosarcoma), and 52% for visceral sarcomas. In visceral sarcomas, the metastases are rarely limited to the liver.[3] The majority of cases of recurrence of GIST are intra-abdominal, mainly liver metastases and sarcomatosis, and 60% of patients with liver metastases have concomitant sarcomatosis or local recurrence.[36]

MELANOMA

In metastatic melanoma, the liver is affected in 25% of cases. Cutaneous melanoma has a lower incidence of liver metastases compared to uveal melanoma. In cutaneous melanoma, liver-only metastases represent only 1% to 4% of cases.[37,38] With disease progression in uveal melanoma, liver metastases will occur in 60% to 90% of patients.[39]

HEAD AND NECK TUMORS

In head and neck cancer, distant metastatic disease is observed in 10% to 18% of patients (lungs, bones, liver, and skin, in order of frequency). Among patients with liver disease, metastases confined to the liver are present in 45% of cases, while disease associated with other sites is seen in 55% of cases.[40]

LUNG AND THYROID TUMOR

The reported incidence of metastatic liver disease in lung cancer (mainly small cell carcinoma) at initial presentation is around 50%.[41] In recurrent metastatic lung cancer, the disease is restricted to the liver in 5% of cases.[42] With thyroid cancer, 4% of patients have metastases at initial presentation; the principal sites are the lungs, bones, brain, and liver. The main thyroid cancers with metastatic dissemination are the anaplastic and medullary subtypes.[43]

UNKNOWN PRIMARY TUMORS

Liver metastases of unknown primary tumors are defined as histologically proven malignant metastases without identified extrahepatic primary site. Adenocarcinomas are the most common histology (80%), and after the lymph nodes, the liver is the second most common site of metastases.[44]

PRESENTATION

Small metastatic lesions within the liver are usually asymptomatic and are difficult to detect with conventional imaging techniques. Patients with advanced disease usually present with a combination of upper abdominal discomfort, weight loss, and general malaise. Pain may be due to unremitting rapid growth of large metastases (occasionally referred to the right shoulder). Central necrosis and infarction of metastases may also cause pain and pyrexia, but these are usually only transient symptoms. Hepatomegaly is indicative of advanced disease and may occasionally be accompanied by fulminant hepatic failure if the metastases are rapidly growing. Evidence of advanced liver failure can include jaundice, ascites, and occasionally portal hypertension, which are late signs and are indicative of an extremely poor prognosis.

INVESTIGATIONS

The aim of a thorough preoperative work-up and routine follow-up after resection of a primary tumor is to identify metastases as early as possible, in order to select patients who may benefit from further surgery or adjuvant or palliative

chemotherapy, and exclude those for whom such treatment may not be helpful.

SERUM MARKERS

The specificity of each serum marker varies according to the primary tumor (**Table 1**). Independent of the primary lesion, serum levels of carcinoembryonic antigen (CEA), alkaline phosphatase, aspartate aminotransferase, and, occasionally, alpha-fetoprotein may be increased in the presence of non-colorectal non-neuroendocrine liver metastasis.[45–52]

IMAGING

As patients with colorectal liver metastasis are typically considered for hepatic resection, much of the data on the imaging modalities is based on the findings of these patients.

Among the various imaging modalities available, transabdominal ultrasound (TUS) is the most widespread and useful test. It is inexpensive and non-invasive, and is reliable in distinguishing solid from cystic lesions. It is operator dependent for interpretation. The characteristic aspect of metastasis relies on a hypoechogenic nodule with a hyperechogenic center.[53] It has a sensitivity of 94% for lesions over 2 cm in size, but this drops to 56% for lesions of less than 1 cm.[54]

Contrast-enhanced tomography (CE-CT) using multi-slice CT scanners may allow for more detailed definition of smaller (<1 cm) lesions compared to TUS. CE-CT scan achieves an accuracy of 80-93% for lesions over 1 cm, and this falls to 68% for lesions smaller than 1 cm.[55] CT scan arterio-portography (CTAP) involves selective catheterization of the superior mesenteric artery (SMA), followed by bolus contrast injection and CT scanning of the liver during the portal phase. The need to perform angiography in order to deliver the contrast agent and the high rate of false positive have restricted its use, although CTAP is particularly helpful for detecting lesions less than 5 mm in diameter, and may allow precise localization of the tumor within the hepatic segments.[56] Typical liver metastases are hypodense on CT scanning, but may be surrounded by a hyperdense ring due to contrast uptake in the compressed surrounding parenchyma. Unenhanced CT scanning may detect hepatic metastases, but some are only seen after contrast enhancement. Occasionally, a metastasis may appear due to hemorrhage or calcification, and if there is extensive central necrosis they may also appear cystic. Most liver metastases are hypovascular and therefore may be distinguished from hypervascular lesions such as hepatocellular carcinomas, adenomas, and focal nodular hyperplasia. CE-CT remains the most useful and reproducible procedure at present for the routine detection of liver metastases and extrahepatic disease.[53]

The role of magnetic resonance imaging (MRI) in the detection of liver metastases is rapidly increasing. It is non-invasive, and has sensitivity and specificity ranging from 80-95%.[57] MRI scans of liver metastases are characterized by a prolonged relaxation time T1 and T2. On T1-weighted images metastatic lesions appear hypointense, but a strong T1 signal is observed in hemorrhagic tumors or tumors with a very high protein content (hepatocellular carcinoma), fat (adenoma), or melanin (melanoma).[53] On the other hand, T2-weighted images tend to be hyperintense compared to the surrounding normal liver parenchyma.[56] Tumors with a high water content (cystic lesions, hemangiomas, certain hypervascular tumors) would exhibit an hyperintense signal on T2, whereas the majority of liver metastases, particularly those that are hypovascular, exhibit a weak or moderate T2 signal. Ferumoxide-enhanced MRI has been found to be superior to unenhanced MRI at detecting lesions of less than 1 cm after inconclusive CE-CT scanning.[56] One study found that MRI had an accuracy equivalent to CTAP for liver lesion detection.[58] Although MRI is near universally available, the cost of these enhanced MRI techniques probably precludes its routine use as a screening tool for liver metastases. However, it is extremely useful in characterizing equivocal suspicious lesions detected by cheaper modalities in these patients.

Contrast enhanced ultrasound (CEUS) provides detailed information during the arterial and early portal phase. However, the contrast behavior is different at delayed phase for reasons not currently well understood, probably related to the fact that at delayed phase the iodine and gadolinium are extracellular, while Sonovue® could be sinusoidal.[59] At a delayed phase, CEUS permits, with good reliability, differentiation of metastases from benign tumors. In fact, 91-95% of hypoechogenic tumors at delayed phase after injection of contrast correspond to metastases.[60–62] CEUS is the only technique that allows real time study of the vascularization of a tumor, compared to CT and MRI in tumor characterization. A prospective study revealed that the percentage of tumors

Table 1. Predictive serum markers for detection of hepatic metastases specific to primary cancer.

Gastric [46]	Ampullary [51,152]	Breast [47,50]	Ovarian [49,52]	Uveal melanoma [48]
CEA CA 19-9 CA 72-4	CEA CA 19-9	CEA AST	CA 125 CEA	LDH Alkaline phosphatase GGT

CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen; LDH: Lactic dehydrogenase; GGT: Gamma glutamyltransferase.

characterized correctly increased from 60% to 85% with CEUS, while CT and MRI correctly diagnosed 78% of cases.[63] CEUS often highlights hypovascular metastases in a hypervascular peripheral halo at the early phase, an element that is characteristic of metastasis. One problem with CT is the differential diagnosis between small hypervascular metastases and hypervascular benign tumors (focal nodular hyperplasia, adenoma, angioma). Theoretically, CEUS is technically more capable for this differentiation, because with delayed time the metastases appear hypoechogenic.[53]

The correct characterization of tumoral vascularization is an essential element in NCNNLM investigation. CEUS and MRI enable the study of the tumor vasculature. There are hypervascular metastases and hypovascular metastases. Those that are hypervascular are classically metastases of neuroendocrine and carcinoid tumors; kidney, breast, and thyroid metastases; and sometimes lesions originating from sarcomas. Conversely, metastatic lesions originating from a primary tumor of the lung, prostate, bladder, or pancreas are hypovascular (**Table 2**).[53]

Positron emission tomography – computed tomography (PET-CT) scanning was initially considered a promising technique for detecting liver metastases. The scan relies on the uptake of fluorodeoxyglucose (FDG), which is high in the liver and in tumor deposits. PET-CT scanning has been used in the detection of pancreatic metastases, and was found to have an accuracy of 90%.[64] In one study, PET-CT demonstrated a higher accuracy than CE-CT or CTAP in identifying intrahepatic metastases.[65] PET-CT is not yet widely available, but may prove to be the investigation of choice for detecting occult disease recurrence in patients with rising tumor markers, yet no obvious lesion in the liver (or elsewhere) on routine CT or MRI.

Several studies have confirmed that intraoperative ultrasound (IOUS) is highly sensitive and specific for detecting liver metastases compared with preoperative ultrasound, CT scan, or palpation at laparotomy.[66] Previously undetected lesions may be seen and, prior to resection of known lesions, it is possible to clearly delineate anatomical landmarks in relation to the tumor. IOUS may also be useful for identifying lesions deep within the liver, particularly those less than 10 mm in diameter,[67] and these findings may tip the balance against a curative resection. Anatomical variations that may make the resection more difficult, such as accessory hepatic veins or common origins of the portal pedicle, may also be identified.[67] Also, additional liver metastases may be found.[68] The benefits of IOUS for laparoscopy are similar to those for open operation, allowing for peritoneal inspection and assessment of liver parenchyma, extrahepatic disease, and vessel invasion, thereby improving the selection of candidates for curative resection. An obvious benefit is the avoidance of unnecessary laparotomy and improved organization of theatre time.

In conclusion, an initial CT scan or MRI (in case of contraindication to CT scan) should be done following the detection of metastases. Sometimes, ultrasound alone may be sufficient if it can provide the necessary information, particularly when ultrasound is associated with contrast. If ultrasound fails to yield the necessary information, the next evaluation modality should be MRI. This is the preferred methodology, as it has a high sensitivity for these lesions. In cases of hypervascular metastases, the CT scan or MRI must comprise an arterial phase (three phasic CT or MRI). Nodule characterization by MRI and contrast ultrasound is more efficient compared to CT scan. For the evaluation of intrahepatic extension of the NCNNLM, CT scan and/or IRM are useful techniques. Depending on the case, a PET scan can be added before a surgical treatment is planned. There is no specific morphological strategy for each primitive tumor; it must be individual for each patient, and it depends on the initial quality of ultrasound and/or CT scan, iodine allergy, and MRI contraindications (pacemaker, claustrophobia). The approaches on imaging are the subject of continuing studies to assess the potential benefits of each modality.

BIOPSY

Routine use of biopsy is not be advocated as part of the diagnostic process. This is especially true for patients who are thought to have potentially resectable lesions because of the danger of peritoneal seeding. Therefore, liver biopsy is not recommended if a patient is being considered for curative resection. However, it could be worthwhile in some doubtful situations of uncertain diagnosis when chemotherapy has a real potential to downsize the liver metastases. In such situations, a protected liver biopsy is preferable to minimize the risk of seeding.

Table 2. Vascularization of hepatic metastases from non-colorectal non-endocrine tumors on radiological imaging. (Adapted from Kunstlinger et al.[53])

Hypervascular metastases	Hypovascular metastases	Hypo- or hypervascular metastases
Neuroendocrine Kidney Thyroid Sarcomas Melanoma	Bladder Lung Prostate	Pancreas (70% hypovascular) Breast (70% hypervascular)

TREATMENT

The variety of clinical factors – such as individual tumor site and histology, patient age, disease-free interval between treatment of the primary tumor and diagnosis of the metastases, intrahepatic tumor burden, response to chemotherapy, and the presence of extrahepatic disease – makes the decision process very complex. Therefore, it is critical that treatment decisions for patients with metastases from non-colorectal non-endocrine tumors should be made by a multidisciplinary team including at least medical oncologists, radiologists, and surgeons.

CHEMOTHERAPY

In contrast to the treatment of colorectal liver metastases, where chemotherapy acts as an adjuvant treatment to surgery, the reverse situation is currently observed for non-colorectal non-endocrine liver metastases. Here, systemic chemotherapy plays the key role and surgery acts as an adjuvant therapy, and mainly – with the emergence of effective therapies for most tumors – the prognostic value of chemotherapy response is of major importance in the decision-making process. In practice, liver surgery for non-colorectal non-endocrine metastases should be considered only when the metastatic disease is well controlled or responsive to systemic therapy. The following are some considerations of chemotherapy for metastatic disease, according to each primary site:

Gastrointestinal tumors

In general, adenocarcinoma of the esophagus is treated by analogy to gastric cancers. For metastatic squamous cell carcinoma, the combination of cisplatin and irinotecan is recommended due to its good tolerability and high response rate (overall response of 57% and complete response of 6%).[69] In one study, the use of oxaliplatin and capecitabine demonstrated an objective response rate of 35%.[70] In patients with poor clinical condition, paclitaxel is suggested, with overall response of about 15%.[71]

Like adenocarcinoma of the esophagus, gastroesophageal junction tumors are treated according to gastric tumor guidelines. Recent advances in the treatment of these tumors include targeted therapies such as bevacizumab. In one study, the use of bevacizumab combined with irinotecan and cisplatin demonstrated response rates of 65% and median survival of 12.3 months.[72] Further studies of chemotherapy in combination with bevacizumab are ongoing. The addition of trastuzumab to chemotherapy in patients with HER-2 positive advanced gastric cancer or gastroesophageal junction tumor increased the median survival in a phase 3 study.[73] The benefit of trastuzumab was greater among patients with HER-2 overexpression.

Spontaneous survival in cases with synchronous bilobar liver metastases from gastric cancer is four months, and seven to eight months in the case of unilobar liver metastatic disease.[74] A recent meta-analysis demonstrated a gain in overall survival in patients undergoing chemotherapy versus best supportive care for metastatic gastric cancer. This study established the superiority of combination regimens with cisplatin on 5-fluorouracil (5-FU) monotherapy.[75] On the other hand, hepatic metastases from gastric cancer are modestly sensitive to chemotherapy. The CF regimen (cisplatin and 5-FU) remains the most popular regimen in Europe, and is still used as a control arm in several studies. A randomized study included oxaliplatin, capecitabine, or epirubicin combined with cisplatin and 5-FU, with similar response rates among the regimens.[76] Regimens containing irinotecan or docetaxel were also tested in randomized studies in patients with advanced disease and had variable results.[77–80] The oxaliplatin-based chemotherapy (FOLFOX) showed objective response of 43% in first-line treatment, consistent with other first-line regimens.[81] As with breast cancer, approximately 20% of gastric tumors show overexpression of HER-2. A randomized study assessed the role of trastuzumab in first-line treatment for patients with HER-2 positive gastric cancer, and there was an increase in overall survival (13.8 vs. 11.1 months, P=0.0046) with trastuzumab.[73]

More than half of patients diagnosed with tumors of the small intestine present with locally advanced or metastatic disease including the liver. In the past, systemic treatments similar to those described for cancers of the stomach were used in cases of more proximal cancers, and similar treatment of colon cancer in cases of distal. However, the use of platinum combined with 5-FU appears to confer survival advantage to these patients.[82] A recent study evaluated the combination of capecitabine and oxaliplatin (CAPOX) with objective response rate of 50%, time to progression of 11.3 months, and median survival of 20.4 months.[83]

Biliary and pancreatic tumors

In metastatic biliary tract cancer, fluoropyrimidine-based regimens achieve response rates of 10% and median survival of approximately 6 months.[84–86] The addition of platinum agents appears to increase survival and response rates.[87,88] A recent meta-analysis of 104 clinical trials[89] suggested differences in biological behavior of tumors of the biliary tract, with gallbladder carcinoma being more sensitive to systemic chemotherapy than cholangiocarcinoma (objective response of 36% vs. 18%), but with a tendency for shorter median survival (7.2 vs. 9.3 months). The superiority of gemcitabine-based regimens compared to other regimens, particularly in combination with platinum agents, was also demonstrated in this meta-analysis. The combination of gemcitabine and capecitabine also proved to be active, with

response rates around 30%.[90] Overexpression of the receptor of epidermal growth factor receptor (EGFR) has been observed in advanced tumors of the biliary tract, suggesting that the combination with cetuximab may increase effectiveness of chemotherapy. A study that evaluated the activity of GEMOX (Gemcitabine – Oxaliplatin) in combination with cetuximab showed an objective response rate of 63%.[91]

Hepatic metastases from pancreatic cancer are modestly sensitive to chemotherapy. The use of gemcitabine is associated with a low objective response, with clinical benefit in only 24% of patients. A recent meta-analysis evaluating the combination of gemcitabine with other drugs showed a benefit in progression-free survival and objective response with combination chemotherapies.[92] The addition of gemcitabine to biological agents (tipifarnib[93] and marimastate[94]) resulted in no benefit in overall survival compared with gemcitabine alone. One exception was a study that compared gemcitabine combined with erlotinib or placebo.[95] The combination demonstrated superiority in terms of overall survival (6.2 vs. 5.9 months, P=0.038) and survival free progression (3.8 vs. 3.5 months, P=0.004). Based on these data, erlotinib was approved for the treatment of metastatic pancreatic cancer.

Breast tumors

Patients with predominantly visceral metastases from breast cancer are sensitive to chemotherapy, and prolonged remissions are obtained in about 50% of cases; however, isolated hepatic metastases from breast cancer are uncommon. Therefore, evaluation of results is difficult to achieve. Recent advances include trastuzumab as first-line treatment in combination with chemotherapy (paclitaxel or anthracyclines and cyclophosphamide) with increased response rates, progression-free survival, and overall survival.[96]

Reproductive system tumors

In metastatic uterine cancer (endometrial), response rates with progestins correlate with tumor grade and the state of the progesterone receptor (37% vs. 8% with no expression).[97] For patients with aggressive disease, such as hepatic metastases, combined chemotherapy is recommended with agents such as doxorubicin, cisplatin, and paclitaxel.[98]

The most active cytostatic agents in metastatic ovarian cancer consist of cisplatin, carboplatin, and paclitaxel, and the most widely used alkylating agent is cyclophosphamide. The number of cycles depends on the stage of disease and on the antitumor response obtained. Drugs such as docetaxel, gemcitabine, adriamycin, and 5-FU are active to a lesser extent.[99]

Urologic tumors

In metastatic bladder cancer, the combination of carboplatin and gemcitabine has been shown to have an efficacy similar to MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) in terms of overall and five-year survival,[100,101] and regimes using carboplatin/gemcitabine/paclitaxel are equally active in metastatic disease.[102]

The use of interleukin-2 (IL-2) in high doses for metastatic renal cancer has shown a complete response of 9.3%, partial response of 9.7%, and overall response of 19%.[103,104] The combination of IL-2 and interferon (IFN) shows similar response rates.[105] Recently, targeted therapies with sunitinib[106], pazopanib[107], or temsirolimus[108] have been recommended as first-line treatment.

The treatment of metastatic prostate cancer is complex, taking into account patient age, PSA values, and tumor aggressiveness (Gleason score). Essentially, prostate cancer involves a hormone sensitive tumor that is androgen-dependent, and the treatment initially consists of hormone therapy by surgical castration or drugs. When the disease becomes hormone-resistant, chemotherapy can be indicated.[109]

In metastatic disease of testicle tumors, the treatment necessarily involves bleomycin, etoposide, and cisplatine (BEP) schemes. Despite the higher myelotoxicity, the VIP system (etoposide, ifosfamide and cisplatin) has the same efficacy as BEP in metastases response.[110,111]

Sarcoma and gastrointestinal stromal tumors (GIST)

Today, the chemotherapeutic treatment for sarcomas is based on histological type. Liposarcomas have increased sensitivity to anthracyclines[112,113] and have a high response rate to trabectedin-based treatments.[114,115] Leiomyosarcomas respond well to combinations of gemcitabine with docetaxel[116–119] and to trabectedin.[115] The most active drug in the treatment of synovial sarcoma is ifosfamide,[120] and targeted therapies with pazopanib and sunitinib have been tested for metastatic disease.[121]

Angiosarcomas are highly responsive to taxanes, isolated[122,123] or in combination with other drugs such as docetaxel and gemcitabine.[124] Dermatofibrosarcoma protuberans appears to be responsive to imatinib, with an objective response rate of 36%.[125]

Metastases from gastrointestinal stromal primary tumors (GIST) have a high objective response rate (over 50%) to imatinib; up to 70% of responding tumors remain in remission up to three years post treatment.[126] The relevance of the initial dose of imatinib in patients with advanced disease has been evaluated in several studies,[127,128] with an increased progression-free survival (with no difference in overall survival) with higher doses of imatinib.

Melanoma

Chemotherapy agents with activity in melanoma, with overall response rates between 10% and 20%, include dacarbazine (DTIC), temozolomide, carmustine, lomustine, vinblastine,

and taxanes, but the response rate of hepatic metastases, particularly in uveal melanoma, is less than 5%.[129] Non-responding patients (to chemotherapy) may respond to IFN or high doses of IL-2.[130] Studies involving combined biological agents to standard chemotherapy have shown an overall response of 40-60% and complete response of 10-30%.[131,132]

Immunotherapy agents have demonstrated to improve overall survival for patients with metastatic melanoma.[133] Also, target therapies play a major role in the systemic management o subtypes of melanoma, especially BRAF-mutant melanomas.[134]

Head and neck tumors

Randomized studies (conducted before the era of cetuximab) demonstrated that polychemotherapy had no benefit in overall survival compared to monochemotherapy in metastatic head and neck cancer, despite higher response rates with combined regimens.[135] The actual recommendation of adding cetuximab to chemotherapy in stage IV patients is based on a randomized study that demonstrated that adding cetuximab provided an advantage in overall survival compared to chemotherapy alone (10.1 vs. 7.4 months, P=0.036).[136]

Lung tumors

Combined or isolated chemotherapy for non-small cell lung carcinoma in the metastatic context has shown an increase in survival rates,[137] but evaluation of results in isolated hepatic metastasis is difficult to achieve because liver-only dissemination occurs in about 5% of metastatic cases.[137] The use of combined regimens has a lower toxicity, and these combinations include carboplatin, paclitaxel, cisplatin, docetaxel, gemcitabine, and vinorelbine.[137] Targeted therapies have also been evaluated, and the combination of chemotherapy with agents such as gefitinib, erlotinib, and bevacizumab has resulted in better response rates compared to chemotherapy alone.[138]

RESECTION OF HEPATIC METASTASES

So far, several authors reporting on the results of surgery for liver metastases have suggested that hepatic resection for NCNNLM is safe and as effective as hepatic resection for colorectal liver metastases, with reported five-year survival rates between 12% and 45%. [42,139–157] However, it is important to know that the majority of these studies on patients with non-colorectal liver metastases treated with hepatic resection have a limited number of patients, as well as a considerable heterogeneity in terms of primary tumors often including patients with endocrine tumor metastases. In total, only few studies with five-year survival reports can be identified that focus on more than 100 patients with only non-colorectal non-endocrine metastases treated with hepatectomy (**Table 3**).[143,154,155,157–165]

The efficacy of hepatic resection for patients with NCNNLM

The efficacy of hepatic resection for patients with NCNNLM is supported by outcomes observed in patients selected for hepatic resection, which are better than those achieved with current available non-surgical therapies – suggesting that resection may provide an independent survival benefit.

A study of the French Surgical Society[157] determined that overall survival following hepatic resection was 36% at five years and 23% at 10 years (**Figure 1**). Disease-free survival at the same intervals was 21% and 15%, respectively,

Table 3. Studies with more than 100 patients undergoing resection of NCNNLM.

Author	Year	N	Operative Mortality (%)	Operative Morbidity (%)	5-Year Survival (%)
Elias[143]	1998	120	2	NR	36
Weitz[154]	2005	141	0	33	57
Ercolani[155]	2005	142	0	21	34
Yedibela[158]	2005	150	9	29	26
Adam[157]	2006	1452	2	29	36
Lendoire[159]	2007	106	2	NR	19
O'Rourke[162]	2008	102	1	21	39
Lehner[163]	2009	242	2	21	28
Groeschl[164]	2012	420	2	20	31
Takemura[165]	2013	145	18	1.4	41
Slotta[160]	2014	101	1	23	30
Hoffmann[161]	2015	150	1	37	42

with a median disease-free survival of 13 months (**Figure 2**). During post-hepatectomy follow-up, recurrent liver metastases were identified in 49% of patients. These metastases were solely intrahepatic in 24% of patients and were associated with extrahepatic metastases in 25% of patients. From the group with only intrahepatic recurrences, 32% underwent a second hepatectomy. Initial extrahepatic metastases were surgically treated in 23%, and subsequent recurrences were surgically treated in 37%. Following first hepatectomy, the five-year and 10-year recurrence-free survival rates were 14% and 10%, respectively, with a median recurrence-free survival of 11 months (**Figure 3**).

Outcomes of resection based on the primary tumor site

According to the study of the French Surgical Society [157] patients following hepatic resection for liver metastases from primary breast tumors, patients showed five- and 10-year survival rates of 41% and 22%, respectively, with a median survival of 45 months. Patients with resected liver metastases that originated from gastrointestinal primary tumors experienced favorable to intermediate survival, including an overall five-year survival rate of 31% and a median survival of 26 months. However, within the gastrointestinal category, some groups experienced better survival rates (e.g., small bowel tumors had a five-year survival of 49%), whereas others had poorer outcomes (e.g., gastroesophageal junction five-year survival was 12%). Metastases from urologic primary tumors were associated with a five-year survival rate of 48% and a median survival of 51 months. In descending order, adrenal, testicular, and renal metastases were associated with five-year survival rates of 66%, 51%, and 38%, respectively. For melanomas, including choroid melanoma and cutaneous melanoma, the five-year survival rates were 21% and 22%, respectively. Patients with gynecologic primary tumors showed a five-year survival of 48%; however, the five-year survival for patients with ovarian primary tumor sites (50%) exceeded that of patients with uterine primaries (35%). Patients with primary tumors of pancreatic or biliary origin experienced an intermediate five-year survival of 27%. Only patients with metastases from primary ampullary tumors had a favorable five-year survival (46%). Patients with liver metastases from primary pancreatic tumors had a five-year survival of 25%, and the subset with pancreatic adenocarcinoma had a five-year survival of 20%. Patients with liver metastases from head, neck, and pulmonary primary tumors (squamous cell histology) experienced poor outcomes following hepatic resection, with five-year survival less than 15%. Resected liver metastases from tumors of unknown origin

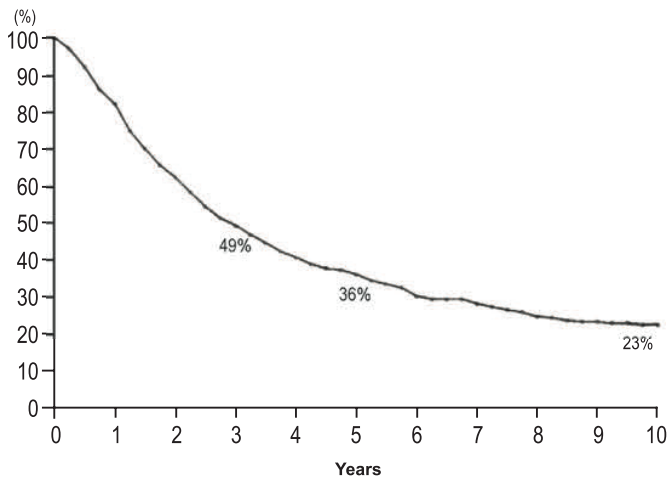


Figure 1. Overall survival for patients with non-colorectal non-endocrine liver metastases (NCNNLM) following hepatic resection. (Adapted from Adam et al.[157])

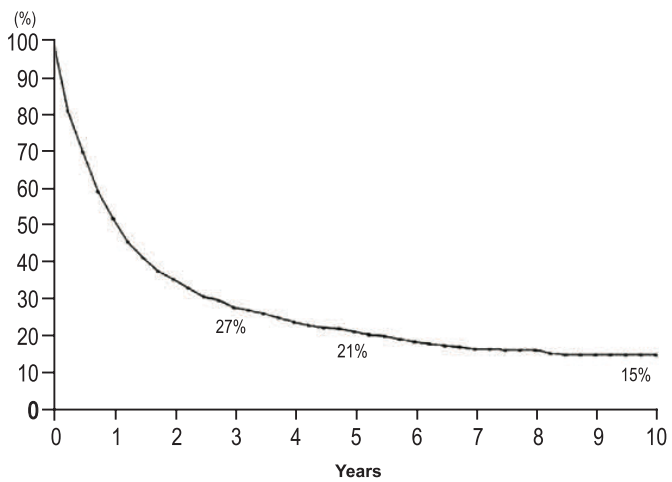


Figure 2. Disease-free survival for patients with non-colorectal non-endocrine liver metastases (NCNNLM) following hepatic resection. (Adapted from Adam et al.[157])

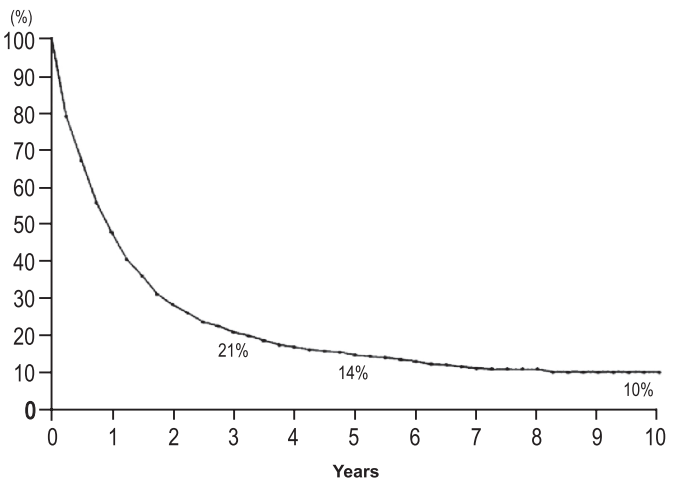


Figure 3. Recurrence-free survival for patients with non-colorectal non-endocrine liver metastases (NCNNLM) following hepatic resection. (Adapted from Adam et al.[157])

were associated with a five-year survival rate of 38% (**Table 4**). Results of a systematic review including over 3.500 patients are depicted in **Table 5.**[166]

Outcomes of resection based on tumor histology

Tumor histology appears to have a great impact on outcomes following hepatic resection. The analysis of outcomes based on primary tumor histology demonstrated that the highest five-year survival rates were observed in patients with stromal (mainly GIST) tumors (70%), adenocarcinomas (36%), and sarcomas (31%), while intermediate five-year survival rates were seen in patients with melanoma (21%) and squamous cell tumors (19%) (**Table 6**).

Morbidity and mortality after resection

The risk of hepatic resection has diminished despite the extension of indications. Surgical series and studies of NCNNLM resection[157 42,149–157] report mortality rates from 0% to 9%, with a morbidity from 8% to 33%. In the above-noted multicentric French series,[157] during the two-month period following hepatectomy, local complications were reported in 14% of patients and general complications were reported in 15% of patients, with mean postoperative hospitalization of 14 days (range 1–106 days) and perioperative mortality of 2.3%. Multicenter studies commonly report higher mortality rates than smaller, single-center studies.[139,142,151,152]

Contraindications to liver resection

Resection may be considered in patients fit enough to tolerate general anesthesia, with no major comorbidity and normal liver function. Absolute contraindications for resection of non-colorectal non-neuroendocrine liver metastases have not been clarified; however, liver resection should not be offered to patients with uncontrolled primary disease and/or multifocal bilateral hepatic involvement.

Relative contraindications to surgery include technically challenging situations such as caudate lobe involvement or tumors invading the inferior vena cava. Tumor involvement

Table 4. Five-year and median survivals for patients with NCNNLM based on individual primary tumor sites [classified as Favorable (Group 1), Intermediate (Group 2), and Poor (Group 3) outcomes]. (Adapted from Adam et al.[157])

Primary tumor	N	5-year survival (%)	Median survival (mo)
All patients	1452	36	35
Group 1 (5-year survival >30%)			
Adrenal	28	66	63
Testicular	78	51	82
Ovarian	65	50	98
Small bowel	28	49	58
Ampullary	15	46	38
Breast	454	41	45
Unknown	28	38	30
Renal	85	38	36
Uterine	43	35	32
Group 2 (5-year survival 15-30%)			
Gastric adenocarcinoma	64	27	15
Exocrine pancreatic	40	25	20
Cutaneous melanoma	44	22	27
Choroid melanoma	104	21	19
Duodenal	12	21	34
Group 3 (5-year survival <15%)			
Gastroesophageal junction	25	12	14
Pulmonary	32	8	16
Esophageal	20	32*	16
Head and neck	15	24*	18

* Three year survival

of the portal vein confluence would also limit the potential curability of the resection. Bilobar distribution and large size of metastasis are relative contraindications but do not necessarily limit resectability.

Risk Model

The aim of developing a risk model is to stratify outcome, to define in which tumor (within the broad range of non-colorectal non-neuroendocrine tumors that metastasize to the liver) is hepatic resection most useful. Based on the results of a multivariate prognostic factor analysis, a risk model was created by the multicentric French group.[157] Numeric scores were given for six sets of variables.

One point was assigned for the presence of each of the following factors: **extrahepatic metastasis present prior to or at the time of hepatectomy**, **major hepatectomy**, and **R2 resection** (macroscopic residual disease). Absence of these factors resulted in an assignment of 0 points for these categories.

Two factors, **patient age** and **length of disease-free interval between treatment of the primary tumor and diagnosis of metastasis** were stratified on a three-point scale. Patients less than 30 years of age were assigned 0 points, while those 30 to 60 years of age were assigned 1 point, and patients older than 60 years were assigned 2 points. Patients with a disease-free interval greater than 24 months were assigned 0 points, while those with a disease-free interval between 12 and 24 months were assigned 1 point, and patients with a disease-free interval less than 12 months were assigned 2 points.

Finally, the **primary tumor characteristics** (site and histology) were stratified on a four-point scale. Patients with breast primary tumors were assigned 0 points, patients with squamous histology were assigned 2 points, and patients with melanoma were assigned 3 points. All other patients were assigned 1 point.

Based on this system, a scale of 0 to 10 points was obtained with an estimated 5-year survival decreasing from 69% for patients with 0 points to 0% for patients with 10 points. Estimated 5-year survival was 30% for patients

Table 5. Expected median survival after resection of NCNNLM. (Adapted from Fitzgerald et al.[166])

Primary tumor group	Primary tumor type	N	Median survival, months (minimum – maximum)
Breast	Breast	1281	44.3 (8 – 75)
Gastrointestinal		684	22.3 (5 – 58)
	Esophagus	23	16.3 (16 – 18)
	GE junction	25	14 (14 – 14)
	Gastric	481	20.6 (8.8 – 58)
	Pancreas	55	18.1 (13 – 20)
	Duodenum	38	32.4 (23 – 38)
	Cholangiocarcinoma	13	28 (28 – 28)
	Gallbladder	21	26.2 (5 – 42)
	Small bowel	28	58 (58 – 58)
Genitourinary		549	63.4 (5 -142)
	Testicular	153	61.6 (5 – 82)
	Ovary	119	67.8 (26 – 98)
	Renal	234	67.9 (16 – 142)
	Uterine	43	32 (32 – 32)
Other		1082	23.7 (10 – 72)
	GIST	106	32 (39 – 40)
	Sarcoma	189	53.8 (23 – 72)
	Melanoma	646	21.8 (10 – 41)
	Lung	36	16.1 (16 -17)
	Head and neck	15	18 (18 – 18)
	Adrenal	90	40.9 (23 – 63)

GE: gastroesophageal; GIST: gastrointestinal stromal tumor.

Table 6. Five-year and median survivals for patients with NCNNLM based on individual primary tumor histology. (Adapted from Adam et al.[157])

Primary tumor	No	5- year survival %	Median survival (mo)
All patients	1452	36	35
By histology			
Stromal	33	70	NR
Adenocarcinoma	703	36	36
Sarcoma	125	31	32
Melanoma	148	21	20
Squamous cell	71	19	17
Other	92	57	88

NR: Not reached

having 0 to 3 points, 10% to 30% for those having 4 to 6 points, and 10% for those having 6 points. This stratification was strongly associated with outcome. Patients with 0 to 3 points had a 5-year survival of 46% (range 36%–69%), while patients assigned 4 to 6 points had an intermediate 5-year survival of 33% (range 5%–46%), and patients with more than 6 points experienced a 5-year survival of only 2% (range 0%–11%) (P<0.0001) (**Table 7**).

Recently, this score has been validated in a German series.[161]

For example, an older patient with significant intrahepatic tumor burden from a non-breast primary tumor, particularly of squamous histology, is likely to have a high recurrence rate and experience poor survival following hepatic resection. In contrast, a young patient with limited metastases from a breast primary adenocarcinoma can expect significant benefits from hepatic resection in terms of both recurrence-free and overall survival.

Other factors may also play a role in the outcome following liver resection of NCNNLM. In a recent series with 420 patients lymphovascular invasion and metastases ≥5 cm were found to be associated with poorer overall survival.[164]

TRANSPLANTATION

Unlike liver metastases from endocrine or carcinoid tumors, liver metastases from non-colorectal and non-neuroendocrine cancer are not good indications for liver transplantation (LT). A consensus conference[167] about the indications of liver transplantation concluded that the place of LT in dealing with malignant tumors other than HCCs is uncertain because of multiplicity of etiologies, heterogeneity of staging, and insufficient available data. A customary survival at five years of 50% allows to perform transplantation in patients with hepatoblastoma, hemangioendothelioma epithelioid, or metastases of carcinoid tumor (evidence level grade C).

Still, hepatic metastases from non-colorectal non-endocrine cancer do have similarities in terms of post-surgical results with colorectal metastases, representing an implicit contraindication, considering the poor results seen with LT performed in the past for colorectal metastases (5-year survival of 18% in the European Registry of Liver Transplant – www.eltr.org). The context of shortage of organs does not allow to go against this implicit rule.

It is in fact exceptional to perform OLT for liver metastases from non-colorectal non-endocrine cancer. Among more than 50,000 liver transplantations performed in Europe from 1968 to 2004, only 34 (0.07%) were performed for hepatic metastases of non-colorectal digestive cancer (n=15) or hepatic metastases of non-digestive cancer (n=19) (www.eltr.org). These transplants accounted for 0.5% of transplants performed for malignancy during this period. The overall survival at five years was 34% (33% for non-colorectal digestive

Table 7. Estimated survival following hepatic resection for NCNNLM as a function of Risk Model Score. (Adapted from Adam et al.[157])

Score	5-Year Survival (%)		
	Minimum	Mean	Maximum
0	69	69	69
1	46	54	62
2	36	45	55
3	26	36	46
4	17	27	37
5	10	19	28
6	5	12	19
7	2	7	11
8	1	4	6
9	0	1	2
10	0	0	0

cancer and 26% for non-digestive cancers). There is no report in the literature regarding this subject. Serralta et al.[168] recently reported three cases of liver transplantation for non-resectable GIST hepatic metastases. The three patients had recurrence in less than three years after the transplant, but thanks to imatinib, all three are alive at 92, 48, and 46 months after transplantation.

OTHER ADJUNCTIVE TREATMENTS

Radiofrequency ablation and destructive therapies

Radiofrequency ablation (RFA) is a relatively recent and not fully validated technique in the treatment of the most common malignant liver tumors such as hepatocellular carcinoma and colorectal metastases. Data regarding treatment by radiofrequency in non-colorectal and non-endocrine liver metastases are even more preliminary and partial, because the local treatment of these metastases is rarely offered (such as radiofrequency, cryotherapy, and laser or even surgical resection).

There is a reporting on the use of radiofrequency as an exclusive treatment for non-colorectal and non-endocrine liver metastases concerns metastases of breast cancer origin.[169] A major issue was the incidence of continuous and/or adjacent tumor recurrence after ablation in relation to the size of the lesions treated (mainly lesions with diameter >4 cm). Another series[170] described the use of percutaneous laser destruction of hepatic metastases from breast cancer. In these series, the effectiveness of local treatment was 92% and 97.7%, respectively. These results are similar to those obtained with the local treatment of HCC and colorectal liver metastases.

In the series using laser therapy,[170] the average survival was 4.2 years with 96 %, 63%, and 41% survival at one, three, and five years, respectively. This survival is comparable with the largest surgical series,[171] in which the median survival was 34 months and the survival at three and five years was 50% and 34%.

There are series of combined radiofrequency ablation and surgery or cryotherapy and surgery. In these series with patients treated by radiofrequency[172] or cryotherapy,[148] metastases from different origins (colorectal, non-colorectal, and endocrine) were included.

Pawlik et al.[172] used intraoperative radiofrequency in addition to resection. The group of patients with non-colorectal metastases (20% of which were endocrine tumors) had a median survival significantly higher than the metastatic colorectal group: 59 months versus 37.3 months, respectively. Overall survival was negatively influenced by lesions greater than 3 cm in diameter.

The use of cryotherapy was reported by Goering et al.[148] The non-colorectal group of the analysis included 22% of endocrine tumors treated by resection alone, cryoablation alone, and a combination of resection and cryoablation. There was no statistical difference in survival at five years, with the resection group at 40% and the two groups with cryoablation at 37%.

Factors to be considered in the indication of percutaneous radiofrequency ablation include the diameter of lesions, the presence of extrahepatic disease, and sensitivity to medical treatment. A less aggressive disease with a tumor progression-free interval exceeding 24 months may be a factor to encourage aggressive local treatments.[150,154]

Chemoembolization

Chemoembolization is a therapeutic modality that can be used in association with percutaneous ablation techniques, surgical resection, or chemotherapy. While there is no reported series with improved survival in patients with NCNNLM treated by chemoembolization, it is, in the majority of cases, well tolerated and can induce a durable response, especially in hypervascular metastases. Tumor regression in patients initially considered non-resectable can enable secondary resection. Thrombosis of the main portal branches is a classical contraindication to chemoembolization, although super-selective chemoembolization decreases the risk of parenchymal necrosis. Severe hepatic insufficiency (Child C) may decompensate after chemoembolization.[173]

FINAL CONSIDERATIONS

The interpretation of available data suggests that the dogma that "there is no role for the surgical treatment of liver metastases from non-colorectal non-endocrine tumors" is no longer valid. However, in contrast to the treatment of colorectal liver metastases where surgery has the key role and chemotherapy could act as an adjuvant treatment, it is likely that the reverse situation is currently observed for non-colorectal non-neuroendocrine metastases, where systemic chemotherapy plays the key role and surgery acts as an adjuvant therapy. As such, increased utilization of surgery in the multimodality treatment of patients with metastatic liver tumors will depend on continued progress in the development of active systemic treatments. In current practice, liver surgery for non-colorectal non-endocrine metastases should be considered only when the metastatic disease is well controlled or responding to systemic therapy. When applied in these situations, surgery may be able to offer selected patients a real benefit in long-term survival.

SUGGESTED READING

Page, A. J., Weiss, M. J. & Pawlik, T. M. Surgical management of noncolorectal cancer liver metastases. *Cancer* **120**, 3111–3121 (2014).

Comprehensive review on the surgical management of non-colorectal liver metastases.

Adam, R. *et al.* Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann. Surg.* **244**, 524–535 (2006).

This multi-institutional series from the Association Française de Chirurgie is the largest series published so far for patients undergoing resection of non-colorectal non-neuroendocrine liver metastases. A multivariate risk model was developed analyzing prognostic factors and long-term outcomes of 1452 patients treated in 41 centers. Factors associated with poor prognosis were patient age >60 years, nonbreast origin, melanoma or squamous histology, disease-free interval <12 months, extrahepatic metastases, R2 resection, and major hepatectomy. A prognostic model based on these factors effectively stratified patients into low-risk (0-3 points, 46% 5-year survival), mid-risk (4-6 points, 33% 5-year survival), and high-risk (>6 points, <10% 5-year survival) groups (P = 0.0001).

Groeschl, R. T. *et al.* Hepatectomy for noncolorectal non-neuroendocrine metastatic cancer: a multi-institutional analysis. *J. Am. Coll. Surg.* **214**, 769–777 (2012).

Retrospective review from 4 major liver centers in United States. The analysis includes 420 patients and breast cancer followed by sarcoma are the major indications. Similar survival is reported among various tumor types. Size of the largest metastases ≥ 5 cm and lymphovascular invasion were associated with poorer overall survival on multivariate analysis. With a median overall survival of 49 months and postoperative morbidity and mortality rate of 20% and 2%, respectively, hepatic resection of NCNNLM is safe and feasible.

Fitzgerald, T. L. *et al.* The benefits of liver resection for non-colorectal, non-neuroendocrine liver metastases: a systematic review. *Langenbeck's Arch. Surg.* **399**, 989–1000 (2014).

Systematic review of 73 studies and 3596 patients discussing the benefits of liver resection for NCNNLM.

Kassahun, W. T. Controversies in defining prognostic relevant selection criteria that determine long-term effectiveness of liver resection for non-colorectal nonneuroendocrine liver metastasis. *Int. J. Surg.* **24**, 85-90 (2015).

Review article addressing the various prognostic factors that might influence the outcome following resection of NCNNLM.

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13 Hepatocellular Cancer

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- *Hepatocellular carcinoma (HCC) is effectively a wide range of diseases, occurring in a wide range of underlying liver diseases. The combination of these problems requires attention to details of tumor location, extent and anatomy, as well as attention to subtleties of liver function limitations and variable causes of the underlying liver diseases.*
- *Most patients have competing causes of death - HCC and underlying liver disease - and treatment of the cancer is impacted by existing liver disease/dysfunction.*
- *Given the wide range of etiologies and underlying liver conditions, presentation can vary from an incidental finding, to a fever, to mass effect of massive tumor, to signs of liver dysfunction, to paraneoplastic syndromes.*
- *Several staging systems for HCC take into account tumor factors and liver factors relevant to prognosis among candidates for treatment and those best treated with supportive care.*
- *Among interventional therapies, intra-arterial therapies, percutaneous ablative therapies, and more aggressive potentially curative therapies (partial hepatectomy or liver transplantation) reflect the wide range of presentations and problems with small tumors in advanced liver disease patients vs. extensive cancer in patients with preserved underlying liver function.*
- *Proper management of HCC patients thus requires deep and expansive multi- and inter-disciplinary care designed to apply the best options to individual patients.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide and affects more than 600,000 people annually.[1] The prevalence is highest in Europe, Asia, and Africa. In the United States, 16,000 cases of HCC are expected this year. In the United States, a decline in alcoholic liver disease and an increase in hepatitis B virus (HBV) immunization have led to a lower incidence of HCC related to these causes, yet the incidence of HCC overall in the United States doubled between 1975 and 1998, most likely because of an increase in hepatitis C virus (HCV) infection [2] and possibly as a result of an increase in steatohepatitis-related HCC. In the majority of patients with HCC, the disease develops in fibrotic or cirrhotic livers, and cirrhosis, regardless of etiology, represents the strongest predisposing factor for HCC.

The behavior of HCC is as variable as the known causes of the disease. Doubling time for HCC tumor volume can vary from a few weeks to several months, and the natural history of untreated disease varies according to the stage at presentation and the degree of underlying liver disease. The prognosis is poor for patients with untreated HCC, even those with early-stage disease, particularly when underlying liver disease is advanced.[3,4] Resection of tumor with negative margins is the treatment most likely to result in long-term survival; reported 5-year survival rates are 50% and higher[5–8] after liver resection and up to 70% after ortothopic liver transplantation.[9,10]

Hepatic resection remains the main curative option for patients with preserved hepatic function and can be

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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applied to patients with large and multifocal tumors and, in highly selected cases, to patients with major vascular invasion and extrahepatic disease (**Figures 1** and **2**). Unfortunately, most patients who present with HCC are not candidates for surgical extirpation because of late diagnosis of cancer, advanced underlying liver disease at the time of proposed treatment, or both (**Figure 3**).[11] Fortunately, the proportion of patients who can undergo safe liver resection is growing as a result of better perioperative care, improved imaging, advanced methods of patient preparation for surgery, and advances in surgical technique. Liver transplantation is generally the best extirpative option for patients with early HCC and significantly impaired liver function, but liver transplantation is not appropriate for patients with advanced HCC, and its use remains limited by limited graft availability and patient factors that represent relative or absolute contraindications for transplantation (e.g., advanced age, comorbid conditions).

Nonsurgical treatments for HCC include systemic therapy, transarterial therapies, ablative therapies, and radiation therapy. In rare instances, systemic therapy enables cure of HCC. When possible, liver-directed therapies for HCC are complementary. Transarterial embolization (TAE) can be used for more advanced HCC, multifocal tumors, and in preparation for resection or transplantation; however, its use is limited to patients with adequate hepatic reserve, and it rarely leads to cure. Percutaneous ablation has gained momentum as a treatment for small unresectable tumors, and results with this treatment are improving; however, pathologic analysis of explanted tumor shows that cure is rare with this modality, and this treatment cannot be used effectively to treat multifocal or large HCCs.[12,13] Radiation therapy (external beam radiation therapy and transarterial radioembolization) is an investigational treatment used only in highly selected cases.[14]

This chapter covers the epidemiology, clinical presentation, diagnosis, staging, and treatment of HCC and includes in-depth analysis of the indications for, techniques of, and outcomes of hepatic resection and nonsurgical treatments for HCC.

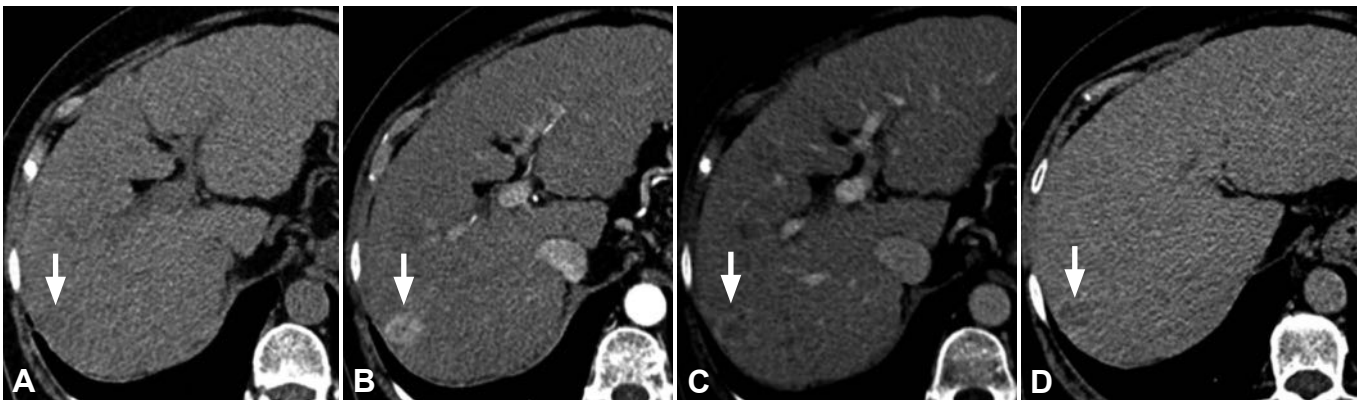


Figure 1. Usual aspect of small hepatocellular carcinoma (arrows) on dynamic computed tomography (CT). **A**) Isodense tumor on unenhanced CT; **B**) Hyperdense lesion on hepatic arterial phase; **C**) Washout on portal phase and; **D**) Tumor slightly hypodense on late phase. (*Courtesy of Dr Gustavo Luersen, Hospital Moinhos de Vento, Porto Alegre, Brazil*)

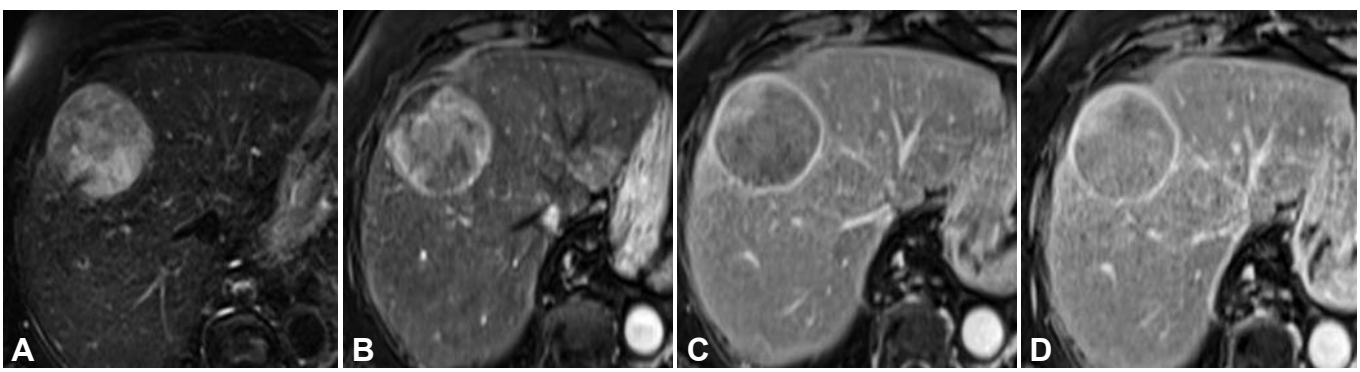


Figure 2. Typical aspect of a large hepatocellular carcinoma (arrows) on dynamic magnetic resonance imaging. **A**) T2 image depicts a hyperintense lesion; **B**) T1 image shows enhancement during arterial phase; **C**) T1 image on portal phase demonstrates contrast washout and lesion becomes hypointense with a rim enhancement and; **D**) T1 image on late phase with persistence of rim enhancement. (*Courtesy of Dr Gustavo Luersen, Hospital Moinhos de Vento, Porto Alegre, Brazil*)

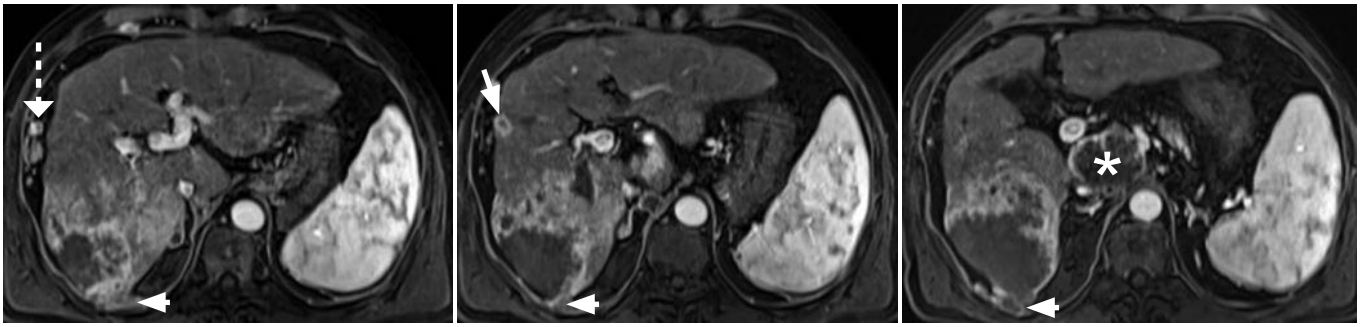


Figure 3. Advanced hepatocellular carcinoma in the setting of cirrhosis. Arterial phase of dynamic MRI demonstrates a large tumor on right hemiliver, with extracapsular invasion (arrowheads). Note the presence of intrahepatic metastasis (solid arrow), peritoneal nodule (dashed arrow) and retroperitoneal nodal involvement (asterisk). Dysmorphic liver and splenomegaly resulted from cirrhosis. Non-tumoral portal vein thrombosis is identified. (*Courtesy of Dr Gustavo Luersen, Hospital Moinhos de Vento, Porto Alegre, Brazil*)

EPIDEMIOLOGY AND RISK FACTORS

HCC incidence varies greatly among different geographic regions of the globe and probably among different ethnic groups. The incidence of HCC is highest in Eastern and Southeastern Asia and sub-Saharan Africa, where HCC is diagnosed at a frequency of 50 to 150 cases per 100,000 individuals per year.[15] In Latin America and developed countries, the incidence of HCC has traditionally been low, at less than 10 cases per 100,000 individuals per year, except in the countries bordering the Mediterranean basin, where HCC occurs with intermediate frequency. In the United States, despite a fall in the prevalence of some known causes of HCC (HBV infection and alcohol abuse), recent evidence demonstrates a rising prevalence of HCC, a twofold rise in the incidence of HCC between 1980 and 1998, and a 37% increase in mortality due to HCC between 1997 and 2001.[16] Similar trends have been observed in the United Kingdom and France.[17] In both the United States and Europe, rising incidence has been attributed to the rise in the incidence of HCV infection and to the rise in the incidence of nonalcoholic steatohepatitis (NASH).

The geographic differences in rates of liver disease and HCC are largely explained by differences in the prevalence of HBV infection worldwide: areas where HBV infection is endemic have the highest HCC incidence, and where HBV infection incidence is lower, HCV infection and alcoholic cirrhosis are the leading causes of HCC. It has been observed that the increase in the prevalence of HCC in the Western world occurred 20 to 30 years after the HBV and HCV epidemic of the 1960s and 1970s.[16]

Up to 90% of patients with perinatal HBV infection, acquired by vertical transmission from the mother to the newborn, have a chronic course of infection. Patients with perinatal HBV infection are at higher risk for HCC than patients who acquire HBV later in life through sexual or parenteral routes, in whom more than 90% of acute HBV infections resolve spontaneously.

The risk of cirrhosis-related HCC varies with the cause of the cirrhosis. HBV-related and HCV-related cirrhosis are associated with a high risk of HCC: 3% to 5% per year.[18] Hemochromatosis is associated with an annual HCC risk of 7% to 9% [19]; this risk may be reduced but does not disappear with optimal medical management of the hemochromatosis. Other genetic conditions, including tyrosinemia and α1-antitrypsin deficiency, also increase the risk of the development of HCC. In men with alcoholic cirrhosis, the risk of HCC is 1% to 4% per year.[20] In women with alcoholic cirrhosis, the risk of HCC appears to be lower. For other causes of cirrhosis, such as autoimmune hepatitis, primary biliary cirrhosis, and Wilson's disease, the risk of HCC is less clear. Over the past decade, there has been increased documentation of HCC among patients with NASH; this risk is less clear as this association was only recently identified.[16,21]

A number of factors unrelated to cirrhosis have also been linked to the development of HCC, including exposure to aflatoxin B1.[22] Aflatoxins are mycotoxins from *Aspergillus flavus* and *Aspergillus parasiticus* and are among the most common naturally occurring carcinogens. Aflatoxins are commonly found in grain in African and Asian countries when grain is stored in hot and humid conditions. There is also some evidence that long-term use of oral contraceptives and anabolic steroids may be associated with the development of HCC. Smoking has also been identified a risk factor for HCC among patients with chronic liver disease.[18] Obesity and diabetes are also believed to be important in the development of HCC and may be linked to the presence of fatty liver disease and subsequent NASH.[16,23]

MECHANISMS OF CARCINOGENESIS

It has been proposed that mechanisms of carcinogenesis differ between HBV-related and HCV-related HCC.[24]

Following infection with HBV, carcinogenesis is believed to be initiated by integration of HBV proviral DNA into the host DNA. Integration of HBV double-stranded DNA into the host genome enhances expression of the c-*myc* and n-*myc* oncogenes and appears to inactivate the tumor suppressor gene *p53*. Cell cycle control, signal pathways, and apoptosis are altered, leading to an increased risk of carcinogenesis. In contrast, HCV is an RNA virus that is not integrated into the host DNA. Rather, HCV most likely leads to carcinogenesis by inducing fibrosis and subsequent cirrhosis, thereby creating a "field of cancerization." Whereas HBV-related chronic liver diseases tend to subside with seroconversion, HCV-related chronic liver diseases are characterized by persistent inflammatory activity with little decrease in their carcinogenic potential, which suggests that HCV probably leads to HCC through chronic inflammatory stimulation. Coinfection with HBV and HCV appears to cause much more severe liver disease and more rapid clinical decompensation than infection with either HBV or HCV alone. In fact, dual HBV and HCV positivity is an independent and significant risk factor for the development of HCC.[24]

The mechanisms of carcinogenesis in patients with NASH-related HCC remain to be elucidated. Carcinogenesis in patients with NASH was initially thought to result from NASH-related (cryptogenic) cirrhosis.[25] The inflammatory features of NASH regress once cirrhosis is established, making it difficult to establish the link from cryptogenic cirrhosis back to NASH when cirrhosis is discovered late in the sequence. However, recent studies suggest that patients are increasingly being identified with NASH-related HCC without cirrhosis, which supports the concept that NASH leads to HCC via a necroinflammatory mechanism. Of further concern is that some obese patients with some but not all the features of NASH may develop HCC.

The etiology of HCC in patients with normal underlying liver or only adenoma - no cirrhosis, no hepatitis, no fatty liver, and no other known risk factor for HCC - is also unknown. In patients with good liver function, a wider range of treatment options and more extensive surgery is often feasible.

Taken together, these distinct mechanisms of carcinogenesis may explain the clinically relevant differences in clinicopathologic features between patients with HCC with different hepatitis profiles and between patients with HCC with or without cirrhosis, NASH, or other known causes of HCC (see the next section).

CLINICAL PRESENTATION

The manner in which patients with HCC present - presentation with symptoms of advanced liver disease versus presentation with tumor-related symptoms versus HCC discovered incidentally - significantly affects treatment planning. HCC is usually diagnosed during the fifth and sixth decades of life, presumably as a consequence of the time needed to first develop liver cirrhosis then HCC (or HCC directly). The age at diagnosis of HCC appears to be younger in HBV-positive patients than in HCV-positive patients,[26] and the age at diagnosis of HCC is 10 to 20 years earlier in areas with a high incidence of HCC than it is in areas with a low incidence. Again, while HCC in HCV patients arises mostly in the setting of cirrhosis, 12% to 50% of patients with HBV-related HCC have no underlying cirrhosis.[27] For most etiologies, HCC has a male predominance; HCC is reported to be four to eight times as common in males as in females in low-prevalence regions and eight times as common in males as in females in high-prevalence regions.

Because the liver can shift function to the non-affected side, symptoms of HCC generally do not appear until either the primary tumor becomes large enough to invade extrahepatic structures or distant metastasis occurs. Further, none of the symptoms or signs attributable to HCC are unique to HCC. Historically, therefore, HCCs were often detected at an advanced stage, and continue to be detected at an advanced stage in most of the underdeveloped world. Fortunately, improved imaging and more effective surveillance programs in high-risk patients have increased the proportion of patients with HCC diagnosed at an early, asymptomatic stage. Indeed, Inagaki et al.[28] found that the frequency of all presenting symptoms of HCC was lower in the late 1980s than before. Recent reports indicate that in areas with active screening programs, the proportion of patients who are asymptomatic at diagnosis is 43% to 60%.[29,30]

It is estimated that 80% of patients with HCC in the West have co-existing cirrhosis and thus often present with symptoms of cirrhosis. The subtypes of HCC that are not associated with cirrhosis, such as fibrolamellar variants in young adults and de novo HCCs in the elderly, are exceptions.

SYMPTOMS AND SIGNS OF CIRRHOSIS

Clinical features and presenting symptoms typically differ depending on HCC etiology, most likely because of differences in HBV- and HCV-related tumorigenesis and the age at which patients acquire the infection. The presence of coexisting cirrhosis and the severity of any coexisting cirrhosis strongly affect the clinical symptoms and signs at presentation, and there is a clear relationship between symptoms and signs of cirrhosis and both the functional hepatic reserve and tumor volume. When patients present with symptoms of advanced cirrhosis (symptoms of liver failure and portal hypertension, jaundice, ascites, tremors, confusion and disturbances of consciousness, or frank encephalopathy), little can be offered in terms of treatment unless HCC is early stage and liver transplantation is feasible.

Peripheral stigmata of liver insufficiency - such as ankle edema, palmar erythema, and caput medusae - are signs of very advanced liver disease. Hepatomegaly can be evident on abdominal examination or cause respiratory symptoms, often with pleural effusion. Arteriovenous fistula can cause a bruit identified on auscultation of the abdomen. This can be differentiated from an aortic bruit in that the bruit resulting from arteriovenous fistula is heard throughout the liver, independent of patient position.[31]

In Southeast Asian and African populations, underlying liver cirrhosis appears to be milder; often, it does not produce symptoms and is discovered only coincidentally during diagnostic work-up. Indeed, in these areas where the incidence of HCC is high, the usual findings at presentation are symptoms related to tumor growth and features of advanced malignancy, such as weight loss, dysphagia, fever, anorexia, and malaise (the so-called constitutional syndrome); abdominal distension from ascites is a common co-existing feature.

PAIN

When large tumors stretch the hepatic capsule or impinge on the diaphragm, they cause a common manifestation of advanced HCC: right upper quadrant pain, which can be referred to the shoulder. This pain can be described as a sensation of discomfort; a dull ache; or a severe, unrelenting pain that requires narcotics for relief. Abrupt onset of pain may also be triggered by complications related to the tumor, such as intratumoral hemorrhage or necrosis. Rarely, acute-onset pain results from tumor rupture and massive hemorrhage. This is one of the most dramatic and life-threatening presentations of HCC. Rupture is usually spontaneous, but it may occur after mild blunt abdominal trauma [32] or abnormal muscular exertion. Rupture with hemoperitoneum is more common in regions where healthcare is less accessible, such as sub-Saharan Africa and southeast Asia; in those regions, spontaneous rupture of HCC is the most common cause of spontaneous hemoperitoneum and occurs in approximately 10% of patients with HCC.[33] In contrast, rupture with hemoperitoneum is rare in the West, where it occurs in only 3% of patients with HCC.[34] Untreated, tumor rupture with hemoperitoneum leads to hypovolemic shock and death in most cases. Less acute bleeding is much more common in patients with advanced HCC, and at the time of autopsy, more than 50% of patients with advanced HCC have blood-stained ascites.[35]

BLEEDING

Variceal bleeding, generally regarded as a complication of advanced cirrhosis and portal hypertension, is the first clinical manifestation of a previously silent HCC in approximately 3% of patients with HCC.[36] A causal relationship between the HCC per se and the bleeding episode cannot be defined; however, 33% to 76% of patients with HCC who present with gastrointestinal bleeding have radiological evidence of portal vein invasion by tumor, which is thought to aggravate the underlying portal hypertension associated with cirrhosis. The reported in-hospital and 1-year mortality rates after variceal bleeding in patients with HCC are extremely high - 20% and 80%, respectively - as a result of both uncontrollable hemorrhage at first bleed and repeated episodes of bleeding after endoscopic sclerotherapy. Other patients develop liver failure as a direct consequence of the bleeding episode or resuscitation. Duodenal ulceration is an additional source of life-threatening bleeding in patients with cirrhosis due to HCC.[37] Major portal invasion can lead to stigmata of massive portal hypertension, venous insufficiency in the intestine, gastrointestinal venous bleeding (from small bowel and colon as well as varices), and liver failure.

JAUNDICE

Jaundice is described in 5% to 44% of patients with HCC.[38] Two classes of jaundice are associated with HCC - jaundice resulting from hepatocellular (parenchymal) insufficiency and jaundice resulting from direct tumor obstruction of the bile ducts.

Most cases of jaundice (90%) in patients with HCC result from hepatocellular (parenchymal) insufficiency. This type of jaundice may result from cirrhosis with the addition of HCC or from extensive tumor infiltration of a cirrhotic liver; in rare cases, the jaundice is a result of reactivation of underlying viral hepatitis or alcohol- or drug-induced hepatitis. The prognosis for patients with jaundice resulting from hepatocellular insufficiency is grave - no treatment can be offered to such patients, and 90% of them die within 10 weeks of presentation.[38]

In patients with jaundice related to direct tumor obstruction of the bile ducts, the jaundice is unremitting, is progressive, and typically overshadows other symptoms and signs. The reported incidence of obstructive jaundice in patients with HCC ranges from 0.5% to 13%. Interventions may improve this type of jaundice. Lau et al.[39] classified obstructive jaundice into three different types. Type 1 jaundice is caused by intrabiliary extension of the tumor to the common duct (**Figure 4**). Free tumor in the duct and bleeding related to the tumor can cause colicky, intermittent pain. Type 2 jaundice is caused by hemobilia, also a result of tumor invasion of the bile duct. Type 3 jaundice is characterized by extraluminal compression of the biliary tree by tumor either encasing or compressing the ducts. Occasionally, type 3 obstruction is described as a result of compression of the extrahepatic bile duct by neoplastic lymph nodes.

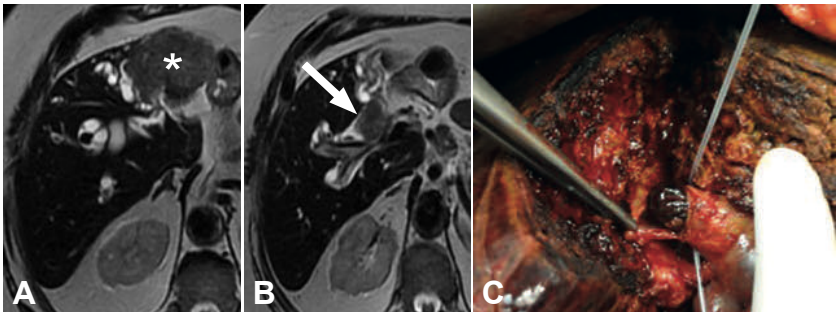


Figure 4. Hepatocellular carcinoma of the hepatic left lobe causing jaundice due to biliary confluence involvement. **A** and **B**) MRI showing a large tumor (asterisk) and extension into the biliary confluence (arrow). **C**) Tumor is seen inside opened right bile duct during left hepatectomy associated to biliary resection and reconstruction. (*Courtesy of Dr Silvio M P Balzan, Hospital Moinhos de Vento, Porto Alegre, Brazil*)

FEVER

Intermittent fever without another cause accompanied by leukocytosis has been reported in 6% to 54% of patients with HCC and may be the presenting symptom in a patient with HCC. This is generally termed "tumor fever" for lack of any other clear explanation for this symptom, which may be related to tumor necrosis.[40]

SYMPTOMS RELATED TO TUMOR INFILTRATION OF VEINS

Invasion of the hepatic veins and vena cava is a well-recognized and relatively common complication of advanced HCC. When a tumor reaches through the hepatic veins to the vena cava, Budd-Chiari syndrome can manifest.[41] Extension of a caval thrombus to the atrium can cause acute episodes of dyspnea and can also cause sudden death. Compression of the superior vena cava by metastatic nodes in the mediastinum, resulting in signs and symptoms of superior mediastinal syndrome, has also been reported.[42]

SYMPTOMS RELATED TO METASTASIS AND PARANEOPLASTIC SYNDROMES

Some patients with HCC present with symptoms related to metastasis of HCC or to paraneoplastic syndromes related to the primary tumor. Metastatic spread via lymphatics or blood vessels to the abdominal and thoracic lymph nodes, lung, bone, adrenal glands, meninges, or brain can produce a wide range of symptoms depending on the location of the metastatic disease.

During the course of the disease, up to 20% of patients with HCC manifest paraneoplastic syndromes, and in approximately 50% of cases, these may be identified at the time of diagnosis. Paraneoplastic phenomena may occur as a result of metabolic dysfunction or production of hormone-like proteins. Hypoglycemia and hypercalcemia are the two paraneoplastic syndromes most often found in patients with HCC. Erythrocytosis can result from ectopic production of erythropoietin or its substrate by tumor cells or from reduced inactivation of erythropoietin by the hepatic parenchyma.[43] Thrombocytosis (platelet count > 400,000/mm^3) associated with increased levels of human thrombopoietin has been described in 2.7% of cases of HCC.[44] Systemic arterial hypertension has recently been reported in a few patients with HCC,[45] as have electrolyte abnormalities as a consequence of watery diarrhea from increased production of secretory peptides.[46] Male patients with HCC can on rare occasions present with features of feminization, including sexual precocity in boys, gynecomastia (although this may be related to co-existing cirrhosis), or florid feminization. Other paraneoplastic syndromes seen in patients with HCC include hypercholesterolemia (serum cholesterol > 250 mg/dL), which is seen in 13% of cases of HCC, cryofibrinogenemia, dysfibrinogenemia, and carcinoid syndrome.

CUTANEOUS MANIFESTATIONS

Various cutaneous manifestations, though not specific, have been described in patients with HCC.[47–49] Examples include pityriasis rotunda, dermatomyositis, porphyria cutanea tarda, pemphigus foliaceus, and the Leser-Trélat sign (abrupt eruption of multiple seborrheic keratoses).

SCREENING AND DIAGNOSTIC STRATEGIES

For patients with known cirrhosis, surveillance ultrasonography every six months is recommended; the goal is to identify HCC at an early stage, when potentially effective treatment can be offered.[50] Serum alpha-fetoprotein (AFP) monitoring every six months is used as well because AFP is detected in more than 80% of HCC cases, at levels ranging from within the reference range to up to 10^7 ng/mL. It is recognized, however, that AFP levels can be up to 500 ng/mL and occasionally higher in adult patients who have hepatitis or cirrhosis with high necroinflammatory activity but who do not have HCC. AFP levels greater than 10 ng/mL have been reported in up to 40% of patients with cirrhosis without HCC. Thus, AFP level alone is neither sufficiently sensitive nor sufficiently specific for HCC screening. However, the presence of an AFP level greater than 200 ng/mL together with characteristic imaging findings is nearly 100% sensitive

for the diagnosis of HCC, and when AFP measurement is used as part of a rational screening program, trends in AFP level can be used to determine whether more intensive testing is warranted.

Ultrasonography is the most commonly used screening modality for HCC. It is noninvasive, sensitive, and relatively inexpensive, and does not involve ionizing radiation. Ultrasonography can detect very small liver lesions, although various sonographic features that have been described as typical for HCC ("mosaic" pattern, peripheral halo, lateral shadows, and posterior echo enhancement) may not be present in small nodules (< 2 cm), which generally appear simply as hypoechoic or, less frequently, hyperechoic abnormalities. This lack of typical HCC features in small nodules poses a significant issue in the screening of patients with cirrhotic livers, in which the ultrasound appearance of nonmalignant regenerative and dysplastic nodules is indistinguishable from that of small HCCs. As a rule, any new liver mass identified by ultrasound in a cirrhotic patient should be carefully investigated with further imaging (e.g., CT or MRI) to determine whether it represents a new HCC. Even with these limitations, ultrasonography is the backbone of effective HCC screening in high-risk patients, and screening appears to reduce the mortality associated with HCC in screened populations.[51]

For nodules larger than 2 cm, multiphasic cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) most reliably establishes a diagnosis of HCC when a nodule exhibits arterial enhancement followed by a contrast washout in the delayed venous phase (**Figures 1** and **2**). High signal intensity on T2-weighted MRI images is usually associated with HCC rather than a benign nodule. If the vascular profile on dynamic imaging is not characteristic and the AFP level is less than 200 ng/mL, a fine-needle aspiration (FNA) biopsy might be considered; close follow-up with serial imaging would be another appropriate option. If imaging is nondiagnostic, but AFP is high, biopsy might also be appropriate.

For nodules smaller than 1 cm, when cross-sectional imaging does not demonstrate the diagnostic pattern of contrast enhancement (arterial enhancement followed by a contrast washout in the delayed venous phase), close follow-up with repeat cross-sectional imaging every 3 to 4 months is generally indicated, particularly when biopsy is not feasible.

For nodules of intermediate size -1 to 2 cm - a diagnosis of HCC is established when the same features characteristic of HCC are detected on two different dynamic imaging studies (CT, MRI, or contrast-enhanced ultrasonography). Almost half of HCCs measuring 1 to 2 cm do not exhibit a diagnostic contrast enhancement pattern. In these cases, an FNA biopsy may be necessary to establish the diagnosis. Negative findings on FNA biopsy do not exclude the diagnosis of HCC; if the biopsy findings are equivocal, options include imaging follow-up with CT or MRI at three to six months or repeat biopsy.

The risk of tumor seeding along the biopsy needle track is no longer an argument against performing FNA; with modern techniques, this event occurs in less than 1% of cases. Furthermore, the risk of bleeding with FNA is low. In cases in which the diagnosis is uncertain, the risks associated with major resection or transplantation for a patient who turns out to have benign disease may outweigh the risks associated with FNA biopsy. Alternatively, serial imaging studies can be used to follow the evolution of suspicious nodules; an enlarging lesion with features typical of HCC can confidently be considered HCC.[52]

STAGING AND PROGNOSTIC FACTORS

Accurate staging of HCC provides prognostic information and also may facilitate the selection of patients for specific treatments. Commonly used staging systems include the Okuda staging system, the Cancer of the Liver Italian Program (CLIP) classification, the Barcelona Clinic Liver Cancer (BCLC) classification, and the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) tumor, node, metastasis (TNM) classification. Of these, the AJCC/UICC classification is the most widely recognized internationally. The AJCC/UICC classification combines clinical and pathologic data to provide the most accurate staging and prognostic scoring system for resectable or transplantable HCC. Only the AJCC/UICC system has been validated both in patients treated with liver resection and in patients treated with liver transplantation. The AJCC and the UICC unified their staging systems in 2003,[53] and the AJCC/UICC system was updated in 2009.[54]

In 2003, the Americas Hepato-Pancreato-Biliary Association (AHPBA) and the AJCC issued a consensus statement recommending the use of the AJCC/UICC staging system to stratify patients who had undergone resection or transplantation.[55] This same consensus statement also recommended that the CLIP system be used to stratify patients with advanced disease who are not candidates for resection or transplantation, in whom pathologic staging cannot be done. In 2010, participants in the Consensus Conference on Multidisciplinary Treatment of Hepatocellular Carcinoma - sponsored by the AHPBA and co-sponsored by the Society of Surgical Oncology, the Society for Surgery of the Alimentary Tract, and the University of Texas MD Anderson Cancer Center - recommended that the AJCC/UICC system be used for candidates for liver resection or transplantation but advised use of the BCLC scheme for nonsurgical patients.[56] The major staging systems are described in detail below.

OKUDA STAGING SYSTEM

The Okuda system stratifies patients on the basis of both tumor extent and liver function. This system, proposed in 1985, divides patients into three groups based on tumor extent, absence or presence of ascites, serum albumin level, and serum bilirubin level **(Table 1).**[57] While this was the first classification system to take into account both tumor factors and liver function, the staging system was devised on the basis of an analysis predominantly of patients with advanced-stage HCC. The Okuda staging system does not include factors that affect prognosis in patients with early-stage, resectable HCC; therefore, its utility is limited to assessing the prognosis of patients with advanced, unresectable disease.

CLIP STAGING SYSTEM

The CLIP staging system was derived from findings in a retrospective study but has subsequently been validated prospectively. Like the Okuda system, the CLIP system takes into account both liver function and tumor extent.[58] The CLIP score is based on four categories: the Child-Pugh classification of liver function, tumor morphology (both size and number of nodules), AFP level, and the presence or absence of portal vein thrombosis (**Table 2**). The range of possible scores is 0 to 6. Patients with CLIP scores of 0, 1, 2, 3, and 4 to 6 have median survival times of 36, 22, 9, 7, and 3 months, respectively. The CLIP system was selected by the AHPBA as the optimal clinical staging system for patients who are not candidates for radical resection. Like the Okuda system, the CLIP system is based on findings in patients with advanced disease (**Figure 3**); it is not as applicable to patients who present with early-stage disease and are eligible for surgical resection.

Table 1. Okuda staging system.

		Points
Tumor extent (% liver involvement)*	> 50% < 50%	1 0
Ascites	Yes No	1 0
Serum albumin level*	< 3 gm/dL > 3 gm/dL	1 0
Serum bilirubin level*	> 3 mg/dL < 3 mg/dL	1 0
Okuda stage	I II III	0 1 or 2 3 or 4

*Although not indicated in the original manuscript from Okuda, it is understood that exactly 50% tumor involvement, 3 gm/dL albumin and 3 mg/dL bilirubin belong to the 0 point group.[57]

BCLC CLASSIFICATION

The BCLC classification was developed as a "staging system" for HCC, but it has been criticized as being a treatment algorithm rather than a true staging system for patients who undergo surgical therapies. In fact, the BCLC was created by correlating outcome with treatment for HCC.[59,60] However, this system, which takes into account both liver function and tumor extent, may be valuable for staging patients who are not candidates for surgical therapies. The BCLC system first divides patients into two groups: those with earlier-stage/good-performance-status disease (BCLC stages A-C) are candidates for potentially curative treatment, and those who have advanced disease (BCLC stage D) are designated for palliative or symptomatic treatment only. BCLC stages A-C include patients who have Okuda stage 1 or 2 disease, an ECOG (Eastern Cooperative Oncology Group) performance status of 0-2, and a Child-Pugh classification of A or B. Patients in BCLC stages A-C are further stratified for treatment on the basis of tumor status. The BCLC has been modified in an attempt to incorporate new treatments (e.g., sorafenib), but careful study shows repeatedly that it is not BCLC "stage" but the allocated treatment that determines patient outcome; thus, the BCLC classification is not a true staging system.

Unfortunately, patientSs with higher "stage" of disease in the BCLC classification have a better prognosis than patients with lower "stage" when aggressive treatments (e.g., surgery) are performed, but the BCLC treatment algorithm calls for

Table 2. Cancer of the Liver Italian Program (CLIP) staging system.

Category	Score		
	0	1	2
Child-Pugh class	A	B	C
Tumor morphology	Uninodular; extension ≤ 50%	Multinodular; extension ≤ 50%	Massive or extension > 50%
Alpha-fetoprotein level, ng/mL	< 400	≥ 400	
Portal vein thrombosis	Absent	Present	

Each patient is assigned a score (from 0 to 6) by adding the points from the 4 categories listed.

patients with higher "stage" of disease to be allocated to palliative or experimental therapies. This issue is the basis for the AHPBA's consensus recommendation to use the AJCC/UICC staging system for surgical patients and the BCLC system only for nonsurgical patients.

Some examples will help illustrate the issues with the BCLC: In the BCLC algorithm, only patients with solitary lesions and normal portal pressure are allocated for resection; patients with more than one lesion are excluded from resection. Additionally, many patients who meet the Milan criteria for liver transplantation (see "Liver Transplantation" below) are assigned by the BCLC algorithm to receive radiofrequency ablation (RFA) or ablation with alcohol. Patients with "intermediate-stage" disease are considered to be candidates for chemoembolization or randomized trials. Patients with slightly more advanced-stage disease, particularly those with extrahepatic disease, are designated to receive experimental agents or be entered into randomized trials. Continuous revision of the BCLC algorithm has failed to bring it up to the standard such that outcomes are related to the tumor stage rather than the treatment advised by the algorithm, largely because the BCLC algorithm remains biased toward palliative therapies and tends to undermine the multidisciplinary assessment and treatment of patients.

The failure of the BCLC classification to accurately stratify surgically treated patients in terms of prognosis may relate to its failure to effectively separate two problems: liver disease and cancer. Patients with good liver function and advanced tumors are candidates for aggressive treatment and may have good outcomes, but the Barcelona algorithm allocates all patients with advanced tumors to palliative treatments irrespective of liver disease. At the other end of the spectrum, patients with advanced liver disease but early cancer respond to liver transplantation. Thus, although the BCLC classification tries to encompass the wide breadth of patients with HCC and liver disease, the treatment determines the outcome more than the BCLC stage does, which limits the utility of the BCLC classification for prognostication in patients who undergo aggressive treatments. For patients who are not candidates for surgery or transplantation, however, Barcelona may be the best prognostic scoring system.[56]

AJCC/UICC STAGING SYSTEM

The AJCC/UICC TNM classification system for HCC was introduced in 1988, but failed to stratify patients according to prognosis and was very complex.[61,62] In 2002, Vauthey et al. analyzed the outcomes of 557 patients from an international cohort who underwent surgical resection for HCC and identified vascular invasion, tumor number, tumor size, and the presence of fibrosis or cirrhosis as independent predictors of survival.[8] The study group traveled to each center, verified data, and reviewed pathologic slides centrally for every patient in the study. On the basis of these analyses, a new simplified staging system was proposed and adopted by both the AJCC and the UICC and published in the sixth edition of the *AJCC Cancer Staging Manual*.[8,53] This system has subsequently been validated in several cohorts of European and Asian patients [63–66] and is the only surgical staging system validated in both resection and transplantation cohorts.[67]

A further refined AJCC/UICC staging system appears in the seventh edition of the *AJCC Cancer Staging Manual*, published in 2010 (**Table 3**).[68] Most aspects of the sixth-edition system remain, such as the fact that patients with a single tumor of any size and no vascular invasion are classified as having T1 disease (**Figure 5**). Patients with evidence of intratumoral microvascular invasion and those with multiple tumors that are 5 cm or smaller are classified as having T2 disease. In a change from the sixth edition, the T3 category has been divided to reflect the difference in prognosis between patients with multifocal large HCCs and patients with HCC with major vascular invasion. The T3a category includes patients with multiple tumors larger than 5 cm; the T3b category includes patients with single or multiple tumors of any size involving a major branch of the portal vein or hepatic vein. The T4 category is unchanged, including tumors with direct invasion of adjacent organs (other than the gallbladder), including ruptured tumors. Changes in these classifications were made on the basis of previously published data [8,64,69] and data presented to the AJCC regarding the prognosis of patients with multinodular HCC versus HCC with major vascular invasion (M. D. Anderson).

In the seventh edition of the staging system, the N

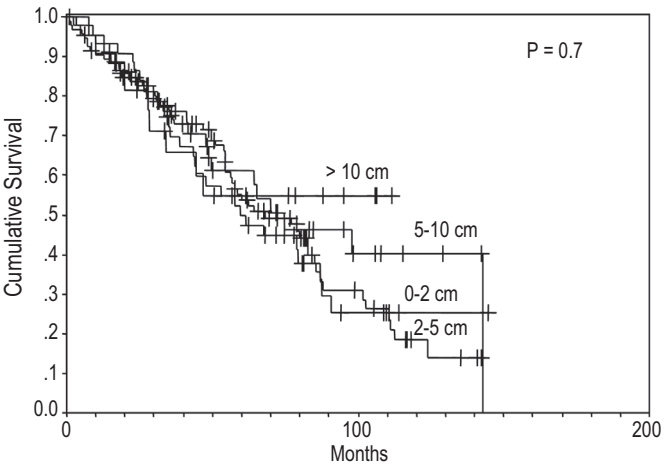


Figure 5. Impact of tumor size on survival after resection in patients with T1 hepatocellular carcinoma (HCC) according to the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) staging system. There is no difference in survival after resection of solitary HCC regardless of size, in the absence of vascular invasion. This formulates the basis for the T1 classification in the unified AJCC/UICC staging system. (Adapted from Vauthey et al.[8], with permission)

(regional lymph node) classification remains simply N0, no regional lymph node metastasis, and N1, regional lymph node metastasis. However, in the seventh edition, inferior phrenic lymph nodes are classified as regional nodes, not "M" nodes, as in the sixth edition. The M (distant metastasis) classification is typical for TNM: M0, no distant metastasis, and M1, distant metastasis.

In the absence of lymph node metastasis (N0) and distant metastasis (M0), T1 and T2 tumors correspond to stage I and stage II disease, respectively (no change from the sixth edition). Changes in the T3 classification led to the following changes in the stage III groupings: Stage IIIA includes only T3a (N0, M0), stage IIIB includes only T3b (N0, M0), and T4 N0 M0 is shifted from stage IV to stage IIIC to reflect the better prognosis for this type of disease. Stage IV now includes all patients with metastases, whether nodal or distant, separated into IVA (N1) and IVB (M1).[54]

Another important feature of the sixth-edition AJCC/UICC staging system that remains in the seventh edition is the provision for a separate reporting of fibrosis. Although fibrosis is not yet a formal part of the staging system, fibrosis is noted because fibrosis status affects survival within every T classification (**Figure 6**).[8] Among patients with stage I disease, the 5-year survival rate is 64% for patients without underlying fibrosis (F0) versus 49% for patients with moderate to severe fibrosis (F1). Among patients with stage II disease, the 5-year survival rate is 46% for F0 patients but only 30% for F1 patients; among patients with stage IIIA disease, the 5-year survival rate is 17% for F0 patients and 9% for F1 patients. Thus, the new AJCC/UICC criteria provide a more precise means of evaluating the effect of fibrosis and cirrhosis on prognosis. Compared to other HCC staging systems, the AJCC/UICC system better stratifies patients, especially those with early disease, into prognostic groups.[64–66]

Table 3. American Joint Committee on Cancer/Union Internationale Contre le Cancer Tumor, Node, Metastasis Staging System (AJCC/UICC TNM).

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors (none > 5 cm)
T3a	Multiple tumors (> 5 cm)
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Fibrosis Score (F)	
F0	Ishak grade 0-4 fibrosis (none to moderate)
F1	Ishak grade 5-6 fibrosis (severe fibrosis or cirrhosis)

Stage Groupings			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	any T	N1	M0
Stage IVB	any T	any N	M1

Fibrosis score is not formally included in assessment of stage, but the staging manual recommends notation of fibrosis score because it stratifies prognosis for each stage grouping. (Adapted from *AJCC Cancer Staging Manual*, 7th ed [68])

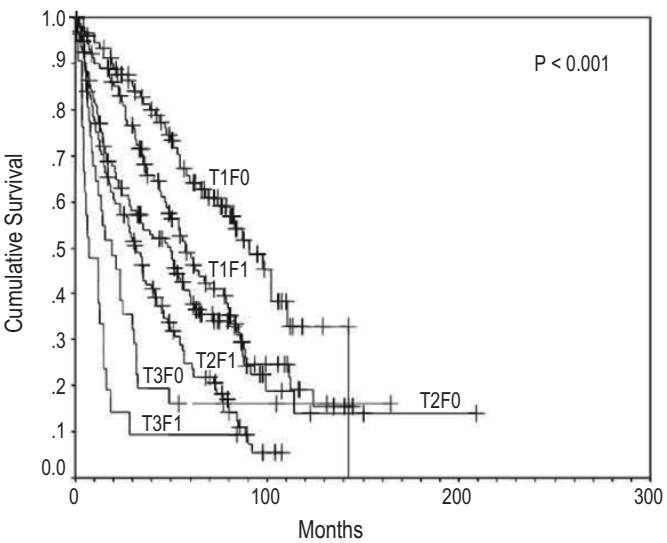


Figure 6. Impact of fibrosis on outcomes after resection in patients with hepatocellular carcinoma (HCC). The presence of severe fibrosis or cirrhosis in the underlying liver in patients with HCC treated with resection lowers the survival within each T classification in the American Joint Committee on Cancer/Union Internationale Contre le Cancer system. F0: fibrosis grade 0-4; F1: fibrosis grade 5-6, according to Ishak. (see text; Adapted from Vauthey et al.[8], with permission).

ALBI GRADE

On the horizon is a new, evidence-based grading system that recognizes the importance of liver function in prognosis of HCC therapy. Current liver function measures vary widely; this led an international study group to develop a simple, objective grade for liver function in patients with HCC that is, in fact, strongly prognostic for survival for HCC patients across a wide spectrum. Only bilirubin and albumin are utilized in the score that was developed upon analysis of 1313 Japanese patients with HCC. The authors of the study proceeded to validate ALBI in more than 5000 patients from around the world (in cohorts similar to the initial study patients) and in other cohorts (525 patients treated with resection, 1132 treated with Sorafenib for advanced disease). In an effort to distinguish the importance of liver function on outcome regardless of therapy for HCC, known prognostic factors related to TNM stage were excluded; cox regression modeling revealed albumin and log10 bilirubin to be powerful outcome predictors. The linear predictor was calculated to = (log10 bilirubin x .66) + (albumin x -.085) with bilirubin in micromole/L and albumin in g/L. Cutpoint analysis revealed three grades: ALBI grade I ≤ -2.60, grade II >2.60 to ≤ -1.39, and grade III > -1.39.[70]

After application to training and validation sets of the initial Japanese cohorts, ALBI was further validated in the above described large international datasets, and proved to be discriminatory in all studied groups. Of note was that two distinct prognostic groups were found among Child-Pugh A patients across all regions. Emphasizing the value of an objective liver function measure was that survival in ALBI categories differed across regions (HCC outcomes can differ region to region); however, ALBI was discriminatory in every region and group tested.[70]

The objective nature and simplicity of ALBI may diminish interobserver variation and refine prognostic systems (such as Child-Pugh for which assessment of ascites, for example, is highly variable); of particular value is the utility of the objective ALBI system in patients with better liver function. Whereas MELD, also an objective liver function measure, is effective in predicting death from liver failure in advanced liver disease patients, ALBI is a liver function assessment that appears to have prognostic value particularly in patients with HCC and including those with good liver function.[70]

SURGICAL TREATMENTS

Surgical resection is an effective treatment for HCC, but it can be offered to only 15% to 30% of patients with this disease. Basic principles guiding resection of HCC include use of anatomic resection when feasible (i.e., systematic resection of the entire tumor-bearing hepatic segment or subsegment, including the supplying portal territories that might contain venous metastases or daughter micronodules); vascular inflow occlusion; and low central venous pressure anesthesia. Liver transplantation, the other surgical treatment for HCC, can be offered to only a tiny minority of patients with this disease because of the limited utility of liver transplantation for advanced disease and the limited availability of organs for transplantation. Although this chapter focuses on liver resection, merits and limitations of liver transplantation are discussed herein as well.

PREOPERATIVE EVALUATION AND PATIENT PREPARATION FOR SURGERY

Clinical Evaluation

Identification of candidates for surgical resection of HCC must be done carefully to minimize postoperative morbidity and mortality and optimize long-term survival. Determining whether a patient is a proper candidate for resection requires systematic assessment of tumor extent, general medical fitness, and underlying liver function. When major hepatectomy is being considered, assessment of remnant liver volume is also crucial.

Patient age per se does not define candidacy for liver resection, but comorbidities increase the operative risk and should be carefully considered. Patients with an American Society of Anesthesiology (ASA) score of greater than 1 have more than three times the mortality and twice the morbidity of patients with a score of 1.[71] The operative risk may be prohibitive in patients with certain comorbidities or combinations of comorbidities, especially congestive heart failure, severe chronic obstructive pulmonary disease, or significant chronic renal failure.

Assessment of Liver Function

HCC typically occurs in patients with cirrhosis. In patients with cirrhosis, after a patient is found to be a candidate for surgery on the basis of overall health and comorbidities, liver function must be assessed. In patients without cirrhosis or underlying liver disease, liver function must be assessed when major hepatectomy is being considered.

The most widely used classification for liver function in patients with cirrhosis is the Child-Pugh classification. The Child-Pugh classification [72,73] takes into account presence and grade of encephalopathy, presence and degree of ascites, total bilirubin and albumin levels, and international normalized ratio (INR) (**Table 4**). Together, these factors provide an estimate of the gross synthetic and detoxification capacity of the liver. Child-Pugh class has been repeatedly validated as an overall predictor of survival after surgery in patients with cirrhosis. Child-Pugh class can also predict the risk of death after other treatments, including portovenous shunt surgery and arterial embolization in patients with cirrhosis.

In general, patients with Child-Pugh class A liver function tolerate hepatic resection. Patients with class B liver function may tolerate minor hepatic resection but generally do not tolerate major hepatic resection. Patients with class C liver function are at significant risk from anesthesia and laparotomy, and resection is rarely (though not never) advised in such patients. Operative mortality rates for patients with Child-Pugh class A, B, and C liver function undergoing abdominal operations are approximately 10%, 30%, and 82%, respectively.[74] Recent hepatectomy series in patients with Child-Pugh class A liver function have reported a wide range of perioperative mortality rates, from 0% to 16%.[75,76] Critics have pointed out that two aspects of the scoring system are ambiguous: the assessment of ascites and the grading of encephalopathy. Consequently, the Child-Pugh classification is used cautiously because it may underestimate the surgical risk. The Liver Cancer Study Group of Japan uses a modified Child-Pugh classification that also takes into account indocyanine green (ICG) retention,[77] although that modified classification is not widely used in the West because of the limited availability of ICG dye.

The Model for End-Stage Liver Disease (MELD) is a more objective classification of liver function than the Child-Pugh classification and has been used as an alternative to the Child-Pugh system to assess the mortality risk from hepatic resection as an extension from its use in candidates for liver transplantation. MELD combines serum bilirubin level, serum creatinine level, and the international normalized ratio in a mathematical formula to yield a whole-number score. MELD does not directly take into account ascites and encephalopathy. MELD was originally developed to assess the risk of mortality in patients undergoing a transjugular intrahepatic portosystemic shunt procedure [78] and was later adopted to improve patient allocation for liver transplantation by classifying patients according to their risk of mortality at three months while waiting for a transplant. A low MELD score correlates with lower risk of mortality while awaiting liver transplantation, whereas a score of 40 is associated with 100% mortality.[79,80] After the adoption of MELD to stratify patients according to their risk of death while waiting for liver transplantation, MELD has also been used to assess the risk of mortality after hepatic resection. Though more objective than Child-Pugh, MELD generally performs similarly to Child-Pugh in the prediction of outcome after liver resection in patients with cirrhosis,[81] but MELD is slightly less consistent than Child-Pugh for this indication.[82] Furthermore, most studies using MELD to predict outcomes after hepatic resection (including one study in which serum sodium level was also taken into account to enhance accuracy) have included primarily patients undergoing minor resection (< two segments; in the latest study, 66% of patients had resection of < one segment, 12% two segments, and 12% three segments),[81] which limits the utility of MELD for the selection of patients for major resection.

Portal hypertension, which may be significant even in patients with Child-Pugh class A liver function, increases the risk of hepatic insufficiency and liver failure after hepatectomy. Portal hypertension can lead to hemorrhage and coagulopathy. In one study, only hepatic venous pressure gradient (the ratio of the wedged hepatic venous pressure to the free hepatic vein pressure), a surrogate measurement of portal venous pressure, predicted hepatic decompensation after hepatic resection.[83] Of note in this prospective study of patients with Child-Pugh class A liver function was that hepatic decompensation developed in 11 of 15 patients with a hepatic venous pressure gradient greater than 10 mmHg, versus none of the 14 patients with a hepatic venous pressure gradient less than 10mmHg ($P < 0.002$). This finding reinforces the concern that Child-Pugh class may in some cases underestimate resection risk. Fortunately, in patients with Child-Pugh class A liver function, readily evident preoperative clinical or radiological signs of portal hypertension, including splenomegaly, abdominal collaterals veins thrombocytopenia (platelet count < 100,000/mm^3), and esophagogastric varices, are reliable indicators of clinically occult portal hypertension. Such signs are relative contraindications for major hepatic resection and, in most patients, any hepatic resection. Surgeons must be attentive to these imaging findings as surgical planning proceeds.

Active hepatitis is another important risk factor for liver failure after hepatic resection. After hepatectomy for HCC, mortality has been shown to be almost six times as high in patients with cirrhosis and active hepatitis as it is in patients with cirrhosis alone.[84] Furthermore, although it

Table 4. Child's-Pugh classification of hepatic functional reserve.

Clinical or Laboratory Measurement	1 Point	2 Points	3 Points
Encephalopathy, grade	0 (absent)	1-2	3-4
Ascites	Absent	Slight	Poorly controlled
Bilirubin level, mg/dL	< 2.0	2.0-3.0	> 3.0
Albumin level, mg/dL	> 3.5	2.8-3.5	< 2.8
International normalized ratio	< 1.7	1.7-2.2	> 2.3

Each feature is assigned 1, 2, or 3 points.[72,73]

is well recognized that an aspartate aminotransferase level greater than 100 IU/L [85] or an alanine aminotransferase level at least twice the upper limit of normal [86] may signal that major hepatic resection is associated with unacceptable risk, serum transaminase levels may not correlate with clinically significant hepatitis. A bilirubin level greater than 2 mg/dL is a contraindication for hepatic resection, and patients with bilirubin levels between 1.1 and 2.0 mg/dL should be carefully screened and considered only for limited resection.

Several other tests have been used to evaluate global liver function, including evaluation of urea-nitrogen synthesis rate, evaluation of galactose elimination capacity, bromsulphalein and aminopyrine breath tests, and evaluation of ICG clearance. ICG is a dye that is cleared from the circulation by the liver, and its clearance is an indicator of hepatocyte function. ICG clearance is the most studied test used to select cirrhotic patients for hepatic resection, though it is used mostly in Asia. Makuuchi et al.[77,87] advocate selecting cirrhotic patients for minor resection on the basis of the presence or absence of ascites, stratified according to the total serum bilirubin level and ICG 15 value (that is, the percentage of dye clearance in 15 minutes). Patients with high bilirubin levels and low hepatic clearance of ICG are considered for limited resection or alternative locoregional ablative treatments. These studies may be of more limited value in selecting patients for major resection because they assess global hepatic function, although this approach was prospectively validated in 107 patients: the 30-day mortality rate was zero, and there were no major complications (although only one patient with cirrhosis underwent resection of four or more segments).[88] This "Makuuchi" algorithm has been used successfully by many centers to effect safe minor resection in patients with cirrhosis, though it is not the standard for planning for major resection.[77,87]

Assessment of Tumor Extent

Assessment of tumor extent is essential for determining resectability and the appropriate type of surgical resection. At MD Anderson, disease is first staged with multiple-phase CT of the thorax and the abdomen because this study provides superior image resolution of extrahepatic sites and excellent detail of the liver anatomy. MRI is the imaging modality of choice when contrast agents are contraindicated or further lesion characterization is needed. CT or MRI images can be used for liver volume assessment when indicated (discussed in the next section).

At major hepatobiliary centers, eligibility criteria for resection have expanded to permit resection in selected patients with tumors once considered unresectable, such as patients with large HCCs, patients with multinodular and bilobar HCCs, and highly selected patients with HCCs with portal vein or hepatic vein involvement (**Figure 7**). Extrahepatic disease and tumor thrombus extending significantly into the inferior vena cava generally remain contraindications for resection. Patients are considered for resection when the assessment of tumor extent indicates that all tumor nodules can be safely removed with negative margins and the volume and function of the portion of the liver that will remain after resection are adequate.[56]

Assessment of Future Liver Remnant Volume

Assessments of global liver function and liver reserve - such as the assessments done to determine Child-Pugh class or MELD score and assessment of ICG clearance - do not predict the function of the future liver remnant (FLR), the liver that will remain after resection. Although the Makuuchi algorithm [87] described above is highly effective in stratifying patients according to the risk associated with minor resection, another approach is necessary when major resection is being considered in patients with preserved liver function and little or no portal hypertension.

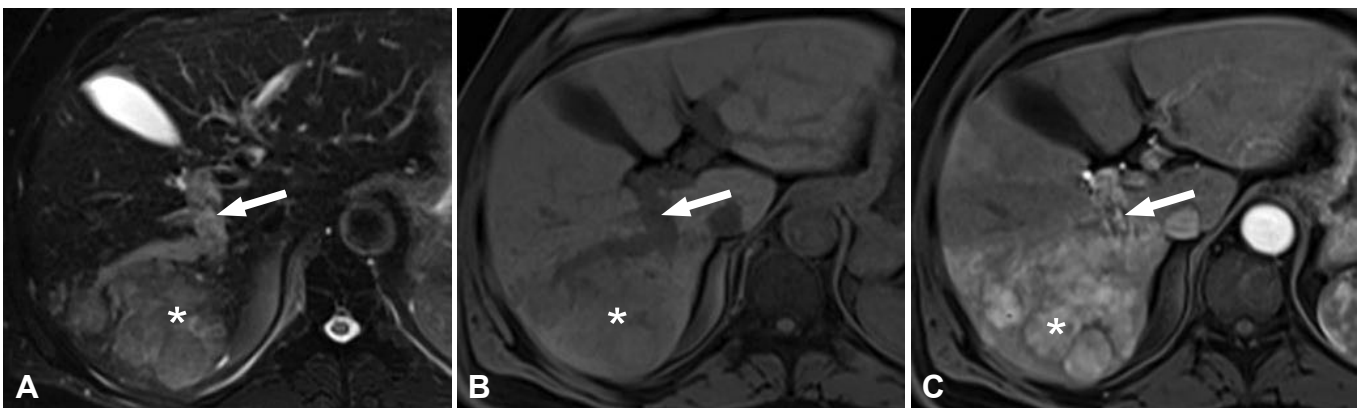


Figure 7. Large hepatocellular carcinoma (asterisks) on posterior sector of the liver with malignant portal thrombosis (arrows) on magnetic resonance imaging. **A**) T2 weighted image; **B**) T1 weighted image; **C**) dynamic T1 weighted image on arterial phase. (*Courtesy of Dr Gustavo Luersen, Hospital Moinhos de Vento, Porto Alegre, Brazil*)

Importantly, in patients being considered for major hepatic resection, such as right or extended right hepatectomy, the FLR volume can vary widely because of the normal variation in segmental liver volumes [89] and because of compensatory hypertrophy resulting from vascular involvement by the tumor in the liver to be resected. Resection leaving a small FLR results in increased portal pressure and flow, endothelial and Kupffer cell injury, and release of proinflammatory cytokines,[90] which contribute to hepatocellular injury and impaired liver regeneration. In short, a "small for size" FLR does not support the metabolic demands of the patient after resection, and hepatic insufficiency or liver failure follows. Thus, appropriate selection of patients for major hepatic resection requires accurate measurement of FLR volume.[56]

The objective of FLR volume measurement is actually not simply to measure volume but rather to predict the function of the FLR after resection. So that the FLR volume can be used to predict function, the FLR is measured using 3-dimensional CT volumetry, then standardized to the total liver volume (TLV). The ratio of FLR volume to TLV has been shown to be the most useful indicator of FLR function. TLV determination thus impacts the utility of the FLR/TLV measurement. Therefore, accurate measurement of the TLV is critically important for surgical planning for several reasons.[91] First, liver volume in cirrhotic patients is often altered as a result of the underlying fibrosis (which makes the liver smaller) or hepatocellular ballooning (which makes the liver larger); thus, the measured TLV may not be useful as an index to which FLR volume should be standardized. Direct TLV measurement also requires that the tumor volume be measured and subtracted from the TLV, which can introduce additive mathematical errors in volume calculation.[92] The magnitude of such errors is greater in patients with multiple tumors and patients with biliary dilatation in the portion of the liver to be resected. An alternative, more accurate method is to calculate TLV using a mathematical formula that relies on the linear correlation between liver size and body surface area (BSA): TLV (cm^3) = -794.41 + 1,267.28 x BSA (m^2).[91] Though many formulas exist for calculating TLV, this particular formula was shown to be the least biased and most precise formula for the estimation of TLV in adults in a recent meta-analysis of formulas developed for this purpose.[93] This method of measuring the FLR using CT volumetry and then dividing the measured FLR by the calculated TLV is termed "standardized FLR volumetry"; the measure that results is termed the "standardized FLR volume."

The standardized FLR volume has been validated as a useful predictor of FLR function in several studies. An analysis of patients with normal underlying liver who underwent extended right hepatectomy showed that complication rates were directly related to the standardized FLR volume.[94] Specifically, patients with a standardized FLR volume of greater than 20% had a complication rate of 13%, compared to 50% in patients with a standardized FLR volume of less than or equal to 20% **(Figure 8)**. Recently, data on 301 consecutive extended right hepatectomies were reported from M.D. Anderson Cancer Center.[95] This study reinforced the correlation between complications and liver insufficiency, objectively defined on the basis of validated data,[96] and standardized FLR volume. Direct comparison of patients with normal liver with small (≤ 20%), intermediate (>20% to 30%), and large (≥ 30%) FLR volumes demonstrated higher risk for liver insufficiency and postoperative death in patients with small-standardized FLR volumes (vs. intermediate or large liver volumes) but not in patients with intermediate standardized FLR volumes (vs. large liver volumes).[95] Thus intermediate volumes (>20% to 30%) are clearly adequate in patients with normal liver.

Data on cirrhotic patients undergoing major hepatectomy further substantiate a correlation between liver volume and liver function. Kubota et al.[97] demonstrated that cirrhotic patients with normal preoperative liver function who underwent major hepatectomy developed hyperbilirubinemia when standardized FLR volumes were small but did not develop hyperbilirubinemia when standardized FLR volumes were large (> 40%). Shirabe et al.[98] took this line of inquiry one step further, in a subsequent study of cirrhotic patients who had undergone right hepatectomy. They demonstrated that patients who died of liver failure had significantly smaller standardized FLR volumes than patients who did not die of

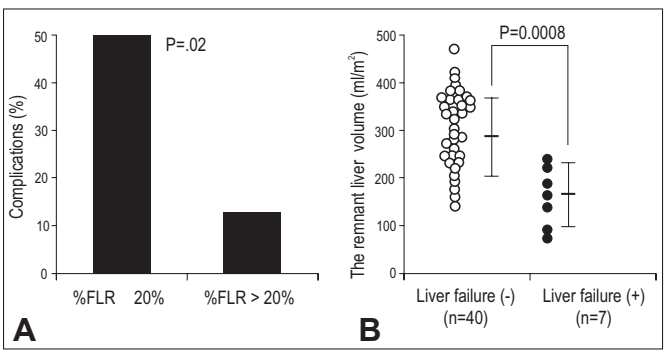


Figure 8. Impact of future liver remnant (FLR) volume on outcome after major hepatic resection in patients with hepatocellular carcinoma (HCC). Inadequate FLR volume is associated with an increase in complications. **A**) In patients with normal underlying liver, the risk of complications (but not mortality) increases when the FLR volume is less than or equal to 20% of the total liver volume standardized to the patient's body surface area (Adapted from Abdalla et al.[94], with permission). **B**) In patients with cirrhosis, mean FLR volume was significantly smaller in patients who died of liver failure (open circles) than in patients who did not die (solid circles) (mean ± standard deviation: 163 ± 63 mL/m^2 vs. 285 ± 82 mL/m^2, P = 0.0008). No deaths from liver failure occurred in patients with standardized FLR volumes greater than 250 mL/m^2. (Adapted from Shirabe et al.[98], with permission)

liver failure (P< 0.008). Further, using a method in which the FLR volume was directly standardized to BSA, they demonstrated that the incidence of liver failure was 38% in patients with an FLR volume of less than 250 mL/m^2 BSA, versus 0% in patients with an FLR volume of greater than 250 mL/m^2 BSA (P < 0.001) **(Figure 8)**.[98]

Analysis of liver volume variability reinforces the importance of FLR volumetry: in the absence of compensatory hypertrophy, segments 2 and 3 represent less than 20% of the TLV in more than 75% of patients, and the left liver represents less than 30% of the TLV in 25% of patients and less than 20% of the TLV in 10% of patients.[89]

Portal Vein Embolization

When major or extended resection is considered appropriate on the basis of clinical evaluation, assessment of liver function, and tumor extent, but FLR volume is inadequate, portal vein embolization (PVE) is considered. PVE is a procedure designed to divert portal blood flow to the FLR before liver resection in order to increase the volume and function of the FLR.[92] PVE is indicated when the standardized FLR volume is below the limit considered safe for resection - specifically, when the standardized FLR volume is less than or equal to 20% in patients with normal liver, less than or equal to 30% in patients with intermediate liver disease, or less than or equal to 40% in patients with well-compensated cirrhosis without significant portal hypertension (**Figure 9**).[56,99,100] PVE is generally performed percutaneously by an interventional radiologist with the patient under conscious sedation or general anesthesia. Most centers with significant experience recommend ipsilateral access to the portal vein (access on the side of the liver to be resected) to avoid potential damage to the FLR. A contralateral percutaneous approach or intraoperative transileocolic approach can be used, but these are generally not preferred because they require puncture of the portal vein in the FLR (percutaneous approach) or laparotomy (transileocolic approach). At M.D. Anderson Cancer Center, the targeted segments are embolized with microparticles plus coils to occlude distal and proximal flow. Liquid embolization is used at some centers.[101,102] Portal vein ligation, a surgical approach to portal flow diversion, is a less efficient method of inducing FLR hypertrophy and has little role in cirrhotic patients as it would require a second period of general anesthesia and laparotomy or laparoscopy in most patients.[103] The result of PVE is that portal flow is diverted to the FLR, which leads to hypertrophy of the nonembolized liver and, to some degree, atrophy of the embolized liver. PVE-induced FLR hypertrophy leads to improved FLR function as measured by increased bile production,[104] increased technetium-Tc-99m-galactosyl human serum albumin uptake,[105] and improved postoperative liver function.[106]

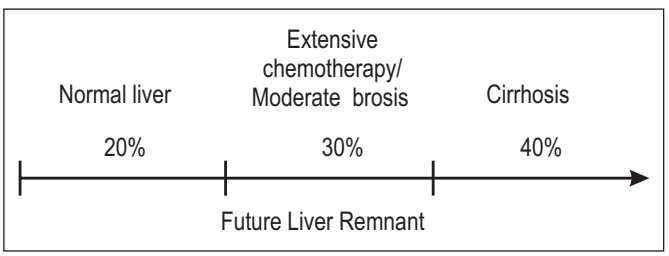


Figure 9. Continuum of indications for preoperative portal vein embolization (PVE) based on extent of underlying liver disease. (Adapted from Zorzi et al.[100], with permission)

After a prospective study revealed a decrease in complications and hospital stay after right hepatectomy with PVE versus right hepatectomy without PVE in patients with cirrhosis,[107] we examined both the perioperative and oncologic impact of PVE before major hepatectomy for HCC.[108] In our study of 54 patients who underwent major resection (≥ three segments), 21 patients who underwent preoperative PVE were compared to 33 patients who underwent resection without PVE. The PVE and non-PVE groups had similar distributions of disease stage according to the sixth edition of the *AJCC Cancer Staging Manual* and similar rates of fibrosis or cirrhosis, hepatitis, and preoperative transarterial chemoembolization (TACE). The overall rates of postoperative complications and positive margins were similar (P-values all non-significant). However, there were no perioperative deaths in the PVE group versus 6 (18%) in the non-PVE group (P = 0.038). The median follow-up time was 21 months. Excluding perioperative deaths, overall survival rates at 1, 2, and 5 years were 94%, 82%, and 72% in the PVE group and 93%, 63%, and 54%, respectively, in the non-PVE group (P = 0.35). Disease-free survival was not significantly different between the groups: disease-free survival rates at 1, 3, and 5 years were 84%, 56%, and 56% in the PVE group and 66%, 49%, and 49%, respectively, in the non-PVE group (P = 0.38) **(Figure 10)**. Thus, PVE before major hepatic resection for HCC was associated with improved perioperative outcomes, enabling safer major surgery without decreasing survival.[108] The beneficial effects of PVE are well recognized, but ours was the first study to demonstrate that oncologic outcome is similar with and without PVE and suggested that longer survival than was previously suggested can be achieved when major resection is required for HCC **(Figure 10).**

Theoretical limitations of the utility of PVE in patients with HCC have been discussed. First, the effect of PVE in patients with cirrhosis may be limited because the cirrhotic liver has less capacity to regenerate than the noncirrhotic liver.[109] Second, it has been theorized that the known compensatory increase in hepatic arterial flow after PVE could lead hypervascular HCC to grow, which would be

an unintended consequence of portal occlusion.[110] Third, concern has been raised that arterioportal shunting in patients with cirrhosis and in patients with HCC might diminish the flow-diversion effect of PVE, decreasing its efficacy in generating contralateral hypertrophy of the nonembolized liver. Clinical studies have failed to support these concerns (as discussed above),[108,109,111–113] though further attention to these potential problems prompted investigation of the combination of arterial embolization (specifically TACE) with PVE.[114,115] In a report on that approach, the authors proposed that TACE be used not only to treat the tumor (to prevent progression during the waiting period for hypertrophy after subsequent PVE) but also to occlude arterioportal shunts before PVE to enhance the hypertrophy-atrophy effect.

Assessment of the Change in Standardized FLR Volume after PVE

Not only the standardized FLR volume but also the change in the standardized FLR volume as a result of PVE (also known as the degree of hypertrophy) is of critical importance in predicting liver function after resection.[56] Volume changes after PVE help to define the regenerative capacity of the liver in patients with normal underlying liver, in patients with cirrhosis, and possibly in patients with underlying liver disease that lies somewhere between the extremes on the spectrum of liver disease (**Figure 9**).

The first observation that PVE-induced change in the FLR volume affects outcome was made in a series of 14 patients with cirrhosis who underwent PVE followed by right hepatectomy.[107] The authors noted that the one patient with liver failure and the one other patient who died after hepatectomy had minimal or no growth of the FLR after PVE. A subsequent study from the same group expanded on this finding.[112] In this study, patients underwent PVE only or TACE plus PVE prior to right hepatectomy. All postoperative deaths and all severe complications occurred in patients with cirrhosis and a degree of hypertrophy less than 10%. In contrast, no patient with cirrhosis and a degree of hypertrophy greater than 10% suffered a major complication or death. Among patients with lesser liver disease, the risk of complications after resection appeared to be low in patients with a degree of hypertrophy greater than 5% after PVE.

We subsequently analyzed 112 patients without severe underlying liver disease and confirmed that complications were rare in patients with a degree of hypertrophy greater than 5% after PVE.[116] Further, patients in whom PVE resulted in both a standardized FLR volume greater than 20% and a degree of hypertrophy greater than 5% had markedly better outcomes than patients in whom PVE failed to produce either or both of these outcomes. Specifically, in patients with standardized FLR volume after PVE greater than 20% and degree of hypertrophy after PVE greater than 5%, major complications were markedly less common (14% vs. 47%, P = 0.01), hepatic insufficiency was rare (1.9% vs. 20%, P = 0.03) and no deaths occurred within 90 days of major hepatectomy (vs. 13%, P = 0.049).

Thus, it has been shown that the combination of standardized FLR volume after PVE and degree of hypertrophy after PVE are the best predictors of the risk of hepatic insufficiency and death after major hepatic resection. Current guidelines advise using these criteria to assess the risk associated with major resection for HCC.[56]

Utility of TACE plus PVE

Two recent studies investigated the use of TACE followed by PVE in patients with cirrhosis and HCC scheduled to undergo right hepatectomy.[111,112,114] In both studies, TACE was used to treat the liver tumor, and then PVE was performed, usually three to four weeks after TACE. In the first study using this technique, by Aoki et al.,[114] 17 patients with advanced HCC (11/17 with multinodular tumors, 15/17 with tumors larger than 5 cm in diameter, and 6/17 with major vascular invasion) underwent TACE followed approximately two weeks later by PVE, and 16 of these patients subsequently underwent resection. The average degree of hypertrophy of the FLR after TACE plus PVE was 22%. Only four patients (25%) experienced minor complications postoperatively, no patient experienced

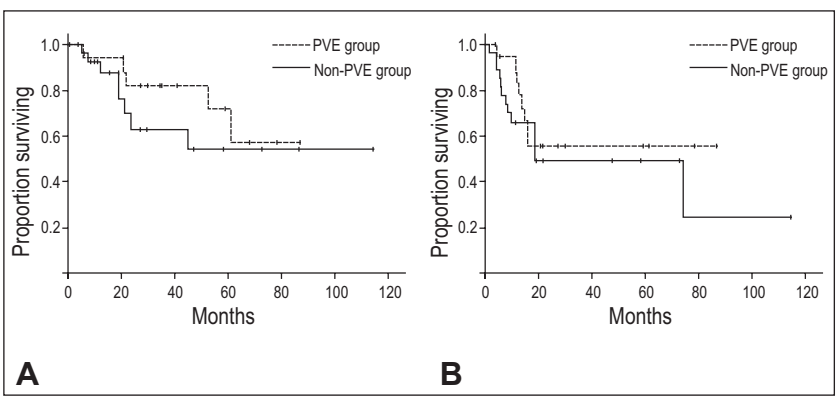


Figure 10. Survival after major hepatectomy for hepatocellular carcinoma (HCC) with and without preoperative portal vein embolization (PVE). There were no postoperative deaths in the PVE group, 6 postoperative deaths in the non-PVE group. **A**) The overall survival rates at 1, 3, and 5 years were 94%, 82%, and 72%, respectively, in the PVE group and 93%, 63%, and 54%, respectively, in the non-PVE group, excluding postoperative deaths (P = 0.35). **B**) The disease-free survival rates were also similar with and without PVE (P = 0.35). (Adapted from Palavacino et al.[108], with permission)

subsequent liver failure, and outcomes were excellent: the 5-year overall survival rate was 56%, and the 5-year disease-free survival rate was 47%.[114]

A subsequent study of 18 patients treated with TACE plus PVE versus 18 patients treated with PVE alone expanded on Aoki et al.'s findings. This study, by Ogata et al.,[112] revealed a significantly greater degree of hypertrophy after double embolization than after PVE only (12% vs. 8%). Importantly, all perioperative deaths occurred in patients with degree of hypertrophy less than 10%. In addition, the proportion of patients who experienced degree of hypertrophy greater than 10% was larger with TACE plus PVE (67%) than with PVE alone (28%). Improved hypertrophy with the double embolization approach may relate to changes in arterial flow after TACE but more likely relates to closure of arteriovenous shunts within large HCCs, allowing more effective portal flow diversion to the FLR with the subsequent PVE.

Oncologic results in the study by Ogata et al.[112] were similar to those in the study by Aoki et al.[114], and the pathologic complete necrosis rate with TACE plus PVE in patients in the Ogata et al. study who underwent resection was impressive: 83% with TACE plus PVE compared to 6% with PVE alone. The 5-year disease-free survival rate was also higher with TACE plus PVE (37% vs. 19%), providing an oncologic basis for considering the combined embolization approach. In M.D. Anderson Cancer Center experience, no patient who underwent resection after TACE plus PVE had a recurrence.[108]

Thus, the combination of TACE and PVE appears not only to increase the degree of hypertrophy over that observed with PVE alone and thus increase the safety of major resection for HCC but also to improve oncologic outcome. Given these findings, TACE plus PVE, rather than TACE alone, could become a definitive treatment for patients with unresectable HCC and adequate liver reserve, as well as being used as a step towards resection to improve outcomes. These studies not only provide evidence that PVE is of significant clinical utility in patients with cirrhosis but also suggest that TACE plus PVE might be an approach that should be considered in the future, a conclusion supported in the most recent consensus statement of the Americas Hepato-Pancreato-Biliary Association (AHPBA) (**Figure 11**).[56]

LIVER RESECTION

Technical Aspects

Advances in anesthetic and surgical techniques, in addition to improved patient selection and preparation for surgery, most likely explain improvements in the safety and surgical outcomes of liver resection for HCC. Recognition that surgical technique affects outcome has led to the development and study of approaches that enhance the probability of not only good surgical outcome but also better oncologic outcome. Established techniques include the use of intraoperative ultrasonography (IOUS), low central venous pressure anesthesia, and hepatic vascular occlusion. Increasingly accepted approaches include portal-oriented anatomic resection, the anterior approach with hanging maneuver for major resection, and parenchymal transection techniques that permit complete resection of tumors with less blood loss.

Intraoperative Ultrasonography

IOUS is generally considered to be an essential component

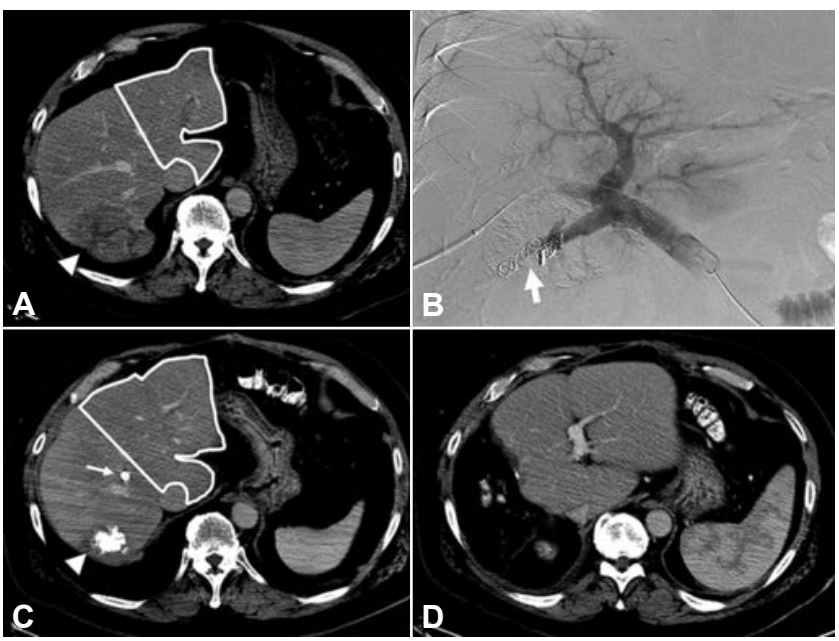


Figure 11. TACE plus PVE prior to right hepatectomy for HCC in a cirrhotic patient. **A**) Pretreatment CT scan reveals tumor abutting the diaphragm (arrowhead). The future liver remnant (FLR), outlined area, represents 32% of the total liver volume. **B**) Portogram after right PVE with coils (arrows). **C**) Postembolization CT scan. The FLR represents now 40% of the total liver volume. The arrowhead indicates the lipiodolized tumor and the arrow indicates a coil. **D**) Postoperative CT scan after right hepatectomy with uneventful postoperative course. Specimen pathologic examination revealed a 6-cm residual tumor with satellite nodules and microscopic vascular invasion and free surgical margins (>2cm). The patient remained without disease recurrence more than 3 years after resection and with alpha-fetoprotein of 6.8 ng/mL (pretreatment was 10,393 ng/mL)

of modern liver surgery. In addition to providing anatomic information necessary to guide resection (i.e., information about the relationship between tumors and intrahepatic vascular structures), IOUS identifies additional nodules in up to 30% of patients,[117] although only about a quarter of newly identified nodules are malignant. Even IOUS-guided biopsy may not definitively differentiate early HCC from dysplastic or regenerative nodules. Although HCC is generally characterized by a "mosaic" pattern with lateral shadowing and posterior enhancement, a significant proportion of nodules lacking these characteristics are found to be malignant. In fact, nearly 30% of hypoechoic nodules, and up to 18% of hyperechoic nodules, are found to be malignant on pathologic examination of explants.[117,118] Not yet available in the United States is contrast-enhanced ultrasonography, which appears to significantly improve the detection and the characterization of lesions using IOUS.[119] There is no debate regarding the utility of IOUS in ensuring margin-negative resection.

Anesthetic Technique

Intraoperative blood loss is one of the most powerful independent predictors of major morbidity and death from hepatectomy in patients with cirrhosis. Maintenance of low central venous pressure, usually less than 5 cm H_2O, has been shown to reduce blood loss from hepatic veins and hepatic parenchyma during liver transection.[120,121]

Hepatic Vascular Occlusion Techniques

The impact of blood loss and transfusion as independent predictors of morbidity and mortality from surgery (particularly in patients with cirrhosis) has led to the investigation of techniques designed to reduce blood loss during liver surgery. Hepatic vascular occlusion is the most common method used to decrease blood loss during parenchymal transection.

Most often used is the Pringle maneuver, also termed pedicle or portal triad clamping. Pedicle clamping has been studied prospectively and has been shown to reduce blood loss and to be safe in patients with cirrhosis, typically when clamping is performed in cycles of 15 minutes of occlusion followed by five minutes of reperfusion, an approach commonly described as "intermittent Pringle occlusion".[122] Pedicle clamping is extremely well tolerated because caval flow is not interrupted;[123] thus, no special anesthetic management is required except for continuous monitoring of arterial blood pressure. Unclamping of the hepatic pedicle is associated with a decrease in blood pressure due to deactivation of the reflex produced by clamping as well as ischemia/reperfusion effects.[124] Usually, blood pressure decreases for a few minutes then returns toward pre-clamp values. In patients with a normal liver, continuous interruption of hepatic inflow is safe for up to 60 minutes.[125] However, intermittent clamping is preferred,[126] 15 to 20 minutes clamped alternating with 5 minutes unclamped, and permits total ischemia time up to 120 minutes [127]or beyond.[128] No reliable data exist regarding the true limits for clamping in patients with a normal liver, though decreased tolerance for intermittent clamping after extended periods - greater than 1 hour of total ischemia - manifests as a more significant decrease in systemic blood pressure when the clamp is replaced and a slower return to baseline after the clamp is removed, similar to the "reperfusion syndrome" in liver transplantation.[129] Tolerable total ischemia times in patients with cirrhosis are shorter, usually about 60 minutes. Intermittent clamping is advised in patients with cirrhosis, as continuous clamping is very poorly tolerated in most patients with any degree of portal hypertension.

Total vascular exclusion, which combines inflow occlusion with complete outflow occlusion (clamping of the suprahepatic and infrahepatic vena cava), causes significant hemodynamic consequences (it may not be tolerated in 10% to 15% of patients because of severe hypotension); is associated with a significant increase in complications; and has not been shown to decrease blood loss compared to pedicle clamping alone.[129] Further, total vascular exclusion is poorly or not at all tolerated in patients with underlying liver disease. Thus, total vascular exclusion is recommended only when necessary because tumor involvement of the hepatocaval junction necessitates vascular control at this juncture for safe resection. The dissection techniques used to expose and control hepatic vascular structures (portal vein, hepatic vein) prior to major resection permit ligation and division of the structures prior to parenchymal transection, which further decreases blood loss and can obviate the need for vascular occlusion affecting the FLR.[129]

On the opposite end of the spectrum is hemihepatic or segmental vascular clamping, which can be used to decrease blood loss and ischemia of the FLR in selected patients based on the anatomic resection planned.[129] Many techniques exist to define portal territories, including "counterstaining" by portal branch injection of ink to define specific vascular territories,[130] ultrasonographic hooking,[131] and ultrasonographic compression of the segmental branch.[131] Each technique has its advantages and disadvantages, mostly defined by surgeon preference, but any of these techniques can be used successfully to optimize the accuracy of resection and to minimize the extent or degree of vascular clamping of the liver to avoid postoperative liver dysfunction.

Portal-Oriented Resection

HCC has a tendency to invade the portal and hepatic veins; thus, tumor spread is primarily through the bloodstream - first via the portal vein to cause porto-portal metastasis,

and later extrahepatically to the lungs, adrenal glands, and bones. In light of the concept of portal extension of HCC, Makuuchi et al.[132] championed the concept of anatomic resection of HCC when feasible, i.e., systematic resection of the entire tumor-bearing hepatic segment, including the supplying portal territories that might contain venous metastases or daughter micronodules. The outcome advantage of anatomic over nonanatomic resection has been clearly demonstrated,[133–135] and a segment-oriented anatomic resection should be considered the standard approach to HCC whenever it is technically and functionally possible. Importantly, anatomic resection does not necessarily mean major resection; lateral bisegmentectomy and single-segment or subsegment resection based on portal territory can also be considered (and are included in studies that examine anatomic vs. wedge resections). Clamping and vascular identification/isolation techniques, including ultrasonographic compression, hooking, and counterstaining,[133–135] can improve the surgeon's ability to identify and completely resect an involved portal territory. The oncologic value of the anatomic approach is emphasized by the finding that after resection with negative parenchymal transection margins, the rate of postoperative tumor recurrence is related not to margin width but rather to microvascular invasion or the presence of microsatellites in or around the resected tumor.[136] Large series comparing anatomic versus nonanatomic resection of HCC revealed that anatomic resection is an independent predictor of disease-free survival and overall survival rates.[133–137] The sole situation in which anatomic resection may not be possible is when a patient has insufficient hepatic reserve. When anatomic resection is not possible, a 1 cm wide negative parenchymal margin is advised, though outcomes relate more to achievement of a negative margin than to the width of the negative margin.[136]

Anterior Approach

Newer surgical approaches to large right-sided tumors represent a significant advance in liver surgery. The conventional approach to right-sided tumors involves mobilization of the right liver from the retroperitoneum and anterior surface of the inferior vena cava, which requires manipulation of the tumor-bearing liver; compresses the FLR; and, in the case of large and very posterior tumors, may give suboptimal access to adhesions to the diaphragm. With the alternative "anterior" approach, proposed as early as 1992 by Ozawa,[137] after extrahepatic control of hilar inflow to the right liver is achieved, the liver is transected anterior-to-posterior, in situ, without liver mobilization. A randomized study of patients with HCC tumors larger than 5 cm requiring right hepatectomy revealed less intraoperative blood loss, lower transfusion requirements, a lower in-hospital death rate, and significantly higher overall and disease-free survival rates with the anterior approach than with the conventional approach to resection.[138]

An important modification of this technique, developed by Belghiti et al.,[139] takes advantage of the consistent absence of hepatic vein branches draining the liver in the midline directly posterior to the liver (**Figure 12**).[140] The "liver-hanging maneuver" is performed in preparation for the anterior approach. First, the space between the right and middle hepatic veins is opened. Next, after inflow vascular control is achieved (usually by division of the right hepatic artery, right portal vein, right biliary pedicle, or some combination of these), the peritoneum is opened over the inferior vena cava inferior to the liver at the level of the caudate liver. Through this avascular space anterior to the inferior vena cava and posterior to the liver capsule, a vascular clamp [139] or - a modification of the technique that we prefer - a pediatric suction-tip catheter [141] is gently passed inferior-to-superior, blindly, to emerge between the right and middle veins. If obstruction is met, IOUS can be used to identify small veins and the course of the clamp or catheter can be altered.[142] A tape is then passed through the dissected space, and the liver is suspended during the parenchymal transection, which facilitates exposure and hemostasis of the structures along the line of transection, particularly improving control and division of posterior structures.

Parenchymal Transection

Many parenchymal dissection techniques are used in hepatic

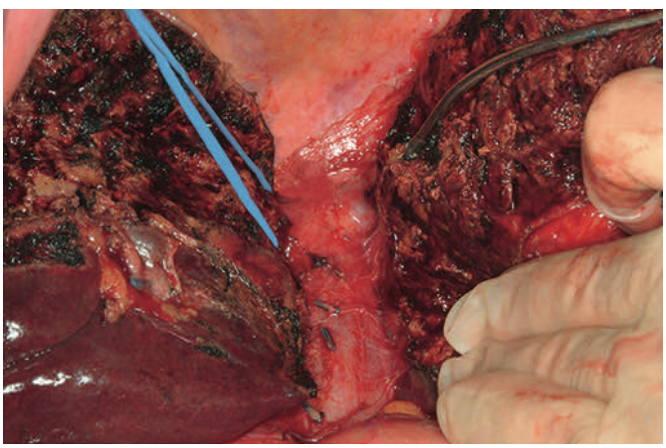


Figure 12. Anterior approach to right hepatectomy. The anterior approach to resection of large hepatocellular carcinomas (or any major hepatectomy) allows the liver to be cut front to back, with or without the hanging maneuver. This image demonstrates the liver cut in situ, with the right hepatic vein in the blue tape. The avascular plane near the midline anterior to the vena cava described by Couinaud (see text) is evident where the clamp or pediatric suction-tip catheter is passed behind the liver to facilitate the hanging maneuver. After the liver has been cut, it is released from the right hypochondrium, minimizing the risk of tumor rupture.

surgery. No one technique is perfect for every liver; for example, some techniques work better in hard, scarred, cirrhotic livers, while other techniques work better in soft, friable, fatty livers. Furthermore, operator preference and the availability of technology in a given center affect the choice of liver-cutting techniques. Common to all approaches, however, should be the effort to minimize blood loss and to expedite hepatic resection. Commonly used instruments include the ultrasonic aspirator, the water-jet cutter, the argon beam coagulator, and the saline-linked cautery device. Our preferred approach separates the two aspects of liver transection: dissection and hemostasis. For dissection, we use the ultrasonic dissector, a handheld device that dissolves hepatocytes by cavitation and aspirates the liquefied tissue. Vessels and biliary ducts, which contain less water, are preserved so that they can be addressed on the basis of their type, size, and orientation. For hemostasis, we use the saline-linked cautery device, in which a metal probe is used to deliver radiofrequency energy conducted through a slow drip of saline. We combine these instruments to increase the efficiency of transection, which has led to decreased blood loss. The primary surgeon dissects the hepatic parenchyma using the ultrasonic dissector, while the second surgeon operates the saline-linked cautery device. Vessels smaller than 3 mm in diameter are coagulated and divided using the saline-linked cautery, while vessels 3 to 5 mm in diameter are controlled with titanium clips and divided sharply. Larger vessels and portal triads are sutured with 3-0 silk ties in continuity and divided sharply. This two-surgeon technique [143] resulted in a significant decrease in blood loss and total operative time and can be applied to most liver types, fibrotic or soft. The decreased need to pass instruments back and forth, as with a similar technique using bipolar cautery,[144] may also contribute to a shorter transection time and, thus, shorter ischemic occlusion time and less blood loss.[145]

Laparoscopic resection

Laparoscopic liver resections are gaining acceptance for benign and malignant diseases (minor and major resections). Despite the absence of randomized clinical trial comparing open and laparoscopic resection for HCC, matched controlled analyses suggest non-inferior perioperative and long-term outcomes. Actually, some studies reported even less blood loss, shorter hospital stay, and lower morbidity rates using laparoscopic approach for HCC resection [146–149]. For further information on the principles of laparoscopic liver surgery please refer to **Chapter 27**.

Outcomes

Outcomes for resection of properly selected patients with HCC are excellent (**Table 5**).[7,150–155] Consideration must be given to the population studied, however. As such, high-risk or advanced HCC should be considered separately from early or recurrent HCC. These three groups are considered below.

High-Risk HCC

Patients with high-risk HCC for whom surgical resection may be considered can be divided into 3 basic groups: patients with large lesions (> 5 cm), patients with multinodular tumors, and patients with major vascular invasion of the portal and/or hepatic veins.

Large tumors (> 5 cm) remain common despite

Table 5. Recent series reporting survival and perioperative mortality after resection of hepatocellular carcinoma.

Author, year	N	Note		5-year Overall Survival (%)	Perioperative Mortality (%)
Grazi, 2001[150]	107	Before 1992		32	9.3
	157	After 1992		49	1.3
Zhou, 2001[151]	1000	≤ 5 cm		63	1.5
	1366	> 5 cm		37	3.7
Poon, 2001[7]	36	≤ 5 cm	Before 1994	26	13
	82	> 5 cm		11	
	103	≤ 5 cm	After 1994	30	2.5
	132	> 5 cm		21	
Taura, 2007[152]	127	Noncirrhotic		81	2
	166	Cirrhotic		46	4
Yang, 2009[153]	135	Solitary ≤ 5 cm		48	0
	260	Solitary > 5 cm		38	0.02
Lee, 2010[154]	130	Cirrhotic		52	0.8
Lee, 2015[155]	679	2002 - 2005		55%	3.2
	916	20 06 - 2010		72%	2

screening for HCC.[156–160] Large tumors are usually discovered in patients with preserved liver function and can exceed 10 cm before symptoms develop. Large tumors are considered a form of high-risk HCC because tumor size correlates with the incidence of vascular invasion;[161,162] however, outcomes after aggressive treatment of large tumors can be excellent, particularly when vascular invasion is absent. Patients with T1 HCC according to the AJCC/UICC staging system, i.e., solitary tumors of any size without vascular invasion, have excellent survival. Tumor ablation, embolization, and transplantation are generally not options for patients with large HCCs. The risks associated with resection of large tumors and incorrectly perceived oncologic risk have led some groups, including the persuasive Barcelona group, to advise against resection of large HCCs.[163] However, major centers perform resection in patients with preserved liver function and large HCCs with excellent results, as detailed below.

Early reported survival rates in the range of 17% to 33% after resection of HCCs larger than 5 cm [134,164] most likely led some surgeons away from considering resection for patients with large HCCs. However, subsequent data revealed excellent results after resection of large HCCs, including 5-year survival rates of greater than 70% when vascular invasion was absent. Primary tumor size (> 5 cm vs. < 5 cm) does affect the probability of survival, primarily because of the higher risk of vascular invasion with larger tumors, but this fact does not imply that patients with tumors larger than 5 cm should not undergo resection. Data from resection of more than 400 HCCs at high-volume centers revealed that the 5-year overall survival rate was 58% for small (< 5 cm) solitary HCCs versus 39% for large (> 5 cm) HCCs, both of which outcomes are excellent.[165] Subsequent data from resection of 300 HCCs larger than 10 cm demonstrated an operative mortality rate of only 5% and excellent survival despite the need for major or extended hepatectomy in 60% of the studied patients.[157] These findings are corroborated by many other series (**Table 6**).[63,138,156–160,165,166]

The impact of underlying liver disease on prognosis after resection is reinforced by the AJCC/UICC staging system's recommendation that fibrosis be taken into account, a factor corroborated in many studies. For example, work by Ishizawa et al.[167] showed that the 5-year survival rate after resection was 58% in patients with Child-Pugh class A liver function and multiple HCCs versus 19% in comparable patients with Child-Pugh class B liver function and multiple HCCs.

Multinodular HCC presents particular oncologic and technical challenges. Multiple nodules may represent independent tumors arising *de novo* throughout the liver or may be a manifestation of advanced disease with intrahepatic metastasis. Bilateral tumor location adds to the technical challenge when resection is considered. Consequently, in patients with multinodular or bilateral HCC, major resection is often necessary to encompass all lesions. Clearly, for patients selected for resection, tumor size and tumor number affect prognosis. Among patients with multinodular HCC, the 5-year overall survival rate after resection is 37% for patients with a maximum tumor diameter of less than or equal to 5 cm but only 15% for patients with a maximum tumor diameter of greater than 5 cm.[8] Patients with more than three nodules, regardless of the size, and patients with two or three nodules, one of which exceeds 3 cm in diameter, have been considered unsuitable for resection by some groups, including the influential Barcelona group.[50] Ng et al.[165] recently analyzed the outcomes of 380 such patients who underwent resection

Table 6. Prognosis after resection of very large (≥ 10 cm) hepatocellular carcinomas in series reporting on more than 100 patients undergoing resection.

Author, year	N	Overall Survival Rate (%)		Negative Prognostic Factors
		5-year	10-year	
Poon, 2002[158]	120	28	Not reported	Multiple tumors, vascular invasion
Yeh, 2003[159]	211	17	14	Absence of tumor capsule, elevated AFP level, presence of satellites around main tumor, vascular invasion, cirrhosis
Zhou, 2003[160]	621	26	18	Multiple tumors, absence of tumor capsule, vascular invasion
Chen, 2004[156]	525	17*	2.9*	Absence of tumor capsule, vascular invasion, presence of satellites around main tumor
Pawlik, 2005[157]	300	27	18	Multiple tumors, elevated AFP level, vascular invasion, cirrhosis
Hwang, 2015[166]	471	35	19	Elevated AFP, hypermetabolic uptake on positron emission tomography, satellite nodules, microvascular invasion

* Low 10-year survival attributed to inclusion of a large proportion of patients who underwent portal thrombectomy (105/525, 20%). Abbreviations: AFP, alpha-fetoprotein.

for HCC and found that the perioperative mortality rate was 2.4% and the 5-year survival rate was 39%, which challenges the BCLC-supported concept that these patients should only be considered for palliative treatment. In a series of 39 patients with bilobar tumors, Wu et al. reported 6-year disease-free survival and actuarial overall survival rates of 31% and 43%, respectively, after radical resection, further emphasizing this point. Several other studies including more than 300 patients with multinodular HCC revealed an identical 5-year overall survival rate of 24%.[8,64,69,165,167–170] Thus, when liver function permits and when clearance of all tumor nodules is possible, en bloc extended hepatectomy, multiple bilobar resections, or hepatectomy plus local ablation of contralateral nodules should be considered for patients with multinodular or bilateral HCC (**Table 7**).[8,64,69,167,168]

Major vascular invasion, i.e., invasion of a main portal trunk or hepatic vein extending as far as the vena cava, presents a difficult problem. Survival in patients with this feature has generally been poor; however, a very select minority of patients can derive a significant benefit from hepatectomy with extraction of caval thrombi or hepatectomy in the presence of segmental portal vein thrombosis. Furthermore, unlike microscopic vascular invasion, tumor invasion of the hepatic or portal veins can be detected preoperatively, which has led some authors and treatment algorithms to direct all patients with this finding toward palliative medical therapies with new antitumor agents in the setting of randomized controlled trials.[163,171] However, resection should not be abandoned in all patients with major vascular invasion. In properly selected patients with major vascular invasion who have adequate hepatic reserve, the survival probability is very reasonable. Minagawa et al.[172] reported a median survival of 3.4 years and a 5-year survival rate of 42% in a series of 23 patients with tumor extension into the portal vein who were treated with partial hepatectomy. In a multicenter series of 102 patients with major portal or hepatic vein involvement, we reported a 5-year survival rate of 23% in patients without cirrhosis.[173] The small number of reported patients who were candidates for resection underscores the factors that lead to selection for surgery underscores the rigorous nature of patient selection for surgery, though a significant benefit can be derived by treating patients individually rather than algorithmically. Furthermore, in the treatment of patients with major vascular invasion, ablation has no role, liver transplantation is contraindicated, and the gold-standard systemic therapy (sorafenib) results in an increase in survival measured only in weeks.[174] Thus, among patients with major vascular invasion who are potential candidates for resection, surgery should be considered before a patient is assigned to investigational therapy even though only a small minority of patients is likely to be able to undergo surgery.

Table 7. Outcomes after resection or transplantation for solitary versus multiple hepatocellular carcinomas.

Author, year	Type of HCC		N	Overall Survival Rate (%)		P
				5-year	8-year	
RESECTION						
Nagasue, 1993[69]	Solitary Multiple		229	32 24	27 24	
Vauthey, 2002[8]	Solitary Multiple		370 180	45 24		< 0.001
Poon, 2003[64]	Solitary Multiple		376 142	54 24		< 0.0001
Wang, 2008[168]	Solitary Multiple		487 112	58 30		< 0.0001
Ishizawa, 2008[167]	Solitary Multiple	Child's A	259 105	68 58		0.035
	Solitary Multiple	Child's B	49 21	45 19		0.013
Ng, 2005[165]	Solitary Multiple		308 72	46.9 month median 14.3 month median		< 0.0001
TRANSPLANTATION						
Yamamoto, 1999[170]	Solitary Multiple		144 126	118 months median 69 months median		

Child's: Child-Pugh class; HCC: hepatocellular carcinoma.

Other morphologic, serologic, and pathologic factors affect the prognosis after resection of patients with high-risk HCC, including the gross appearance of the tumor,[175,176] the presence of satellite nodules surrounding the main tumor,[136] and elevated AFP level.[175,177,178] To date, however, these factors have not been particularly useful as a guide to treatment planning.

Early HCC

Treatment of early HCC is generally surgical and is guided by the degree of underlying liver disease. Among patients with severe underlying liver disease, those with early HCC generally meeting the Milan criteria (a solitary HCC smaller than 5 cm in diameter or a maximum of three tumors, each less than 3 cm in diameter, without macroscopic vascular involvement or distant disease[9]) are considered for liver transplantation. Patients with early HCC without liver disease or with well-compensated liver disease are generally treated with liver resection. Following is an overview of outcomes after liver transplantation and liver resection in patients with early HCC, together with a brief discussion of the controversy surrounding the selection of treatment for these patients.

Based on the seminal study of Mazzaferro et al.,[9] which followed Bismuth et al.'s suggestion that transplantation be considered for patients with early HCC,[179] liver transplantation is now considered by many to be the ideal treatment for early HCC in patients with cirrhosis. The findings of such an influential study should be considered carefully. Only 48 patients were studied, and only 4-year survival was reported. Three patients died within one month of transplantation. The median tumor size was small (only 1.5 cm), and no patient was found to have vascular invasion. The disease-free survival rate was higher than the overall survival rate because 12 of the 14 deaths that occurred outside the perioperative period were unrelated to tumor recurrence. Because overall survival, not disease-free survival, captures all the causes of death in patients with HCC (including deaths from both cancer and underlying liver disease), disease-free survival may not be of great value in comparing outcomes after transplantation and resection. In addition, mortality from liver transplantation is not insignificant, and despite improvements in immunosuppression, deaths from complications of infection, graft-versus-host disease, and recurrent cirrhosis or hepatitis remain issues with liver transplantation for HCC.

Once the Mazzaferro (or Milan) criteria were adopted, however, subsequent series reported good results for liver transplantation for early HCC, including 5-year overall survival rates of about 65%.[67,180] Unfortunately, however, raw data from the Organ Procurement and Transplantation Network (accessed August 20, 2010) reveal that the 5-year overall survival rate for patients who undergo transplantation in the United States for malignancy is only 54%, far below the rates quoted above, and the corresponding 1-year overall survival rate is only 86%.[180] Though these contemporary survival figures for liver transplantation in the United States may include an occasional patient with HCC more extensive than specified by the Milan criteria and perhaps a few patients with non-HCC malignancy, these figures suggest that the reality of survival after liver transplantation for HCC is not the reality purported by individuals who advocate use of liver transplantation *as an alternative* to liver resection. Further, when intention-to-treat analysis is performed and drop-out is considered in the survival analysis for liver transplantation for HCC, the 3-year overall survival rate decreases from 80% to only 60% in one series,[171] and the 2-year survival rate decreases to only 73% in a more recent report.[181] Finally, only about 20% of the approximately 6000 liver transplantations performed each year in the United States are performed for HCC. The problem of donor shortage has not been solved with living donor transplantation, results of which have been disappointing, and risk to the donor adds to the complexity of the treatment decisions.

In comparing outcomes after liver resection and liver transplantation, it is not appropriate to include liver-resection series that included patients with large or advanced HCCs given that liver transplantation is performed for early HCC. When analysis is limited to liver-resection series that include only patients with small HCCs, results are good, whether they are compared to results after liver transplantation or considered as stand-alone results. A small series of 36 patients who underwent liver resection for HCC that was pathologically confirmed to meet the Milan criteria revealed a 5-year overall survival rate of 69% and a five-year disease-free survival rate of 48%.[182] A larger series of 135 patients age 65 years or younger who underwent resection of "transplantable" HCC between 1989 and 1999 was reported from Hong Kong.[183] All patients had disease that was pathologically confirmed to meet the Milan criteria. Overall survival rates at 5 and 10 years were 70% and 35%, respectively, and the corresponding disease-free survival rates were 36% and 22%, respectively. Of note was that among the 67 patients with recurrence, 53 (79%) were considered eligible for salvage transplantation, and decompensation from Child-Pugh class A to class B or C disease without HCC recurrence occurred in only six patients. Worse outcomes were found in patients with more advanced cirrhosis, reinforcing the finding that patients with advanced liver disease are better served by liver transplantation. In contrast, patients with Child-Pugh class A liver function had 5-year survival rates similar to the best published rates in patients treated with liver transplantation, and salvage transplantation was at least a theoretical possibility in the majority of patients who

experienced recurrence.

Recent series that "compare" liver transplantation and liver resection confirm the good results of both treatments. Lee et al.[154] recently reported on 87 liver transplantations and 130 liver resections for HCC. The study groups were not balanced; patients undergoing liver resection were significantly older, had AFP levels four times those in patients undergoing transplantation, had higher-grade tumors, had higher-stage tumors, and were less likely to have undergone preoperative TACE. Despite these differences, however, overall survival was not significantly different between the transplantation and resection groups (3-year overall survival, 78% after liver transplantation vs. 75% after liver resection, P = 0.207). Disease-free survival rates did differ, but the liver resection patients had more advanced cancer, and again, disease-free survival may not be the endpoint of interest for patients with HCC. The operative mortality rate for liver transplantation (5.1%) exceeded that for liver resection (0.8%).

In summary, liver transplantation and liver resection for early HCC are realistically complementary treatments. Liver resection is best used in patients without liver disease or with well-compensated liver disease, whereas liver transplantation is best used in patients with more advanced liver disease. Issues of donor availability, waiting-list dropout, and lifelong immunosuppression associated with liver transplantation are balanced against the risk of liver insufficiency and in-liver recurrence after liver resection.[184]

Recurrent HCC

Intrahepatic recurrence is the main type of treatment failure after resection of HCC. Overall 5-year recurrence rates after potentially curative resection range from 70% to 100%, and up to 90% of recurrences include intrahepatic recurrence.[69,175] Whether these recurrences result from porto-portal intrahepatic metastases or from the development of new primary tumors in the liver as a result of hepatitis or cirrhosis is unknown.

In the case of isolated, limited intrahepatic recurrence, repeat hepatectomy is considered in about 20% of patients. Repeat resection is challenging in the previously resected liver but has been shown to be safe and provide good outcomes in selected patients.[185–187] The same criteria are generally used to select patients for repeat resection as are used for the first resection of HCC, and basically the same factors are prognostic; additional factors associated with improved prognosis in patients undergoing resection for recurrent HCC are a single tumor (vs. multiple tumors) at the first resection and a disease-free interval between the first resection and recurrence of at least one year. Although only a minority of patients with recurrent HCC are considered candidates for resection, the overall 5-year survival rate after a repeat hepatectomy in the largest reported series (of 67 patients) was 56%, a rate similar to those reported in many series of initial resection.[186]

In patients who are not appropriate candidates for repeat resection, aggressive nonsurgical treatment with ethanol injection, in situ ablation, and TACE may yield favorable results. RFA is often considered in this setting as well because recurrences found in patients undergoing surveillance are often small.

LIVER TRANSPLANTATION

Advanced cirrhosis often eliminates liver resection as a treatment option for HCC. In such cases, liver transplantation can be considered. Indications for liver transplantation are guided by the seminal proposal of Bismuth et al.,[179] which was subsequently formalized by Mazzaferro et al.[9] Mazzaferro et al. proposed that liver transplantation be limited to patients with a solitary HCC less than 5 cm in diameter or a maximum of three tumors, each less than 3 cm in diameter, without macroscopic vascular involvement or distant disease. These selection criteria, known as the Milan criteria, have resulted in 5-year survival rates of 71% to 75% in some centers and of about 60% in analyses based on registry data from Europe and the United States.

The major advantages of liver transplantation over liver resection are the treatment of the underlying liver disease and the complete removal of the "field at risk" for development of de novo cancer.[188] These advantages are counterbalanced by the 13% 1-year mortality rate in adults, the severe shortage of organ donors, and the cost and morbidity of lifelong immunosuppression. Progression of HCC while patients wait for a suitable donor organ can lead to "dropout" or loss of opportunity for transplantation; in fact, the rate of tumor progression leading to dropout among patients waiting for liver transplantation is reported to be 15% to 33%. Because of progression and dropout, the 2-year intention-to-treat survival rate is 84% for patients with 62 days of waiting time but only 54% for patients with 162 days of waiting time. Recent intention-to treat analyses of a large cohort of patients found 5-year survival rates of 47% to 62%, far below the 70% survival rates for liver transplantation that are frequently quoted.[171]

Expansion of the morphologic selection criteria for liver transplantation has been considered, and some authors have suggested incorporating biologic factors such as grading and genotyping into the patient selection process. A detailed discussion of the pros and cons of these controversial approaches is beyond the scope of this chapter, but encouraging results of early studies are counterbalanced by the difficulty of identifying good-prognosis tumors among patients with HCC more extensive than that defined by the Milan criteria.

In practice, as mentioned earlier in this chapter, liver

resection and liver transplantation are complementary, not competing, treatments. Patients with preserved hepatic function are generally considered for liver resection as first-line treatment. Conversely, those with poor liver function and early HCC are eligible for liver transplantation. Despite the complementary nature of these treatments, debate continues regarding resection versus transplantation as the optimal initial treatment for patients with preserved liver function and HCC that meets the Milan criteria.[183,189,190] Factors that favor resection include the discrepancy between organ supply and demand; problems associated with liver transplantation, such as graft rejection, recurrent viral hepatitis, immunosuppression-related opportunistic infections, and long-term medical complications; and the potential value of liver resection followed by "salvage" transplantation for patients with recurrence of HCC or deterioration of hepatic function. Majno et al.'s[191] Markov-based decision analytic model, which showed a life expectancy of 8.8 years for patients undergoing primary liver transplantation versus 7.8 years for patients undergoing primary resection and salvage transplantation, added fuel to the controversy. The problem of more advanced HCCs arising in the setting of advanced cirrhosis remains unsolved by either liver resection or liver transplantation.

Outcomes after liver transplantation for HCC have changed little since the standardized application of Milan criteria for liver transplantation (see above). Mortality for liver transplantation remains an issue of concern; some early series reported 90-day mortality rates up to 22%, primarily related to immunosuppression-related complications, but those rates have fallen to closer to 2% in more modern series.[192]

For further reading on transplantation on malignant liver tumors refer to **Chapter 30**.

FIBROLAMELLAR HCC

Fibrolamellar HCC is a rare subtype of HCC that deserves brief separate mention because of differences in treatment strategies for fibrolamellar versus conventional HCC. Fibrolamellar HCC generally occurs in younger patients with normal underlying liver. The AFP level is typically normal. Fibrolamellar HCC does not appear to be related to typical risk factors for HCC, such as hepatitis. Paraneoplastic syndromes are not uncommon with fibrolamellar HCC. At presentation, up to 70% of patients have metastatic lymphadenopathy, and mass-related symptoms are common. Diagnosis is often made on the basis of imaging that reveals fairly well defined or lobulated masses, sometimes with central scar or calcification, and typically in the background of normal underlying liver. Biopsy reveals well-differentiated HCC with deeply eosinophilic cytoplasm and macronucleoli with abundant fibrous bands.

Surgery is the mainstay of treatment for fibrolamellar HCC. Both resection and transplantation are viable options. Liver resection should include lymphadenectomy; in patients with nodal or lung metastases at diagnosis or at recurrence after initial resection, surgery to remove the metastases is of value. Resection yields excellent 5-year overall survival rates (up to 65%), and orthotopic liver transplantation can yield similar results (5-year overall survival rate, 50%).[193]

NONSURGICAL TREATMENTS

ABLATIVE THERAPIES

A significant proportion of patients with HCC are not eligible for liver resection or liver transplantation. For some patients who are not candidates for surgery and who have limited and small tumors, ablative therapies can be considered. Some authors utilize one form of ablative therapy, radiofrequency ablation (RFA), to delay progression of HCC while patients await liver transplantation.[12,13]

Advantages of ablative therapies are generally low morbidity and the potential for percutaneous treatment. The major disadvantages of all ablation techniques are the difficulty of evaluating treatment margins and the need to obtain negative treatment margins in three dimensions. All ablation techniques are associated with higher local recurrence rates than resection. Although ablative therapies may also be used to treat resectable HCC, their efficacy has not been established as equivalent to that of resection or transplantation. However, ablative therapies are an important complement to these potentially curative therapies.

The oldest, best-known, most widely used, best-studied, and least expensive ablative therapy for HCC is percutaneous ethanol injection.[194] Injection of absolute ethanol via a fine needle under imaging guidance leads to cellular dehydration, necrosis, and vascular thrombosis causing tumor cell death. Percutaneous ethanol injection is most effective for small HCCs; complete ablation rates of 90% to 100% have been reported for HCCs smaller than 2 cm, but the complete ablation rate falls to 70% for tumors between 2 and 3 cm and 50% for tumors between 3 and 5 cm. Incomplete ablation may result from inadequate ethanol infiltration related to imperfect needle placement or from imperfect diffusion of ethanol throughout the tumor because of the presence of intratumoral septae. Severe complications of percutaneous ethanol injection are rare, and the treatment-related mortality rate has been reported to be 0.09% to 0.1%. More recent ablation methods include cryoablation, radiofrequency ablation, and microwave

ablation.[195,196]

RFA is the most utilized mode of ablative therapy. RFA uses heat to destroy tumors: a needle electrode inserted into the tumor delivers a high-frequency alternating current, which generates rapid vibration of ions, frictional heat, and, ultimately, coagulative necrosis. For small (< 2 cm) tumors, the efficacy of RFA is similar to that of percutaneous ethanol injection, but for larger tumors, RFA is significantly more effective than percutaneous ethanol injection.[197] Even when ablation with RFA is apparently complete, however, explant analysis of ablated tumors (in patients who underwent RFA for HCC in cirrhosis as a bridge to liver transplantation) consistently shows tumor persistence after RFA in 45% to 53% of cases (37% to 38% for HCCs < 3 cm); in fact, the cumulative probability of HCC persistence rises with time after RFA, to 70% by 18 months after treatment.[13] The main drawbacks of RFA are its relatively high cost; its higher rate of complications compared to percutaneous ethanol injection (0% to 12%), which can include pneumothorax, pleural effusion, hemorrhage, subcapsular hematoma, hemobilia, biliary stricture, and liver abscess; and the treatment-related mortality rate of up to 1%. Despite these shortcomings, RFA remains an important and effective treatment for unresectable small HCCs; in addition, because of percutaneous treatment and retreatment options and lesser impact on liver function than liver resection, RFA remains an important tool for treatment of limited cancer in patients with severely diseased livers. For patients who have a tumor recurrence after surgical treatment and who are not candidates for resection, RFA is probably the best "salvage" technique and may induce remission. As previously mentioned, RFA is also used in some patients to prevent tumor progression while patients are awaiting liver transplantation.[198]

Ultimately, I am of the opinion that although RFA has limited ability to completely destroy HCC, RFA in cirrhotic patients adequately controls small tumors. Patients with cirrhosis have a competing risk for death (liver failure), and RFA can safely control tumors without a high risk for development of liver failure. Certainly, when resection can be offered, it is a better oncologic treatment than RFA, but if resection comes at the cost of liver failure, this better "oncologic" treatment comes at an unacceptable risk. Again, decision-making about treatment must take into account both of the problems of cirrhotic patients with HCC: liver disease and cancer.[199]

TRANSARTERIAL THERAPIES

Bland Embolization and Chemoembolization

For HCC not amenable to liver resection, liver transplantation, or RFA – especially for multifocal HCC – transarterial therapies (also known as intraarterial therapies) can be considered. The transarterial therapeutic approach is attractive for HCC because the preferential arterial blood supply to HCC enables delivery of anatomically targeted treatments while (theoretically) sparing hepatic parenchyma and thus reducing the incidence and severity of hepatic and systemic side effects. One form of transarterial therapy, TACE, is also used as a modality to control (or perhaps to downsize) HCC in patients awaiting liver transplantation.

Three categories of transarterial therapies for HCC have been used: (1) delivery of bland embolic particles (TAE); (2) delivery of chemotherapy as an infusion or, more commonly, with an embolic component (TACE); and (3) a newer approach, in which radioactive particles are delivered (radioembolization). All involve delivery of transarterially targeted embolic agents, chemotherapeutic agents, or both into the liver or selectively into hypervascular liver tumors. TAE, TACE, and radioembolization are discussed only briefly here as they are discussed in detail elsewhere in this book.

TACE is a technique that combines transarterial chemotherapy and embolization of selected vessels feeding tumors within the liver. Chemotherapeutic agents, such as doxorubicin or cisplatin, are combined with iodized oil (lipiodol) and delivered transarterially to intrahepatic branches of the hepatic artery. This is typically followed by delivery of an embolic agent, such as gelatin sponge (Gelfoam), polyvinyl alcohol, or starch microspheres. The procedure results in extensive tumor necrosis in over half of patients treated. Randomized controlled trials from Hong Kong [200] and Barcelona [201] demonstrated significant improvements in overall survival in patients treated with TACE compared with those treated symptomatically or with TAE alone. These studies demonstrated 3-year survival rates of 26% (Hong Kong) and 29% (Barcelona) after TACE, compared to 3% (Hong Kong) and 11% (Barcelona) after symptomatic treatment alone. The difference in outcomes between the two studies reflects the selection of patients for embolization in each trial - patients in the Hong Kong trial had more advanced disease than those in the Barcelona trial. Both trials show a survival advantage for TACE, despite differences in the studies. Although the study from Barcelona demonstrated equivalent 3-year survival rates for TACE and TAE alone, there were fewer deaths in the TACE group secondary to tumor progression. This led to the conclusion that TACE was superior to TAE. Both studies relied on careful patient selection to identify those who would tolerate chemoembolization and benefit from treatment. In a more recent study, 100 patients with unresectable HCC were randomly assigned to TACE or systemic doxorubicin, and the results suggested a benefit for TACE in terms of treatment-related mortality, response rate, and progression-free survival. Median overall survival was not statistically prolonged with TACE (38 weeks)

versus systemic chemotherapy (32 weeks, P = 0.08).[202]

Of all patients with unresectable HCC, fewer than 30% are candidates for TACE. These include patients with relatively well-preserved hepatic function, adequate renal function, and no evidence of extrahepatic metastatic disease. Patients with advanced HCC and poor hepatic function are susceptible to liver failure after TACE. Main portal vein occlusion is another relative contraindication for TACE, although patients with suspected portal vein or hepatic vein occlusion can be treated selectively (and were included in the Hong Kong trial).

Because of the recent lack of availability of lipiodol worldwide, many groups have converted to using drug-eluting beads for TACE. Mounting evidence suggests that TACE using doxorubicin-eluting microspheres is more effective than TAE and results in tumor response rates and tumor control rates similar to or superior to those observed in historic, larger studies of lipiodol-based TACE.[203,204] There is a suggestion that postembolization syndrome (pain, fever, and nausea) may be less common with TACE with drug-eluting beads than with conventional TACE. In any case, the current lack of availability of lipiodol has led most centers to shift to TACE with drug-eluting beads by necessity. The ongoing PRECISION V trial is a phase III trial of TACE with drug-eluting beads that is accruing patients well and is expected to definitively demonstrate the utility of this newer TACE approach.[205]

TACE is also used as a tumor control method for patients awaiting liver transplantation for HCC (see the next paragraph); in combination with RFA to achieve adequate tumor control in selected patients; and in combination with PVE as a strategy for preparing patients for major hepatic resection (see the section "Utility of TACE plus PVE" above).

The utility of TACE as a bridge to transplantation is debated, but TACE is widely used for this purpose. The duration of time waiting for transplantation affects the relative value of TACE: patients with short wait times most likely do not benefit from any bridge treatment as disease progression during a short waiting period is unlikely to cause drop-out from candidacy for liver transplantation. One study included 48 patients whose disease initially met the Milan criteria and 15 patients whose disease did not initially meet the Milan criteria but who had 50% or greater reduction in tumor volume after TACE and were thus ultimately considered for transplantation.[206] At the time of publication, 41 patients had undergone liver transplantation, and 46 patients were alive. Of the patients whose disease initially met the Milan criteria, none were removed from the waiting list because of tumor progression after a mean wait time of 178 days. The 5-year intention-to-treat survival rate was 93%, and only one patient (2.4%) had a recurrence. Among the patients with initially advanced disease, the dropout rate was 20%; among the patients with initially advanced disease who underwent transplantation, 30% had a recurrence. Others have shown that in the majority of patients, TACE maintains initially Milan-compatible disease within the Milan parameters and downstages up to 63% of cases of advanced disease so that they meet the Milan criteria.[207]

Finally, some authors suggest that response to TACE is a valuable tool for selecting patients for transplantation. A small study of 27 patients with HCC treated with TACE or TACE plus another ablative modality found no difference in progression or survival with or without TACE (wait time was 214 days in the TACE group vs. 133 days in the non-TACE group). However, progression while waiting for transplantation (irrespective of TACE) was associated with shorter overall survival.[208] In short, TACE is viewed as a means to help patients with prolonged wait times avoid being dropped from the waiting list for liver transplantation. Further study is needed to define the expected wait duration that mandates bridge treatment with TACE versus no bridge treatment. Further, as liver transplantation allocation guidelines change, wait-list duration will change, which will affect the need for effective bridge therapy.

Radioembolization

Gaining favor since the development of two commercially available spheres embedded with yttrium-90 (^{90}Y) is embolization with radioactive particles. One product is a glass microsphere that is non-biodegradable and has a small diameter (25 ± 10 micrometers, Therasphere). Because of their small size, these glass spheres lodge at the arteriolar level, generally in the periphery of tumors, where they emit radiation over a maximum diameter of about 10 mm around the sphere for about 10 days. The other product is a non-biodegradable resin sphere with a diameter ranging from 29 to 35 micrometers (SIR-sphere). SIR-spheres have lower activity per sphere than Theraspheres, and there are technical differences in delivery of the two agents (for details, see **Chapter 7**). Several studies have demonstrated the efficacy and toxicity of ^{90}Y radioembolization for HCC. Fatigue, pain, nausea and vomiting, and elevated bilirubin level are reported in a significant proportion of patients (over 20% and in some series up to 60%). Other problems, including cholecystitis and leucopenia, have also been reported, and the mortality rate is up to 7%.[14] Long-term effects (liver failure) when tumor control is achieved have not been clearly reported, but the possibility of liver failure remains a concern with this treatment in light of the experience with radioembolization for treatment of other tumor types.[198] In patients with multinodular disease that would have required many TACE procedures but was instead treated with sequential lobar radioembolization or whole liver radioembolization, response rates and

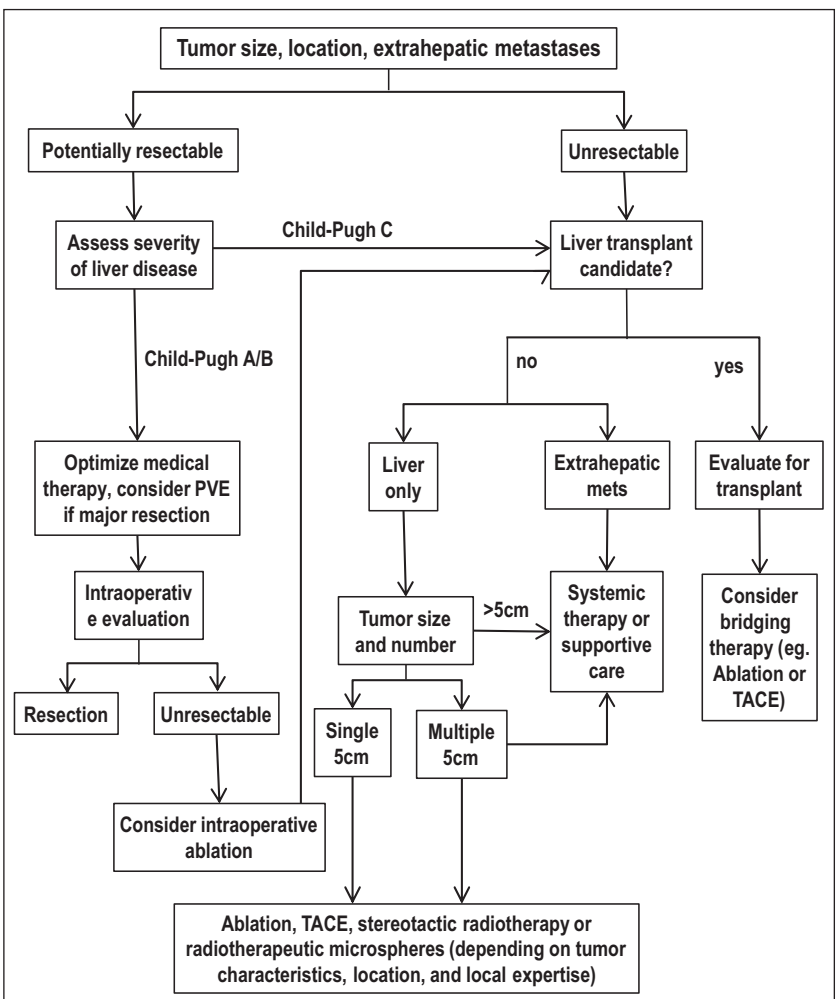
outcomes are promising. Combined partial and complete response rates are in the 50% range.[14,209,210] Survival after radioembolization is generally measured in months but may reach two years in patients with better liver function (Child-Pugh class A or Okuda stage I disease).

SYSTEMIC THERAPY

Systemic chemotherapy has been disappointing as an approach to advanced HCC. Cytotoxic chemotherapy has marginal antitumor activity against HCC. Various clinical trials investigating the role of single agents - such as 5-fluorouracil, doxorubicin, cisplatin, vinblastine, and etoposide - in the treatment of unresectable HCC have reported short-lasting, modest responses in 0% to 20% of patients. Doxorubicin is considered the most active single agent and has produced an overall response rate of 19%. However, neither doxorubicin nor any other chemotherapeutic agent or combination has produced improved patient survival rates.

A subgroup of patients with advanced HCC but preserved liver function may benefit from systemic chemotherapy (**Figure 13**). A phase II trial of a combination of cisplatin, interferon alpha-2b, doxorubicin, and fluorouracil (PIAF) in such patients yielded promising results: an overall response rate of 26% and a complete pathologic response rate of 8%. Although a subsequent randomized phase III study failed to demonstrate an improved survival duration or a significantly higher response rate for PIAF (8.7 months and 21%) versus doxorubicin alone (6.8 months and 11%),[211] a remarkable 28% of patients with initially unresectable HCC treated with PIAF experienced downsizing of their disease so that it became resectable and then underwent salvage resection (in the doxorubicin-alone group, the rate of downsizing to resectable disease was only 12%).[212]

For fibrolamellar HCC, 5-fluorouracil and interferon alpha have been used and have produced modest response rates.[213]



PVE: Portal vein embolization; TACE: transarterial chemoembolization.
Notes: Resection on patients Child-Pugh B is controversial; patients initially outside transplant criteria could be reassessed after downstaging therapy; systemic therapy include sorafenib or clinical trial.

Figure 13. Treatment algorithm for hepatocellular carcinoma.

The most recent advance in the treatment of unresectable HCC is the use of the oral multikinase inhibitor sorafenib. This advance was based on the results of a phase III randomized, placebo-controlled study demonstrating that sorafenib could prolong survival (although only by a few weeks) in patients with advanced HCC.[214] Sorafenib blocks tumor cell proliferation through an antiangiogenic effect derived from blockade of vascular endothelial growth factor receptors 2 and 3, and blockade of platelet-derived growth factor-beta. The study included primarily patients with Child-Pugh class A disease, and median survival was extended modestly but statistically significantly over that seen with best supportive care alone (median overall survival was 10.7 months with sorafenib vs. 7.9 months in the placebo group, $P < 0.001$). Time to progression was prolonged as well (5.5 months with sorafenib vs. 2.8 months in the placebo group). Side effects, including diarrhea, hand-foot syndrome, and fatigue, were not insignificant. Subset analysis suggested greater benefit in patients with HCV than in patients with other causes of HCC, and there is some interest in and there was some suggestion of an antiviral effect of sorafenib on HCV, which remains to be confirmed. Sorafenib is actually the first drug to be approved for treatment of advanced HCC, and despite the modest effect of the drug, this advance has opened the door to new treatment approaches to HCC using molecularly targeted agents and other treatment combinations. From a surgical perspective, there is interest in sorafenib as a post-treatment adjuvant therapy after TACE, RFA, or resection; this strategy may be pursued in upcoming clinical trials.

Systemic therapies remain difficult to deliver in patients with advanced liver disease, but advances in targeted therapies continue to open doors to new treatment approaches that could enable downsizing before treatment or adjuvant therapy after definitive therapy to reduce the risk of recurrence. Many other molecularly targeted agents are under study for HCC, though advances in systemic treatment for this disease continue to occur slowly.[215]

Finally, of growing interest is antiviral therapy as an "adjuvant" therapy. Attention is being again raised to the importance of viral control even in surgery for HCC as a result of a recent randomized, controlled trial of patients with hepatitis B and HCC who underwent R0 resection.[216] Patients were randomly assigned to receive adefovir 10 mg/d (n=100) or placebo (n=100) following complete surgery. Those who received antiviral therapy experienced longer overall survival (63% vs. 42%, $P = 0.001$) and longer recurrence-free survival (46% vs. 27%, $P = 0.026$). After adjustment for confounders in a COX model, patients who received antiviral treatment experienced significantly decreased relative risk for recurrence [0.651, 95% Confidence Interval (CI): 0.451-0.938, $P = 0.021$] and decreased relative risk for death (0.42, 95% CI 0.271-0.651, $P < 0.001$). Further suggesting the true effect of the therapy was that there was no protective effect of antiviral therapy on early tumor recurrence (likely governed by tumor factors), but there was a protective effect of antiviral therapy on late recurrence (thus effect of reducing risk for new disease, not recurrent disease). [216]

RADIATION THERAPY

External-beam radiation therapy has limited utility in the treatment of HCC. Whole-liver radiation therapy is not effective for any liver disease and may be associated with radiation hepatitis. Newer methods, including conformal, "4-dimensional" planning techniques and proton therapy, have shown promise in terms of tumor control, and radiation therapy can provide relief from symptoms in highly selected patients with HCC. Interest is increasing in selective internal radiation therapy through intra-arterial injection of iodine 131-labeled lipiodol or yttrium-90-labeled microspheres (the latter termed "radioembolization"). The impact of these therapies on survival has not been established, and they are considered investigational. Radioembolization is discussed above in the section "Transarterial Therapies" and is discussed in greater detail elsewhere in this book.

FINAL CONSIDERATIONS

HCC remains a major health issue worldwide. Improving outcomes are certainly linked to effective screening, which permits diagnosis at an early stage, when potentially curative treatment can be offered. In addition, advances in treatment have given a growing proportion of patients with more advanced disease the opportunity to undergo aggressive treatment and experience prolonged survival. Many treatments for HCC are complementary and increasingly used in combination. Following multidisciplinary team evaluation a suggested algorithm for patients with HCC is shown in **Figure 13**. Liver resection is the treatment of choice in cirrhotic patients with preserved liver function (Child-Pugh class A disease) across a spectrum of patients with early to more advanced HCC. Selected patients with large or multinodular tumors can undergo resection with excellent results; carefully selected patients (usually without cirrhosis) with macroscopic vascular invasion and bilobar tumors also may undergo resection and experience acceptable outcomes. The safety of resection relates to the function of the underlying liver (absence, presence, and degree of underlying liver disease) and, critically, to the volume of the liver that will remain after resection. In patients with an inadequate FLR, PVE is indicated to reduce the morbidity and mortality of major hepatectomy. Combination treatment with TACE and PVE followed by resection addresses oncologic factors (tumor

downsizing) and liver factors (augmentation of FLR volume and function), further expanding resection options and the safety of major hepatectomy for HCC. Advances in surgical techniques, including use of the anterior approach with hanging maneuver and improved liver-cutting techniques, appear to have improved both short- and long-term outcomes for patients with HCC undergoing major resection. Liver transplantation remains the treatment of choice for early HCC in patients with advanced underlying liver disease, but organ shortage limits the use of transplantation, and transplantation is only useful for early HCC. Systemic therapies are disappointing, and transarterial treatments, including TACE and radioembolization, are increasingly used in patients with unresectable disease but relatively preserved liver function. Ablation plays an important role in the treatment of small, unresectable tumors. The largest proportion of patients with advanced underlying liver disease and advanced HCC are in need of better treatment options.

Future advances in the surgical treatment of HCC are likely to arise from a growing understanding of the interactions between liver volume and liver function and the variable causes and biology of HCC. The integration of systemic, liver-directed, and surgical therapies and the improved definition of biologic factors contributing to cirrhosis and to HCC are likely to guide future therapies in this challenging patient population.

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SUGGESTED READING

Vauthey, J. N. *et al.* Simplified staging for hepatocellular carcinoma. *J. Clin. Oncol.* **20**, 1527–1536 (2002).

This is the seminal paper on which the modern TNM staging system for HCC is based. The system has been modified minimally since, but this is the backbone of the present AJCC and UICC staging systems for HCC.

Mazzaferro, V. *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl. J. Med.* **334**, 693–699 (1996).

This paper formulated the basis for the "Milan" criteria, the basis of present guidelines for transplantation for HCC in cirrhosis.

Llovet, J. M., Bru, C. & Bruix, J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin. Liver Dis.* **19**, 329–338 (1999).

This is the initial presentation of the Barcelona staging classification – not so much a staging system but a treatment algorithm designed to aid in treating patients in a more systematic way. This is criticized for producing prognosis based on assigned treatment (ie. Being a treatment algorithm not staging system) but the Barcelona integration of performance status, liver disease and tumor extent proves valuable in assessment of non-surgical patients with HCC.

Abdalla, E. K., Hicks, M. E. & Vauthey, J. N. Portal vein embolization: rationale, technique and future prospects. *Br. J. Surg.* **88**, 165–175 (2001).

This seminal review on PVE secured the place for this preoperative liver-remodeling approach to patients that require extensive hepatectomy. The review recognizes the critical work done primarily in Japan leading up to integration of PVE into standard practice for major hepatic resection.

Aoki, T. *et al.* Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. *Arch. Surg.* **139**, 766–774 (2004).

This first to combine portal and arterial embolization initiated a wave in surgical and non-surgical patients with HCC with relatively preserved liver function. Subsequent evidence confirms the value of doub le embolization in enhancing safety and improving outcome of major resection for HCC in cirrhosis. The double embolization therapy may be highly therapeutic in some non-surgical patients as well.

Liu, C. L., Fan, S. T., Lo, C. M., Tung-Ping Poon, R. & Wong, J. Anterior approach for major right hepatic resection for large hepatocellular carcinoma. *Ann. Surg.* **232**, 25–31 (2000).

This randomized controlled trial demonstrated that surgical technique (anterior approach to resection of large right liver tumors) not only improved safety but probably oncologic outcome for resection of large HCC.

Llovet, J. M. *et al.* Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* **359**, 378–390 (2008).

This is the seminal SHARP trial which established sorafenib as the first drug approved for treatment of advanced HCC, if only extending survival by a few weeks.

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14 Hilar Cholangiocarcinoma

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- *Hilar cholangiocarcinoma is a complex disease for which the only curative treatment is complete surgical resection.*
- *Staging and evaluation of resectability of hilar cholangiocarcinoma require preoperative determination of tumor extent to the biliary tract, portal vein, and hepatic artery.*
- *R0 resection is of utmost importance and has been associated with improved survival. Major hepatic resection is needed to achieve complete longitudinal and radial negative margins. Portal vein involvement and bilateral biliary extent to secondary branches are not contraindications for curative intent surgery.*
- *Preoperative portal vein embolization and selective or total biliary drainage are available tools to increase resectability rate and minimize surgical morbidity.*
- *Orthotopic liver transplantation can benefit a subgroup of patients with unresectable small hilar cholangiocarcinoma.*
- *Palliative therapies include surgical biliary drainage procedures, endoscopic or percutaneous bile duct stenting, and local ablative methods (such as chemotherapy and photodynamic therapy).*

INTRODUCTION

Cholangiocarcinomas are malignancies of the biliary duct system and further classified as i) intrahepatic, ii) perihilar (also named Klatskin tumor, or hilar cholangiocarcinoma, or proximal extrahepatic cholangiocarcinoma), and iii) distal, according to their location. Despite the incidence of cholangiocarcinomas varying greatly across different countries, these tumors represent less than 3% of all digestive cancers. Cholangiocarcinomas involving the biliary confluence are the most common (nearly 60%) and represent the focus of this chapter.[1,2] Intrahepatic cholangiocarcinomas are discussed in **Chapter 15**.

Hilar cholangiocarcinoma (HC) usually originates in the absence of risk factors, but it may be associated with locally inflammatory conditions such as primary sclerosing cholangitis, ulcerative colitis, or parasitic infestation.[3]

Hilar tumors are usually slow growing, with lymph nodal, hematogenic, and peritoneal spread occurring late in the course of disease. However, due to its position on the hepatic hilum, it tends to be locally invasive, with early involvement of vascular regional structures. The frequent involvement of hilar structures and adjacent liver parenchyma makes surgical resection complex, even for small tumors. Despite a typically high surgical morbidity (nearly 50%) and mortality (up to 10%), curative resection remains the treatment of choice for HC, resulting in an overall 5-year survival rate of approximately 45%.[4–6] A minority of patients (30-40%) are candidates for curative resection at the moment of diagnosis,

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mainly due to advanced hilar involvement. Survival with palliative therapies is poor, with a 15% survival rate at two years.[4,6,7] Selected patients with unresectable HC are candidates for adjuvant radiotherapy with chemosensitization followed by liver transplantation, as discussed later in this chapter.

EXTENSION MODE

Longitudinal extension

Longitudinal tumor extension along the mucosa and sub-mucosa of the bile duct occurs in most hilar cholangiocarcinomas, reaching up to 15 mm from the main macroscopic tumor. Periarterial and perineural tumor spread is typical with HC.[8–11]

Longitudinal tumor extension is responsible for the high rate of microscopically compromised resection margin (R1) and justifies the dissection at the porta hepatis and around the pancreatic head, with skeletonization of the vascular axes, performed during HC resection. Hepatic pedicle lymph node involvement is also part of longitudinal extension. The Bismuth-Corlette classification for HC is based on longitudinal extension (**Figure 1**).

Vertical extension

Vertical extension of HC includes involvement of the hepatic parenchyma of the right and/or left hemiliver, and also extension forward and backward (i.e., segments 1 and 4). The hepatic pedicle can be directly invaded, including the involvement of the portal vein at its bifurcation, the hepatic artery (especially the right branch), and the floor and roof of the hilum (segments 1 and 4, respectively).

These primary modes of extension explain the role of major hepatectomy, regional lymphadenectomy, resection of the common bile duct, and occasionally resection of the portal vein with vascular reconstruction (**Figure 2**).

DIAGNOSIS AND STAGING

Diagnosis of HC is required before surgical treatment. Diagnostic criteria for HC include the presence of biliary stricture suggesting malignancy associated with one of the following: i) endoluminal biopsy or cytology positive for cholangiocarcinoma; ii) polysomy by fluorescent in situ hybridization; iii) mass lesion on cross-section imaging at the location of the biliary stricture; and iv) carbohydrate antigen (CA) 19-9 greater than 100 UI/L. Before liver transplantation for HC, biopsy or cytology should confirm cholangiocarcinoma.[12,13]

CLINICAL PRESENTATION

Patients with hilar cholangiocarcinoma typically present with jaundice. However, clinical nonspecific manifestations can develop early, including weight loss, abdominal pain, or pruritus. Most of hilar bile duct stricture associated to jaundice represent hilar cholangiocarcinoma. Cholangitis is a very uncommon presentation in the absence of instrumentation of biliary tree.

Serum bilirubin and alkaline phosphatase are typically elevated. Tumor markers, such as CA 19-9 and carcinoembryonic antigen (CEA) are not specific to hilar cholangiocarcinoma, but they are helpful to determine the presence of malignancy. The sensitivity and specificity of CA 19-9 in differentiating between a benign versus malignant

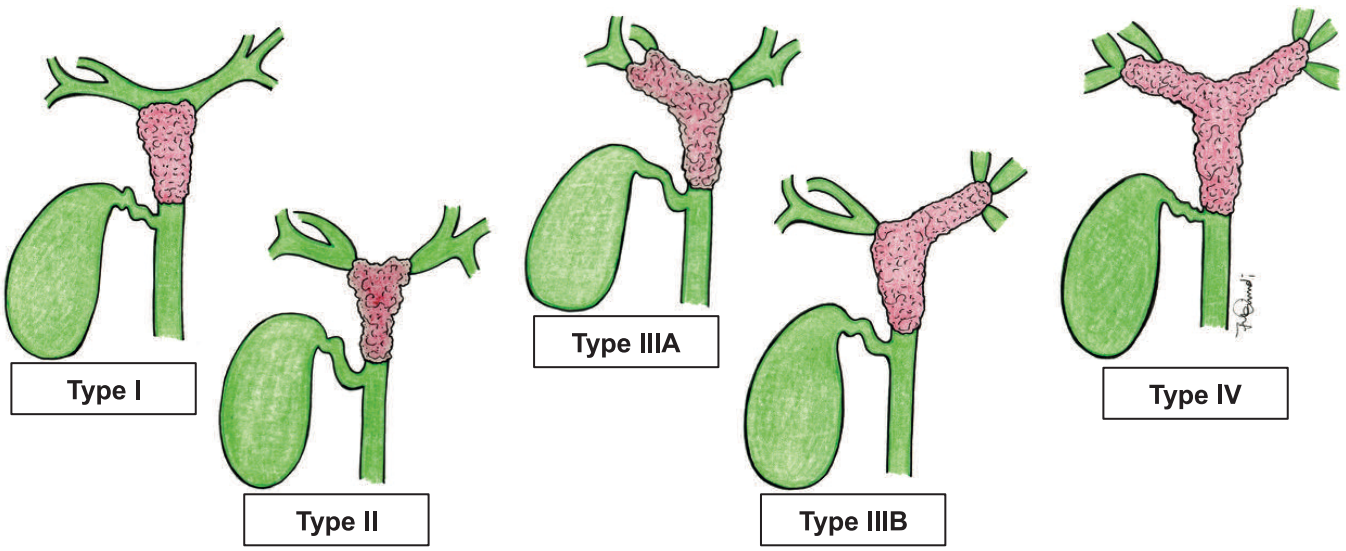


Figure 1. Schematic representation of Bismuth-Corlette classification. Type I: the biliary confluence is reached but not interrupted. Type II: interruption of the biliary confluence. Type III: obstruction of the right (a) or left (b) secondary confluence. Type IV: obstruction of both the right and the left secondary bile ducts.

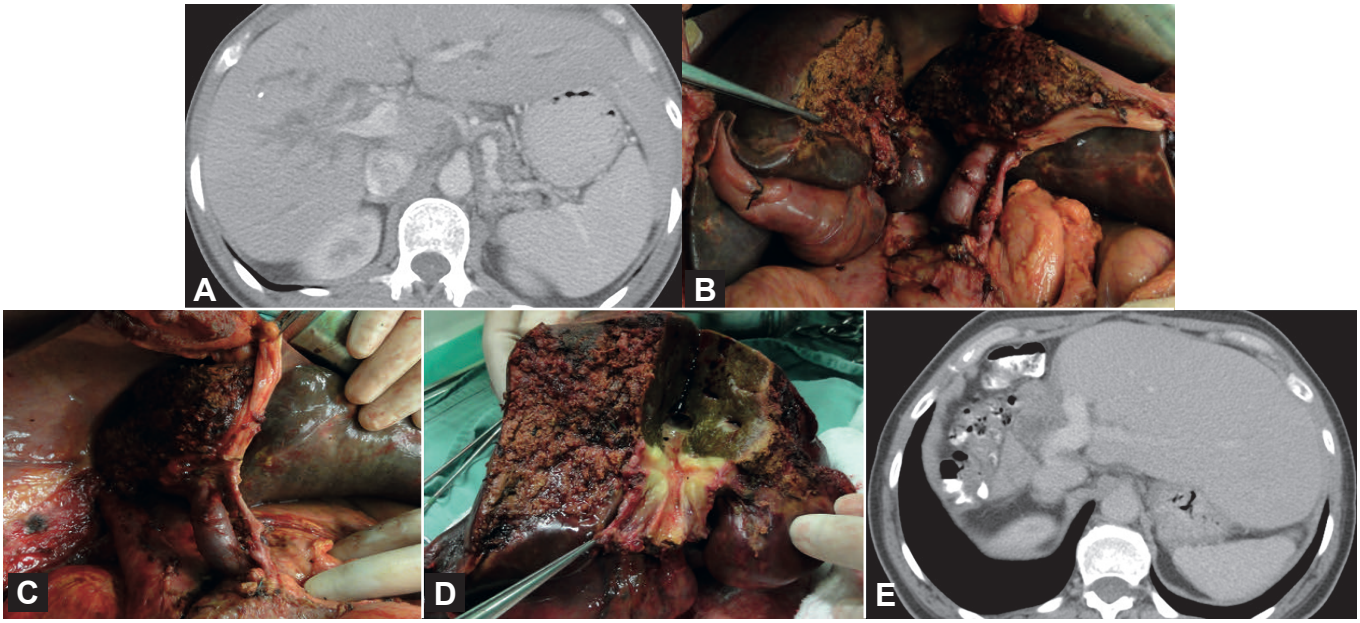


Figure 2. Illustrative case of a hilar cholangiocarcinoma Bismuth-Corlette type IIIa without vascular invasion showing a standard resection for hilar cholanciocarcinoma. **A**) Preoperative computed tomography (CT) showing a predominant extension for secondary right biliary radicles. **B**) Intraoperative aspect showing en bloc resection of the hepatoduodenal ligament (except vascular structures), hilum (including the biliary confluence), and segments 4 to 8 plus segment 1 of the liver. **C**) Intraoperative view after the resection was accomplished showing the vascular skeletonization. **D**) Surgical specimen with a nodular-infiltrating cholangiocarcinoma (macroscopic and pathological free margins of 5 mm). **E**) CT four years after resection with no evidence of recurrence.

stricture is 76 and 92%, respectively.[14] Additionally, tumor marker levels are associated with tumor stage, predicting a worse overall survival.[14,15]

HISTOLOGICAL EVIDENCE OF CANCER

Most cases of proximal bile duct strictures are due to hilar cholangiocarcinoma. However, an alternative etiology is seen in 5-15% of hilar biliary strictures, including benign strictures and other malignancies, even in jaundiced patients (**Table 1**).[16–18] Clinical diagnosis of HC can be challenging, particularly in patients with primary sclerosing cholangitis, in which mass lesions are often identified on imaging without significant intrahepatic biliary dilatation.[19]

It is often difficult to obtain histological evidence of malignancy HC, mainly due to the frequent pattern of submucosal extension in bile ducts, the small size of tumors, and the presence of intrahepatic bile duct dilatation.[20,21] Additionally, a negative cytology does not exclude HC.[21–23] Preoperative methods for tissue diagnosis include percutaneous biopsy of a mass and brushing of bile ducts (by percutaneous or endoscopic access). Endoscopic ultrasound (EUS) can be used to guide biopsies through the stomach or duodenum, but similarly to percutaneous access, there is a risk of peritoneal tumor seeding. Percutaneous biopsies and endoscopic brush cytology have low sensitivity for HC diagnosis (40-70%).[24] Molecular biology and fluorescence in situ hybridization (FISH) may increase the sensitivity of cytology to 86%.[25] Transperitoneal biopsy or fine needle aspiration (FNA) can lead to tumor seeding and is usually contraindicated.

The identification of morphological findings associated with malignancy of hilar lesions (e.g., involvement of biliary secondary branches, vascular encasement, and liver parenchyma atrophy) and an adequate knowledge of diseases mimicking HC allow for correct diagnosis without the need of

Table 1. Differential diagnoses of hilar cholangiocarcinoma.

Benign hilar strictures	Malignant hilar strictures
Iatrogenic injury (biliary injury after cholecystectomy)	Gallbladder cancer with hilar extension
Primary sclerosing cholangitis	Lymph node metastases
Autoimmune, infectious, or ischemic cholangitis	Peritoneal carcinomatosis
Mirizzi syndrome	Liver metastases (segment 4 or 1)
Portal biliopathy	
Hepatic pseudotumors	

biopsy in most cases.[5,17] In fact, in a recent prospective study focusing on perioperative management of HC, preoperative knowledge of the malignant nature of the hilar tumor was missing in 80% of patients.[5] Thus, histological diagnosis should not be mandatory before surgical exploration, even in cases of doubt and especially for small resectable lesions, since most hilar strictures are due to HC.

RADIOLOGICAL ASSESSMENT (Figures 3 to 7)

Patients with HC typically present with jaundice, and intrahepatic (but not extrahepatic) dilatation is seen on imaging.

Biliary anatomy can be evaluated by non-invasive methods, such as magnetic resonance imaging cholangiography (MRI-cholangiography) or computed tomography cholangiography (CT-cholangiography), or by invasive direct cholangiography through endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic cholangiography (PTC). Tumor local extension, vascular involvement, parenchymal atrophy, and metastatic disease can be assessed using computed tomography (CT) or magnetic resonance imaging (MRI). Positron emission tomography (PET) has low sensitivity for detection of regional and distant metastases from HC and is not routinely used.

Ultrasonography is usually performed as the first imaging study for evaluation of jaundice or other non-specific abdominal symptoms. The most prevalent ultrasonographic finding on HC is intrahepatic biliary dilatation (unilateral or bilateral) with non-dilated extrahepatic ducts. Also, a mass, liver parenchyma invasion, or tumor inside the portal vein may be seen on ultrasound.

Contrast-enhanced CT can usually identify the level of biliary obstruction and can detect the presence of parenchymal atrophy, mass, or vascular involvement.[26,27] Contrast retention in delayed phases is a characteristic finding with cholangiocarcinomas. Accuracy in portal venous and hepatic artery involvement is 96% and 93%, respectively.[28] Despite the effectiveness of CT in determining resectability, the proximal extent of biliary involvement is not always accurate.

MRI-cholangiography is non-invasive and has high sensitivity for the preoperative assessment of HC.[29] MRI and MRI-cholangiography identify obstructed or isolated bile ducts, properly determine the level of proximal biliary involvement, and assess vascular invasion, nodal involvement, and distant metastases.[30–32]

Typical imaging modalities used to evaluate vascular extension (arterial and venous), lymph node metastasis, and liver dysmorphia are detailed in **Table 2**.

The usefulness of PET with focal accumulation of nucleotide tracer 18-fluorodeoxyglucose (FDG) is unclear, particularly in infiltrating tumors. However, PET scans would lead to a change in surgical management in up to 30% of patients evaluated for cholangiocarcinoma due to the detection of unsuspected metastases.[33] Nevertheless, the results of a PET scan must be interpreted with caution in patients with primary sclerosing cholangitis or with biliary stents in place, due to a high rate of false positivity.[33–36]

Direct imaging of the bile ducts can be obtained with percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiography (ERC). However, these methods have been restricted to special situations, such as the need for preoperative biliary drainage. The risk of contamination of otherwise sterile bile ducts is a possible complication, mainly with ERC.

EXPLORATORY LAPAROSCOPY

Unresectable HC can be discovered at the time of exploration despite extensive preoperative evaluation including ultrasound, CT, and MRI. Peritoneal carcinomatosis and/or small intrahepatic metastases are undetectable with conventional preoperative evaluation. Of patients who are undergo exploration with curative intent, up to 60% are ultimately non-resectable, which has motivated close evaluation of the role of staging laparoscopy for patients with HC.[37,38] The yield and accuracy of staging laparoscopy is 25% to 42% and 42% to 53%, respectively.[38] This surgical approach is validated in terms of operative time, length of hospital stay, time of access to chemotherapy[37,38] and cost. The yield of laparoscopy (i.e., the proportion of patients correctly classified) depends on the completion of

Table 2. Radiologic features on hilar cholangiocarcinoma.

Method	Features and possible findings
Ultrasonography	- intrahepatic bile duct dilatation upstream the stenosis - no extrahepatic bile duct dilatation - local thickening of the bile duct walls - tumor hilar mass - vascular evaluation by US-Doppler - nodal, hepatic, peritoneal extension
Computed tomography	- intrahepatic bile duct dilatation upstream the stenosis - long biliary stenosis with thickened walls (>1.5mm) with delayed contrast enhancement - hilar mass with extension to the segment 4 - adequate vascular evaluation - nodal, hepatic, peritoneal extension - liver atrophy
Magnetic resonance imaging	- intrahepatic bile duct dilatation upstream the stenosis - no extrahepatic bile duct dilatation - thickening of bile ducts with moderate hyperintensity on T2 phase, enhancement especially in the late phase - extension to adjacent liver parenchyma - adequate evaluation of longitudinal extension

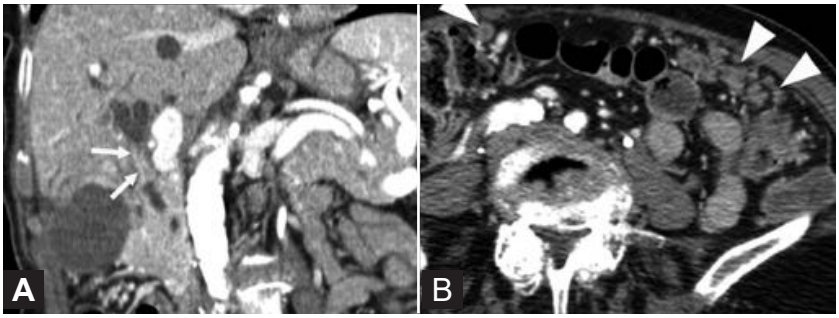


Figure 3. Hilar cholangiocarcinoma Bismuth-Corlette type I. Computed tomography (CT) on portal phase showing stenosis of the proximal bile duct. **A**) Coronal reformation showing thickening of the bile duct wall with contrast enhancement (arrows). **B**) Axial image showing nodules of carcinomatosis (arrowheads).

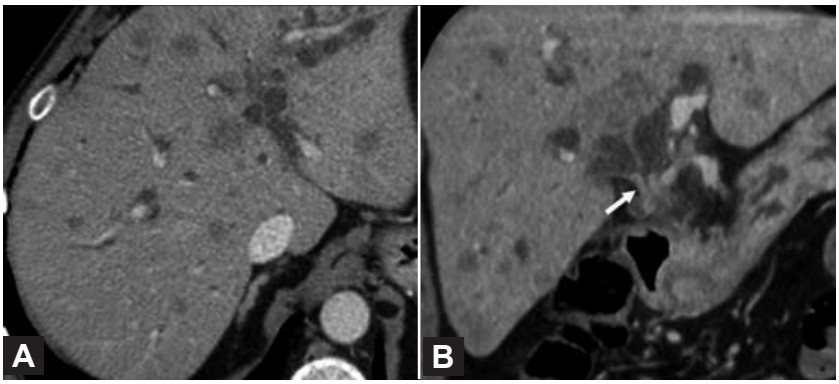


Figure 4. Hilar cholangiocarcinoma Bismuth-Corlette type II. Computed tomography (CT) on portal phase showing biliary stenosis and tumor extension to the biliary confluence (arrow). **A**) Axial image. **B**) Coronal reformation. Note the multiple hypodense hepatic lesions (metastases).

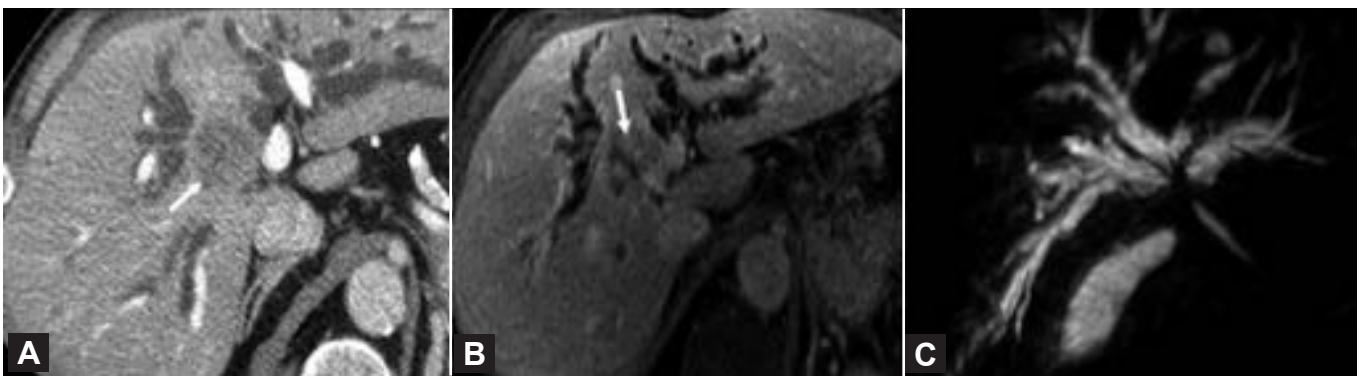


Figure 5. Hilar cholangiocarcinoma Bismuth-Corlette type IIIa. **A**) Axial computed tomography (CT) on portal phase showing a hypodense tumor extended to segment 4 and the right hepatic duct, responsible for intrahepatic bile duct dilatation. **B**) Axial T1-weighted magnetic resonance imaging (MRI) after injection of gadolium in the late phase. **C**) 3D MRI-cholangiography of the same patient.

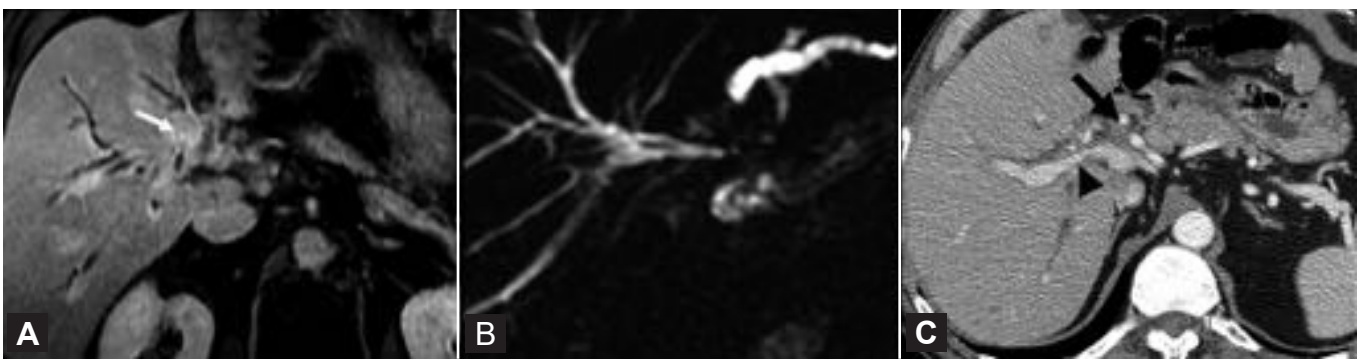


Figure 6. Hilar cholangiocarcinoma Bismuth-Corlette type IIIb. **A**) Magnetic resonance imaging (MRI) in axial T1-weighted after gadolinium in the late phase showing hilar tumor (arrow) extended to the intrahepatic left bile ducts with ipsilateral parenchyma atrophy. **B**) 3D MRI-cholangiography showing marked bile duct dilatation on the left side. **C**) Axial computed tomography in portal phase of the same patient showing portal compression by the tumor (arrowhead) and perivascular infiltration (arrow).

a laparoscopic intraoperative ultrasound. A prospective study showed that the yield of laparoscopy was 25% in patients with HC (36% in patients with HC classified T2/T3 stage and 9% in those classified as stage T1).[38]

CLASSIFICATION AND STAGING

Despite attempts to establish a staging system able to predict outcomes and resectability, all available systems present weaknesses.

Pathological classification of HC includes three subtypes: i) sclerosing, ii) nodular, and iii) papillary. Most HCs are sclerosing (concentric thickening of the bile duct and periductal infiltration) or nodular (tumor projection directly into the lumen of the bile duct) tumors. Papillary lesions are rare.

The **Bismuth-Corlette classification** (**Figure 1**), described in 1975,[39] is based on the level and extension of the hilar tumor along the biliary tree. Lesions are classified as i) type I when only the common hepatic duct below the biliary confluence is involved; ii) type II when the biliary confluence is involved; iii) type IIIa or IIIb when the right hepatic duct or the left hepatic duct is involved, respectively; and iv) type IV when both right and left hepatic ducts are involved together with the confluence. This classification has been widely adopted; however, since it only evaluates the biliary system involvement, regardless of the presence of vascular involvement and/or parenchymal atrophy and/or distant metastases, it is not predictive for tumor resectability and survival.[40]

The **Memorial Sloan Kettering Cancer Center** (MSK-CC) developed another preoperative T-staging system (**Table 3**) that takes into account portal vein involvement, lobar atrophy, and ductal extent of the tumor.[40] The accuracy of this classification for preoperative local tumor extent was 86% in the original report, which included 225 patients. This classification does not take into account the nodal and arterial involvement and presence of distant metastases, but this T-staging system is predictive of resectability, the likelihood of nodal or distant metastases, and overall survival.[6,40–42]

The **TNM staging system** (**Table 4**), revised in 2009

Table 4. TNM staging of extrahepatic bile duct tumors according to the AJCC/UICC 7th edition.

	Description
T	TX - The primary tumor cannot be assessed T0 - No evidence of a primary tumor Tis - Carcinoma in situ T1 - Tumor confined to the bile duct histologically T2a - Tumor invades the surrounding adipose tissue beyond the wall of the bile duct T2b - Tumor invades the adjacent hepatic parenchyma T3 - Tumor invades unilateral branches of the portal vein or hepatic artery T4 - Tumor invades the main portal vein or its branches bilaterally, the common hepatic artery, the second-order biliary radicals bilaterally, or the unilateral second-order biliary radicals with contralateral portal vein or hepatic vein involvement
N	NX - Regional lymph nodes cannot be assessed N0 - No regional lymph node metastasis N1 - Regional hilar lymph node metastatis (cystic duct, common bile duct, common hepatic artery, and portal vein nodes) N2 - Metastasis to periduodenal, peripancreatic, superior mesenteric artery, and/or celiac nodes
M	M0 - No distant metastasis M1 - Distant metastasis

Stage grouping	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-T2b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-T3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T Any T	N2 Any N	M0 M1

Table 3. Hilar cholangiocarcinoma staging according to the Memorial Sloan Kettering Cancer Center (MSKCC) classification.

Tumor stage (T)	Description
T1	- The tumor involves the biliary confluence with unilateral involvement up to secondary biliary radicles. - No portal vein involvement or liver atrophy
T2	- The tumor involves the biliary confluence with unilateral involvement up to secondary biliary radicles. - There is ipsilateral portal vein involvement or ipsilateral hepatic lobar atrophy. - No main portal vein involvement.
T3	- The tumor involves the biliary confluence with bilateral involvement of secondary biliary radicles, OR unilateral extension to secondary biliary radicles with contralateral portal vein involvement, OR unilateral extension to secondary biliary radicles with contralateral hepatic lobar atrophy, OR main/bilateral portal vein involvement.

by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), is based on pathological findings and its preoperative use is very limited.

Another recent classification from the International Cholangiocarcinoma Group, reported by Deoliveira et al.,[7] tried to establish a predictive classification of resectability, available preoperatively, based on the tumor size, the extent of the disease in the biliary system, the involvement of the hepatic artery and portal vein, the involvement of lymph nodes, distant metastases, and the volume of the remnant liver after resection. Nevertheless, this new staging system still needs to be validated and accepted.

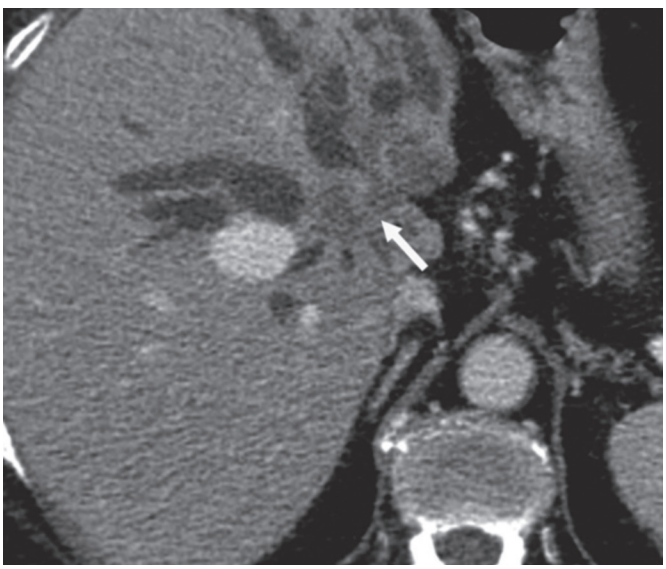


Figure 7. Hilar cholangiocarcinoma Bismuth-Corlette type IV. Axial computed tomography (CT) in portal phase projection MinIP. Hilar tumor extended to segment 4 (arrow) invading the right and the left hepatic ducts. Bilateral intrahepatic bile duct dilatation.

PREOPERATIVE MANAGEMENT

CLINICAL ASSESSMENT

Potential surgical candidates should be carefully evaluated to their fitness to surgery, since comorbidities are frequent. According to estimated surgical risk, detailed cardiologic and respiratory evaluation is undertaken. Correction of associated malnutrition and coagulopathy is performed preoperatively.[43] Standard laboratory tests should include total serum bilirubin levels and serum albumin.

PREOPERATIVE BILIARY DRAINAGE (Figure 8)

Several reports have shown that liver resection in patients with obstructive jaundice and cholangitis is associated with severe complications, including intraoperative bleeding, postoperative abscesses due to biliary fistula, and liver failure. The theoretical roles of preoperative biliary drainage (BD) are: i) to decrease serum bilirubin level (and restore intestinal bile flow whenever possible), ii) to treat biliary infection, iii) to obtain better assessment of intraductal extent of tumor, and iv) to allow hypertrophy after portal vein embolization (PVE). Currently, there is a consensus to consider BD in the following situations: i) when the future remnant liver (FRL) is less than 40% of the total liver volume and if a PVE is considered; ii) presence of cholangitis resistant to antibiotics; and iii) malnutrition, renal failure, or hypoalbuminemia.

There are two methods of biliary drainage with HC: percutaneous transhepatic biliary drainage (PTBD) and endoscopic retrograde biliary drainage (ERBD). PTBD has possible adverse effects, including i) tumour seeding,

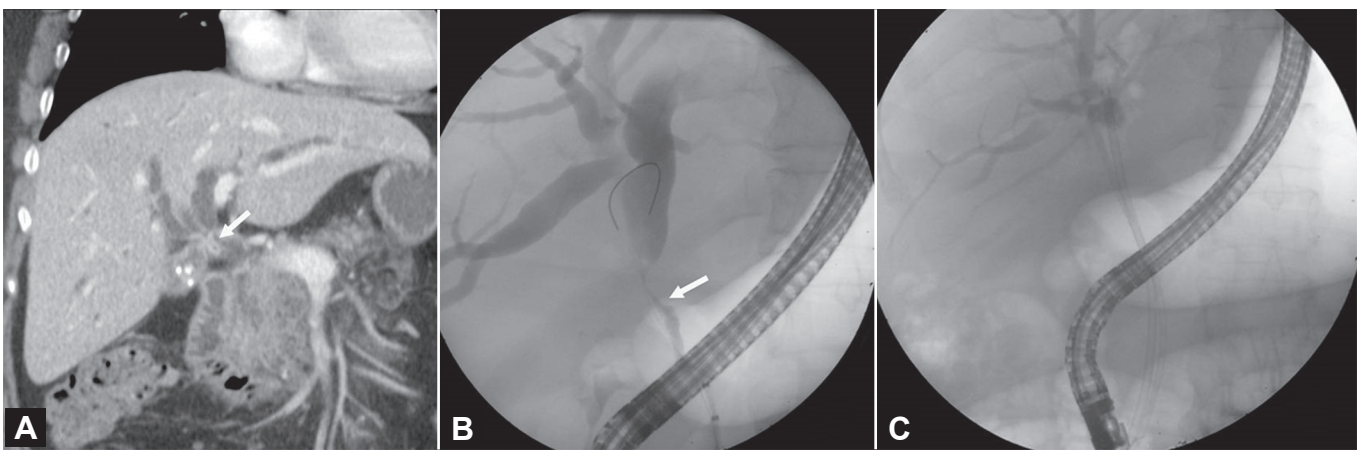


Figure 8. Endoscopic biopsy and drainage of a hilar cholangiocarcinoma Bismuth-Corlette type II. **A**) Coronal computed tomography on portal phase showing the tumor at the biliary confluence (arrow). **B**) Endoscopic retrograde cholangiography (ERC) showing a tight and irregular narrowing of the proximal common bile duct (arrow). **C**) Endoscopic placement of two plastic stents.

ii) bleeding due to hepatic puncture, iii) infection, iv) pseudoaneurysm, v) fistula, vi) hemobilia, and vii) prolongation of hospital stay. Although successful ERBD may achieve efficient drainage with low morbidity and a shorter hospital stay,[8] this procedure is rarely feasible in patients with complete obstruction and involvement of secondary biliary ducts.[9] Biliary drainage is usually selective (drainage of the hemiliver to be preserved) in order to accelerate compensatory hypertrophy of the remnant liver. However, if segmental cholangitis occurs after selective biliary drainage, total biliary drainage is performed.

The optimal duration of preoperative biliary drainage has not been established. Surgery is usually performed after resolution of jaundice (even if serum bilirubin is two or three times the upper limit of normal values), which occurs typically after 4-6 weeks. The recovery of hepatic function depends on the duration of biliary decompression and the duration of jaundice before biliary drainage. However, long-term biliary drainage increases the risk of drainage malfunction and perioperative septic complications. A recent systematic review demonstrated no clinical benefit of preoperative biliary drainage and an increased risk of postoperative complications.[44] Another study suggest that biliary drainage before right-sided hepatectomy could reduce the risk of postoperative liver failure while before left-sided hepatectomy it could increase the risk of infectious complications.[45]

In fact, there are few studies addressing liver resection for HC in the presence of cholestatic livers.[46,47] While some centers advocate routine preoperative biliary drainage, others recommend biliary drainage only in selected patients. Biliary drainage is a procedure carrying non-negligible morbidity and even mortality, mainly related to the risk of sepsis, and it is likely that patients with a short period of jaundice could tolerate a major hepatectomy without preoperative biliary drainage.[48]

PREOPERATIVE PORTAL VEIN EMBOLIZATION (Figure 9)

The purpose of preoperative portal vein embolization (PVE) is to initiate compensatory hypertrophy of the FRL and thus minimize postoperative liver failure. Currently, there is no randomized controlled trial supporting routine use of PVE before resection of HC, but there is general agreement that PVE should be considered when the anticipated FRL is less than 40% of the total liver volume. The desired FRL in patients with biliary obstruction is higher than for other indications (25% of the total liver volume if no underlying chronic liver disease is present).[49]

Most preoperative PVE in the context of HC is performed before a right trisectionectomy, frequently indicated for hilar tumors originating from the biliary confluence or from the right bile duct. PVE is rarely indicated before a left hepatectomy because the right liver usually represents more than 50% of the total liver volume. Even when an extended left trisectionectomy is indicated PVE is rarely necessary, since HCs in this context have usually produced considerable atrophy of the left liver, and hypertrophy of the right liver and right posterior sector (this representing the FRL). Almost all series reporting their experience of PVE in HC underline that requirements for PVE include: i) serum bilirubin lower than twice the normal upper range, and ii) biliary drainage of the FRL if biliary obstruction is present. It has been shown that liver hypertrophy is deteriorated in the presence of cholestasis. There have been attempts to further improve the efficacy of PVE by combining it with arterial embolization[50] or embolization of hepatic veins.[51] These approaches have potential drawbacks, still need evaluation, and are not performed by most centers.

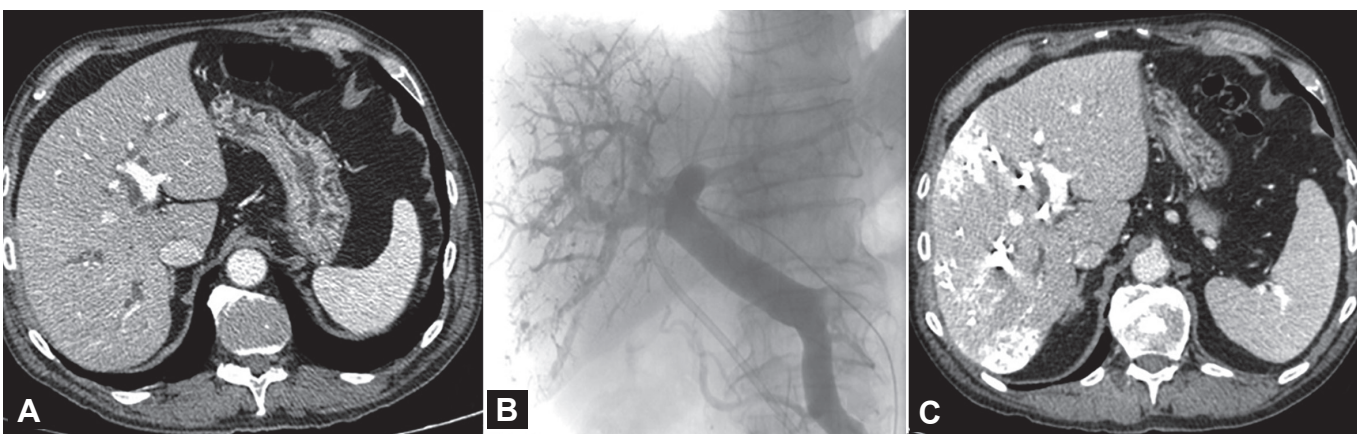


Figure 9. Preoperative right portal vein embolization (PVE). **A**) Axial computed tomography (CT) at portal phase before portal vein embolization. **B**) Portography after placement of a portal catheter. **C**) CT four weeks after right PVE showing hypertrophy of left hemiliver, however insufficient for a safe right trisectionectomy. Additional embolization of portal branches to segment 4 was then performed.

SURGICAL RESECTION

Complete surgical resection (R0) is the only potentially curative treatment for HC. Globally, most patients are considered unresectable at diagnosis. However, reported resection rates vary widely, from 35 to 94%, probably due to differences in preoperative imaging techniques, different referral systems and patient populations, surgical team expertise, and criteria of resectability, among other factors.[4,8,40,52–58] Similarly, operative morbidity and mortality rates are variable, but usually higher than those reported for liver resection due to other causes. Nowadays, standard operations for HC include resection of involved bile ducts (and skeletonization of hepatoduodenal ligament), en bloc liver resection (including at least segments 1 and 4, but usually major hepatectomies), and lymphadenectomy (**Figure 1**). R0 resection is clearly associated with better survival, and it is now accepted that major hepatic resection allows higher rates of R0 resection, which can reach up to 95% of cases.[49,59,60]

CRITERIA OF RESECTABILITY AND CONTRA-INDICATIONS

Contraindications to resection include: i) the presence of liver or extrahepatic metastases, and ii) the technical impossibility to preserve a sufficient amount of liver parenchyma with normal arterial and portal inflow.[61] Bilateral extension of the tumor to the secondary biliary bifurcations is not in itself an absolute contraindication for surgical resection, but usually precludes an R0 resection.

Proved or suspected lymph node involvement represents a challenging condition on the clinical practice. It is largely accepted that surgical resection should not be recommended in the presence of compromised lymph nodes beyond the portal pedicle. No long-term survivor has been identified when retropancreatic, coeliac, superior mesenteric, para-aortic, or para-caval nodes are involved. However, it is usually difficult to determine lymph node involvement preoperatively. Lymph nodes may be enlarged without tumor involvement in patients with biliary obstruction. Staging laparoscopy or biopsy guided by ultrasound-endoscopy may be useful.

Typical causes of non-resectability at the preoperative stage are: i) bilateral involvement of hepatic arterial or portal venous branches, ii) a combination of unilateral hepatic arterial involvement with contra lateral biliary spread, and iii) intra- or extrahepatic metastases. Portal vein involvement and bilateral intrahepatic bile duct involving left and right segmental branches are no longer absolute contraindications. In a retrospective study including 390 patients who underwent major resection (>3 liver segments), a tumor size greater than 3 cm in multivariate analysis was associated with invaded resection margins (R1) as well as early death (<12 months) (personal data).

CURATIVE RESECTION

Complete (R0) surgical resection is the only potentially curative treatment available for HC. For that, in addition to resection of the involved bile ducts, R0 resection usually requires en bloc liver resection, due to the biliary confluence being embedded in the hilar plate. Local excision without associated liver resection could only be accepted on the rare cases of small tumors confined to the wall of the bile duct and Bismuth-Corlette type I papillary HC. Also, regional lymphadenectomy is routinely performed and portal vein and/or hepatic artery resection and reconstruction may be necessary. The complex and intimate anatomical relations of the bile duct and vascular hilar structures make resection of HC a very challenging surgery. Complete resection including the whole liver followed by liver transplantation is an emerging therapy for highly selected patients (see discussion below).

Hepatic resection

Curative resection of HC generally comprises a major hepatectomy including the resection of hepatic segment 1 (caudate lobe) and the inferior part of segment 4.[60] There is clear evidence that the rates of R0 resections increase with the rates of associated major hepatectomies for HC.[62] Left or right trisectionectomy or central hepatectomy is performed according to the extension to intrahepatic bile ducts and the vascular involvement. Also, segment 1 is involved in HC in 40-58% of cases and it should be routinely resected.[60,63] The strategy of associate hepatic resection during HC surgery was proposed by Nimura et al.,[64] and resulted in an increase in resectability rates.

Vascular resection

Portal vein resection and reconstruction have been performed for HC with conflicting results. Although several retrospective series have shown no difference in operative mortality between patients who undergo portal vein resection and patients who do not,[65] the impact of portal vein resection on long-term survival remains still unclear. Neuhaus et al.[66,67] proposed the resection of portal bifurcation as part of a "no-touch" resection of tumor and adjacent tissue, achieving a wide tumor-free margin **(Figure 10)**. In their series, portal vein resection was an independent positive prognostic factor in patients undergoing R0 resection. However, other studies have shown equivalent or worse survival in patients undergoing en bloc resection of the portal vein, and further studies are needed.[65,68]

Hilar en bloc resection with the "no-touch" technique is associated almost exclusively with right trisectionectomy,

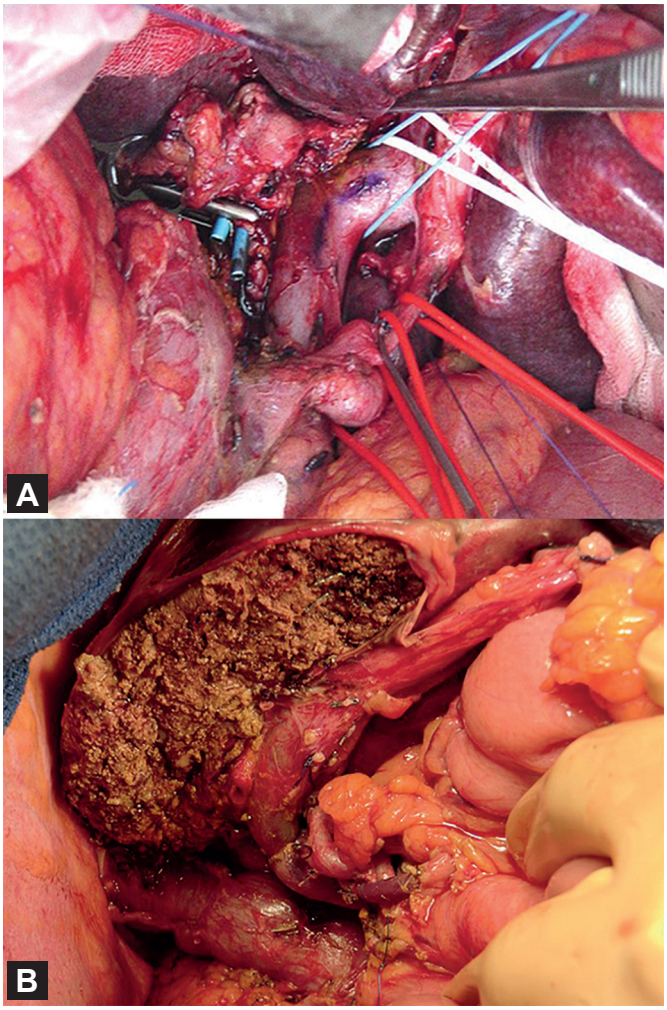


Figure 10. Intraoperative aspect of a right trisectionectomy for hilar cholangiocarcinoma using the "no-touch" concept. **A**) The left portal vein (blue lac) and main portal vein are encircled before en-bloc resection of the portal bifurcation. **B**) Surgical view after resection and end-to-end anastomosis between the main portal vein and the left portal vein.

due to the longer length of the left hepatic duct and the need of right hepatic artery reconstruction when resection is associated with left trisectionectomy. The right hepatic artery is sectioned at its origin. The main portal vein is divided proximal to bifurcation and the left portal vein sectioned at the level of umbilical fissure, without dissecting the portal vein bifurcation. After this, an end-to-end portal vein anastomosis is performed.

Most authors recommend portal vein resection only when necessary to obtain a complete resection, i.e., when the portal vein cannot be freed from the tumor during the vascular skeletonization of the hepatoduodenal ligament.[65,69] Five-year survival does not significantly differ if the portal vein is actually invaded or not.[68] Hepatic artery resection and reconstruction during HC surgery is usually not recommended, since it seems result in high morbidity and mortality with no proven benefit.[68,70–72]

Lymphadenectomy

Metastases to regional lymph nodes are common in HC and represent an important prognostic factor for poorer survival after resection.[73,74] Survival in patients with nodal involvement beyond the hepatoduodenal ligament is very poor, with 5-year survival rates of 0-12%.[73,75,76] Routine dissection of hepatoduodenal ligament lymph nodes is recommended, at least to achieve accurate staging and prognosis. The intraoperative finding of nodal involvement confined to the hepatic pedicle or the hepatoduodenal ligament is not a contraindication to complete HC resection, but nodal involvement of hepatic artery and para-aortic usually preclude more extensive surgery. However, the Nagoya group suggests routine extended nodal dissection (i.e., para-aortic nodes from the level of celiac axis to the mesenteric inferior vein) since they found a 5-year survival of 12% for patients with para-aortic nodal metastases.[75]

Hepato-pancreato-duodenectomy may be indicated for selected patients with locally extended HC with the goal of obtaining negative surgical margins.

Roux-en-Y hepaticojejunostomy is performed to reestablishment of biliary-enteric continuity.

SURGICAL MORBIDITY AND MORTALITY

Due to the complexity of biliary and hepatic resections required to obtain complete resection in HC, as well as the usually impaired general condition of patients secondary to jaundice and sepsis, perioperative morbidity and mortality rates have usually been greater than 50% (14-66%) and 10% (0-19%), respectively.[4,6,8,40,52–58,64,66,77,78] However, a recent publication of a study including 574 patients reported a reduction of mortality from 11% before 1990 to 1.4% after 2006.[79] Perioperative morbidity includes bleeding, bile leakage, liver failure, and infectious complications (such as wound infection, cholangitis, intra-abdominal abscess, and pulmonary infection). Infectious complications are particularly common and account for 50-80% of all complications.[5] Mortality is usually related to postoperative liver failure and/or sepsis. Infectious complications are probably associated to the high prevalence of bactibilia (spontaneous or more often resulting of preoperative direct biliary cholangiography or drainage). Thus, prolonged course (five days) of antibiotic prophylaxis, adapted to intraoperative bile samples cultures, is recommended, despite no proven benefit.[80]

LONG-TERM OUTCOMES

Recent studies have published 5-year survival rates ranging from 25 to 50%.[4,40,57,69,79,81–84] The largest published series of

resection of HC reports a increasing on 5-year survival rate from 23% before 2000 to 38% after 2001.[79] Local recurrence is the more common pattern of failure. Many factors have been shown to have positive impact on long-term outcome, including R0 resection,[4,49,52,66,84–87] concomitant liver resection,[40,53,61,79,85] absence of nodal involvement,[4,40,61,69,87] lower AJCC T-stage,[88] well-differentiated tumor grade,[4,40,61,87] papillary tumor morphology,[40] absence of blood transfusion,[79] and lack of perineural invasion.[4,40,61,87] Complete resection with histologically negative margins is the main modifiable factor, and is therefore the central goal of surgical therapy.[19] Concomitant liver resection seems to increase the rate of R0 resections. The 5-year survival rate in the Nagino et al.[79] report reached 67% for patients resected after 2000, with R0 resection and without lymph node or distant metastases.

The effect of R1 resection versus no resection on outcome has been controversial in the surgical literature,[56,89,90] with some recent studies reporting improved survival after R1 resection compared with patients with unresected disease.[19,55,84]

ADJUVANT AND NEOADJUVANT THERAPIES

There is currently no validated indication for adjuvant or neoadjuvant chemotherapy, radiotherapy or combined chemo- and radiotherapy. However, given the growing evidence efficacy of chemotherapy[91] and radiotherapy,[92,93] prospective trials are underway.

LIVER TRANSPLANTATION

Initial experience with liver transplantation (LT) for HC was very disappointing, with early tumor recurrence and poor 5-year overall survival (except for the rare cases of small HC incidentally discovered on a resected specimen after LT for primary sclerosing cholangitis). Consequently, HC was considered a contraindication to LT.

More recently, a new approach has been established, whereby patients with unresectable early-stage hilar cholangiocarcinoma are first treated with chemoradiation (external-beam radiation with concomitant 5-fluorouracil chemosensitization followed by transcatheter iridium brachytherapy) and subsequently transplanted. This so-called "Mayo Protocol" led to encouraging results, with overall survival reaching 70% at five years for *de novo* hilar cholangiocarcinoma.[13,94,95] However, selection criteria are extremely strict to achieve these results: i) the tumor should be less than 3 cm, ii) it should not have been biopsied (except via the retrograde endobiliary route), and iii) there should be no lymph node invasion. Indeed, this approach has also received some criticism because patients with small HC and filling the criteria of non-resectability could be considered resectable for others, with favorable outcomes.[79] Another difficulty is to obtain a liver graft soon after completion of the neoadjuvant therapy to prevent the high rate of drop out (up to 11% per three months and near 30% at 12 months) from the transplant protocol before transplantation.[96] Considering the complexity of this approach, it is only performed in a very limited number of institutions worldwide.[97]

PALLIATIVE PROCEDURES

Patients that are not candidates for curative resection (with or without liver transplantation) should receive palliative treatment for jaundice.

PALLIATIVE SURGICAL TREATMENT

If radical resection is not considered, permanent biliary drainage (BD) is needed. When non-resectability is discovered intraoperatively, a palliative surgical BD can be considered in patients in good general status. The palliative surgical options for BD include segment 3 cholangiojejunostomy, right sectoral duct bypass, and transtumoral tube placement. Studies concerning segment 3 cholangiojejunostomy reveal a surgical complication rate ranging from 17% to 55%, and a surgical mortality from 0% to 17.6%. Relief of jaundice was achieved in at least 70%.[98]

ENDOSCOPIC AND PERCUTANEOUS STENTING

No stent should be placed before high quality imaging has been obtained, and only plastic stents should be used before a formal and validated contraindication to resection has been identified. In the palliative setting, metallic stents are the most used as they have a longer patency than plastic stents, a larger diameter and allow drainage of side branched biliary ducts of the biliary tree through the mesh.

Few studies have compared percutaneous with endoscopic stenting procedures.[99] Percutaneous technique has the theoretical advantages of precise segmental placement, possible lower risk of cholangitis, and need of only a minimal sedation. However, complications related to the puncture site and the risk of biliary peritonitis are additional concerns with the use of percutaneous approach.

PHOTODYNAMIC THERAPY

A photosensitizer is first introduced intravenously and it accumulates within in the target malignant tissue, which is thereafter illuminated at a specific wavelength of light. The photosensitizer undergoes a photochemical reaction that generates reactive oxygen species and cell apoptosis (**Figure 11**). Two prospective randomized trials comparing

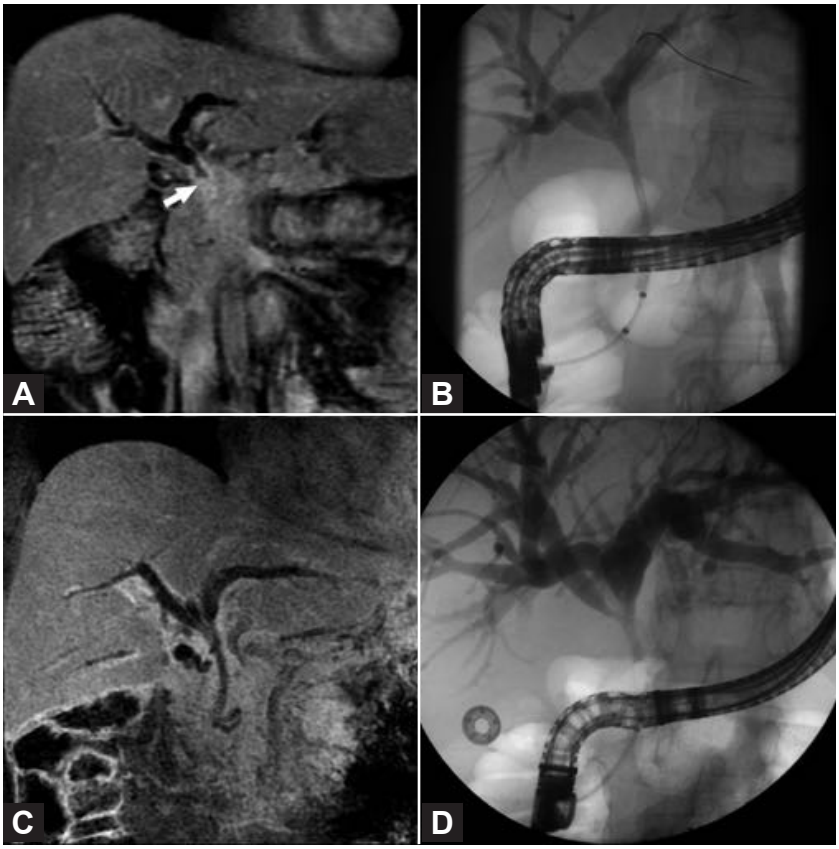


Figure 11. Photodynamic therapy (PDT) for a hilar cholangiocarcinoma. **A**) Magnetic resonance imaging (MRI) with gadolinium in the late phase showing hilar biliary stenosis (arrow). **B**) Endoscopic retrograde cholangiography (ERC) of the same patient before therapy. **C**) MRI after 9 months of the first session of PDT with reduction of the biliary obstruction. **D**) ERC aspect after 9 months of PDT. A second session of PDT was performed.

photodynamic therapy (PDT) with biliary stenting alone in patients with unresectable cholangiocarcinoma have suggested a prolongation in survival following PDT.[100] However, data on palliative PDT are currently very limited. Randomized studies on a larger scale are required to determine more efficiently its place in the therapy strategy of patients with HC.

SYSTEMIC CHEMOTHERAPY

A recent randomized trial has established gemcitabine/cisplatin as a standard for first-line chemotherapeutic regimen for unresectable cholangiocarcinoma.[91] This study confirms a previous pooled analysis of 104 trials (representing 2,810 patients with advanced biliary tract cancers and treated with chemotherapy in the last 35 years) that found that combination of gemcitabine and platinum regimens yielded the highest response rates and tumor control rates.[100] Targeted agents are also under investigation.[101,102]

FINAL CONSIDERATIONS

Surgical resection remains the mainstay treatment for HC. Negative resection margins should be achieved and for that major hepatic resections and occasionally vascular resection and reconstruction (in particular of the portal veins) are required. Perioperative mortality is usually high and preoperative biliary drainage and portal vein embolization represent useful tools in the attempt to reduce risk in selected cases. Adjuvant treatments may in the future improve long-term outcomes but require accurate evaluation.

SUGGESTED READING

Regimbeau, J. M. et al. Surgery for Hilar Cholangiocarcinoma: A Multi-institutional Update on Practice and Outcome by the AFC-HC Study Group. *J. Gastrointest. Surg.* **15**, 480–488 (2011).

This paper presents an overview of the management of hilar cholangiocarcinoma established on a recent and short inclusion series of patients. The need of proper indication of preoperative biliary drainage and portal vein embolization is underlined.

De Jong, M. C. et al. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. *Cancer* **118**, 4737–47 (2012).

This large series of curative-intent surgery for hilar cholangiocarcinoma supports the benefits of radical surgery. Outcomes after resection including extrahepatic bile duct resection, hepatectomy, and portal vein resection in selected cases were more favorable than after extrahepatic bile duct resection alone.

Neuhaus, P. et al. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. *Ann. Surg. Oncol.* **19**, 1602–8 (2012).

The authors suggest a radical approach to resection of hilar cholangiocarcinoma with hilar en bloc resection including portal vein resection without hilar dissection.

Nagino, M. et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. *Ann. Surg.* **258**, 129–40 (2013).

One of the largest series of hilar cholangiocarcinoma resection, showing that indication of surgical resection has expanded, surgical mortality diminished, and survival increased.

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15 Intrahepatic Cholangiocarcinoma

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- *Clinical presentation and management of intrahepatic cholangiocarcinoma (IHCC), the second most frequent primary liver tumor (after hepatocellular carcinoma), depend on the location of origin (juxtahilar to end-order biliary branches).*
- *In addition to classical risk factors for IHCC (such as parasitic infections, bile duct ectasia, and primary sclerosing cholangitis), hepatitis B and C virus infection, cirrhosis, obesity, diabetes, and genetic polymorphisms seem to play a role in IHCC origin.*
- *The three pathological subtypes – mass-forming, periductal-infiltrating, and intraductal-growth tumors – present different biological behavior and imaging characteristics.*
- *Surgical resection of IHCCs carries high morbidity and mortality rates, but it is currently the only curative treatment for IHCC, with a 5-year overall survival rate of 27%. Recurrence is frequent, rarely amenable for repeat surgery, and usually associated with death. The role of liver transplantation is controversial.*

INTRODUCTION

Intrahepatic cholangiocarcinoma (IHCC) is the second most frequent primary tumor of the liver, after hepatocellular carcinoma (HCC). Together, HCC and IHCC account for more than 95% (and up to 99% in certain areas of the world) of primary liver tumors. IHCC has, however, received much less attention than HCC until recently. Its lower incidence is of course an explanation, but the main reasons for the previous relative lack of interest in IHCC were its difficult pathological characterization, irrelevant staging, and dismal prognosis.

Until the late 1980s, there was a lack of immunohistological markers that could pinpoint the biliary origin of adenocarcinoma, and therefore IHCCs were probably frequently considered liver metastases of an adenocarcinoma of unknown origin. As a consequence of this, the unique characteristics of IHCC have been overlooked. Although HCC and IHCC have distinct pathological codes, they were assigned the same TNM (Tumor-Node-Metastasis)/UICC (Union for International Cancer Control) staging systems until recently. Finally, the prognosis of IHCC is traditionally poorer than that of HCC, in part because of its delayed diagnosis, but also because of its particular mode of spreading, which is frequently overlooked.

There have, however, been three profound changes over the past few years. First, it is possible to accurately diagnose IHCC based on cytokeratin expression on a biopsy. Second, a pTNM staging specific to IHCC has been designed and validated. Third, a randomized trial has demonstrated the efficacy of chemotherapy for this type of tumor.

It should, however, be noted that the current knowledge that we have regarding this type of tumor is still fairly limited. Apart from Japan, where it has been extensively studied, sources of information in other areas of the world – in Europe in particular – are relatively scarce.

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GENERALITY

According to both the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) TNM (tumor-node-metastasis), IHCC is considered a primary intrahepatic liver tumor, along with HCC. This differentiates them from malignancies of the biliary confluence (Klatskin tumor) that are stratified as extrahepatic tumors, along with malignancies of the gallbladder and the common bile duct. The definition of IHCC (primary tumor of the intrahepatic bile ducts) implies that it encompasses all malignancies developed from the intrahepatic bile ducts, starting from the second order branches and up to the Hering ducts (intrahepatic bile ductules). This heterogeneity of origins readily explains that the clinical presentation and management of this tumor are quite heterogeneous, depending on whether the tumor originates from the end-order peripheral branches or from the juxtahilar branches. The former is likely to be more frequent than the latter, at least partly because as bile structures divide, their numbers increase. However, the proportion of each is still ill-defined, because mass-forming type IHCCs may behave as hilar malignancies as a result of their location in the vicinity of the biliary confluence or centrifugal extension along the Glissonean pedicles. Two words of caution should be given on the sources of information available in the medical literature. First, the figures that will be presented in this chapter relate, as a rule, to patients who have been operated on for IHCC, and not just the general population with IHCC. As a matter of fact, virtually all series or registries of IHCC patients are surgical series. They have the advantage of focusing on patients with pathologically proven tumors, but there is very little information on non-surgically treated IHCC. Second, most data originate from single surgical centers and usually include a limited number of patients gathered over a fairly large period of time (typically 10-20 years). The three exceptions are the North American and Japanese[1] registries, as well as recent Italian[2] and French multi-institutional surveys.[3]

EPIDEMIOLOGY

FREQUENCY

It has been widely assumed in the past, in particular in surgical series, that IHCCs account for a very small proportion (approximately 10%) of all bile duct malignancies.[4] This view is challenged worldwide by more recent epidemiological databases, and in particular the latest edition (published in 2007) of *Cancer incidence in five continents*, which covers the period 1998-2002.[5] In France, for example, the incidence of IHCC in 11 French registries ranges between 0.5 and 1.3 per 10^5 for men and 0.2 and 0.9 per 10^5 for women, whereas the respective incidences of all extrahepatic bile duct malignancies ranges between 0.6 and 1.3 and 0.7 and 2.3 per 10^5. These data need to be interpreted with caution, but they do suggest that IHCCs are almost as frequent as all extrahepatic bile ducts in men and only about half as frequent in women.[5] The same holds true in most other countries, except in those where the incidence of gallbladder cancers are particularly high. Worldwide, the incidence of cholangiocarcinoma (CC) varies greatly.[6,7] Countries such as Thailand, in Southeast Asia, have the highest incidence of cholangiocarcinoma – as high as 113 per 100,000 men and 50 per 100,000 women – whereas in Western countries such as Australia, the incidence is low – at 0.2 per 100,000 men and 0.1 per 100,000 women.[6,8] Differing exposure to risk factors is thought to account for the varying geographic incidences, with parasitic infections (*C. Sinensis and O. Viverrini*) and hepatolithiasis being more prevalent in Asia.[6,8] As far as primary liver tumors are concerned, it has recently been estimated that IHCC is 15 times less frequent than HCC. This figure is in between that observed in the United States (8 times less frequent than HCC) and that reported in Japan (23 times less frequent than HCC), where the prevalence of HCC is particularly high. These variations are indeed more influenced by the numerator (i.e., the incidence of HCC, which is highly variable in different areas of the world) than by the denominator (i.e., the incidence of IHCC, which is fairly constant except in South East Asia, where distomatosis is endemic).

INCIDENCE

A number of epidemiological studies have suggested that the incidence of IHCC has increased over the past 20-30 years. It is, however, unclear if this increase is genuine or artificial. Most of this increase is probably related to the fact that a number of IHCCs were misdiagnosed in the past: before the unique immunophenotype of biliary cells was identified, many IHCCs were probably considered liver metastases of unknown primaries. Another source of confusion is the evolution of the International Classification of Diseases (ICD) for Oncology. Changes in ICD classification may be influencing observed changes in intrahepatic and extrahepatic bile duct tumor incidence rates. Coding misclassification is also likely to have been skewing cholangiocarcinoma registration to an intrahepatic site, thereby contributing to the previously reported rise in intrahepatic tumors.[9] Consequently, no definitive statement can be made on the temporal trends of IHCC in most world regions in the absence of marked, consistent trends.[10] In the United States, Welzel et al.[11] reported that misclassification of Klatskin tumors had contributed to the temporal trends of increasing IHCC and decreasing extrahepatic cholangiocarcinoma

(EHCC) between 1992 and 2000. Furthermore, recent Surveillance, Epidemiology and End Results (SEER) data (2000-2005) suggest that the temporal trends are reversing, with decreased IHCC and increased EHCC incidence.[12]

RISK FACTORS

The classically established risk factors for IHCC include parasitic infections, Caroli disease, hepatolithiasis, and primary sclerosing cholangitis (PSC).[10,13] These turn out, however, to account for only a minor proportion of IHCC in the West. New risk factors include hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, obesity, and diabetes. In most patients with IHCC, however, no risk factor can currently be identified.

CLASSICAL RISK FACTORS

Parasitic Infections

The hepatobiliary flukes, *Opisthorchis viverrini* and *Clonorchis sinensis*, are associated with a very high risk of development of cholangiocarcinoma, particularly in Southeast Asia. In some areas of Thailand, the incidence may be as high as 100 per 100,000 inhabitants (as compared to 0.5 to 3 per 100,000 in most other areas of the world). A recent meta-analysis performed by Shin et al. pooled 912 cases and 4909 controls, and confirmed the strong association between *C. sinensis* and cholangiocarcinoma (OR: 4.7; 95% CI: 2.2-9.8). In endemic areas, the population-attributable risk, based on this study, was as high as 27.9% for men and 16.2% for women.[14]

Bile-Duct Ectasia

Bile duct cysts (i.e., choledochal cysts) are rare congenital disorders characterized by cystic dilatation of the extrahepatic and/or intrahepatic bile ducts. The risk of malignancy decreases after complete choledochal cyst excision; however, these patients are still at an increased risk of developing cholangiocarcinoma, compared with the general population.[15–17] In a SEER-Medicare study, Welzel et al. observed a strong association between choledochal cysts and increased risk of both IHCC and EHCC, with ORs of 36.9 (95% CI: 22.7-59.7) and 47.1 (95% CI: 30.4-73.2), respectively.[18]

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC), an autoimmune disease that results in the stricturing of extra and/or intrahepatic bile ducts, is an established risk factor for cholangiocarcinoma. Chronic inflammation, proliferation of biliary epithelium, production of endogenous bile mutagens, and bile stasis are postulated mechanisms of carcinogenesis.[19] The lifetime incidence of cholangiocarcinoma among PSC patients ranges from 6%-36%.[20,21] Although PSC is known to be a strong risk factor for cholangiocarcinoma, no more than 1–10% of cholangiocarcinoma is attributed to PSC.[2,3,21] It is unclear whether the duration of PSC correlates with the risk of developing cholangiocarcinoma; in fact, most cases present relatively soon after the diagnosis of PSC.[10] Smoking and alcohol consumption have also been examined as potential risk factors for cholangiocarcinoma in patients with PSC. However, there are no definitive data to suggest that this is the case.[10]

Hepatolithiasis

Hepatolithiasis is the presence of calculi or concretions located proximal to the confluence of the right and left hepatic ducts. Hepatolithiasis is an established risk factor for IHCC in Asian countries, with 2-10% of patients with hepatolithiasis developing IHCC.[22] There are less data available on the relationship between hepatolithiasis and ICC in Western countries,[23] but an Italian hospital-based case control study also showed a significant association between hepatolithiasis and ICC, with an OR of 6.7 (95% CI: 1.3-33.4).[24]

Toxins

The currently banned carcinogenic agent Thorotrast, a radiographic contrast agent used primarily from 1930 to 1960, has been strongly associated with an increased risk of developing cholangiocarcinoma (usually 30 to 35 years after exposure).[25] Occupations including the auto, rubber, and chemical industries have been less strongly associated with an increased incidence of cholangiocarcinoma.

NEW RISK FACTORS

IHCC has traditionally been considered a malignancy developing in a normal liver, in contrast to HCC. However, newly established risk factors pinpoint to a background liver disease. These include HCV or HBV infection, cirrhosis, obesity, diabetes, and genetic polymorphisms. The data also suggest that in Western countries, HCV is consistently associated with IHCC and not EHCC. In Asian countries, it appears that HBV may be associated with IHCC. Cirrhosis is the most consistently illustrated risk factor for IHCC, but not EHCC. A recent meta-analysis of published literature revealed the summary relative risks of hepatitis B virus and hepatitis C virus to be 2.6 (95% CI: 1.5–4.6), and 1.8 (95% CI: 1.4–2.4), respectively.[26] Available data suggest that diabetes and heavy alcohol drinking may confer an increased risk for cholangiocarcinoma.[27] Welzel et al.[28] recently showed that metabolic syndrome is a significant risk factor (OR=1.56; 95% CI: 1.32-1.83, P<0.0001) for development of IHCC in the general US population. The lack of an accurate, consistent cholangiocarcinoma classification system may have hindered the conduct and interpretation of risk factors in epidemiological studies.[10] Despite the identification of these new risk factors, most IHCCs currently remain unexplained.

PATHOLOGICAL SUBTYPES

Three pathological subtypes have been described **(Figure 1)**:

i) ***Mass-forming tumors,*** which represent the most frequent form, are described as tumors with clear macroscopic borders between malignant and non-malignant tissues (these borders are, however, much less clear microscopically, and the tumor invades the adjacent parenchyma and portal tracts).

ii) ***Periductal-infiltrating tumors*** are described as more infiltrative and extend along peri-bile duct tissues without forming a discrete nodular mass. These are very rare, whereas the mixed mass-forming/periductal infiltrating variant is frequent. One problem, however, as detailed below, is the lack of a standardized definition of this infiltrating component.

iii) ***Intraductal-growth type tumors*** are characterized by papillary growth within the bile duct lumen; this variant corresponds to what is also called papillomatosis.

These three sub-types seem to have different proliferative activity and different biological behavior: the *mass-forming* type develops intrahepatic metastases as a result of localized vascular invasion (**Figure 2**), whereas the *periductal* type has an infiltration spread via the Glissonean sheath and pedicle lymph node metastases. In addition, frequency of lymph node metastases is higher in the mass-forming and periductal types than in the *intraductal* type.[29]

CLINICAL PRESENTATION

As a rule, IHCC tends to be diagnosed at an advanced stage because the tumor remains clinically silent for a long time. It is therefore important to know when the question of diagnosis should be raised.

AGE AND GENDER

Peak incidence occurs between the age of 55 and 75 years, and this tumor is extremely rare before the age of 45 (<10% of patients). It is equally present in men and women. Although the sex ratio may fluctuate slightly around 1 in different areas of the world (0.9 in the Western world and 1.5 in Asia), this may simply reflect, at least in part, the corresponding age-adjusted sex ratio of the population. In France, the male/female ratio is 1.2.[1] Therefore, unlike HCC, which is 5 to 6 times more frequent in males, there is no gender influence on this type of tumor.

PRESENTATION

Patients with IHCC tend to remain clinically in fair overall condition despite having large tumors. In surgical series where the mean tumor diameter typically ranges between 5 and 7 cm, one third to one half of patients are asymptomatic. Circumstances of diagnosis therefore frequently include the evaluation of non-specific abdominal symptoms or of abnormal liver function tests. Symptoms, when present, include abdominal pain, malaise, night sweats, asthenia, nausea, and weight loss. Interestingly, the presence of symptoms does not have the same detrimental impact on outcome that it has for other malignancies, such as HCC or colorectal liver metastases. It should, however, be underlined that these data are derived from series of patients who have undergone surgery. If one considers all patients with IHCC, most of whom are not amenable to surgery, the proportion of asymptomatic patients is – not unexpectedly – much lower. Altogether, these data suggest that the course of the disease might be more indolent than previously thought, and offer some explanation as to why this tumor is usually discovered at an advanced stage. When symptoms do develop, the tumor is frequently unresectable.

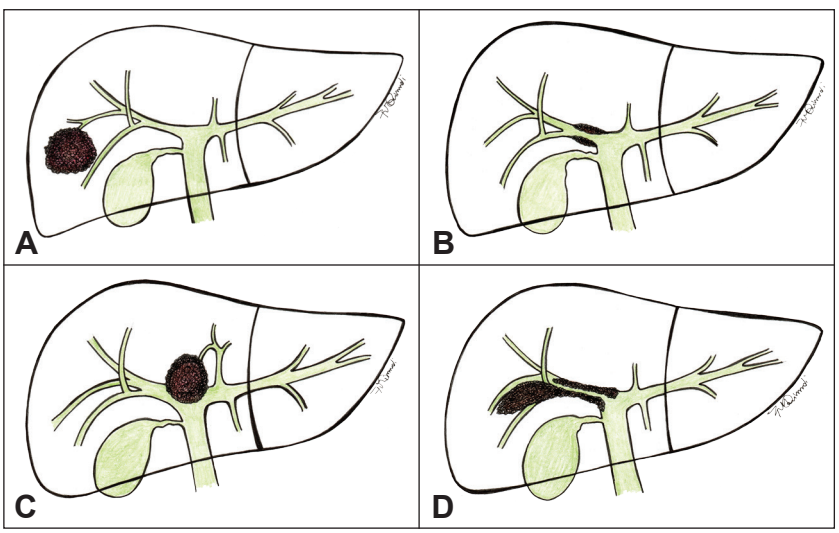


Figure 1. Heterogeneity of the morphological presentation of intrahepatic cholangiocarcinoma (IHCC). **A**) Mass-forming type of an IHCC originating from the end division of the intrahepatic bile ducts. **B**) Periductal infiltrating type of an IHCC originating from the proximal segmental or sectional bile ducts, resembling a Klatskin tumor. **C**) Mass forming type IHCC developed from small bile ducts in liver segments adjacent to the biliary confluence. **D**) Mass forming and periductal infiltrating mixed type IHCC, with extend along the Glissonean pedicles.

Although IHCC by definition excludes tumors located within the biliary confluence or first order branches (left or right bile duct), jaundice is present in 10–15% of patients. It may result from protrusion or migration of tumor material within the bile duct lumen, or compression of the common bile duct by metastatic lymph nodes. However, the most frequent cause of bile duct obstruction is compression of the bile duct confluence by tumors located in the liver segments adjacent to the biliary confluence (segments 4 and 1) or carcinomatous infiltrating extension along the Glissonean sheath of segmental or sectional bile ducts **(Figure 1)**.

Liver function tests are non-specific, even though an increase in liver enzymes may be the only initial finding in some patients. Gama-glutamil transferase levels at least are always above the normal upper range, although this increase might be slight. This feature is, however, common to any space-occupying lesion of the liver (except hemangioma).

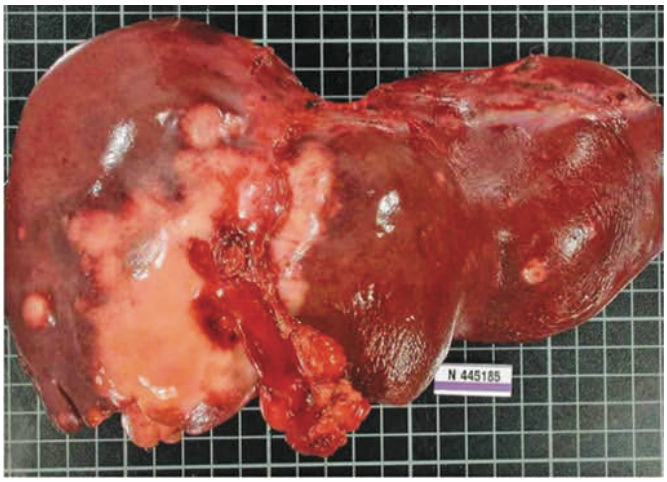


Figure 2. Macroscopic finding of a resected mass-forming type IHCC developing in the left liver. Note the retraction of the capsule around the round-ligament and the presence of satellite nodules.

METHODS OF DIAGNOSIS

IMAGING

The diagnosis of most IHCC is usually fairly obvious on imaging studies, mainly computed tomography (CT) and/or magnetic resonance imaging (MRI). It typically presents as a liver tumor that has three distinctive features: i) it is fibrotic and therefore enhances at the delayed phase of the injection, and is associated with a retraction of the capsule and an encasement of the vascular and biliary structures (**Figures 3 to 6**); ii) it is frequently associated with satellite nodules that predominate at the periphery of the tumor; and iii) enlarged lymph nodes in the hepatic pedicle (in particular at its right inferior part) or above the junction of the common and proper hepatic arteries are frequent. The main differential diagnosis is colorectal liver metastases (and to a lesser extent, liver metastases of breast cancer).

On CT scanning (**Figure 4**), the typical appearance is of a hypodense mass on unenhanced images, with irregular margins, peripheral rim enhancement in the arterial phase, and progressive hyperattenuation on venous and delayed phases. Theses findings reflect the usual presence of fibrosis. On MRI (**Figures 5 and 6**), IHCC appear hypointense on T1-weighted images and hyperintense on T2-weighted images. Central fibrosis can appear as hypointensity on T2-weighted images. Contrast dynamic is similar to that

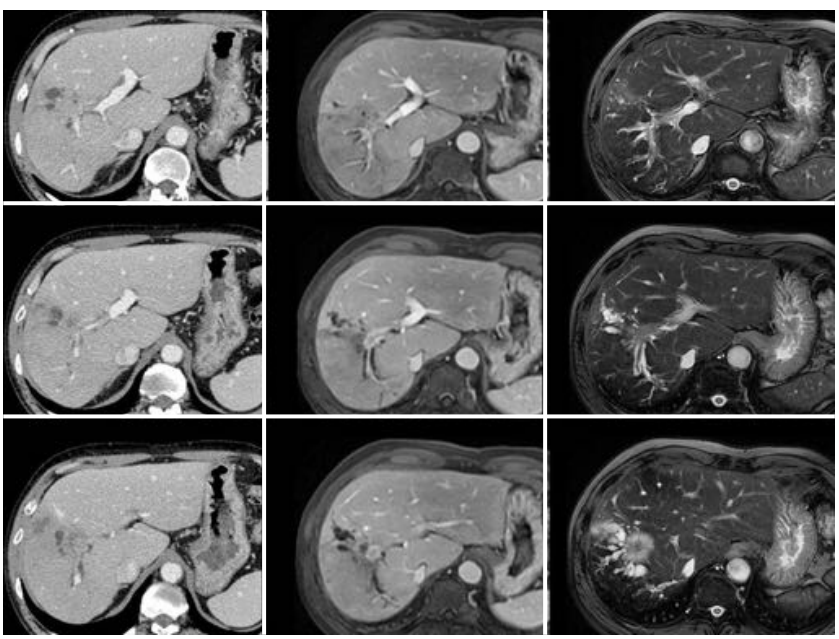


Figure 3. Imaging findings on CT-scan (left column) and MRI of a mass-forming type intrahepatic cholangiocarcinoma developing in the right liver. Note the extension along the right anterior Glissonean pedicle. This is much more clearly visible on MRI than on CT scan.

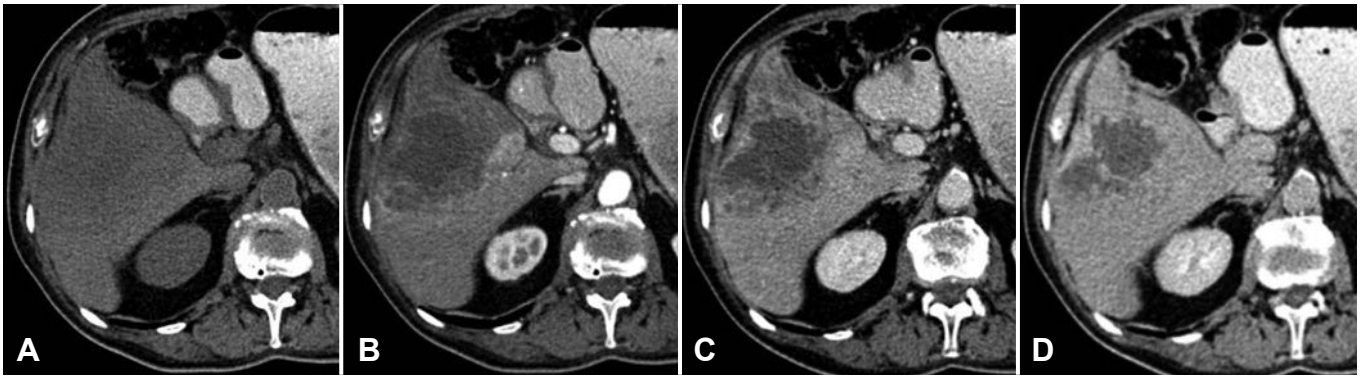


Figure 4. Dynamic computed tomography (CT) scan showing typical features of a large intrahepatic mass forming type cholangiocarcinoma on the right liver . **A**) Unenhanced CT, **B**) arterial phase, **C**) portal phase, and **D**) venous phase. The lesion is seen as a slightly hypoattenuating mass on unenhanced phase. After contrast injection there is a ragged and gradual centripetal filling that persist on late phases. Central fibrosis remain hypodense on late phases. Capsular retraction is evident on hepatic surface. (*Courtesy of Dr. Gustavo Luersen*)

observed with CT. Pooling of contrast on delayed images is indicative of fibrosis and suggestive of IHCC.[30] Positron emission tomography (PET) scan is not accurate for early diagnosis, and its role in tumor staging remains controversial.

Depending on the context, there are two options to invasively confirm the diagnosis. The first is to perform a colonoscopy to rule out a colon cancer. The second is to perform a biopsy of the tumor (and of the adjacent liver) with immunostaining for cytokeratins (CK) 7 and 20. IHCC are CK7 positive CK20 negative, whereas colorectal metastases are CK7 negative and CK20 positive (**Figure 7**). CK7 is indeed expressed relatively late during embryogenesis by cells that have differentiated into biliary cells (unlike CK19, which is expressed very early on and is a marker of undifferentiated cells).

TUMOR MARKERS

Tumor markers are of little help in the diagnosis of IHCC because of their lack of sensitivity, as well as specificity.[30] The most widely used are the carcinoembryogenic antigen (CEA) and carbohydrate antigen (CA) 19-9, but neither has in fact been very extensively studied. Overall, CEA levels are above 20 and above 100 in 15% and 5% of patients, respectively.[1] CA19-9 levels are between 100 and 1000 in 25% of patients and above 1000 in a further 30%, but these values have not been stratified for the serum bilirubin level. Alpha fetoprotein (AFP) levels are below 200ng/ml in 95% of patients.[1]

STAGING OF IHCC

SATELLITE NODULES

In surgical series, IHCCs are often multiple, but 65% of IHCCs are unique and this rate is similar in Japan and in Western countries. However, the multifocality of IHCC is unclear in different series because the terminology used is highly variable, including terms such as "multifocal tumor", "satellite nodules", and "intrahepatic metastases". Indeed, it is difficult to differentiate multiple nodules corresponding to a multifocal carcinogenesis of multiple nodules, corresponding to an extension by contiguity, from a primary tumor. This

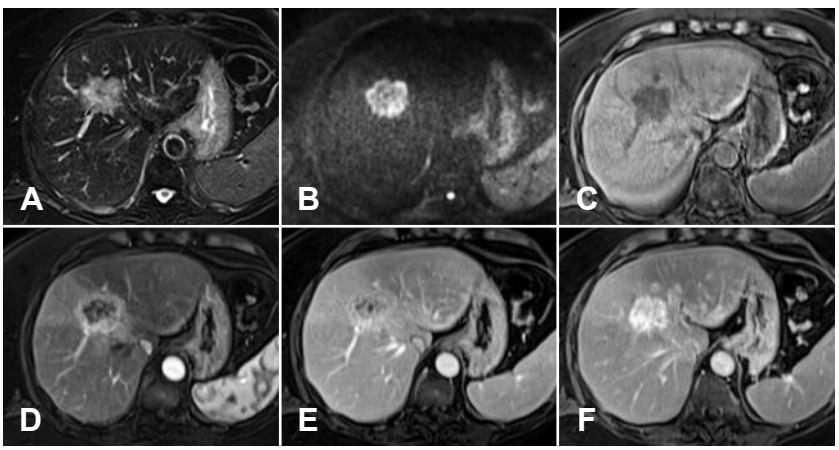


Figure 5. Magnetic resonance imaging (MRI) of a mass-forming intrahepatic cholangiocarcinoma on the right liver. **A**) T2-weighted image shows a hyperintense lobulated mass, **B**) diffusion weighted imaging (DWI), **C**) Unenhanced T1-weighted image with hypointense lesion, **D**, **E** and **F**) Dynamic contrast-enhanced T1-weighted images. On the arterial phase (D) there is an irregular rim enhancement, followed by a gradual centripetal enhancement on portal (E) and venous (F) phases. Note the wedge-shaped transient hyperenhancement peripheral to the tumor, due to portal compression. (*Courtesy of Dr. Gustavo Luersen*)

latter hypothesis seems to be the most common due to the mode of spread. These satellite nodules are mainly observed in large,[31] peripheral,[32] and mass-forming tumors.[33]

VASCULAR EXTENSION

Unlike HCC with vascular thrombus, the vascular extension of IHCC is infiltrative in the vast majority of cases. However, macroscopic vascular thrombi have been reported.[34,35] Frequency of vascular invasion in IHCC (mainly portal vein invasion) has reached nearly 33% in Western series,[36–38] 58% in Japanese series,[39,40] and 15% in Korean series.[41] Resection of the inferior vena cava or portal vein during major hepatectomy for IHCC resulted in short- and long-term outcomes similar to hepatectomies without vascular resection in a retrospective cohort.[42] A recent report[43] identified an association between tumor size and microscopic vascular invasion (more than 30% of tumors larger than 5 cm had vascular invasion). Tumor size was also associated with worse tumor grade.

CAPSULAR EXTENSION

Although peritoneal rupture is rare,[44] peripheral IHCC is frequently associated (nearly 50%)[1] with capsular retraction. Nevertheless, this capsular retraction is associated with adjacent organ invasion in nearly 25% of cases.[45]

BILIARY EXTENSION

Unlike HCC, microscopic biliary extension is observed in more than half of patients with IHCC (versus only 3% in HCC),[1] including common bile duct invasion in 8%.

PERINEURAL EXTENSION

Some Japanese surgeons claim that perineural extension has the same significance as lymphatic extension in IHCC.[46] Its frequency is inconstantly specified and ranges from 20–100%.[39] Given the pedicle and juxtahilar predominant location of the neural network, perineural extension is more frequent in proximal IHCC compared to peripheral IHCC (about 30% versus 85%).[47,48]

LYMPH NODE EXTENSION

The proportion of positive lymph nodes is 40% in surgical series of IHCC when lymphadenectomy is performed routinely. This high propensity for lymphatic extension has two consequences. The first is that "N" status is likely to outweigh some of the "T" characteristics of IHCC (a "small" tumor that is N positive will have a poorer prognosis than a "large" tumor that is N negative). The second consequence, which is even more problematic, is that accurate surgical staging

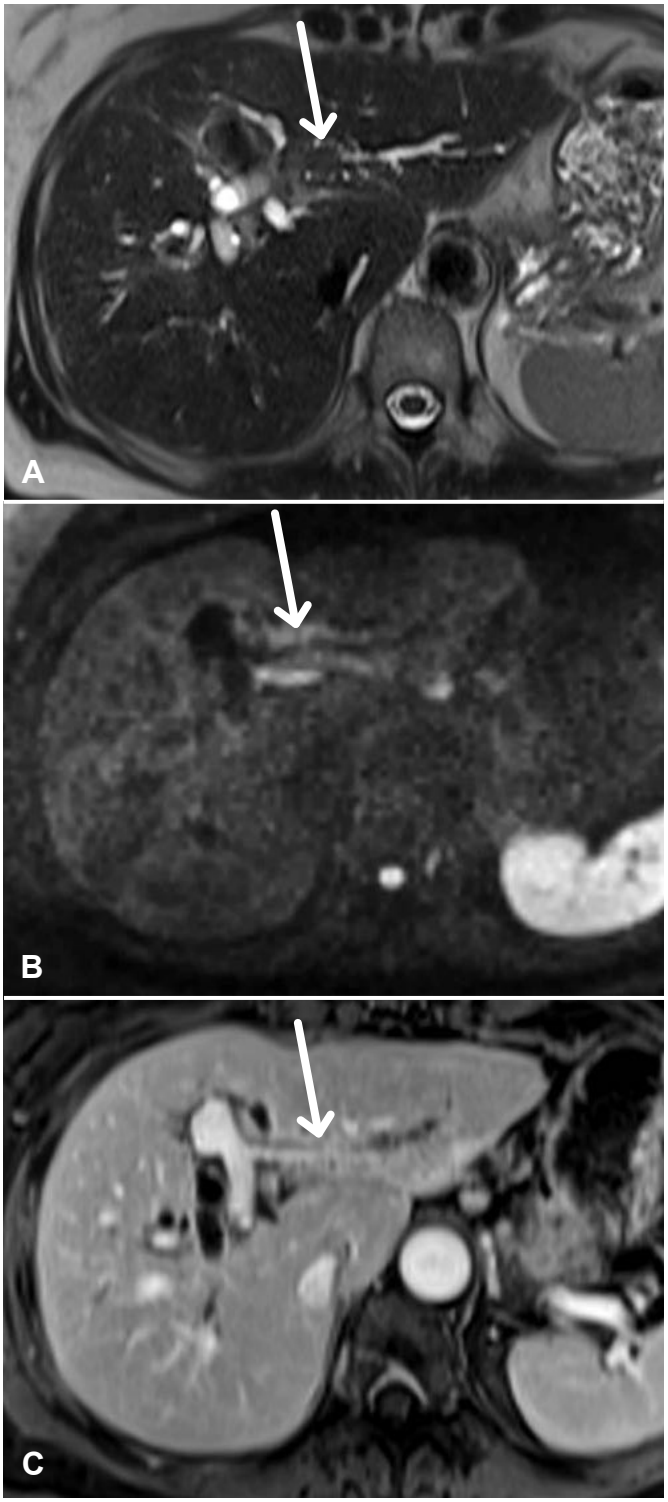


Figure 6. Periductal infiltrating intrahepatic cholangiocarcinoma (arrows) on magnetic resonance image (MRI). **A**) T2 weighted MRI with ill-defined bile duct obliteration on left liver and dilated peripheral duct. **B**) Diffusion MRI showing infiltrative periductal lesion with abnormal restriction around the bile duct. **C**) Portal phase of dynamic MRI reveals narrowing of left portal vein and bile duct, with dilatation of peripheral intrahepatic bile ducts. (*Courtesy of Dr. Gustavo Luersen*)

of IHCC requires that all surgically treated patients undergo lymph node dissection.[48] This is still not the case, and the accuracy of imaging studies to predict lymph node invasion is low. Hence, although some have considered patients who did not have lymph node dissection as being N negative, these patients in fact have a prognosis intermediate between a true N positive and true N negative, suggesting that some of them are indeed N positive. In a recent multicenter series including 11 institutions (from the US, Switzerland, Italy, Belgium, and Portugal), only approximately a half of patients undergoing surgery (at any of the major hepatobiliary centers) had their lymph nodes evaluated.[49] To ensure accuracy, hepatic surgeons should strongly get in the habit of sampling lymph nodes routinely at the time of surgery, as nodal extension of IHCC is much more prevalent than for other tumors that they are used to dealing with.[50] This lymphadenectomy should include harvesting of hepatoduodenal ligament for right-sided tumors and harvesting of cardia and lesser curvature nodes for left-sided tumors (**Figure 8**). Although the removal of metastatic nodes may decrease locoregional recurrence, the implication of removing these nodes is mainly to allow accurate staging.

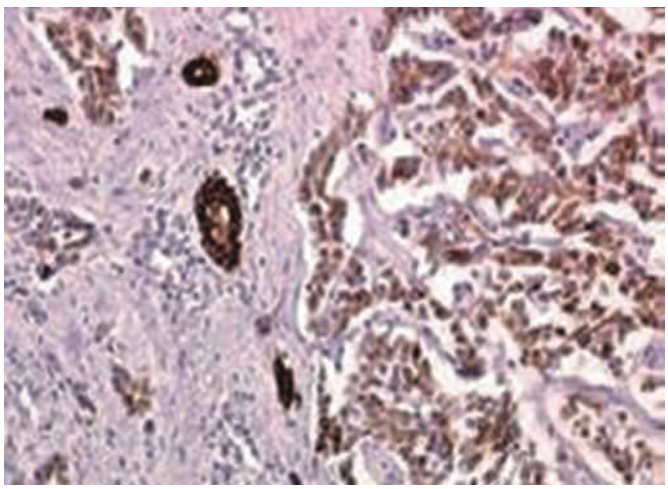


Figure 7. Immunostaining for cytokeratins 7 in intrahepatic cholangiocarcinoma. Note the staining of the tumor cells signing their biliary origin.

STAGING SYSTEMS

In contrast to cholangiocarcinoma of the extrahepatic bile ducts, IHCC is considered by the World Health Organization (WHO) as an intrahepatic liver malignancy, along with HCC. With the latter being more frequent than IHCC, and the diagnosis of IHCC being rather unreliable until the late 1980s, staging systems for intrahepatic malignancies have initially been developed based on the clinical, pathological, and therapeutic characteristics of HCC. However, different staging systems for HCC have proven to be both inappropriate and inaccurate for IHCC because only a very low proportion of IHCCs measure smaller than 2 cm, and also because of the high propensity for lymphatic extension. In 2010, the 7th edition of the AJCC implemented a unique staging system for IHCC (**Table 1**).[51] It was designed following a retrospective analysis of the SEER database and was found superior to the two Western and two Japanese pTNM classifications that had previously been used.[52] This new edition of the AJCC ensured a more coherent distribution of patients on TNM stages I, II, and III. Recently, this new system has been validated using a highly selected group of patients

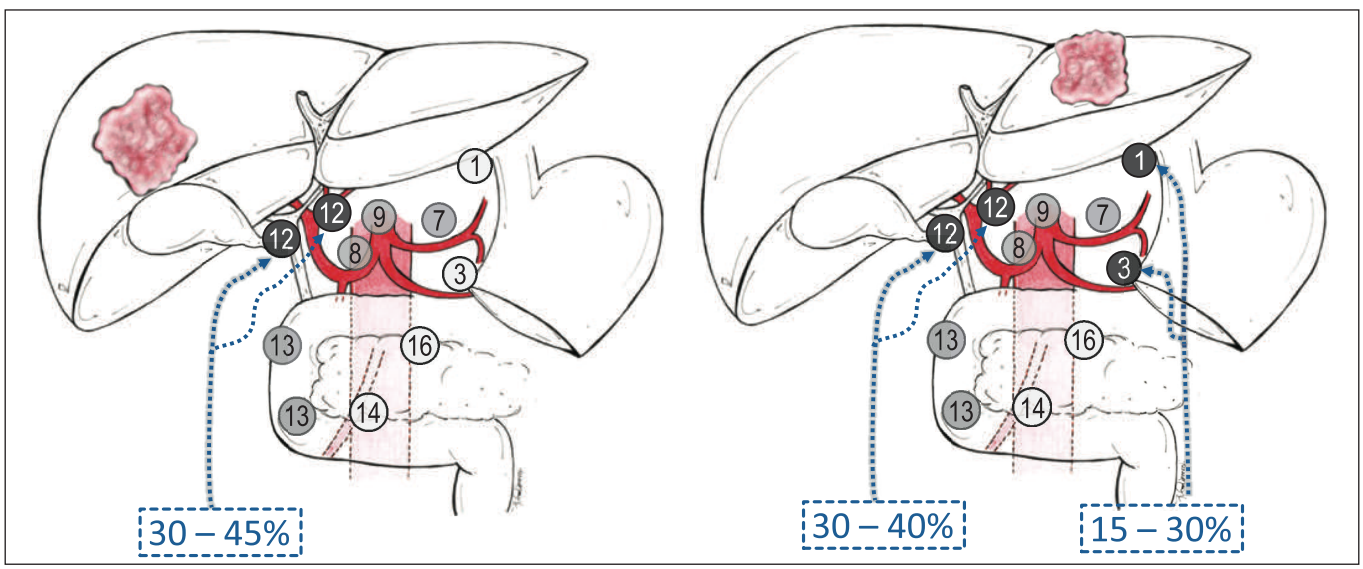


Figure 8. Lymph node extension in intrahepatic cholangiocarcinoma. Incidence and topography according to the location of the tumor (right or left hemiliver). Lymph nodes: 1: right cardia, 3: lesser gastric curvature, 7: left gastric artery, 8: hepatic artery, 9: celiac trunk, 12: hepatoduodenal ligament, 13: retropancreatic, 14: mesenteric, 16: aortic.

and shown to be more accurate in predicting survival after resection than the previous systems.[53] According to this new edition, 28% of the patients had stage I tumors, and their five-year survival was 62%. In contrast, 6% of the patients were stage IV and none of them survived two years after surgery. Therefore, the rationale for operating on these latter patients is questionable. The remaining stage II and III patients, who comprised two thirds of the population, had a median survival of 53 and 16 months, respectively, and their estimated five-year survival was 27% and 14%, respectively. Although the seventh edition of the TMN staging system has introduced important changes resulting in a better contrast, the majority of IHCC patients are distributed in either T1 or T2. Recently, a prognostic nomogram based on a retrospective study on 367 resected IHCCs was undertaken by Wang et al.,[54] including tumor markers, vascular invasion, nodal metastasis, direct invasion, and number and diameter of nodules. Accuracy was better than other staging systems but requires external validation, especially in Western countries. A standardized definition of the periductal infiltrating component is needed to further improve this classification.

Table 1. TNM staging of intrahepatic cholangiocarcinoma according to the AJCC/UICC 7th edition.

	Description		
T	TX - Primary tumor cannot be assessed T0 - No evidence of a primary tumor Tis - Carcinoma in situ T1 – Solitary tumor without vascular invasion T2a – Solitary tumor with vascular invasion T2b – Multiple tumors, with or without vascular invasion T3 – Tumor perforating the visceral peritoneum or involving the local extrahepatic strutures by direct invasion T4 – Tumor with periductal invasion		
N	NX - Regional lymph nodes cannot be assessed N0 - No regional lymph node metastasis N1 - Regional lymph node metastasis		
M	M0 - No distant metastasis M1 - Distant metastasis		
Stage grouping	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-T2b	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
Stage IVB	Any T	Any N	M1

TREATMENT OPTIONS

Tumor resection is currently the only effective treatment for IHCC. As for other liver tumors, there is no randomized controlled trial to support this statement. However, the three-year survival rate is virtually nil without resections, whereas it is close to 40% in patients whose tumors have been removed. In fact, there is little alternative to surgery in the treatment of IHCC, in contrast to HCC for which liver transplantation, percutaneous ablation, and transarterial chemoembolization are all valid treatment options (**Table 2**). These alternatives to surgery have failed to achieve good results in terms of survival for IHCC and therefore to have a role in its management. In fact, treatment decisions for this type of tumor were for a long time fairly simple, as the two main options were surgical resection and palliation. In addition, there is a widespread belief that resection should be attempted at all costs (given the few alternatives to surgery), that some patients could benefit from incomplete resection,[55,56] and that the prospect of narrow hepatic resection margins should not exclude patients from being considered for surgery.[36,57] However,

Table 2. Available data on the management of IHCC and HCC according to the cumulative French and Japanese registries.

	IHCC	HCC
Male / Female ratio	1	5
Age (peak incidence) (years)	55 - 75	65 - 75
Cirrhosis	10%	85%
Mean diameter (cm)	6	3
France (FRANCIM registry)		
Tumor resection	29%	13%
% of R0 resection	60%	83%
Transplantation	1%	3%
Ablation	0%	4%
Survival (5-year) in all patients	7%	7%
Survival (5-year) in R0 resected patients	40%	40%
Japan (LCSGJ registry)		
Tumor resection	68%	34%
% of R0 resection	78%	91%
Transplantation	0.2%	0.3%
Ablation	2%	31%
Survival (5-year) in all patients	19%	35%
Survival (5-year) in R0 resected patients	43%	NA

IHCC: intrahepatic cholangiocarcinoma; HCC: hepatocellular carcinoma; FRANCIM: The French network of cancer registries; LCSGJ: The liver cancer study group of Japan.

since modern chemotherapy enables a median survival of 12 months, the utility of surgery at any cost can legitimately be questioned, particularly in patients with a dismal prognosis.

SURGICAL RESECTION

Since tumor resection is currently the first-line treatment for IHCC, it is important that physicians be aware of its efficacy and limits that have four specificities compared to other indications for liver surgery.

First, the efficacy of surgery for IHCC is usually assessed in terms of patient survival up to five years after surgery. There are little data on survival beyond five years or on disease-free survival rates. In fact, the latter has not been considered a very necessary end point, as the vast majority of deaths are related to recurrence and very few recurrences are amenable to repeat surgery. According to series published over the past decade in the international medical literature, the 1-, 3-, and 5-year survival rates following resection of IHCC are 67% (CI: 63-71), 38% (CI: 34-42), and 27% (CI: 23-31), respectively. Results for surgical resection of IHCC are detailed in **Table 3**.[49,58–68] These figures are very much the same in different areas of the world. Accordingly, the prognosis of resected IHCC is a little less than that of other liver malignancies. The 5- and 10-year survival rates for HCC treated by hepatic resection (liver transplantation excluded) are, for example, 53% and 28% in the Japanese registry.[1] Corresponding figures for colorectal liver metastases are 42% and 26% in an international registry. It is of course possible that these differences witness selection bias towards the most suitable patients, as there are other treatments than surgery for HCC and colorectal metastases, whereas surgery is the main or only treatment for IHCC. Nevertheless, there is general agreement amongst surgeons that there is a place for improved patient selection and neoadjuvant or adjuvant treatments for IHCC patients.

The second specificity of surgery for IHCC is the fairly high risk associated with the procedure (mortality ranging from 1 to 14% and morbidity ranging from 6 to 43%).[69] When pooling data from different geographical areas, the mortality rate turns out to be the same (6%) in the Western world (United States and Europe), in Japan, in Korea, and in France. This figure is higher than that of liver resection in normal livers (actual figures for colorectal metastasis or HCC without underlying liver disease are around 1-2%) and comparable to that of liver resection in cirrhotic livers (the majority of resections for HCC). The main complications after resection for IHCC are liver failure and sepsis.[70] As a matter of fact, hepatectomy for IHCC usually consists of a major hepatectomy, removing more than three liver segments in 75–80% of patients. Further, a significant number of patients have an associated removal of segment 1 (30–50%), the common bile duct (20–40%), or vascular structures (10–20%) to achieve complete resection.[70,71] Indeed, IHCCs are usually large at the time of surgery and have ill-defined borders that infiltrate the surrounding parenchyma and lack a clear tumor capsule.[47] Without accurate imaging (in particular MRI), these are generally overlooked and only discovered upon laparotomy.

The third specificity is that both the resectability and curability rates of IHCC are somewhat less than for other malignancies. In approximately 20–30% of patients operated on for IHCC, incidental liver metastases or peritoneal deposits that have been missed by preoperative imaging and that

Table 3. Results for surgical resection of intrahepatic cholangiocarcinoma.

Author	Year	Country	n	Median survival (mo)	1-year overall survival (%)	3-year overall survival (%)	5-year overall survival (%)
Cherqui [58]	1995	France	14	27	100	-	-
Pichlmayr [59]	1996	Germany	32	13	-	-	-
Casavilla [60]	1997	USA	34	-	60	37	31
Madariaga [61]	1995	USA	34	19	67	40	35
Chu [62]	1999	Hong Kong	39	12	57	24	16
Kawarada [63]	2002	Japan	37	31	54	34	24
Ohtsuka [64]	2002	Japan	48	-	62	38	23
Lang [105]	2005	Germany	16	46	94	82	-
De Oliveira [4]	2007	USA	34	28	-	-	63
Endo [66]	2008	USA	80	36	-	-	-
Ercolani [67]	2010	Italy	72	-	91	62	48
Farges [68]	2011	France	212	58	77	43	28
De Jong [49]	2011	International	449	27	77	44	31

contraindicate resection will be discovered. The prognosis of these patients is dismal, with no 3-year survivors. Among resected patients, approximately 25% will have an R1 or R2 resection. Survival following an R2 resection is usually comparable to, and occasionally worse than, that of non-resected patients. Median survival following an R1 resection is in most series close to 12 months, and the 3-year survival rate is nil.

The fourth specificity is that, in contrast to other liver malignancies such as HCC or colorectal liver metastases, there is little or no evidence that the prognosis of IHCC following liver resection has clearly improved over the past 10 years, and it may be useful to understand why. For HCC, 5-year survival has increased from 30% to 50-60%. The main reasons are better patient selection and preparation (portal vein embolization to test the ability of the liver to regenerate), improved oncological surgery techniques (such as anterior approach to avoid mobilization of the tumor), refined definition of the optimal surgical margins (anatomical resection with 2 cm margins), and active treatment of recurrence. For colorectal liver metastases, 5-year survival has increased similarly. The main reason is the more liberal use of highly effective adjuvant or neoadjuvant chemotherapies, again active treatments of recurrences. As a rule, none of these features has developed to a comparable level for IHCC. There is limited information available on the location and kinetics of recurrence (although they account for the majority of postoperative deaths). Confusing data have been reported on their risk factors. There is currently evidence that the efficacy of chemotherapy is improving, and several series have recently reported IHCC recurrences following resection amenable to repeat resection or to radiofrequency ablation.

ALTERNATIVES TO SURGERY

Local ablation

Radiofrequency ablation (RFA) and microwave ablation have recently been estimated to be used as frequently as (or slightly more frequently than) resection in the treatment of HCC. There are, in contrast, two main reasons why it is exceptionally indicated and performed for IHCC. The first is anatomical and relates to the typically large diameter of IHCC at the time of diagnosis. Any tumor larger than 3 cm is unlikely to be efficiently destroyed by currently available devices. Besides, the frequent proximity between IHCC and Glissonean pedicles both limits the efficacy of ablation (through the so-called cooling effect) and increases the risk of biliary complications. The second is the usual absence of a severe underlying liver disease. The risk of post-hepatectomy decompensation of the underlying liver disease was the main rational for the development of ablation for HCC. In contrast, the incidence of underlying cirrhosis is much less in IHCC, and the justification to use a less aggressive treatment than surgical resection is therefore limited. In the Japanese registry,[1] this treatment was performed in 2% of IHCC patients, compared to 31% of HCC patients. When performed, incomplete response to ablation was twice as frequent in the former group than in the latter (36% vs. 18%). However, some recent series have reported on use of radiofrequency ablation in unresectable IHCC with encouraging results (overall survival nearly 60 months).[72,73] The only circumstance when ablation has been successfully used for IHCC is with single and small hepatic recurrence following resection.[74,75]

Transarterial chemoembolization (TACE)

TACE, which is widely used and increasingly effective for HCC, is, as a rule, not indicated for IHCC. Being mainly fibrotic, this type of tumor is not hypervascular at the arterial phase of the contrast injection, and therefore there is no blush to help identify the feeding artery. Besides, chemoembolization is less likely to induce tumor necrosis of non-hypervascular tumors, which is the case with IHCC. Finally, although Child-Pugh C cirrhosis (which is a formal contraindication to TACE) is rare in patients with IHCC, significant portal or biliary involvement by the tumor is more frequent and may represent relative or absolute contraindication. In the latest edition of the Liver Cancer Study Group of Japan, chemoembolization was actually performed in only 4% of patients, and the morphological response was either minor or absent in two thirds of these patients. There are, however, some IHCCs that are at least partly hypervascular and could benefit from TACE as a palliative treatment.[76,77] Encouraging results have also been recently reported using doxorubine-eluting beads[78] or Yttrium-90 microspheres.[79–81]

Liver transplantation

Liver transplantation has been infrequently used to treat IHCC, and it is extremely difficult to form a clear idea regarding its results. One reason is that patients with IHCC are usually grouped with patients with hilar cholangiocarcinoma in liver transplant series. In a recent French national survey, IHCC accounted for 30% of all patients transplanted for a cholangiocarcinoma while 70% had been transplanted for a Klatskin tumor. All cholangiocarcinoma patients (peripheral and hilar) themselves account for less than 1% of all liver transplantation in the North American and European liver transplant registries. Five-year survival following transplantation is usually around 30%, and in the recent French survey, survival curves of patients with hilar and peripheral cholangiocarcinoma were almost exactly the same.[82] This survival figure is considered much too low by the transplant community in a context of graft shortage to justify this indication. In contrast, liver transplantation for very small IHCCs that are incidentally discovered on

the resected specimen, or have been mistaken for HCCs, achieves good results.[83] However, as indicated previously, this situation is exceptional, as only approximately 5% of IHCCs measure less than 2 cm in diameter. The major risk factor of recurrence after transplantation is lymph node involvement. In a series by Pichlmayr et al.,[59] 1-, 3-, and 5-year survival rates were 89%, 56%, and 44% after transplantation in LN-negative patients, whereas 3- and 5-year survival rates were nil in LN-positive patients. Based on these results, some authors have suggested performing a lymph node sampling during laparotomy prior to transplantation.

SYSTEMIC CHEMOTHERAPY

Most trials assessing the effectiveness of chemotherapy for IHCC have been carried out in groups of heterogeneous patients with extrahepatic cholangiocarcinoma, IHCC, or gallbladder or pancreatic cancer. Therefore, there is little specific evaluation of chemotherapy for IHCC. Ercolani et al.[67] retrospectively showed improved survival in patients who received adjuvant gemcitabine after resection (5-year survival: 65% vs. 40%).

Although current guidelines have not established a standard first-line chemotherapeutic regimen for unresectable IHCC, recent publications have shed light on potential options. A recent randomized trial established the superiority of combined gemcitabine and cysplatin compared to gemcitabine alone in patients with locally advanced or metastatic biliary cancer.[84] The combination treatment was well tolerated, had encouraging antitumor activity, and enabled secondary resection in a third of patients. A recent pooled analysis of 104 trials (representing 2810 patients with advanced biliary tract cancers and treated with chemotherapy in the last 35 years) found that combination gemcitabine and platinum regimens yielded the highest response rates and tumor control rates.[85,86] While gemcitabine/cysplatin has now become the standard regimen for cholangiocarcinoma, many trials are evaluating the role of targeted therapies in the treatment of patients with advanced disease, including sunitinib,[87] cetuximab,[88] bevacizumab, and erlotinib.[89] The series are supported by the series by Guedj et al.[90] showing that hilar cholangiocarcinoma and IHCC display different specific protein profiles, especially regarding VEGF expression. This suggests a potential benefit for anti-angiogenic therapies in IHCCs.

PROGNOSTIC FACTORS

Many investigators have used multivariate analysis to determine useful prognostic factors for IHCC after surgical resection. These results are detailed in **Table 4**.[36,38,39,56,57,66,67,91–96] Indeed, since systemic chemotherapy enables survival for more than 12 months, the utility of surgery can legitimately be questioned, particularly in patients with a dismal prognosis.

LYMPH NODE INVOLVEMENT

Lymph node metastasis has been reported to be one of the most significant independent prognostic factors for patients with IHCC.[66,91,94,97,98] A multicenter analysis conducted by the Study Group for Hepatic Surgery of the Japanese Society of Hepatobiliary Surgery[98] showed that, of 139 patients with IHCC who had lymph node involvement, only seven patients survived for more than four years, and only three patients survived for more than five years (5-year survival 7%). Other series have reported that no patients with nodal involvement survived for more than five years, [38,67,92,95,97] and others have reported a 5-year survival rate that ranged from 6% to 17%.[29,40,47,56,91,94,95,99] Based on these results, some investigators have reported that radical resection should be contraindicated for patients with nodal involvement.[100] When De Jong et al. examined the cumulative effect of multiple tumors, vascular invasion, and nodal disease, they found that patients who had none of these risk factors had 5-year survival of 38% compared to 27% for patients with one risk factor, and 18% for patients with two or three risk factors. When patients were stratified according to nodal status, among patients with no nodal metastasis, the other two risk factors were still able to stratify patients with regard to prognosis. In contrast, when patients with positive nodal disease were examined, the authors noted that presence of multiple tumors or vascular invasion either alone or together failed to discriminate patients into discrete prognostic groups.[49] Therefore, N1 status does not only adversely affect overall survival but also influences the relative effect of tumor number and vascular invasion on prognosis.

SURGICAL MARGINS

The incidence of R1 resections in patients with mass-forming type IHCC is as high as 24%,[100,101] and there is evidence that it is not improving over time.[66] This incidence probably reflects IHCC's particular mechanism of spreading. Indeed, IHCCs are usually large at the time of surgery and have ill-defined borders that infiltrate the surrounding parenchyma and lack a clear tumor capsule.[47] Other specific pathological features of IHCC have been associated with an increased likelihood of R1 resection; these include the presence of satellite nodules,[102] bile duct extension,[103] or a periductal infiltrating-type tumor.[94] The influence of IHCC R1 resection on outcome is controversial, with approximately half of the published studies reporting that it is not an independent predictor.[36,39,55,66,67,92,93,102,103] We have recently shown that the surgical margin's influence is highly dependent on context.[68] In patients with nodal metastasis, R1 resection has no impact

on survival, as previously suggested.[41,102] In contrast, an R0 resection is a significant independent predictor of survival in patients with no nodal metastases, even apparent in patients with risk factors for poor outcomes, such as tumor multiplicity or vascular invasion. There is very little data available on the influence of the surgical margin width. However, this margin width seems to have no influence in patients with pathological nodal positive disease but was correlated with the outcome in patients with no nodal extension.[68] In patients with no nodal involvement, a margin of less than 1 mm was equivalent to R1 resection in terms of outcome. The question even arises as to whether it is justified to attempt resection when preoperative imaging or intraoperative assessment clearly indicates that the result will be R1. The median survival time of R1-resected patients was 12 months, and none survived for three years; these figures are hardly better than those observed in non-resected patients. Rather than operate on these patients, one option could be to enroll them in trials of short courses of neoadjuvant chemotherapy. Finally, curative R0 resections with wide margins (10 mm or more) is the only chance of cure for patients with IHCC and any effort must be undertaken to achieve this. The benefit of performing surgery alone in patients with nodal invasion (whether formally proven preoperatively or incidentally discovered on frozen sections intraoperatively) or in whom resection is likely to be R1 is questionable; there is a need for prospective trials of adjuvant or neoadjuvant chemotherapy in these patients.

PERIPHERAL VERSUS HILAR IHCC

Some authors suggested that proximal IHCC are more aggressive with in particular more periductal-infiltrating types[104] and more lymph node involvement,[47,92] but these results have not been confirmed in other series.[104] Similarly, the 5-year survival rate of patients with peripheral IHCC has been shown to be significantly higher than that of patients with proximal IHCC,[40,47,56,66] although others, including a multicenter study from nine Japanese high-volume centers,[98] reported that 5-year survival rates between the two groups did not differ.

SELECTION OF PATIENTS FOR SURGERY

Evaluation of risk factors for recurrence is the cornerstone of patients' selection for surgery. Somewhat conflicting results

Table 4. Prognostic factors after resection for intrahepatic cholangiocarcinoma.

Author	n	Curative resectability (%)	Nodal involvement (%)	Median survival (mo)	5-year survival (%)	Prognostic factors by multivariate analysis
Shimada, 2007 [96]	74	69	46	24	31	IM, MT
Endo, 2008 [66]	82	85	9	36	-	LN, IM, TS
Uenishi, 2008 [91]	133	83	47	18	29	LN, IM, R
Tamandl, 2008 [36]	74	80	31	31	28	TS, IM
Shirai, 2008 [39]	59	85	54	-	-	LN, G, IM, PNI
Nakagohri, 2008 [92]	56	75	38	22	32	IM
Choi, 2009 [93]	64	86	27	39	40	G
Yedibela, 2009 [38]	45	80	13	37	35	LN, R, BL, BT
Guglielmi, 2009 [94]	52	83	27	40	20	LN, VI
Lang, 2009 [56]	83	64	34	26	21	Gender, R
Shirabe, 2010 [95]	60	72	43	-	31	G, LI
Ercolani, 2010 [67]	64	83	29	57	48	Year of operation
Saxena, 2010 [57]	40	70	28	33	28	LN, CA19-9, G
Zhang, 2010 [97]	40	75	28	25	28	LN, TS
Cho, 2010 [106]	63	94	30	-	32	Age, CA19-9, LI, R
Uchiyama, 2011 [98]	341	80	50	20	29	LN, CA19-9, IM, R
Murakami, 2011 [104]	44	61	45	28	31	LN
Farges, 2011 [68]	212	76	37	58*	45*	TNM
De Jong, 2011 [49]	449	81	30	27	31	LN, R, IM, VI

LN: nodal involvement; CA19-9: carbohydrate antigen 19-9; IM: intrahepatic metastasis; R: pathologically curative resection; LI: lymphatic invasion; TS: tumor size; G: pathological grading of differentiation; VI: vascular invasion; BL: blood loss; BT: blood transfusion; PNI: perineural invasion; MT: macroscopic type; IDPCC: intraductal papillary carcinoma component. * in R0 resections.

have however been reported in the literature and the validity of the results are further hampered by the discordance between the limited number of patients and the high number of variables evaluated. Nevertheless, the presences of satellite nodules or of positive lymph nodes are determinants and when both conditions are present, survival is so low that surgery might not be justified. Selection criteria however need to be validated and refined.

DEVELOPMENT OF CHEMOTHERAPY

The efficacy of surgery, although obvious, has its limits considering the high rate of R1 resections and of recurrence. Further improvement will require more active use of chemotherapy, either as a neoadjuvant or adjuvant treatment. Inclusion of patients into randomized controlled trials should be encouraged.

FINAL CONSIDERATIONS

IHCC is the second-most frequent primary liver tumor and is increasingly recognized because of both better identification and rising incidence. Diagnosis should be suspected in either male or female patients in their 60s, with no or minimal symptoms, and fibrotic liver mass. Surgery is currently the only effective treatment and may yield a 5-year survival of 40%, provided that the resection is curative (R0). Unfortunately, this occurs in as little as 20% of patients due to delayed diagnosis or technical difficulties in achieving safe margins. Improvement in prognosis may require a higher index of suspicion and an earlier referral to specialized surgeons, who should aim to achieve wide margins and the development of innovative chemotherapy regimens.

SUGGESTED READING

De Oliveira, M. L. et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann. Surg. **245**, 755–762 (2007).

Large study including patients with intrahepatic (8%), perihilar (50%), and distal (42%) cholangiocarcinoma.

Shin, H.-R. *et al.* Epidemiology of cholangiocarcinoma: an update focusing on risk factors. *Cancer Sci.* **101**, 579–585 (2010).

An important meta-analysis evaluating the association between cholangiocarcinoma and and infections with liver fluke, HBV, or HCV.

Weber, S. M. et al. Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. J. Am. Coll. Surg. **193**, 384–391 (2001).

A study including 53 intrahepatic cholangiocarcinomas treated in a single institution. Risk factors of poor survival are identified (vascular invasion, positive margin, and multiple tumors).

De Jong, M. C. et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J. Clin. Oncol. **29**, 3140–3145 (2011).

A large multi-institutional study including 449 patients that underwent surgery for intrahepatic cholangiocarcinoma (IHCC). The authors suggest consider lymphadenectomy during resection of IHCC due to the high frequency of nodal involvement.

Wang, Y. et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J. Clin. Oncol. **31**, 1188–1195 (2013).

A prognostic nomogram is proposed based on a multivariate analysis including 367 patients who underwent hepatictomy for intrahepatic cholangiocarcinoma. Survival was affected by tumor markers level, tumor diameter and number, vascular invasion, lymph node involvement, local invasion, and extrahepatic metastasis.

Farges, O. et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC--IHCC-2009 study group. Ann. Surg. **254**, 824–829 (2011).

A large multi-institutional series of patients with intrahepatic cholangiocarcinoma (mass-forming type) who underwent curative resection. The poor outcomes in the presence of nodal involvement or R1 resection is highlighted.

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16 Gallbladder Carcinoma

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- *Gallbladder (GB) carcinoma is 5th most common malignancy of the gastrointestinal tract and its incidence varies widely worldwide. Long-term survival can only be achieved with complete surgical resection, which is guided by the T stage.*
- *In early GB cancer T1a tumors can be treated with a simple cholecystectomy while T1b or T2 tumors demand an extended cholecystectomy (associated or not with bile duct resection). Advanced GB cancer (T3 or T4) usually requires extended major hepatectomy and common bile duct resection and reconstruction. Associated regional lymphadenectomy has potential therapeutic and prognostic benefits.*
- *Radical surgery has no proven benefit in metastatic disease (including lymph nodes outside the hepatoduodenal ligament).*
- *The high rate of recurrence after curative resection of GB carcinoma justifies the use of adjuvant therapy (except for T1 disease), despite the scarcity of data.*
- *The majority of patients with GB carcinomas present with advanced disease and palliative treatment of symptomatic jaundice, pain, or gastrointestinal obstruction is frequently required.*

INTRODUCTION

Historically, gallbladder (GB) cancer has been associated with a dismal prognosis. This is partially explained by the typical advanced stage at presentation, often with locally invasive and unresectable tumors with disseminated disease. Further, there is no proven effective systemic therapy for carcinoma of the GB, either for metastatic disease or as adjuvant therapy for high-risk patients after surgical resection. Despite progress in the multimodality treatment of other solid malignancies of the gastrointestinal tract over the past several decades, the only reasonable chance for long-term survival in patients with GB carcinoma is for it to be discovered at an early stage when complete surgical resection can be achieved. From the time of the original description of GB cancer in 1778 to more recent series, the overall 5-year survival in patients remains around 5% with median survival of approximately 6 months.[1–5] Complete resection offers the only chance for long-term survival. As stated above, the role of systemic chemotherapy, radiation therapy, and other non-surgical treatment modalities are unproven and seemingly ineffective in the treatment of GB cancer.

For surgeons treating GB cancer, the critical decision is to determine which patients will potentially benefit from complete resection in order to offer this select group of patients that do not have advanced, disseminated disease a chance for cure. The improvements in non-invasive imaging (multi-detector computed tomography [CT], magnetic resonance imaging [MRI], ultrasound [US], positron emission tomography [PET], etc.) over the past several decades have allowed surgeons to more accurately stage patients preoperatively to make this selection process more accurate.

In this chapter, we will first review the natural history and epidemiology of GB cancer and discuss the relevant anatomic considerations for the surgeon treating GB cancer. Next, we

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will review the clinical presentation, staging, laboratory and radiologic workup of the patient with suspected or proven GB cancer. We will then focus on the surgical management of GB cancer in the following common presentation scenarios: i) incidentally discovered GB cancer either during laparoscopic cholecystectomy for presumed benign disease, ii) incidentally discovered GB cancer on final pathology after laparoscopic cholecystectomy (usually early stage), and iii) preoperatively suspected or discovered GB cancer (either incidentally discovered, asymptomatic GB mass on imaging for other reasons, or discovered on imaging for specific abdominal/GB complaints). We will conclude with a discussion on the outcomes and appropriate follow-up of patients with GB cancer, including the role of adjuvant therapy and the treatment of unresectable disease. The final figures in this chapter (**Figures 8** to **11**) serve as a summary/flowchart of our institutional practice in the workup, treatment, and follow-up of patients with GB cancer and can be referred to when reading the various sections.

EPIDEMIOLOGY

GB cancer is the 5th most common malignancy of the gastrointestinal tract and the most common tumor of the biliary tree in the United States.[6] The annual incidence is 1.2 cases per 100,000 persons per year, resulting in approximately 3,000 deaths per year. Analysis of registry data from 33 states in the United States reveals that Caucasian males have a significantly lower age-adjusted incidence of GB cancer compared with other racial and ethnic groups,[7] including Native Americans, Alaska natives, and Asian-Pacific Islanders. Also noted was a gradual reduction in the incidence of GB carcinoma between 1993 – 2002 when compared to 1973 – 1992.

Worldwide, the incidence of GB cancer varies widely (by as much as 25-fold) by geographic and ethnic regions.[8] The highest reported rates are found in India (21.5 cases per 100,000 persons per year),[5] Pakistan (13.8 cases per 100,000 persons per year),[5] East Asia (~0.5%),[9] and Native Americans in New Mexico (9.8-14.5 cases per 100,000 persons per year).[10] Rates higher than other Western countries are also found in cancer registries in Eastern Europe.[5] Despite the decreased incidence of GB cancer in the United States noted in the aforementioned population-based analysis,[7] there have been no such trends found worldwide.[11,12] Women are approximately three times more likely to develop carcinoma of the GB when compared to men,[13,14] and this holds true across all geographic regions worldwide. GB cancer is a disease nearly exclusively of advancing age, with the incidence peaking over the age of 60.[3,15–17] There are rare reports of pediatric [18] and familial GB cancer,[19,20] but the vast majority of cases occur sporadically in late adulthood. There are also other rare associations of GB cancer in patients with GB polyps and primary sclerosing cholangitis (PSC),[21] inflammatory bowel disease,[22] and polyposis syndromes,[23] but these observations have not translated into a significantly elevated clinical risk of the development of GB carcinoma in these groups in larger, population-based studies.

ETIOLOGY

Gallstones are present in 90% of patients with GB carcinoma.[14,24–26] However, there is no direct evidence showing that gallstones are the etiologic factor in the pathogenesis of GB cancer. Several case-control and cohort studies have shown that the relative risk for the development of GB cancer in the setting of asymptomatic cholelithiasis is approximately 5 – 7 times that of the general population.[12,27–33] When this is coupled with the already low incidence of GB cancer in the general population, the incidence of GB cancer in patients with gallstones is still very low (0.3-3%). Patients with GB cancer tend to have significantly larger stones,[34] multiple stones,[35] and a higher aggregate weight of gallstones when compared to patients with asymptomatic and symptomatic cholelithiasis.[35]

Other inflammatory conditions of the GB have also been associated with GB cancer, such as typhoid fever,[36–38] cholecystenteric fistula,[39] and a long common channel between the pancreatic and bile ducts.[40–42] Chemical carcinogens, such as methyldopa,[43] oral contraceptives,[44] isoniazid,[45] heavy metals,[46] and occupational exposure,[47] have also been associated with GB cancer, but not proven causally. Obesity is associated with cholelithiasis and GB cancer, as it is with many other types of malignancy.[48]

Similar to colorectal cancer, there is some, albeit less, evidence of an adenoma-carcinoma sequence in the development of GB cancer in that there is severe dysplasia and carcinoma *in situ* adjacent of most GB carcinomas.[14] In contrast to colorectal cancer, however, this adenoma-carcinoma sequence occurs at a much lower frequency, as the association of polypoid lesions of the GB and the development of cancer is rare. Yang et al.[49] found an 8% incidence of GB malignancy in cholecystectomy specimens with GB polyps, all > 1 cm and solitary, resulting in current practice recommendations of performing cholecystectomies for GB polyps ≥ 1cm in size.[50] More recently, Konstantinidis et al.[51] had similar findings, with 14% of cholecystectomy specimens with GB polyps harboring malignancy, all of which were > 1 cm. The presence of multiple GB polyps supports the diagnosis of pseudopolyps, which carry no increased risk of malignancy and can be safely observed if they continue to be asymptomatic.[24,51–53]

The presence of calcification within the GB wall (porcelain GB) has historically been thought to be a

marker of associated GB cancer. Older series reported a 10-50% incidence of carcinoma in radiographically discovered porcelain GBs;[54] however, more modern series demonstrate a lower risk of 5-10%,[55,56] or have failed to find an association.[57–59] Calcification is considered the end-process of chronic inflammation. Thus, the higher incidence of GB cancer in patients with porcelain GB may be due to the long-standing inflammation and irritation of the GB epithelium, resulting in the development of malignancy. The standard of care for porcelain GB should be cholecystectomy, unless there is a contraindication. However, these more modern series suggest that close follow-up for more benign patterns of calcification or high-risk patients may be acceptable.[56,58] Further, since there is low risk of malignancy in the setting of porcelain GB, a laparoscopic approach is acceptable, with a low threshold for conversion if a difficult dissection is encountered or malignancy is suspected.

Taken together, the presence of any underlying factor that causes inflammation of the GB may be a risk factor for the development of GB cancer. The factors mentioned above may lead to GB epithelial irritation and inflammation, thus initiating the sequence of dysplasia leading to malignancy.[13,60,61] In animal models, the addition of known carcinogens to inflammatory conditions leads to dramatically increased rates of GB cancer,[62] suggesting that environmental exposure, coupled with an inflammatory state (from stones or any other factor), may lead to higher rates of malignancy.

ANATOMIC CONSIDERATIONS

The way in which carcinoma of the GB grows locally, and spreads regionally and distantly, is directly related to the anatomy of the GB and surrounding structures. The detailed anatomy of the GB and liver are reviewed elsewhere. However, several points directly related to this point are worth emphasizing.

First, the GB is partly intraperitoneal and lies attached to the undersurface of the liver (segments 4b and 5). There is no peritoneal covering overlying the GB where it is applied to the liver surface and the muscular wall of the GB is very thin, such that a tumor in this location lies in very close proximity to the lymphatics of the GB wall and liver parenchyma. In that location lies the cystic plate,[63] an area of fibrous connective tissue between the GB muscularis and the liver. When a routine cholecystectomy is performed, this layer is the plane of dissection, which is inadequate in the case of malignancy. Thus, simple cholecystectomy is not sufficient save for the earliest stages (carcinoma *in situ* or malignancy confined to the lamina propria) of GB cancer. Invasive tumors of the body and fundus of the GB may be resected with negative margins with a limited resection of segments 4b and 5, as they are usually of sufficient distance from the structures of the porta hepatis such that the bile duct, hepatic arteries, and portal venous structures can be avoided. Tumors of the infundibulum and cystic duct, contrastingly, often invade the porta hepatis, rendering them resectable only with a major liver and bile duct resection or are unresectable due to severe involvement.

Second, the progressive lymphatic drainage of the GB is well understood and is important in the staging and treatment of GB cancer. The first draining lymph nodes to the GB are to the pericystic and pericholedochal nodes (N1). From there, the general progression of drainage is from the pericholedochal to the pancreaticoduodenal and retroportal nodes (N2).[64] Spread to the superior mesenteric from the pancreaticoduodenal and the celiac from the retroportal nodes is the next stepwise progression (also N2). From all of these nodes, spread to the aortocaval nodes occurs, which is also considered N2 disease (see staging section below). Importantly, some lymphatic drainage occurs directly from the choledochal nodes directly to the aortocaval nodes, which may explain why even small GB cancers present with advanced metastatic spread. Both Ito et al.[65] and Uesaka et al.[66] describe the main cholecysto-retropancreatic lymphatic drainage. This includes the main route from the anterior surface of the bile duct to the right or passing straight down from the posterior surface of the bile duct to the terminal retroportal nodes, as well as a cholecysto-celiac route to the left, through the hepatoduodenal ligament to the celiac nodes. They also describe the aforementioned cholecysto-mesenteric route to the left in front of the portal vein to the superior mesenteric lymph node station. As will be expanded upon below, the lymphatic drainage pattern of the GB has important staging and treatment implications that must be taken into account both when deciding to operate and in deciding how extensive of an operation (lymphadenectomy) to perform.

PATHOLOGY AND HISTOLOGY

PRE-MALIGNANT GB LESIONS

The malignant potential of GB polyps (**Figure 1**), as discussed in previous sections of this chapter, is more controversial. The incidence is low, and varies between approximately 0.1 and 1% in several series.[53,67,68] GB polyps have been noted in approximately 5% of patients undergoing ultrasound evaluation, but most are cholesterol polyps.[52,69] Polyp size of >1 cm is associated with cancer and forms the basis of the recommendation for cholecystectomy for such lesions.[51–53,70–75] The incidence of carcinoma associated with non-adenomatous polyps (cholesterol polyps, hyperplastic polyps, and

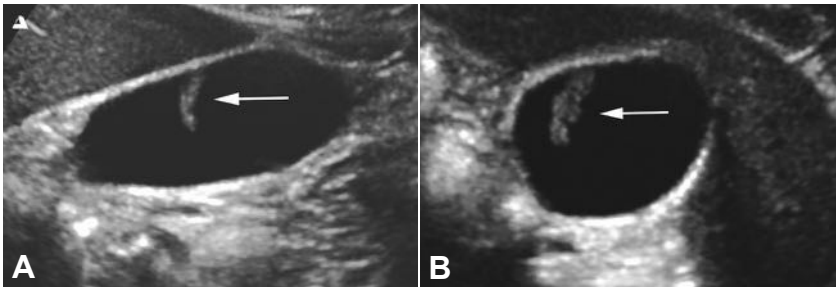


Figure 1. Transabdominal ultrasound of the GB in a 58-year-old male patient with symptoms of biliary colic. Long- (**A**) and transverse-axis (**B**) images demonstrate a 1.39 x 0.5 cm, hypervascular, intraluminal polyp (arrows) in the GB. The patient underwent an uneventful laparoscopic cholecystectomy and final pathology revealed a benign, hypervascular polyp.

inflammatory polyps) is near zero.[49,65,69] In one study of 123 GB polyps, 21 (17%) were found to be adenomatous and 7 (6%) harbored malignancy.[70] The risk of malignancy was associated with older age, polyps > 1cm, and the presence of a single polyp. Taken together, these studies indicate that the progression from adenoma to carcinoma in GB polyps accounts for a very small minority of all GB cancers.

At our institution, Ito et al. found that in 214 patients with GB polyps discovered on ultrasound, only 10% had adenomatous polyps and carcinoma *in situ* was found in one patient with a 14-mm lesion.[53] Most patients had either pseudopolyps (58%) or no polyp (32%). Thus, the association between the presence of GB polyps and malignancy is small and the current practice recommendation of cholecystectomy being reserved for polyps ≥ 1cm seems justified.

GROSS MORPHOLOGY

The gross findings of early GB cancer often mimic that of chronic cholecystitis, with a thickened GB wall appearing like chronic inflammation (**Figure 2**). Oftentimes, patients are taken to the operating room with a preoperative diagnosis of biliary colic or chronic cholecystitis, only to discover on final pathology a diagnosis of GB cancer. The findings of incidentally discovered GB cancer discovered during cholecystectomy for presumed benign disease varies between 0.1 and 1% in the literature.[76–78]

More advanced GB cancers can lead to different gross presentations, depending on the growth of the tumor. The mass can grow into the GB lumen (endophytic) and distend the GB with tumor, or it can grow out into the liver (exophytic) and collapse the GB (**Figure 2**). Either can lead to cystic duct, and sometimes common bile duct (CBD), compression and obstruction. Approximately 60% of tumors originate from the fundus of the GB, 30% from the body, and 10% from the neck.[79,80] There are five described subsets of gross descriptions of GB cancer: infiltrative, nodular, nodular-infiltrative, papillary, and papillary-infiltrative.[81] Infiltrative tumors spread subserosally and can involve the entire GB wall. They also extensively invade the liver. Papillary tumors can grow quite large, and are often endophytic, but generally have a better prognosis due to their less invasive nature into the wall of the GB.[82]

HISTOLOGY

Table 1 lists the various histologic subtypes of GB cancer.[83] Commonly, there is more than one histologic subtype present. The majority of GB cancers are adenocarcinomas (**Figure 1**), with less common variants of papillary, mucinous, squamous, and adenosquamous carcinomas.[82,84–88] Over a 10-year period at our institution, consisting of 435 patients with GB cancer, 391 cases (90%) were adenocarcinoma.[89] Other histologies included: 18 cases (4%) of squamous/adenosquamous carcinoma, 13 cases (3%) of neuroendocrine carcinoma, 7 cases (1.6%) of sarcoma/adenosarcoma, 5 cases (1.1%) were unspecified, and 1 case (<1%) of melanoma.

Similar to other gastrointestinal malignancies, GB cancer progresses from dysplasia, to carcinoma *in situ*, to invasive cancer in the GB epithelium.[68,79] The majority

Table 1. Histologic subtypes of gallbladder cancer.

EPITHELIAL TUMORS
Adenocarcinoma
Well-differentiated
Papillary
Intestinal
Pleomorphic giant cell
Poorly differentiated (small cell)
Signet ring
Clear cell
Colloid
Choriocarcinoma-like
Squamous Cell Carcinoma
Adenosquamous Cell Carcinoma
MESENCHYMAL TUMORS
Embryonal rhabdomyosarcoma
Leiomyosarcoma
Malignant fibrous histiocytoma
Angiosarcoma
OTHER TUMORS
Melanoma
Carcinoid

(Adapted from D'Angelica and Jarnagin[83])

of GB carcinomas harbor areas of severe dysplasia or carcinoma *in situ* in adjacent sections.[90] There are two predominant types of metaplasia in the GB mucosa that are precursors to malignancy: pseudopyloric and intestinal,[85] with the intestinal type demonstrating higher rates of carcinoma. Consistent with this progression of dysplasia to carcinoma, patients with invasive cancer are 15 and 5 years older than patients with dysplasia and carcinoma *in situ*, respectively.[90]

Papillary adenocarcinomas tend to have a better prognosis than other subtypes, likely due to their less invasive growth pattern.[82,91] However, when they do become invasive, papillary cancers display metastatic potential. The non-epithelial (mesenchymal, carcinoid, melanoma) tumors of the GB are extremely rare and are only described in case reports in the literature.

GB cancers are grouped into a spectrum from well- to poorly-differentiated. This histologic grading system does not have a correlation with survival, with the exception of the fact that most papillary tumors are well-differentiated.[82] Taken together, the histologic types and grade of GB cancer do not offer much prognostic information with respect to outcomes and survival.

MOLECULAR ANALYSIS OF GB CANCER

There is limited knowledge of the precise genetic mutations and pathways responsible for the development of GB carcinoma from dysplastic lesions. It is known, however, that GB cancer arises from multiple genetic defects.[14,92,93] **Table 2** summarizes the various genes known to be altered in GB cancer.[94–107] There are multiple oncogenes and tumor suppressor genes altered in GB cancer. Further, pathways known to be altered in other solid malignancies (angiogenesis, microsatellite instability [MSI], adhesion molecules, etc.) are also mutated in GB carcinoma. Goldin & Roa [108] provide

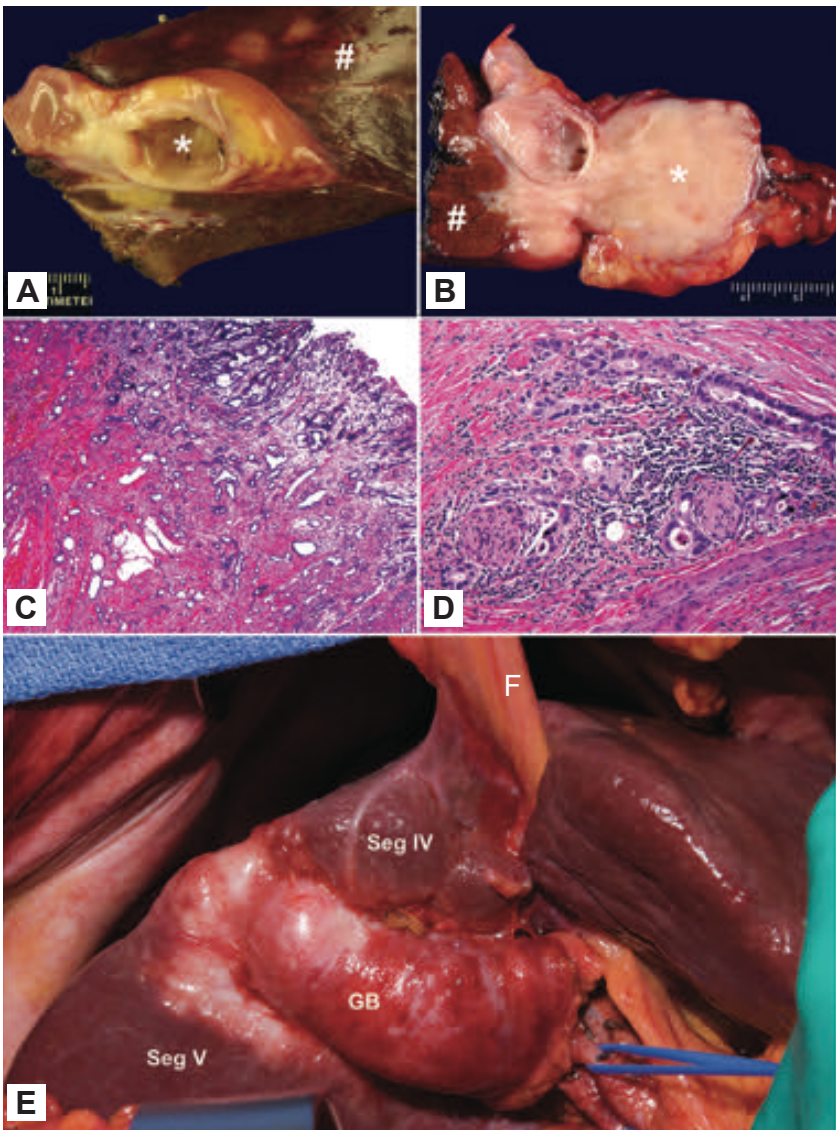


Figure 2. Gross, microscopic, and intraoperative photos of GB adenocarcinoma. **A**) Gross picture of a radical cholecystectomy and en bloc liver resection of a GB adenocarcinoma in the neck of the GB leading to symptoms of cholecystitis. The lumen (*) of the GB is seen and the tumor directly invades the surrounding liver (#) tissue. **B**) Gross picture of an exophytic GB adenocarcinoma obliterating the GB lumen (*) and invading the adjacent liver (#). Low- (**C**) and high- (**D**) powered views of GB adenocarcinoma, characterized by nests of poorly-differentiated epithelial cells with visible mitotic figures invading into the muscular layer of the GB wall, including lymphovascular structures. (Photos courtesy of Laura Tang, M.D., Department of Pathology, Memorial Sloan-Kettering Cancer Center). **E**) Intraoperative photo of a GB cancer in a 62-year-old female with an incidentally discovered, asymptomatic GB mass concerning for malignancy on chest CT performed for pneumonia. Intraoperatively, the falciform ligament (**F**) is being retracted superiorly and the mass can be seen originating from the fundus of the GB, invading segments 4 and 5 of the liver. The cystic duct (upper) and an accessory right hepatic artery (lower) are encircled with vessel loops. An R0 resection was achieved via cholecystectomy with en bloc partial hepatectomy consisting of a IVb/V liver resection and portal lymphadenectomy. Final pathology demonstrated a T3N0 moderately differentiated GB adenocarcinoma. (*courtesy of William Jarnagin, M.D., Department of Surgery, Memorial Sloan-Kettering Cancer Center*)

an excellent overview of these mutations in a recent review.

Several groups have identified polymorphisms (CA242 and CA125) that achieve high levels of sensitivity and specificity for discriminating patients with GB carcinoma from those with cholelithiasis.[109] Other serum markers (hypoxia-inducible factor-1α, the 'D' allele of lipoprotein receptor associated protein (LRPAP1), the NAT2 slow acetylator phenotype, the X(+) D haplotype of apolipoprotein B, and the 'H' allele of the ATP-binding cassette sub-family G member 8 (ABCG8) D19H polymorphism) may also identify patients at risk of developing GB cancer independent of the presence of gallstones.[110–114]

CLINICAL PRESENTATION

Patients with GB cancer usually fall into one of three presentations categories: i) incidentally discovered GB cancer found on pathologic examination of a routine cholecystectomy specimen, ii) GB cancer discovered intraoperatively during cholecystectomy for presumed benign disease, and iii) GB cancer suspected preoperatively.[84] In 435 patients with GB cancer treated at our institution over a 10-year period, 47.4% were discovered incidentally at laparoscopic cholecystectomy and 52.6% presented with either locally advanced (16%) or disseminated (36.6%) disease.[89] It is important to note that these percentages can vary widely based on a medical center's geographic location, ethnic breakdown of patients, and referral patterns. The large number of GB cancers discovered incidentally after laparoscopic cholecystectomy justifies the routine inspection of the GB mucosa by the surgeon in the operating room, with frozen-section analysis of any suspicious lesions.

GB cancer is generally asymptomatic in its early stages, as tumor growth and invasion do not elicit specific symptoms unless the tumor growth leads to either obstruction of the cystic duct, in which case it can mimic cholecystitis, or obstruction of the CBD, in which case it leads to jaundice. Thus, patients are often misdiagnosed with benign cholecystitis or present at an advanced, often incurable, stage. Nearly 75% of patients with GB cancer present with either locally advanced or metastatic disease.[84,115]

When symptomatic, GB cancer often leads to constant right upper quadrant pain, which on careful history can be differentiated from the typical episodic pain of biliary colic. Symptoms of advanced disease include jaundice, anorexia, and weight loss.[116] In 82 patients presenting with jaundice and GB cancer at our institution, only 6 (7%) were found to be resectable, and of those, all had recurred within 2 years and died within 3 years.[117]

Table 2: Genetic alterations in gallbladder cancer.

Gene	Gene Type	Alteration	% Expression in GBC	Comments
K-ras[94]	Oncogene	Activation Mutation	40-50%	Increased with anomalous pancreaticobiliary duct
p53[95]	Tumor Suppressor	Inactivating Mutation	27-70%	Increased at late stage disease
p21/CDKN1A[96]	Oncogene	Activating Mutation	28%	Decreased survival when co-expressed with p27 and p53
p16/CDKN2[97]	Tumor Suppressor	Inactivating Mutation	50%	Decreased prognosis when mutated
COX-2[98]	PG pathway	Increased Expression	70%	Decreased prognosis with increased expression
MSI[99]	--	Presence of MSI	10%	Present in 33% of metaplastic lesions and 83% of dysplastic lesions
VEGF[100]	Angiogenesis	Increased Expression	Unknown	Increased expression with more advanced tumors
iNOS[101]	Inflammatory Mediator	Increased Expression	70.8%	Present in many cases of chronic GB inflammation
FHIT[102]	Tumor Suppressor	Inactivating Mutation	100%	Possibly involved early in pathogenesis
hTERT[103]	Telomerase Subunit	Increased Expression	93%	Increased expression in pre-malignant lesions
c-erb-B2[104]	Oncogene	Activation Mutation	10-46.5%	Decreased prognosis with presence of mutation
Cadherins[105], Catenins[106]	Adhesion Molecules	Decreased Expression	14-40%	Early stage of tumor progression and metastases
DNA Methylation[107]	--	Presence of DNA Methylation		Decreased prognosis when certain genes (p73, FHIT, others) are methylated

COX = cyclooxygenase, FHIT = fragile histidine triad gene, GBC = GB cancer, iNOS = inducible nitric oxide synthase, MSI = microsatellite instability PG = prostaglandin, VEGF = vascular endothelial growth factor.

LABORATORY AND RADIOGRAPHIC EVALUATION

LABORATORY INVESTIGATIONS

The initial laboratory workup in the patient with suspected GB cancer should include a complete blood count, comprehensive metabolic profile, coagulation panel, and type and screen. This allows for a thorough evaluation of the patients overall health and hepatic function, should a major resection be undertaken. The findings of anemia, hypoalbuminemia, and elevated bilirubin and/or alkaline phosphatase suggests advanced disease.[118] There are no serum markers that are either sensitive or specific enough for GB cancer to be used as a screening or confirmatory diagnostic tool. In one study, carcinoembryonic antigen (CEA) was found to be 90% specific, but only 50% sensitive for GB cancer.[119] The CA 19-9 is both 75% specific and sensitive for GB cancer, although when jaundice is present, the utility of an elevated CA 19-9 is minimal.[120] In combination, tumor markers (CA-125, CA 19-9, and CA-242) achieve sensitivity and specificity as high as 100% and 69%, respectively.[121] However, the cost and marginal benefit of such analysis is questionable and of limited utility. The most useful role for tumor markers, if elevated preoperatively, is to monitor for tumor recurrence post-resection and/or to monitor response/progression during systemic treatment.

RADIOGRAPHIC INVESTIGATIONS

Prior to the advances of high-resolution cross-sectional imaging over the past 20 years, including CT, MRI, US, and PET, GB cancer was often diagnosed intraoperatively during exploration for symptoms, often with the findings of advanced disease. In the modern era, any patient with either suspected or incidentally discovered GB cancer should have some, if not multiple, high-resolution cross-sectional imaging studies for proper staging. The goals of any radiographic study are to evaluate for resectability and any distant spread of disease. Of note, in addition to the GB-focused imaging modalities discussed below, patients with suspected GB cancer should also have, at the very least, PA and lateral chest radiographs to screen for occult pulmonary metastases. However, the presence of pulmonary metastatic disease, in the absence of locally advanced or intraabdominal metastatic disease, is rare.[122–126] **Table 3** summarizes the various imaging modalities commonly utilized in the workup of GB cancer.

US is a readily available modality that is excellent at evaluating the various layers of the GB wall. It has the ability to detect small polyps (**Figure 1**) and early mucosal-based lesions,[127] as well as large masses with invasion into the liver. Findings on US can include the presence of gallstones and the presence of a mass filling the GB lumen and/or invading the adjacent liver.[128] US is also an excellent modality to evaluate for tumor invasion into major hepatic biliary and vascular structures. In a study of 203 patients with GB cancer, preoperative US demonstrated a mass in 177 (87%) patients.[129] However, unlike the other modalities discussed below, US quality is highly operator dependent.

CT is a relatively inexpensive cross-sectional imaging modality that provides detailed anatomic information about the local extent of disease as well as any distant metastatic spread. It can readily detect enlarged regional lymph nodes with accuracy of >80%, but is less well-suited to detect small peritoneal deposits of tumor.[130] GB cancer is generally characterized as a low-attenuation mass in the right upper quadrant. Often this replaces or involves most of the GB. There can be various levels of contrast enhancement, corresponding to viable and necrotic areas of tumor (**Figure 3**). In early stages, the often encountered asymmetric GB wall thickening can be difficult to distinguish from chronic cholecystitis.[128,129] CT is 71-84% accurate in staging GB cancer. In a study of 118 patients from Korea, CT was found to be 79.3, 92.7, and 100% accurate in differentiating T1 vs. T2, T2 vs. T3, and T3 vs. T4 GB cancers, corresponding to specificities of 98.8%, 86%, and 100%.[125] In another study, CT had a sensitivity, specificity, and overall accuracy in determining resectability of 72.7%, 100%, and 85%, respectively.[131] Importantly, there was 100% correlation between CT and surgery in determining hepatic parenchymal and vascular invasion.

MRI has gained popularity in the past decade in the evaluation of biliary tract malignancies, mainly due to

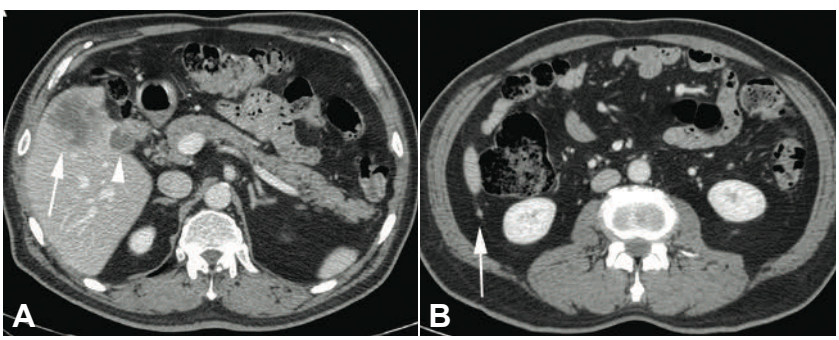


Figure 3. Abdominal computed tomography images in a 64-year-old female who presented with back pain. **A**) The GB (arrow head) is seen to be shrunken with abnormally enhancing soft tissue, suspicious for malignancy. There is direct tumor spread into segments 4b e 5 (arrow). **B**) Several sub-centimeter, nodular, soft tissue masses (arrow) were seen within the pericolonic fat and mesentery, suspicious for carcinomatosis. The patient was found to have diffuse peritoneal carcinomatosis on diagnostic laparoscopy.

the advent of MRI-angiography (MRI/MRA) and MRI-cholangiopancreatography (MRCP). Typically, GB carcinomas appear hypointense on T1 images and heterogeneous on T2 images. The area of outermost contrast uptake correlates well with the extent of the tumor.[128] MRI has a sensitivity of 70-100% for diagnosis of hepatic parenchymal invasion and 60-75% for regional lymph node metastases.[132,133] In a study from Korea the sensitivity and specificity of MRI/MRA and MRCP in 41 patients with GB cancer was 100% and 89% for involvement of the bile duct, 100% and 85% for involvement of major vascular structures, 67% and 89% for hepatic parenchymal invasion, and 56% and 89% for lymph node metastases.[123] Another study from our institution demonstrated sensitivities of 100% and 92% for hepatic parenchymal and lymph node involvement, respectively.[133] However, the added benefit of MRI over CT is unclear. One study of 25 consecutive patients with GB cancer showed that MRI/MRCP did not provide any additional information with respect to preoperative staging.[134] MRI is probably best suited to evaluate the bile ducts and major vascular structures when contemplating resection in a patient presenting with jaundice, as the addition of MRA and MCRP does provide additional detail that can be especially helpful to the surgeon and interventional radiologist when planning interventions, either for curative resection or operative/interventional palliation.

Most GB cancers demonstrate increased uptake of ^{19}F-deoxyglucose (FDG), and are thus **PET**-avid tumors. The experience with PET in GB cancer is limited, but has the theoretical advantages of distinguishing between malignant and benign lesions, as well as detecting areas of extrahepatic spread. However, PET is limited in that it cannot differentiate between benign inflammatory conditions, including normal postoperative changes after cholecystectomy, and malignancy.[135] In a study of 16 patients with GB cancer in Japan, PET had a sensitivity and specificity of 75% and 88%, respectively,[136] and was only 50% sensitive for extrahepatic metastases. In another study of biliary malignancies, including cholangiocarcinoma and GB cancer, the addition of PET to standard CT scans for patients' preoperative evaluation changed management in 17% of cases and PET was 56% sensitive for extrahepatic metastases, detecting intra-abdominal metastases in 3 of 6 patients with histologically-confirmed carcinomatosis.[137] In a different study of 31 patients, PET was 86% sensitive for detecting the primary tumor, 87% sensitive for detecting metastatic

Table 3: Imaging modalities commonly used in gallbladder cancer.

Modality	Accuracy	Pros	Cons
Ultrasound (U/S)	87%[A]	• No ionizing radiation • Inexpensive • Good detail of GB wall and small lesions or polyps	• Operator dependent • Poor evaluation of regional LN and CBD involvement
Computed Tomography (CT)	• 71-84% overall[B,C] • 79.3% T1 v. T2[C] • 92.7% T2 v. T3[C] • 100% T3 v. T4[C]	• Detailed anatomic information • Inexpensive • Evaluation for extrahepatic disease • Evaluation of regional LN spread	• Low sensitivity for peritoneal disease • Inflammatory changes can mimic malignant involvement
Magnetic Resonance Imaging (MRI)	• 100% Se, 89% Sp for CBD invasion[D] • 100% Se, 87% Sp for VI[D] • 67% Se, 89% Sp for HI[D] • 56%% Se, 89% Sp for LN involvement	• No ionizing radiation • Combination of MRA and MRCP improves detail of imaging • Excellent for evaluating bile duct and vascular involvement	• Expensive • Not readily available • No proven increased yield over CT • Low sensitivity for peritoneal disease
Positron Emission Tomography (PET)	• 75-86% Se[E] • 50-88% Sp[E] • Changes management in 17-23% of cases[E] • 57% Se, 94% Sp[F]	• Evaluation of extrahepatic disease • Evaluation of suspicious findings on CT or MRI	• Expensive • Cannot distinguish inflammatory from malignant findings • No proven yield over CT or MRI

[A]U/S demonstrated a mass in 87% of patients with histologically-proven GB cancer.[120]
[B]CT was 71-84% accurate for diagnosing T stage of GB cancer.[125,131]
[C]CT sensitivities for differentiating various stages of histologically-proven GB cancer.[131]
[D]Sensitivities and specificities of MRI for GB tumor involvement.[132]
[E]Sensitivity and specificity of PET in diagnosing GB cancer preoperatively.[135,136]
[F]Sensitivity and specificity of PET in diagnosing metastatic GB cancer preoperatively.[126]
CBD = CBD, HI = hepatic invasion, LN = lymph node, MRA = magnetic resonance angiography, MRCP = magnetic resonance cholangiopancreatography, VI = vascular invasion, Se = sensitive, Sp = specific

disease, and changed operative management in 23% of patients.[135] Currently, our practice is to utilize PET scanning in instances where CT or MRI leads to suspicious findings that are not completely evaluated. In these circumstances, PET may be helpful in delineating suspicious areas as benign or malignant, which may then guide further invasive diagnostic and therapeutic procedures.

In patients who are deemed resectable based on the aforementioned workup, a tissue diagnosis/biopsy is not necessary. GB cancer has a propensity to spread to the peritoneum and biopsies may introduce tumor spread to biopsy tracts and port sites, potentially spreading an otherwise localized tumor.[138–140] Further, the results of such a biopsy would rarely change management: a positive biopsy would lead to the planned surgical resection, but a negative biopsy would likely not be trusted and either repeat biopsy or planned surgical resection would be the next logical step. In the setting of advanced, unresectable disease, percutaneous, image-guided (CT, US, etc.) biopsy can be undertaken, of either the primary or a metastatic deposit of tumor, to establish a tissue diagnosis in preparation for systemic therapy. The accuracy of these techniques is approximately 90%.[141] The sensitivity and specificity of bile cytology has been evaluated, but is not sufficiently accurate to justify the necessity of an added endoscopy with instrumentation of the biliary tree, which has significant morbidity, to perform this technique.[141–143]

In summary, patients with suspected or proven GB cancer being properly staged and considered for require a comprehensive laboratory evaluation. There is no utility for routine tumor markers. US is an excellent modality to evaluate the gallbladder and the relationship of the mass to the bile duct and liver parenchyma. All patients should have dedicated, high-resolution cross-sectional imaging, consisting of either CT or MRI, primarily to evaluate for liver invasion, relationship to the vascular structures of the liver, and to assess for metastatic disease. The use MRA/MRCP is reserved for cases where standard imaging requires further detail to determine involvement of the biliary tree and major vascular structures. PET scanning should not be routinely obtained in all patients with GB cancer, but may be helpful in circumstances where CT or MRI yields suspicious findings. Preoperative biopsy is rarely, if ever, indicated when a suspicious mass is found on imaging concerning for GB cancer. In the setting of advanced disease, CT-guided or laparoscopic biopsy to establish a tissue diagnosis prior to the induction of systemic therapy may be required.

STAGING

There are several proposed staging schemes for GB cancer, including the American Joint Committee on Cancer (AJCC) [144], the Japanese Biliary Surgical Society system [145], the Nevin [146] and modified Nevin [147] systems. Historically, this led to much confusion in comparing results across various institutions and countries utilizing different system. Currently, the AJCC TNM staging system (7th Edition) [144] is the standard reporting mechanism for GB cancer. It is summarized in **Table 4**. This system utilizes Tumor depth (T), lymph node involvement (N), and presence of metastatic disease (M) to pathologically stratify GB cancer into four stage groups.

T1 tumors invade the GB lamina propria (T1a) and/or muscular layers (T1b). T2 tumors invade through the muscular layers of the GB wall and into, but not beyond, the connective tissue layers (i.e. into the serosa of the GB or the cystic plate). T2 tumors do not extend into the liver parenchyma. T3 lesions perforate the serosa of the GB, invade the liver tissue, involve the extrahepatic bile ducts, and/or directly invade one adjacent organ (stomach, colon, etc.). T4 lesions invade multiple extrahepatic organs and/or involve major vascular structures (main portal vein or hepatic arteries), which nearly always indicates unresectable disease.

N stage is split into N0 (no evidence of regional nodal metastases), N1 (positive evidence of hilar nodal metastases), and N2 (positive evidence of regional nodal metastases). N1 includes metastases along the cystic duct, hepatic artery, common bile duct, and/or portal vein, while N2 comprises disease within the pericaval, periaortic, superior mesenteric artery, and/or celiac artery nodes. M stage is split into M0 (no evidence of distant metastatic disease) and M1 (positive distant metastases).

The T, N, and M groupings are arranged into stages that group similar patients together (Table 4). Stage I includes node-negative T1 (Stage Ia and Ib) tumors. Stage II includes T2 node negative disease. Stage III includes T3 node negative (Stage IIIa) and T1-3N1 (Stage IIIb) disease. Stage IV includes T4 tumors (Stage IVa) and any T/N stage with the presence of metastatic disease (Stage IVb). In the seventh edition of the AJCC staging system, tumor stage correlates with overall survival and nodal status is the most suggestive of prognosis.

SURGICAL MANAGEMENT

Complete resection is the only treatment modality that has the potential for cure in patients with GB cancer. As was mentioned previously, patients with GB cancer can generally be divided into one of three groups: i) incidentally discovered GB cancer either during laparoscopic cholecystectomy for presumed benign disease, ii) incidentally discovered GB cancer on final pathology after laparoscopic cholecystectomy (usually early stage), and iii) preoperatively suspected or discovered GB cancer (either incidentally discovered, asymptomatic GB mass on imaging for other reasons, or discovered on imaging

for specific abdominal/GB complaints). Each of these scenarios will be addressed in the following sections. What is common to all GB cancer, irrespective of presentation status, is that T stage, in the absence of metastatic disease, is the best prognostic factor in determining the presence of micrometastatic disease and dictates the principles of operation. For example, in the patient in whom a T1a GB cancer is discovered after routine laparoscopic cholecystectomy, no further surgery is recommended, as the incidence of microscopic invasion into the liver or microscopic lymphatic spread is minimal. This is in contrast to T2 lesions, which because of the thin nature of the GB wall and the absence of a peritoneal surface along the GB-liver interface, simple cholecystectomy alone results in high rates of loco-regional recurrence; thus, more extensive surgical resection, as will be discussed below, is recommended. The recommendations discussed below are largely based on several large, retrospective institutional reports on the outcomes of patients with GB cancer undergoing surgical resection. These studies are summarized in **Tables 7** to **9** and will be discussed in the next section on "Outcomes".

GB POLYPS

Polyps are a common finding in patients undergoing US of the GB for complaints of biliary colic (**Figure 1**). Most polyps are benign, including fibromas, lipomas, hemangiomas, cholesterol polyps, inflammatory polyps, and adenomyomas. Adenomyomatosis, which arises from extension of the normal architecture of Rokitansky-Aschoff sinuses through the muscular wall of the GB, is a diffuse, benign process often discovered on ultrasound.[148] The only GB polyps that carry a risk of malignancy are true adenomatous polyps.

US does not, however, have the ability do discriminate between benign and potentially malignant (adenomatous) lesions. Clinically, the question facing the treating physician is when to recommend cholecystectomy for the finding of a GB polyp on imaging. Numerous reviews have looked retrospectively to identify factors associated with malignant GB polyps. The most consistent predictors include presence of a single polyp, size greater than 1 cm, and age > 50.[49,75,149] A study from our institution of 417 patients with polypoid lesions of the GB discovered on US found neoplastic/adenomatous polyps in 10% of patients.[53] Of

Table 4: American Joint Committee on Cancer (AJCC) Staging System for gallbladder cancer*.

T Stage (Primary Tumor)			
Tis	Carcinoma in situ		
T1	Tumor invades lamina propria (T1a) or muscle layer (T1b)		
T2	Tumor invades perimuscular connective tissue. No extension beyond the serosa or into the liver		
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ (i.e. stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts)		
T4	Tumor invades the main portal vein or hepatic artery or invades multiple extrahepatic organs		
N Stage (Regional Lymph Nodes)			
N0	No regional lymph node metastases		
N1	Metastases to nodes along the cystic duct, CBD, HA and/or PV		
N2	Metastases to periaortic, pericaval, SMA and/or celiac artery lymph nodes		
M Stage (Distant Metastases)			
M0	No distant metastases		
M1	(+) Distant metastases		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1, T2, T3	N1	M0
Stage IVA	T4	N0, N1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

*7th Edition, 2010 [144]

these patients, 143 had follow-up US studies, and polyp growth was only found in 8 (6%) patients. Eighty patients underwent cholecystectomy for polyp size <1cm (21%), abdominal symptoms (23%), patient-initiated factors (such as patient anxiety or intolerance with recommendations of close follow-up) with polyps <1cm (14%), or cholecystectomy in combination with another operation (43%). Carcinoma *in situ* was identified in one patient with a 14-mm GB polyp. It is our institutional practice to recommend laparoscopic cholecystectomy for patients with GB polyps >1cm, as the risk for malignancy in sub-centimeter polyps is extremely low. The only exception to this recommendation is that GB polyps in the setting of primary sclerosing cholangitis have a higher rate of malignant transformation, so the threshold for cholecystectomy is lower, although it remains incompletely undefined.[21] Further, patients must be counseled that US only has a 50-70% positive-predictive value for diagnosing GB polyps,[150] so the final pathology report carries a significant chance of not showing any abnormality.

Most GB polyps are asymptomatic, so if they are discovered on US evaluation for abdominal symptoms, other etiologies should be investigated. If no other cause of the patient's abdominal pain is elicited, laparoscopic cholecystectomy should be recommended, with the caveat that surgical removal of the GB may not lead to resolution of the patient's symptoms. In the asymptomatic patient with sub-centimeter GB polyps or adenomyomatosis, follow-up US has traditionally been recommended at 6-12 month intervals, with recommendations for cholecystectomy in the setting of polyp growth. The length of follow-up is not well defined, but long-term follow-up of stable disease does not seem warranted based on an analysis of multi-institutional radiology and cancer registries that included over 70,000 patients who underwent GB US. In this series, the prevalence of GB cancer in Caucasian patients with polypoid lesions of the GB was 0.08% making the role of long-term, routine US surveillance questionable.[151] Conversely, Kubota et al.[152] found that patients with malignancy in association with a GB polyp demonstrated polyp growth of 1.4 - 4 times on repeat US 4 - 12 months after the initial US study. Thus, our recommendation is to obtain a follow-up US study at 6 - 12 month intervals for 1-2 years and, if stable, to stop routine surveillance US and perform subsequent studies only for new clinical findings or symptoms. If malignancy is suspected on US evaluation, high-resolution cross-sectional imaging (CT, MRI) should be obtained to completely clinically stage the patient.

If cholecystectomy is undertaken for GB polyps >1cm, the surgical approach (open versus laparoscopic) is somewhat controversial. Proponents of the laparoscopic approach argue that most GB cancers found in the setting of GB polyps are either *in situ* or T1a lesions that are cured by simple cholecystectomy. Opponents of the laparoscopic approach argue that laparoscopic dissection of the cystic plate during a laparoscopic cholecystectomy is not precise enough to ensure a complete resection, especially around the polyp, and if there is spillage, the patient is at higher risk for peritoneal dissemination of malignancy. As laparoscopic cholecystectomy has become standard practice, it has been our recommendation to perform laparoscopic cholecystectomy for the majority of patients with >1cm GB polyps with no suspicion of invasive cancer on US, reserving a lower than average threshold for conversion to an open procedure. Patients are counseled regarding conversion to open cholecystectomy for any suspicious findings or inability to safely and adequately perform the operation laparoscopically. Frozen section analysis is routinely performed, with conversion to open, definitive resection for findings of carcinoma.

INCIDENTALLY DISCOVERED GB CARCINOMA EITHER DURING OR AFTER CHOLECYSTECTOMY FOR PRESUMED BENIGN DISEASE

The finding of GB cancer on pathologic analysis of a cholecystectomy specimen, usually laparoscopic and performed for presumed benign disease, ranges from 0.27 - 2.1% of all laparoscopic cholecystectomies.[89,153–155] If GB cancer is diagnosed on frozen section analysis intraoperatively and the operating surgeon is not prepared to perform a curative operation, including possible liver and/or bile duct resection, no further dissection should be performed and the patient should be transferred to a center with hepatobiliary surgical expertise.[84] An analysis from our institution showed that there was no difference in mortality, complications, and long-term survival in patients presenting initially or after prior non-curative operation (usually simple cholecystectomy) with GB cancer.[16] A report from Japan had similar findings.[154]

The majority of patients presenting with a diagnosis of GB cancer discovered incidentally after laparoscopic cholecystectomy have early stage tumors. In a Japanese study of 498 patients who underwent initial laparoscopic cholecystectomy with a final diagnosis of GB cancer, 34% had T1a disease, 14% had T1b, 41% had T2, 8% had T3, and 2% had T4 disease.[155] All patients require a complete clinical staging workup (laboratory and radiographic studies) as described above. If there are no contraindications to further surgery (patient co-morbidities or findings of distant spread), further treatment recommendations are based on the T stage of the primary tumor and the status of the cystic duct margin. If negative margins are obtained and the lesions are confined to the lamina propria, cure rate after simple cholecystectomy is 85-100%.[156–158] In this subset of patients, no further treatment is recommended.

However, for T2 and greater lesions, there is substantial risk of residual disease, loco-regional recurrence, and

progression to systemic disease, so simple cholecystectomy is not considered curative. In a multi-institutional series of 115 patients, increasing T stage was associated with the risk of finding: any residual disease on re-resection – T1 38%, T2 57%, T3 77%, residual liver parenchymal invasion – T1 0%, T2 10%, T3 36%, and locoregional lymph node metastases – T1 13%, T2 31%, T3 46%.[159] Similarly, Kai et al.[160] found that lymphatic, vascular, and perineural invasion increases with T stage. In a small study of patients with T2 tumors undergoing repeat surgical resection, patients who underwent resection with lymphadenectomy had improved survival compared to patients who did not undergo lymphadenectomy.[161]

The role for additional surgery is less clear for T1b lesions, as the recurrence rates in the literature after simple cholecystectomy is mixed. Principe et al.[162] report a 50% 1-year survival in patients with T1b GB cancer treated with simple cholecystectomy. However, in other series, the rates of cure for T1b GB cancer approach those for T1a lesions (90-100% at 5-years).[163] In a prospective registry comprised of incidental GB cancers, T1b tumors (n=72) undergoing re-resection had a statistically significant survival advantage with 5-year survival rate increasing from 42% to 79%.[164] Further, in a Surveillance, Epidemiology, and End Results database analysis of T1 tumors, T1b tumors (n=536) who underwent either radical cholecystectomy or cholecystectomy and lymphadenectomy compared to only a simple cholecystectomy had benefit in disease specific survival and in overall survival.[165] Based on the above studies, in patients with T1b or greater lesions fit for surgery we generally recommend re-operation with hepatic resection of the GB fossa (segments 4b and 5) in conjunction with a portal lymphadenectomy, which is referred to as an extended cholecystectomy (**Figure 4**).

If the cystic duct margin was positive bile duct resection with biliary reconstruction is indicated. Similarly, if there is concern for malignancy at the cystic duct margin on re-exploration, frozen section specimens should be obtained and, if positive, bile duct resection and reconstruction performed. Although resection of the extrahepatic bile duct has not been proven to improve survival in all patients,[159,166] it is the only method to ensure complete tumor clearance in the face of a positive cystic duct margin. Further, studies that have not found a survival advantage comparing patients undergoing routine bile duct resection have not specifically addressed the issue of a positive cystic duct margin. Thus, it is our routine to recommend bile duct resection in the presence of a positive cystic duct stump margin, either on pathologic review of the cholecystectomy specimen or intraoperatively on re-exploration. Also, when re-exploring a patient after previous cholecystectomy, it is important to review the preoperative imaging (which often only consists of an US) in order to determine the location of the tumor, which may guide the subsequent resection. We also find it helpful to discuss the case with the surgeon who performed the initial cholecystectomy to further detail and clarify the intraoperative findings. Of significant importance, it is prudent to discuss with the patient about the possibility of not finding residual malignancy in the resected specimen. A summary of our institutional treatment recommendations for patients found to have GB cancer either during or on pathologic analysis after cholecystectomy is presented in **Table 5**.

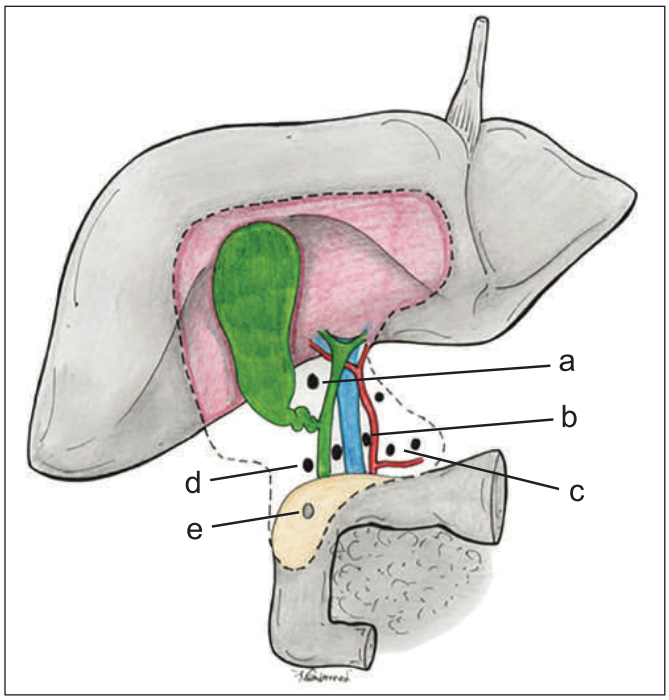


Figure 4. Diagrammatic representation of the extent of resection in an extended cholecystectomy. Colorful area represents the extent of node clearance. a = cystic duct (Calot's) node, b = superior periportal lymph nodes, c = hepatoduodenal ligament lymph nodes, d = inferior periportal lymph nodes, e = superior pancreaticoduodenal lymph nodes. (Adapted from D'Angelica and Jarnagin, W.R.[83], with permission)

ROLE OF STAGING LAPAROSCOPY

The majority of patients with a new diagnosis of GB cancer present with advanced stage disease based on radiographic findings of locally unresectable or metastatic disease. This is reflected in the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database, indicating that of the greater than 1,900 patients with extrahepatic bile duct and GB cancers, only 28% presented with potentially resectable, localized disease.[167] However, only 50-75% of these patients are confirmed to have resectable and curable disease during surgical exploration due to a combination of sub-radiographic metastatic disease (distant lymph node [LN] or peritoneal implants) and/or sub-radiographic locally unresectable tumors.[168]

This high incidence of occult metastatic disease has led surgeons to utilize staging laparoscopy to prevent futile laparotomies. The goals of staging laparoscopy are predominantly two-fold: i) to identify occult, sub-radiographic peritoneal tumor deposits and; ii) to identify LN spread outside of the peri-portal region. To some extent, laparoscopy can also identify locally advanced tumors that are unresectable; however, this is generally appreciated on high-quality preoperative imaging. A prospective analysis of 409 patients diagnosed with primary GB cancer by Argawal et al.[169] found the yield of laparoscopy to be 23%. Staging laparoscopy identified 94% of detectable lesions and prevented 56% of patients with unresectable disease an unnecessary laparotomy. Metastatic disease is often present in primary GB cancer, thus these patients should undergo staging laparoscopy as long as disseminated disease is not seen on preoperative imaging.[169]

However, metastatic disease is uncommon in patients with incidental GB cancer. An analysis of staging laparoscopy for incidental GB cancer from our institution included 136 patients. Of whom 46 patients underwent staging laparoscopy, 10 had disseminated disease, and 2 patients were diagnosed by staging laparoscopy (yield=4.3%). Further, patients with poorly differentiated, T3 or positive-margin gallbladder tumors were found to be at high risk for disseminated disease.[170] Although disseminated disease is rare in incidental GB cancer, the yield of staging laparoscopy is greater in high-risk patients and should be considered for this group.

The issue of palliation in patients with unresectable disease is an important one, as there is no benefit in performing laparoscopy if a surgical biliary or gastric bypass is required for palliation. Procedures for palliation will be expanded upon below, but for the sake of this discussion, it is suffice to say that the combination of short median survival (< 5 months) in patients with liver and/or peritoneal implants, combined with the ability of endoscopic and percutaneous techniques to relieve biliary and gastric outlet obstruction and the significant morbidity of surgical bypass procedures, translate into very few patients requiring such surgical interventions.[171,172]

EXTENT OF RESECTION AND LYMPHADENECTOMY

As has been briefly discussed above, a curative operation for GB cancer for all lesions that have invaded into or beyond the muscular wall of the GB (T1b - T4) begins with extended cholecystectomy to include segments 4b and 5 of the liver, along with a peri-portal lymphadenectomy. This approach was originally described by Glenn and Hays in 1954 as a "wedge resection" of the GB bed and "regional lymphadenectomy of the hepatoduodenal ligament".[83] However, the rarity and often discovered unresectable nature of GB cancer led to much confusion during the middle- to late-20th century as to the best operative approach in patients with GB cancer. A survey of surgeons in the early 1990s showed that only 49% recommended lymph node dissection and only 64% recommended any form of liver resection for T2-4 tumors.[173] Despite this confusion, there is much evidence in the literature to support the use of liver resection and regional lymphadenectomy for GB cancer without evidence for distant metastases on preoperative imaging and staging laparoscopy. This has led to modest improvements in survival over time, likely due to improved and safer surgical resections.[118,174] In the following section, we will separately discuss the extent of resection by stage, the role of lymphadenectomy, the role of liver resection, and the role of bile duct resection.

Table 5: Treatment recommendations for gallbladder carcinoma based on pathologic T stage discovered incidentally after cholecystectomy.

T Stage*	Recommended Operation	Comments
Ia	Simple cholecystectomy (no further treatment).	85 – 100% cure with simple cholecystectomy.
Ib, II	Cholecystectomy with limited hepatic resection of the GB fossa (segments 4b e 5) with en bloc regional[#] lymphadenectomy. Possible bile duct excision with biliary reconstruction.[$]	Bile duct excision if positive cystic duct margin.
III	As above, with higher likelihood of bile duct excision and/or major hepatectomy (right- or extended-right) and biliary reconstruction.[$] Any adherent organ or structure should also be resected.	More likely to involve cystic duct margin, bile duct, or right-sided vascular structures and mandate major liver and biliary resection with reconstruction.
IV	As above, if resectable.	Generally unresectable due to invasion of hilar vascular structures.

* Based on pathologic analysis of the cholecystectomy specimen. Note that Stage III tumors are generally defined by radiographic findings of hepatic involvement. [#] includes portal lymphadenectomy proximally to the level of the intrapancreatic CBD. [$] Generally a Roux-en-Y hepaticojejunostomy.

EXTENT OF SURGICAL RESECTION BY STAGE

As was discussed in the prior section on "Incidentally Discovered GB Carcinoma Either During or After Cholecystectomy for Presumed Benign Disease," T stage of a resected cholecystectomy specimen correlates well with the incidence of residual, occult hepatic and lymphatic disease. In 136 patients undergoing surgical resection for GB cancer after simple cholecystectomy at our institution, the probability of finding residual disease on re-exploration increased with T stage (T1 = 50%, T2 = 61%, T3 = 85%, and T4 = 100%).[89] However, the high rate of finding residual disease in patients with T1 disease may be skewed by the small number of patients in this group (n = 4) and the fact that 75% (3 of 4) were stage T1b.

Our institutional treatment recommendations are summarized in **Table 5**. In general, simple cholecystectomy is only considered curative for T1a tumors. T1b, T2, and T3 tumors are treated with complete resection of any residual tumor or GB bed; with an *en bloc* segments 4b/5 liver resection and regional lymphadenectomy (see later section for detailed definition and description of lymphadenectomy).[165] The management of either a positive cystic duct margin and/or residual tumor along the cystic duct stump at the time of re-operation requires an extrahepatic bile duct resection with biliary reconstruction for complete tumor clearance. It is important to note that, at the time of surgical exploration, thorough clinical staging is important and major resections should be abandoned if distant nodal or other metastases are discovered.

When T3 tumors are encountered, they may require not only liver resection, as will be discussed below, to achieve hepatic tumor clearance, but can also be found to have direct invasion into other surrounding organs, such as the duodenum, stomach, or colon. If this is encountered, *en bloc* resection should be performed, if the patient is deemed fit to tolerate such an operation. This may include combinations of major hepatectomies, bile duct reconstructions, along with partial gastrectomy, colectomy, and sometimes pancreaticoduodenectomy. In 104 patients undergoing surgical resection at our institution, 21 (20%) were found to have direct invasion of other organs and underwent concurrent *en bloc* resection (9 partial colectomies, 4 partial duodenectomies, 3 partial colectomies with concurrent partial duodenectomy/gastrectomy, 2 pancreaticoduodenectomies, 1 partial duodenectomy with concurrent wedge resection of the pancreas, and 1 partial colectomy with concurrent partial duodenectomy with pancreatic wedge resection).[175] It is important to note that when adhesions between the GB and other organs are found, 50% will contain foci of cancer, stressing the importance of an *en bloc* resection. There was no significant difference in cumulative survival between patients with and without adjacent organ resection. When a complete resection is attained, 5-year survival rates of 30-50% can be achieved in patients with T3 tumors.[16,84,145,176]

ROLE OF LYMPHADENECTOMY

The lymphatic drainage of the GB, as was described previously, is somewhat variable, but generally follows the pattern of pericystic to pericholedochal to pancreaticoduodenal, retroportal, and pancreaticoduodenal and superior mesenteric nodes. Finally, drainage is to the periaortic and pericaval nodes.[64] Historically, there has been wide variability in the recommendation for extent of lymphadenectomy in resection for GB cancer, ranging from simple resection of the cystic duct node to a complete periportal lymphadenectomy combined with pancreaticoduodenectomy.[177] The recommendation for more extensive resections is based on the finding that lymphatic spread to the retropancreatic and aortocaval nodes often occur early and that pancreatic resection improves the clearance of these LN. However, because the prognosis for patients with nodal disease is in general poor, and especially so for nodal disease outside of the porta-hepatis, this radical approach is not recommended. Based on this fact, the first step in any operation for GB cancer is a thorough assessment for distant metastases and LN metastases outside of the aforementioned "extended cholecystectomy" field (**Figure 4**). This includes "Kocherizing" the duodenum to assess the aortocaval and retropancreatic LN. If suspicious LN are found in this area, they are sent for frozen section analysis and, if positive, the operation is terminated.

For the sake of this discussion, "regional lymphadenectomy" includes removal of LN in the porta hepatis, gastrohepatic ligament, and retroduodenal space, which are considered N1 disease in the current AJCC staging system.[144] In patients with T1b and greater tumors, regional lymphadenectomy is associated with improved survival compared to patients undergoing extended cholecystectomy alone.[24,153,154] In these studies, the rate of positive nodal disease in T1b-T3 tumors is 16-30%. In an analysis of 104 patients undergoing resection for GB cancer at our institution, 90% underwent regional lymphadenectomy and 33% had positive LN on final pathology,[161 175] thus supporting the inclusion of regional lymphadenectomy when performing an extended cholecystectomy for GB cancer, both for accurate staging and potential therapeutic benefit. It is important to note, however, that there is no literature to support that lymphadenectomy improves survival. This will be discussed further in subsequent sections detailing outcomes after surgery for GB cancer.

Despite this data, a SEER database study found that adequate lymphadenectomy (defined by AJCC as ≥ 3 LN) was only obtained in 5.3% of patients undergoing surgical resection for GB cancer.[178] T1 stage (compared to T2, HR=0.48, 95% CI 0.27-0.83), and year of resection (> 1988,

HR=1.20, 95% CI 1.14-1.26) were associated with adequate lymphadenectomy. Similarly, only 6% of patients with T2 or T3 tumors underwent lymphadenectomy, and 45% (T2) and 75% (T3) of all *en bloc* resections contained 0-2 LN. Thus, the vast majority of patients with potentially curable GB cancer did not undergo the recommended oncologic standard surgical procedure for resectable GB cancer. However, this study may overestimate this trend due to the limitations of addressing this question using the SEER database, which relies on proper coding of surgical procedures to capture treatment variables.

ROLE OF LIVER RESECTION

The lack of a peritoneal layer between the muscular layer of the GB and the liver parenchyma allows for direct tumor extension of a GB carcinoma directly into the liver tissue. "Extended cholecystectomy" is defined as a cholecystectomy and *en bloc* resection of segments 4b and 5 to encompass the GB bed.[122,179] Intraoperative US can be helpful in guiding the resection to delineate major vascular and biliary structures. The pedicles to segments 4b and 5 can be taken within the liver substance, or the segment 4b pedicles can be isolated and divided in the umbilical fissure and divided prior to parenchymal dissection, although this is rarely necessary to achieve tumor clearance.[83] Distal branches of the middle hepatic vein, encountered at the deep intrahepatic margin, can lead to major bleeding and must be carefully secured. Care must be taken to avoid injuring the main right anterior sectoral pedicle and the branches to segment 8.

If extended cholecystectomy would result in an inadequate margin, a right- or extended-right hepatectomy would be required. This is generally true for large tumors at the base of the cystic plate near the GB neck.[84] If the tumor encroaches on the porta hepatis, concurrent bile duct resection may also be required. Because the bifurcation of the right portal vein lies in close proximity to the GB fossa, large tumors of this area also often require right hepatectomy. This can be especially relevant if a prior cholecystectomy has been performed, where tumor cannot be distinguished from inflammation and scar tissue. It is our practice to perform a formal hepatectomy, either right or extended right, in the following circumstances: i) when prior cholecystectomy has resulted in significant inflammation in the triangle of Calot, resulting in the inability to perform a safe, oncologically sound operation, ii) in the rare circumstance when patients present with preoperative jaundice from biliary obstruction and a resectable lesion, and iii) when patients present with a large mass invading into the liver parenchyma, in close proximity to the right portal vein or biliary confluence. Extended hepatectomy can be performed safely in patients fit for major liver resection. Reddy et al.[179] reported on 11 patients with stage I and II GB cancer who underwent extended hepatectomy for large tumors (n=5), positive or unknown cystic duct margin after prior cholecystectomy (n=4), preoperative jaundice and biliary obstruction (n=1), known node-positive disease before hepatic resection (n=4), or significant inflammation in the triangle of Calot after simple cholecystectomy (n=1). They found no significant differences in morbidity, mortality, or long-term survival when compared to historical controls undergoing extended cholecystectomy (minor hepatectomy). An analysis of 104 patients from our institution showed that there was no difference in outcomes based on extent of hepatic resection. Independent predictors of survival included T and N stage of the resected tumors, histologic differentiation, and common bile duct involvement.[175] However, morbidity and mortality increased with more extensive resections. Thus, it is our practice to perform only the extent of hepatic resection necessary to achieve tumor clearance.

ROLE OF BILE DUCT RESECTION

Routine bile duct resection for all cases of GB cancer is not recommended.[180] Although it facilitates a complete regional lymphadenectomy, it also increases morbidity.[166,181] Further, there is no difference in the number of lymph nodes harvested in comparing regional lymphadenectomy alone or in combination with bile duct resection.[159,166,175]

In general, CBD resection is reserved for cases where the tumor infiltrates into the porta hepatis or when inflammation from prior surgery makes it impossible to differentiate this from tumor. In this circumstance, a Kocher maneuver is performed, with division of the bile duct at the level of the duodenum with complete dissection of all soft tissue superiorly in order to skeletonize the hepatic artery and portal vein. Reconstruction is generally with a Roux-en-Y hepaticojejunostomy.[83] In the circumstance where invasion of the CBD, with preoperative jaundice, is encountered, a bile duct resection would be required. However, given the low likelihood of a complete resection and the dismal prognosis in this circumstance,[117] a palliative approach should be considered.

CBD resection is also indicated if the cystic duct stump margin is positive or in the rare circumstance where the cystic duct stump margin is unknown and the tumor location is in the GB neck. Patients with a microscopically positive cystic duct stump margin were more likely to have residual disease in the CBD (42%) when compared to those with a negative cystic duct stump margin (4%).[159] Although bile duct resection has not been shown to improve survival in this patient group,[166] the results are confounded by other strongly prognostic factors (such as LN involvement) that make these results difficult to analyze. On multivariate analysis, stage of disease and the presence of residual tumor in the liver bed (but not the bile duct margin) were associated with poor

survival. Also, bile duct resection is the only way to achieve complete tumor clearance in these patients.

In 109 patients undergoing surgical resection for GB cancer at our institution, excision of the CBD was performed in 68 patients (65%).[175] Clinical involvement of the CBD mandating resection was present in 36 patients, while 32 had a CBD excision performed empirically. CBD excision was not associated with clinical or pathologic variables. Patients with CBD involvement had median survival of 19 months and predicted 5-year survival of 20%, which is significantly worse when compared to 62 months and 49% for patients without CBD involvement. Similarly, Sakamoto et al.[166] compared 29 patients with CBD involvement to 58 patients without CBD involvement, all with T2-T4 GB cancer treated with extended cholecystectomy and CBD excision. Survival was less with CBD involvement (5-year overall survival of 10% vs. 55%, P=0.0001). Taken together, these series emphasize the point that stage of disease, not extent of surgery (assuming an R0 resection), determines survival in resected GB cancer.

PORT SITE AND INCISIONAL RECURRENCES

Patients with GB cancer diagnosed after laparoscopic cholecystectomy for presumed benign disease may be predisposed to early peritoneal spread or port site seeding. This problem could theoretically be accentuated by operative spillage of bile or stones.[138,182] In a study of 409 patients who underwent laparoscopic cholecystectomy for presumed benign disease but were found to harbor malignancy on final pathology, laparoscopic port site recurrences occurred in 17% of patients at a median of 180 days after surgery.[183] Based on this observation, some surgeons recommend port site removal upon re-operation for GB cancer. However, rarely (if ever) does a port site recurrence occur in isolation and should be considered a marker for subsequent peritoneal and metastatic disease;[184–187] thus, it may be considered as a staging tool. As such, it is not our practice to routinely recommend excision of prior port sites during re-exploration for GB cancer.

OUTCOMES

Historically, the overall prognosis for all patients with GB cancer has been dismal. Most notably, this is due to the vast majority of patients presenting with advanced stage disease. The overall 5-year survival is consistently less than 5% for all patients, with a median survival of 5 - 8 months,[2,4,188,189] although there is some suggestion that survival is improved somewhat in the modern era,[167] likely due to better recognition of curable disease and improved surgical technique. An analysis of patients treated at a single institution in the United States showed a modest improvement in overall survival from 3 months in 1915 - 1935, compared to 10 months in 1990 - 2000.[118]

From 1995 - 2005, 435 patients presented to our institution with GB cancer. 36.6% presented as AJCC stage IV.[89] Median overall survival of the entire cohort was 10.3 months (95% CI 8.8-11.8 months) with a median follow-up of 26.6 months. Median survival for those presenting with stage Ia-III disease was 12.9 months (95% CI 11.7-15.8 months) and 5.8 months (95% CI 4.5-6.7 months) for those presenting with stage IV disease. Median survival for all patients discovered incidentally at laparoscopic cholecystectomy was 15.7 months (95%

Table 6: Summary of 435 patients referred to Memorial Sloan-Kettering Cancer Center with a diagnosis of gallbaldder cancer from 1995 – 2005.[89]

Patient Group	Median Overall Survival (months)	95% Confidence Interval
All patients (n=435)	10.3	8.8 – 11.8
Stage Ia-III on Presentation (n=276)	12.9	11.7 – 15.8
Stage IV on Presentation (n=159)	5.8	4.5 – 6.7
Patients Presenting After Laparoscopic Cholecystectomy (n=206)	15.7	12.4 – 18.4
Patients with no residual disease after re-resection (n=35)	72.0	34 - ∞
Patients with residual disease undergoing subsequent R0 re-resection (n=49)	19.0	12.9 – 28.0[$]
Patients with residual disease undergoing subsequent R1/R2 re-resection (n=53)	12.7	8.2 – 15.7[$]
Patients undergoing "curative surgery" alone (n=99)[#]	30.3	21.8 – 43[%]
Patients undergoing "curative surgery" plus adjuvant therapy (n=24)*	23.4	15.7 – 47[%]

[#] "Curative" surgery either as an initial procedure or following prior cholecystectomy. * Of patients receiving adjuvant therapy, 11 (46%) were node positive, 9 (37.5%) had unknown nodal status, and 6 (25%) were node negative. Eight patients (33%) had an R1 resection or had excision of a metastatic site. [$] P < 0.0001. [%] P = 0.4.

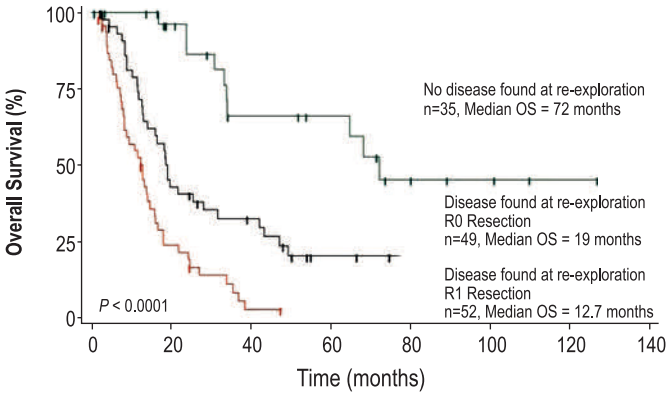


Figure 5. Overall Survival (OS) in 136 of 435 patients undergoing surgical resection for GB cancer from 1995 – 2005 at Memorial Sloan-Kettering Cancer Center. (Reprinted with permission from Duffy, A. et al.[89])

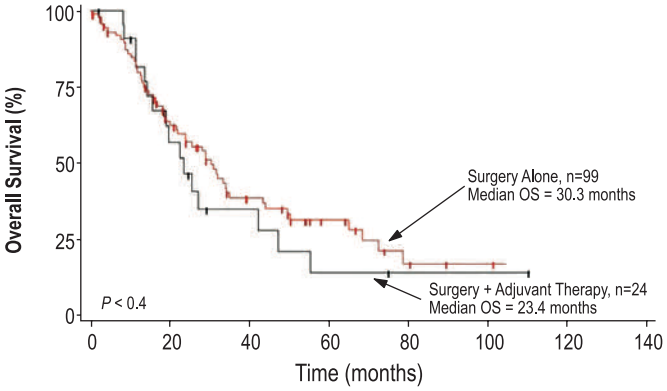


Figure 6. Overall Survival (OS) in 123 of 435 patients undergoing curative surgical resection with or without adjuvant therapy for GB cancer from 1995 – 2005 at Memorial Sloan-Kettering Cancer Center. (Reprinted with permission from Duffy, A. et al.[89])

CI 12.4-18.4 months). For those who subsequently underwent re-exploration, the median survival was 72 months (95% CI 34-∞) for those who were found to have no pathological evidence of disease, 19 months (95% CI 12.9-28.0 months) if an R0 resection was obtained, and 12.7 months (95% CI 8.2-15.7 months) if an R1 or R2 resection was performed (P<0.0001). In a separate analysis of 104 patients undergoing curative resection for GB cancer, T and N stage (along with histologic differentiation and CBD involvement) were strong independent predictors of outcome.[175] Our institutional results are summarized in **Table 6** and **Figures 5** to **7**.

The aforementioned studies represent the typical advanced nature of GB cancer at the time of diagnosis. Important to the treating surgeon, however, is the prognosis for patients after surgical resection, based on intraoperative findings and final pathology. There are several prognostic factors that predict survival after resection, of which T stage of the original cancer is the single best predictor of outcome. Fong et al.[16] have shown that in patients who had a non-curative laparotomy, patients with T2 disease had a 59% 5-year survival rate, compared with 21% for those with T3 disease. Nodal disease is also associated with poor prognosis, with only two patients of the 36 with nodal disease surviving beyond 5 years in the same study. Below, we will discuss stage-specific survival and comment on survival for various other scenarios (patients presenting after laparoscopic cholecystectomy, node positive disease, presence of jaundice on presentation).

OUTCOMES IN PATIENTS WITH T1 GB CANCER

The results of selected modern series of patients with T1 GB cancer are shown in **Table 7**.[155,163,190–194] Survival is generally excellent, with 5-year overall survival in the 70 – 100% range. Most of the patients in this category presents with incidental findings of malignancy after pathologic evaluation of simple cholecystectomy specimens. By definition, they do not penetrate through the muscular layer, such that a simple cholecystectomy is curative for T1a lesions. These tumors are rarely spread to lymph nodes. The most common method of spread is sub-mucosally, involving the cystic duct margin,[157] with T1b tumors showing a higher risk of recurrence. As stated previously, simple cholecystectomy is appropriate for T1a tumors, but our recommendation is to treat T1b lesions with extended

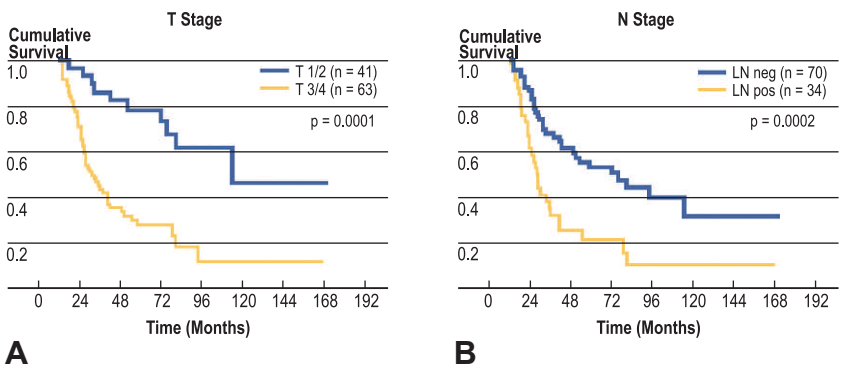


Figure 7. Disease-specific survival for 104 patients with gallbladder adenocarcinoma treated at Memorial Sloan-Kettering Cancer Center by resection stratified by (a) T stage (1/2 versus 3/4) and (b) N status. (Reprinted with permission from D'Angelica, M. et al.[175])

Table 7: Survival after resection of T1 gallbladder cancer from select modern series.

Reference	Patients	Treatment	3-year OS (%)	5-year OS (%)
Ogura, 1991*[190]	366	NS	87	78
Shirai, 1992 [191]	39	100 % SC	100	100
De Aratxabala, 1997 [192]	32	69% SC 31% EC	94	94
Ouchi, 2002*[155]	234	82% SC 18% EC	NR	97
Toyonaga, 2003 [193]	22	100% SC	100	100
Kang, 2007 [163]	24	100% SC	NR	95
Shindoh, 2014*[194]	46	NS	86.1	86.1

*Multi-institutional series. EC: extended cholecystectomy, NR: not reported, NS: not specified, OS: overall survival, SC: simple cholecystectomy.

cholecystectomy, unless the patient's overall medical condition contraindicates additional surgery, in which case close observation is reasonable.

OUTCOMES IN PATIENTS WITH T2 GB CANCER

The results of selected modern series of patients with T2 GB cancer are shown in **Table 8**.[16,116,155,156,163,191,193,195–197] Patients with T2 GB cancer, which are also often discovered incidentally at the time of cholecystectomy for presumed benign disease, are not thought to be cured by simple cholecystectomy, as the subserosal plane of dissection has been shown to be involved with tumor.[156] Accordingly, this group of patients is most likely to benefit from extended cholecystectomy. Long-term survival is generally achieved in 60 - 100% for patients undergoing an extended resection compared to less than 50% survival in patients undergoing simple cholecystectomy. Further, at least one-third of all patients with T2 disease demonstrate nodal metastases,[16,198] highlighting the importance of a thorough regional lymphadenectomy for potentially therapeutic and certainly diagnostic purposes.

OUTCOMES IN PATIENTS WITH T3 AND T4 GB CANCER

The results of selected modern series of patients with T3/T4 GB cancer are shown in **Table 9**.[16,145,155,163,168,175,177,190,194,196,197,199] The most controversial aspect in the care of a patient with GB cancer is the role of surgical resection in patients with advanced (T3 and greater) tumors, either suspected based on preoperative imaging in the new patient, or discovered intra- or postoperatively in the patient taken to the operating room for presumed benign disease. Historically, these patients have extremely poor survival, and surgery was thought to be futile. However, several case series have documented improved survival with surgical resection in highly selected patients. Typically, this improvement in survival has been found in Asian series, possibly due to the more extensive use of radical surgical procedures, including biliary and vascular resections and reconstructions,[145,191,200] although more recent Western series have shown similar findings.[16,173] It is also important to note that most 3- and 5- year survival rates in the majority of reported series (**Table 9**) are identical, indicating that

Table 8: Survival after resection of T2 gallbladder cancer from select modern series.

Reference	Patients	Treatment	5-year OS (%)
Shirai, 1992 [191]	35 10	SC EC	41^ 90^
Yamaguchi, 1992 [156]	25	100% SC	36
Oertli, 1993 [116]	17	100% SC	24
Fong, 2000 [16]	16 37	SC EC	19^ 61^
Ouchi, 2002* [155]	48 153	SC EC#	70 for all patients$
Toyonaga, 2003 [193]	25 18	SC EC	65^ 38^
Suzuki, 2004 [195]	20	100% EC	77
Foster, 2007 [196]	10 9	SC EC	38^ 78^
Kang, 2007 [163]	19 33	SC EC	56^ 75^
Goetze, 2010* [197]	161 139	SC EC	25^ 41^

* Multi-institutional series. # One patient had EC + extended right hepatic resection. $ Trend toward improved survival with EC (P = 0.051). ^ Statistically significant difference (P ≤ 0.05). EC = extended cholecystectomy, NR = not reported, NS = not specified, OS = overall survival, SC = simple cholecystectomy.

most recurrences occur early and disease-free survival at 3 years strongly predicts long-term cure.

Clearly, the majority of patients with T3/T4 GB cancer have metastatic disease on presentation and surgery is rarely curative. However, in the patient in whom metastatic disease is not found on thorough preoperative workup, including diagnostic laparoscopy, radical surgery offers the only chance of cure. Thus, in the fit patient, we recommend attempted surgical resection. It should also be stressed that patients with lymph node metastases outside of the hepatoduodenal ligament should not undergo resection.

SIGNIFICANCE OF PRESENTATION OF GB CANCER DISCOVERED INCIDENTALLY AFTER CHOLECYSTECTOMY

Due to the aforementioned poor outcomes of patients presenting with GB cancer, the notion of re-exploration after prior cholecystectomy has been questioned. Many felt that prior surgery was either a contraindication to secondary exploration or, at the very least, portended a worse prognosis. A review of 410 patients with GB cancer at our institution, 248 of whom presented after prior operation elsewhere, demonstrated no differences in operative morbidity, mortality, and overall survival. Only resectability and stage were independent predictors of long term survival, irrespective of presentation status.[16] Further, patterns of recurrence were similar among patients presenting after prior operation elsewhere compared to those undergoing primary operation at our institution, indicating that prior operation does not predict poor outcome, as has been suggested based on the notion of tumor spillage during the initial operation. Similar findings have been reported by other investigators,[159,181,201,202] supporting re-exploration for patients with GB cancer found incidentally without evidence for metastatic disease on complete clinical staging.

SIGNIFICANCE OF POSITIVE LYMPH NODES

A recent review of the German Society of Surgery registry of 439 resected cases of GB cancer demonstrated that long-term survival after resection for all stages of GB cancer was only achievable with a complete surgical resection of the gallbladder bed combined with dissection of the lymph nodes of the hepatoduodenal ligament.[197] Similar results have been found in other large registry series, such as the SEER database.[178] As was discussed previously, among 104 patients with GB cancer at our institution, T and N stage represent the strongest predictors out outcome [175] and is illustrated in **Figure 7**. Taken together, these data suggest that positive lymph nodes, along with initial T stage, are the major determinants of survival after potentially curative resection for GB cancer.

Table 9: Survival after resection of T3 and T4 gallbladder cancer from select modern series.

Reference	Patients	Stage	3-year OS (%)	5-year OS (%)
Ogura, 1991* [190]	453	IV	18	8
Matsumoto, 1992 [177]	8 27	III IV	38# 25#	NR
Onoyama, 1995 [145]	12 14	III IV	44^ 8	44^ 8^
Bartlett, 1996 [168]	8 7	III IV	63^ 25^	63^ 25^
Wakabayashi, 2004 [199]	8 13	III IV	83^ 46^	83^ 46^
Fong, 2000 [16]	58	III/IV	28	28
Ouchi, 2002$ [155]	40 11	III IV	NR	20^ 0^
Foster, 2007 [196]	4	III	NR	25
Kang, 2007 [163]	26	III	NR	15
D'Angelica, 2009 [175]	63	III/IV	NR	25
Goetze, 2010 [197]	46	III	NR	17
Shindoh, 2015*[194]	131	III	34.1	26.3

* Multi-institutional series. $ All diagnosed after laparoscopic cholecystectomy. # No statistically significant difference (P > 0.05). ^ Statistically significant difference (P ≤ 0.05). NR: not reported, OS: overall survival.

SIGNIFICANCE OF JAUNDICE ON PRESENTATION

The clinical presentation of jaundice with a diagnosis of or suspicion for GB cancer is an ominous sign, as it suggests tumor involvement of the porta hepatis. In 240 patients presenting with GB cancer at our institution, 82 (34%) were found to be jaundiced. These patients were more likely to have advanced stage disease. Only 6 patients (7%) were resected with curative intent, and only 4 of these 6 had negative surgical margins, which differed significantly from the 89% negative margin rate in the resected non-jaundiced patients.[117] The median disease-specific survival in patients presenting with jaundice was 6 months, which was significantly worse than the 16-month disease-specific survival in the non-jaundiced group (P<0.0001) and there were no disease-free survivors at 2 years in the jaundiced group. Thus, undertaking resection for GB cancer in the jaundiced patient should be done with the expectation of finding incurable disease. Rarely, the cause of jaundice may be from an impacted stone in the CBD or a small cancer at the origin of the cystic duct or infundibulum of the GB, in which case a complete resection could be achieved. The general poor prognosis of these patients is generally attributable to extensive lymphatic metastases and diffuse biliary involvement with tumor. Attention should be paid to a complete preoperative workup and consideration of palliative strategies to relieve jaundice.

ADJUVANT THERAPY

The high rate of recurrence, generally systemic, after curative resection for GB cancer makes adjuvant therapy a rational approach. At our institution, 85% of recurrences included distant sites as part of the recurrence pattern.[203] Currently, however, there are no proven regimens that have been shown to affect survival.[204,205] Due to the rarity of gallbladder cancer, there are limited prospective randomized studies assessing adjuvant therapy. There is only a single phase III randomized clinical trial evaluating adjuvant chemotherapy in resectable gallbladder cancer, in which complete surgical resection with or without adjuvant mitomycin C and 5-FU were compared. The treatment group had improved 5-year overall (26% versus 14.4%) and disease-free (20.3% versus 11.6%) survival.[206] However, this trial was limited by a small sample size (140 patients with GB cancer as a subset analysis of a larger trial) and the inclusion of patients with incomplete (R1 and R2) resections; thus, this adjuvant regimen has not gained favor amongst most oncologists. Subgroup analysis demonstrated that patients who underwent an R0 resection had no survival advantage with adjuvant therapy.

A recent SEER database analysis of 4,000 patients with GB cancer, found a survival benefit for the use of adjuvant radiotherapy in patients with node-positive or ≥ T2 stage (15 months versus 8 months), which remained significant on multivariable analysis (HR = 1.46, 95% CI 1.07-1.98, P=0.014).[207] However, it is difficult to draw meaningful conclusions from a large database trial studying the use of a local therapy for a disease in which survival is dictated by systemic spread.

At our institution, there were no differences in overall survival in 123 of 435 patients undergoing curative surgical resection with (n=24) or without (n=99) adjuvant therapy (16/24 chemoradiation alone, 8/24 chemotherapy alone; **Figure 6**).[89] However, these findings must be taken in the context of the fact that patients treated with adjuvant therapy had higher rates of positive lymph nodes, incomplete (R1 and R2) resections, and had higher stage disease.

Given that there is no standard of care, much of the current therapy is guided by extrapolating results from the metastatic setting, which will be discussed below. Our current practice is to offer all patients with resected GB cancer a consultation with a medical oncologist for consideration of gemcitabine-based or fluorpyrimidine-based chemotherapy, with or without concurrent radiation depending on nodal status, or inclusion in a clinical trial.[180] For all but the earliest disease (T1), the high rates of recurrence compared with the limited toxicity of these regimens, argues for some form of systemic adjuvant treatment.

PALLIATIVE MANAGEMENT

The majority of patients with GB cancer present with advanced, incurable disease and many are not candidates for surgical resection. In these patients, the primary objective should be alleviation of symptoms related to the patients' incurable GB cancer. They often suffer from symptomatic jaundice, pain, and gastrointestinal obstruction. Efforts should also be made to prevent serious complications such as cholangitis. For symptomatic obstructive jaundice or gastrointestinal obstruction, endoscopic or percutaneous interventions are the preferred approach to palliation in order to minimize morbidity.[84,208–210] Of note, these patients have very high complication rates after such interventions, which argues for these procedures to only be performed in symptomatic patients. A prospective study from our institution of 109 patients undergoing percutaneous biliary drainage for malignant obstruction demonstrated a 58% rate of major complication with two procedure-related deaths.[211] There was 10% and 28% mortality at 4 and 8 weeks post-procedure, respectively. These procedures were found to successfully alleviate pruritus (i.e. symptomatic jaundice), but have a high risk

of morbidity and mortality, arguing against routine use for asymptomatic biliary obstruction. In some cases, though, these minimally invasive approaches may not be possible and therefore palliative surgery may be necessary. Symptomatic obstructive jaundice due to biliary obstruction can be alleviated with surgical bypass to segment 3 of the liver. This has been shown to be an effective strategy in a series of 41 consecutive segment 3 bypass for patients with advanced GB cancer with a 87% success rate with 12% mortality and 51% morbidity rate having been reported.[2,12] Intestinal bypass should be performed only in patients who have symptomatic obstruction. Endoscopic stenting of the gastrointestinal tract, or percutaneous feeding and/or drainage tube insertion should be favored over surgical bypass. It is important to stress that patients with advanced GB cancer resulting in obstructive symptoms have a very short life expectancy, measured in days-to-weeks. Thus, treatment should be performed at symptoms, and not laboratory and radiographic findings.

As in the adjuvant setting, palliative chemotherapy and radiation therapy offer little benefit in GB cancer. Chemotherapy has shown poor response rates of 10-20%.[213] A phase III randomized controlled trial of 410 patients with locally advanced or metastatic biliary tract cancers showed improved overall survival (11.7 months versus 8.1 months) in patients treated with gemcitabine and cisplatin versus gemcitabine alone, respectively. Within this study, GB cancer patients (n=149) who received gemcitabine and cisplatin had superior survival and were 39% less likely to die than those treated with gemcitabine alone (hazard ratio 0.61, 95% confidence interval: 0.42-0.89).[214] Further, improved overall survival has been reported in unresectable gallbladder cancer patients treated with gemcitabine and oxaliplatin compared to conservative therapy or treatment with 5-fluorouracil and folinic acid.[215] The NCCN guidelines recommend gemcitabine and cisplatin for first line chemotherapy in advanced or metastatic biliary cancers, although other gemcitabine or fluoropyrimidine-based regimens may be used. Additionally, chemoradiation may be considered, however there is limited clinical trial data to show definitive benefit or specific regimens.

FOLLOW-UP

Due to the fact that there are no effective medical or surgical treatments for recurrent disease, there is little rationale and no data to support aggressive surveillance following resection of GB cancer. However, for consideration of novel, and potentially beneficial, clinical trials or adjuvant treatments, we generally follow-up patients every 4 - 6 months for two years, and annually thereafter, recognizing that that majority of recurrences occur early.

FINAL CONSIDERATIONS

Our institutional treatment recommendations for the workup, treatment, and follow-up of patients with GB cancer are presented in **figures 8** to **11**. Although the overall picture of GB cancer is poor, significant advances have been made since the nihilistic view from Dr. Alfred Blalock, who said in 1924 that "in malignancy of the GB, when a diagnosis can be made without exploration, no operation should be performed, inasmuch as it only shortens the patient's life".[216] Localized GB cancer can be cured with an extended resection. However, if not caught at an early stage, such as an incidental finding of GB cancer after laparoscopic cholecystectomy for presumed benign disease, GB cancer is rarely curable.

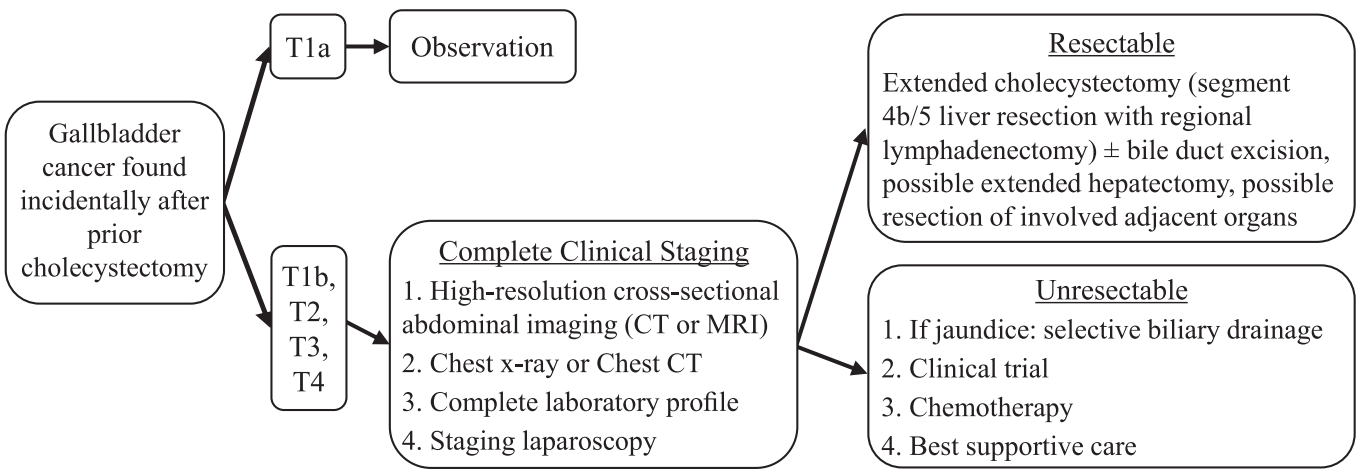


Figure 8. Memorial Sloan-Kettering Cancer Center (MSKCC) treatment scheme for GB cancer found incidentally after prior cholecystectomy. Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging.

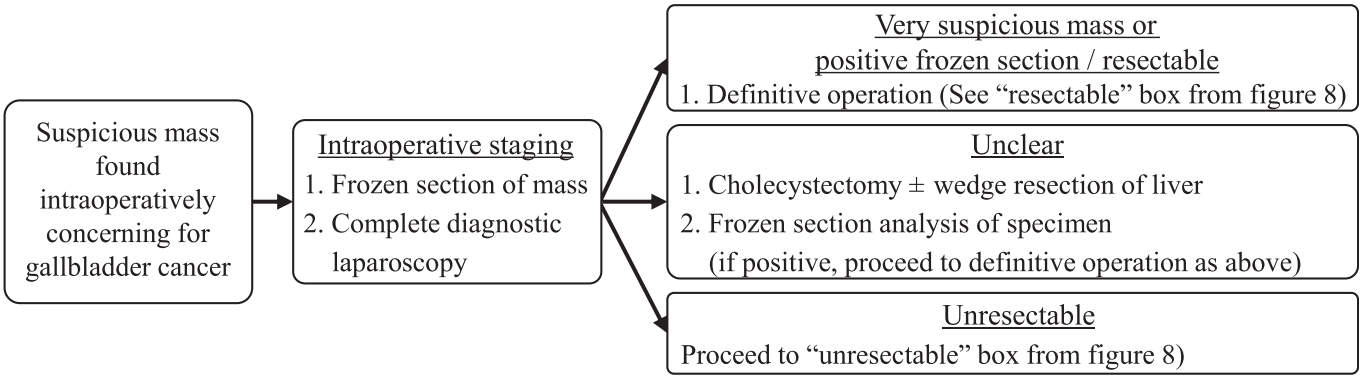


Figure 9. Memorial Sloan-Kettering Cancer Center (MSKCC) treatment scheme for a suspicious mass concerning for GB cancer found intraoperatively.

Simple cholecystectomy is curative for T1a lesions. However, for T1b - T4 lesions with no evidence of metastatic disease, more extensive surgery is required for potential cure. The proper operation to treat GB cancer has been thoroughly discussed and involves a liver resection to encompass the tumor with a negative margin. This usually involves a resection of parts of segments 4b and 5; however, if the tumor dictates further resection to achieve tumor clearance, major hepatectomy and/or CBD resection and reconstruction may be required and are justified. Any such operation should also include a complete regional lymphadenectomy, for potential therapeutic and certain diagnostic/prognostic benefit. Lymph node disease outside of the described regional lymphadenectomy is considered metastatic disease and precludes further surgical resection. More advanced tumors should be approached with the expectation to find occult metastatic or locally advanced and unresectable disease. Every effort should be made to select only those patients who will benefit from extensive surgery for exploration, which includes the use of high-resolution preoperative imaging and staging laparoscopy.

There are no proven systemic treatments for GB cancer. Every effort should be made to refer patients with metastatic or unresectable disease and patients' status-post surgical resection to a medical oncologist for discussion of novel agents/regimens, ideally in the setting of a clinical trial. The surgeon's role in the management of such patients is to facilitate palliative treatments to improve their quality of life, such as endoscopic biliary and gastric outlet stenting.

Due to the advanced nature of GB cancer on presentation, research efforts should be focused on the earlier detection of biliary malignancies and the development of effective systemic agents. In the past several decades, we have shown the ability to safely perform resections for localized GB cancer with low rates of morbidity and mortality and excellent long-term survival. What we desperately need are ways to diagnose a larger portion of GB cancer at such early, curable stages and to develop effective systemic therapy to decrease

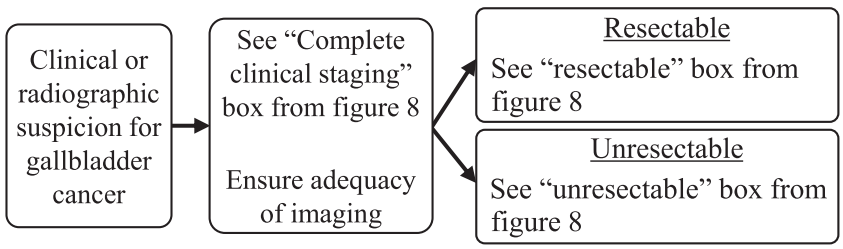


Figure 10. Memorial Sloan-Kettering Cancer Center (MSKCC) treatment scheme for clinical or radiographic findings concerning for GB cancer.

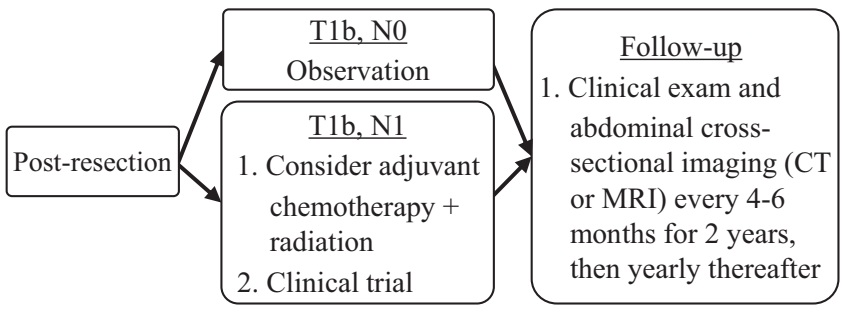


Figure 11. Memorial Sloan-Kettering Cancer Center (MSKCC) treatment scheme for adjuvant therapy and follow-up of patients after resection for GB cancer clinical or radiographic findings concerning for GB cancer.

the rate of recurrence after such operations. As GB cancer is an overall rare malignancy, it is not realistic to screen entire (or even high risk) populations. However, better education to consider the diagnosis in patients presenting with signs and symptoms of GB cancer may improve the detection of earlier stages of disease.

SUGGESTED READING

Fong, Y., Jarnagin, W. & Blumgart, L. H. Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann. Surg.* **232**, 557–569 (2000).

An analysis of 410 patients presenting with gallbladder cancer to a single institution over a 14-year period demonstrating that radical resection can provide long-term survival, even for large tumors with liver invasion. Importantly, the authors showed that long-term survival can be achieved for patients presenting after prior non-curative surgical exploration.

Ito, H. et al. Polypoid lesions of the gallbladder: diagnosis and followup. J. Am. Coll. Surg. **208**, 570–575 (2009).

An analysis of 417 patients with polypoid lesions of the gallbladder (GB) demonstrating the low (10%) rate of neoplastic polyps/adenomas and the finding of in situ cancer in one patient. This establishes the routine of observation of patients with sub-centimeter GB polyps.

Dixon, E. *et al.* An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. *Ann. Surg.* **241**, 385–394 (2005).

An analysis of 104 cases of resected gallbladder cancer from a single institution demonstrating the independent predictive value of T stage, N stage, histologic differentiation, and common bile duct involvement on disease-specific survival in GB cancer.

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17 Other Malignant Primary Tumors of the Liver

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- *The most common malignant hepatic tumor is by far hepatocellular carcinoma, followed by intrahepatic cholangiocarcinoma. However, other primary malignancies can occur and require specific approaches.*
- *Cystadenocarcinoma is a cystic tumor that usually develops from hepatic biliary cystadenoma. In both cases, radical surgical resection is the treatment of choice.*
- *Primary hepatic lymphomas are very rare (contrary to the frequent secondary involvement of the liver in disseminated non-Hodgkin lymphoma) and frequently associated with hepatitis C virus infection. Chemotherapy is efficient for most tumors and surgical resection indicated for complete resection of limited tumors or to reduce tumor burden before systemic therapy.*
- *Most cases of hepatoblastoma occur in childhood. Prognosis in adults is much poorer due to late diagnosis. Treatment is based on complete surgical resection.*
- *Hepatic epithelioid hemangioendothelioma is a rare vascular tumor with variable degrees of aggressiveness. Surgical resection (including liver transplantation) is the best approach when no extrahepatic involvement is present.*
- *Angiosarcoma, the most common primary hepatic sarcoma, represents up to 2% of primary liver malignancies, occurs more frequently in aged patients, and carries a very poor prognosis. Surgical resection is the best option in resectable cases, although recurrence is very common. Chemotherapy and trans-arterial therapy are used alone (to prevent bleeding and avoid tumor growth) or in combination with surgery.*

INTRODUCTION

Although hepatocellular carcinoma and cholangiocarcinoma comprise the majority of malignant primary hepatic tumors, a variety of less common primary hepatic malignancies can occur. Treatment and outcomes of uncommon hepatic tumors remain quite controversial. It is important to understand these conditions in order to recognize them and guide adequate management. In this chapter, we will review key topics and present current data about the following primary hepatic malignancies: cystadenocarcinoma, primary hepatic lymphoma, hepatoblastoma, hepatic epithelioid hemangioendothelioma, angiosarcoma, and other less common hepatic sarcomas.

CYSTADENOCARCINOMA

Biliary cystadenoma (BCA) and cystadenocarcinoma (BCAC) are rare cystic neoplasms, classified as epithelial tumors of the liver, which usually arise in the liver or, less frequently, in the extrahepatic bile ducts or the gallbladder. They are estimated to comprise approximately 5% of liver non-parasitic cysts.[1]

The estimated incidence of biliary BCAC is less than 1% of primary liver tumors.[2] Since the first report by Willis[3] in 1943, more than 100 cases have been published in the global literature.[4] The pathogenesis of biliary cystadenocarcinoma remains controversial and the only known predisposing factor for BCAC development is BCA,[4,5] which has a potential malignant transformation of 25%.[6] Most BCAC has occurred

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in women (60%), and at a mean age of 56 years.[4]

BCAC consists of a similar biliocyte-derived epithelial cell population which has atypical and, at least in some cases, visible invasive growth. The biliocyte origin of BCAC is underlined by the expression of cytokeratin 19, and is thought to originate from smaller ducts in the liver and from periductal glands in extrahepatic ducts. This tumor may develop large masses; the size of tumors ranges from 1.2 to 40 cm.[4,7] BCAC can be histologically classified into three groups: 1) primary malignant tumor originating from the intrahepatic bile duct; 2) cancer developing from an intrahepatic biliary BCA; and 3) cancer developing from congenital intrahepatic biliary malformation. Concerning adjacent invasion, tumor growth is confined to cysts in 48% of cases, whereas invasive extension into the adjacent liver or neighboring organs can be seen in 52% of cases.[4] Based on detectable invasion, two prognostic groups of BCAC (non-invasive and invasive) have been proposed.[8] Although histochemical and immunohistochemical techniques have not revealed any difference between the two groups, there is a significant difference in prognosis.

Clinical manifestations are variable and non-specific; the most common symptoms include abdominal pain, dyspepsia, anorexia, nausea, vomiting, and, occasionally, jaundice as a result of progressive displacement of the liver parenchyma or major bile duct compression by the neoplasm. Although uncommon as a presenting symptom, jaundice is the most common symptom of presentation in extrahepatic biliary cystadenocarcinoma. Less common symptoms at initial presentation are weight loss, fever due to cyst superinfection and/or cholangitis, and ascites due to the development of portal hypertension. The majority of patients affected by BCAC have a palpable upper abdominal mass. Liver function tests (aminotransferase, alkaline phosphatase, gammaglutamyl transpeptidase, bilirubin) are altered in approximately 25% of patients.[4] While serum alpha-fetoprotein level is usually within normal limits, levels of carbohydrate antigens (CA125 and CA-19.9) and carcinoembryonic antigen (CEA) can be significantly elevated in 36% and 14% of patients, respectively.[4,9]

Typical BCA and BCAC imaging usually consists of a solitary, large, multilocular cystic lesion, with a thick fibrous capsule and internal septa. Though BCA has thinner septa and more regular walls than BCAC,[10] it is nearly impossible to distinguish one from the other. With this in mind, every diagnostic attempt should be made to discriminate these tumors from other lesions of the liver.[11] The absence of internal septa or papillary projections helps distinguish simple cysts from BCA and BCAC. In cases of hemorrhagic cysts, computed tomography (CT) or ultrasound scans are often not reliable in ruling out biliary cystic neoplasms, whereas magnetic resonance imaging (MRI) can detect high signals from clot formation (in both T1 and T2 weighted sequences) and permits differentiation of complicated cysts from BCAC.[12] In the presence of complicated or multiloculated hepatic cysts, a useful complementary tool is fine needle aspiration and analysis of intracystic fluid; atypical cells, mucinous material, and elevated levels of CEA and CA 19.9 in the cystic fluid have been observed both in BCA and BCAC, but not in hepatic simple cysts.[13] Nevertheless, intracystic fluid examination alone is not sensitive and specific enough to diagnose biliary cystic neoplasms, and should always be evaluated together with imaging.[11] Ultrasound finding of a large lesion with hypoechoic central area can make differential diagnosis between giant hemangioma and giant BCA or BCAC difficult. CT scan and MRI usually enable the correct diagnosis by showing an enhancing rim with centripetal filling, with sparing of the large central lacunar areas.[14] Occasionally, hepatocellular carcinoma and cholangiocarcinoma may present as a large hypodense and multiloculated mass on CT scans. In these cases, arterial phase enhancement and portal phase washing-out on dynamic CT are diagnostic.[15]

Once a diagnosis of biliary cystic neoplasm is made, a radical complete surgical resection should be performed not only in the case of BCAC, but due to its potential malignant degeneration, also in the case of BCA (**Figure 1**). Incomplete excision or enucleation of BCA or BCAC results in a higher rate of recurrence compared to radical resection (22% versus 5.5%, respectively).[4,12] If the tumor is confined to the liver, no further treatments are required. Chemotherapy and/or radiotherapy might be administered to patients who are not suitable for radical excision because of tumor recurrence or metastasis. Experience with liver transplantation for BCAC is limited to a single case report;[16] the patient died two months after transplantation due to aortic aneurysm rupture. However, because of the relatively benign course of BCAC, liver transplantation could be proposed in unresectable cases due to the degree of hepatic involvement.

PRIMARY HEPATIC LYMPHOMA

Primary hepatic lymphoma (PHL) is defined as a lymphoma confined to the liver, without lymphomatous involvement of the spleen, lymph nodes, bone marrow, or other lymphoid structures.[17]

Although liver involvement may be detected in up to 40% of patients at the time of diagnosis in disseminated non-Hodgkin lymphoma (NHL),[18] PHL is a rare entity; indeed, it constitutes 0.4% of cases of extra-nodal NHL, and only 0.016% of all cases of NHL.[19] Since the first report of primary hepatic lymphoma in 1965,[20] nearly 300 cases have been described in the literature.[21] PHL commonly presents at 55 years of age (range 5-87 years), with a male to female

ratio of 2.3:1.[22]

Though the pathogenesis of PHL is still unknown, previous observations pointed toward underlying immune abnormalities in some patients. Thus, PHL has been associated with systemic lupus erythematosus,[23] primary biliary cirrhosis,[24] immunosuppressant administration,[25] and AIDS.[26] In all of these situations, the possible inciting factor is the loss of T-cell surveillance and uninhibited B-cell proliferation.[22,26]

Recent reports have described an increased incidence of PHL in hepatitis C virus (HCV)-positive patients.[27,28] Possible explanations are: 1) HCV virus causes chronic B-cell stimulation, leading to polyclonal, and eventual monoclonal, B-cell expansion; 2) HCV may induce a chromosomal translocation, leading to bcl-2 overexpression and monoclonal IgH rearrangement;[29] and 3) HCV may produce alteration in the transcriptional regulation of genes like p21, p53 and H-ras by the viral core and/or NS5 proteins.[30,31] Another virus that has been associated with the pathogenesis of PHL in immunocompromised patients is Epstein-Barr virus (EBV), because of the deficient regulatory T-cell function, which normally limits B-cell proliferation due to EBV infection.

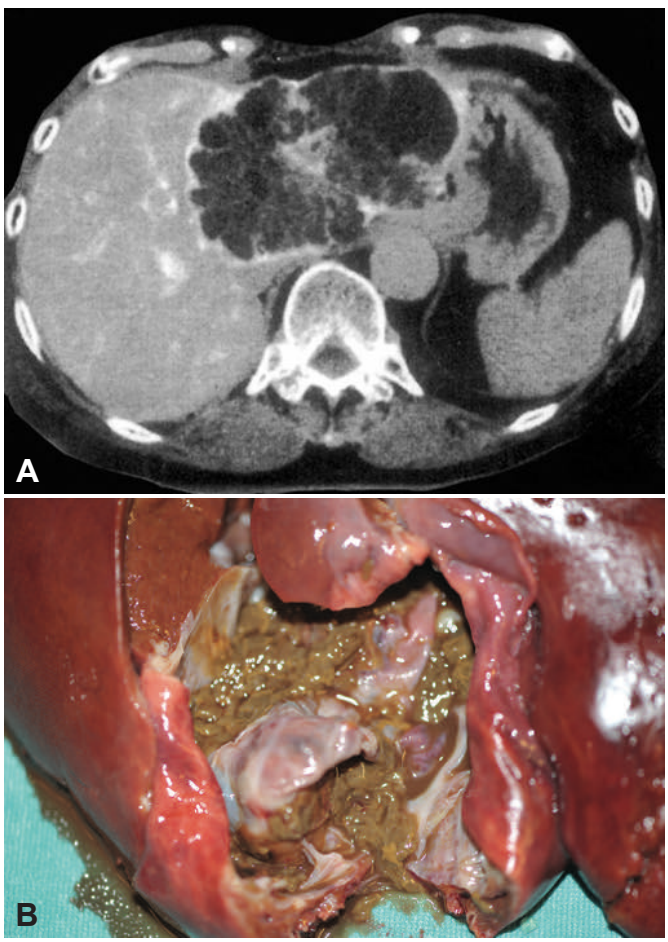


Figure 1. A) CT scan of a patient with cystoadenocarcinoma of the left hemiliver. **B**) Surgical specimen showing a solitary, multilocular cystic lesion, with a thick fibrous capsule, internal septa and inhomogeneous content.

PHL has been hypothesized to originate from Kupferr cells and transformed lymphocytes. The majority of cases of PHL are non-Hodgkin's type. Diffuse B-cell lymphoma is the most commonly encountered histological subtype; other histological types, described in less than 5% of cases, include diffuse mixed small and large cell, lymphoblastic, diffuse immunoblastic, diffuse histiocytic, mantle cell, Burkitt, and mucosa associated lymphoid tissue (MALT) lymphoma. T-cell PHL is less common; the subtypes are peripheral T-cell, anaplastic T-cell, and hepatosplenic T-cell lymphoma. Microscopically, the tumor cells may have a nodular or a diffuse growth pattern.[32]

According to Lei,[22] three criteria must be met to establish PHL diagnosis: 1) signs and symptoms related to liver involvement at presentation, including laboratory abnormalities and right upper quadrant mass or pain; 2) absence at presentation of palpable adenopathy and of distant lymphadenopathy on radiological studies; and 3) absence of leukemia on peripheral smear.

Clinical manifestations are variable and non-specific; abdominal pain or discomfort occurs as a presenting symptom in 39-70% of the cases.[22,26] Other symptoms include fever, night sweats, jaundice, ascites, anorexia, malaise, and weight loss. PHL rarely presents as acute liver failure (ALF).[33] Liver function tests are altered in 70% of patients.[21] Other frequent laboratory findings include abnormal lactate dehydrogenase, C-reactive protein, erythrocyte sedimentation rate, and β-2-microglobulin. Adverse prognostic factors at the time of diagnosis are patient age, bulky disease, elevated lactate dehydrogenase, and comorbidities such as chronic hepatitis, cirrhosis, HIV, and immunosuppressant use.[21]

PHL can present radiologically in three ways: i) as a solitary liver mass; ii) as multiple liver lesions; and iii) as a diffusely infiltrated liver. The most common appearance is as a single, well-defined lesion, and the least common is as diffuse infiltration (**Figure 2**).[21] Positron emission tomography (PET) scan with fluorodeoxyglucose is useful because the level of uptake correlates with disease activity and tumor proliferation, and it helps to exclude sites of disease outside the liver.[34,35] However, due to the non-specific clinical presentation, laboratory findings, and imaging, pathologic examination is the only way to provide diagnosis of PHL.

The pattern of liver involvement is the most important prognostic factor; in fact, 1- and 3-year survival is 70% and 57%, respectively, for patients with nodular growth, versus 38% and 18%, respectively, for patients with diffuse disease.[32] Treatment options for PHL include surgery, chemotherapy, radiation, or a varying combination of these. Indications for surgery include localized disease that can be completely excised or cases in which the tumor burden can be reduced

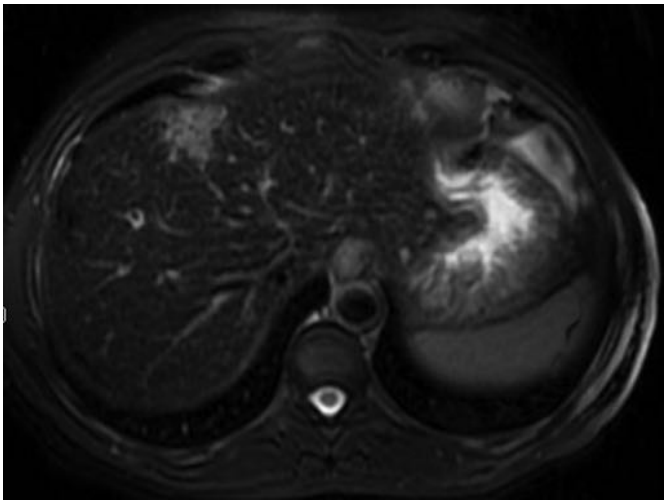


Figure 2. MRI of a patient with primary hepatic lymphoma. In the pre-contrast phase, a 4 cm area with irregular profiles, hyperintense in T2-weighted images, was displayed. Even after administration of hepato-specific contrast, the lesion was interpreted as an infiltrating form of hepatocellular carcinoma.

prior to adjuvant treatments. PHL is a chemosensitive tumor; for aggressive subtypes, anthracycline-based chemotherapy seems the most appropriate treatment, possibly reinforced by rituximab.[21] Because of the natural indolence of PHL rising in HCV positive patients,[33] the first therapeutic attempt that should be used is antiviral therapy with interferon plus ribavirin; this treatment is effective in eliminating IgH rearrangement, t(14;18), and translocation.[27,36] Patients presenting with ALF secondary to diffuse PHL have a poor prognosis.[37] While systemic lymphoma is a contraindication to liver transplantation because of the high risk of recurrence, this prohibition should not be applied to patients affected by PHL and decompensated liver failure.[33]

HEPATOBLASTOMA

Hepatoblastoma (HB) is the most common pediatric hepatic malignancy, accounting for 1% of all pediatric malignant tumors and for 80% of liver cancers in children younger than 15 years. The male/female ratio ranges from 1.2-3.6:1.[38] This tumor is rare in adults, and prognosis is much worse in adulthood than in childhood because diagnosis is usually late.[39,40]

HB derives from undifferentiated embryonal tissue, with 90% of cases clinically manifesting by the age of 4 years. An association with prematurity and low birth weight has been observed.[41] There are five histologic subtypes of HB: pure fetal, embryonal, mixed epithelial, mesenchymal-macrotrabecular, and small cell undifferentiated. The pure fetal type has the most favorable prognosis,[42] while the small cell undifferentiated type has the worst.[43]

HB has associations with some familial syndromes, such as Beckwith-Wiedemann syndrome, suggesting a role for genetic aberrations of chromosome 11,[44,45] hemihypertrophy, and familial adenomatous polyposis (FAP), suggesting a role for aberrations of chromosome 5.[46] Other biological markers may include Trisomy 2, 8, and 20, and translocation of the NOTCH2 gene on chromosome 1.[47]

At diagnosis, about 20% of patients show metastases, the lung being the most common site, followed by brain and bone. HB is often asymptomatic, and presentation with weight loss, anorexia, vomiting, and abdominal pain is usually associated with large liver mass and/or advanced disease.

The radiological identification of HB is based on abdominal ultrasound, CT scan, CT-angiography and/or MRI, which depict the extent and possible multicentricity of the tumor, and its relationship with Glissonean pedicles and hepatic veins. HB usually appears as multinodular masses with tendency for expansion, well demarcated from the normal liver but without a capsule. Vascular invasion occurs mainly into the hepatic veins, causing spreading to the lungs or, through the liver capsule, to contiguous tissues and organs.

Serum alpha-fetoprotein (AFP) level is elevated in 90% of children with HB, while lack of elevation of AFP at diagnosis is correlated with greater aggressiveness.[48] However, a liver biopsy is recommended in all patients with HB, especially to discriminate between this tumor and hepatocellular carcinoma.[49]

The traditional American staging system continues to be used by the Children's Oncology Group (COG) and depends upon extent of surgery at the time of initial diagnosis. Stage I indicates complete gross resection at diagnosis with clear margins; Stage II indicates complete gross resection at diagnosis with microscopic residual disease at the margins of resection; Stage III indicates biopsy only at diagnosis, or gross total resection with nodal involvement, or tumor spill, or incomplete resection with gross intrahepatic disease; Stage IV indicates metastatic disease at diagnosis.[50]

The traditional COG staging system has been criticized for being rather subjective, depending to a large extent on the surgeon rather than the tumor.[51,52] A risk-based stratification of treatment has been proposed as follows: low risk (Stage I/II without any unfavorable biological feature); intermediate risk (Stage III or Stage I/II with small cell undifferentiated histology); and high risk (Stage IV or Stage I/II/III with AFP < 100 ng/mL at diagnosis).

The International Society of Pediatric Oncology Liver Tumor Study Group (SIOPEL) has used two broad categories of risk stratification for several years: standard risk and high risk. Assignment to the standard or high-risk group depends upon PRETEXT (pretreatment extent of disease) group and biological variables. The PRETEXT classification of liver

tumors is shown in **Figure 3**.[53] Standard risk tumors are PRETEXT I, II, or III. SIOPEL high-risk tumors are defined as tumors involving all four hepatic sectors (PREVEXT IV), or any tumor with metastasis (m), invasion of the vena cava (v), invasion of the portal vein (p), or contiguous extrahepatic disease (e), and tumors that fail to express AFP (AFP < 100 ng/mL at diagnosis).

Even if unresectable at diagnosis, most HBs are unifocal and chemosensitive, especially to "platinum" derivative chemotherapeutic agents. With the routine addition of cisplatin to the chemotherapy in the late 1980s, overall survival in HB increased from 30% to 70%.[54,55] Because tumor cells may become resistant to chemotherapy after prolonged exposure, and because cumulative chemotherapy toxicity may be relevant, prolonged (more than 44 cycles) courses of neoadjuvant chemotherapy are discouraged by all study groups. Early referral for complex surgical planning may be indicated for large invasive tumors potentially requiring transplantation.[56]

Even patients presenting with metastatic disease are potentially curable with a combination of chemotherapy, complete tumor resection (by partial hepatectomy or transplantation), and pulmonary metastasectomy.

The role of pulmonary metastasectomy is not completely clear, but it seems that surgical removal of lung metastases may be more likely to cure patients with disease present at diagnosis but persistent after neoadjuvant therapy rather than patients with pulmonary relapse.[51]

COG study P9645 showed 3-year event-free survival of 90% for Stage I–II, 50% for Stage III, and 20% for Stage IV.[57] In the European SIOPEL II study, 3-year survival was 90% for standard risk tumors and 50% for high-risk tumors.[58] However, a newly designed preoperative chemotherapy regimen, alternating cycles of cisplatin and carboplatin plus doxorubicin (seven cycles preoperatively plus three cycles postoperatively) and delayed tumor resection, showed that a great proportion of tumors became resectable, and, in comparison with previously published results, led to an improved survival in patients with high-risk HB. Indeed, 3-year overall survival was 69% for the whole group.[59]

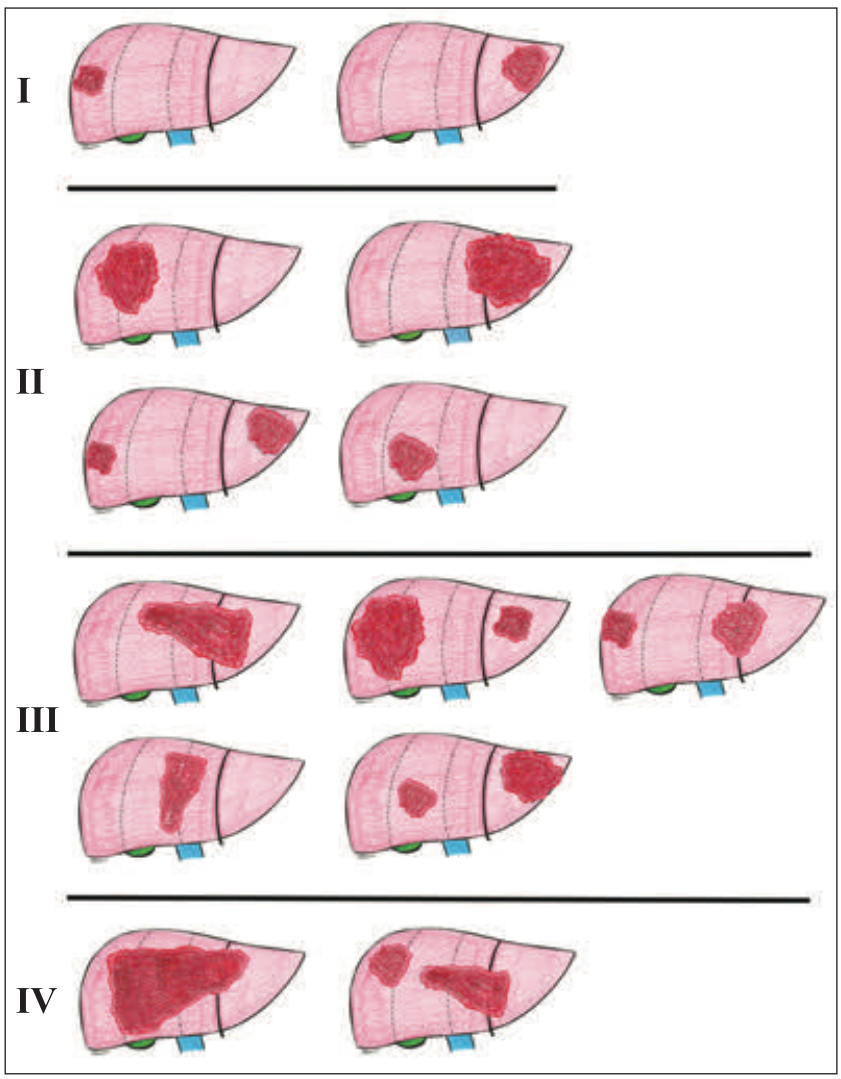


Figure 3. PRETEXT (pretreatment extent of disease) classification for hepatoblastoma. I: Three contiguous sectors of liver tumor free. II: Two contiguous sectors of liver tumor free. III: One sector of liver tumor free. IV: No sector of liver tumor free. +C: Caudate lobe involvement. +V: Invasion of all three hepatic veins. +P: Invasion of main portal vein. +E: Invasion of extrahepatic organ(s). +M: Distant metastatic disease.

Cure of HB demands a complete gross resection of the primary tumor at some point during the treatment regimen (**Figure 4**). Two main strategies exist. In the United States, tumor resection at diagnosis, whenever possible, has been advocated because i) toxicity of chemotherapy can be reduced; ii) some tumors may become resistant to prolonged chemotherapy; and iii) the highest survival rates have historically been observed in patients with initially resected tumors.[60] The strategy proposed with COG surgical guidelines advocates definitive surgical resection at diagnosis for localized, unifocal PRETEXT I and II tumors, followed by chemotherapy. In PRETEXT stages III or IV, multicentric tumors, portal or hepatic venous invasion, or pulmonary metastatic lesions, the chance of curative resection may be improved by neoadjuvant treatment and delayed primary resection.

Conversely, the SIOPEL study group discourages initial resection of HB in favor of neoadjuvant chemotherapy in all patients because chemotherapy often decreases tumor size and increases resectability, which offsets the toxicity of neoadjuvant chemotherapy.[56]

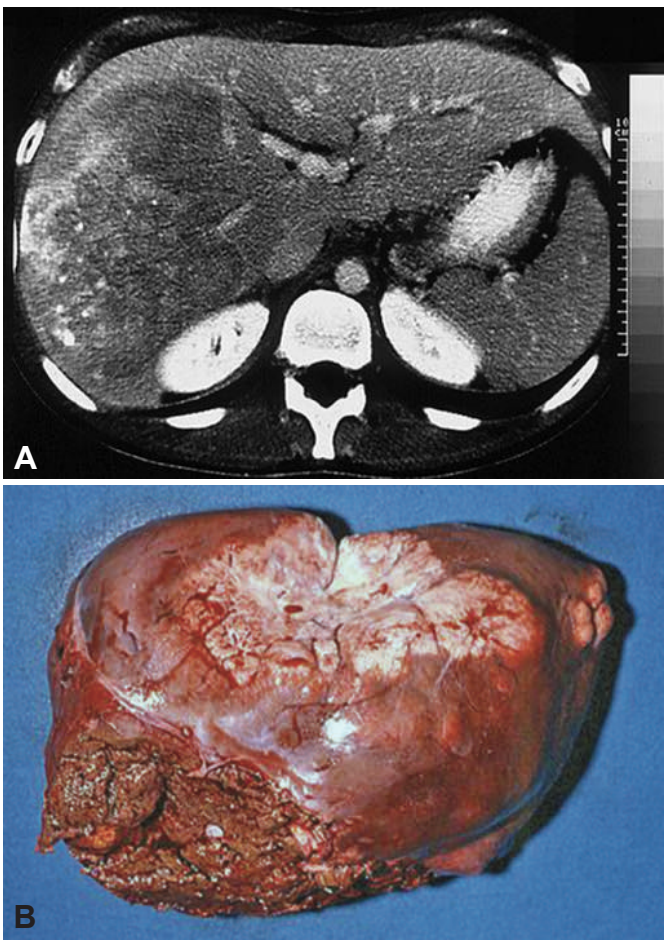


Figure 4. A) CT scan of a 16-year-old patient presenting with abdominal pain and a large mass in the right lobe of the liver. **B**) Surgical specimen (right hepatectomy). The final diagnosis was hepatoblastoma.

Growing experience with liver transplantation (LT) has shown that this is a good treatment option in children with unresectable primary tumors in the absence of metastatic disease after neoadjuvant chemotherapy and pulmonary metastasectomy, if necessary. In HBs invading all four sectors of the liver, LT has resulted in long-term disease-free survival rates of up to 80%.[61] Certainly, major resections would avoid the need for long-term immunosuppression linked to LT, but attempts at partial hepatectomy in children with major venous involvement or with extensive multifocal tumors should be discouraged.[62–64] This latter strategy should only be considered in experienced centers with easy access to LT.[64]

HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular neoplasm of the liver that arises from endothelial cells, with an estimated incidence of around 1 per million people.[65,66] This tumor is considered to have unpredictable malignant potential, with behavior between the benign epithelioid hemangioma and the highly aggressive epithelioid angiosarcoma.[65–69]

The median age of occurrence of HEHE is 40 years, with a female-to-male ratio of 3:2. It is rarely reported in patients younger than 15 years of age.[65,69]

The etiology of HEHE is unclear, there does not seem to be any relationship with a background of chronic liver disease. However, association with contraceptive drugs, exposure to vinyl chloride, or major hepatic trauma are assumed to play a role in the pathogenesis of HEHE.[65,67,69–71]

HEHE is classified into solitary nodular and diffuse nodular types, the latter probably being the natural evolution of former (**Figure 5**).[72,73] The typical appearance of HEHE is that of a large, slow growing lesion in peripheral location, with extension to the liver capsule with capsular retraction, a tendency for tumoral nodules to merge with each other.[74–77]

The lesions typically have ill-defined, infiltrative margins. The cross-section is often gray and white with hard consistency. The surrounding liver parenchyma is always normal in the solitary nodular type, but in the diffuse form, compensatory hepatic hypertrophy is a common complication and cirrhosis or focal nodular hyperplasia may develop.[66,67] Common tumor markers, such as AFP, carcinoembryonic antigen, and CA 19.9 are usually within normal ranges and are used only for ruling out other liver tumors.[65,69]

Histopathological studies are needed to diagnose HEHE.[65–67,69,70] Two main histological features typically characterize HEHE: i) the presence of dendritic and/or epithelioid cells with evidence of vascular differentiation

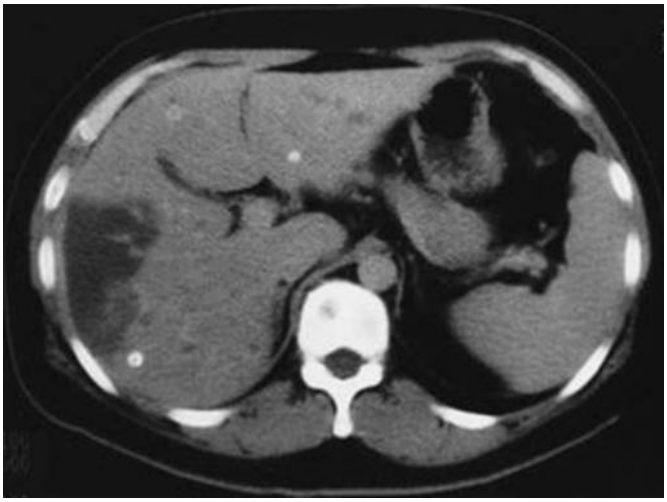


Figure 5. CT scan of a 40-year-old patient showing multiple, hypodense hepatic nodules with calcifications. The patient was finally diagnosed as having an epithelioid hemangioendothelioma.

Imaging techniques can help in the differentiation of HEHE from other tumors. Solitary or diffuse nodular lesions can be seen, with a predilection for peripheral subcapsular growth and nodular confluence. The "halo" sign after contrast enhancement on CT or MRI, presence of calcifications, and capsular retraction are other relatively frequent findings. HEHE is usually hypoechoic relative to adjacent hepatic parenchyma.[78] On CT scans, lesions appear hypodense, while on MRI they show low signal intensity on unenhanced T1-weighted sequences, and high intensity signals at the periphery of the lesions with hypodense center in the T2-weighted sequences intermediate to high signal intensity on T2W1.[79]

The clinical manifestations of HEHE are usually unspecific and variable, ranging from complete absence of symptoms (25%) to portal hypertension or hepatic failure.[65,69]

The course and prognosis of HEHE are also variable and unpredictable, ranging from a favorable disease with prolonged survival, even without therapy, to a rapidly progressive disease with fatal outcome. In some cases of no treatment, or after ortothopic liver transplantation (OLT) with positive nodes or vascular invasion, long-term survival has been reported.[67,69,80] Spontaneous regression of the lesions has also been reported.[67,81]

There are no clinical or histological criteria by which the evolution of the disease can be predicted. Extrahepatic spreading of the disease at the time of diagnosis was encountered in more than 35% of the patients and metastases occur more frequently in lungs, regional lymph nodes, peritoneum, bone, and spleen.[65]

The management of this uncommon liver tumor remains debated, especially for bilobar disease extending into the liver and in the case of extrahepatic spreading. Over the past two decades, different surgical and non-surgical treatment options have been proposed, including liver resection (LR), orthotopic liver transplantation (OLT), thermoablation, percutaneous ethanol injection therapy, immunotherapy, chemotherapy, radiotherapy, and hormone therapy;[65,67,74,82] however, due to the rarity of the disease and the usually natural indolent course relative to other hepatic malignancies, the effectiveness of curative strategy is currently difficult to define.[74]

Laparoscopy should probably be recommended to obtain a precise evaluation of the disease extension into the liver (especially with evaluation of small subcapsular lesions) in order to select patients suitable for LR in curative intent therapy.

Radical LR has been indicated as the treatment of choice whenever possible.[67] While this is probably true for solitary and/or unilobar disease, LR has a questionable role in diffuse nodular types, because unsatisfactory long-term outcome is usually achieved after major hepatectomies.[83]

OLT seems to be the treatment of choice for bilobar, multifocal HEHE, especially if there is no evidence of extrahepatic extension of the disease.[80] Recently, results of the largest reported multicenter transplant series, including 59 patients, were found to be excellent with 1-, 5-, and 10-year patient survival rates of 93%, 83%, and 72%, respectively.[84] In such series, microvascular invasion significantly reduced survival after OLT.[84] OLT should be considered even if a limited extrahepatic disease, such as small pulmonary metastases, is present.[83,84]

Interferon (IFN) has been used in combination with extended LR[85] and has been discussed prior to OLT as an option to reduce tumor growth.[67] Chemoembolization followed by OLT can also be effective in the management of HEHE.[86]

Furui et al.[73] reported five cases of diffuse HEHE without extrahepatic metastasis, treated with intra-arterial chemotherapy or transarterial chemoembolization using mitomycin and adriamycin or 5-fluorouracil, while Lauffer et al.[74] reported good results in eight patients treated with 5-fluorouracil by intrahepatic arterial infusion and six patients treated by transcatheter arterial embolization.

Other systemic chemotherapeutic agents, such as cyclophosphamide, adriamycin and thalidomide, have also been used to treat HEHE,[87–90] but overall results are still unclear and should be substantiated by larger studies. Bearing this in mind, the role of anti-angiogenic drugs such as anti-vascular endothelial growth factor-antibodies or rapamycine as immunosuppression after LT should be elucidated.

HEHE should be distinguished from infantile hepatic hemangioendothelioma, which is the most common vascular tumor of the liver in children,[91] representing 1–2% of all pediatric hepatic neoplasms. Infantile hepatic hemangioendotheliomas are vascular lesions that show a clinical course intermediate between a hemangioma and

an angiosarcoma. There are two types of infantile hepatic hemangioendothelioma. Type I is the most common vascular lesion in children, and typically these lesions will involute and regress.[91] Type II lesions are more aggressive and can metastasize. Histologically, type II lesions are more disorganized, and the differentiation between type II lesions and angiosarcomas can be difficult.[92]

Congestive heart failure is present in up to 50% of patients with this type of tumor and is a leading cause of death. Kasabach–Merrit syndrome, a consumptive coagulopathy, is common and can cause severe bleeding complications.[93] Hypothyroidism can be present, resulting from thyroid hormone catabolism by the tumor. Skin hemangiomas are present in 10–40% of patients with hepatic hemangioendotheliomas.[94,95]

Treatment of infantile hepatic hemangioendothelioma is necessary only if the lesion is symptomatic and cannot be managed conservatively while waiting for the expected involution to occur in type I tumors. Medical therapy for high output congestive heart failure, hypothyroidism, or coagulopathy has to be considered.

To accelerate the involution process, corticosteroids can be initially used, while IFN can be considered in the case of no response.[49] In patients with massive hemangioendotheliomas without congestive heart failure, chemotherapy and radiotherapy have been used with varying success.[96]

Hepatic artery embolization, hepatic artery ligation, and LR are reserved for patients requiring ventilatory support, or in symptomatic patients in whom pharmacotherapy is unsuccessful. LR is also indicated if the tumor is indistinguishable from a malignant mass on preoperative imaging.[49]

Type II infantile hemangioendotheliomas are difficult to identify preoperatively. If the diagnosis is correct, liver resection is indicated because of the potential progression similar to that of angiosarcomas. OLT should be considered in patients with infantile hepatic hemangioendothelioma if all other treatment strategies fail.[49,96]

Patients with type I infantile hepatic hemangioendothelioma have an excellent prognosis, especially in the case of spontaneous regression after the first year, with an expected long-term survival of 70%.[49,91] Negative prognostic factors are asymptomatic masses, congestive heart failure, jaundice, multiple tumor nodules, and the absence of cavernous differentiation on histology.[49]

ANGIOSARCOMA

Angiosarcoma is the most common primary sarcoma in the liver, accounting for 2% of primary hepatic tumors.[97–101] It is more frequent in patients aged 60–70 years, but can also occur in younger patients.[98,99,102] The male/female ratio is 4:1.[99]

In most patients, no risk factor for the appearance of hepatic angiosarcoma is documented.[98,99,103] However, in a minority of cases this tumor has been associated with environmental carcinogens (such as Thorotrast, vinyl chloride, and arsenic compounds)[104,105], hemochromatosis, use of anabolic steroids, chronic inflammation, and evolution of hematomas.[106–109]

Patients usually present with non-specific symptoms, including abdominal pain, weakness, fatigue, anorexia, and weight loss. Hematologic abnormalities, including microangiopathic haemolytic anemia and thrombocytopenia, are frequently associated.[99] Erythrocytes are thought to be traumatized in the poorly organized neoplastic vessels, and platelets may be trapped. Occasionally, this localized coagulopathy results in the development of systemic disseminated intravascular coagulation.[99,108] Tumor rupture with hemoperitoneum can be present and represents a dismal prognosis.[110]

Most patients have metastatic lesions at the time of presentation. The most common sites of metastases are the lung and the spleen.[99] It is sometimes difficult to determine whether the liver or the spleen is the site of the primary neoplasm.

Because of the vascularity of the lesion, diagnosis by means of liver biopsy has been reported as non-diagnostic and involves risk of hemorrhage.[99,111]

The gross appearance of angiosarcoma is characterized by the presence of necrosis and hemorrhage. Four types of growth patterns are described: multiple nodules (**Figure 6**), a large dominant mass, mixed patterns of a dominant mass with nodules, and a diffusely infiltrating micronodular tumor.[112,113]

Microscopically, angiosarcoma is characterized by spindle-shaped cells that form vascular channels, which show a wide spectrum of patterns, from excessively dilated sinusoidal or cavernous spaces resembling cavernous hemangioma to slit-like, freely anastomosing vascular channels.[98,112,113] These various vascular patterns are usually simultaneously present. Fibrosis and deposition of hemosiderin are frequently observed in solid portions of the tumor.[112,113]

In the case of Thorotrast exposure, on unenhanced CT scan tumors are hypoattenuating, but residual Thorotrast can appear as a hyperattenuating linear network.[100,104,105] In patients without Thorotrast exposure, angiosarcoma is hypoattenuating compared with the surrounding hepatic parenchyma on unenhanced CT scan.

On contrast-enhanced images, most lesions are hypoattenuating compared with normal liver tissue, but some lesions can be hyperattenuating.[114–116] In some cases, progressive centripetal enhancement similar to that of cavernous hemangioma has been described.[117] MR imaging shows the hemorrhagic, heterogeneous, and hypervascular nature of the tumor. On T1-weighted images, hemorrhage appears as irregular areas of high-signal intensity within

dominant masses, while on T2-weighted images hemorrhage is indicated by the presence of fluid-fluid levels. On T2-weighted images, a heterogeneous architecture, with focal areas of high intensity among variously shaped areas of low intensity, is demonstrated.[118] On dynamic contrast-enhanced MRI, tumors usually show heterogeneous enhancement on the arterial and portal phases. At delayed phase, a progressive enhancement of the lesion compared with that of the early phase is present.[118]

Especially on MRI, a differential diagnosis between angiosarcoma and hypervascular metastases, such as neuroendocrine tumors and hepatocellular carcinoma, is sometimes difficult. In contrast to hepatocellular carcinoma, however, angiosarcoma demonstrates continuing, progressive enhancement on delayed-phase images. Splenic metastases and absence of cirrhosis help in suggesting the presence of angiosarcoma instead of hepatocellular carcinoma.

When angiosarcoma appears as multiple nodular lesions on CT, most lesions are hypoattenuating, and foci of enhancement may be present, but they are clearly distinguishable from the nodular enhancement in benign hemangiomas.[118]

Despite being an aggressive tumor that generally carries a poor prognosis, angiosarcoma has an indication for surgical resection when completely removable (nearly 20% of cases), because this is the only definitive treatment that can improve survival.[110,119,120] However, even after complete resection recurrence is generally the rule, and median survival is 17 months.[118–120] Chemotherapy is often applied alone or in the adjuvant setting, but its effectiveness is still low, especially for all high-grade hepatic sarcomas.[121]

Transarterial embolization (TAE) and transarterial chemoembolization (TACE) have been suggested to control tumor growth and to prevent the risk of bleeding, which is rather high with such neoplasms compared to other hypervascular tumors.[118] These two strategies may be applied in cases of solitary masses, while the presence of multiple nodules seems to be a poor prognostic factor for tumor mass control.

Liver transplantation is rarely used to treat angiosarcoma (**Figure 6**). In an analysis of the US Israel Penn International Transplant Tumor Registry, six patients receiving live transplantation after treatment of angiosarcoma were identified. Recurrence was universal and all patients died due to recurrence, with a median survival of less than six months. Therefore, liver transplantation is a poor therapeutic choice for primary hepatic angiosarcoma.[122]



Figure 6. A and **B**) Surgical specimen of a 21-year-old woman initially presumed to have an epithelioid hemangioendothelioma. The tumor occupied the whole liver and the patient underwent liver transplantation, with a final diagnosis of angiosarcoma.

OTHER SARCOMAS

UNDIFFERENTIATED EMBRYONAL SARCOMA

Undifferentiated embryonal sarcoma of the liver (UESL) is the third-most common malignant tumor of the liver in childhood (**Figure 7**), accounting for about 9% to 15% of all hepatic malignancies.[123,124] However, it is a rare tumor and, since its first description in 1978,[123] only about 150 cases have been reported in the literature;[125] fewer than 70 cases of adult UESL have been also described.[126] UESL occurs mainly between five and 10 years of age, without gender predilection. There are no recognized genetic or syndromic abnormalities associated with UESL.

The histogenesis of UESL is still under debate. Microscopically, mesenchymal cells without any evidence of specific differentiation are observed. Tumor cells may be compactly or loosely arranged, with an abundant mucopolysaccaride matrix. Characteristic of this tumor are the globules of eosinophilic material, which are present both within the cytoplasm of the tumor cells and the intercellular matrix.[123] Tumor size often exceeds 10 cm.[127]

There are no specific clinical features; common presenting symptoms include abdominal mass and abdominal pain. Other complaints, such as fever, nausea, anorexia, diarrhea, malaise, or jaundice have been reported. Spontaneous

rupture of UESL, which can occur in rare cases, is an important complication affecting the prognosis and may be fatal.[128] Laboratory tests are usually nonspecific as well; mild leukocytosis, anemia, and elevated liver enzymes may be observed. Typically, the serum level of AFP is within normal limits and enables differentiation of UESL from hepatoblastoma and hepatocellular carcinoma.

Discrepancies in the appearance of the mass on ultrasound scans versus CT scans are the hallmark of UESL. In fact, UESL is characteristically isoechoic or hyperechoic on ultrasound, which confirms the solid nature of the tumor, while CT scan usually shows a hypodense cystic mass with water attenuation.[129] MRI localizes the lesion more accurately, better characterizes the tumor, and assists in surgical planning, detecting vascular invasion, biliary obstruction, or hilar adenopathy.[130]

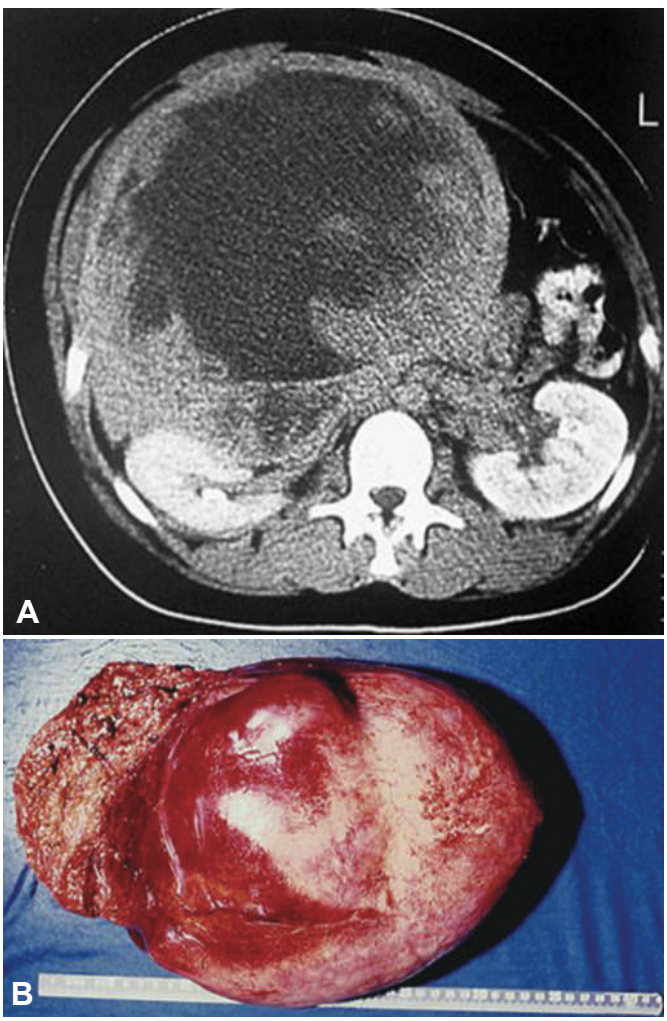


Figure 7. A) CT scan of a 15-year-old boy presenting with abdominal pain and fever. A large liver tumor (undifferentiated embryonal sarcoma) with cystic areas was detected. **B**) The patient underwent right hepatectomy and no tumor recurrence was detected after a 20-year follow-up.

Since multimodal treatment (surgical resection, neoadjuvant/adjuvant radiotherapy and chemotherapy) has been introduced, the prognosis of patients affected by UESL has improved considerably.[126,131] In particular, Bisogno et al.[131] reported that 70% of patients treated with multimodal therapy were alive at the end of follow-up (range 2-20 years), compared to 37% of patients treated with surgical intervention alone.[132] Limited data exists on the role of liver transplantation in children with UESL.[133] However, this option may be considered, after chemotherapy and in the absence of metastatic lesions, when complete surgical resection is not feasible.

RHABDOMYOSARCOMA

Biliary rhabdomyosarcoma (RMS) is a very rare tumor, accounting for 0.8% of all RMS and 1.3% of all liver tumors.[134] Since its first description in 1875,[135] at least 100 cases have been reported in the literature. Biliary RMS almost exclusively occurs in children under five years of age, with clear predominance of male patients; about 2% are present at birth. Noonan syndrome, Costello syndrome, and related disorders have been associated with an increased risk for RMS development.[136]

RMS arises from precursor cells for striated muscle. Though histological subtypes are embryonal, alveolar, botryoid, pleomorphic, and anaplastic, biliary RMS is of embryonal or botryoid types in 96% of cases.[137] It is found to be greater than 5 cm in the majority of the cases, and it arises from the common bile duct in about one half of cases. Other primary sites include the hepatic and cystic duct, intrahepatic bile ducts, and gallbladder, as well as the ampulla of Vater.

The most common presenting symptom is jaundice,[137] which may be accompanied by acholic stools and hepatomegaly, mimicking infectious hepatitis. Other symptoms are fever, abdominal discomfort, nausea, and vomiting. Liver function tests can be mildly altered. Favorable prognostic factors are patient's age < 10 years, tumor size < 5 cm, botryoid histology, and absence of distant metastases.

Possible findings on abdominal ultrasound are dilated bile ducts and a mass or stones in the affected biliary tract; CT scan and MRI are usually able to show a mass growing inside the biliary ducts.[138] Percutaneous transhepatic cholangiography permits biliary drainage in cases of obstructive jaundice and may be helpful in planning the surgical approach.

In the majority of cases, a complete and safe surgical resection is not feasible at the time of diagnosis, due to tumor size and involvement of nearby organs.[139] In addition, it is generally recognized that an initial aggressive surgery in patients with advanced RMS does not provide advantage in terms of outcome. For these reasons and because of RMS

radio- and chemo-sensitivity, some authors recommend surgical exploration only to confirm the diagnosis, making a biopsy of the tumor and determining the regional extent of the disease,[137] leaving surgical resection as a complementary procedure for eliminating residual disease after neoadjuvant treatment.[140,141]

LEIOMYOSARCOMA

Primary hepatic leiomyosarcoma (LMS) is a very rare mesenchymal tumor (**Figure 8**); since the first case reported in 1968,[142] nearly 70 cases have been published in the literature.[143] Hepatic LMS usually occurs in middle-aged patients, without gender predilection. Though hepatic LMS development is not associated with cirrhosis or other liver diseases, a relationship between this tumor and HIV infection or Epstein-Barr virus infection in immunocompromised patients has been reported.[144,145]

Hepatic LMS originates from smooth muscle cells of intrahepatic vascular structures, bile ducts,[146] or ligamentum teres.[147] Microscopically, the tumor is composed of intersecting bundles of elongated, spindle-shaped cells. Immunohistochemistry stains are positive for desmin, vimentin and smooth muscle actin, and negative for keratin, S-100 protein, and neuron-specific enolase.[148] LMS of the liver is generally large and located in the right lobe.[149]

The most common presentation symptom is right upper quadrant pain, associated with hepatomegaly. Other common complaints are weight loss, anorexia, epigastric fullness, jaundice, and ascites.[150] Tumors arising from the hepatic veins may lead to Budd-Chiari syndrome and have worse prognosis than those from other origins.[151] Liver function tests are variable and therefore not useful in diagnosis. Carcinoembryonic antigen and AFP are in the range of normality.

Primary hepatic LMS appears on CT scan as a large, well-defined, hypodense mass with internal and peripheral enhancement, occasionally displaying central necrosis or cystic appearance.[146,150] MRI shows a mass with homogeneous or heterogeneous hypointensity on T1-weighted images and hyperintensity on T2-weighted images.[143] Since most LMS detected in the liver are metastatic lesions from neoplasms developed in other sites, exclusion of extrahepatic lesions is mandatory to diagnose primary hepatic LMS.

Although surgery seems to be the only treatment that offers hope for long-term survival, the prognosis of patients affected by primary hepatic LMS is generally poor, with a mean survival that ranges from 10 months to three years.[147,148,150] Chemotherapy is the alternative treatment for inoperable patients; gemcitabine and gemcitabine-taxotere combinations are promising agents for the treatment of advanced LMS.[152] Given the high tumor recurrence rate and poor survival, liver transplantation is not recommended.[153]

MALIGNANT FIBROUS HISTIOCYTOMA

Although malignant fibrous histiocytoma (MFH) is one of the most common soft tissue sarcomas of the late adult life, primary hepatic localization is very rare. In fact, since its first description in 1985,[154] fewer than 40 cases have been described in the literature. Hepatic MFH usually occurs in the fifth and sixth decades of human life (mean age 58 years), with no sex predilection.[155]

MFH is composed of a mixture of cells with pleomorphic nuclei, resembling fibroblasts and histiocytes, arranged in a storiform pattern. According to the histopathological features, MFH has been categorized into storiform-pleomorphic, myxoid, inflammatory, giant cell and angiomatoid subtypes.

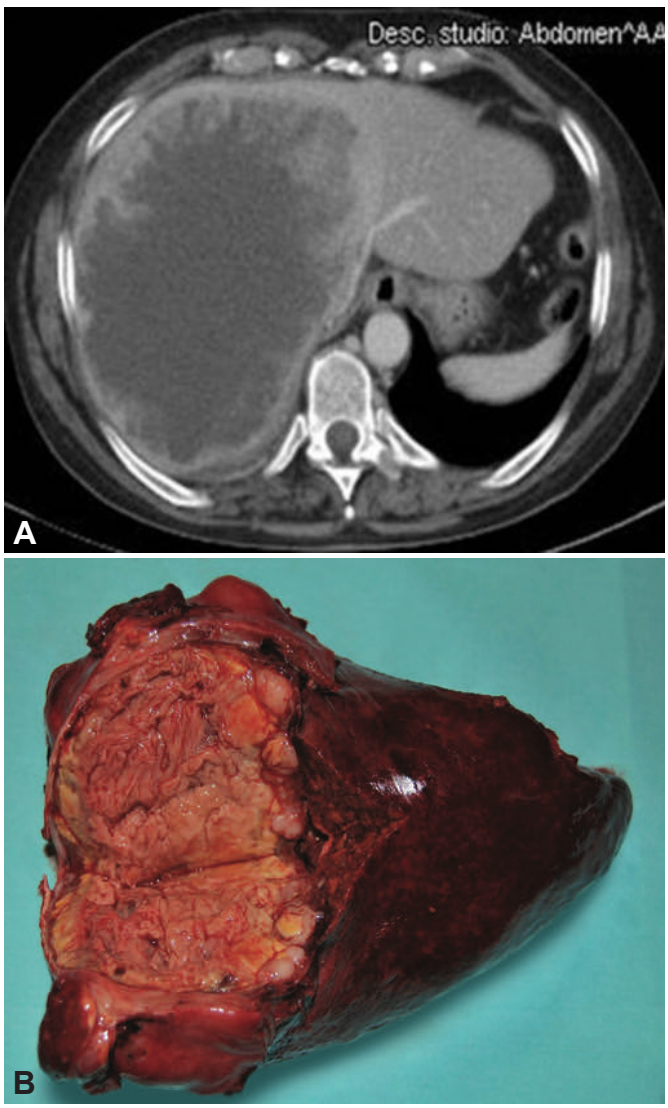


Figure 8. A) CT-scan of a 69-year-old woman showing a large, well--defined, hypodense mass with peripheral enhancement, displaying central necrosis. **B**) Surgical specimen (extended right hepatectomy) of the same patient. Final diagnosis was primary hepatic leiomyosarcoma.

The storiform-pleomorphic variant is the most common. Ezrin, a cytoskeleton linker protein, has been recently identified as a growth and metastasis regulator of soft tissue sarcoma, including MFH.[155,156] Ninety-one per cent of hepatic MFH tumors are large solitary lesions, with a median diameter of 12 cm.[155] They often involve adjacent organs at the time of diagnosis, without regional lymph node metastasis.

According to Li et al.,[155] diagnostic criteria to define primary hepatic MFH are: 1) solitary or multifocal liver lesion, without evidence of primary localization in any other part of the body; 2) histology compatible with the spectrum of MFH; 3) mesenchymal differentiation at immunohistochemical examination, without a well-defined cellular line of derivation; and 4) presence of fibroblast-like, histiocyte-like, or undifferentiated cells, with no evidence of any other well-differentiated cell type.

The clinical presentations include abdominal pain or discomfort and systemic symptoms, such as fever, malaise, anorexia, and weight loss. Negative prognostic factors are large tumor size, adjacent organ invasion, distant metastasis, and high ezrin expression score at the initial presentation.

Hepatic MFH usually appears hypoechoic on ultrasound, and hypodense on non-contrast CT scan; the presence of extensive necrosis may mimic a cystic tumor, while intratumoral hemorrhage can be confused with hematoma.[143] Differential diagnoses include sarcomatoid hepatocellular carcinoma,[157] cholangiocarcinoma, and other types of sarcoma, such as angiosarcoma and leiomyosarcoma.

Surgery is the only effective treatment for hepatic MFH confined to the liver, but the prognosis is poor; most patients die of tumor recurrence within one year after diagnosis, with a median survival of four months.[155] Ding et al. reported a 2-year overall survival rate of 60%, with half of the remaining patients suffering from local recurrence.[158] Chemotherapy and radiotherapy have been attempted, neither is effective.[159]

SUGGESTED READING

Läuffer, J. M. et al. Biliary cystadenocarcinoma of the liver: The need for complete resection. Eur. J. Cancer **34**, 1845–1851 (1998).

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Noronha, V., Shafi, N. Q., Obando, J. A. & Kummar, S. Primary non-Hodgkin's lymphoma of the liver. Crit. Rev. Oncol. Hematol. **53**, 199–207 (2005).

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18 Benign Solid Focal Lesions and Incidentalomas of the Liver

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- *Hemangioma (the most common benign solid hepatic tumor) and Focal Nodular Hyperplasia (FNH) seldom pose a clinical significant risk requiring a surgical procedure.*
- *Hepatic adenoma is a rare tumor that may cause significant morbidity from bleeding, rupture, or malignant transformation. It represents the most frequent indication for surgical intervention among solid benign hepatic tumors.*
- *Oral contraceptives have been associated with hepatic adenoma and FNH. Nonetheless this association is not clear for hepatic hemangiomas.*
- *Other benign solid tumors are of exceedingly low frequency. They are difficult to diagnose and exceptionally require surgical treatment.*
- *Despite most of hepatic incidentalomas in patients with and without known cancer are benign, some of them require follow-up or treatment and management of incidentalomas is challenging.*

INTRODUCTION

Focal lesions of the liver are detected with increasing incidence due to the frequent use and technical advances of imaging studies of the abdomen.

The technical improvements (mainly contrast and spatial resolution), associated to an increasing number of imaging examinations performed, lead to an increase in the detection of incidental findings (incidentalomas).

Benign focal lesions can originate from hepatocytes, bile duct epithelium, mesenchymal tissue, or a combination of these. Cystic diseases, the most common focal hepatic lesions, are discussed on chapters 19 (Non-Parasitic Cystic Diseases of the Liver) and 20 (Parasitic Hepatic Cysts).

The most frequent benign solid tumors of the liver are hemangioma, focal nodular hyperplasia (FNH), and adenoma. Also, inflammatory pseudotumor, peliosis hepatis, focal fatty infiltration, hamartoma, and other rare conditions can appear as focal solid lesions in imaging studies. (**Table 1**)

Table 1. Main benign liver tumors.

Origin		Tumor
Epithelial	Hepatocellular	Focal nodular hyperplasia Hepatocellular adenoma Regenerative nodules
	Biliary	Bile duct adenoma Biliary cystadenoma Biliary cyst
Mesenchymal	Endothelial	Hemangioma Hemangioendothelioma
	Mesothelial	Benign mesothelioma
	Adipocyte	Lipomatous tumors
Other		Biliary hamartoma

Hepatic hemangioma and FNH are more frequent than hepatic adenoma, but symptoms are uncommon for any

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of them. While hemangioma rarely presents diagnostic difficulties, differentiation between FNH and adenoma can be challenging.

In contrast to hemangioma and FNH, hepatic adenoma usually requires surgical resection due to the significant risk of morbidity from bleeding, rupture, or malignant transformation.

The presence of an underlying chronic liver disease (such as chronic hepatitis or cirrhosis) is uncommonly found in patients with benign hepatic lesions, and it should raise the suspicious of a malignant tumor.

This chapter encompass the main features on benign focal hepatic diseases and incidentalomas, including decisional algorithms and radiological examples of a diversity of focal hepatic lesions (**Figures 1** to **36**).

HEPATIC HEMANGIOMA

INTRODUCTION

Hepatic hemangioma is the most common benign solid focal lesion of the liver. It is found in 2% to 4% of the general population and up to 20% of necropsies.[1] It can be a single lesion (60% of cases) or multiple, ranging in size from some millimeters to many centimeters (more than 20 cm). Those with more than 5 cm are designated giant hemangiomas. Although hemangiomas can occur at all ages, they are diagnosed more frequently in individuals aged 30-50 years. Infantile hemangiomas, seen in 5-10% of children aged 1 year, typically regress during childhood.

The hepatic hemangioma is composed of masses of blood vessels that are atypical or irregular in arrangement and size, making the blood flow slower than in the normal hepatic parenchyma. Although uncertain, its etiology is probably a consequence of a congenital vascular malformation.

Despite the absence of a clear association with hormonal factors, steroids and estrogen (including pregnancy) can increase the size of an already existing hemangioma. In addition, hemangiomas occur more frequently in females, and symptoms are more likely in childbearing women.[2,3]

CLINICAL FEATURES

Hemangiomas of the liver are usually small and asymptomatic. They are most often discovered during imaging studies (mainly ultrasonography and computed tomography) performed for another reason. They will require a therapeutic intervention only exceptionally.

Despite the rarity of symptoms, pain or fullness may occur when large and/or multiple lesions exist. Up to 40% of patients with hemangiomas greater than 4 cm, and up to 90% of those with lesions greater than 10 cm, might have symptoms. However, even in the large hemangiomas, symptoms attributed to hepatic lesions can be due, in fact, to other gastrointestinal diseases, such as irritable bowel syndrome. Early satiety, nausea, and vomiting may occur when large lesions compress the stomach. Single large lesions are more likely to produce persistent pain, truly related to the hepatic hemangioma. Pain can occur due to thrombosis, infarction or hemorrhage into the lesion, or compression of adjacent tissues or organs. Globally, a third of hemangiomas will increase in size, specially single lesions.[4]

The physical examination is generally not remarkable. Rarely a hemangioma can present as an abdominal mass with or without an arterial bruit over the right upper quadrant. Other atypical presentations include cardiac failure (from massive arteriovenous shunting), jaundice (from compression of the bile ducts), gastrointestinal bleeding (from hemobilia), and fever of unknown origin.

Seldom, hemangiomas can occur in association with clinical syndromes. The Kasabach-Merritt syndrome is characterized by tumor bleeding, thrombocytopenia, and coagulopathy (due to intravascular coagulation). The Blumgart-Bornman-Terblanche syndrome is characterized by an inflammatory process with fever and abdominal pain. These syndromes can evoke minor and major complications and should be treated surgically in most of cases. The Osler-Rendu-Weber disease is characterized by numerous small hemangiomas on the face, nares, lips, tongue, oral mucosa, gastrointestinal tract, and liver. Also, in Klippel-Trenaunay-Weber syndrome, hepatic hemangiomas occur in association with congenital hemiatrophy and nevus flammeus, with or without hemimeganencephaly. Von Hippel-Lindau disease is marked by cerebellar and retinal angiomas, with lesions also in the liver and pancreas. Multiple hepatic hemangiomas have been reported in patients with systemic lupus erythematosus.[5]

Rupture, spontaneous or traumatic, is awfully atypical and can lead to acute hemorrhagic shock with upper abdominal pain. Reported spontaneous rupture occurred in lesions with a mean size of 11 cm. The overall mortality rate associated with rupture is 60-75%, with a 30 - 40% operative mortality rate in this situation.[6]

Hemangioma can be mistaken for other hypervascular lesions, including focal nodular hyperplasia, hepatic adenoma, hemangioendothelioma, metastasis, and hepatocellular carcinoma. Differentiation of each individual lesion is important as hemangioma and other lesions can coexist. Tumor markers, such as alpha-fetoprotein, CEA, CA19.9, are typically at normal levels. Their increase should raise the suspicious of a malignant condition. It is of note that malignant transformation of hemangioma has not been reported.

Hemangiomas are uncommon in cirrhotic livers, probably due to the fibrotic process.

IMAGING

The modalities that usually help in the diagnosis of hepatic hemangiomas include ultrasonography (US), dynamic contrast-enhanced computed tomography (CT) scanning, nuclear medicine studies using technetium-99m (^{99}Tc)-labeled red blood cells (RBC), magnetic resonance imaging (MRI), hepatic arteriography, and digital subtraction angiography. Some atypical hemangiomas may require multiple imaging tests due to patterns similar to other hypervascular hepatic lesions, such as hepatocellular carcinoma and certain metastases, especially from neuroendocrine tumors.

Ultrasonography

Hepatic hemangiomas are usually well circumscribed and uniformly hyperechogenic on conventional US (**Figure 5**), but their appearance can be variable. In large hemangiomas, heterogeneous areas occur within the hyperechoic mass. Changes of the hepatic parenchyma, such as diffuse steatosis, can make a typical hemangioma appear as a hypoechoic lesion.[7] Also, atypical features can include hypoechoic lesions with a thin hyperechoic rim or a thick rind and scalloped borders.[8] Color Doppler might improve specificity and sensitivity of US.

Contrast-enhanced ultrasonography (CEUS) provides data on blood flow and tissue perfusion. The accuracy of CEUS for the diagnosis of hepatic hemangioma is high (from 82% to 95%).[9–11]Hemangiomas show peripheral puddles and pools of enhancement that expand in a centripetal pattern during the portal phase. Later scans usually show a complete filled in lesion. The absence of complete enhancement might occur in large lesions due to central thrombosis or scarring. On the other hand, small lesion can present with complete and rapid centripetal enhancement during arterial phase.

Computed Tomography

Hemangiomas have characteristic dynamic features with the administration of contrast media. The typical triple phase CT with delayed imaging of a hepatic hemangioma shows: i) hypodense lesion on precontrast phase, ii) peripheral enhancement (ring or globular) of the lesion in arterial phase with hypodense center, iii) and progressive centripetal enhancement in portal phase and delayed images. The center of hemangioma may only become hyperdense in delayed images. The pattern of a peripheral, discontinuous, intense nodular enhancement during the arterial-dominant phase with progressive centripetal fill in on CT scans is considered pathognomonic for hemangiomas (**Figures 19** and **20**).

Wedge-shaped subcapsular or segmental perilesional enhancement may be noted adjacent to high-flow hemangiomas. These findings are possibly due to hemodynamic alterations in the liver.[12] Atypical features of hemangiomas include the presence of arterioportal shunts and capsular retraction.[13,14] Rarely, a centrifugal pattern of contrast enhancement is seen.[15]

On CT, such as on CEUS and MRI, small hemangiomas can show intense and uniform enhancement in arterial phase (**Figure 17**) and thus be mistaken for other hypervascular liver tumors such as hepatocellular carcinoma, FNH, adenoma, and hypervascular metastases.

Magnetic Resonance Imaging

MRI is a highly sensitive and specific method in the diagnosis of hepatic hemangioma. Hemangiomas appear as smooth, lobulated, homogeneous, sometimes septated, hypointense lesions on T1-weighted images. On T2-weighted images, they appear highly hyperintense relative to the liver. When gadolinium is used as an intravenous contrast agent, hemangiomas enhance in a similar fashion to that seen on dynamic CT, although the enhancement pattern is more easily depicted on MRI (**Figure 18**). Lesions of less than 2 cm may show a homogeneous enhancement on early phase images that persist on delayed images and can sometimes be indistinguishable from other hypervascular lesions. The sensitivity of MRI for detection of hepatic hemangioma is 90% to 100% and the accuracy is higher than 90%.[16]

Large hemangiomas may show cystic areas on MRI or CT as a result of hemorrhage or myxomatous degeneration. Exceedingly slow blood flow through the lesion can favor sedimentation of blood cells with the development of internal fluid levels.[17,18]

Nuclear Imaging

Planar scintigraphic studies using Tc-99m labeled red blood cells have an adequate accuracy in diagnosis of hemangiomas larger than 2 cm.[19] The association of single-photon emission computerized tomography (SPECT) using Tc-99m pertechnetate-labeled RBCs is even more accurate. SPECT seems to be more specific than MRI, but less sensitive. This is particularly true for lesions near the heart or major blood vessels.[20]

Arteriography

The diagnostic accuracy of noninvasive tests has obviated the use of angiography in most cases. Hemangiomas have early opacification of irregular areas, with persistence of a dense and nodular pattern into the venous phase. Branches of the hepatic artery may be displaced and crowded together or stretched around the lesion, with normal vascular tapering.

Practical use of imaging studies

MRI with extracellular contrast agents is the most accurate radiologic study to establish the diagnosis of a small hepatic hemangioma.

Patients with a typical hemangioma on US and no history of liver disease or malignancy may repeat the US within three

to six months to assure stability. Otherwise a confirmatory test such as CT o r MRI should be performed.

The sonographic diagnosis of a probable hemangioma can be confirmed by MRI and/or nuclear medicine studies. MRI is the test of choice in most centers.

CEUS is gaining acceptance as an emerging method for diagnosis of hemangioma.

Imaging in patients with cirrhosis requires greater caution due to the higher probability of hepatocellular carcinoma (HCC). Hemangioma-like lesions seen on CT and/or SPECT on cirrhotic patients with normal alpha fetoprotein proved to be HCC on fine needle aspiration biopsy.[21] On this setting, MRI may be useful for better lesion characterization.

BIOPSY

Percutaneous biopsy of a hepatic hemangioma carries an increased risk of hemorrhage and should be avoided, specially in large superficial lesions.[22,23] Percutaneous or laparoscopic biopsy may be reasonable to perform in cases where a small liver lesion must be differentiated from HCC (radiologic studies and alpha fetoprotein testing equivocal). Whenever possible the needle should pass through liver parenchyma before sampling the target lesion to diminish the risk of bleeding.

MANAGEMENT

Most hepatic hemangiomas remain asymptomatic and do not require any kind of treatment. It is unclear if radiological follow-up is needed, even in patients exposed to estrogen overload or large tumors (greater than 10 cm). However, any patient known to have a hemangioma presenting with a new onset of abdominal pain requires a contemporary imaging study in order to exclude some sort of complication.[2,24]

Although rare, treatment of hepatic hemangioma may be required in: i) symptomatic patients, ii) rapidly growing tumors, iii) doubt regarding the possibility of malignancy, and iv) the presence of complications.[25,26]

Unfortunately, it is difficult to assure if the symptoms are truly caused by the hemangioma. Some authors have advocated resection for large (greater than 10 cm) asymptomatic lesions because of the potential risk of spontaneous rupture, intratumoral hemorrhage, or high-output congestive heart failure. Although, these complications are seldom reported in the literature and a recent retrospective study concluded that operative treatment should be reserved for patients with severe symptoms or complications of their disease.[27] This cohort, including 289 patients with hemangiomas greater than 4 cm demonstrated that 23% of the 233 patients in the non-operative group reported hemangioma-related symptoms, but life-threatening complications occurred in only 2%. On the other hand, 7% of the 56 patients submitted to surgery experienced life-threatening complications.

Whenever needed, the main treatment option for hepatic hemangiomas is surgical resection. Very selected cases might benefit from non-surgical therapies, such as arterial embolization, radiofrequency ablation, and hepatic irradiation. There are even few reports of ortothopic liver transplantation in very exceptional circumstances.

Spontaneous rupture of a hemangioma is a feared and potentially life-threatening event. The approach in this exceedingly rare situation is challenging. Immediate surgical resection is associated with a very high mortality rate. Thus, hemorrhagic shock and associated coagulopathy should be treated before definitive tumor resection. Techniques used to reduce bleeding allowing hemodynamic stabilization include control of the arterial hepatic inflow and can be obtained by radiology (percutaneous arterial embolization) or surgery (hepatic artery ligation).[6] In exceptional cases liver packing and damage control could be considered.

The Kasabach-Merritt syndrome is characterized by consumptive coagulopathy caused by the hemangioma. Thus, the treatment goals include: i) control of coagulopathy and thrombocytopenia, and ii) tumor resection. Surgery is often difficult, but resection of the tumor is the treatment of choice and usually curative.[28]

Surgical resection

Surgical resection of hemangioma can vary from enucleation to anatomical resection. The choice of the procedure relies mainly on the size and location of the lesion. Typically, surgical resection is performed using an open approach, but laparoscopic surgery can be used in selected cases and probably associated with less morbidity. For further reading on laparoscopic approach refer to **Chapter 27** (Principles of Laparoscopic Liver Resections). Seldom, surgical resection requires total hepatectomy followed by liver transplantation.[29,30]

Mortality rates for surgical resection can reach zero in large series. Morbidity rates are typically low and dependent of factors such as the extent of resection. The average length of hospital stay is shorter than one week.[31,32]

A useful maneuver to reduce intraoperative bleeding during definitive surgery of a large and/or ruptured hemangioma is to control blood tumor inflow before resection (hepatectomy or enucleation). This can be accomplished by preoperative percutaneous arterial embolization or intraoperative extrahepatic surgical ligation of feeding vessels as the first step of surgery.[6,33]

Arterial embolization.

Arterial embolization of hemangioma is a safe procedure resulting in shrinkage of the lesion, that continue until 12 months after the procedure. [34] It is performed percutaneously with embolization of hepatic artery branches done with polyvinyl alcohol, pingyangmycin-lipiodol emulsion, or other

substances.[34–36] Morbidity includes transient impairment of liver function, which recovers in 2-4 weeks, and abscess formation. Both are seen more frequently in case of large tumors. Also, pain, fever, and nongranulomatous arteritis with eosinophilic infiltration are recognized complications.

The use of arterial embolization as a sole treatment option is useful for patients carrying a prohibitive surgical risk (severe comorbidities, massive or diffuse nature of the lesion, and vicinity to some vascular structures). In a series of 98 patients submitted to arterial embolization of hepatic hemangiomas, Zeng et al.[34] reported relieve of symptoms in all the 53 symptomatic individuals. Although, long-term efficacy of isolated arterial embolization (without subsequent resection) has not been proved.

Other treatments

Alternative therapies can be used in very selected cases. Percutaneous or laparoscopic radiofrequency ablation has been reported to reduce the lesion size in selected symptomatic patients.[37–39]

Irresectable tumors can eventually be treated by hepatic radiation therapy (15-30 Gy over several weeks) resulting in symptom relief and lesion regression with minimal associated morbidity. [40,41] Its use in young patients is a matter of concern due to the increased risk of secondary malignancy development. Although, selected cases of Kasabach-Merritt syndrome in childhood might benefit from this approach.

It should be noted that currently there is no approved medical therapy to reduce the size of hepatic hemangiomas.

FOCAL NODULAR HYPERPLASIA

INTRODUCTION

Focal nodular hyperplasia (FNH) is found in up to 8% of the general population. Following hemangioma, FNH is the second most common benign solid hepatic tumor. FNH is 8 to 9 times more frequent in women than men. The majority of them are seen among 20 to 50 year-old individuals. [42] FNH comprises up to 2% of liver tumors in children.[43] Most frequently FNH is solitary (80 to 95%) and with less than 5 cm in size. Although, multiple lesions and larger than 10 cm may also occur.

It is accepted that FNH represents a hyperplastic or regenerative response to hyperperfusion, probably due to a vascular anomaly. In fact, an anomalous central artery is commonly identified.[42,44] The association with hereditary telangiectasia (Osler-Weber-Rendu disease) strengthens the hypothesis of a congenital vascular anomaly.

Histologically, all the regular components of the liver parenchyma are present but in an abnormal organized pattern. This might be useful for diagnostic purposes since Kupffer cells are not typically seen in certain tumors eventually misdiagnosed with FNH, such as hepatic adenoma and HCC. A characteristic finding on pathology, the central stellate scar, might be present along with an disproportionately large artery with multiple branches radiating to the periphery. Its margin is usually sharp without capsule and may eventually be pedunculated.

Most of FNH are asymptomatic and incidentally diagnosed. FNH rarely presents with acute onset of hemorrhage, necrosis, or infarction. Despite its little clinical significance, FNH must be differentiated from other lesions.

Malignant transformation of FNH has not yet been reported. However it may be misdiagnosed with fibrolamelar hepatocellular carcinoma as they may share some imaging and gross features. The differential diagnosis between FNH and adenoma may be also challenging.

DIAGNOSIS FEATURES

The main diagnostic feature of FNH is the demonstration of a central scar. Unfortunately, a typical central scar is not always present (it is absent in 20 to 50% of cases). Non-classical variants comprise up to 20% of FNH and they almost always lack the central scar. On the other hand, a central scar may be found in fibrolamellar hepatocellular carcinoma, hepatic adenoma, and intrahepatic cholangiocarcinoma. Also, hypervascular metastasis, hemangioma, and regenerative nodules in a cirrhotic liver, may mimic FNH on imaging studies.

The most common variant was the telangiectatic type (often present in multiple FNHs, and associate to obesity and hepatic steatosis). This variant is characterized by the absence of nodular architecture and the presence of plates of hepatocytes fed by anomalous arteries. The telangiectatic type carries a risk of bleeding similar to that observed in patients with a hepatic adenoma.[45] In fact, telangiectatic FNHs are nowadays classified as inflammatory hepatocellular adenomas, described below in this text. Some authors suggest even to ban this term.[46]

Biochemical liver tests are frequently within the normal range, although minor elevations can be seen. Alpha-fetoprotein is not elevated.

IMAGING

Ultrasonography

US findings usually rise suspicious for FNH diagnosis. US is particularly useful when combined with duplex Doppler (**Figure 6**), and may even preclude from additional tests. Doppler differentiation of the arterial or venous flow may distinguish FNH from hepatic adenoma. In the setting of malignancy additional imaging studies, such as CT, MRI,

angiography, and radionuclide imaging, are needed to improve the diagnostic yield. It is of note that only 1% of FNHs have calcifications.

On conventional US, FNH can appear as a hyper, hypo, or isoechoic lesion with a central scar identified in only 20% of cases. The use of contrast-enhanced ultrasonography (CEUS) improves characterization of focal liver lesions, and might be useful when FNH is suspected.

Computed Tomography

Dynamic CT with non-enhanced and enhanced phases may be highly suggestive of FNH when a central scar is seen (**Figure 21**). On non-enhanced CT scans, FNH may appear as an isodense or slightly hypodense mass. Typically, FNH becomes hyperdense compared to the surrounding liver in the arterial phase. In the portal venous phase FNH is less conspicuous and becomes isodense compared with the hepatic parenchyma and keeps this pattern in the delayed phase.

The stellate central scar is hypodense with a core and radiating fibrous septa and becomes hyperdense in the portal venous and/or delayed phases. Central scar is identified by CT in only 15 to 33% of patients. The central artery traversing the central scar may show early enhancement in the arterial phase.

CT features of FNH can mimic other benign and/or malignant lesions (**Figure 7**).

Magnetic Resonance Imaging

Since FNH has the same components found in normal liver, its enhancement patterns on MRI are similar to those seen on CT. Typical FNH is isointense on T1-weighted images, and isointense or slightly hyperintense on T2-weighted images. Central stellate scar is more commonly seen on MRI and it is typically hyperintense on T2-weighted due to vessels or edema. The dynamic seen after gadolinium infusion is similar to that observed on enhanced-CT (**Figure 22**).

MRI with liver-specific contrast agent has higher sensitivity (97%) and specificity (100%) than US or CT for the diagnosis of FNH (**Figure 23**).[47] The use of gadolinium-based liver-specific contrast agents (Gd-BOPTA and Gd-EOB-DTPA), with both dynamic and hepatobiliary studies, increases the accuracy of MRI by providing functional and morphological features on FNH. Most nodules appear iso-hyperintense to the liver on hepatobiliary phase and central scar become hypointense due to lack of hepatocytes. The central scar is even more commonly seen on hepatobiliary phase.[48]

In most cases MRI can differentiate hypervascular liver lesions. However, false-positive diagnosis of FNH may occur with HCC (fibrolamellar and other well-differentiated forms), adenoma, and hypervascular metastases.

Nuclear Imaging

The detection of FNH using radionuclide scans with technetium-99m sulfur colloid depends on the burden of Kupffer cells in the lesion. As the concentration of these cells in FNH is not uniform, the uptake of technetium sulfur colloid is variable. On the other hand, hepatic adenomas will occasionally harbor Kupffer cells. Thus, in many centers, nuclear imaging has been largely replaced by Gd-BOPTA-enhanced MRI or dynamic multi-phase CT.

Angiography

Angiography has a little role in the diagnosis of FNH. The typical spokelike appearance (a dilated main feeding artery perforating the center of the tumor and peripheral arteries branching from it) is seen in only a third of cases. Up to 10% of FNHs are avascular. Vascularity may be decreased within the central stellate scar. Characterization of small FNHs is even more difficult. In small lesions, the supplying arteries break up into small branches, which appear to permeate the tumor, and form a reticular pattern.

LIVER BIOPSY

Findings on needle biopsy may substantially overlap those of well-differentiated HCC. Thus, open biopsy or surgical resection might be recommended when the imaging diagnosis is not clear.

MANAGEMENT

Since FNH is not associated with malignant potential and very few cases of complications have been reported, these lesions almost always do not require any intervention.[50] FNHs generally remain stable in size, although they can occasionally become smaller or bigger over time.

The uncommon symptomatic FNH should be treated by resection. Also, surgical resection or open biopsy should be considered for patients with unclear diagnosis.

Despite an inconsistent association, estrogen overload has been linked to FNH enlargement. Thus, it is reasonable to discourage the use of oral contraceptives and/or perform a follow-up examination every 6 to 12 months. Regarding pregnancy, small FNHs do not appear to pose any significant threat but close observation is strongly advised. It is wise to treat large lesions (more than 8 cm) with resection before pregnancy.

HEPATOCELLULAR HEPATIC ADENOMA

INTRODUCTION

Hepatocellular adenoma (HCA) is an uncommon benign hepatocellular neoplasm of presumable epithelial monoclonal

origin. Kupffer cells, whenever present, are reduced in number and usually nonfunctional. Despite its low frequency (approximately 0.004% of the general population) HCA represents the third most common benign focal hepatic lesion and the second most common benign hepatocellular neoplasm, after FNH. The risks of bleeding and malignant transformation reinforce its clinical importance. Overall, up to 30% of HCAs may bleed and almost 10% undergo malignant transformation.[45] Symptoms, specially right upper quadrant discomfort, may be present in up to 50% of patients with HCAs.[51]

Most HCAs are solitary and non-encapsulated, with size ranging from less than 1 cm to more than 20 cm.

There is a strong association between HCAs and estrogen overload (such as oral contraceptives and pregnancy). They occur mostly in women (female:male ratio 8-10:1) of childbearing age and are rarely seen in adult men and children.[52,53] Most of patients with HCA (85 to 95%) have used oral contraceptives (OCs) for more than 2 years.[54,55]

Oral contraceptives containing a high dose of estrogen, and even those with a low dose, especially when used for a long time, increase the risk of HCA.[56] According to Rooks et al.[57] the annual incidence of HCA among women who had never used OCs was 1.3 per million, while among long-term users of OCs this rate was much higher (34 per million). Also, HCAs are more numerous, larger, and more likely to bleed in patients who take OCs.[58–60] Despite HCAs can eventually be diagnosed after previous exposure to OCs, its discontinuation can lead to HCA regression.[61] During pregnancy HCAs can grow remarkably, increasing the risk of rupture and/or hemorrhage, and posing a threat for the mother and the fetus.[62]

HCAs are more frequent among patients with metabolic liver diseases, such as glycogen storage disease (GSD), tyrosinemia, galactosemia, steatohepatitis, and hemochromatosis.[63,64]Also, anabolic androgen steroid intake and familial adenomatous polyposis are associated to HCA.[65–68]

Actually, genetic studies indicate that HCAs comprise a group of tumors with specific pathologic abnormalities and biology. Therefore, HCAs are currently categorized into four distinct genetic and pathologic subtypes: i) inflammatory HCA, ii) hepatocyte nuclear factor 1 alpha (HNF-1α) HCA, iii) β-catenin-mutate HCA, and iv) unclassified HCA.[69,70]

Inflammatory HCA (I-HCA)

I-HCA represents 40 to 50% of all HCAs. They are seen predominantly in women, in association with obesity, alcohol use, and hepatic steatosis. Most of patients with this subtype have used OCs.[66]

Symptomatic individuals can present with a clinical systemic inflammatory syndrome (fever, leukocytosis, and elevated serum C-reactive protein levels), anemia or nephrotic syndrome. [71]The serum level of gama-glutamyl transferase may be elevated. Characteristic imaging is of a hypervascular hepatic mass with persistent enhancement in the portal venous and delayed phases. They are markedly hyperintense on T2-weighted images (corresponding to areas of sinusoidal dilatation). On CEUS, I-HCAs show arterial hypervascularity with centripetal filling and peripheral rim of sustained enhancement with delayed central washout. Many of these HCAs were misclassified as "telangiectatic focal nodular hyperplasia" in the past.

Inflammatory HCAs carry a definite increased risk of bleeding (up to 30%) and a risk of malignant transformation (5 to 10%).[65,72,73]

HNF1α inactivated HCA (HNF-HCA)

Hepatocyte nuclear factor-1 alpha (HNF1α) mutated HCA subtype represents 35 to 50% of HCAs. They occur exclusively in women and most of them have a history of OC use. HNF-HCA can also be associated with familial adenomatosis and maturity onset diabetes of the young type 3 (MODY3). Familial cases of adenomatosis can also occur in HNF-HCA. [74,75] They are characterized by diffuse intralesional steatosis (due to suppression of gluconeogenesis, activation of glycolysis, and promotion of fatty acid biosyntesis secondary to hepatocyte nuclear factor-1-alpha mutation). Thus, HNF-HCA may appear as a liver mass containing fat, which is better characterized on MRI than on CT. On CEUS, HNF-HCA is homogenously hyperechoic with mild to moderate arterial hypervascularity and becomes isoechoic on the portal venous phase.[65]

HNF-HCA may be multiple in up to 50% of cases.[65] It carries a low risk of bleeding, but there is no risk of malignant transformation.

β-catenin mutated HCA.

This subtype of HCAs (10 to 18% of all HCAs) originates from sustained activation of beta-catenin due to a gene mutation. Beta-catenin plays a major role in hepatocyte development, differentiation, zonation, proliferation, and regeneration. This aberrant activation is also seen in HCCs and hepatoblastomas. β-catenin mutated HCAs affect primarily male patients with glycogen storage disease and those individuals on androgen treatment. Up to 75% of patients with glycogen storage disease (type IA, II, IV and VI) may develop HCAs.[76]

HCAs with beta-catenin mutations may appear as homogeneous or heterogeneous hypervascular tumors that lack intralesional fat. Intense arterial enhancement may persist in delayed phases of dynamic CT and MRI. The presence of arterial enhancement and washout can simulate a HCC.

β-catenin mutated HCAs have a greater propensity than other subtypes to undergo malignant transformation (hepatocellular carcinoma): 5% to 10%.[51,52,77] In fact, 20 to 30% of malignant HCAs show beta-catenin mutations.[51,76,78]

Unclassified Adenomas

About 10% of all HCA do not have known genetic alterations or specific histological phenotype to be classified as I-HCA, HNF-HCA, or β-catenin mutated HCA.

The clinical impact of this histologic classification needs to be validated. Despite being the main feature of a subtype (β-catenin mutated HCA) the β-catenin mutation can also be found in 10% of I-HCAs. This predisposing condition to malignant degeneration is not present in HNF-HCAs. In the near future the typical radiological findings might define the approach for low and high-risk lesions of malignant transformation. Current evidence suggests that MRI and CEUS will be used with a high predictive value in subtype stratification of HCAs.[79,80]

HEPATIC ADENOMATOSIS

Hepatic adenomatosis (HA) is defined as the presence of more than 10 adenomas in the absence of classic risk factors for HCA (such as estrogen overload) in an otherwise normal liver. Patients with glycogen storage disease are excluded from this definition. Hepatic adenomatosis is very uncommon and affect equally men and women.[81]

HA is characterized by the development multiple HNF-HCA or I-HCA. These individuals should be submitted to periodical screening for early detection of diabetes. The mutation of the gene Hepatocyte Nuclear Factor 1-alpha (HNF 1-alpha), found in half of patients with HA, is associated with the development of maturity onset diabetes of the young type 3 (MODY3).

Differential diagnosis includes other multiples hypervascular tumors, such as multifocal HCC, FNH, or metastases. CT and MRI features can strongly suggest the diagnosis of adenomatosis.[82]

The rates of complications (bleeding and degeneration) for each individual lesion in adenomatosis are similar to those found on solitary HCAs. Therefore, the therapeutic approach should be based on the assessment of each nodule, considering its subtype and size, rather than the total number of hepatic lesions. [83] Currently, some authors suggest do not consider hepatic adenomatosis as a specific entity, and the term should mean many HCAs (more than 10).[9,65]

As for solitary HCA, resection is recommended for lesions greater than 4-5cm. Liver transplantation can eventually be needed in case of malignant degeneration, progressive liver failure, or unresectable disease.

CLINICAL FEATURES

Most of hepatic adenomas are asymptomatic and found incidentally during an abdominal imaging study for an unrelated reason. Although there is a clear distinction among the histological subtypes, they are not used yet to define the clinical approach. Pain and bleeding are the most common symptoms. Although rare, mass effect can be responsible for symptoms, such as early satiety and abdominal bloating.

Pain and bleeding

In general, right upper quadrant pain is present in 20-25% of cases and associated to hemorrhage in 30-40% of them. In this subset of patients hemorrhage is intralesional in one third and subcapsular or intraperitoneal in two third of cases. Bleeding into the lesion does not represent a life-threatening event in most of cases, however subcapsular and intraperitoneal haemorrhages need immediate evaluation and treatment to avoid fatal complications. The global risk of bleeding from HCA is likely to be between 20% and 40%.[84]

The risk of relevant clinical hemorrhage increases in adenomas larger than 4-5 cm and during pregnancy, but massive bleeding from lesions of only 3.5cm had already been reported. Every patient known to have HCA should undergo a new imaging examination in case of new setting of abdominal pain or clinical signs of hypovolemia. Also, evidence of minimal silent intratumoral bleeding is often present. Lesions near the surface of the liver are more prone to cause hemoperitoneum. In a systematic review including a total of 1176 patients, the overall frequency of hemorrhage was 27.2% (15.8% of all lesions). Rupture with intraperitoneal bleeding was reported in 17.5% of patients. [85] Rupture and acute bleeding of a previously unknown adenoma can occur at 10-30% of cases and is associated with a mortality of up to 8%. [86]In case of intraperitoneal bleeding leading to shock a mortality rate of 25 to 30% can be expected. Adenoma rupture during pregnancy is associated with high rates of maternal and fetal mortality.[87–89]

Malignant transformation

The estimated global risk of malignant transformation is 4% to 10%.[90,91]This risk is not completely understood, but it is enhanced in patients with male hormone use, familial polyposis, and β-catenin mutated subtype of HCA.[87]

Large lesions (greater than 5 cm), even in asymptomatic patients, carry an increased risk of complications (bleeding and malignancy).

IMAGING

The imaging methods with the best yield for HCA diagnosis are MRI and CEUS (**Figure 26**). It is difficult to describe typical radiological findings as the imaging features of HCAs vary on the basis of associated complications and pathologic subtype.

The absence of Kupffer cells may be a hint for the HCA diagnosis. HCAs usually have large blood vessels on

the surface and a fibrous capsule may be present or not. The capsule absence may predispose to intrahepatic or extrahepatic hemorrhage. Necrosis may be seen in lesions that outgrow their arterial blood supply.

The subtype classification can be suggested by MRI and CEUS. HNF-HCAs are typically associated to diffuse fat distribution (intralesional steatosis) and I-HCAs present sinusoidal dilatation.[80,92]

The similar patterns of enhancement can become a real challenge in the differentiation of HCA from FNH and well-differentiated HCC. The typical findings of an uncomplicated HCA (isointense or isodense lesion, with homogeneous enhancement at the arterial phase and becoming isointense or isodense at the portal venous phase) can be seen also in FNH and well-differentiated HCC. Imaging is useful to identify high-risk lesions, such as HCA that are large, peripheral on the liver, and without lipid content. It is of note that more than one type of HCA can be present in the same patient.

Magnetic Resonance Imaging (MRI)

The use of gadolinium-based liver-specific contrast agents (Gd-BOPTA and Gd-EOB-DTPA) in MRI facilitates the differentiation of HCA and FNH (sensitivity of 92% and specificity of 91%).[93] However, the differentiation from well differentiated HCC may be problematic in some cases.

The MRI is able to identify steatotic and hemorrhagic components in the lesions. The aspect of HCAs on MRI is heterogeneous, but some patterns are useful to characterize the main subtypes of HCAs.

The most common subtype of HCA is the inflammatory, characterized by intense plymorphous inflammatory infiltrates, marked sinusoidal dilatation or congestion, and thick-walled arteries. They appear at MRI as lesions diffusely hyperintense on T2-weighted images, with a higher signal intensity in the periphery of the lesion (correlating with dilated sinusoids). These lesions are isointense or mildly hyperintense on T1-weighted images. There is an intense enhancement during the arterial phase after administration of gadolinium, which persists in the portal venous and delayed phases.[69,80,94] These findings provide a sensitivity of 85% and a specificity of 87% for I-HCA.

The HNF-HCA subtype is predominantly hyper- or isointense on T1-weighted images, with diffuse signal drop-off with use of a chemical shift sequence, due to the intracellular steatosis.[69] Also, the hepatic parenchyma commonly presents steatosis. HNF-HCAs appear isointense to slightly hyperintense on T2-weighted images. After gadolinium injection moderate enhancement occurs in the arterial phase, with no persistent enhancement in the portal venous and delayed phases (sensitivity 86% and specificity 100%).[69,80]

Notably, b-catenin-HCAs have no specific MRI pattern. They show homogeneous or heterogeneous hyperintensity on T1- and T2-weighted images, according to the presence of hemorrhage and/or necrosis.

No specific image patterns are identified on unclassified HCAs.

MRI characteristics according to HCA subtype are depicted in **Table 2**.

HCAs with hemorrhage may have hyperintense T1-weighted imaging with subcapsular hemosiderin rings in 30% of patients.

Non-Contrast-Enhanced Ultrasonography

Regular ultrasonography has no specific findings for HCA. The lesions may be hypoechoic, isoechoic, or hyperechoic relative to liver parenchyma. Doppler flow patterns in HCAs are venous, as compared to the arterial pattern noted in FNH.

Contrast-Enhanced Ultrasonograhy (CEUS)

The main subtypes of HCAs (I-HCA and HNF-HCA) have typical CEUS patterns.

I-HCAs show arterial hypervascularity with centripetal filling, a peripheral rim of sustained enhancement, linear vascularities, and central washout in the late venous phase. These findings provide a sensitivity of 64% and specificity of 100% for diagnosis of I-HCA.[95,96]

The CEUS aspects of HNF-HCAs are of homogeneous hyperechoic lesions with isovascularity or moderate hypervascularity with mixed filling in the arterial phase,

Table 2. MRI features of subtypes of hepatocellular adenoma. (Modified from Katabathina et al.[69])

Subtype	T1-weighted Gradient-Echo	T2-weighted	Gadolinium-enhanced T1-weighted
Inflammatory	Isointense or mildly hyperintense, without signal loss on chemical shift imaging	Diffusely hyperintense	Intense enhancement during arterial phase that persists in the portal venous and delayed phases
HNF-1α-mutated	Hyper- or isointense, with diffuse signal loss on chemical shift imaging	Isointense to slightly hyperintense	Moderate enhancement in the arterial phase, with no persistence enhancement in the portal venous and delayed phases
β-Catenin-mutated	No specific MRI patterns; may mimic HCC (strong enhancement during arterial phase, with portal venous washout)		

MRI: Magnetic Resonance Imaging; HCC: Hepatocellular carcinoma.

and isoechogenicity in the portal and late portal venous phases. The homogeneous hyperechogenicity correlates with diffuse fat infiltration and provide a sensitivity of 88% and specifity of 91% for diagnosis HNF-HCA. This pattern may be misdiagnosed with hemangioma.[95]

Like in MRI, b-catenin-HCAs and unclassified HCAs have no specific patterns on CEUS.

Computed Tomography (CT)

Most HCAs are encapsulated on CT scan. The lesions can have a central necrotic area or calcifications.

Non-enhanced CT images generally show HCAs as well-circumscribed isodense or hypodense lesions. After contrast injection a heterogeneous or centripetal pattern of enhancement is seen on arterial phase, and the lesions become iso- or hypodense on portal venous and delayed phases.

The CT scan is not useful to distinguish the HCAs subtypes.

Nuclear Imaging

Nuclear imaging can be useful to differentiate HCA from FNH and HCC. Typically, HCAs and HCCs appear as defects on sulfur-colloid scans, due to their low content or absence of Kupffer cells. With the use of hepatobiliary radiotracers, HCAs can be distinguished from HCC as they appear hot on early and delayed images. For differentiation between HCA and FNH, nuclear imaging has been replaced by MRI with liver-specific contrast agents.

Angiography

Currently, angiography does not have a significant role in the diagnostic workup of HCA.

BIOPSY

HCAs are a mass of normal-appearing hepatocytes and the conventional histologic evaluation has a low yield for its diagnosis. However, immunohistochemistry testing can be helpful not only to differentiate HCAs from other lesions, but also to identify its subtypes. In fact, the immunohistochemistry results can guide the approach of HCAs.

In selected cases resection may be required as the most specific way to confirm diagnosis.

OTHER TESTS

Liver function tests are typically normal. However, serum aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase levels can be mildly elevated in multiple adenomas. These findings can also be observed when intratumoral bleeding and/or a mass effect are present. Tumor markers, such as alpha-fetoprotein, are within the normal range.

MANAGEMENT

Regardless of the management strategy, in all cases of HCAs the offending drugs (such as oral contraceptive pills and androgens) should be stopped whenever possible. Although complete resolution is atypical, this allows regression in the size of the majority of the tumors. However, the risk of malignant transformation remains even after the contraceptive or steroid use has been discontinued.[52,97]

The approach of HCAs should be based on the presence of symptoms and the risk of complications (bleeding and malignant degeneration). In case of more than one lesion, the characteristics of each individual HCA, rather than the total number of lesions, should guide the therapeutic approach.

Asymptomatic HCA

Most HCAs are incidental findings in asymptomatic patients. These individuals can be managed according to the algorithm in **Figure 1**.

Size greater than 5 cm is associated with a high risk of bleeding and malignant transformation.[52,65] Also, men and patients with glycogen storage disease (GSD) have a higher risk of malignant degeneration (up to half of HCAs in men and ¾ of HCAs in patients with GSD).

Thus, all HCAs occurring in men and those greater 5 cm, irrespective of gender, should be treated by surgical resection.[52,65,98]

An individualized approach of HCAs with less than 5 cm in females is based on its subtypes. The imaging features

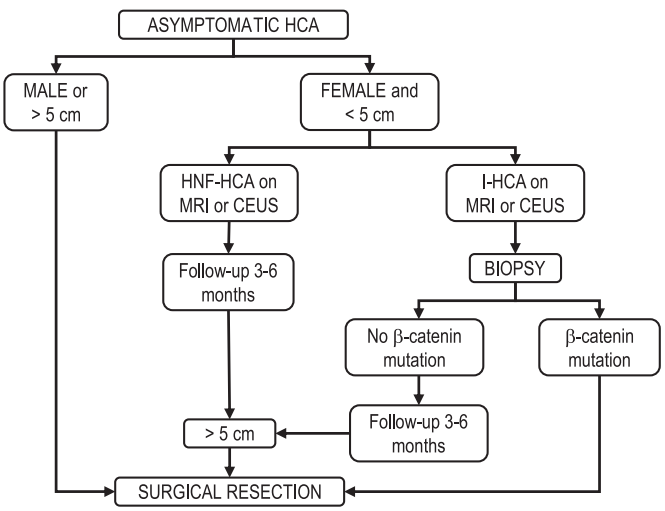


Figure 1. Individualized approach to asymptomatic hepatocellular adenoma. HCA: Hepatocellular adenoma; HNF-HCA: Hepatocyte nuclear factor-1 alpha mutated HCA; I-HCA: inflammatory HCA; MRI: magnetic resonance imaging; CEUS: contrast-enhanced ultrasonography. (Note: if biopsy or immunohistochemistry is unavailable HCAs with less than 5 cm in females should be followed and surgical resection considered for growing lesions – see the main text).

in this population can suggest the subtype and guide the need of a biopsy. HNF-HCAs on MRI or CEUS carry a very low risk of b-catenin mutation and can be precluded from biopsy.[52,77,86]

On the other hand, I-HCAs on imaging should be biopsied to explore the risk of malignant degeneration. All HCAs with evidence of b-catenin activation should be resected due to the risk of malignant degeneration. HCAs with no evidence of b-catenin mutation can be followed with regular year imaging (MRI) examination until menopause, at least.

The individualized approach of HCAs according to their subtypes relies on imaging technics and sophisticated immunohistochemistry analysis of tumor samples. However, tumor biopsy carries risks such as tumor rupture/seeding, hemorrhage, and sampling errors. Also, the lack of widespread adequate immunohistochemistry and the occasional difficulties on differential diagnosis with core biopsy limit the clinical application of biopsy-based approach.

For those centers where biopsy and/or immunochemistry are not available, the traditional approach should still be used. In this setting HCAs with less than 5 cm in asymptomatic females should be followed after stopping offending drugs.

It is judicious to treat lesions diagnosed as HCAs in patients with elevated alpha-fetoprotein irrespective of size and/or symptoms.

HCA and pregnancy

The estrogen overload during pregnancy represents an increased risk of HCA growth and bleeding. Thus, the management of HCAs in women of childbearing age requires particular attention.

The natural history of HCAs during pregnancy and labor is poorly understood due to the rarity of the situation. Prognostic factors on rupture and malignant degeneration during pregnancy remain unknown. The traditional management guidelines have been based on case reports and/or retrospective small case series, most of them of complicated patients.

Lesions greater than 5 cm, as for non-pregnant women, should be treated before pregnancy, with resection whenever possible or other less invasive techniques (rafiofrequency ablation, arterial embolization). However, the management of small HCAs during pregnancy remains controversial. Current data suggest that it is acceptable to observe lesions of up to 4-5cm. In a recent prospective series of 17 pregnancies (12 patients) only 5 of more than 30 HCAs grew during pregnancy. Thus, pregnancy should not be completely discouraged to all women with small HCAs, as long as the risks are discussed with the patient and close follow-up performed (imaging every 6 weeks). It seems reasonable to treat only growing lesions that reach over 5 cm. Although elective surgical treatment of benign liver tumors carries a low morbidity and mortality risk in non-pregnant women, non-urgent surgical procedures in pregnant ones, especially during the second trimester, seem to be safe with laparoscopy being an important emerging tool. Other options in case of growing HCA include radiofrequency ablation, cesarean section, and arterial embolization. Treatment options should be tailored according to gestational age and risks related to radiation exposure.

Rupture and bleeding of an HCA during pregnancy is a life-threatening situation for both, the mother and fetus. Rupture occurring during pregnancy should be managed as in non-pregnant patients.

HCA and hemorrhage

Hemorrhage associated with HCAs may be limited to the tumor (intralesional bleeding) or not (subcapsular hematoma and/or hemoperitoneum). Diagnosis of bleeding is easily confirmed by abdominal imaging methods. Although rare, HCA rupture with hemodynamic instability might occur. All patients with HCAs who present with abdominal pain and/or signs of bleeding must undergo immediate imaging assessment.

The **intratumoral bleeding** is more common and generally does not need immediate procedures. Symptomatic patients should be given analgesics and observed. In the absence of pain relief a new imaging study should be performed.

Tumoral rupture can result in **subcapsular hematoma and/or hemoperitoneum.** These are life-threatening situations requiring immediate management.

The initial approach includes the assessment of hemodynamic stability and ordinary resuscitation management. Patients with hemodynamic instability require an immediate procedure to stop the bleeding. Whenever possible, selective arterial hepatic embolization should be the procedure of choice in this setting.[99–101] In case of failure or unavailability of arterial embolization urgent laparotomy should be performed.[102] Indeed, even patients without hemodynamic instability will benefit from selective arterial hepatic embolization to stop or limit the bleeding and to reduce the tumor mass. Occasionally, patients with no signs of shock and/or active bleeding can be managed without arterial embolization during the acute phase with rest and observation.

Elective surgical resection is the definitive treatment of choice for ruptured adenomas. The reabsortion of the hemoperitoneum and/or hematoma, generally 4-6 weeks after the acute event, allows a safer and more limited hepatic resection.[65,101] Lately, some authors have favored a non-surgical approach after a successful embolization resulting

in small tumor size (less than 5 cm).[99] Patients with high-surgical risk can be managed with transarterial embolization or radiofrequency ablation.

Summary

In summary, surgical resection of HCA is warranted in the following cases: i) male gender, ii) lesions greater than 5 cm, iii) growing tumors, iv) b-catenin mutated adenomas and, v) elevated serum AFP.[25,73,103]

TREATMENT OPTIONS

Usual therapeutic procedures for HCAs include surgical resection, local ablation, and arterial embolization.

Surgical resection

Surgical resection is the definitive treatment of choice for HCAs. Complete tumor clearance of the target lesions abolishes the risk of bleeding and malignant degeneration. Once an HCA is completely resected, the rare event of recurrence is associated with lesions that had already degenerated.[104] After a first resection of HCA up to 25% of patients require another surgery due to another lesion.[91,105]

Limited segmental hepatic resection is enough in most of cases. Major liver resections can be needed in case of large and/or central lesions. Elective resection of benign tumors carries a low morbidity (approximately 13%) and mortality (less than 1%). [91,105]On the other hand, in case an emergency hepatic resection is performed, the mortality rate is exceedingly high (5-25%). [103,106,107]

Feasibility of laparoscopic approach for benign liver tumors has already been shown. The preference of open or laparoscopic procedures should be based on localization and size of the tumor as well as the team expertise. For further details refer to **Chapter 27** (*Principles of Laparoscopic Liver Resections*).

Seldom, liver transplantation has been described as an alternative for the treatment of patients with multiple adenomas and glycogen storage disease.[81,108]

Emerging approaches

Less invasive emerging approaches for the treatment of HCAs include selective arterial embolization and local ablation by radiofrequency.

Selective arterial embolization is the treatment of choice for the management of acute bleeding. Outside the emergency setting, selective arterial embolization has been proposed for the management of multiple HCAs not amenable to surgical resection, poor surgical candidates, and for reduction of tumor volume. Although selective arterial embolization can be used as a sole treatment it is unknown if the reduction of the size of the lesion represents a truly reduction in the risk of malignant degeneration.

Local radiofrequency ablation seems to be efficient for the treatment of small lesions. Large tumors can be treated with multiple ablations or after size reduction by previous selective arterial embolization.[109] Long-term results are still lacking, but it is reasonable to consider this less invasive approach for poor surgical candidates or those that would require a major liver resection.

FOLLOW-UP

Despite the lack of evidence, all patients with diagnosis of HCA and lesions left in situ should undergo regular follow-up. There are no clear guidelines for the optimal interval, duration and screening methods, but it is suggested yearly imaging (US or MRI) and assessment of alfa-feto-protein until menopause, at least. It is also reasonable to follow patients that underwent surgical resection of HCA due to the risk of de novo lesions in up to 25% of patients.[51,65,109–111]

OTHER SOLID BENIGN TUMORS

Among the less common solid benign tumors and pseudotumors of the liver are included the inflammatory pseudotumor, the lipomatous tumors, and the nodular regenerative hyperplasia. Other rare benign tumors will not be discussed here.

INFLAMATORY PSEUDOTUMOR

Inflammatory pseudotumor of the liver is a localized mass of proliferating fibrovascular tissue infiltrated by inflammatory cells.[112,113] It represents a chronic inflammatory lesion of uncertain histogenesis and may be secondary to portal phlebitis, such as originated from recurrent cholangitis.[114] Inflammatory pseudotumor is a benign lesion and can present spontaneous regression, but usually mimic other hepatic tumors on imaging.[115–117]

LIPOMATOUS TUMORS

Lipomatous tumors of the liver, such as lipoma, hibernoma, angiolipoma, myelolipoma, angiomyelolipoma, angiomyolipoma, angiomyomyelolipoma, present different elements in variable proportions.[118] The variability of the different tissue components rend radiological images heterogeneous. In fact, the heterogeneity of these tumors makes difficult the diagnosis even by needle biopsy. MRI is the most specific radiological method for the detection of lipomatous component. However, the definitive diagnostic is the histopathologic study, associate to immunohistochemical markers,

of the resected specimen.[119]

Despite most of **angiomyolipomas** are asymptomatic and found incidentally; some of them may reach a large size and cause symptoms. Abdominal discomfort, nausea, hepatomegaly, and even Budd-Chiari syndrome were reported.[120] The combined study of dynamic CT, MRI and contrast-enhanced US allows for the detection of a vascular pattern with a prominent efferent tumor vein. [119,121,122] The specificity of this vascular pattern, however, has not been documented yet. Asymptomatic angiomyolipomas no need treatment and should be monitored on regular basis, since rupture or malignant transformation are exceeding rare.

Epithelioid angiomyolipoma is a mixed mesenchymal tumor that usually occurs in the kidney.[123] It is characterized by a triad of tortuous, thick-walled blood vessels, smooth muscle cells, and adipose tissue in varying proportions.[118] Most of angiomyolipomas has no propensity for metastasis or malignant potential. Multiple hepatic angiomyolipomas are found in patients with tuberous sclerosis and particularly in those with multiple renal angiomyolipomas.[124]

NODULAR REGENERATIVE HYPERPLASIA

Nodular regenerative hyperplasia is characterized by diffuse hyperplastic nodules composed of cells resembling normal hepatocytes, without fibrosis around the nodules. Nodular regenerative hyperplasia is of uncertain etiology and represents a regenerative hepatocellular activity. Nodular regenerative hyperplasia is usually associated with organ transplantation myeloproliferative or lymphoproliferative diseases, or autoimmune processes, and lesions usually enhance similar to the liver parenchyma on radiological studies. Computed tomography and MRI can show multiples nodules mimicking metastatic disease or cirrhosis. It can present with portal hypertension.[125,126] This condition should be differentiating from large **regenerative nodules**, which are often associated with Budd-Chiari syndrome and result in contrast enhancing liver lesions. Regenerative nodules do not present fibrosis between the nodules.[127,128]

SUMMARY

In fact, the main clinical challenge during evaluation of a hepatic focal lesion is the exclusion of a primary hepatic or a metastatic malignancy. Efforts should be directed to obtain preoperative diagnosis based on imaging and/or needle biopsy, with special immunohistochemical markers when necessary. If definitive diagnosis is not established, the approach should be based on the clinical scenario additionally to radiological features, that even when not diagnostic, a stratification risk of worrisome may be possible. Approach to incidental hepatic lesions is suggested below.

HEPATIC INCIDENTALOMA

INTRODUCTION

Hepatic incidentaloma refers to asymptomatic hepatic lesions identified incidentally. Hepatic incidentalomas (HI) are most commonly detected during radiological investigations for other pathologies although eventually they may be identified during a laparotomy or laparoscopy. HI are identified on up to 15% of radiological studies and most of them are non-threatening benign lesions, however some of them will require additional evaluation, follow-up, or even treatment. Indeed, approximately 10% of HI are malignant lesions. Workup of HI can be challenging since additional studies or procedures may lead to unnecessary costs and risks, and even be misleading.[129–132]

MANAGEMENT

The approach of HI aims to identify significant lesions, i.e. malignant tumors or benign lesions with potential for complications (mainly bleeding and malignant degeneration). There are no evidence-based guidelines regarding the best approach to HI. However, it is usually possible distinguish hepatic incidental lesions with no clinical meaning from those that require a specific treatment or follow-up. The clinical scenario, including anamnesis, physical examination, simple laboratory tests, review of imaging already performed, and selective use of further imaging are the basis for the management of HI.

Thus, the initial approach should be based on the clinical scenario, the imaging modality performed, and the lesion features.

The clinical scenario

Patients can be stratified according to the presence of known risk factors for potentially significant lesions. Mainly, hepatocellular carcinoma, liver metastasis, and adenoma have well-known risk factors. Thus, three groups can be depicted: i) **high-risk group** includes patients with a known malignancy with a propensity to metastasize to the liver (including gastrointestinal and breast tumors, and melanoma), cirrhosis of any etiology, or other hepatic risk factors (chronic viral hepatitis, autoimmune hepatitis, sclerosing cholangitis, hemochromatosis, hemosiderosis, hepatic dysfunction, long-term oral contraceptive or anabolic steroid use); ii) **moderate-risk group** comprises patients older than 40 years of age without known malignancy and no hepatic risk factors; and iii) **low-risk group** includes young patients (<40 years-old), with no malignancies or other hepatic risk factors.[133]

Tests that might be useful for the inclusion of a patient into one of the three groups include liver function tests, serum ferritin, serological tumor markers (CEA, alpha-fetoprotein, CA19.9) and serological markers of viral hepatitis and autoimmune hepatitis. In a similar way, radiological signs of chronic underlying liver disease can be informative. Other tests, such as upper endoscopy, colonoscopy, mammography, and chest imaging, should be used very selectively when a liver metastasis is suspected in a patient without known malignancy.

IMAGING MODALITIES AND LESION FEATURES

Hepatic incidentaloma may be detected on different imaging methods, most frequently US, CT and MRI. The first imaging examination is commonly enough for adequate characterization of the lesion and for definition of the clinical significance or even of the definitive diagnosis of a HI.

An algorithm based on the imaging modality that detected the incidental lesion and the lesion features is summarized on **Figure 2** and discussed below.

PROPOSED ALGORITHM TO APPROACH OF HI

The algorithm represented on **Figure 2** is based on imaging modalities and lesions features. Numbers cited on specific items of the flowchart are used to locate the respective discussion of these items in the text below.

The outcomes of this approach include no-need of further evaluation (discharge), follow-up imaging, or additional evaluation. Treatment and follow-up according to specific diagnosis are discussed in other chapters of this textbook.

HI on ultrasonography (US)

Hepatic incidentalomas are frequently found on US. This method is useful to distinguish cystic ① from solid ② lesions.

Cystic lesions ① can be classified as simple or complexes. Simple cyst ③ (**Figure 3**) is sharply delimited, anechoic, homogeneous, with posterior reinforcement, and with no vascular flow with Doppler US. A complex cyst ④ (**Figure 4**) is characterized by the absence of simple cyst features, presence of septae, mural nodules, heterogeneous content, or solid component.

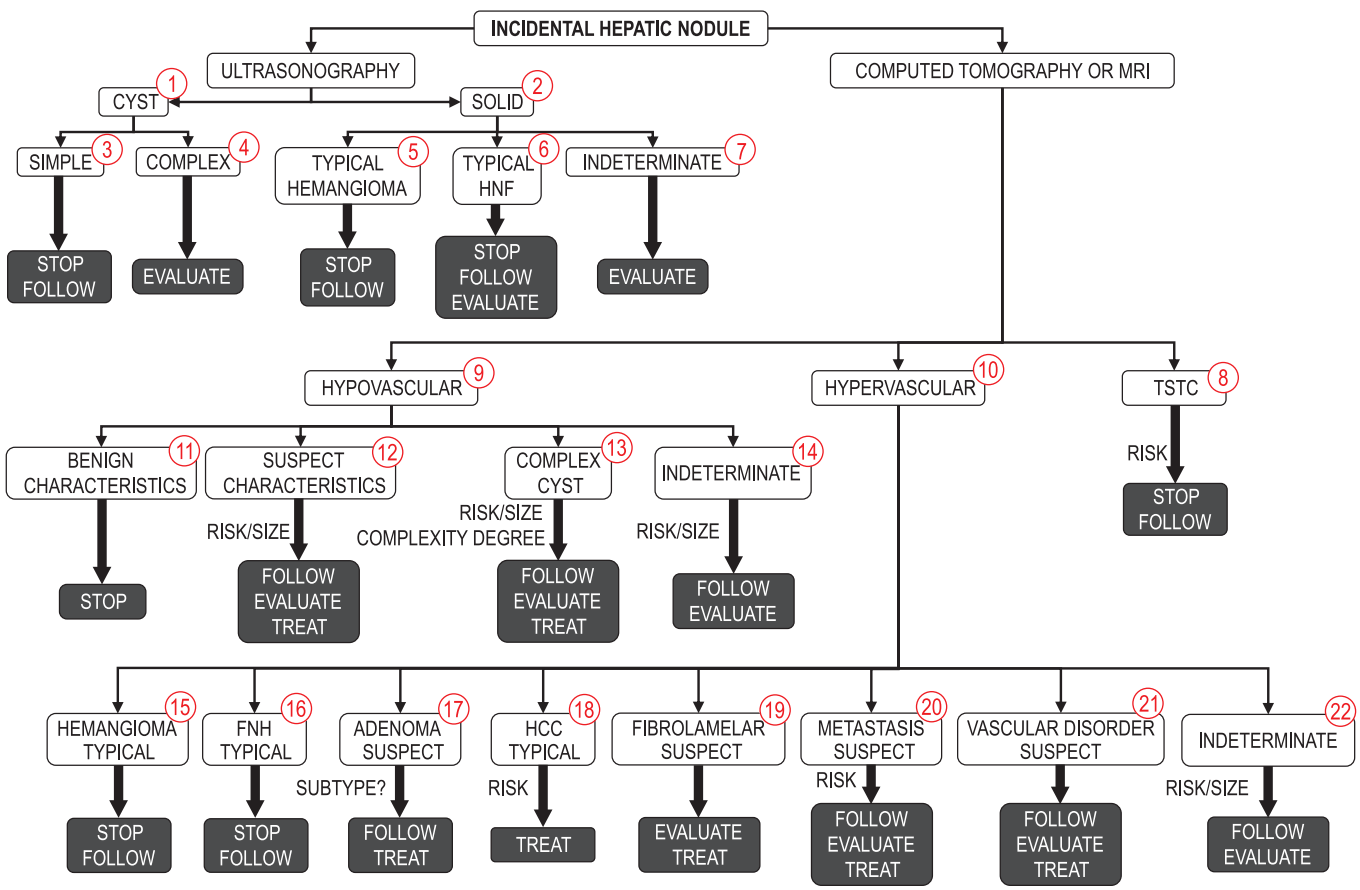


Figure 2. Approach to hepatic incidentaloma according to imaging features. Numbers are used to locate details on the main text. MRI: Magnetic resonance imaging; TSTC: to small to characterize; FNH: Focal nodular hyperplasia; HCC: hepatocellular carcinoma.

Solid lesions ② may be ultrasonographically characterized as typical for hemangioma, typical for focal nodular hyperplasia (FNH), or indeterminate. Typical hemangioma ⑤ (**Figure 5**) is sharply delimited, homogeneous, hyperechogenic, with posterior acoustic reinforcement, and no signs with Doppler US. Typical features of a FNH ⑥ (**Figure 6**) are a homogeneous nodule, with variable echogenicity, with no hypoechogenic halo (capsule), with a central scar that may be hyper- or hypoechogenic and that presents arterial flow with Doppler US. Solid nodules with unspecific ultrasonographic characteristics are indeterminate lesions ⑦ (**Figure 7**).

Complex cysts ④ and indeterminate nodules ⑦ should be evaluated with a dynamic study, such as contrast enhanced CT or MRI.

HI on Computed Tomography (CT) and Magnetic Resonance Imaging (MRI).

These are largely available and useful methods to characterize hepatic lesions. Hepatic nodules can be classified as: i) to small to characterize (TSTC) ⑧, ii) hypovascular nodules ⑨, and iii) hypervascular nodules ⑩. Accuracy of MRI seems better than that of CT for detection and characterization of focal hepatic lesions. Thus, some indeterminate nodules on CT might have a distinct classification using MRI. Main features of each group of HI found on CT or MRI are described below.

Lesions to small to characterize (TSTC) ⑧ (Figures 8 and 9)

Lesions TSTC are generally indeterminate due to their small size and atypical imaging features and usually their categorization is not reliable. They also called subcentimeter lesions, however this is not a size-based classification. Indeed, the progress on imaging methods has more frequently allowed characterization of nodules of less than one centimeter.

In a study [134] published in 1992 comprising 1,500 patients that underwent abdominal CT, TSTC lesions were found in 17% of cases. No TSTC was identified in patients with no known primary malignancy. Among those with known primary malignancy, the number of TSTC lesions was associate with the risk of malignancy, i.e., for 1 TSTC lesion

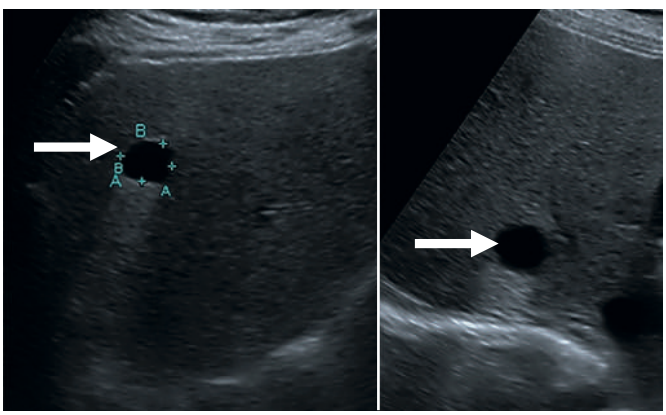


Figure 3. Simple cysts on ultrasound (arrows): anechoic, homogeneous, sharply delimited, and with posterior reinforcement.

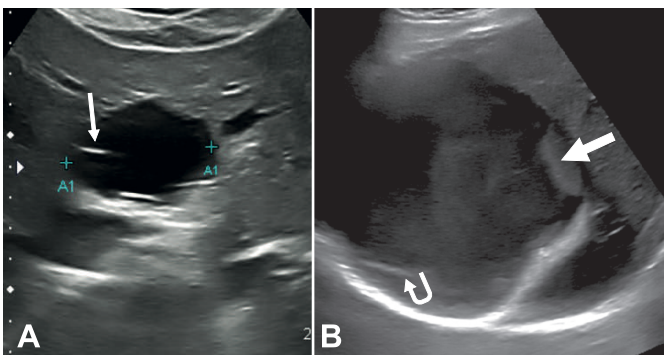


Figure 4. Complex cyst on ultrasound. **A)** Anechoic cyst with thin septum (arrow). **B)** Large cyst in the right liver with a thick septum (curved arrow), echogenic content (asterisk) and mural nodule (arrow).

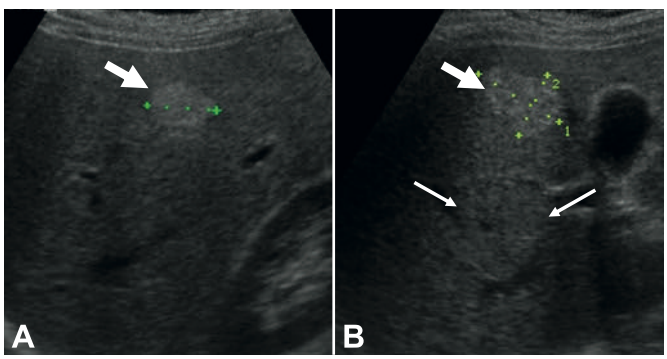


Figure 5. Typical hemangioma on ultrasound. **A** and **B**) Well-defined, homogeneous and hyperecogenic nodule (thick arrows) with posterior acoustic enhancement (thin arrows) and no signal on Doppler scan. (*courtesy of Dra. Iara R. S. Lucena, Hospital de Clínicas, Porto Alegre, Brazil*)

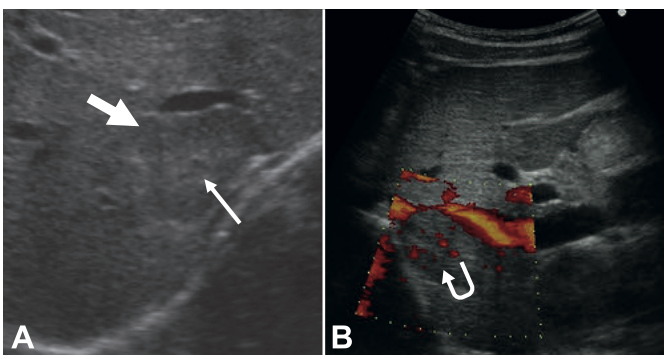


Figure 6. Typical focal nodular hyperplasia (FNH) on US. **A** and **B**) Homogeneous lesion (thick arrow) with variable ecogenicity and with no peripheric hypoecogenic halo (capsule). A hypoecogenic central scar (thin arrow) with arterial vessels on Doppler US (curved arrow), a characteristic finding on FNH, is seen.

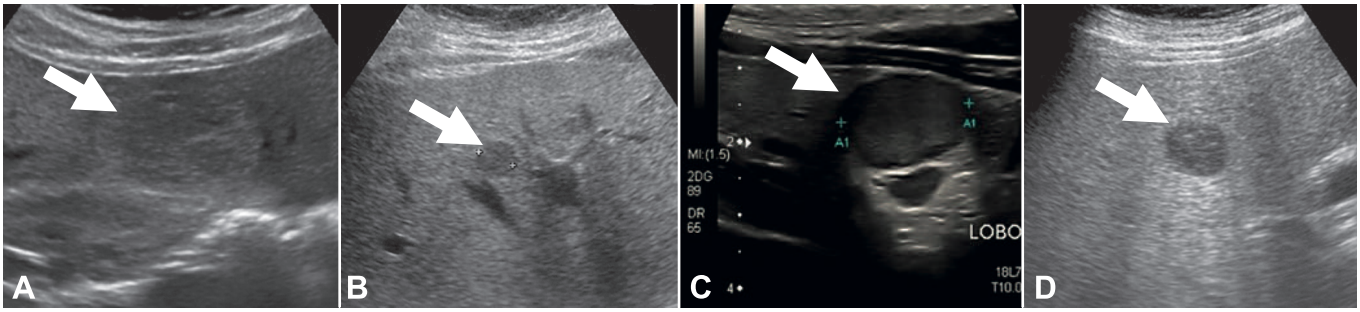


Figure 7. Indeterminate nodules on ultrasound. Nodules that do not fit features for specific diagnosis on ultrasound (US) should be considered indeterminate and evaluated by a dynamic imaging method. A large range of benign and malignant lesions may have similar US appearance becoming specific diagnosis impossible. **A**) Hemangioma. **B**) Focal nodular hyperplasia. **C**) Liver metastasis from endocrine tumor. **D**) Hepatocellular carcinoma.

the risk of malignancy was 5%, for 2 to 4 TSTC lesions this risk increased to 19%, and for those with 5 or more TSTC lesions the risk of malignancy reached 76%. However, it is of note that this study was performed before the advent of multidetectors CT. Another study [130], published in 1999, including 2,978 patients with known primary malignancy, reported a prevalence of 12% of TSTC lesions, and only 12% of them (1.4% of patients) were metastases. TSTC were more frequently malignant when the primary site was a breast tumor. This found is in agreement with the observation that liver metastases from breast cancer are usually small and multiple, in opposition of those from colorectal origin, for example.

More recently, a study [135] reported a correlation between the size and edge aspect of TSTC lesions and the risk of malignancy, as summarized on **Table 3**. Also, a cohort including breast cancer patients with no known liver metastasis found that those with TSTC lesions (present in 35% of cases) developed liver metastasis in 28% of cases.[136] This risk was similar to those patients with no TSTC after a median follow-up of 584 days. Thus, despite most of TSTC lesions are benign, multiple TSTC lesions in patients with known malignancy represent an increased risk to malignancy.

Hypovascular nodules ⑨

Hypovascular nodules represent a large group of lesions, including most of liver metastases. On the flowchart hypovascular lesions were classified as i) benign ⑪, ii) suspicious ⑫, iii) complexes cysts ⑬, and iv) indeterminate ⑭.

Table 3. Probability of a lesion being benign using size and edge as characterization. (Modified from Robinson et al.[135])

Size	Ill-defined	Sharply defined
<5mm	90%	94%
5-10mm	71%	81%
10-15mm	62%	71%

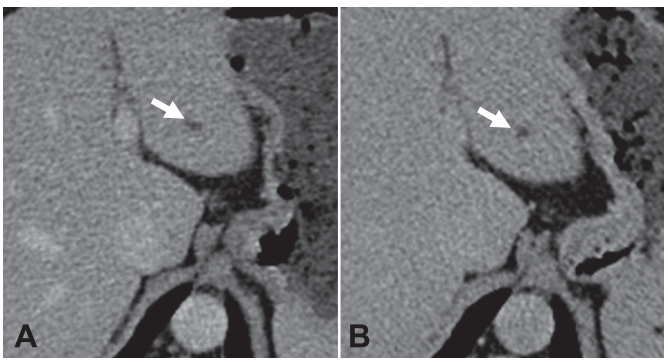


Figure 8. A small nodule (arrows) on portal-venous (**A**) and delayed (**B**) phases of dynamic CT. The nodule remains hypodense and shows the same aspect on both phases, suggesting a cyst.

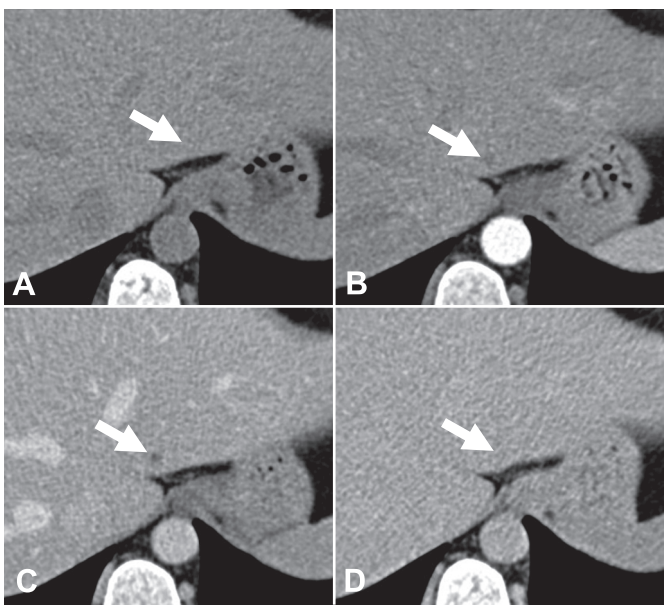


Figure 9. To small to characterize (TSTC) nodule. A small nodule (arrows) on pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of a dynamic CT. The nodule shows contrast enhancement, however, it is not possible to characterize the pattern of enhancement.

Typical benign hypovascular nodules ⑪ (**Figure 10**) are sharply defined, homogenous, with low density (up to 20 HU) on CT, and with no contrast enhancement. Margins may be irregular but well defined. Hepatic cysts are the more common lesions in this category.

Suspicious hypovascular nodules ⑫ (**Figures 11** to **14**) have ill-defined margins, contrast enhancement (more than 20 HU), and heterogeneity. Metastasis is the more frequent lesion in this category and most metastases presents with these imaging features. However, this group is heterogeneous and include many different diagnosis. Cholangiocarcinoma for example normally is included in this category. Inflamatory pseudotumor, a benign lesion, usually also shows imaging features of this category.

Complex cystic lesions ⑬ (**Figures 15** and **16**) are characterized by the presence of septa and wall thickening with contrast enhancement, heterogeneous content, calcifications, and solid component. Complex cysts can be subdivided according to the degree of complexity into mild, intermediate and accentuate. Mild complex cysts have non-perceptible walls, with thin septa (less than 3 mm) and no solid compound. Intermediate complex cysts have little thicker wall and/or septa (between 3 and 5 mm), without solid compound. Finally, accentuate complex cysts have thick (more than 5 mm) and irregular walls and/or septa and may have solid compound that enhances after contrast

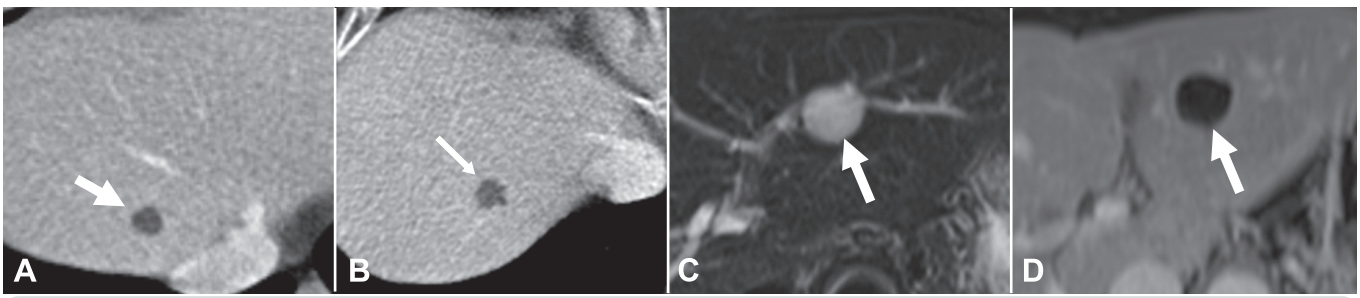


Figure 10. Benign hypovascular lesions. **A**) Portal-venous phase CT showing a well-defined and homogeneous nodule (arrow), with low density (lower than 20 HU) and no contrast enhancement. **B**) Portal-venous phase CT showing a nodule with irregular, but sharply defined, margins (arrow). **C** and **D**) MRI of a well-defined and homogeneous nodule (arrows), hyperintense on T2-weighted image (C) and with no enhancement on dynamic post-contrast scan (D).

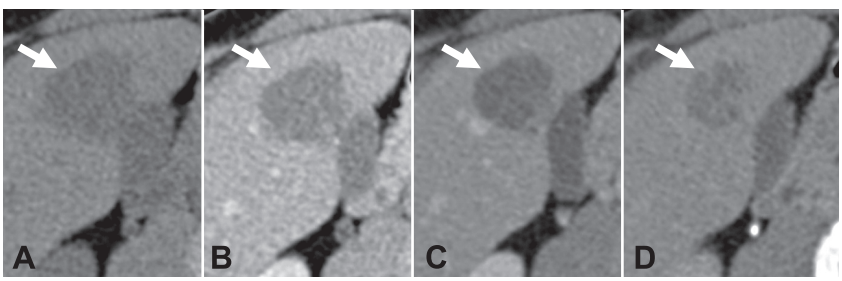


Figure 11. Suspicious hypovascular lesion on dynamic CT. Nodule (arrows) with ill-defined margins, heterogeneity, and contrast enhancement (better appreciated on delayed phase). Lesion was proved to be a colorectal metastasis. Pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of dynamic CT.

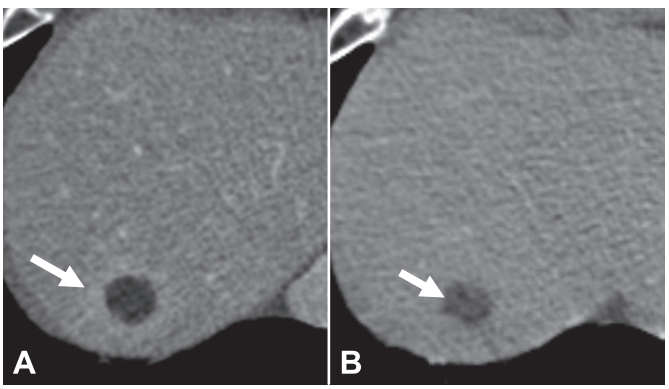


Figure 12. Suspicious hypovascular lesion on dynamic CT. **A**) portal-venous phase showing subtle peripheric enhancement (arrow). **B**) Delayed phase with little enhancement (better noticed by reduction of lesion's size). It was proved to be a metastasis from pancreatic cancer.

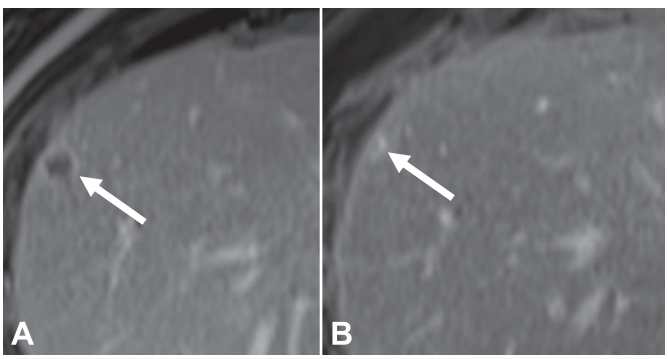


Figure 13. T Suspicious hypovascular lesion on portal-venous phase of dynamic MRI (MRI). **A**) Initial imaging showing a nodule with peripheric enhancement (arrow). **B**) After chemotherapy there was a size reduction (arrow). The nodule was a liver metastasis from breast cancer. Increasing of size on follow-up study or reducing of size after treatment are suspicious characteristics.

media administration. Etiology of complex cysts is variable and includes complicated simple cyst (bleeding or infection of simple cyst), ciliated cyst, hydatid cyst, abscess, bilioma, hematoma, cystadenoma, cystadenocarcinoma, cystic primary hepatic tumors, and cystic metastases. Management of complex cysts depends on clinical features and specific characteristics. For example, a hepatic cyst with calcified wall and no contrast enhancement in a patient from an endemic area is probably a hydatid cyst.

Indeterminate hypovascular lesions ⑭ represent the other hypovascular lesions, which its characteristics are not included in the former hypovascular categories. They might be submitted to additional evaluation or follow-up, according to their size and group of risk of the patient.

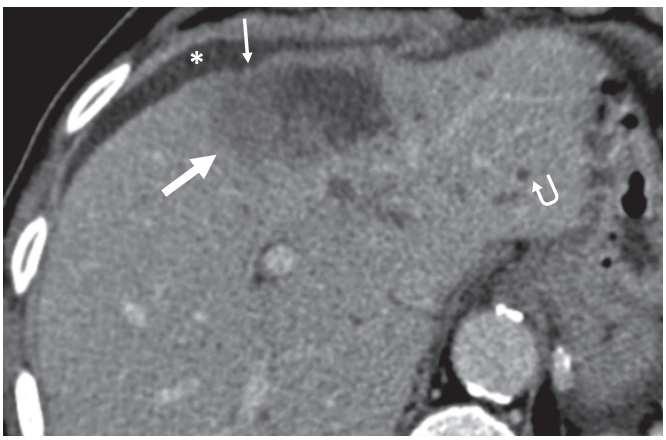


Figure 14. Suspicious hypovascular lesion on portal-venous phase of dynamic CT. An ill-defined and heterogeneous lesion (thick arrow) is shown, associated to minimal capsular retraction (thin arrow), intrahepatic biliary dilatation (curved arrow), and ascites (asterisk). The lesion was an intrahepatic cholangiocarcinoma, a diagnosis usually found on this category.

Hypervascular nodules ⑩

Hypervascular lesions are further divided in: i) typical hemangioma ⑮, ii) typical focal nodular hyperplasia (FNH) ⑯, iii) suspicious adenoma ⑰, iv) typical hepatocellular carcinoma ⑱, v) suspicious fibrolamelar carcinoma ⑲, vi) suspicious metastases ⑳, vii) suspicious vascular disorder, and viii) indeterminate ㉒.

Typical **hemangiomas** ⑮ (**Figures 17** to **20**) may present three patterns of contrast enhancement. In type I, typical of small (less than 1.5 cm) hemangiomas, there is an intense and uniform contrast enhancement of the lesion during the arterial phase, followed by a progressive slow reduction of the enhancement, but remaining hyperdense/hyperintense in late phase, in a similar way of vascular structures. There may be perfusion abnormalities surrounding the nodule during arterial phase. In type II, most frequent on hemangiomas up to 5 cm, the lesion enhancement is nodular, initially peripheral and non-homogeneous, with progressive centripetal enhancement resulting in a homogeneously isodense/isointense aspect to the vessels in late phases. Type III enhancement is found in large hemangiomas and characterized by nodular, initially peripheral and non-homogeneous, with centripetal enhancement on subsequent images, similar to type II lesions, however, in this pattern a central scar is present, with no enhancement even in late phases. Atypical patterns of enhancement are not discussed here; however they usually have non-specific imaging findings leading its diagnose challenging and unsafe. Usually the pattern of enhancement of hemangiomas is better characterized by MRI than by CT. The typical signal hyperintensity on T2-weighted images might be useful for the diagnose of hemangioma on MRI. In type III lesions, the central scar is even more hyperintense on T2-weighted images.[137]

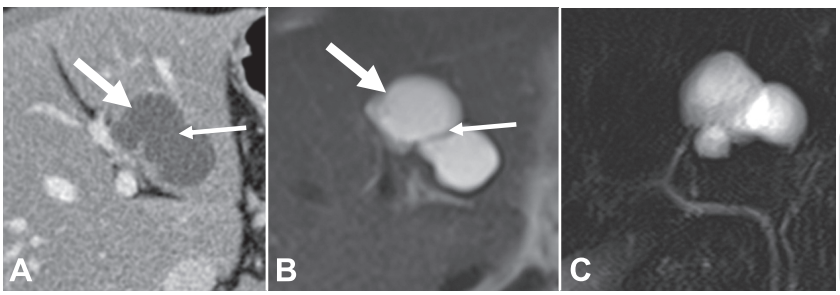


Figure 15. Complex cyst (thick arrows) on portal-venous phase of dynamic CT (A), T2-weighted MRI (B), and T2-weighted MRI cholangiography (**C**). Note the lobulated contour and the thin septum (thin arrow, better depicted on MRI).

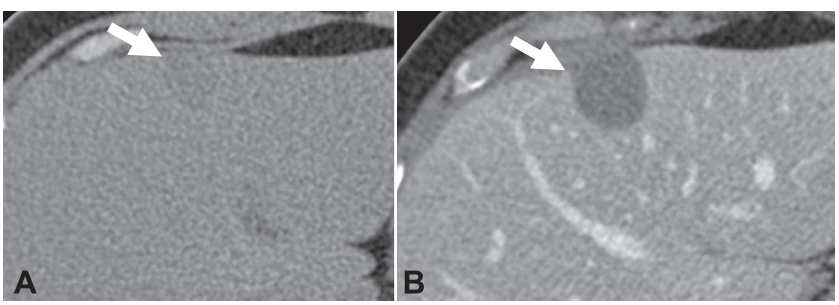


Figure 16. Complex cyst on pre-contrast (A) and portal-venous (B) phases of dynamic CT. A dense cyst (45 HU without contrast enhancement) on this location should raise suspicion for ciliated cyst.

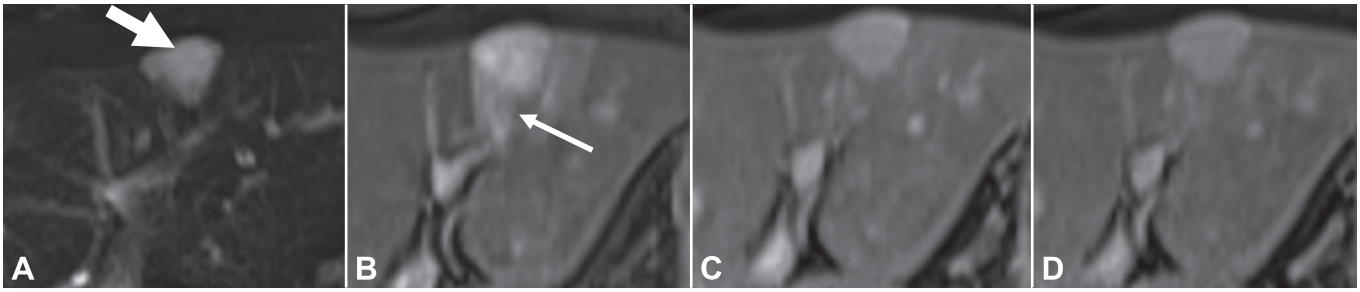


Figure 17. Type I hemangioma on dynamic MRI. **A**) T2-weighted image showing a well-defined hyperintense nodule (arrow). **B**) Arterial phase with intense enhancement and peripheric perfusion abnormality (arrow). **C** and **D**) Hyperintensity remains on portal-venous (C) and delayed (D) images, similar to the vessels.

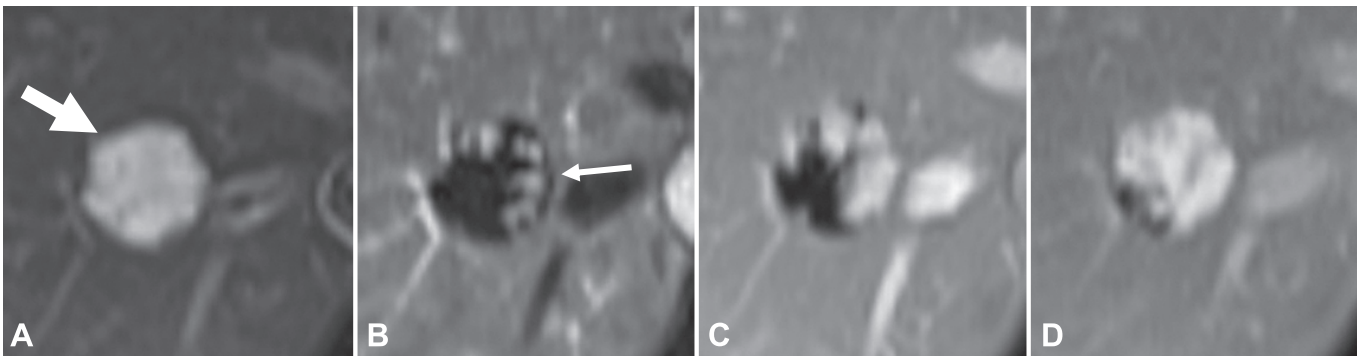


Figure 18. Type II hemangioma on MRI. **A**) T2-weighted image showing an hyperintense well-defined nodule (arrow). **B**) Arterial phase showing intense peripheric discontinuous nodular enhancement areas (thin arrow). **C**) On portal-venous-phase those nodular areas increase in size and tend to converge centripetally. **D**) On delayed phase the lesion tends to become homogeneously hyperintense, similar to the vessels.

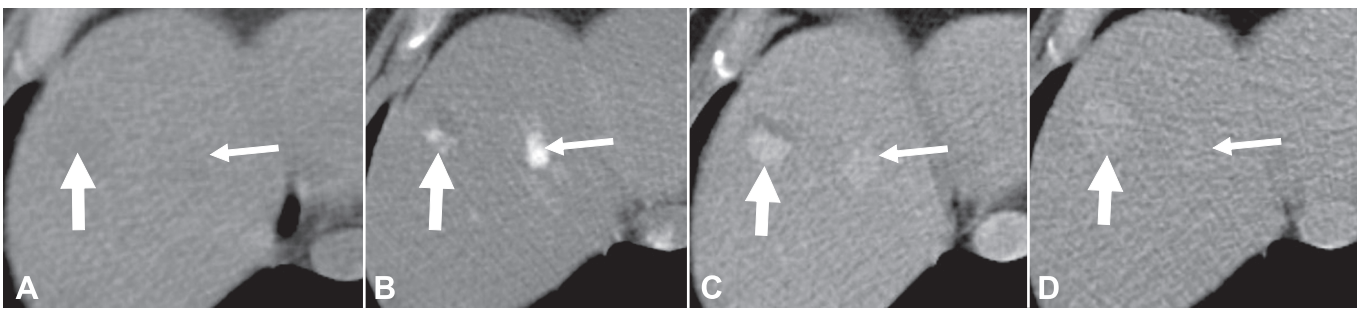


Figure 19. Type I (thick arrows) and type II (thin arrows) hemangiomas on dynamic CT. Pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases are shown. Note the enhancement of lesions similar to that of vessels.

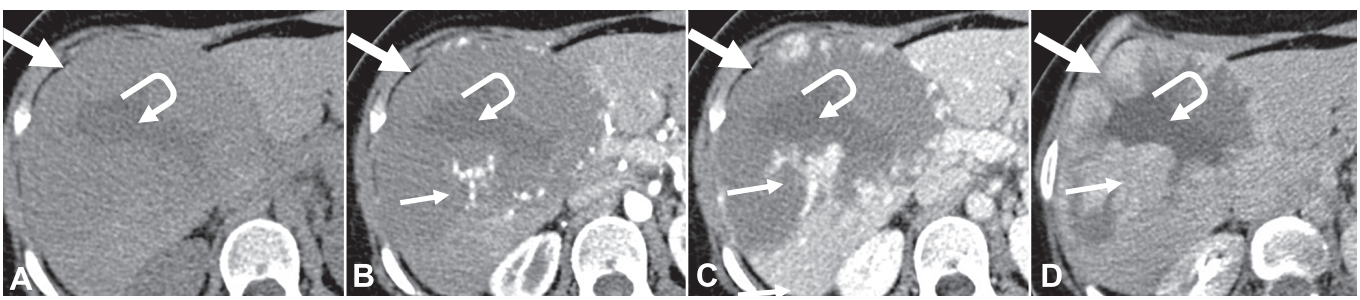


Figure 20. Type III hemangioma on pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of dynamic CT. A large liver lesion (thick arrow) with similar enhancement pattern of type II hemangioma (Centripetal discontinuous nodular enhancement – thin arrows). However, there is a "central scar", which is more hypodense than the lesion itself and do not enhance, even on delayed images. In MRI that "central scar" would be brighter than the lesion on T2-weighted images.

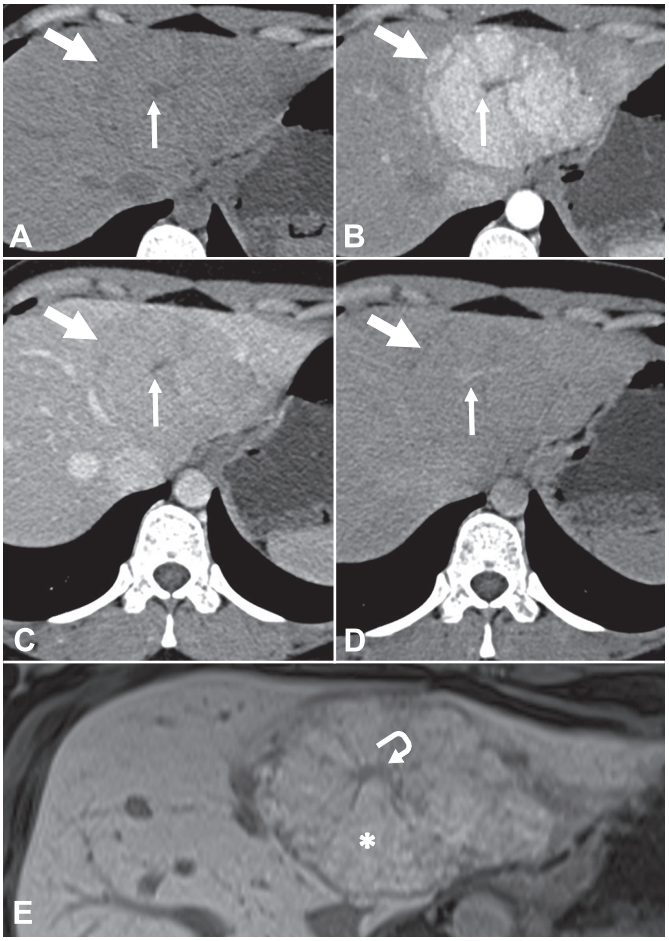


Figure 21. Typical focal nodular hyperplasia (FNH). **A** to **D**) Dynamic CT. The nodule has density close to liver parenchyma on pre-contrast phase (A), intense enhancement on arterial phase (B) and again density similar to liver parenchyma on portal-venous (C) and delayed (D) phases. A central scar (thin arrow) and radiating septa are seen, hypodense on pre-contrast and arterial phases, with progressive enhancement that is persistent on delayed phase. **E**) MRI after hepatobiliary contrast. Uptake is seen in the lesion (asterisk) but not in the central scar and septa (curved arrow). FNH usually has lobulated contour.

On CT, typical **FNH** ⑯ (**Figures 21** to **23**) appears as an isoattenuating nodule on images with no contrast (except if the rest of the liver is fatty, when FNH may appears hyperattenuating). The lesion is enhanced rapidly and transiently during the arterial phase, becoming isodense on portal and late phases. The central scar is hypodense on early phases and become iso- or hyperdense on delayed phases. Enlarged central arteries may be seen. On MRI, typical FNH is homogenous, well delineated, with lobulated aspect, and with signal intensity similar to liver parenchyma on T1-weighted and T2-weighted (or slightly low signal on T1-weighted and high signal on T2-weighted).

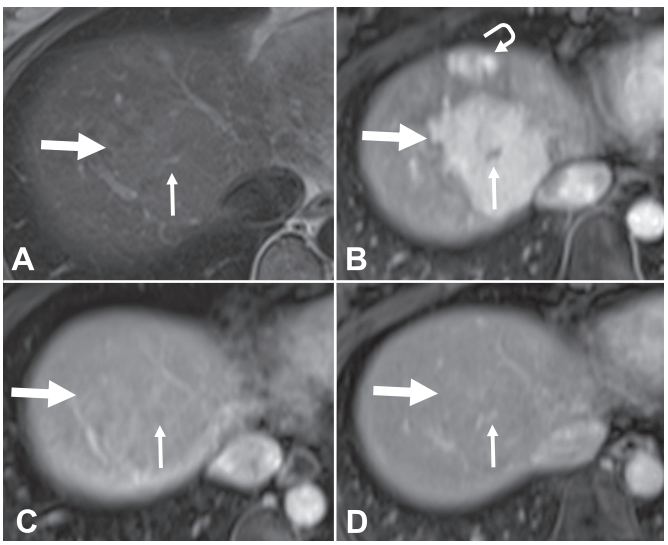


Figure 22. Typical focal nodular hyperplasia (FNH) on MRI. **A**) On pre-contrast T2-weighted the nodule has signal intensity close to liver parenchyma (thick arrow). **B** to **D**) Similar to CT, there is intense enhancement on arterial phase (B), and signal similar to the liver parenchyma on portal-venous (C) and delayed images (D). The central scar (thin arrows) is hyperintense on T2-weighted image (A) and no contrast enhancement occurs on arterial phase (B); on delayed phase it becomes hyperintense. The adjacent small nodule (curved arrow) seen on arterial phase (B) is another FNH.

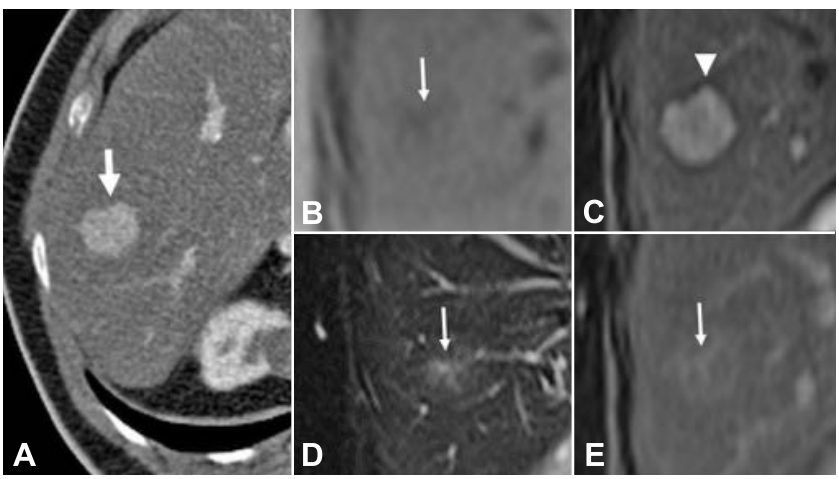


Figure 23. Focal nodular hyperplasia (FNH). **A**) Arterial phase of dynamic CT showing an indeterminate hypervascular nodule (arrow), not visible on the other phases (not shown). **B** to **E**) MRI depicted a central scar (arrows) with hypointensity on T1-weighted (B) and hyperintensity on T2-weighted (C) pre-contrast images. On post-contrast images the hypervascular nature of nodule (arrowhead) is depicted on arterial phase (D). On delayed phase (E) the central scar remains enhanced (arrow). These founds on MRI allows diagnosis of FNH.

Pattern of enhancement is similar to that of CT. The central scar is more frequently identified on MRI than on CT, and is typically high signal on T2-weighted when recognized.[137]

Suspected hepatic **adenoma** ⑰ (**Figures 24** to **26**) demonstrates early and relatively homogeneous enhancement returning to near isodensity on portal venous and delayed phase image. A peripheral halo may be seen in adenomas, contrarily to FNH. Fat and blood may also be found especially in large, complicated, and peripheral lesions. Microscopic fat can be detected using chemical shift on MRI. Also MRI can be helpful on distinguish histopathological and genetic subtypes: i) **inflammatory** adenomas are usually isointense or slightly hyperintense on T1-weighted, without loss of signal intensity on chemical shift imaging, and diffusely hyperintense on T2-weighted; there is intense enhancement during the arterial phase that persists on delayed images; ii) **HNF-1 (Hepatocyte Nuclear Factor 1) alpha-mutated** adenomas are usually hyper- or isointense on T1-weighted images, with signal loss in chemical shift imaging, and are isointense or slightly hyperintense on T2-weighted, with moderate enhancement during arterial phase and without enhancement persistence on delayed phases. The intensity of enhancement during the arterial phase varies according to the amount of fat inside the tumor, and nodules with large amount of fat may even do not show arterial enhancement.; iii) **beta-catenin-mutated** adenomas have no specific pattern on MRI and

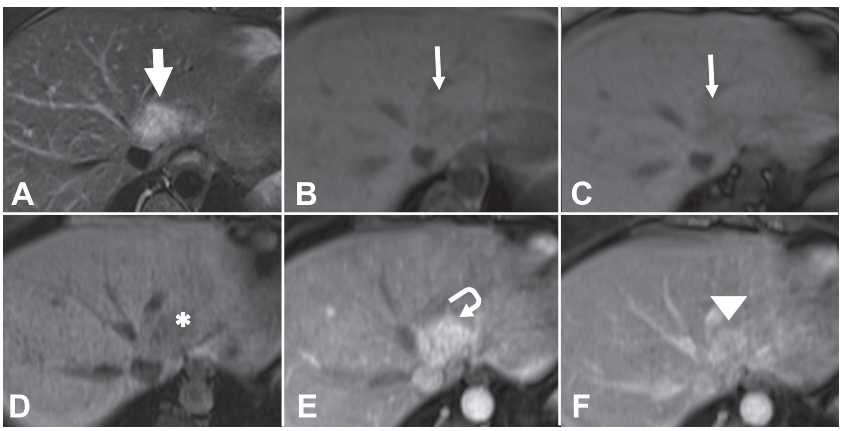


Figure 24. Suspected hepatic adenoma. MRI showing usual imaging features of inflamatory adenoma, presented as an hyperintense heterogeneous nodule (thick arrow) on T2-weitghted image (**A**), with no fat (thin arrow) on in-phase (**B**) and out-of-phase (**C**) images. The nodule is hypointense (asterisk) on pre-contrast phase (**D**), with intense enhancement (curved arrow) on arterial phase (**E**), that persist hyperintense (arrowhead) on portal-venous (**F**) and delayed phase (not shown)

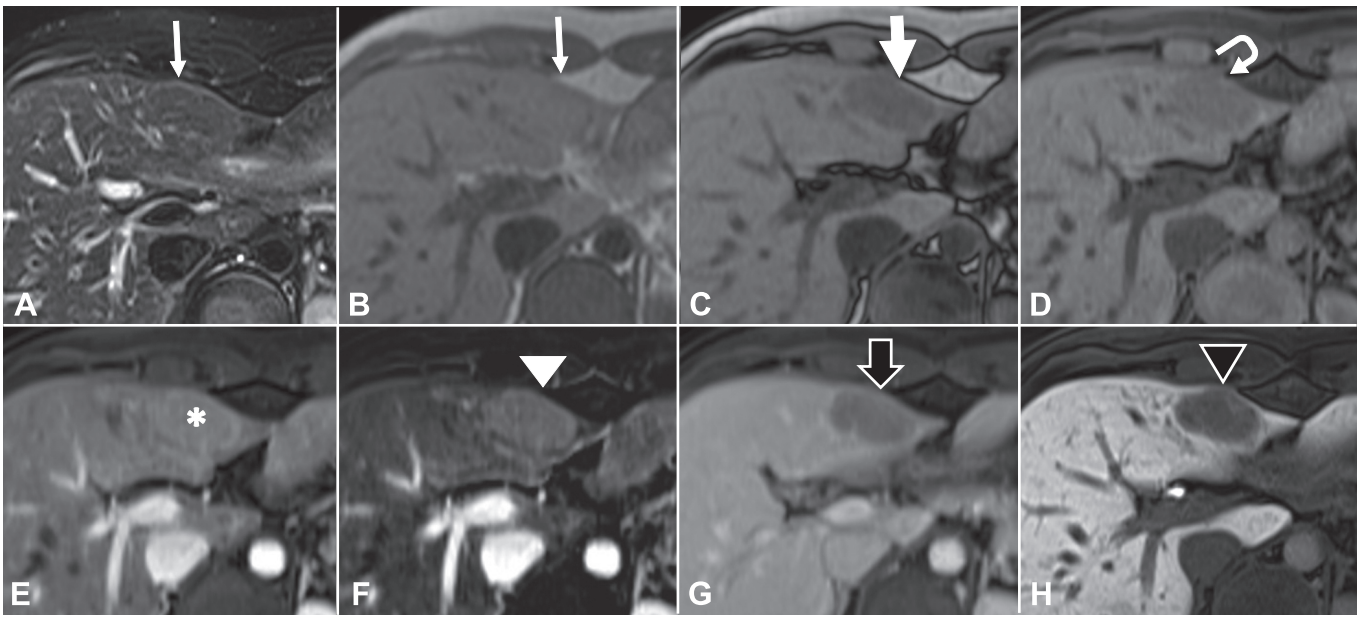


Figure 25. Suspected hepatic adenoma. MRI showing usual imaging features of HNF-1α-mutated adenoma. Signal intensity on T1- and T2-weighted images varies according the amount of fat inside. This nodule have signal intensity similar to liver (thin arrow) on T1-weighted (**A**) and T2-weighted (**B**) images. There is a signal drop (thick arrow) of the lesion on out-of-phase image (**C**) related to fat and a loss of signal (curved arrow) on fat-suppressed pre-contrast phase (**D**). On dynamic contrast images, the intensity of enhancement (asterisk) on arterial phase (**E**) is related to the amount of fat, better seen (arrowhead) in this case on subtracted image (**F**). There are hypointensity (open arrow) on portal-venous phase (**G**) representing washout and reduced contrast uptake (open arrowhead) on hepatobiliary phase (**H**).

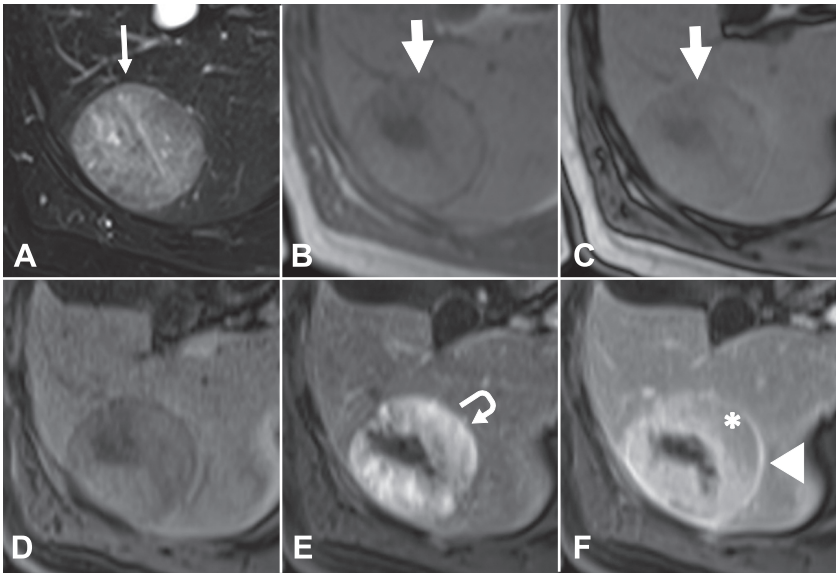


Figure 26. Hepatic adenoma (diagnosis proved after resection) with imaging features similar to hepatocellular carcinoma. There is mild heterogeneous hyperintensity (thin arrow) on T2-weighted image (**A**), with no evidence of fat (thick arrow) on T1-weighted in-phase (**B**) and on out-of-phase (**C**) images. On dynamic contrast study (**D** to **F**), there is arterial enhancement (curved-arrow) on arterial phase (**E**), with hypointensity (asterisk) and pseudo-capsule (arrowhead) on portal-venous phase (**F**).

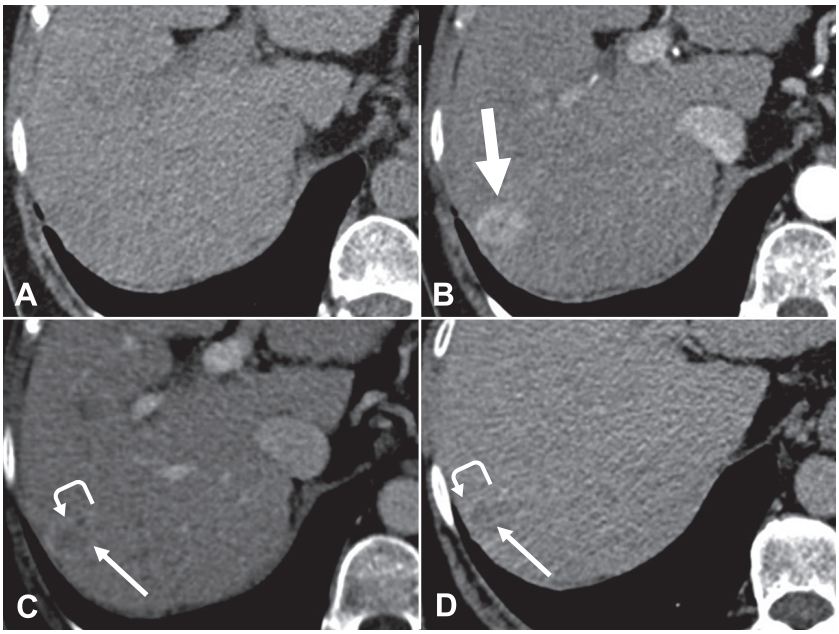


Figure 27. Typicaly hepatocellular adenocarcinoma on CT. Pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of a dynamic CT showing a typical small HCC with three major features: arterial enhancement (thick arrow), "washout" (thin arrow) on portal-venous and delayed phases (hypodensity related to the liver parenchyma), and pseudocapsule (curved arrow) on portal-venous and delayed phases. These features are in keeping with a LI-RADS 5 lesion.

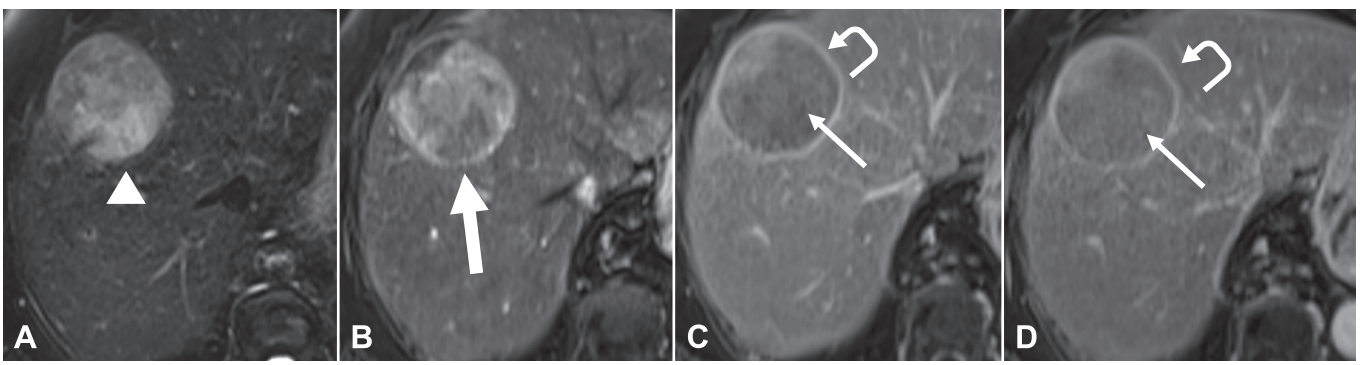


Figure 28. Typicaly hepatocellular carcinoma (HCC) on MRI. T2-weighted (**A**), arterial (**B**), portal-venous (**C**) and delayed (**D**) MRI images showing a typical large HCC with three major features: Intense enhancement (thick arrow) on arterial phase, "washout" (thin arrow), and pseudocapsule (curved arrow) on portal-venous and delayed phases. On T2-weighted image, the lesion is hyperintense and heterogeneous (mosaic architeture). These features correspond to a LI-RADS 5 lesion.

differential diagnosis with hepatocellular carcinoma is difficult. Of note that nearly 10% of adenomas are not included in the cited subtypes.

Hepatocellular carcinoma (HCC) ⑱ (**Figures 27** and **28**) features are discussed on **Chapter 13** (*Hepatocellular Carcinoma*) and this tumor should be included on the differential diagnosis of any hypervascular hepatic nodule. Typically HCC shows enhancement during arterial phase and non-homogeneous contrast washout during portal and/or delayed phases, with enhanced pseudocapsule on late phases. MRI is more accurate than CT on detecting HCC on chirrosis. LI-RADS (Liver Imaging Reporting and Data System) classification of nodules in patients at risk of HCC should be used to stratified risk according to imaging characteristics. Typical HCC represents category LI-RADS 5 with 100% certainty for HCC.

Fibrolammelar carcinoma ⑲ (**Figure 29**) should be included in differential diagnosis of nodules that are large, heterogeneous, with calcifications (70% to 95% of these tumors), with large central scar (usually more than 2 cm) which is hypointense on T2-weighted images on MRI, associate to increased hilar lymphnode (65% of cases), and occurring in non-cirrhotic liver.

Hypervascular liver **metastases** ⑳ (**Figures 30** and **31**) can be originated especially from renal clear cells tumor, melanoma, and endocrine tumor. Less frequently hypervascular metastases are from carcinoma of breast, pancreas, colon and lung, also from coriocarcinoma and sarcomas. Large metastases may present hypovascular central area in case of necrosis.

Vascular disorders ㉑ (**Figures 32** and **33**) on the liver may present diffusely or focally, sometimes mimicking focal lesions. Transient hepatic attenuation difference (THAD), hepatic infarction, arterio-portal shunt, passive congestion, peliosis hapatis, Budd-Chiari syndrome, hereditary hemorrhagic telangectasia (Osler-Weber-Rendu Syndrome), superior vena cava obstruction are examples of vascular disorders that occasionally may simulate focal lesions on radiological images.

Indeterminate hypervascular lesions ㉒ (**Figures 34** and **35**) should be evaluated according size of the nodule and the patient group risk. Small lesions on patients with low risk are usually benign and no additional evaluation or treatment is required. Large lesions or those occurring in patients with high risk should receive further evaluation.

Additionally, fat liver disorders may result on radiological images that simulate focal lesions (**Figure 36**). Focal area of steatosis or spared area on steatotic liver simulating focal lesions usually occur on hepatic peripheral or perivascular area, mainly adjacent to gallbladder, porta hepatis and falciform ligament, with no expansive effect, and generally with a triangular or geographical aspect. The MRI is the method of choice in doubtful cases.

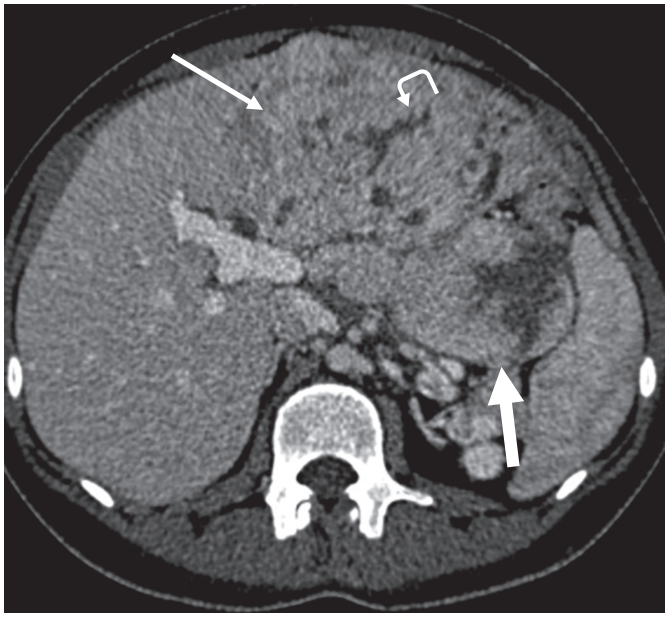


Figure 29. Fibrolamelar hepatocellular carcinoma. It should be suspected when there is a large heterogeneous nodule (thin arrow), usually with calcifications and/or large central scar (curved arrow) in a liver without characteristics of chirrosis. Enlarged lymph nodes are comum (thick arrow).

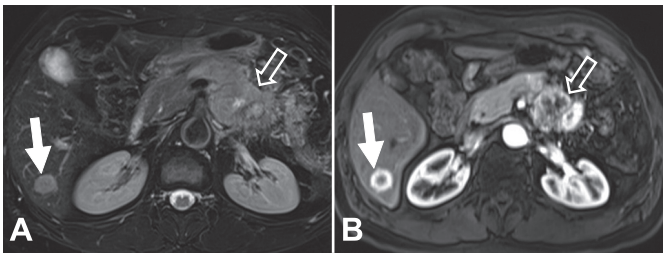


Figure 30. Hypervascular metastasis. Hepatic nodule (arrow) slightly hyperintense on T2-weighted image (**A**) with intense rim enhancement (arrow) on arterial phase of dynamic study (**B**), proved to be a metastasis. The primary tumor is depicted in the body/tail of pancreas (open arrow).

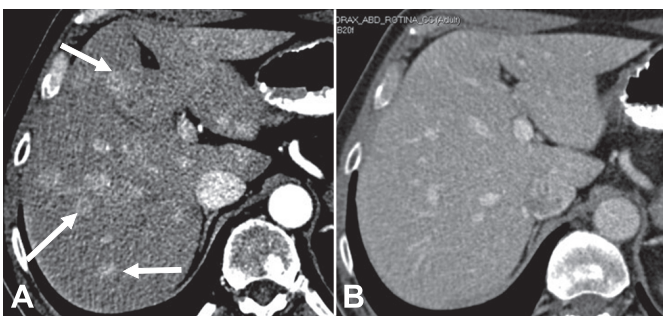


Figure 31. Hypervascular metastasis. **A**) Arterial phase of dynamic CT showing several hypervascular metastases from a bronchial endocrine tumor (some of them with a rim enhancement pattern). **B**) Portal-venous phase of dynamic CT at the same level of (A). No lesion is visible on this phase, disclosing the need of the arterial phase to detect some liver lesions.

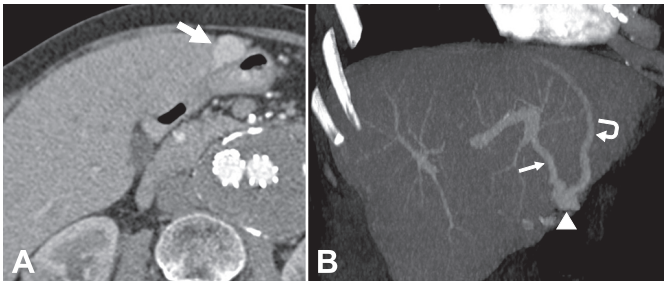


Figure 32. Portal-systemic shunt. **A**) Arterial phase of dynamic CT with a hypervascular nodular image in the left liver. **B**) MIP reformatation showing the communication (arrowhead) between a left portal vein branch (thin arrow) and the left hepatic vein (curved arrow), which has prompt enhancement due to the vascular shunt.

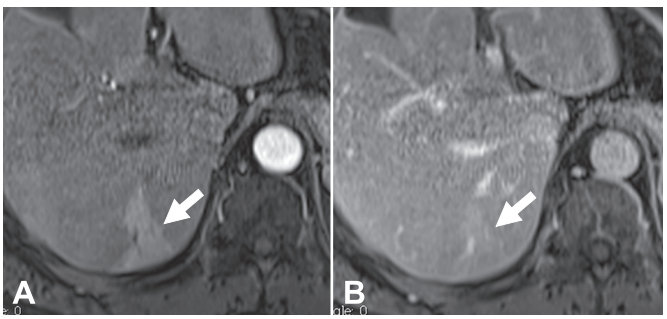


Figure 33. Transient hepatic attenuation/intensity differences (THAD/THID). Arterial (**A**) and portal-venous (**B**) phases of dynamic MRI showing a peripheric wedge-shaped area (thick arrow) of enhancement on arterial phase that become homogeneous on subsequent phases in keeping with a perfusion abnormality. Care should be taken about concomitant nodule (specially in the apex of wedge-shaped area), which can be the cause of the perfusion abnormality.

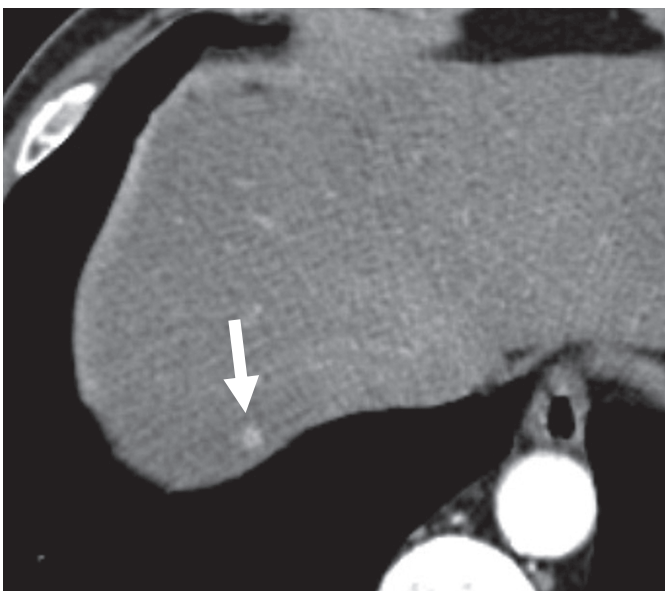


Figure 34. Hypervascular indeterminate nodule. Arterial phase of dynamic CT showing a tiny liver nodule visible only on this phase, in keeping with an indeterminate hypervascular nodule.

ADDITIONAL EVALUATION

Despite only a minority of incidental lesions requires supplemental investigations for a definite diagnosis, some methods may be helpful on management or definitive diagnosis of incidentalomas.

Hepatic MRI with liver-specific contrast

This method has replaced otheHHr radiological methods such as labeled red blood cell scans, sulfur colloid scans, and visceral angiography. Liver-specific contrast MRI combines vascular and hepatocyte-specific properties, being called bimodal contrast agents. Liver-specific contrast MRI is particularly useful in hypervascular lesions that are not hemangioma. Sensitivity and specificity to distinguish FNH and adenoma are up to 96% and 100%, respectively.[47,93] A recent meta-analysis evaluating the accuracy of MRI with liver-specific contrast agent for HCC detection showed an area under the ROC curve of 0.98 for overall HCC, 0.98 for HCC in patients with cirrhosis, and 0.99 for HCC 2.0 cm or smaller in diameter.[138] However, severe hepatocellular dysfunction (cirrhosis Child C) and cholestasis may prevent sufficient contrast uptake to obtain an adequate hepatocellular phase. In summary, liver-specific contrast play a special role on hepatocellular adenoma, focal nodular hyperplasia, hepatocellular carcinoma (mainly small one), and liver metastases. Biliary leakage may also be evaluated by these liver-specific contrast agents due to their partially biliary excretion of contrast, however, usually more delayed images are required.

Positron emission tomography – computed tomography (PET/CT).

18F-fluorodeoxyglucose (FDG) PET/CT has been used in the management of liver lesions, particularly it has a high sensitivity and specificity for detection of liver metastases from a range of primary cancers. Detection of additional metastases, intra- or extrahepatic, may change clinical management. However, false negatives can be seen in small lesions (less than 1 cm) and tumors that exhibit low glucose uptake (such as metastases from well-differentiated neuroendocrine tumors and some hepatocellular carcinomas) or have suffered significant necrosis.[139] False positive results are rare, but were described for abscesses and other inflammatory lesions (especially granulomatous ones) and liver adenomas.[93,140,141] Other biomarkers than FDG has been explored to increase sensitivity of PET/CT for hepatocellular carcinoma and other tumors.

Technetion-99m Labelled Red Blood Cell (RBC)

Labelled RBC Scintigraphy has a high specifitiy and positive predictive value for hepatic hemangioma. The standard pattern of images on this radiological method is a perfusion/

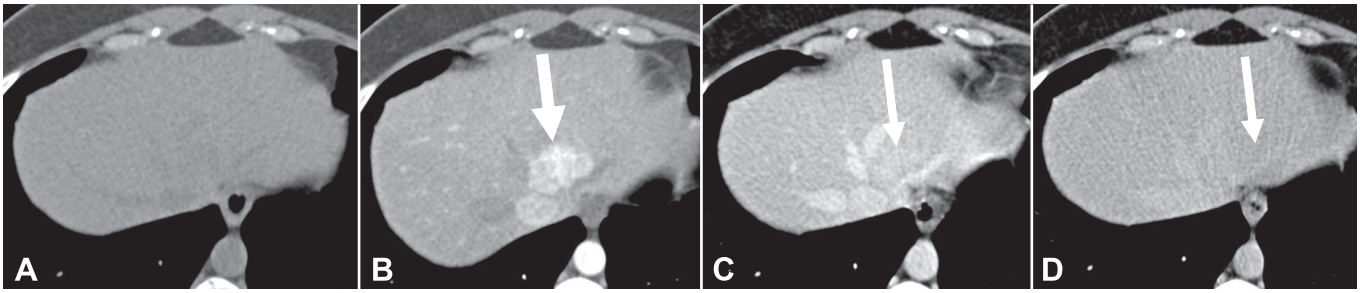


Figure 35. Hypervascular indeterminate nodule. Pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of a dynamic CT showing a large hypervascular liver nodule in segment 4, which has arterial enhancement (thick arrow) and becomes isodense to liver on the later phases. There is no sufficient specific findings to a precise diagnostic. This lesion should be considered a indeterminate nodule on CT. Further MRI (not shown) showed features suggesting adenoma and diagnosis confirmed after resection.

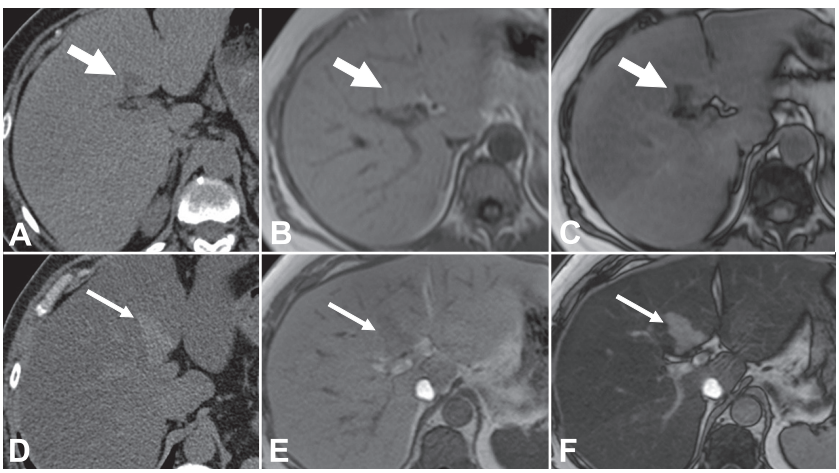


Figure 36. Hepatic steatosis. **A** to **C**) Area of focal steatosis on pre-contrast CT (A), in-phase T1-weighted MRI (B), and out-of-phase T1-weighted MRI (C). **D** to **F**) Area spared of steatosis (another patient) on pre-contrast CT (D), in-phase T1-weighted MRI (E), and out-of-phase T1-weighted MRI (F).

blood pool mismatch, i.e. a decreased perfusion on early dynamic images and a gradual increase in activity on blood pool images. This pattern of activity is rarely seen in other causes of liver nodules. On the other hand, labeled RBC scintigraphy has a limited sensitivity for the detection of small hemangiomas or those located adjacent to the heart or major vessels. Also, false negative results may occur on large hemangiomas with extensive thrombosis or fibrosis.

Technetion-99m Sulphur Colloid Scintigraphy

Uptake of technetion-99m sulphur colloid is seen in around 80% of patients with FNH and may be useful in evaluating indeterminate liver lesions. However, it has limited utility in differentiating FNH and adenoma, because adenomas occasionally demonstrate tracer uptake.

Pathological diagnosis

Sample tissue for histologic assessment can be obtained through biopsy or tumor resection. Most of the data on percutaneous biopsy comes from patients with known or suspected malignancies, when its global accuracy is close to 90%. However, it carries a non-negligible risk of morbidity (mainly bleeding and tumor seeding) of 2 to 4.8% and even mortality (0.05%).[142–145] Nonetheless, modern imaging methods can reach similar or even greater accuracy than percutaneous biopsy. Thus, needle biopsy is most appropriate in patients with an apparent malignancy of unknown origin in whom resection is clinically contraindicated or not technically possible.

For small size HI percutaneous biopsy can be challenging due to the technical issues and the difficulties for the pathologist to give a definitive diagnosis with limited samples. Moreover, very rarely pathological analysis of HI results in a modification of the patient management. Whenever necessary, tissue sample is more appropriate obtained by surgical excision. Despite of that, percutaneous biopsy could have a place in patients not candidates for a surgical resection.

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A review including discussion of the clinical differential diagnosis of the most common liver masses.

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19 Non-Parasitic Cystic Diseases of the Liver

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- *Non-parasitic cystic lesions of the liver are common (up to 5-20% of the population), mainly simple cysts, and increasing in incidence with age. Most of them are asymptomatic and diagnosed incidentally at abdominal surgery or radiological studies for unrelated disease.*
- *Symptomatic simple cysts and polycystic liver disease are frequently treated by deroofing or partial hepatectomy (associated or not with deroofing of residual cysts). In selected cases, liver transplantation can represent the only definitive treatment, especially if portal hypertension or cirrhosis is present. Percutaneous aspiration, with or without sclerotherapy, can be useful to determine if symptoms are related to the cysts to be treated, or it can be used rarely as a definitive treatment (when associated with sclerotherapy).*
- *Neoplastic cysts include benign biliary cystadenoma and cystadenocarcinoma. Cystadenoma originates from intrahepatic bile ducts and may undergo malignant transformation to biliary cystadenocarcinoma, and therefore require more aggressive management.*
- *Cystic biliary dilatation of Caroli's disease is frequently associated with complications, especially hepatolithiasis and recurrent cholangitis. Liver resection is the treatment of choice for unilobar disease, and it can be associated with contra-lateral clearance of stones in bilobar disease. Treatment of diffuse disease is challenging, sometimes requiring liver transplantation as a definitive treatment.*
- *- Other rare cystic lesions of the liver include cystic metastases or primary tumors and post-traumatic cysts among others. They should have individualized treatment.*

INTRODUCTION

Non-parasitic cystic lesions of the liver are relatively common, occurring in up to 5-20% of the population and increasing in incidence with age.[1–5] Most of them are asymptomatic and diagnosed incidentally at abdominal surgery or radiological studies for unrelated disease (**Figure 1**). However, symptoms (such as pain, nausea, vomiting, early satiety, or heartburn) and/or complications (such as bleeding, rupture, infection, torsion, malignant transformation, or obstructive jaundice) occur in nearly 5% and invasive therapy is often needed.[6]

The pathogenesis of non-parasitic cystic liver disease is related to its etiology. Hepatic cysts can originate from congenital malformations (simple cysts), genetic mutations (polycystic liver disease), and trauma to the intrahepatic biliary tree (traumatic cysts) or be of unknown etiology (benign biliary cystadenoma and biliary cystadenocarcinoma). Cysts may be solitary, multiple or diffuse and of variable size.

Simple cysts are the most frequently non-parasitic cystic lesions of the liver with a prevalence of 2.5 to 18% of the population. Simple cysts are lined by cuboidal or columnar epithelium, contain serous fluid and tend to be singular. They do not communicate with the intrahepatic biliary tree and are surrounded by normal hepatic tissue. They are thought to arise from the abnormal development of intrahepatic bile ducts in-utero. Malignant transformation of the lining epithelium has also been known to occur. Adenocarcinomas, squamous cell carcinomas and sarcomas have all been described.[7–9]

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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Other less common diseases, benign and malignant, must however be considered and include a variety of diseases, such as polycystic liver disease (prevalence of 0.1% to 0.6% of the population), biliary cystic tumors (5% of all hepatic cysts),[10] hepatic abscesses, Caroli's disease (incidence of 1:1,000,000), cystic liver metastasis or primary hepatocellular carcinoma, post-traumatic cysts, hamartomas (also called von Meyenburg complexes, prevalence of 0 to 2.8% of the population), intrahepatic pancreatic pseudocysts, ciliated hepatic foregut cysts (some 100 reported cases), epidermoid cyst, lymphangiomas, biloma, endometrial cysts, and biliary intraductal papillary mucinous tumor.

CLINICAL FEATURES ON NON-PARASITIC HEPATIC CYSTS

Despite sometimes challenging, the differential diagnosis among the etiologies of hepatic cystic lesions is often necessary since the approach differs. Characterization of liver cysts is provided mainly by imaging tests including ultrasonography, computed tomography, magnetic resonance imaging and, rarely, endoscopic retrograde cholangio-pancreatography or magnetic resonance cholangio-pancreatography. More recently positron emission tomography has shown promising in the diagnosis of hepatic lesions, but its role in managing cystic disease is limited. The diagnosis of benign non-parasitic cystic disease of the liver remains frequently one of exclusion and involves ruling out other more sinister pathology by non-invasive imaging.

Abdominal ultrasonography differentiates cystic from solid lesions (**Figure 2)**; computed tomography and magnetic resonance imaging with intravenous contrast are useful to detect the size, number and nature of lesions as well as to further define precise anatomical location. The optimal reconstructed section thickness for detection of liver lesion on computed tomography is of 5mm or less.[11] Endoscopic retrograde cholangio-pancreatography and magnetic resonance cholangio-pancreatography are only used if doubt concerning biliary communication or evidence of biliary obstruction are present. Laparoscopy allows direct visualization of certain liver lesions and can be combined with intraoperative ultrasound, especially to plan surgical management.

Although radiological characterization of cystic hepatic pathology is generally accurate, a high index of suspicion of neoplastic disease should always be maintained. Radiological differentiation between a simple cyst with intra-cystic hemorrhage and a cystadenoma may be challenging. Routine liver function tests are almost invariably within normal limits in patients with non-parasitic cystic liver disease. Complicated cysts may present with a mild increase in serum transaminases or alkaline phosphatase levels. There is no role for biopsy or fine-needle aspiration for the diagnosis of cysts since this is potentially associated with hemorrhage, sampling error, misdiagnosis, and also may be responsible for infection of a non-complicated cyst. In fact, formal definitive diagnosis may not be ascertained until the lesion has been resected, partially (by deroofing) or completely.

GENERAL MANAGEMENT OF NON-PARASITIC HEPATIC CYSTS

Globally, the management of non-parasitic cysts of the liver varies from simple observation or few invasive techniques (such as percutaneous aspiration and sclerosing) to more aggressive procedures (such as open or laparoscopic



Figure 1. CT undertaken for other intra-abdominal pathology showing multiple asymptomatic small cysts throughout liver.

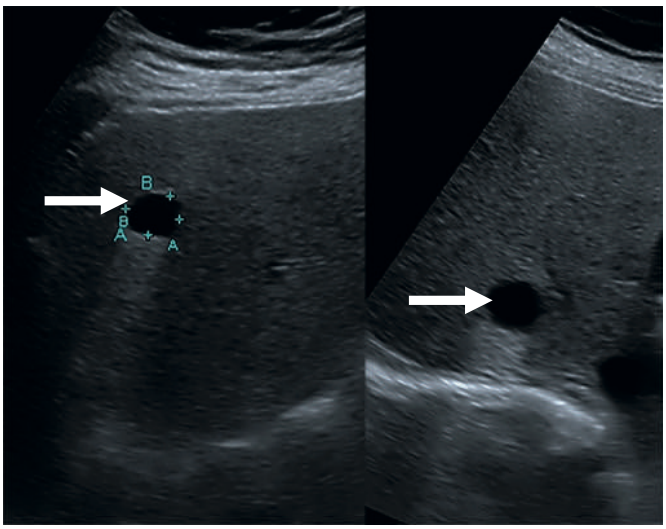


Figure 2. Simple cysts on ultrasound (arrows): anechoic, homogeneous, sharply delimited, and with posterior reinforcement.

deroofing, hepatic resection, or even liver transplantation). Thus, the surgeon should be thoroughly familiar with clinical features and natural history of each etiology of non-parasitic hepatic cysts, as well as the therapeutic options available.

There is little rationale for performing percutaneous aspiration alone (without sclerosing agents) on non-parasitic hepatic cysts. However, this procedure can be useful in selecting patients that might benefit from definitive treatment of simple cysts.[12] Percutaneous aspiration followed by instillation of a sclerosing agent injection (diluted 1:4 with the aspirated fluid and re-aspiration after 10-15min) is said to represent a relatively non-invasive method of management of certain non-parasitic hepatic cysts. Despite the frequently reported high recurrence rates following this procedure it could be used for short-term relief of symptoms whilst awaiting definitive treatment or as definitive treatment in patients not fit for surgery. Complications of percutaneous needle aspiration include inadvertent perforation of gallbladder or colon, cyst infection, and irreversible sclerosing cholangitis if the sclerosing agent is injected in the presence of undetected biliary communication.[13,14]

Cyst deroofing or fenestration (by open or laparoscopic technique) can provide definitive management of some cystic liver disease, such as in selected cases of simple cysts or polycystic liver disease. One or more cysts are aspirated then deroofed to achieve volume reduction.[15] Since the first description of the laparoscopic technique on the treatment of cystic liver disease, in 1991,[16] this technique has become the preferred method for cyst deroofing. It is associated with lower rates of morbidity (11% to 50%), lower re-operation rate, and shorter postoperative stay compared with open surgical techniques.[15,17,18] Complications include hemorrhage, ascites, bile leak, and pleural effusion but the majority of complications occur when deeper located cysts are treated.[15,18] The best indications for laparoscopic deroofing include symptomatic simple cysts and polycystic liver disease type I and II of Gigot classification (see below). Deroofing of cystic lesions located posteriorly on the liver, in segments 7 and 8, are prone to recurrence because early adhesion of the fenestrated cyst with the diaphragm eliminates the communication with the peritoneum. Cyst deroofing of remnant lesions is often performed in association with hepatic resection for polycystic liver disease.

Liver resection may be considered when either percutaneous drainage with sclerotherapy and laparoscopic or open deroofing procedures are unsuccessful or not indicated. Liver resection is the treatment of choice for biliary cystic tumors (cystadenoma and cystadenocarcinoma) due to the risk of recurrence and malignancy. It may also be the preferred approach in diffuse polycystic liver disease when cysts predominate in one side of the liver (usually in combination with deroofing or remnant cysts). Postoperative liver dysfunction is uncommon after hepatectomy for cystic liver diseases but consideration must be given to the amount of functional remnant liver, especially in polycystic liver disease. Morbidity rates are low (nearly 17%),[19] and liver resection has become more popular as the preferred management in many centers. Hepatectomy for polycystic liver disease is challenging due to the distortion of the anatomy and compression of vascular and biliary structures. As a result, patents are susceptible to developing postoperative ascites, bile leakage and sepsis, which can be difficult to manage, as discussed below. In selected cases of polycystic liver disease, liver transplantation represents the best therapeutic choice. Gall et al.[17] reviewed a large series of non-parasitic hepatic cysts and proposed a rationale algorithm for treatment based on the etiology and pattern of diseases.

In summary, there has been no general consensus on the optimal approach to management of symptomatic hepatic cysts due to their low incidence in the general population, and patients have been treated on an individual basis. In symptomatic or complicated cases of simple cysts or polycystic liver disease there is considerable debate about the best approach. On the other hand, there is no doubt that complete resection of biliary cystic tumors of the liver (cystadenoma and cystadenocarcinoma) is the best definitive treatment. The ideal approach to more rare pathologies lacks of consensus.

SIMPLE CYSTS OF THE LIVER

ETIOLOGY AND PATHOGENESIS

The prevalence of simple cystic disease in the general population is 3.6% to 18% [2,20–22], with a female to male ratio of 4:1 in non-symptomatic cases. This ratio rises to 10:1 in symptomatic or complicated cases.[21] Huge or giant cysts almost exclusively affect women over the age of 50 years (**Figure 3**). The cause of simple liver cysts is unknown, however they are believed to be congenital in origin and may develop from micro-hamartomas that fail to develop normal connections with the biliary tree, continue to secrete intraluminal fluid and progressively dilate.

Macroscopically, simple cysts appear as unilocular fluid filled lesions without septa that are distinctly separate from the surrounding hepatic parenchyma with a smooth and translucent external surface. The adjacent hepatic tissue may atrophy as the cyst enlarges (**Figure 4**). Large or giant cysts can occupy an entire lobe of the liver, resulting in compensatory contralateral hypertrophy. Also, these can be pedunculated and carry a risk of torsion.

Histologically, simple cysts have an outer layer of thin

fibrous tissue and are lined by a single layer of cuboidal or columnar epithelium, similar to biliary epithelium, that continually secretes serous fluid. (**Figure 5**) This fluid does not contain bile, amylase or white blood cells. Cysts lined by squamous epithelium have been reported and in these circumstances may complicate by the development of squamous cell carcinoma.[23] Malignant transformation to adenocarcinoma and sarcoma has also been reported but such risk would not represent an indication for intervention in the asymptomatic patient.

CLINICAL PRESENTATION

The majority of simple cysts are asymptomatic and are discovered incidentally on radiological investigation for other pathology. However, symptoms are present in 10% to 15% of patients and complications in 5%.[21–31] Large cysts can cause abdominal pain or discomfort in the right upper quadrant, the most common symptom of simple cysts. Other manifestations include anorexia, abdominal bloating, vomiting, and early satiety due to local mass effect. Occasionally, a cyst can be large enough to produce a palpable abdominal mass in the hypochondrium. The most common complications are infection (frequently monomicrobial by E. coli) and intra-cystic hemorrhage.[32,33] Obstructive jaundice is uncommon, but can be caused by external compression of the biliary tree.[23,34,35] Similarly, portal hypertension and acute Budd-Chiari syndrome have been reported as a result of compression of the hepatic veins and portal vein, due to mass effect.[23,36,37] Other rare complications include rupture, acute torsion of a mobile cyst [38], acute pulmonary embolism and malignant transformation, among others.[39,40] Intracystic bleeding is a particular complication that is said to occur more often in elderly patients and can lead to rapid growth of the cyst, acute pain, and compressive thrombosis of the inferior vena cava.[41] This complication also confounds the differential diagnosis with hepatic cystadenoma.[24,42,43] Patients with cyst torsion may present with symptoms of an acute abdomen and those with cyst rupture may develop peritoneal symptoms or secondary infection leading to a similar presentation of hepatic abscess including abdominal pain, fever and leukocytosis.

INVESTIGATION

Diagnosis can be made by abdominal ultrasonography, the most cost-effective imaging method, which typically reveals circular or oval anechoic areas in the liver, with well-defined boundaries, no septations or internal echoes, and posterior acoustic enhancement (**Figure 2**). Cysts can be single or multiple. Simple cysts do not have an evident wall on ultrasonography, unlike parasitic or neoplastic cysts. Simple cysts complicated by intracystic bleeding can present with internal acoustic shadowing and the differential diagnosis with neoplastic lesions (especially cystadenoma or cystadenocarcinoma) can become challenging. Occasionally, two or more simple cysts in direct contact lead to images mimicking intracystic septations that are in fact the wall of adjacent cysts without liver parenchyma between them. Ultrasonography examination of the kidneys in addition to

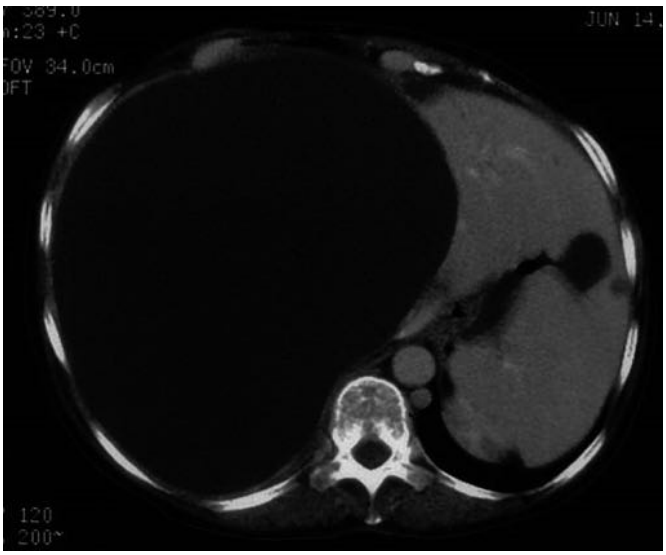


Figure 3. CT demonstrating a large solitary cyst involving entire right liver. There is resulting hypertrophy of the left hemi-liver which enabled laparoscopic radical deroofing of the liver.

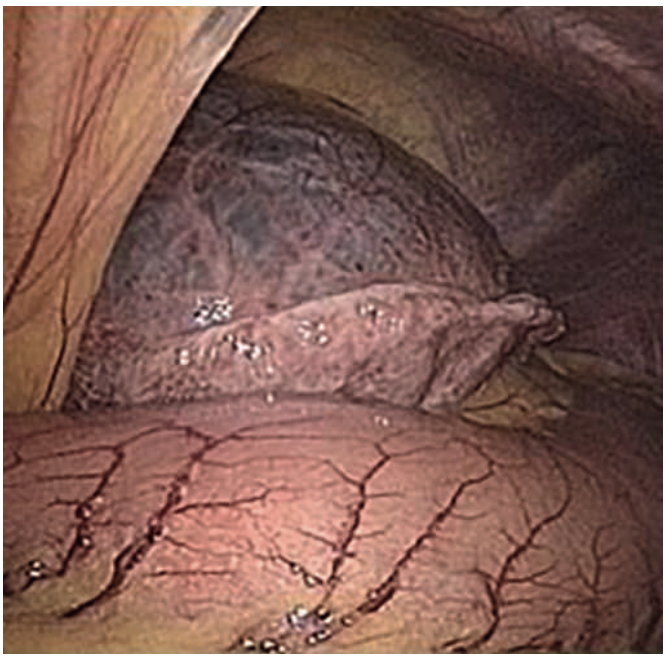


Figure 4. Laparoscopic view showing complete replacement of left lobe by a simple cyst. Note the atrophied residual edge of the liver and the blue doomed appearance of the cyst. Segmental pedicles have been stretched and displaced to reveal them on the cyst wall.

the liver is useful in excluding autosomal dominant polycystic kidney disease. For asymptomatic patients further radiological investigation is seldom required.[21,25,31,44]

If symptoms are present, there is a rapid increase in size, or there is a clinical suspicion of neoplastic origin or transformation, further imaging by computed tomography or magnetic resonance imaging should be performed. These methods can provide additional information about the number of cysts, the amount liver tissue surrounding the lesion and allow accurate location of the cysts in the liver. Simple cysts appear as well-rounded water density lesions without septa on computed tomography imaging. (**Figure 3**) Magnetic resonance imaging is useful for the diagnosis of intracystic complications, such as bleeding or infection. Uncomplicated simple cysts are homogeneously hyperintense on T2 and low intensity on T1. The use of intravenous contrast enhancement confirms the avascularity of these lesions. Hemorrhagic cysts may appear with a relatively thick wall and may contain intracystic debris mimicking other cystic pathology. Cystadenoma, cystadenocarcinoma or carcinoma arising in a simple cyst, can present as a thickening one area of the cyst wall (**Figure 6**). Also, if calcifications are evident on the cyst wall, serological tests for hydatid disease should be performed to exclude parasitic infection on patients from endemic areas.

MANAGEMENT

Asymptomatic simple cysts require no treatment. The size of the cyst itself does not represent an indication for treatment, although large cysts are frequently symptomatic. Treatment methods for symptomatic or complicated cases may be non-surgical (such as percutaneous aspiration with or without sclerosing agent injection) or surgical (such as laparoscopic or open deroofing, and hepatectomy). There is some controversy in determining the treatment of choice for symptomatic simple cysts, but most recent evidence suggests that laparoscopic deroofing is preferred.

Percutaneous aspiration alone is not a definitive treatment since recurrence of cystic fluid is the norm.[14,19,45,46] Also, the procedure is not free of risks and hemorrhage and/or infection can occur. Percutaneous drainage associated with instillation of sclerosing agent (alcohol, minocycline, monoethanolamine oleate, or pantopaque) may prevent the cyst epithelium form producing fluid thereby reduce the risk of recurrence. However, the use of sclerosing agents exposes the patient to the risk of irreversible sclerosing cholangitis if a biliary communication is present. Thus, cystography by injection of contrast after cystic fluid aspiration is recommended before sclerosis. Percutaneous aspiration is useful preoperatively to determine whether the symptoms are attributable to the cyst and it can be an option for patients ineligible for surgery.[45]

Cyst deroofing (excision of the largest possible part of the roof of the cyst), leading to drainage of its fluid content into the peritoneal cavity, provides effective long-term results. Recurrence rates range from 0 to 20%.[47–52] Some authors suggest the association of concomitant epithelial destruction by sclerosing agents (before deroofing) or coagulation (argon beam or electrocoagulation).[48,49,52] However, coagulation of the residual epithelium can result in thermic injury to adjacent biliary ducts and result in bile leakage. Similarly, sclerosing agents must not be instilled for the reasons noted above. Deroofing of the cyst, as opposed to percutaneous

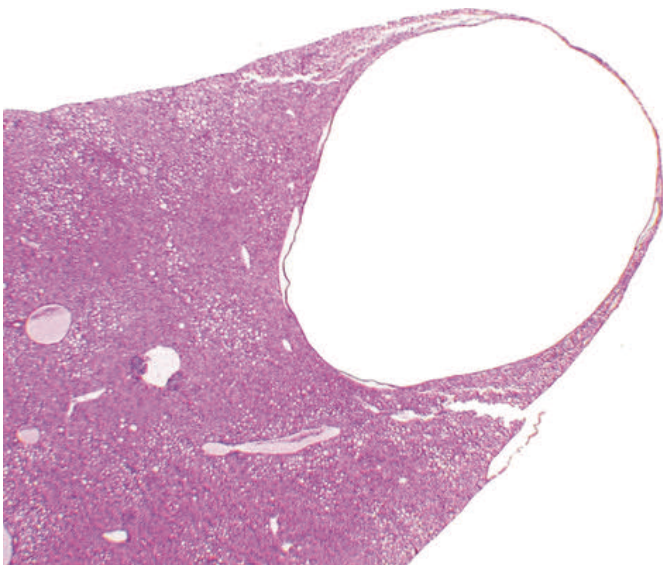


Figure 5. H&E stain of large solitary cyst that demonstrates a single layer of flattened cuboidal cells lining the cyst, the wall of which is comprised by compressed liver cells and some fibrotic tissue.



Figure 6. Computed tomography showing concomitant simple cyst and cystadenoma in a 56 year-old woman. The small simple cyst (arrow head) has homogenous content and no septa. The cystadenoma (arrow) has septations and wall thickness. Patient was treated by left lateral sectorectomy and histology confirmed the diagnosis.

procedures, also has the advantage of direct visualization of the epithelium and permits histopathological analysis of the resected portion of the wall, excluding the diagnosis of other cyst pathology. Deroofing of large central cysts can be associated with parenchymal resection to minimize the risk of recurrence and complication (**Figure 7**).

Laparoscopic deroofing has replaced open surgery with similar long-term results and lower morbidity rates (0 to 25%), shorter postoperative hospital stay and a lower requirement for reoperation.[17,26,27,29,48,49,53,54] Thus, laparoscopic deroofing is considered the treatment of choice in most centers. The disadvantages of incomplete removal of the cyst wall include the potential risk for cyst recurrence, infectious complications and the risk of malignant transformation on the remnant cyst epithelium. However, malignant transformation of simple cysts is anecdotal and has never been observed by the authors. The main long-term complication is recurrence.

A potential limitation to a deroofing procedure (open or laparoscopic) is with involvement of hepatic segments 7 and/or 8, due to the risk of early adhesion to the diaphragm or abdominal wall with resultant loss of the communication created with the peritoneum leading to recurrence. Omentoplasty may prevent recurrence in this situation.[55] The utility of this technique is questionable and it is not evident that it confers additional advantage over radical deroofing and or resection.[56]

In the rare situation of biliary communication between a simple cyst and the biliary tree, where sclerosis is contraindicated, optional methods include suturing of the communication, hepatic resection, or cystojejunostomy.[46]

More radical procedures, such as cystectomy or formal hepatectomy are rarely performed. Complete cystectomy can only be achieved by hepatic resection since a clear plane of dissection between the cyst and the liver is lacking. Liver resection results in excellent long-term outcomes, but is associated with higher rates of morbidity.[17] It should be considered in patients for whom deroofing or a percutaneous approach are more likely to result in recurrence, such as in large cysts on the posterior hepatic segments and in patients submitted to previous abdominal surgery. Liver transplantation for simple cystic liver disease is rarely indicated and more likely to be indicated for complications of previous inadequate intervention rather than uncomplicated simple hepatic cystic disease.

In summary, both laparoscopic deroofing and percutaneous approaches (aspiration with sclerosis) are appropriate treatments for most symptomatic simple cysts of the liver, associated with no mortality, low morbidity, and satisfactory long-term results. Liver resection is rarely necessary.

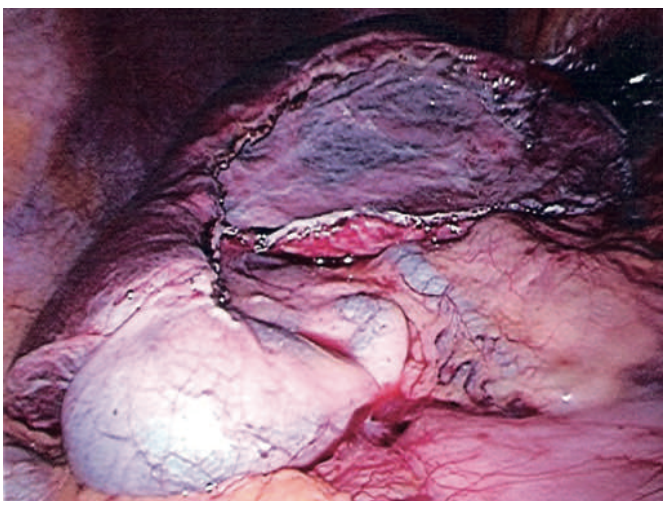


Figure 7. Laparoscopic view of residual cyst wall and right hemi-liver following deroofing of a cyst which required resection of the left liver.

POLYCYSTIC LIVER DISEASE

ETIOLOGY AND PATHOGENESIS

Polycystic liver disease (PCLD) is a genetic disease and its diagnosis is based on the imaging findings of multiple fluid filled cysts scattered throughout the liver parenchyma. PCLD is part of the spectrum of cystic diseases including autosomal dominant polycystic kidney disease (ADPKD). Isolated PCLD is less prevalent than ADPKD (<0.01% *vs* 0.20%).[57] ADPKD may present at any age but is generally a late-onset multisystem disorder characterized by bilateral renal cysts; associated or not with cysts in other organs including the liver, seminal vesicles, pancreas, and arachnoid membrane. In addition, there may be vascular abnormalities including intracranial aneurysms, dilatation of the aortic root, and dissection of the thoracic aorta; mitral valve prolapse; and abdominal wall hernias. ADPKD is characterized by polycystic kidneys and mutations on two genes, *PKD1* and *PKD2*, on chromosomes 16 and 4, respectively.[58] Most patients with ADPKD also have polycystic liver as part of the phenotype, and in a few of them the polycystic liver disease is the main cause of symptoms. Liver cysts are the most common extra-renal manifestation of ADPKD, although for these patients it is the renal disease, which predominates in symptomatology and outcome. Isolated PCLD is caused mainly by mutations on *PRKCSH*[59] or *SEC63* genes, located on chromosome 19 and 6.[60] Liver cystogenesis of PCLD differs from renal cystogenesis and involves over expression of growth factor receptors and loss of adhesion rather than proliferation or deregulated apoptosis.[61]

Macroscopically PCLD cysts are similar to simple cysts of the liver, being lined by biliary type epithelium. Their pathogenesis is attributed to failed involution of excess

intra-lobular bile ducts during embryological development. The cysts of PCLD and ADPKD are often multiple and can extensively replace both lobes of the liver. In addition to macroscopic cysts, there are often numerous microscopic cysts and clusters of multiple bile ductules, referred to as von Meyenburg complexes (see below for more details).

PCLD is rarely seen before puberty and thereafter increase in frequency with age. The diagnosis is made most commonly between the third and fourth decades of life. Once diagnosed, the disease leads a progressive course with cystic growth. In ADPKD, kidney disease always precedes the development of hepatic cysts and the prognosis is much more sinister than simple hepatic cysts because of the risk of renal failure. Despite a similar lifetime risk to develop hepatic cysts, women experience more severe liver disease than men, since estrogens are known to stimulate cyst growth. Pregnancy, oral contraceptives and estrogen replacement increase the risk of severe hepatic cystic disease.

CLINICAL MANIFESTATIONS

Most patients with PCLD have small and sparse cysts and are asymptomatic (up to 80% of cases). In patients with ADPKD, the liver cysts are frequently clinically silent and only become evident during management of the patient's renal disease. The commonest symptoms are related to increase in liver size and mass effect and include; abdominal distension, early satiety and more occasionally dyspnea. Extension of the liver into the pelvis may result in bladder and bowel symptoms but may also result in considerable discomfort when bending, stooping and sitting (**Figure 8**). Hepatomegaly is invariable and a significant abdominal mass is present on examination in three-quarters of patients. Importantly, hepatic function and therefore liver function tests remain remarkably preserved on the whole despite massive hepatomegaly.

Acute complications are uncommon and include bacterial infection of cysts, intracystic hemorrhage, cyst rupture and cyst torsion, and usually manifest by acute pain (**Figure 9**). Spontaneous bacterial infection is a serious complication more commonly found in those immunosuppressed following renal transplantation or under dialysis for ADPKD.[62] Cyst infection should be promptly identified and treated, usually by antibiotic therapy associated with cyst drainage if antibiotics alone fail to control sepsis. However, identification of the infected cyst is frequently difficult, but suggested on computed tomography by the presence of fluid-fluid levels within cysts, cystic wall thickening, or intracystic bubbles.[63–65] Labeled leucocyte imaging (such as In-111 WBC scan) is an option in identifying infected cysts. Intracystic hemorrhage is less common and symptoms can be similar to cyst infection. However, most cases resolve spontaneously. Cyst rupture, cholestasis (due to compression of adjacent biliary ducts), jaundice (due to compression of the common hepatic duct or common bile duct), portal hypertension (secondary to portal or hepatic veins compression), and finally liver failure are rare. Budd-Chiari syndrome and inferior vena cava or right atrium compression have been reported.

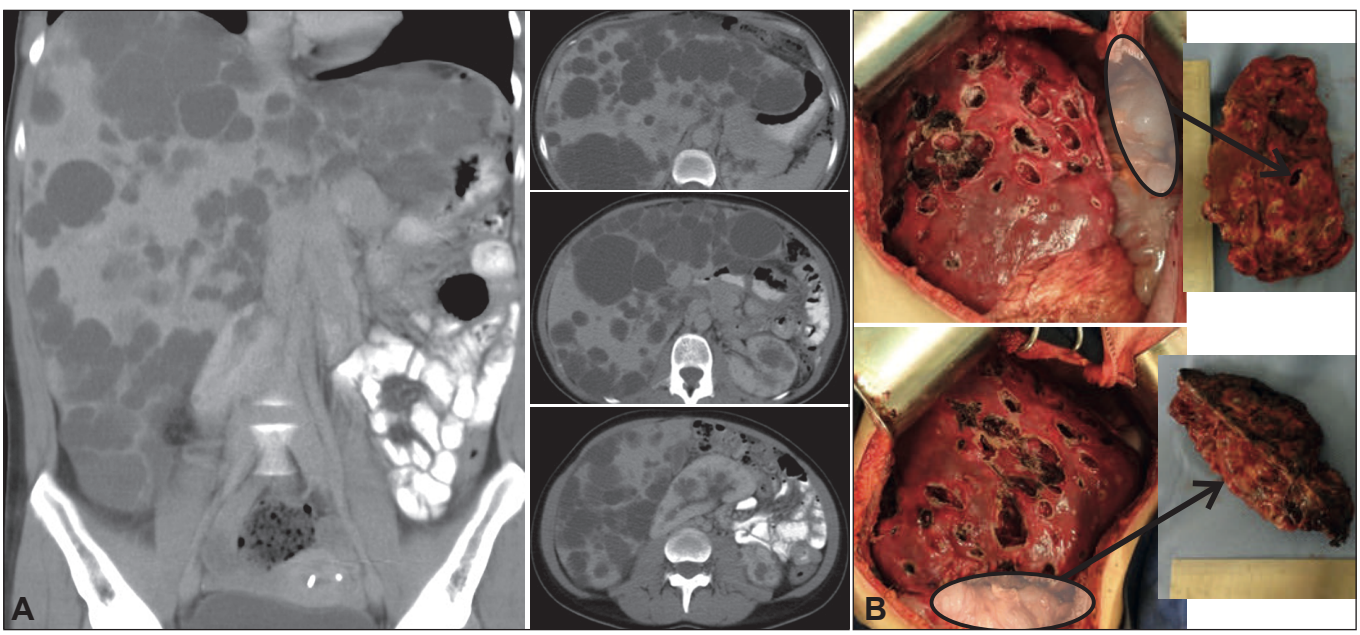


Figure 8. Symptomatic polycystic liver disease (Type C of Schnelldorfer classification). **A**) Preoperative CT shows a liver enlarged by multiple cysts of small and medium size (up to 7 cm) with a relatively preserved right anterior sector. Note the right kidney dislocated. **B**) Intraoperative final view after bilateral hepatic resection combined with deroofing of multiple cysts on the remnant liver. Superior figures show a left lateral lobectomy (small picture showing the specimen). Inferior figures show segmentectomy 6. (*courtesy of Silvio M P Balzan*)

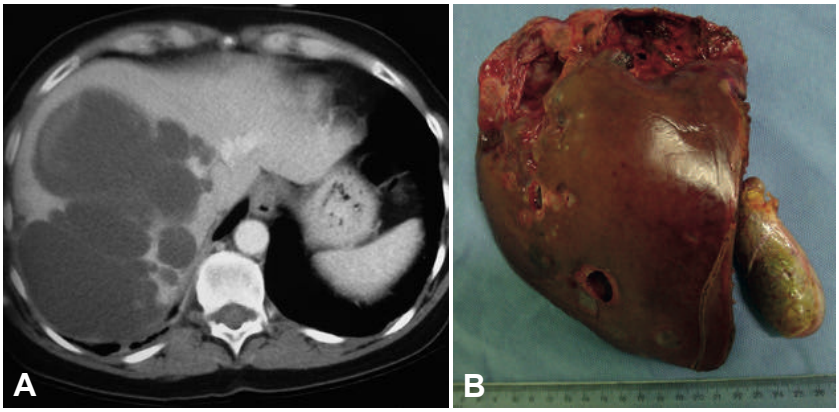


Figure 9. A) Computed tomography of a patient with recurrent acute abdominal pain showing multiple hepatic cysts on the right hemiliver. One of the large cysts presented signs of intracystic bleeding. **B**) Treatment was by right hepatectomy. (*courtesy of Silvio M P Balzan*)

INVESTIGATION

Polycystic liver disease associated with ADPKD should be distinguished from multiple simple cysts of the liver. Hepatic cysts in the context of ADPKD do not occur without the presence of multiple renal cysts. Occasionally, few simple renal cysts may occur concomitantly with simple hepatic cysts.

Ultrasonography, computed tomography and magnetic resonance imaging demonstrate multiple fluid-filled round or oval cysts with sharp well-defined margins in the liver, and also in the kidneys in ADPKD (**Figure 10**). Calcification is unusual. If cystic lesions are identified within the liver on imaging studies it is useful to assess the kidneys and pancreas. Pancreatic cysts occur in up to 9% of patients with ADPKD after 30 years of age, whereas cysts in the spleen, ovaries, and lungs are more rarely present. A diagnosis of ADPKD should prompt a thorough evaluation of the patient and exclude the presence of intracranial pathology (cerebral aneurysms are present in up to 8%) and mitral valve prolapse (present in up to 25%).[66] Computed tomography and magnetic resonance imaging are useful to differentiate polycystic liver disease from neoplastic pathology and from cysts from other etiologies. The presence of a thickened wall is more likely to represent cystadenoma or cystadenocarcinoma. The cysts in PCLD increase in size slowly and unlike simple cysts are not associated with an increased risk of malignant transformation. Imaging studies should also clearly detail the portal, arterial and hepatic venous anatomy of the future remnant liver and the inferior vena cava if hepatic resection is to be considered. Magnetic resonance angiography can be used for this purpose.

MANAGEMENT

Treatment is indicated only in patients with symptoms and/or complications. Interventions are ordinarily aimed at decompression and reduction of liver volume, rather than a specific cyst, or drainage of infected cysts. The most efficacious therapies for PCLD include cyst deroofing, liver resection and liver transplantation. Hepatic intervention will not relieve symptoms related to renal enlargement.[15] Furthermore, liver surgery is made difficult by the distortion of the anatomy. The choice of management is dependent on the size, location and distribution of cysts, total liver volume and volume of preserved hepatic parenchyma, patient co-morbidities, and the vascular anatomy of preserved liver. Detailed preoperative assessment is therefore integral to patient selection. Cyst size alone is of limited value when planning the treatment modality, since multiple small cysts in polycystic liver disease are as likely to require intervention as a large solitary cyst.

Medical management, with the use of lanreotide (a long-acting somatostatin analogue) has been proposed for patients with diffuse PCLD, but its efficacy in reducing liver volume is limited and in many countries it is unlicensed for this indication. There is no strong evidence to avoid

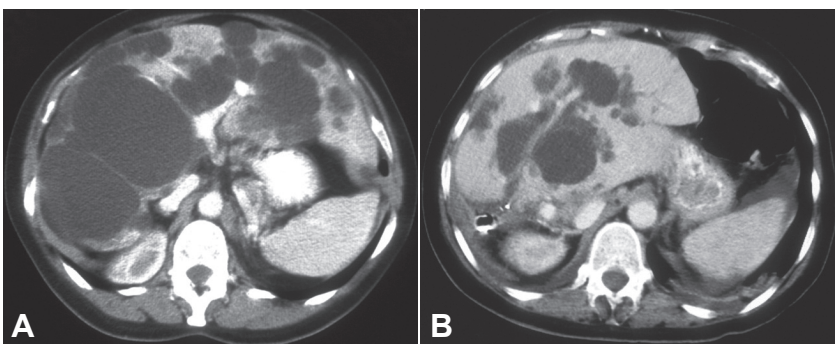


Figure 10. A) Preoperative computed tomography demonstrating multiple cysts involving both lobes of the liver but with predominately larger cysts on the right side. Note that the upper pole of the right kidney is not involved by cystic disease. **B**) Postoperative imaging after right hepatectomy and deroofing of residual cysts of the left hemi-liver.

estrogen intake.

Percutaneous aspiration of cysts, with or without the use of sclerosing agents, rarely produces satisfactory long-term relief of symptoms and therefore has limited application in the management of polycystic liver disease. Sclerosing agents, such as ethanol, ethanolamine oleate, minocycline and tetracycline, induce damage of the epithelial lining and inhibit fluid production. The most suitable patients for this form of management are those with dominant cysts of over 6 cm in diameter and in an accessible location, or those ineligible for a surgical procedure.[67,68] As for simple cysts, preoperative percutaneous aspiration of cysts to be unroofed or resected can be useful to determine the ability of surgery to resolve the symptoms.

Arterial hepatic embolization has been attempted to reduce cyst volume.[69,70] Hepatic artery branches supplying the most affected liver segments results in reduction of cyst volume and in an increase of the unaffected parenchyma. Thus, it is a therapeutic option in selected patients with symptomatic polycystic liver disease and who are not candidates for surgery.

Surgical deroofing

Surgical deroofing or fenestration according to the technique described by Lin et al.[71] has traditionally been the most widely used treatment modality for symptomatic patients (**Figure 11)**. The procedure commences with the deroofing of as many superficial cysts as possible and then neighboring deeper cysts are then stepwise fenestrated through these. The site of fenestration of deeper cysts can be guided by intraoperative ultrasound to minimize the risk of vascular and/or biliary injury, since these structures can be compressed and difficult to visualize between the cysts. Intraoperative cholangiography and/or methylene blue dye biliary injection can be used for detection of biliary leakage. Peritoneal drainage is not used routinely.

The laparoscopic technique of deroofing has been increasingly used in PCLD but there is a high recurrence rate, which results in a less satisfactory long-term outcome. Morbidity and mortality rates are less and hospital stay is shorter when compared to open deroofing. However, cystic lesions in segments 7 and 8 are not always amenable to laparoscopic fenestration due to limited visualization. In our own recent series, laparoscopic deroofing was the most successful operation in terms of length of operative stay, operation time and morbidity. However, 85% of patients who underwent laparoscopic deroofing had recurrent symptoms and 46% of these patients needed further reoperation. Despite this, patients reported that the recurrent symptoms were milder and therefore translated into better physical and psychological quality of life scores when compared to those whom underwent liver resection for polycystic liver disease.[17] However, despite the preference for the laparoscopic approach in the management of simple cysts, many centers including our own, have preferred either open deroofing or hepatic resection as the primary management of polycystic liver disease. Laparoscopic deroofing should be used only in selected patients with most of cysts accessible to this approach. Overall morbidity and mortality for surgical deroofing of polycystic liver disease is nearly 30% and 1%, respectively.[15] Ascites is the most common complication after surgical deroofing. Treatment usually requires diuretics and repeated paracentesis.

Hepatic resection

Resection of most compromised hepatic segments has been proposed to reduce the whole liver volume and to increase parenchymal regeneration of less affected areas. Partial liver resection in polycystic liver disease can be technically challenging and is generally performed in association with fenestrations of cysts of the remnant liver (**figures 8 and 11)**. This procedure results in higher long-term success rates in selected patients compared to fenestration alone. Partial hepatectomy carries a lower reoperation rate and a longer time to recurrence, which may result from the more extensive decompression of normal liver parenchyma.[27,72] However, mortality after hepatectomy in polycystic liver disease is not negligible, ranging from 3% to 10%, and it is

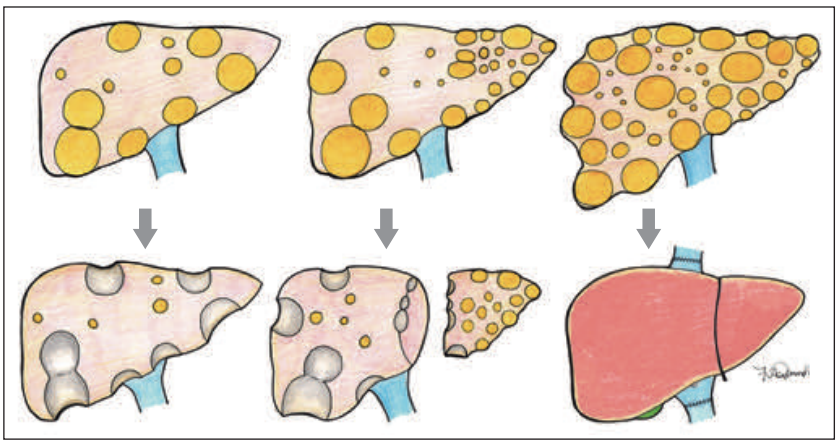


Figure 11. Schematic representation of Gigot's classification for polycystic liver disease and suggested surgical approaches. **A**) Type I. Treatment by cyst deroofing. Deroofing of superficial large cysts gives access to deroofing deeper cysts; **B**) Type II. Treatment by partial hepatic resection and deroofing of remnant cysts; **C**) Type III. Treatment by partial resection or total hepatectomy and liver transplantation.

frequently associated with high morbidity rates, from 20% to 100%.[15] Furthermore, in massive polycystic livers, it can be problematic to determine the optimal extent of resection, since accurate evaluation of the remnant functional parenchyma is difficult.[73] Both extensive resection and fenestration may allow the abdomen to better accommodate the diseased liver, however they can be associated with transient massive ascites in the postoperative period, especially in patients with impaired renal function.[44] Other complications of hepatic resection in polycystic liver disease are hemorrhage, biliary leak, infection, and, more rarely, pancreatitis or Budd-Chiari syndrome.

The technique for hepatic resection in patients with polycystic liver disease differs from that in patients with other disease. The liver is not only larger but also more rigid in polycystic liver disease and therefore less mobile making access to the vascular pedicles and inferior vena cava more difficult. Exposure and mobilization can be optimized by fenestration of selected cysts prior to resection.[74] Cyst fenestration should be performed centrally to avoid vessels running along the intervening septa. Lymphatics are often dilated and should be ligated. The appropriate branches of the portal vein, hepatic artery and bile duct may be identified and divided before proceeding to parenchymal transection. The hepatic veins are usually identified and divided following parenchymal transection, because they are rarely identifiable until this stage. The cavitron ultrasonic surgical aspirator (CUSA™) has been found to be of great use in hepatic resection but even with its use, progression through the liver substance is made difficult by the distorted liver anatomy and presence of multiple small fluid filled cysts. Hepatic resection in polycystic liver disease becomes yet more challenging due to displaced hepatic vessels and bile ducts as well as the development of large intrahepatic collateral veins often traversing the parenchyma. Hemorrhage from small veins or collaterals can be troublesome and bile leak can occur due to disruption of small bile ducts that lie adjacent to these vessels. They require careful suture ligation or placement of surgical clips rather than diathermy to avoid bile duct thermic injury. Partial hepatic resection requires preservation of both the hepatic and portal veins of the remnant liver, which can also be challenging due to distorted anatomy. All cysts adjacent to the remnant vasculature and inferior vena cava need to be fenestrated to ensure postoperative patency by reducing extrinsic compression. Perihepatic drains may be placed to allow drainage of postoperative ascites, fluid collection and potential bile leak; however large losses from drained massive postoperative ascites can complicate management.

Total liver resection followed by liver transplantation is the only curative modality for polycystic liver disease, however this demands lifelong immune suppression and has an inherent mortality. It can be the only option in selected cases, especially for patients with associated renal failure in ADPKD, when renal transplantation is also under consideration, despite usually normal liver function. Simultaneous renal and liver transplantation if hepatic replacement is indicated in patients with ADPKD and mild to moderate renal failure is controversial. Combined liver-kidney transplantation from the same donor could have potential immunological advantages and the postoperative management is easier in patients without renal failure.

It is of note that despite marked hepatomegaly, the functional parenchymal liver volume is mostly normal with preserved hepatic function.[73,75] Therefore, calculated Model for End-Stage Liver Disease (MELD) criteria scores are low, making organ allocation more difficult.[75] Living donor transplantation for highly selected patients may provide a potential alternative.[74] Studies show that 5-year survival after deceased donor liver of combined liver-kidney transplant is approximately 80%, with a good quality of life.[76,77] Currently there are no clinical trials comparing outcome for severely symptomatic patients undergoing liver transplantation versus hepatic resection and fenestration. Late outcomes from each surgical procedure (fenestration, hepatic resection, or liver transplantation) should be weighed against potential surgical morbidity and mortality. Patient and hepatic cystic disease characteristics have been used to guide the best choice of treatment.

Gigot et al.[52,78] have proposed a classification of non-parasitic liver cysts based on preoperative computed tomography and have suggested a therapeutic approach for each type of disease. (**Figure 11**)

They classified PCLD as follows: **type I** (less than 10 large cysts with large areas of non-cystic parenchyma), **type II** (diffuse involvement of liver parenchyma with medium cysts with large areas of remaining non-cystic parenchyma) and **type III** (diffuse liver involvement with small and medium sized cysts with only a few areas of normal parenchyma between). Type I was present in only 10% of cases, but was considered an optimal indication for laparoscopic fenestration. On the other hand, patients with type III have poor liver reduction with fenestration only and hepatic resection should be considered. Fenestration and liver resection represent appropriate options for type II disease. Liver transplantation is reserved for patients with liver failure or recurrence after hepatectomy. Patients with a large dominant cyst pattern located mainly in the anterior segments could be best managed by laparoscopic or open deroofing. For those patients with a diffuse cystic pattern, hepatic resection should be the preferred option.

Another large series published by Schnelldorfer et al.[74] reviewed the management of 141 patients with symptomatic PCLD. They proposed a new classification based on severity of symptoms, cyst characteristics, areas of non-affected parenchyma and blood supply for these areas (**table 1**).

The authors proposed the following management options in each of the classification groups: type A should undergo observation or medical treatment, type B cyst fenestration, type C (**Figure 8**) partial hepatectomy with remnant cyst fenestration and type D, liver transplantation. In patients with a diffuse disease pattern and in whom there is a minimal amount of normal liver parenchyma with significant distortion of the liver anatomy, extended hepatectomy may carry a high risk of liver failure and ortothopic liver transplantation may be the best course of action. Liver transplantation should also be considered in patients with significant fatigue and cachexia or, rarely, in the presence of severe liver failure.[15]

In relation to medical therapy, a recent randomized controlled double-blind trial performed by Van Keimpema et al.[79] has shown that the use of somatostatin analogues and, in particular, lanreotide, show promise in reducing liver volume in patients with both ADPKD and PCLD. They found that patients treated with 6 months of lanreotide demonstrated a 2.9% reduction in liver volume when compared with the placebo group that showed a 1.6% volume increase. Although the gain appeared modest, lanreotide may have promise in holding disease progression whilst providing some volume reduction in patients awaiting surgical management although its use is not licensed for this indication in several countries.

VON MEYENBURG COMPLEXES.

Von Meyenburg complexes (VMC), also called microhamartomas, are characterized by small, non-hereditary nodular cystic lesions scattered throughout the liver. Cysts are typically located peripherally and detected incidentally on radiological imaging. No treatment is warranted. VMC may occur isolated or in the context of PCLD and ADPKD.

VMC are characterized by small embryonic ductal plate malformation remnants (< 1.5cm) or larger (> 1.5cm) hamartomas. Cysts wall is delineated by regular cuboidal epithelium and become separate from the intrahepatic biliary tree.[80,81]

CYSTADENOMA AND CYSTADENOCARCINOMA

ETIOLOGY AND PATHOGENESIS

Biliary cystadenoma (BCA) and biliary cystadenocarcinoma (BCAC) of the liver are biliary cystic tumors that arise from the biliary epithelium. Cystadenomas have a risk of malignant transformation of up to 30%.[2,82]

Cystadenoma of the liver is rare (accounting for less than 5% of nonparasitic cysts of the liver)[4,10], but has a strong tendency to recur and has a malignant potential (cystadenocarcinoma).[83,84] It is usually solitary and mainly affects women over the age of 40 years of age. The etiology of neoplastic liver cysts is unknown and there is no known association with the use of oral contraceptives. BCA and BCAC are often confused with other intrahepatic cystic disease including atypical or complicated simple cysts, atypical hemangioma, hamartoma, and lymphangioma.[85] The majority arises from intrahepatic ducts (generally located in liver segment 4), but 15% may arise from the extrahepatic ducts and gallbladder.

BCA are often multiloculated, unlike simple cysts and the cysts of polycystic liver disease, and may measure up to 35 cm in diameter [84,85], with a smooth external surface (**Figure 12**). Histologically, these are mostly lined by a single layer of mucus secreting cuboidal or columnar cells (**Figure 12**). In some areas the epithelium may form papillary projections into the cavity of the cyst. BCA usually contain blood or dark brown material and their lining is surrounded by a less cellular layer of collagen.[86]

BCAC arise almost exclusively within pre-existing cystadenomas. Malignancy usually affects part of the cyst wall or eventually the entire cyst epithelial lining, and the epithelium is multilayered, with numerous papillary projections. The tumor grows into the liver and metastasis can develop.[87]

Table 1. Classification of polycystic liver disease according to Schnelldorfer et al.[74]

	Type A	Type B	Type C	Type D
Symptoms	absent or mild	moderate or severe	severe (or moderate)	severe (or moderate)
Cyst characteristics	any	limited number large cysts	any	any
Areas of relative normal liver parenchyma	any	≥ 2 sectors	≥ 1 sector	< 1 sector
Isosectoral portal vein or hepatic vein occlusion of preserved sector	any	absent	absent	present
Recommended therapy	observation	cyst fenestration	resection associated or not to fenestration of remnant cysts	liver transplantation

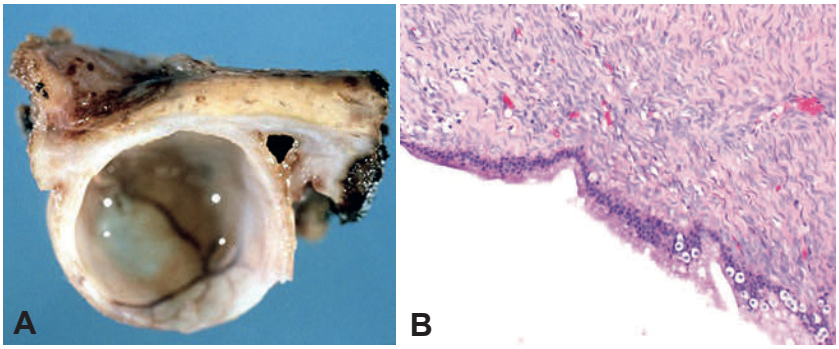


Figure 12. Specimen of partial liver resection for a biliary cystadenoma. **A**) Macroscopic aspect. **B**) Microscopy with H&E stain showing both cuboidal and columnar cells secreting mucus.

CLINICAL FEATURES

Biliary cystic tumors are largely more common in female (85% of cases), but it appears that males with such tumors are more likely to have a BCAC (one third of biliary cystic tumors are BCAC).[84,88] The presenting features are similar to other mass-forming liver pathology, namely abdominal discomfort, anorexia, nausea and abdominal swelling. Occasionally, a large hepatic mass may be palpable on physical examination. Cystadenomas are most commonly found incidentally on abdominal imaging similar to most non-parasitic hepatic cysts. Cystadenomas may progress in indolent fashion however complications can include biliary obstruction, intracystic hemorrhage, bacterial infection, rupture, recurrence following partial excision and malignant transformation.

Diagnosis is based on ultrasonography, computed tomography and magnetic resonance imaging. Ultrasonography characteristics are of a large, anechoic, fluid filled area with irregular margins and multiple internal septations, features not present in simple cysts (**Figure 13**). Internal echoes may be seen due to septa or papillary projection from the cyst wall. Computed tomography provides more accurate anatomical location but may be less sensitive than ultrasonography in demonstrating the thin septations. Occasionally, calcification may be seen on septations or mural nodules.

It is important to differentiate cystadenomas from other cystic lesions (such as simple cysts, hydatid cysts, abscesses, polycystic liver disease, post-traumatic cysts, and cystic metastasis from ovarian or pancreatic adenocarcinoma) prior to management, since the malignant potential and high recurrence rate impose a more aggressive surgical approach. Seo et al.[89] found that the presence of a mural nodule, left lobe location, and increase of serum alkaline phosphatase were useful in differentiating biliary cystic tumor (cystadenoma and cystadenocarcinoma) from atypical hepatic simple cysts. A recent study identified that a tumor marker, TAG-72, measured in the intracystic fluid was useful in differentiating cystadenoma from simple cyst.[90] Other tumor markers, such as CA19.9, are usually elevated in the serum and the cystic fluid in patients with cystadenoma, but they are not accurate. Distinguish cystadenomas from hydatid cysts can be very difficult. Preoperative core needle biopsy is usually not recommended because the low accuracy and the potential risk of needle seeding and dissemination.

Differentiation between cystadenoma and cystadenocarcinoma should be suspected radiologically by the presence of papillary projections into the cyst, septal calcification, intracystic debris, bile duct dilatation, cyst wall enhancement after contrast injection, or mural nodule [91] but no specific radiographic marker is reliable in differentiate BCA from BCAC. The absence of all the above features strongly suggests BCA, but the presence of any of them does not necessarily represent BCAC (i.e. radiological findings has a low positive predictive value).[88] In a large multicentric study, tumor location in the right hemiliver was associated with a greater risk of BCAC relative to BCA. Similarly, serum tumor markers (CEA and CA19-9) tend to be higher in BCAC,[88] and biliary cystic tumors in men are more likely to represent BCAC than in women.[88,92] It is of note that concomitant cystic lesions from different etiologies may be present.



Figure 13. Ultrasonography showing typical features of cystadenoma of liver with internal septa.

occurred after incomplete tumor excision. Overall 5-year survival was 84.2%, and it was worse for BCAC than for BCA. Pinson et al.[97] have reported cyst enucleation without late recurrence and mortality. This may be an alternative approach when hepatic resection is not possible or carries a high risk, however large cystadenomas compress and distorted vascular and biliary structu res, becoming difficult to separate them from the cystadenoma.[98,99] Since accurate preoperative diagnosis is challenging, it would be prudent to perform a frozen section examination during conservative surgery for a presumed simple cyst to exclude biliary cystic tumors.[88]

In summary, biliary cystadenoma should be considered as a possible diagnosis in any hepatic multilocular cystic lesion. Complete excision of suspected biliary cystic tumors is mandatory, as well as long-term surveillance because of the risk of recurrence. Enucleation remains an optional procedure in selected cases.

CAROLI'S DISEASE AND CAROLI'S SYNDROME

ETIOLOGY AND PATHOGENESIS

Congenital intrahepatic bile duct dilatation is a rare disorder resulting from abnormal development of the ductal plate. Biliary dilatation limited to the intrahepatic bile ducts (corresponding to type V of Todani et al. classification) comprises two entities: **Caroli's disease**, characterized by multifocal saccular dilatations of intrahepatic bile ducts without any other associated liver abnormality, and **Caroli's syndrome**, commonly transmitted as an autosomal recessive trait and manifesting as saccular bile duct dilatations that coexist with congenital hepatic fibrosis.[100,101] Both entities result in cystic dilatations that are in continuity with the intrahepatic biliary tree. They therefore do not represent true forms of liver cystic disease. A brief overview is provided however, since dilatations can confound the diagnosis of the true cystic liver diseases. For additional information, it is suggested that **Chapter 21** (Primary Intrahepatic Lithiasis) be reviewed.

In contrast to simple cysts and polycystic liver disease, the intrahepatic dilated ducts predispose to biliary stasis, stone formation, and infection (cholangitis and liver abscesses); these complications ultimately lead to secondary biliary cirrhosis and a tendency to the development of cholangiocarcinoma (prevalence of 6% to 25%).[101–103] The unilobar involvement (mainly left lobe) of congenital intrahepatic bile duct dilatations is more frequently reported, but it possibly represents a referral bias, since bilobar or diffusely affected patients are not usually referred for surgical treatment.[101]

Caroli's syndrome, which is more common than Caroli's disease, is characterized by coexisting congenital hepatic fibrosis (that can lead to portal hypertension) and occasionally renal disease (from tubular ectasia to polycystic kidney disease). Caroli's disease may also manifest with renal cysts. The etiology is uncertain however it probably shares its origins with the family of abnormalities that include congenital hepatic fibrosis and polycystic liver disease.[104] It is usually diagnosed in childhood or early adult life with 75% of affected individuals being male.

CLINICAL PRESENTATION

Caroli's disease usually presents in or after the second decade of life. Patients may remain asymptomatic and with normal liver function tests for many years. However, most patients will present with symptoms of recurrent cholangitis (typically represented by abdominal pain, jaundice and fever). Furthermore, symptoms can result from congenital hepatic fibrosis and its consequences, such as portal hypertension or cirrhosis, or also from intrahepatic abscesses formation.

INVESTIGATION

Serum levels of liver function tests are usually abnormal in symptomatic patients and are mostly related to biliary obstruction. Imaging methods reveal multiple intrahepatic biliary dilatations communicating with the biliary tree. Ultrasonography may detect echoic foci with posterior acoustic shadowing if stones are present. Computed tomography with intravenous contrast enhancement may identify dilated intrahepatic bile ducts with adjacent contrast enhanced radicles of the portal vein, often described as "central dot sign". Magnetic resonance cholangiography is useful in diagnosis and evaluation of the extension and location of bile duct dilatations, intrahepatic stones and strictures. Direct cholangiography methods, such as endoscopic retrograde cholangiography and percutaneous transhepatic cholangiography should be avoided because of the risk of septic complications unless treatment by the same approach is envisaged.

MANAGEMENT

The management of congenital intrahepatic bile duct dilatations is usually challenging. Resection of the affected hepatic segments is the surgical treatment that provides best long-term results. Liver resection is able to treat the bile duct dilatation, associated intrahepatic stones and biliary strictures that eventually present. Therefore, congenital intrahepatic bile duct dilatation without liver fibrosis or cirrhosis should be treated preferably by partial liver resection. Hepatectomy for unilobar Caroli's disease provides satisfactory long-term

results. The approach to bilobar disease is more controversial, but appropriate management options include extended liver resection of the most affected side associated with stones clearance of the less affected liver segments, or even ortothopic liver transplantation. Hepatic transplantation should also be considered in all cases of congenital intrahepatic bile duct dilatations with concurrent hepatic fibrosis, portal hypertension or cirrhosis. Partial or total liver resection reduces substantially the risk of development of intrahepatic cholangiocarcionoma. It is of note that surgical procedures of biliary drainage or strictureplasty have been practically abandoned and more conservative treatments (by percutaneous or endoscopic access) should be limited to patients ineligible for definitive surgery. Relevant points regarding this topic are discussed in **Chapter 21** (Primary Intrahepatic Lithiasis).

Although asymptomatic patients may be observed without any treatment, some authors suggest an early aggressive approach. Early diagnosis and definitive treatment could avoid emergency intervention and minimize the need for endoscopic approaches which are factors associated to septic complications and poor outcome in these patients. On the other hand, patients presenting with septic complications are appropriately managed by antibiotic therapy with or without percutaneous biliary drainage. Ursodeoxycholic acid has been successfully used in the management of Caroli's disease to prevent biliary sludge and stone formation.[105]

In summary, despite some controversy, it seems that early and aggressive treatment of congenital intrahepatic bile duct dilatation results in favorable short-term and long-term outcomes.

TRAUMATIC CYSTS

ETIOLOGY AND PATHOGENESIS

The liver is one of the most commonly injured organs in abdominal trauma and can be injured by either blunt or penetrative trauma. Traumatic cysts of the liver are among the less frequent sequelae of liver trauma. Liver laceration and hematoma would normally resolve with little evidence of long-term scarring or other effect to the liver. The incidence of traumatic cysts has been reported to be less than 0.5% [106] but the literature is sparse and consists mainly of case reports and series of a few patients. Traumatic liver cysts are acquired and most authors suggest that moderately severe trauma to the liver must occur to rupture bile ducts and cause intrahepatic hemorrhage.[107,108] Christopher [109] originally classified liver injury into three categories: central, subcapsular and rupture of liver tissue with its capsule. Traumatic liver cysts usually arise following central injury. In some instances, bile leakage into the cyst continues and the cyst grows progressively. The cystic fluid is therefore composed of either altered blood or bile or a mixture of both or yet, in some instances, the cyst may contain necrotic liver tissue. Unlike simple cysts, polycystic liver disease and biliary tumors there is no true epithelial cyst lining. Traumatic liver cysts are in fact pseudocysts.

CLINICAL FEATURES

There is often a delay of several days to months after the initial hepatic trauma before the patient presents with symptoms of abdominal pain, distension and hepatomegaly. Complications of traumatic hepatic cysts include: obstructive jaundice, abscess formation, hemorrhagic shock or biliary peritonitis due to cyst rupture and resultant bile leakage. The radiological findings of traumatic cysts are similar to that of congenital cysts. A past history of trauma helps in establishing the diagnosis.

MANAGEMENT

Management of traumatic cysts differs from the management of congenital and neoplastic cysts. Traumatic cysts lack a true cyst wall that can continue to produce cystic fluid, and they do not present a risk of malignant degeneration even if are not completely resected. Traumatic cysts can be treated expectantly in asymptomatic patients. Some cases of spontaneous resolution have been reported. Percutaneous or open and laparoscopic drainage, decortication of the cyst wall associated with omentoplasty, and even hepatectomy have been reported with satisfactory results. It is important to consider a differential diagnosis of simple cysts or polycystic liver disease, because the use of sclerosing agent is not indicated, since frequently there is a residual communication between the cyst and the biliary tree.

OTHER RARE CYSTIC HEPATIC LESIONS

Ciliated hepatic foregut cysts are benign lesions that can occur in most of gastrointestinal organs.[110,111] They are extremely rare and the main characteristic is a pseudostratified and ciliated columnar epithelium, similar to that of bronchial tree.[112] Nearly half of patients are asymptomatic and diagnosis incidental, but abdominal pain and abnormal liver function tests can be present in 40% of cases. Radiologically, ciliated cysts appear as unilocular and well-delimited lesions of less than 4 cm, located preferably on hepatic segment 4 (58% of cases) and subcapsular.[113,114] There is a risk of degeneration and thus the preferred treatment is resection.[115]

Cystic hepatic metastases and primary tumors. Hepatic metastases can arise as cystic lesions when these originate from cystic tumors (such as pancreatic or ovary cystadenocarcinomas) or they can become cystic due to intratumoral necrosis. Necrosis can be secondary to a rapid grow of hypervascular tumors (such as sarcoma, melanoma, and neuroendocrine tumors) or due to chemotherapy.[116,117] Also, liver metastases from gastrointestinal stromal tumors (GIST) may appear cystic even before treatment. Diagnosis is usually easy due to the presence of an irregular and thickened wall. Cystic metastases are usually multiple. Primary hepatic malignancy (hepatocellular carcinoma and cholangiocarcinoma) or benign (hemangioma) lesions can eventually have a cystic component.[116–119] Malignant cells may not be present in the intracystic fluid and biopsies, if necessary, should be of the cyst wall. The treatment is individualized for each situation.

Endometrial cysts within the liver [120] are rare but can present as diagnostic challenges. They can mimic mucinous cystic neoplasms of the liver. **Intrahepatic pancreatic pseudocyst**s [121,122] can rarely develop into the liver (**Figure 14**). **Spontaneous hematomas** typically present with acute abdominal pain (**Figure 15**). **Traumatic hematomas** and **biliomas** are usually easily diagnosed by characteristic context.[123,124]

FINAL CONSIDERATIONS

Non-parasitic cystic disease of the liver represent a heterogeneous group of disorders that can originate from congenital malformations (simple cysts), genetic mutations (polycystic liver disease), trauma to the intrahepatic biliary tree (traumatic cysts) or be of unknown etiology (benign biliary cystadenoma and biliary cystadenocarcinoma). The majority of patients with non-parasitic liver cysts are asymptomatic and require no treatment. However, patients with symptomatic lesions or lesions that have the potential for further growth, complications or malignant transformation should undergo prompt surgical management.

The role of percutaneous aspiration alone is limited due to the inevitable risk of recurrence. Percutaneous aspiration with sclerosing agent injection shows more promising results in selected cases but is also associated with high rates of recurrence. However percutaneous aspiration with sclerosing instillation can provide temporary symptomatic relief, and is useful in the management of those not eligible for surgery due to significant co-morbidity or limited life expectancy. Furthermore, percutaneous aspiration can be a useful tool before surgery to determine if symptoms are related to the cyst to be treated.

The majority of simple liver cysts can be managed by laparoscopic deroofing, however there is a definite role for open surgery in selected patients. In patients with polycystic liver disease, open or laparoscopic deroofing is the preferred approach for a dominant cyst pattern, whereas hepatic resection or, indeed, liver transplantation may be necessary for patients with a diffuse cystic pattern. Due to the risk of both recurrence and malignant progression patients with cystadenomas should always undergo primary hepatic resection. Caroli's disease and Caroli's syndrome are preferably managed by surgical resection where unilateral or segmental involvement is evident, however diffuse disease, recurrent cholangitis and associated liver failure may require liver transplantation. More rare cystic lesions of the liver are therefore managed on an individual basis. A suggested treatment algorithm for the surgical management of cystic liver disease is depicted in **figure 16**.



Figure 14. Computed tomography showing an intrahepatic pancreatic pseudocyst in the right hemi-liver in a patient with acute pancreatitis.

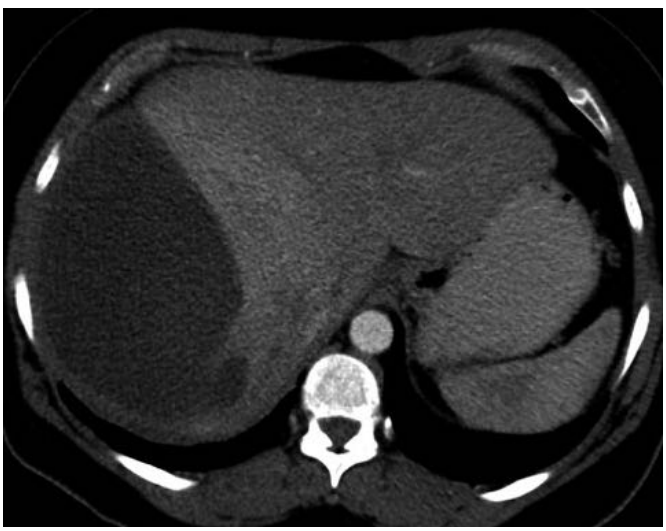


Figure 15. Computed tomography after right arterial embolization for a large spontaneous hematoma.

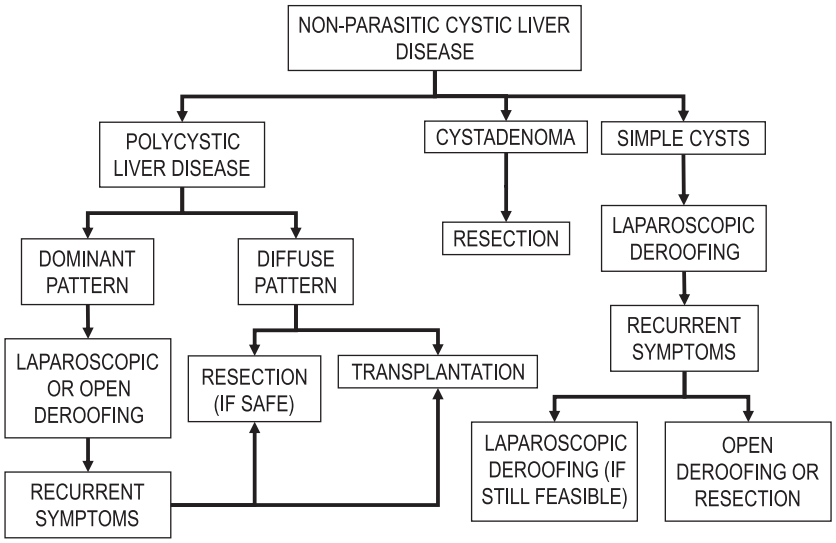


Figure 16. Suggested management algorithm on non-parasitic liver cysts.

The management of non-parasitic cystic liver disease has evolved over the last few decades with the development of new surgical technologies. The choice of management is dependent on many factors. Management is therefore challenging and requires thorough preoperative investigation and evaluation to optimize the success. Treatment should therefore be undertaken within specialist hepatobiliary units using a multidisciplinary approach.

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20 Parasitic Hepatic Cysts and Pyogenic Hepatic Abscess

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- *The most common parasitic hepatic disease that can need surgical treatment is the hydatid cyst, caused by Echinococcus granulosus. Other echinococcosis (alveolar and polycystic) are less frequent.*
- *Hydatid cysts may be multiple and can measure up to 20-50 cm in diameter. Most of them develop in the right lobe of the liver. Commonly, symptoms result from mass effect or cystic complications, such as rupture (into biliary tract, peritoneal cavity, hollow viscera, and lungs) or infection. Diagnosis is suggested especially by radiological findings.*
- *Surgical treatment can be conservative (comprising sterilization of the cyst and treatment of the residual cavity) or radical (including pericystectomy and anatomical liver resections).*
- *Pyogenic liver abscess represents a life-threatening bacterial infection of the liver. Surgical treatment is indicated in case of failure of conservative therapy (antibiotics combined or not with percutaneous drainage), which occurs mainly in multiloculated abscesses and those with biliary communications.*

INTRODUCTION

The liver, the largest gland in the body, seems to be very attractive for many parasites. They either inhabit the organ, or pass through during their normal development without damaging the organ, or may be carried to it leading to its destruction. People in developing countries and tropical areas are commonly exposed to these parasites.[1,2] Because of traveling, immigration and the HIV/AIDS pandemic, parasitic disease can be found anywhere and may even affect inhabitants of developed countries. To combat this worldwide diffusion, some attempts to develop vaccines against these pathogens have been made, but have been hampered by the difficulty inherent to cultivating parasites in vitro, the complexity of their multicellular organization and/or multistage development, and their impressive antigenic variability. Luckily, anti-parasitic drugs treat most parasitic liver diseases. In advanced stages of disease, other therapeutic methods are required to suppress parasites or to manage their complications, as represented by percutaneous, endoscopic, or surgical approaches. Even liver transplantation can be needed for the treatment of advanced cases in which the remnant liver is not large enough to assume normal metabolic activity.

Pyogenic hepatic abscesses are relatively rare and most often polymicrobial. Bacteria may reach the liver through the portal vein, arterial blood, biliary tract, or even direct contact. The development of modern radiology techniques has facilitated diagnosis and management. However, surgical approach still plays a role in the management of selected cases not amenable to treatment through the combination of percutaneous drainage and antibiotic therapy, the standard treatment for this disease.

In this chapter, we will discuss the three main parasitic infestations requiring liver resection (hydatid disease, alveolar echinococcosis and polycystic echinococcosis). Nonetheless, this chapter will cover the surgical approach to treating pyogenic hepatic abscesses.

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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CYSTIC HYDATID DISEASE OR CYSTIC ECHINOCOCCOSIS

ETIOLOGY, PATHOLOGY AND NATURAL HISTORY

Cystic hydatid disease (CHD) is caused by the development of the larval form of *Echinococcus granulosus*, a parasite spread almost all over the world. It is a tapeworm (2-7 mm in length) that resides and grows in the small bowel of dogs and other canines (definitive hosts). It produces eggs that pass through the stool and infect pastures. When ingested by intermediate hosts (mainly sheep and cattle), eggs hatch into oncosphere larva in the duodenum. The larva crosses the intestinal wall and, via the portal system, migrates to the liver, where it grows into a cyst. The definitive hosts are infected by consumption of cyst-containing viscera of slaughtered animals (**Figure 1**).[3–6]

Humans (accidental intermediate hosts) become infected through the ingestion of tapeworm eggs excreted in the feces of infected dogs, either by direct contact with the animal or by consumption of unboiled or unwashed contaminated vegetables (**Figure 1**). In the duodenum, eggs release larvae that go through the intestinal wall and migrate to the liver via the portal system. Reaching the liver, larvae may die or develop into hydatid cysts within months to years. Thus, the liver is the most frequently infected organ in humans (50-77% of cases).[7–9] The hepatic parenchyma is a physical barrier that prevents the spreading of parasites to the whole body. However, in some cases, larvae may pass through the liver, continue their course, and settle in the capillaries of the lungs (17-25% of cases),[10–12] or even reach the systemic circulation and potentially lodge in any part of the body — muscle (5%), peritoneum (4%), mediastinum (3.5%), bones (3%), heart (2%), kidneys (2%), spleen (1%), central nervous system (1%), thyroid (1%), or the adrenals, pleura, bladder, ovaries, or scrotum (<1% each location).[13–26]

Once in the human liver, the parasite's natural course is variable and cysts generally grow slowly (1 mm to 5 mm per year), but they can grow faster (up to 160 mm per year) and can reach very large sizes before they become clinically evident. Cysts can reach 25-50 cm and contain several smaller cysts ("daughter cysts") inside a large cyst ("mother cyst"). On the other hand, cysts can regress and/or become infertile.

CHD is endemic in many areas around the world, mainly in Mediterranean countries such as Morocco, Tunisia, Greece and Turkey, in addition to other regions where sheep and cattle are raised, such as the Middle East, the southern part of South America, Australia, New Zealand, and southern countries of Africa.[27–29]

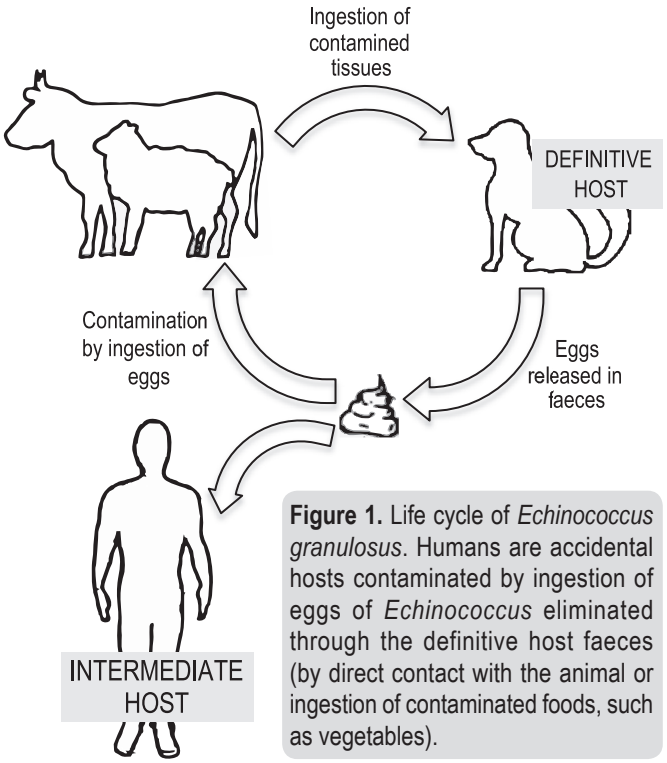


Figure 1. Life cycle of *Echinococcus granulosus*. Humans are accidental hosts contaminated by ingestion of eggs of *Echinococcus* eliminated through the definitive host faeces (by direct contact with the animal or ingestion of contaminated foods, such as vegetables).

In recent decades, echinococcosis incidence decreased owing to improvements in both agricultural and medical habits that followed the economic growth of these countries.[30] The incidence of hepatic hydatid disease in endemic areas ranges from 1-220 cases per 100,000 inhabitants.[7,31–34]

Histologically, hepatic CHD is composed of two main layers (**Figure 2)**:

i) the **pericyst** (or adventitia), composed of host compressed hepatic cells that form a dense fibrous zone secondary to a reaction to the parasite, and
ii) the **parasite-derived endocyst**, which has an outer laminated layer (called the laminated membrane, and formerly called the ectocyst) and an inner germinal layer (called the germinal membrane, and formerly called the endocyst).

The laminated membrane is an acellular elastic layer that allows the passage of nutrients into the cyst.

The single-celled germinal membrane secretes a clear colorless fluid, with a neutral pH, that can contain scolices and is strongly antigenic. Indeed, it can cause anaphylaxis if it makes contact with the circulation of the host. The germinal membrane is responsible for the formation of the laminated membrane, and gives rise to the brood capsules and daughter cysts, both containing scolices (**Figure 3**). Brood capsules are initially attached by a pedicle to the germinal layer, but they may detach from it and grow into daughter cysts. Occasionally, daughter cysts can grow up through the laminated

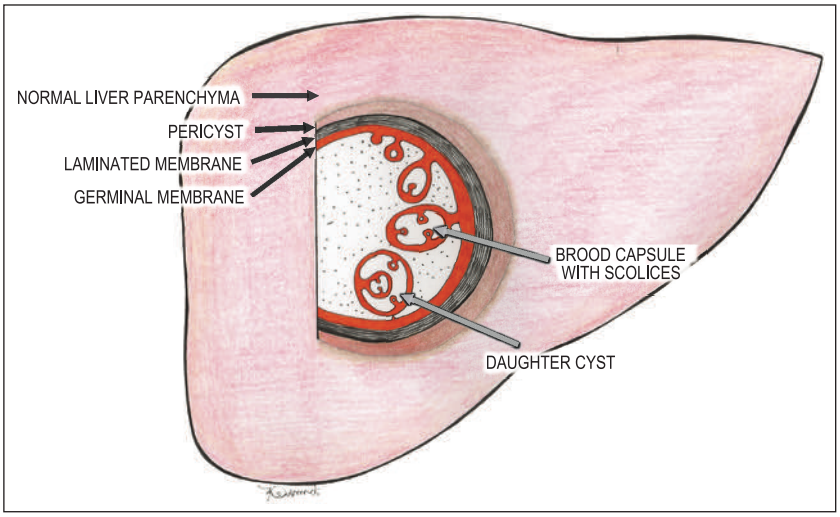


Figure 2. Schematic representation of a viable uncomplicated liver hydatid cyst. Thickened surrounding liver parenchyma forms the pericyst layer. Germinal membrane produces brood capsules and daughter cysts (development of daughter cyst is represented in the cyst in a clockwise sense).

membrane towards the external side of the original cyst, leading to the development of satellite cysts (exogenous daughter cysts). The so-called hydatid sand corresponds to scolices and remnants of membrane from ruptured daughter cysts.

Following the growing phase, hydatid cysts can involute as a consequence of scolices and overproduction of daughter cysts. In this phase the cystic fluid is replaced by scolices and membranes, and the reaction of the host can lead to a progressive calcification around the cyst. Indeed, completely calcified cysts are usually considered "dead cysts", despite the rare presence of fertile daughter cysts. Multiple small single cysts may form clusters resulting in a polycystic or multivesicular appearance, which has to be distinguished from alveolar and polycystic echinococcosis.

SYMPTOMS

Uncomplicated hydatid cysts are usually asymptomatic (50% of cases) and they may be diagnosed incidentally during imaging studies for other reasons.[35] The liver is the most affected organ (up to 70%) and frequently (65% of cases) the hydatid cyst is unique and localized in the right hepatic lobe. Multiple hepatic cysts occur in 20-40% of cases.

Symptoms due to hepatic CHD can be produced by the cyst itself (mainly compressive effects, rupture, and infection). Local or mechanical symptoms depend on location, number, and size of cysts. They generally occur generally when cysts reach more than 5 cm in diameter. Complications occur in about half of hepatic hydatid cysts. Infection and rupture (mainly into the biliary tree, the peritoneal cavity, and the pleural cavity) are the most frequent complications. Symptoms can also develop as a general toxic reaction due to the presence of the parasite (urticaria, anaphylaxis, and asthma, among others).

LOCAL COMPLICATIONS

Compressive effects

Manifestations due to mass effects are initially non-specific abdominal pain, cough and dyspeptic symptoms. In the liver, compressive effects of cysts include right upper quadrant pain (60% of cases) due to the hepatic capsule distension, obstructive jaundice (15% of cases) due to biliary tree compression, portal hypertension due to portal vein obstruction, and Budd-Chiari syndrome due to hepatic veins compression.[36]

Cyst rupture

Cyst rupture occurs in 3-40% of cases and it results from an increased pressure within the cyst. Rupture is habitually to the biliary tree, the peritoneal cavity, or the pleural cavity. (**Figure 4**)



Figure 3. Multiple daughter cysts evacuated from a large hydatid cyst.

Intrabiliary rupture (**Figure 4**). During cyst growth, biliary ducts that pass through pericysts lose their elasticity, and compression of their wall leads to necrosis and fissures. As a consequence, biliocystic communication can occur.[31] This is a major turning-point in hydatid cyst development. The true incidence of communication with bile ducts is not well known but may range from 6.6-37%.[31] This situation represents a well-defined anatomic entity illustrated by various clinical manifestations, depending mainly on size of biliocystic communication. Minor communications lead to cystic fluid drainage while major ruptures allow passing of extra intracystic material. The classic triad of biliary rupture in CHD (biliary colic, jaundice, and urticaria) can eventually be associated with fever (in case of cholangitis), which occurs mainly in major communications. However, jaundice due to biliary compression can be temporarily relieved following biliary communication (reduction of intracystic pressure). On the other hand, eventual bacterial inoculation can result in secondary cyst infection, hepatic abscess, and ultimately severe sepsis. The migration of daughter cysts through the biliocystic communication can lead to jaundice secondary to obstruction at the level of the duodenal papilla. Minor leaks of the cyst can produce flushing and urticaria, and major rupture can lead to a potentially fatal anaphylactic reaction.

Rupture to the biliary tree mainly occurs in centrally located cysts and most frequently into the right hepatic duct branches (55-60%) or left hepatic duct branches (25-30%), but communication can also occur into the hepatic duct confluence, common bile duct, cystic duct, or gallbladder. Diagnosis is usually suggested by the clinical findings described above associated with a combination of dilated bile ducts and a hepatic cystic lesion on imaging studies. Seldom, biliary tract communication can result in fibrosis of the papilla or external biliary fistulas.

Peritoneal rupture (**Figure 4**). Rupture of a hydatid cyst into the peritoneum (1-8% of cases) may occur spontaneously or after blunt trauma and can be followed by anaphylactic shock.[37,38] Large cysts located superficially on the liver are more likely to present peritoneal rupture. Symptoms typically include acute abdominal pain, nausea, vomiting, and urticaria. The presence of bile (due to previous biliary rupture) can lead to hydatid choleperitonitis. Acute peritoneal rupture is suggested on imaging studies by the presence of a collapsed hepatic cyst and peritoneal effusion or daughter cysts. On the other hand, rupture to the peritoneum can be insidious, with no acute manifestation. In this situation the spillage of scolices leads to multiple abdominal daughter cysts, which develop months to years later (secondary echinococcosis).[39]

Intrathoracic rupture (**Figure 4**). Hepatic hydatid cysts near the diaphragm can rupture into the thoracic cavity (0.6-16% of cases). Adhesions occur during cystic erosion (due to pericystic inflammation) and determine the extension of damage. Thus, intrathoracic rupture can lead to myriad findings according to extension of communication (pleural, pulmonary, or bronchial), and include hydatid pleurisy, bronchobiliary fistula, hemoptysis, and cystic or bile expectoration.[40,41] Clinical presentation is predominantly pulmonary, including coughs, expectoration, and dyspnea. Computed tomography scan is useful for diagnosis of thoracic complications from hepatic hydatid cysts.

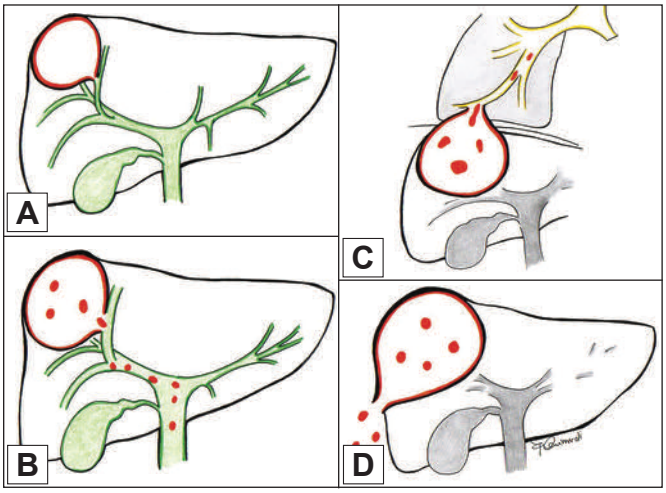


Figure 4. Schematic representation of ruptured hydatid liver cysts: **A**) Rupture to the biliary tree (biliary communication); **B**) rupture to the biliary tree with migration of daughter cysts into the biliary tree; **C**) Rupture to the thorax; **D**) Rupture to the peritoneum.

Secondary bacterial infection

Secondary bacterial infection occurs in approximately 10% of hydatid cysts but it is usually latent and subacute. Right upper abdominal pain, hepatomegaly, and fever can be present. Following secondary bacterial infection a hydatid cyst can become unfertile.

Other complications

Hepatic CHD can fistulize to the skin (with welling of pus and/or hydatid membranes), to the digestive tube with eventual hydatimesis (release of daughter vesicles during vomiting) or hydatid enterica (hydatid cyst in stool), or to blood vessels (such as hepatic veins or vena cava).

DIAGNOSIS

Hydatid liver disease diagnosis is based on a combination of epidemiological data, clinical features, radiological imaging and serologic blood tests.[30,42] Clinical suspicion of liver hydatid disease can be confirmed by imaging (such as ultrasonography, computed tomography, or magnetic resonance imaging), detection of specific antibodies with immunodiagnostic tests (ELISA, arc 5 test, among others), or by examination of material obtained by biopsy puncture.

Radiological imaging

Calcifications are seen in 20-30% of cases on **plain films** of the abdomen. Curvilinear or ring-like pattern calcifications are more common, but a complete calcification can be seen in some cases, frequently indicating death of the parasite. However, all of these findings are non-specific.

Ultrasonography is a well-established and very sensitive and specific tool for liver hydatid cyst diagnosis, being the screening method of choice in endemic area.[1,42–44] Ultrasonography is useful to define number, site, dimensions, and vitality of hydatid cysts. The method is particularly accurate when hydatid sand, daughter cysts, and/or calcifications are seen. Some findings are considered pathognomonic of hydatid disease: i) unilocular anechoic lesion with a cyst wall (laminated layer) and snowflake-like inclusions or floating laminate membranes; ii) multivesicular or multisepate cysts with a wheel-like appearance; and iii) unilocular cysts with daughter cysts with a honeycomb appearance. A cyst with echogenic material that moves according to the patient's position, as well as the imaging of one or more cysts within a cyst, provides a very strong diagnostic probability.

Most classifications of cystic hydatid disease of the liver are based on ultrasound findings. The most widely adopted, especially for surgeons, is the one proposed by Gharbi et al.[45] in 1981 (**Figure 5**).[3,14,17,18,39,45–54]The World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) developed a similar classification based on activity status of cysts suggested by sonographic appearance.[55] Three categories were defined: i) active (CE1 and CE2), indicating fertile cysts containing viable scolices; ii) transitional stage (CE3), owing to compromise of the cyst either by host defense or by chemotherapy; and iii) inactive (CE4 and CE5), having lost their fertility, and being degenerative (**Figure 5).** Both classifications are intended to correlate with the natural history of the disease. It's of note that Gharbi type II cysts correspond to CE3a (WHO-IWGE classification) and vice versa. Also, the WHO-IWGE classification includes the predominantly solid cyst with daughter cysts, which is not explicitly included in Gharbi's classification, in the CE3 group.

Cysts with a visible split wall inside (floating membrane or water lily sign) and those with septations, or with a honeycomb pattern, are pathognomonic of hydatid cysts. On the other hand, simple hepatic cysts with well-defined borders, cyst wall not visible, and uniform anechoic contents (defined as CL on WHO-IWGE classification) are not characteristic of hydatid disease. Similarly, solid heterogeneous masses or cysts (corresponding to CE4 and CE5 with the WHO-IWGE classification, and type IV and type V with the Gharbi classification) can be difficult to differentiate from granulomas or tumors.

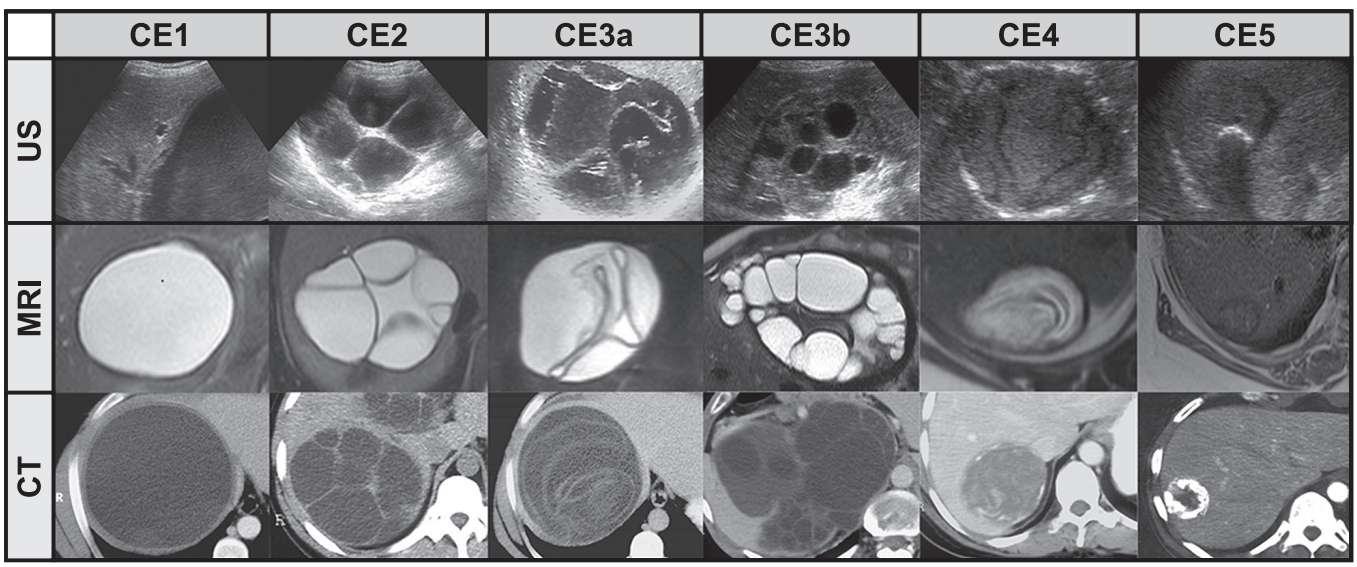


Figure 5. WHO-IWGE (World Health Organization – Informal Working Group on Echinococcosis) classification for liver hydatid cysts. **CE1**: unilocular, simple cysts with liquid content and often with the CE1-specific "double line sign", **CE2**: multivesicular, multiseptated cysts, **CE3a**: cysts with liquid content and the CE3a-specific detached endocyst, **CE3b**: unilocular cysts with daughter cysts inside a mucinous or solid cyst matrix, **CE4**: heterogenous solid cysts with degenerative, CE4-specific canalicular structure of the cyst content, and **CE5**: cysts with degenerative content and heavily calcified wall. Note that CE2 and CE3b correspond to GHARBI III classification (fluid collection with septa and/or daughter cysts), and CE3a corresponds to GHARBI II classification. Additional class on WHO-IWGE classification, cystic lesion (CL), corresponds to cyst with no visible wall and homogeneous anechoic content (not shown in the figure). Despite being considered "inactive", cysts CE4 and CE5 can carry viable scolices. (From: *Stojkovic M, Rosenberger K, Kauczor H-U, Junghanss T, Hosch W* Diagnosing and Staging of Cystic Echinococcosis: How Do CT and MRI Perform in Comparison to Ultrasound? *PLoS Negl. Trop. Dis.* **6**, e1880 (2012).[62]

Abdominal computed tomography (CT) can detect small-sized cysts, as well as visualize membrane detachment and the presence of the multivesicular pattern. CT is indicated in cases in which ultrasound fails due to patient-related difficulties (e.g., obesity, excessive intestinal gas, abdominal wall deformities, previous surgery) or disease complications. CT has a high sensitivity and specificity for hepatic hydatid disease.[56] Specificity can be increased by presence of calcified rim of daughter cysts. CT can be useful when US diagnosis is uncertain, mainly in cysts types CE4 and CE5. In cases of wide cysto-biliary communication CT demonstrates rupture in 77% of cases.[57]

Magnetic resonance imaging (MRI) has accuracy comparable to CT, and both methods bring further anatomical details for surgeons to anticipate their surgical approaches.[7,29,58,59] MRI may, however, be superior to CT in the evaluation of postsurgical residual lesions and recurrences, and also to identify rupture into the biliary tree.[58,60–63]

Serological tests.

Eosinophilia is present in up to 25% of cases (mainly in the presence of cyst rupture). Serological tests detect specific antibodies to *E. granulosus* and circulating hydatid antigen. Antibody assays are useful to confirm presumptive radiologic findings of cystic echinococcosis. However, some patients with hydatid disease do not demonstrate a detectable immune response.[32,64]

Enzyme-linked immunosorbent assay (ELISA) has a high sensitivity to detect antibodies, although it is dependent on the method of antigen preparation, and cross-reactions with other helminthic diseases occur if crude antigens are used. Purified fractions may yield high sensitivity (95%) and specificity (100%).[5,65–67] While approximately 10% of patients with hepatic hydatid cysts do not produce detectable serum IgG antibodies, ELISA is useful in follow-up to detect recurrence. Double diffusion and immune-electrophoresis demonstrate antibodies to antigen 5 (arc 5 test) and provide specific confirmation of reactivity.

Despite high rates of false-negative results (particularly in the early cyst stages, when hydatid fluid is still tightly contained within the endocysts, and in the final stage of involution, when cyst content is solid and the cyst wall largely calcified)[62] and false-positive results of serological tests, they remain very helpful to guide diagnosis in some equivocal cases, especially outside endemic areas,[68] using ELISA as a screening test and immuno-electrophoresis as a confirmatory test.[1,14,17,43]

Diagnostic puncture

Percutaneous fine-needle aspiration (PFNA) can provide definitive diagnosis if scolices are recovered from a suspected hydatid cyst; however, this technique carries a risk of spilling scolices into the peritoneal cavity. PFNA may be helpful to differentiate hydatid cysts, malignancies, and abscesses, particularly in cases with inconclusive imaging appearance and negative serological tests. Puncture should be performed by transhepatic routes and chemotherapy should be used for four days before puncture and for at least one month after puncture.[69]

TREATMENT

Although most patients with LHC are asymptomatic or paucisymptomatic, treatment should be instituted to prevent complications, such as infection, rupture of the cyst to the adjacent structures, or anaphylaxis. Currently, four major approach options are available: surgery, chemotherapy with benzimidazole compounds,[27,38,70–73] interventional approaches (such as radiological percutaneous needle aspiration,[73–79] radiofrequency,[80,81] or endoscopic therapeutics,[82–86] and follow-up with no specific treatment ("wait and see").[2,87] However, there is no consensus for the best approach.[28,30,33,43,55,87,88] Treatment of cystic echinococcosis should be a combination of general goals and rules with individual decisions and indications,[43] tailored according to surgical fitness of patients, characteristics of the cysts, and physician team experience and medical resources available.[3,7,29,47,67,74,89–91] Medical teams should know all available options and opt for the most adequate (individually or in combination), according to each individual situation. However, surgery remains the gold standard treatment for liver hydatid cysts.[3,4,6,7,18,27,30,41,43,47–49,51–54,68,81,84–86,89–102] The main intended goals of treatment of hydatid disease of the liver are to ensure complete elimination of the parasite (including the destruction or resection of the germinal layer) and prevention of recurrent disease with lower morbidity and mortality.

Thus, small cysts that are densely calcified (Gharbi V or CE4 or CE5) could be followed with no specific treatment or excised if the patient has a good performance status; viable but uncomplicated deep small cysts could be treated by chemotherapy or interventional procedures; complicated cysts or peripheral cysts in a fit patient should be treated by surgery.[103]

Surgical approach

Surgery is the treatment of choice especially in large (>10 cm) lesions, complicated cysts (associated with rupture, biliary tree communication, compression of adjacent organs or vessels, secondary infection, hemorrhage), and cysts situated superficially that may rupture spontaneously or as a result of trauma.

The main principles of the surgical treatment are: i) to inactivate scolices contained in the cyst; ii) to prevent spillage of cyst contents during its evacuation; iii) to eliminate all viable elements of the cyst; iv) to manage the residual cavity of the cyst; and v) to search for and manage any

communications with the biliary tract.

Anaphylaxis and secondary recurrence due to accidental spilling of the cyst content are specific complications added to ordinary surgical risks associated with any surgical procedure. Operative mortality rate varies from 0.5% to 4% but increases with repeated intervention. Relative contraindications to surgery include pregnancy, poor clinical status, and diffuse hepatic cysts.

Surgical approach includes **conservative surgery**, when the pericyst is not resected but the germinal and laminated membranes are resected; and **radical surgery**, when the pericyst is included in the resection (pericystectomy and partial hepatectomy). Usually more radical procedures are associated with higher intraoperative risk but lower chance of relapses, and vice versa.

Perioperative chemotherapy. Preoperative chemotherapy could soften the cysts and reduce intracystic pressure, reducing the risk of peritoneal spillage during evacuation of the cysts. Postoperative chemotherapy is useful to reduce the rate of recurrences and should be used for at least one month after the procedure.

Installation and approach. For most cases the patient is positioned supine. No special rolls or padding are necessary. Laparoscopic access may be used; however, usually open laparotomy is preferred through a large incision (a right subcostal incision, extended to the left and/or to the xiphoid process). Depending on the topography and number of cysts on the liver and the possibility of the presence of hydatid cysts in other viscera, the surgeon can proceed to an upper midline incision. In the last decade, studies examining the use of pure laparoscopic approach and hand-assisted technique have been published.[104–108] In fact, these minimally invasive surgical approaches can be performed safely in selected patients with liver hydatid cysts.

The first step after peritoneal access is to explore the peritoneal cavity, the liver, and the extrahepatic biliary tract through both visual, manual palpation, and intraoperative ultrasonography (IOUS) examination.

Concerning the treatment of the hepatic hydatid cysts, numerous surgical techniques have been proposed. These include radical and conservative surgical approaches. The more aggressive options are hepatectomy and total pericystectomy. They involve removing the whole cyst with the pericyst, with unnecessary loss of normal hepatic parenchyma. Conversely, conservative operations aim to unroof the cyst after evacuating its contents, and to manage the residual cavity. Comparisons between radical and conservative techniques remain at the center of many controversies.[28,29,37,55,83,89,100,101,105–107,109] The choice between one of these two approaches depends mainly on the habits and skills of the surgical team and the technology available more than the known results of each procedure.

Scolicide substances. During surgical approach, scolicidal agents can be used to protect surrounding organs and to inactivate the cyst. Potential communication between the hydatid cyst and the biliary tree should be taken into account since most scolicidal agents can cause chemical cholangitis and lead to subsequent sclerosing cholangitis. Formalin was completely abandoned as scolicidal agent owing to its severe complications, such as sclerosing cholangitis.[4,6,36,48,97] Other agents were used in the past, such as alcohol, chlorexidine, cetrimide or silver nitrate solution, but were mostly abandoned.[30,102,108,110] Nowadays the three most used scolicidal agents, depending on surgeons' habits, are: hydrogen peroxide,[4,6,7,40,96,110,111] hypertonic saline 15% or 20%,[4,28,30,33,35,54,64,87,88,97,99] or polyvinyl pyrolidone-iode.[46,89] Studies comparing usual scolicidal agents are rare and not conclusive.[112–114] The use of hydrogen peroxide results in an exothermic reaction and boiling when applied to the larvae or the cavity. Colorless characteristics of this scolicidal liquid help in identifying hydatid fluid that is bile stained.

Conservative approach

The principal aims of conservative surgery are: i) inactivation of viable parasitic elements; ii) evacuation of the cyst cavity leaving part or all the pericyst; and iii) management of the residual cavity and cyst-bile duct communications, if existing.

After complete exploration of the peritoneal cavity, the area around the cyst is covered and isolated with packs immersed in a scolicidal agent. The cyst is then punctured and incised at its most accessible part. Aspect of the liquid is noted; yellowish coloration suggests biliary communication, while purulent content indicates infection, which is frequently associated with biliary fistulae. It is highly recommended to use two suction cannulas (one for cyst contents, the other for eventual spread and leaks around it) and a jar trap to avoid obstruction of aspiration systems. All cyst content is aspirated and the cyst largely opened. The germinal membrane is easily removed with forceps and the cavity is flushed with scolicidal agent for 10 minutes. The pericyst is cleaned by the interior of the cyst and smoothed out, and possible daughter cysts developing in the pericyst are removed. It is prudent to proceed to meticulous operative inspection of the inner surface of the remaining cavity, peeling the laminated membrane to reduce thickness of the pericyst, and remove daughter cysts hidden in the pericyst layer (exogenous daughter cysts). Using hydrogen peroxide to again flush the remaining cavity for at least 10 minutes may play a role in sterilizing remaining exogenous cysts exposed by the peeling procedure. Exogenous vesiculation occurs when the pericyst becomes thicker.[3,90]

Before injection of scolicidal agents it is necessary to look for an eventual fistula. Scolicidal agents should be avoided in case of biliary fistulae because the contact of these agents with the biliary tract can be harmful. Thus, scolicidal agent injection is not recommended while the cyst

is still closed. Many methods can be used to help identify fistulas, such as injection of isotonic serum, methylene blue or air through the cystic duct, or through common bile duct puncture.[52,89,99] The visible biliary openings should be sutured when they are less than 5 mm, or these communications can be treated by directed external fistulization when they are more than 5 mm.[52,82,93,115] If the hydatid fluid is bile stained, after a negative meticulous sought of biliary openings, the possible fistula is left alone and the residual cavity is kept under aspiration during the postoperative period using external drainage. After puncture, the cyst is widely unroofed by excising the projecting part of the pericyst (**Figure 6**).[27,29,37,46,47,82,115–117] Then, the obliteration of the remaining cavity is completed by introflexion or capitonage (increasing the risk of injuring the major duct and vessel passing next to the pericyst), suture of the pericyst with slowly resorbing thread, omentum (**Figure 7**) or muscle flaps, or simple drainage.[7,29,37,46,64,82,93,101,107,117] In some rare cases, cystojejunostomy can be performed by a wide anastomosis between pericystic edges and jejunum.[28,64,82,93,101,107] All of these techniques prevent dead space in the remaining cavity and further potential complications. Filling the inner cystic cavity prevents fluid collection and infection in postoperative period. Cholecystectomy can be performed along with intraoperative cholangiography whenever biliocystic communication is suspected, or in the case of a dilated common bile duct, to ensure the vacuity of biliary tract. A T-tube drain can be placed in the common bile duct (**Figure 8**). A conservative approach can result in a rigid residual cavity due to the thickness of the pericyst. This fibrous tissue can make it difficult to suture eventual biliary communications and can also make it difficult to identify exogenous daughter cysts. Scolices in the common bile duct can be evacuated intraoperatively or postoperatively through endoscopy. The intervention is completed with drainage of the perihepatic area.

In the postoperative period, drainage of the remaining cavity should be maintained until at least the fifth day. If a postoperative external biliary fistula presents during this period, it is appropriate to maintain the drain. Endoscopic sphincterotomy and/or nasobiliary catheter may be very useful in the management of persistent bile leakage by accelerating the healing.[29,89]

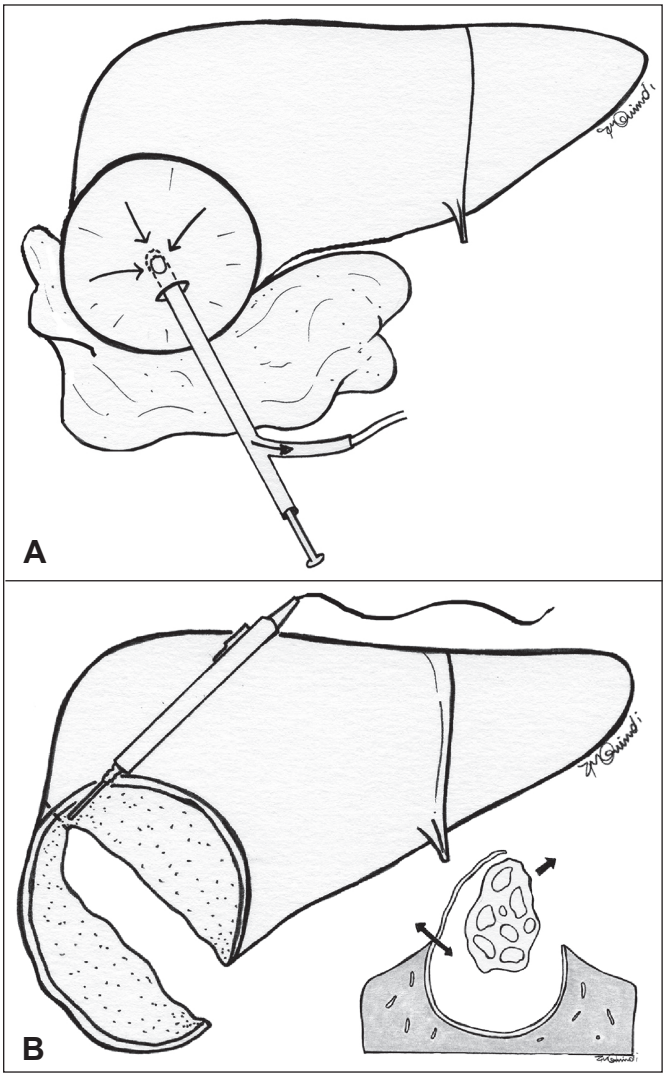


Figure 6. Schematic representation of a conservative surgery for hydatid cyst. **A**) After protection of surroundings of the cyst by packs soaked with scolicidal agent, the cyst is punctured with a trocar with a system for release obstructions, the content of the cyst is aspirated, and if it is not of bilious aspect, the cyst is filled with scolicidal agent for 15-20 minutes. **B**) The cyst is largely opened and the endocyst is removed, then the cyst is unroofed by removing the portion not involved by hepatic parenchyma. Meticulous search for communications with bile ducts and/or exogenous daughter cysts is performed and if present they are treated as described in the text.

Radical approach

The main procedures of radical approach are total pericystectomy and liver resection. With these techniques all objectives of the surgical treatment of hydatid cysts are met. Authors who support radical surgery for liver hydatid cysts report that it results in fewer postoperative complications, such as biliary leakage and recurrence.[33,36,98,107,108] The most common radical approach is pericystectomy (**Figure 9**). In this procedure, the whole cyst (including the pericyst) is removed along with nearby healthy liver parenchyma. This parenchymal margin should be slight, to minimize the loss of liver tissue, representing a non-anatomical liver resection. Whenever it is difficult or risky to manage the intraparenchymal portal pedicle (bile duct and portal vein) due to proximity to the hydatid cyst, an anatomical liver resection is preferred and should follow general rules as detailed in other chapters of this book.

Complete resection of the cyst can be performed either

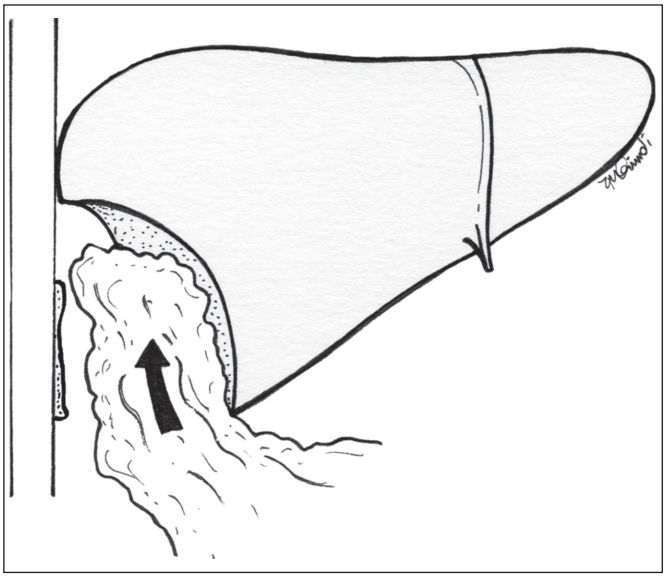


Figure 7. Schematic representation of epiploonplasty as a method of treatment of the residual cavity after unroofing or pericystectomy of hydatid liver cyst.

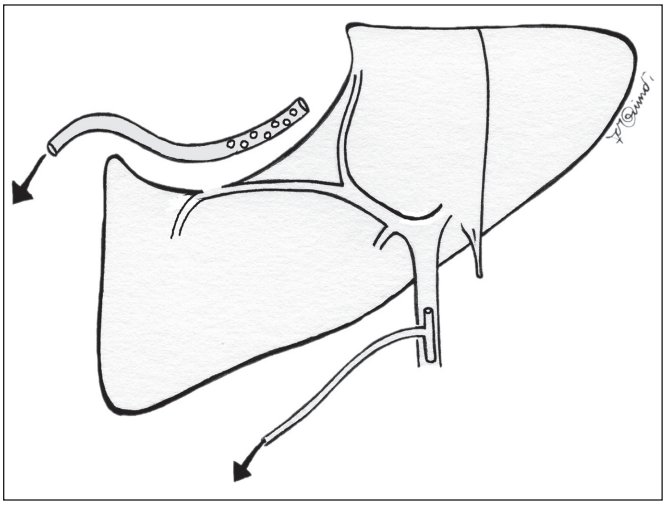


Figure 8. Option for treatment of biliary communication after conservative surgery of hydatid cyst. A "T" tube placed in the main bile duct reduces the pressure in the biliary tree and a tubular drain placed near the suture of the bile duct communication avoid fluid collection until complete healing.

by an "open-cyst" approach (with resection after opening and sterilization of the cyst), or "closed-cyst" approach (without opening of the cyst).[97,100] The open-cyst technique brings the risk of intra-abdominal seeding of scolices, especially if no additional measures are applied as described in conservative approaches (protection and scolicidal agents). In this situation, some benefits of the radical approach are lost. Otherwise, the open technique can reduce the risk of accidental rupture of the cyst during the resection or the mobilization of a closed cyst.

Advantages of pericystectomy include the preservation of normal hepatic parenchyma (in contrast with anatomical liver resections) and the complete resection of the parasite and pericyst, resulting in a resilient residual cavity that is easy to obliterate and allows for adequate treatment of eventual biliary communication. During pericystectomy, a fragment of pericyst can be left in place to avoid dangerous dissection in contact with major vascular or biliary structures (**Figure 10**). Similarly to the conservative approach, the residual cavity can be obliterated. The main indication for anatomical liver resections is complex compromise of the biliary tree or vascular intrahepatic structures. However, a recent large study comparing conservative and radical surgical approaches showed no difference in perioperative complications, nor in recurrence rates.[118]

In endemic areas and less equipped medical facilities, radical approaches can lead to high postoperative morbidity and mortality rates. In addition to the non-malignant aspect of this disease and its slow progression, other reasons could justify conservative approaches, such as the presence of secondary inflammation in the nearby liver resulting from long-term compression by the cyst, and the difficulties in estimating remnant liver function. However, recent technological developments and the generalization of modern surgical techniques, such as intraoperative ultrasonography, ultrasonic dissection, LigaSure, metal bands and radiofrequency, make a strong case for adopting radical approaches. Hepatic resections can be reserved for cysts involving major vascular-biliary structures of the liver (anatomical resection), small cysts located peripherally (pericystectomy), pedunculated cysts, anatomical hepatic segments or sectors with severe damage by a cyst or being the

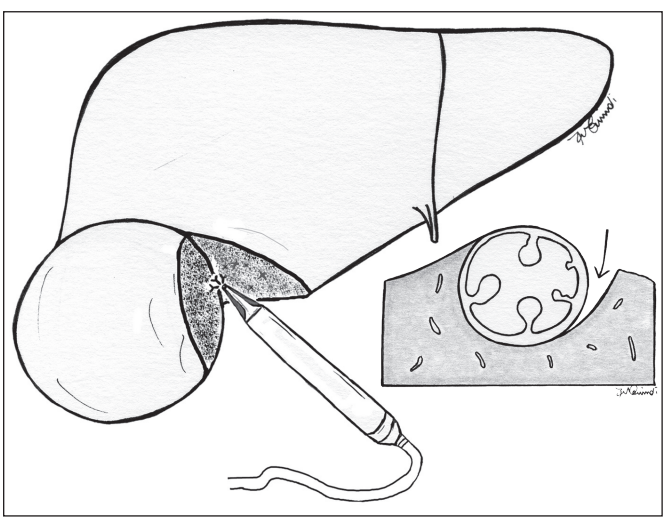


Figure 9. Schematic representation of a pericystectomy. The cyst is completely removed with the pericyst. The residual cavity is more supple than if the pericyst is preserved.

are preferable, such as large cysts rendering liver mobilization impossible or dangerous, blood vessels in a perilous situation, or when there is high risk of trauma to nearby organs (colon, diaphragm, stomach and duodenum). In these situations it is safer to be conservative and to perform an open cyst resection instead of radical removal of the cyst.

Perioperative chemotherapy (using benzimidazole compounds) can reduce recurrence risk. However, despite all precautions, dissemination and spillage of hydatid liquid into the abdomen or wound edges during the intervention can still happen.[3,4,7,29,38,48,87,104]

Laparoscopic approach

Surgery for uncomplicated hydatid cysts of the liver can be performed safely by laparoscopic approach.[119–122] The advantages of this less invasive approach (including shorter hospital stay, lower incidence of wound infection and less postoperative pain) should be weighed against the potential increased risk of spillage of scolices (difficulties in aspirating), difficulties in approaching deeply located cysts and the possibility of eventual increased recurrence rates.[123,124]

Results of surgical treatment

Most studies demonstrate that mortality and morbidity of radical and conservative approaches are similar.[47,48,87,99,125] Generally, mortality ranges from 0 to 6.5%.[73,82,92,125] However, some factors such as perioperative complications, disseminated disease and weight loss seem to be involved.[7,73,91,126] All interventions on liver hydatidosis should be considered as potentially major surgery.[7,90]

Specific morbidity is represented particularly by deep abdominal complications, which range from 10% to 29.5%.[7,28,73,87,109,115,127] Bile leakage represents the main source of immediate postoperative complications. It is related to persistent biliary fistula on a thick, calcified and infected remaining pericyst, and poor or defective drainage of the residual cavity. In most cases, fistulae close spontaneously, or after endoscopic sphincterotomy.

After surgery, all patients should undergo abdominal ultrasound surveillance. It is usually recommended at the first month after discharge, every six months during the first four years, and then annually thereafter, to detect recurrences. In the case of highly suspected liver hydatid disease recurrence on an ultrasound, abdominal CT scan should be performed. Recurrence is defined as the appearance of a new growing cyst, undetected by radiological exploration before the surgery or by the surgeon during the procedure, whether in the first location of the hydatid cyst in the liver or in another liver segment. During follow-up, if cystic areas appear on an ultrasound and/or CT scan without change in size and without evidence of daughter cysts, fine-needle aspiration cytology (FNAC) can be used to confirm recurrence.[68] Immunological tests are less sensitive and specific, and

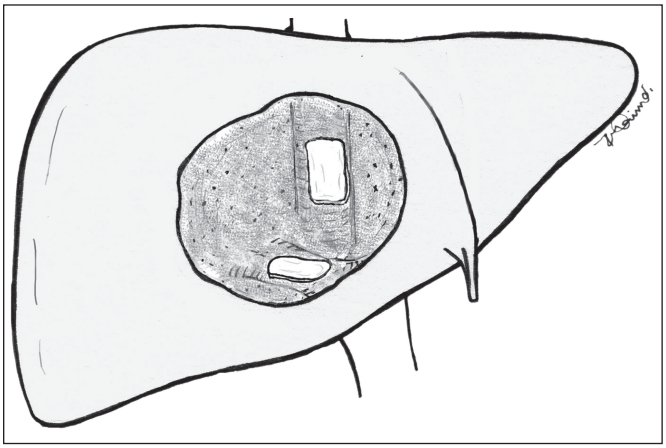


Figure 10. Schematic representation of pericystectomy with partial preservation of pericyst in zones of adherence to vascular structures.

are helpless to recognize recurrence when compared to radiological explorations. Recurrence rates of liver hydatid cysts after surgery range from 0 to 25%.[4,29,46,48,49,70,79,87,91,128–133]

Some authors report a significant high rate of recurrence after conservative approaches and following radical resection.[48,87,97–99] They report that recurrences with conservative procedures are due to the possibility of leaving viable material on the outer surface of the pericyst (exogenous vesiculations).[3,4,52,79,90,129] Some surgeons may fail to ensure a meticulous strategy in order to avoid missing residual vesicles.[3,127] Surgeons' skills and experiences can be another determining factor of recurrences.[29,90,91] Peritoneal soiling during emptying of the cysts can explain some recurrences and seems to be a more complex problem.[3,130] When all described precautions are taken and all parameters are adjusted, no statistically significant difference is observed between radical and conservative approaches in terms of postoperative recurrences.[68] Recurrence may occur many years later, which is the reason why extended follow-up is recommended. Postoperative recurrence can occur anywhere from four months to 35 years after the first surgery. Thus, in patients who have a high risk of developing recurrences, a conservative approach may be preferred because technical difficulties may occur during further hepatic operations, leading to high postoperative morbidity and mortality or a lengthy postoperative stay.[97]

Percutaneous aspiration, injection, re-aspiration (PAIR)

Percutaneous aspiration, injection of scolicidal agent, and re-aspiration (PAIR) for the treatment of hydatid cysts of the liver was introduced in 1980s,[134] and is a low invasive procedure with less morbidity and mortality than surgery.[135] Cyst puncture for treatment of hydatid disease of the liver comprises: i) percutaneous puncture under ultrasonic guidance; ii) aspiration of a substantial amount of cyst fluid;

iii) injection of scolicidal agent; and iv) re-aspiration of the fluid cyst content after 15 to 20 minutes. The PAIR procedure should be accompanied by perioperative chemotherapy to reduce risks of secondary echinococcosis (due to spillage of scolices).[134,136] Some crucial points for the PAIR technique include the use of transhepatic puncture (surrounding liver parenchyma protect against peritoneal spillage) (**Figure 11**) and immediate analysis of the aspirated fluid for traces of bilirubin (since biliary tree communication precludes the injection of scolicidal agents).

PAIR is mainly indicated for hydatid cysts in patients not suitable for surgery and those who refuse surgery. Cysts classified CL, CE1, CE2, and CE3 are good candidates for PAIR. However, cysts that are superficially located, honeycomb-like cysts, cysts with solid patterns or that are calcified, and cysts with associated biliary tree communication are generally refused for PAIR. Superficially located cysts carry a higher risk of spillage and puncture should be avoided, or, if necessary, performed using transhepatic technique (**Figure 11**).

Percutaneous Thermal Ablation (PTA). The percutaneous evacuation of a hydatid cyst of the liver followed by radiofrequency thermal ablation is another percutaneous method that is able to inactivate the germinal layer without the use of scolicidal substances.[76,137]

Chemotherapy

Chemotherapy using benzimidazole compounds can result in significant regression (degeneration or size reduction in up to 70% of cases) or complete disappearance (10% to 30% of cases);[134,136,138] however, some studies found no response in 40% of patients.[136] Relapses after chemotherapy occur in up to a quarter of cases, but are usually sensitive to retreatment. Favorable response is mostly expected in isolated small cysts with minimal surrounding adventitial reaction. Conversely, large, old, or complicated cysts are less likely to respond well to chemotherapy. Thus, it is indicated as a sole treatment in patients with contraindications for surgery or PAIR, or it can be used as a perioperative treatment adjunct to invasive procedures (such as surgery or PAIR). Patients with unfavorable fitness status and/or with multiple simultaneous cysts in other organs or the peritoneum are examples of poor surgical candidates that could undergo a conservative approach by chemotherapy alone. Chemotherapy as sole treatment should be done for at least three months.

The two available benzimidazoles, albendazole (10-15 mg/kg/day) and mebendazole (40-50 mg/kg/day), have demonstrated efficacy, but results for albendazole have been superior (probably due to easer intestinal absorption and penetration into the cysts). Contraindications for the use of benzimidazoles include early pregnancy, chronic hepatic diseases, and bone marrow suppression. Adverse reactions (such as neutropenia, liver toxicity and alopecia) are reversible upon cessation of treatment.

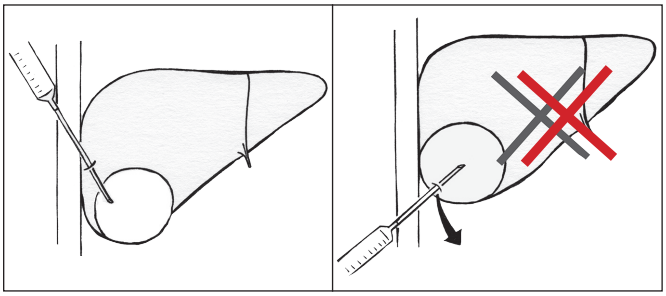


Figure 11. Technique for puncture of hydatid cysts of the liver. Transhepatic technique avoids spillage of parasites in superficially located cysts.

Praziquantel (50 mg/kg/day), an isoquinolone derivative, has a marked in vitro efficacy on reducing scolex viability,[139] and it has been used in combination with albendazole, resulting in more rapid results than benzimidazoles alone.[140–143]

ALVEOLAR ECHINOCOCCOSIS

Alveolar echinococcosis (AE) is caused by the larval stage of *Echinococcus multilocularis*, a tapeworm with a life cycle similar to that of *Echinococcus granulosus*, but having foxes, coyotes, dogs and cats as definitive hosts instead (**Figure 1**). Humans are accidental intermediate hosts (rodents are regular intermediate ones), infected by ingestion of eggs discharged with the feces of definitive hosts, probably by handling definitive hosts or by ingesting contaminated food or water. Despite the worldwide presence of the parasite, mainly in the northern hemisphere, and the high prevalence of definitive hosts in certain areas, alveolar echinococcosis is rare in humans.[144,145] It is considered to be the most pathogenic zoonosis in temperate and arctic regions of the Northern Hemisphere and more recently in Asia and Europe, and it has expanded from rural to urban areas.[145,146] Despite the fact that alveolar echinococcosis is a benign disease, it is well known as potentially fatal.[147]

Once in the liver, nearly exclusively the primary site of AE, the parasite develops, resulting in an alveolar structure, made up by multiple vesicles whose diameter varies from less than 1 mm up to 15-20 cm. Each vesicle has a structure similar to that of cystic hydatid disease, with germinal and laminate layers; however, brood capsules or scolices are uncommon and the small cysts are surrounded by dense connective tissue and granulomas. The disease is characterized by infiltrative local proliferation (exogenous tumor-like proliferation) and the potential to metastasize.

Because the cysts usually grow slowly, parasite infection may not produce any symptoms for many years (**initial**

phase) and may be cured spontaneously or continue growing, resulting in symptoms (**progressive phase**).[148] Initial clinical manifestations include mainly abdominal pain, jaundice and hepatomegaly.[149] In this phase, the liver is largely affected. The **advanced phase** is characterized by liver failure, often associated with portal hypertension, ascites and splenomegaly. The natural course for untreated (or inadequately treated) patients is frequently death, some years after diagnosis. Death eventually results from biliary complications (such as cholangitis, septicemia, and secondary biliary cirrhosis), portal hypertension, Budd-Chiari disease, or complications related to involvement of other distant organs. A **stable phase**, with inhibition of parasite proliferation, can occur in patients undergoing long-term chemotherapy. Also, in some asymptomatic cases, the parasite dies out and the lesion becomes calcified, representing an **abortive phase**.

The clinical diagnosis is based on: i) clinical findings and epidemiological data,[65] ii) lesion morphology shown by imaging techniques (mainly ultrasound examination, CT scan, MR imaging or FDG-PET),[150–152] iii) histopathology and/or nucleic acid detection, and iv) serology.

Typical ultrasound aspects of AE are a pseudotumoral hepatic mass, which is heterogeneous, with irregular edges and scattered calcification. Central necrosis may result in a cystic aspect with surrounding hyperechogenic tissue. CT scanning reveals the morphological aspect of the lesions and is useful for preoperative evaluation of vascular involvement and extension to adjacent structures and metastatic lesions (especially in the lungs and brain). MRI is the method of choice to assess invasion of adjacent structures and is helpful in differential diagnosis from similar lesions from other etiologies. Also, magnetic resonance cholangiography reveals the relationship between the AE lesion and the biliary tree. Intrahepatic biliary obstruction and/or communication with a central necrotic area can also be identified by percutaneous cholangiography or endoscopic retrograde cholangiography. Fluorodeoxyglucose positron emission tomography (FDG-PET) assesses the parasite metabolic activity (but not parasite viability, and in negative exams viable parasite can be present). The different methods of imaging play complementary roles in detecting and characterizing lesions and their complications.

Clinical features have been clearly outlined and updated by the expert consensus for diagnosis and treatment of cystic echinococcosis and alveolar echinococcosis in humans,[99] which established the WHO-IWGE (World Health Organization - Informal Working Group on Ecchinoccocosis) PNM classification system as the international benchmark for standardized evaluation of diagnostic and therapeutic measures.[153,154] This classification takes into account the primary mass in the liver (P), the involvement of neighboring organs and lymph nodes (N), and the presence of metastasis (M) (**Table 1**).

Serological tests are usually positive. Purified *E. multilocularis* antigens allow high specificity and serologic differential diagnosis from *E. granulosus* infection.

Percutaneous needle biopsy is useful in some cases and can confirm the diagnosis if larval elements are demonstrated.[65]

Diagnosis of alveolar echynococcosis is confirmed if at least two of the following four parameters are achieved:[147]

1) Typical organ lesions detected by imaging techniques
2) Detection of *E. spp'* specific serum antibodies by tests of high sensitivity and confirmed by assays with high specificity
3) Histopathology compatible with a metacestode of *E. multilocularis*
4) Detection of the *E. multilocularis* nucleic acid in a clinical specimen.

Guidelines for the management of alveolar echinococcosis have also been recently updated.[149] Anti-parasitic therapy with benzimidazoles (albendazole or mebendazole) over many years (in cases of surgical resection) or lifelong if necessary, combined with interventional procedures, can inhibit disease progression, reduce metastases, and improve both the quality and length of survival.[155,156] Radical surgery combined with anti-parasitic therapy (for two years at least) should be the primary choice, and, when performed in an early stage of the infection, may lead to cure. Interventional procedures (percutaneous bile or abscess drainage, or endoscopic dilatation of the bile duct with or without plastic stents) should be preferred to palliative surgery whenever possible.

To achieve a complete radical surgery, resectability should be carefully analyzed by precise preoperative imaging. The entire parasitic lesion should be excised including a 2 cm safety margin and should be classified according to the quality of resection by histopathology in R0 (no residual disease); R1 (microscopic residual disease); or R2 (macroscopic residual disease).[149]

Hepatic AE can spread by different ways: i) hematogenous; ii) biliary; iii) contiguity; and iv) lymphatic.[157–159] Thus, regional lymph nodes (hepatic and subpyloric) should be included in curative resection (although WHO guidelines provide no instructions on how to deal with regional lymph nodes).[160]

Incomplete resection (R1 or R2) should be avoided; however, it might be useful in some rare cases of sepsis if neither R0 resection nor percutaneous or endoscopic drainage are possible.[161]

Liver transplantation may be proposed in exceptional cases of very advanced alveolar echinococcosis when usual radical liver resection is not feasible.[162,163]

POLYCISTIC ECHINOCOCCOSIS

Polycystic echinococcosis (PE) is a rare parasitosis caused by *E. vogeli* (neotropical echinococcosis) and *E. oligarthrus* (unicystic echinococcosis).[164–169] It is present mainly in tropical areas of South America.[167] The life cycle of this parasite includes the bush dog and some wild mammals as definitive hosts, while human beings are accidental hosts.[169]

Despite the clinical aspects of PE being similar to alveolar echinococcosis, the cysts are relatively large and contain brood capsules and scolices. Diagnosis is performed by enzyme-linked immunosorbent assay (ELISA, high sensitivity) and Western blot (high specificity).

Because of its rarity, management of this disease remains controversial and not well established. Lesions are usually so extensive that surgical resection is always difficult, frequently incomplete, and carries a high mortality rate.[167] However, whenever possible, surgical resection combined with benzimedazoles is the most likely to succeed.

PYOGENIC HEPATIC ABSCESS

Pyogenic liver abscess (PLA) is a relatively uncommon but life-threatening disease. Incidence of PLA appears to have increased over the last decades, possibly due to progress in imaging studies.

PLA results from a bacterial infection of the hepatic parenchyma with subsequent inflammatory infiltration, and formation of a collection of pus.[170] A failure of clearance of bacteria that reach the liver may result on PLA. The most frequent routes for bacterial hepatic invasion are **biliary** (46%) and **portal** (15-25%). Biliary obstacles (benign or malignant), cholecystitis and dysfunctional bilioenteric anastomosis are possible biliary causes of PLA. Portal route occurs following a portal phlebitis from organs with portal drainage, such as with diverticulitis, appendicitis, infected colorectal or pancreatic cancer, and pancreatitis. If no clear risk factor is identified, the abscess is called **cryptogenic** (18-25%). It has been suggested that cryptogenic PLA could be a sign of occult gastrointestinal malignancy.[171,172]

Table 1. PNM classification of alveolar echinococcosis.

P	**HEPATIC LOCALIZATION OF THE PARASITE**
PX	Primary tumour cannot be assessed
P0	No detectable tumour in the liver
P1	Peripheral lesions without proximal vascular and/or biliar involvement
P2	Central lesions with proximal vascular and/or biliar involvement of one lobe [a]
P3	Central lesions with hilar vascular or biliar involvement of both lobes and/or with involvement of two hepatic veins
P4	Any liver lesion with extension along the vessels [b] and the biliary tree
N	**NODAL INVOLVEMENT**
N	Extrahepatic involvement of neighbouring organs [diaphragm, lung, pleura, pericardium, heart, gastric and duodenal wall, adrenal glands, peritoneum, retroperitoneum, parietal wall (muscles, skin, bone), pancreas, regional lymph nodes, liver ligaments, kidney]
NX	Not evaluable
N0	No regional involvement
N1	Regional involvement of contiguous organs or tissues
M	**DISTANT METASTASES**
M	The absence or presence of distant metastasis [lung, distant lymph nodes, spleen, CNS, orbital, bone, skin, muscle, kidney, distant peritoneum and retroperitoneum]
MX	Not completely evaluated
M0	No metastasis [c]
M1	Metastasis

[a] For classification, the plane projecting between the bed of the gall bladder and the inferior vena cava divides the liver in two lobes.
[b] Vessels mean inferior vena cava, portal vein and arteries.
[c] Chest X-ray and cerebral CT negative.

Single abscesses are more likely to be cryptogenic than multiple hepatic abscesses.[173–175] The **arterial** route (5-15%) is uncommon and eventually associated with dental abscesses.[176] PLA due to **direct extension** of a contiguous infection (such as cholecystitis or subphrenic abscess), trauma, or invasive procedures (such as hepatic resection, transarterial chemoembolization, and radiofrequency ablation) are rare (<5%).[177,178]

Symptoms of PLA are variable, from the more classic presentation (with right upper abdominal pain fever, and leukocytosis) to an oligosymptomatic presentation (with progressive fatigue and weight loss). Hepatic abscess due to biliary obstruction usually has more evident and precocious infectious signs. Local complications of PLA include thoracic or peritoneal rupture and fistulization. Sepsis and malnutrition, together with their consequences, may lead to death. Overall mortality for PLA from recent series varies from 2% to up to 32%.[175,179–183] Many risk factors have been suggested, such as the presence of malignancy, advanced stage, multiloculated abscess, and polymicrobial infection.[175,184,185]

Most pyogenic liver abscesses are unique lesions, located in the right liver, and measure more than 5 cm at the moment of diagnosis. However multiple or even diffuse forms can be present at the diagnosis.

Imaging studies have a high accuracy in diagnosing PLA, particularly CT and MRI. A central fluid-like pus collection surrounded by a multilayered hypovascular or hypervascular rim (corresponding to the fibrotic wall or to hyperemic granulation tissue, respectively) is the classic, most frequent radiological finding.[186] A solid pattern can be observed during the initial stage of a PLA, but the infection progressively leads to necrosis and cystic areas. CT and MRI are useful to differentiate solid tumors from solid organizing PLA.[186]

Most often, PLA is polymicrobial. The most common bacterial species cultured are *Escherichia coli*, *Streptococcus*, *Klebsiella pneumonia* and anaerobic agents. However, culture of purulent material can be negative in up to 28-52% of cases,[170,175,176,179] especially if antibiotic therapy is initiated before material sampling. PLA by *Klebsiella spp* has increased in the last decade, especially in Asia and North America, possibly associated with malignancies.[170,175,187] This particular PLA usually has a more aggressive course, with a high propensity to metastatize.

Nowadays, the first choice of treatment for PLA is based on antibiotic therapy alone (for small unilocular abscesses), or combined with imaging-guided percutaneous puncture and drainage.[188,189] Success rates of 70% to 90% are obtained with non-surgical approaches for single and unilocular abscesses, and even for multiloculated ones.[180,182,190]

Risk factors for failure of percutaneous drainage include mainly multiloculated abscesses and abscesses with biliary communication.[179,182,189,191] Percutaneous or surgical drainage of PLA with biliary tract communication should have concomitant treatment of biliary obstruction if present. PLA in the setting of biliary tract cancer is more likely to have a biliary communication and a higher mortality.[185] Biliary obstruction can be treated by percutaneous or endoscopic techniques, but eventually surgical approach is needed. Also, large abscesses containing thick viscid pus are prone to failure by percutaneous treatment.[192] Furthermore, underlying disease treatment is indicate whenever possible, such as in cases of cholecystitis, biliary fistula, pylephlebitis secondary to appendicitis, and malignancies (such as hepatocellular carcinoma, cholangiocarcinoma, liver metastases, gallbladder carcinoma, carcinoma of the papilla, and pancreatic cancer).

Surgical drainage allows the placement of a soft large-bore tube drain, which enables complete drainage of viscid pus and necrotic debris (**Figure 12**) and frequently the treatment of causal disease. Intraoperative ultrasound allows accurate localization, planning of drainage route, localization and avoidance of vascular and biliary structures.[180]

Thus, surgical drainage is indicated mainly for PLA that failed to percutaneous treatment or when surgery is need for the underlying cause of the PLA.[181,193] However, salvage surgery is associated with high mortality rates and should be performed soon if percutaneous drainage is not efficacious.[179,182] Overall surgical mortality for PLA varies from to 2% to 11%.[179,180,194]

Surgical drainage may be the initial treatment of PLA in selected groups of patients. Some authors found better results from initial surgical drainage than from percutaneous drainage in patients with large hepatic abscess (more than 5 cm).[180] Open surgical drainage resulted in fewer treatment failures, less requirement for secondary procedures, and shorter length of hospital stay, but overall morbidity and mortality

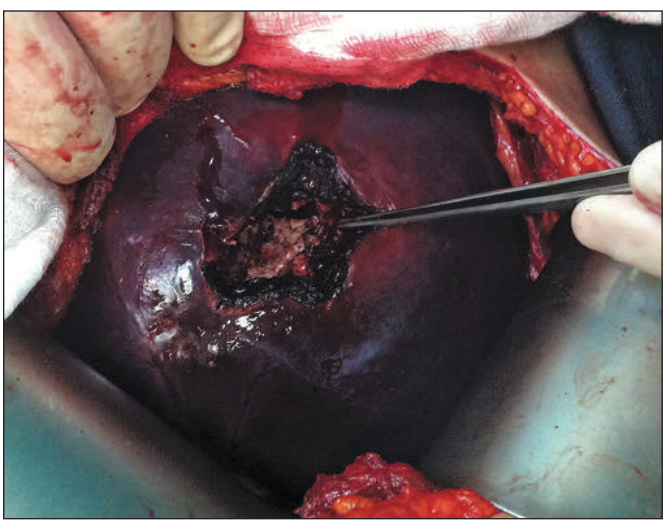


Figure 12. Intraoperative aspect of a single cryptogenic pyogenic liver abscess with necrotic debris, not suitable for percutaneous drainage.

rates were similar to those with percutaneous approach. Hope et al.[188] suggest that surgical treatment should be the first choice for multilocular abscesses of more than 3 cm. Patients with large multiloculated liver abscesses secondary to malignancies should undergo early surgical approach.[184] Initial surgical approach has also been suggested for critically ill patients because of the high mortality of percutaneous approach in this group of patients.[176] Other indications for initial surgical approach are ruptured abscesses and those relating to localization unfavorable to percutaneous access.

Hepatic resection is a safe and efficacious option for PLA that could be exceptionally indicated when the initial presentation is intraperitoneal rupture, when hepatolithiasis is associated, or if severe hepatic destruction is associated.[174,181,195]

SUGGESTED READING

Brunetti, E., Kern, P. & Vuitton, D. A. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop.* **114**, 1–16 (2010).

A well-structured review on the two most important types of echinococcosis: cystic and alveolar. It represents the expert consensus from the World Health Organization (WHO) – Informal Working Group on Echinococcosis (IWGE) for the treatment of these diseases, mainly cystic echinococcosis.

El Malki, H. O. *et al.* Predictive model of biliocystic communication in liver hydatid cysts using classification and regression tree analysis. *BMC Surg.* **10**, 16 (2010).

Paper that evaluates preoperative predictive factors for biliocystic communication. Other results from this large series of 672 patients treated for cystic hydatid disease at a single center can be seen in references 03 and 07.

Mezhir, J. J. *et al.* Current management of pyogenic liver abscess: surgery is now second-line treatment. *J. Am. Coll. Surg.* **210**, 975–983 (2010).

It is a retrospective study of 58 patients with pyogenic liver abscesses. The mortality of salvage surgical treatment after failure of percutaneous drainage was high. The predictors of failure of percutaneous drainage were the presence of cystic yeast and cystic communication with the biliary tree.

Tan, Y. M. *et al.* An Appraisal of Surgical and Percutaneous Drainage for Pyogenic Liver Abscesses Larger Than 5 cm. *Ann. Surg.* **241**, 485–490 (2005).

The authors suggest, in a retrospective study of 80 patients with pyogenic liver abscesses larger than 5 cm, that surgical drainage could provide better results than percutaneous approach in this group of patients.

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21 Primary Intrahepatic Lithiasis

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- *Primary intrahepatic lithiasis (stones originated inside the intrahepatic biliary tree) is endemic in East Asia and much less common in the West. It is usually associated with intrahepatic biliary strictures and is responsible for recurrent episodes of cholangitis, hepatic atrophy, secondary biliary cirrhosis, and intrahepatic cholangiocarcinoma.*
- *Diagnosis of hepatolithiasis is usually established by non-invasive radiological methods. Accurate location of stones, detection of biliary strictures, identification of hepatic segments involved and/or atrophic, suspicion of cholangiocarcinoma, and/or the presence of cirrhosis and portal hypertension will ultimately lead the therapeutic approach.*
- *Treatment is challenging and sometimes controversial, and aims to prevent recurrent cholangitis and consequences of progression of disease (ultimately cholangiocarcinoma).*
- *Liver resection allows remotion of the stones, of the biliary strictures, and of the atrophic parenchyma, and ultimately diminishes the risk of cholangiocarcinoma. It seems to be the best surgical option for treatment of primary intrahepatic lithiasis.*
- *Well-established indications for hepatic resection of primary intrahepatic lithiasis include: i) lithiasis limited to one lobe, sector, or segment; ii) parenchymal hypo-atrophy; iii) presence of liver abscess; iv) failure of previous treatments; and v) suspected cholangiocarcinoma.*

INTRODUCTION

Intrahepatic lithiasis (or hepatolithiasis) is defined as the presence of stones in the biliary tract proximal to the confluence of the right and left main hepatic ducts, irrespective of the presence of stones in the main bile duct or the gallbladder.

Intrahepatic lithiasis is endemic in East Asia (including Taiwan, China, Hong Kong, Korea, Malaysia, and Japan). While in some Asian countries (such as Taiwan) the prevalence of intrahepatic stones can reach up to 50%, in the West it is much less common - closer to 1%.[1–3] However, the incidence of hepatolithiasis is increasing in the Western world, and it seems to be in decline in some Eastern countries. The etiology of hepatolithiasis probably suffers the contributory influence of genetic, dietary, and environmental factors, and trends in incidence can be at least partially explained by migration from endemic areas and by westernization of lifestyle.

Differential diagnosis between primary and secondary intrahepatic lithiasis is extremely important. Intrahepatic stones secondary to extrahepatic biliary strictures related to previous liver surgery (common bile duct stricture or stricture of hepaticojejunostomy), or secondary to stone migration from the gallbladder, can be classified as **secondary intrahepatic lithiasis** (**Figure 1**). This is the most frequent cause of intrahepatic stones in Western patients. Stones may also originate inside the liver, within single or multiple dilations of the intrahepatic biliary tree, in association or not

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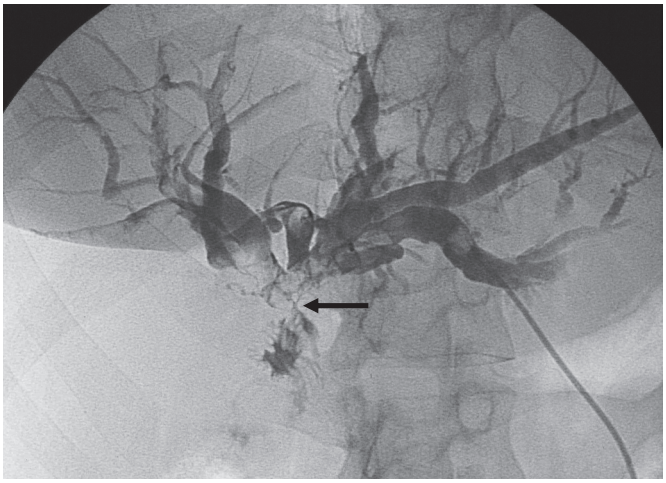


Figure 1. Secondary intrahepatic lithiasis. Percutaneous transhepatic cholangiography (PTC) showing intrahepatic stones above a strictured hepaticojejunostomy (arrow).

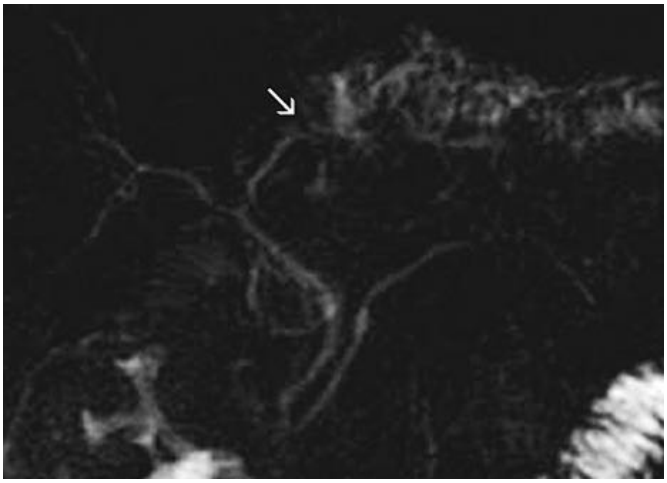


Figure 2. Primary intrahepatic lithiasis (PIL). Magnetic resonance cholangiography (MRC) showing multiple biliary dilations and stones proximal to a stricture on the left biliary hepatic duct (arrow).

with intrahepatic biliary strictures (**Figure 2**). Such cases are classified as **primary intrahepatic lithiasis (PIL)**.

Patients with intrahepatic stones have a typical clinical presentation characterized by abdominal pain and recurrent cholangitis; less commonly, patients present with jaundice, acute pancreatitis, or have asymptomatic disease. Unfortunately, hepatolithiasis is characterized by frequent recurrence, requiring multiple interventions. Therefore, to prevent late complications of the disease (liver abscesses, pyogenic sepsis, hepatic fibrosis resulting in secondary biliary cirrhosis, and cholangiocarcinoma), early aggressive treatment is needed.

Advances in hepatobiliary imaging, especially magnetic resonance imaging (MRI) and magnetic resonance cholangiography (MRC), allow clear diagnosis of hepatolithiasis, precise delineation of the biliary anatomy, and identification of the degree of parenchymal hepatic atrophy. These pieces of information are essential for optimal therapeutic planning.

Treatment of primary intrahepatic lithiasis includes surgical (mainly hepatectomy) and non-surgical (such as percutaneous and endoscopic procedures) approaches. Liver resection is the best surgical treatment for PIL. Hepatectomy allows for remotion of stones, of the bile strictures and of atrophic parenchyma, and ultimately prevents the development of cholangiocarcinoma. Very rarely, liver transplantation is considered.[4–9]

This chapter will focus on the management of primary intrahepatic lithiasis (PIL).

ETIOLOGY AND PATHOLOGY

COMPOSITION OF INTRAHEPATIC STONES

Typically there are two types of intrahepatic stones: calcium bilirubinate stones (brown pigment stones) and cholesterol stones.

Calcium bilirubinate stones, overall the most frequent, are mainly composed of bilirubin, cholesterol, fatty acids, and calcium, and represent the majority of intrahepatic stones (**Figure 3A**).[2] Intrahepatic brown pigment stones contain more cholesterol than similar stones of extrahepatic biliary ducts, suggesting the involvement of an associated altered cholesterol metabolism. Calcium bilirubinate stones are probably associated with biliary strictures, stasis,

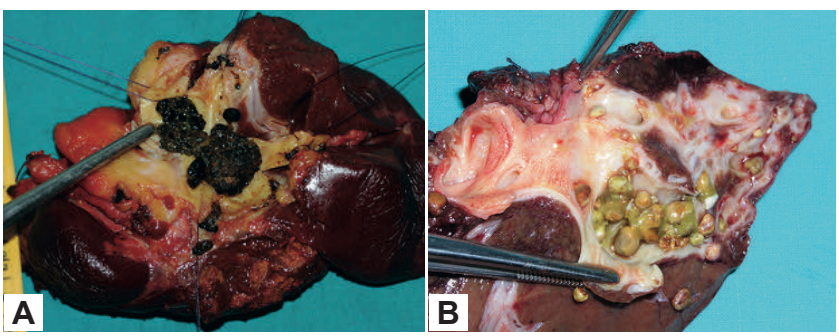


Figure 3. A) Typical calcium bilirubinate stones (brown pigment stones) within the left biliary hepatic ducts in a specimen of left hepatectomy. **B**) Cholesterol stones within the right biliary hepatic ducts in a specimen of right hepatectomy.

and bacterial infection (by β-glucoronidase-producing bacteria).[1,2,10] The histologic changes of the bile ducts containing calcium bilirubinate stones are classified into chronic proliferative cholangitis, suppurative cholangitis, and chronic granulomatous cholangitis.[11] In later stages, atrophic changes are seen, and biliary cirrhosis and portal hypertension can develop if the whole liver is involved. Also, long-standing chronic cholangitis may be related to malignant transformation. In fact, a continuous histologic spectrum may be observed, from papillary growths with low-grade and high-grade dysplasia to carcinoma in situ, and finally invasive cholangiocarcinoma.[12] The prevalence of cholangiocarcinoma in patients with hepatolithiasis is 2.4% to 14%.[10,13–15] Similarly, among patients with cholangiocarcinoma, up to 27% have intrahepatic stones.[16–20]

Intrahepatic cholesterol stones (5.8% to 13.1% of all intrahepatic stones) are more common in Western countries (**Figure 3B**).[2] Cholesterol stones result from an error in biliary phospholipid secretion, which leads to bile supersaturated with cholesterol. They can occur without biliary stenosis or dilations. Pathogenesis of primary intrahepatic cholesterol stones remains unclear. Recent investigations indicate that their formation is based upon the dual defects of up-regulation of cholesterol synthesis and down-regulation of bile-acid synthesis in the liver, possibly in association with defective secretion of phospholipid by its canalicular transporter, multidrug resistance protein (MDR3).[21] Metabolic factors, either acquired or congenital, act synergistically in the development of these intrahepatic stones.[1,22] Bile ducts containing cholesterol stones generally show a milder degree of fibrosis and glandular hyperplasia than ducts containing calcium bilirubinate stones. Foamy cell aggregates and multinucleated giant cells are characteristic findings associated with intrahepatic cholesterol stones.[23] Causal relationship between cholesterol stones and carcinoma is not clear.[24]

BILIARY DUCT FEATURES

Some studies suggest that anatomical features of intrahepatic bile ducts can be involved in the development of hepatolithiasis.

Usual biliary tree anatomy

Intrahepatic stones are more frequent in the left lobe than in the right lobe. The acute angle formed at the junction of the left hepatic duct with common bile duct would tend to induce bile stasis. In fact, a biliary scintigraphy study showed evidence of prolonged time-activity curves in left bile ducts compared to right bile ducts, even in normal livers.[1,25] In the right lobe, the biliary duct of segment 6 seems to be the most frequently involved, and in this case anatomical features could also play a major role. (**Figure 4**).

Biliary tree variations

The confluence of the right posterior bile duct into the left hepatic duct (Norman's anomaly)[26] is likely to be an important factor in the development of PIL (**Figure 5**).[27] However, in a recent comparative study including patients from Taiwan and Japan, anatomic variations of intrahepatic segmental ducts did not seem to play any important role in the pathogenesis of PIL.[28] Although in Western countries anatomic variations of intrahepatic bile ducts are frequently observed in patients with intrahepatic lithiasis, the role of anatomic variations of intrahepatic bile ducts in hepatolithiasis remains unclear.

Biliary anomalies

It is unclear whether primary intrahepatic stones and intrahepatic congenital bile duct dilation represent different features of the same disease. In Western patients, PIL has been reported to be more frequently associated with the presence of congenital intrahepatic bile duct dilation than in Eastern patients, in whom it seems mainly related to biliary infestations and infections.[29]

Congenital bile duct dilation is a rare disorder, in most cases hereditary, resulting from an embryonic disorder known as ductal plate malformation.[30,31] The estimated frequency of this disease is reported to be 1 in 1,000,000 in the whole population.[31] The ductal plate malformation may comprise different segments of the intrahepatic biliary tree (sectorial bile duct, segmental bile ducts, and peripheral bile ducts) leading to different clinicopathological entities defined according to Todani's classification.[32] Congenital bile duct dilation with intrahepatic-only localization corresponds to Todani Type V.[32] This entity was first described by Caroli et al. in 1958.[33] Later, Guntz et al.[34] classified congenital

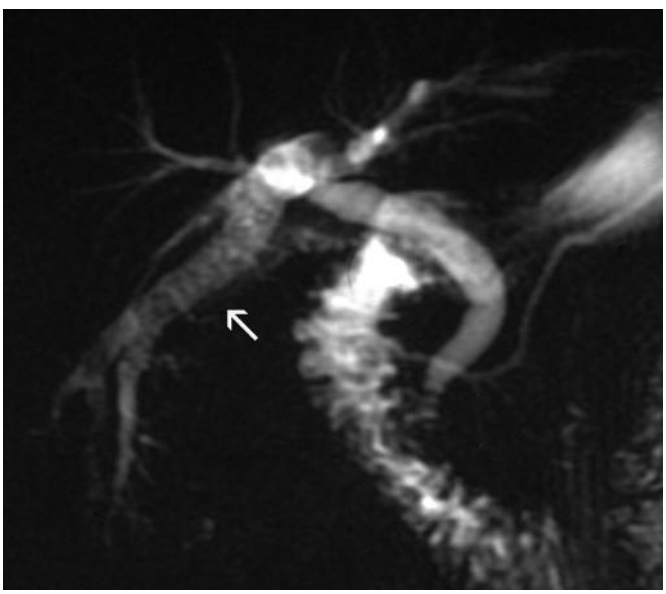


Figure 4. Magnetic resonance cholangiography (MRC) showing dilation of the biliary duct of segment 6 filled with stones (arrow).

intrahepatic bile duct dilations (IHBD) according to the aspect and the extent of dilations: Type 1 (grape-brunch-like saccular communicating dilations of peripheral IHBD); Type 2 (fusiform dilations of large IHBD); and Type 3 (saccular dilations of large IHBD). The original disease described by Caroli corresponds to Type 1, according to Guntz classification.

PARASITIC INFECTION

Biliary parasitic infection (by clonorchis sinensis, ascaris lumbricoides, and opisthorchis) can lead to stone formation (parasite fragments or eggs may act as a nidus). However, evidence of infestation is not commonly found in resected liver specimens.[2]

CLINICAL PRESENTATION

Abdominal pain, either in the right upper quadrant or in the upper abdomen, is the most frequent initial symptom (70% of patients). Other common manifestations of hepatolithiasis include cholangitis, jaundice and acute pancreatitis. Abdominal discomfort and vomiting may occur. However, no clinical manifestation is pathognomonic for intrahepatic stones. Hepatolithiasis may be an incidental finding on abdominal imaging in asymptomatic patients (16%), especially due to advances in diagnostic imaging modalities and their frequent use.

Frequently, patients have a long history of previous biliary operative and/or non-operative treatments and tend to have recurrent pyogenic cholangitis as the most common clinical manifestation. Pyogenic cholangitis may cause further septic complications such as hepatic abscess, and may ultimately result in parenchymal atrophy or secondary sclerosing cholangitis. Indeed, the most frequently observed clinical history of patients with PIL includes several endoscopic treatments by endoscopic retrograde cholangio-pancreatography for recurrent stones of the common bile duct. Patients usually first undergo cholecystectomy and then present with recurrent extrahepatic lithiasis misdiagnosed as migration from the gallbladder. For this reason they usually undergo several endoscopic treatments of the common bile duct stones, frequently without any further complete investigation of the entire intrahepatic biliary tree. Rarely, patients with hepatolithiasis may develop thrombocytopenia and enhanced platelet activation, resulting in coagulation and fibrinolysis disorders that might be particularly severe following liver resection.[35]

The Hepatolithiasis Research Group in Japan has proposed a clinical grade classification to quantify the severity of hepatolithiasis: Grade I: absence of symptoms; Grade II: abdominal pain; Grade III: transient jaundice or cholangitis; Grade IV: persistent jaundice, sepsis, or cholangiocarcinoma.[36]

DIAGNOSIS AND TREATMENT-ORIENTED CLASSIFICATION OF PRIMARY INTRAHEPATIC LITHIASIS

Diagnosis of hepatolithiasis is established by non-invasive radiological methods, mainly ultrasonography, computed tomography scan, and magnetic resonance cholangiography. These methods frequently allow accurate location of stones, detection of biliary strictures, and identification of hepatic segments involved. These data, associated with suspicion of cholangiocarcinoma and/or the presence of cirrhosis and portal hypertension, will ultimately lead the surgical approach. On the other hand, direct opacification methods, such as endoscopic retrograde cholangiography and percutaneous cholangiography, are usually used in case of non-surgical invasive treatments.

ULTRASONOGRAPHY

Ultrasonography (US) is frequently the first technique used to examine patients with PIL. Intrahepatic stones

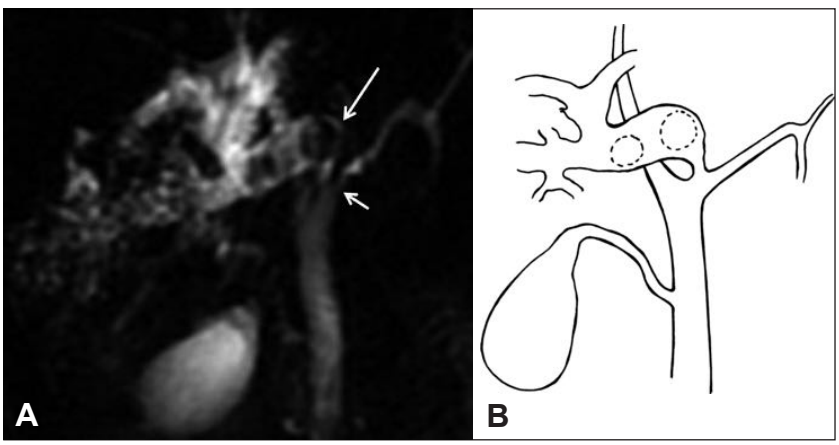


Figure 5. A) Magnetic resonance cholangiography showing primary intrahepatic lithiasis of biliary ducts of the right posterior (RP) sector (long arrow). The RP bile duct drains into the left hepatic duct – Norman's anomaly (short arrow). **B**) Schematic representation of the anomalous drainage of the RP duct into the left hepatic duct.

appear as hyperechogenic spots with a posterior acoustic shadow. Associated biliary dilation is easily identified on US (**Figure 6**). Pneumobilia, as a result of a previous endoscopic procedure with papillotomy or biliary-enteric anastomosis, may make ultrasonography interpretation difficult. Also, stones that do not produce an acoustic shadow cannot be clearly visualized by US, and accurate assessment of biliary strictures might be difficult due to the presence of stones. Liver abscesses can be identified by US.

COMPUTED TOMOGRAPHY

Computed tomography (CT) is the single most cost-effective imaging modality when hepatolithiasis is suspected. CT provides information about location and composition of stones as well as precise liver anatomy, biliary strictures and dilation, the degree of parenchymal atrophy, and the presence and location of abscesses (**Figure 7**). All of these pieces of information are useful in choosing the best therapeutic approach. Images before contrast injection are especially useful to detect stones with low calcium content. Dilated bile ducts appear as low-density, tubular, tortuous branching structures, and they are best appreciated on contrast-enhanced studies. Unlike on US, pneumobilia does not impair CT evaluation of the biliary tree. Strictures appear as thickened duct segments distal to the dilated bile duct. Inflammatory changes on strictures are responsible for contrast enhancement, and differential diagnosis with cholangiocarcinoma can be challenging. Malignancy should be suspected in case of i) periductal soft-tissue density, ii) higher enhancement (on portal phase) compared to adjacent bile duct, iii) ductal wall thickening, iv) portal vein obliteration, and v) lymph node enlargement. These features are associated with the presence of cholangiocarcinoma.[20]

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI), especially magnetic resonance cholangiography (MRC), is accurate in detecting and locating intrahepatic stones, identifying obstructed intrahepatic bile ducts, and defining bile duct anatomy (**Figures 2 and 8**). In a retrospective study by Sugiyama et al., the sensitivity, specificity and accuracy of MRC for detecting and locating intrahepatic stones in hepatolithiasis

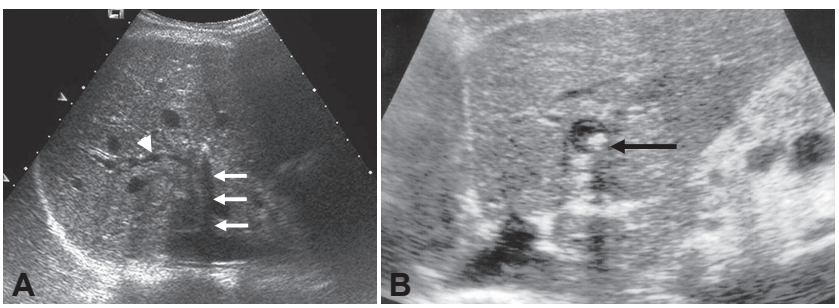


Figure 6. Ultrasonography of primary intrahepatic lithiasis. **A**) Intrahepatic stones appear as echogenic structures that produce acoustic shadow (arrows). Proximal bile duct dilation (arrow head) is frequently identified. **B**) Typical ultrasonographic imaging of stone (arrow) into a dilated bile duct.

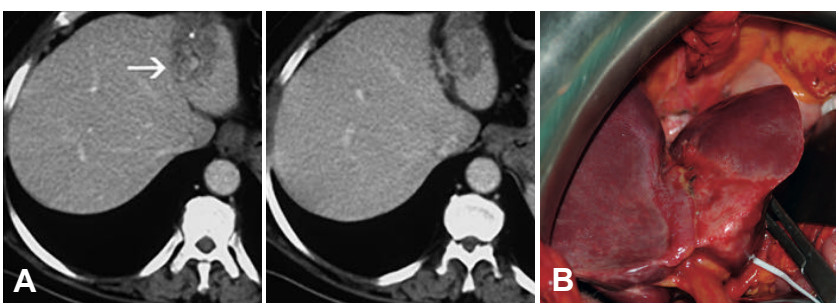


Figure 7. A) Abdominal computed tomography (CT) showing atrophy of the left lateral sector of the liver associated with intrahepatic bile duct dilation and stones (arrow). **B**) Intraoperative view confirming atrophy of the left lateral sector, especially segment 3.

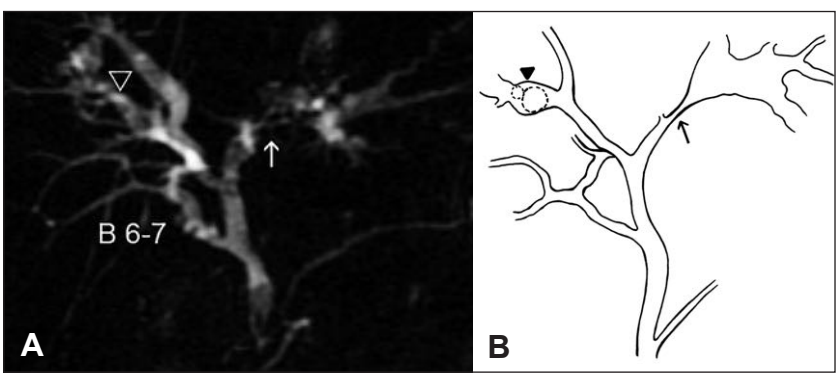


Figure 8. A) Magnetic resonance cholangiography (MRC) showing intrahepatic lithiasis of the left hepatic duct proximal to a biliary stricture (arrow) and of the right anterior biliary duct (arrow head). The right posterior biliary duct (B 6-7) joins the common bile duct, below the main biliary confluence. **B**) Schematic representation of the biliary anomaly. RP: right posterior biliary duct, RA: right anterior biliary duct, L: left hepatic biliary duct.

were 97%, 99%, and 98%, respectively.[37] The sensitivity, specificity and accuracy of MRC for detecting and locating intrahepatic bile duct strictures were 93%, 97%, and 97%, respectively.[37] Similarly to CT, MRI is a valuable tool to detect liver abscesses. However, as with CT, detection of cholangiocarcinoma associated with hepatolithiasis can be difficult with MRI and MRC. Also, pneumobilia can be misinterpreted with intrahepatic stones on MRI. MRC allows the accurate location of intrahepatic stones and of accompanying biliary strictures and it has replaced diagnostic endoscopic retrograde cholangiography in patients with hepatolithiasis.

DIRECT CHOLANGIOGRAPHY

Direct cholangiography can be performed by endoscopic retrograde cholangiography (ERC) (**Figure 9**) or percutaneous transhepatic cholangiography (PTC) (**Figure 10C**), both being invasive techniques that carry considerable morbidity rates (between 1% and 7%). PTC has excellent sensitivity for intrahepatic stones and it provides precise segmental and subsegmental anatomy of the intrahepatic bile ducts and strictures. ERC provides similar diagnostic results if the whole biliary system is opacified; however, biliary obstacles (stones or strictures) can prevent adequate visualization of proximal bile ducts. PTC provides access to therapeutic percutaneous transhepatic cholangioscopy (PTCS) and percutaneous transhepatic biliary drainage (PTBD), both important tools for treatment of cholangitis, stone extraction, stenting of strictures, and biopsy of intraductal lesions. ERC also provides access to therapeutic modalities, such as biliary stent insertion. However, the risks of ERC (especially cholangitis), when compared to the advantages of PTC, make the latter the current method of choice for direct cholangiography in case of hepatolithiasis.

Percutaneous procedures may result in vascular intrahepatic injury, especially in case of non-dilated bile ducts (**Figure 10D**). Selective puncture of bile ducts (including the affected peripheral branches) can be performed percutaneously aided by US, making PTC more useful than ERC for demonstrating peripheral intrahepatic stones with or without biliary strictures.[2,23] Percutaneous cholangioscopy can be performed during PTC with direct visualization of biliary ducts, achieving more detailed information about location and severity of strictures, impacted stones and features of biliary mucosa.[23]

The significant progress in non-invasive radiological methods, especially MRI and MRC, has led to a more restricted use of invasive techniques as diagnostic tools. However, invasive methods remain helpful for therapeutic aims and when non-invasive methods are inconclusive.

TREATMENT-ORIENTED CLASSIFICATION OF PRIMARY INTRAHEPATIC LITHIASIS

The hallmark of PIL is an abnormal bile duct feature characterized by dilation alone or by the association of stricture with proximal dilation. Several classifications of PIL, especially from Eastern countries, have been proposed over the years.

The most simple classification was proposed by the Japan Research Group for the Study of Hepatolithiasis,[23] and divides patients into two groups: patients with stones confined to intrahepatic bile ducts (Type I), and those with stones in intrahepatic and extrahepatic bile ducts (Type IE). The patients are further classified according to the location of stones within the liver: on the right side (Type R), on the left side (Type L), on both sides (Type LR), and on the caudate lobe (Type C).

Tsunoda's classification includes intrahepatic dilation and biliary strictures: Type I, no marked dilation or strictures of intrahepatic ducts; Type II, diffuse dilation of intrahepatic ducts without strictures; Type III, unilateral solitary or multiple cystic intrahepatic dilation accompanied by strictures; and Type IV, similar to Type III but with bilateral involvement.[38] Types I and II correspond originally to secondary hepatolithiasis.

In the classification system recently proposed by Cheon et al.[39], patients with intrahepatic lithiasis were divided into three groups according to stone distribution and presence of associated bile duct stricture: Type A, unilateral solitary or multiple stones with or without intrahepatic dilation and strictures of the intrahepatic bile ducts of the same lobe;

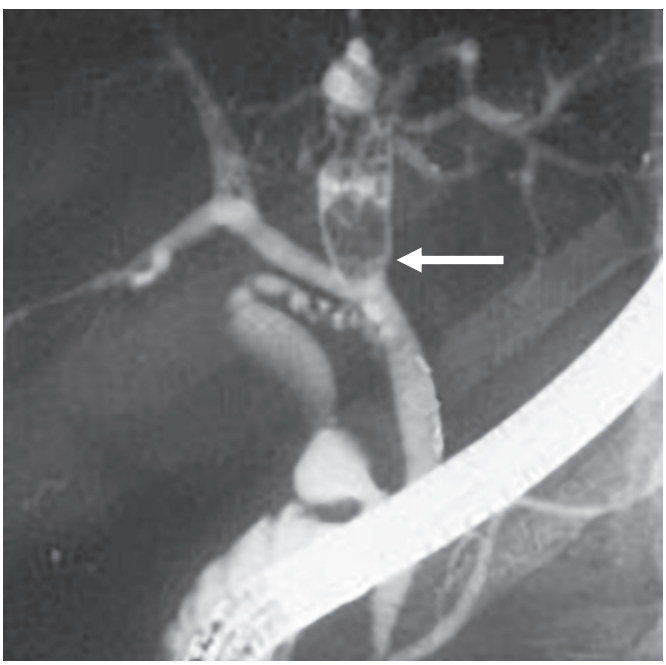


Figure 9. Endoscopic retrograde cholangiography (ERC) showing lithiasis and consequent obstruction of the left biliary duct (arrow).

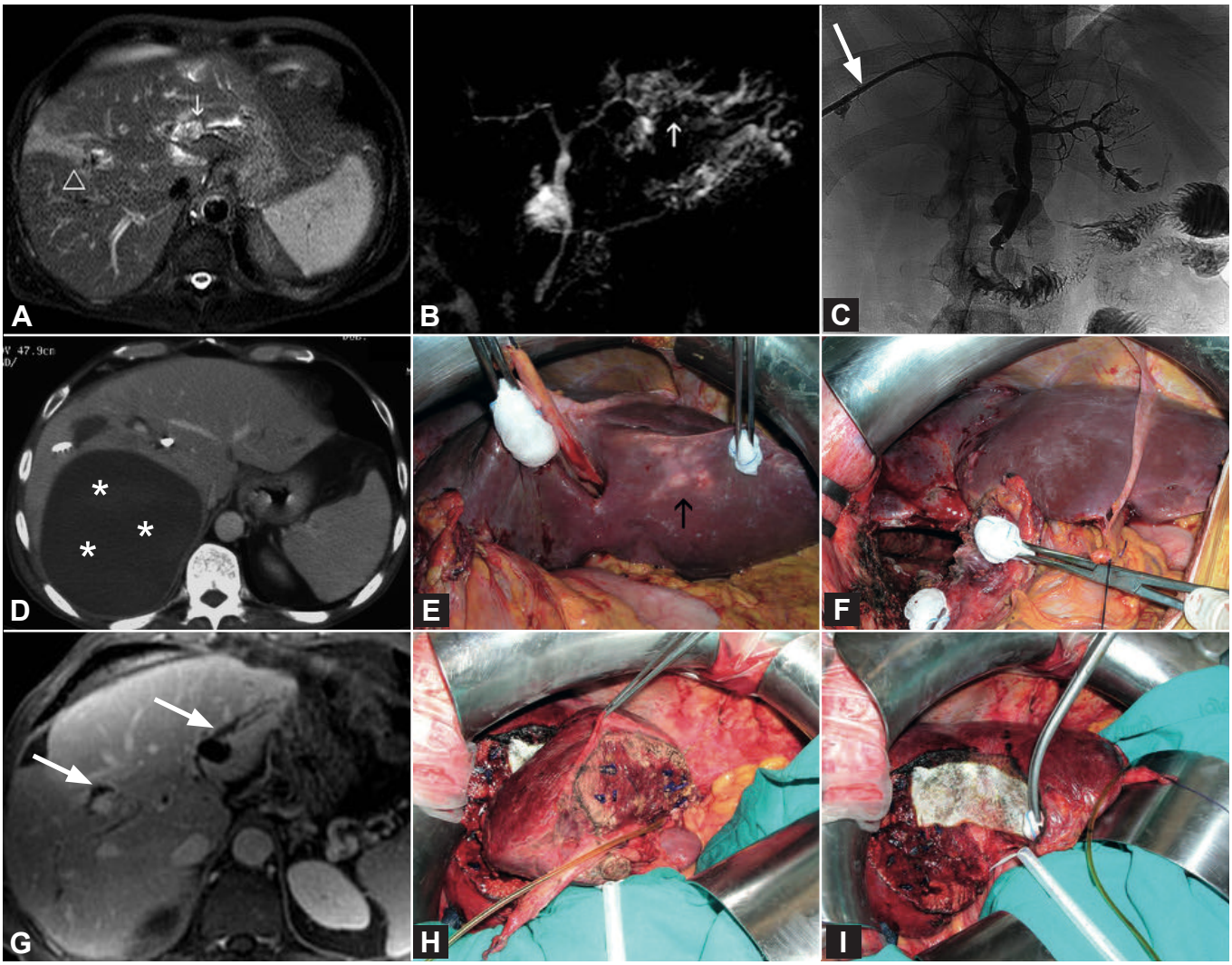
Type B, bilateral multiple stones associated with unilateral stricture of the intrahepatic duct; and Type C, bilateral multiple stones associated with bilateral strictures of the intrahepatic duct (**Figure 11**).[39]

Dong's classification divides localized (Type I) and diffuse (Type II) intrahepatic stones.[40] Additionally, it considers the presence of extrahepatic stones and the functioning of the sphincter of Oddi.

Unfortunately, the various classification systems and the absence of a consensus hampers the possibility of accurately evaluating the outcome of different treatments and series.

PIL TREATMENT ISSUES

The primary goals in the treatment of PIL are to avoid attacks of cholangitis and to prevent progression and sequelae of the disease. Optimal treatment of PIL remains difficult and



Figures 10. 60-year-old male patient who underwent cholecystectomy and endoscopic retrograde cholangiography for treatment of gallbladder and common bile duct (CBD) stones. Endoscopic removal of recurrent CBD stones three months later. Subsequent recurrent episodes of cholangitis. **A**) Magnetic resonance imaging (MRI) demonstrating primary intrahepatic lithiasis of biliary ducts of segments 2 and 3 (arrow) and of segment 5 (arrow head). **B**) Magnetic resonance cholangiography (MRC) confirming these findings. **C**) Percutaneous transhepatic cholangiography (PTC) and percutaneous transhepatic biliary drainage (PTBD) through segment 5 biliary duct after extraction of stones. (Arrow identifies percutaneous biliary drain.) **D**) Computed tomography after PTBD reveals large hematoma on right liver (asterisks). The hematoma caused a large hepatic abscess, responsible for sepsis. **E**) Intraoperative view during laparotomy for surgical drainage of hepatic abscess. Signs of recurrent cholangitis are seen on segment 3 (arrow). **F**) Intraoperative view of remnant cavity after abscess drainage. Patient was discharged in good condition on postoperative day 20. **G**) CT scan five months after surgical drainage, revealing complete resolution of abscess but persistence of intrahepatic lithiasis and dilation of biliary duct of segments 2 and 3 and segment 5 (arrows). **H**) Definitive treatment with surgical resection of segments 2 and 3 (left image) and segment 5 (right image).

controversial. Several surgical, endoscopic, and percutaneous procedures have been reported in the literature, but high recurrence rates are often reported for all of them.

The main steps to be taken in the treatment of PIL to reach its primary goals include: i) complete extraction of stones, ii) elimination of bile duct strictures, iii) removal of affected bile duct drainage areas, and iv) removal of atrophic segments. These procedures will ultimately minimize the risk of repeated cholangitis, liver atrophy, secondary biliary cirrhosis, and cholangiocarcinoma.[41] The procedure most likely to achieve the above-noted goals is resection of affected liver segments. Occasionally, patients with diffuse hepatolithiasis and secondary biliary cirrhosis might be considered for liver transplantation as definitive treatment. On the other hand, less aggressive procedures (surgical or non-surgical) might be helpful in selected cases.

The best approach should be individualized, but some factors - such as the presence of acute cholangitis, stone distribution (hepatic segments involved), presence of bile duct dilations and/or strictures, parenchymal liver atrophy, anatomical biliary variations, suspicion of cholangiocarcinoma, and presence of cirrhosis - affect the choice of treatment.

Approach to patients with **acute suppurative cholangitis** due to PIL is similar to that of cholangitis secondary to gallstones. Antibiotics and biliary drainage are cornerstones in the control of sepsis. PTBD is the most useful method of drainage in case of intrahepatic biliary obstruction, and it is preferable to operative and endoscopic transpapillary drainage approaches (**Figure 10C**).

Concerning **distribution of stones**, most cases of hepatolithiasis are unilateral (61%) and the left side of the liver is more frequently affected (ranging from 58% to 86% of cases) (**Figure 12**).[14,16,31,42–45] As described below, in unilobar disease (especially left liver disease), hepatectomy seems to be the best treatment. On the other hand, treatment of bilateral hepatolithiasis remains controversial. Surgical approaches depend of precise location of stones and strictures and vary from hepaticojejunostomy to bilateral liver resections. Resection of all hepatic segments affected is the best option to reach the ultimate goals in the treatment of PIL. Therefore, once mandatory requirements for a safe resection are met (see **Chapter 22** for further details), resection is the first-choice approach. Frequently, segments to be resected are atrophic and the remnant liver volume is enough. If complete resection of the affected segments is not possible, surgical options include a variety of procedures that can be used alone or in combination, such as resection of the most affected side (generally the left liver) in addition to the complete clearance of remnant bile ducts (by intraoperative cholangioscopy or other perioperative non-surgical procedure), stone clearance and hepaticojejunostomy or hepaticocutaneous jejunostomy or common bile duct T-tube insertion (for postoperative stones extraction), surgical strictureplasty, and even more aggressive approaches with liver transplantation in very selected cases.

Common bile duct stones are present in 27% and gall-

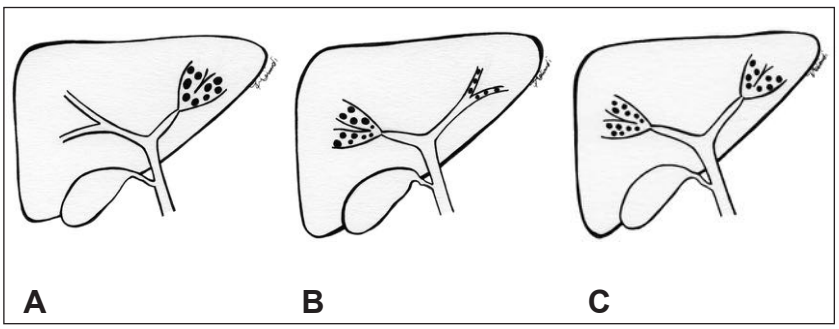


Figure 11. Classification of primary intrahepatic lithiasis based on stone distribution (unilateral or bilateral) and presence of intrahepatic biliary strictures according to Cheon et al. **A**) Type A: unilateral stones with or without intrahepatic biliary dilation and stenosis of the same hemiliver. **B**) Type B: bilateral stones with unilateral biliary stenosis. **C**) Type C: bilateral stones with bilateral biliary stenosis. (Prevalence of Type A, B, and C was 63%, 22%, and 15%, respectively, in a report by Cheon et al.) (Adapted from Cheon et al.[39])

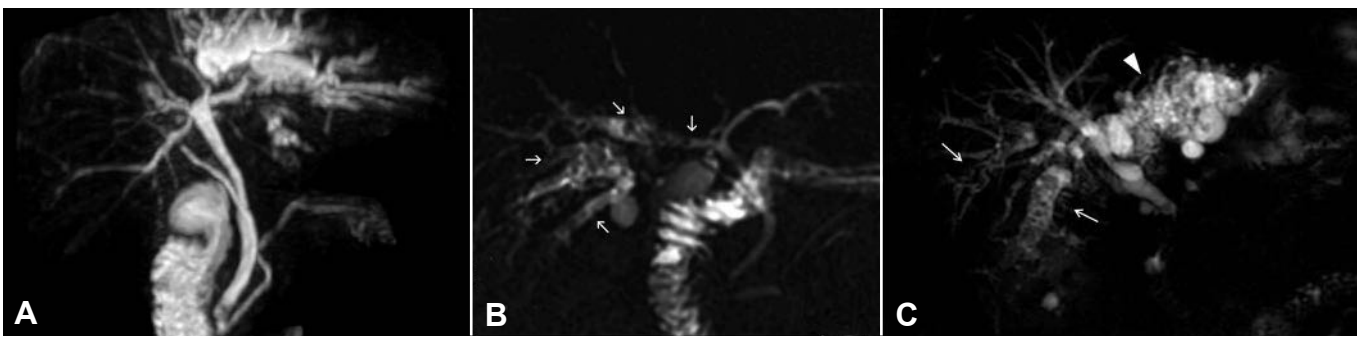


Figure 12. Distribution of stones on primary intrahepatic lithiasis (PIL), demonstrated with magnetic resonance cholangiography (MRC). **A**) Left-sided PIL (biliary dilation and stones on the left hepatic duct). **B**) Right-sided PIL (biliary dilation and stones on the right bile ducts). **C**) Bilateral PIL involving the left bile ducts (arrowhead) and right posterior sector (arrows).

stones in 44% of patients with PIL (**Figure 13**). To avoid the need for a potentially difficult second operation, Lee et al.[9] suggest prophylactic cholecystectomy concomitant to surgical treatment of PIL.

Intrahepatic biliary strictures are frequent (in 27% to 54% of cases)[4,31,39,46–49] and represent a major cause of treatment failure. Residual stones, acute cholangitis, and stone recurrence are more frequent in patients with biliary duct strictures, mainly intrahepatic strictures.[4,6,39,50] Thus, in addition to complete stone clearance, the elimination of biliary duct strictures is necessary to prevent recurrent hepatobiliary complications. More conservative treatment of strictures with balloon dilation does not seem to affect long-term outcomes in patients with biliary strictures.[36]

Repeated episodes of cholangitis lead to **liver atrophy**, **secondary biliary cirrhosis**, and finally end-stage liver disease. Atrophic hepatic segments are usually non-functional and resection of these areas is safe (**Figure 14**). Patients with diffuse hepatolithiasis and secondary biliary cirrhosis should be considered for liver transplantation, which treats the hepatocellular dysfunction and eliminates the possibility of developing cholangiocarcinoma.

The presence of **anatomical biliary variations**, especially with right-sided hepatolithiasis, can make cholangioscopic biliary access difficult. Cranial shift of the right sectorial ducts proximal to the hepatic confluence may be considered an independent risk factor for right hepatolithiasis in the right lobe. It has also been demonstrated that a sharp ductal angle (less than 90° in different views of cholangiography) co-existing with biliary strictures in right-sided hepatolithiasis increases the risk of complications, including severe and/or recurrent cholangitis, liver abscesses, and sepsis.[51] In addition, some anatomical biliary variations can increase the risk of biliary complications in hepatic resections **(Figures 5**, **8 and 14**).

The risk of development of **intrahepatic cholangiocarcinoma** in patients with PIL is well known (prevalence of cholangiocarcinoma in patients with PIL can reach 25%).[16,51] Cholangiocarcinoma associated with hepatolithiasis can be synchronous (depicted preoperatively, intraoperatively by frozen biopsy, or postoperatively as an occasional finding in surgical specimens), or occurs during follow-up after initial treatment (occurring in 1.6% to 12.9% of patients after initial treatment of PIL).[19,52] In fact, most cases of synchronous cholangiocarcinoma are unexpected findings (**Table 1**) (**Figure 15**). The presence of residual stones and bilateral involvement are factors associated with the occurrence of carcinoma.[19]

Preoperative diagnosis of associate cholangiocarcinoma is usually difficult because of hepatolithiasis itself and the related inflammation that hinders clear visualization of bile ducts by imaging techniques. Therefore, especially in patients with biliary strictures where it is very difficult to rule out a malignant stricture, liver resection should always be considered. Cholangioscopy with biopsy can be useful for the diagnosis of malignancies in severe strictures. If malignant stricture cannot be excluded with certainty, liver resection should always be considered. Radical oncological surgery with lymph node dissection is the target treatment when cholangiocarcinoma is suspected or confirmed preoperatively or intraoperatively. Similarly, if malignancy is found postoperatively in the surgical specimen, reoperation to perform a more radical procedure (extended parenchymal resection, resection of main biliary confluence, and lymphadenectomy) should be considered.[53] The prognosis of cholangiocarcinoma secondary to hepatolithiasis is poorer than cholangiocarcinoma alone.[17,39,54]

Regular follow-up after initial treatment (surgical or non-surgical) of PIL could allow early detection of malignancy and it may include tumor markers (such as carbohydrate antigen 19-9 and carcinoembryonic antigen) and imaging modalities (such as US and/or RMI).

HEPATIC RESECTION FOR PIL

Hepatectomy is the most effective treatment for hepatolithiasis. It represents the only treatment that allows com-

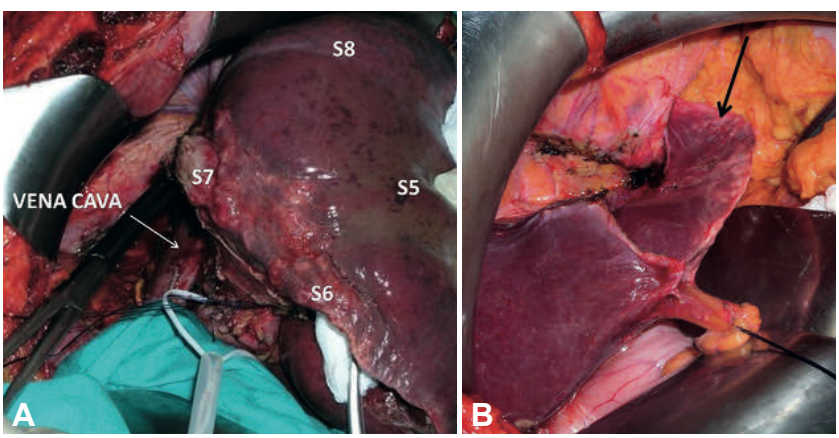


Figure 13. Parenchymal atrophy secondary to primary intrahepatic lithiasis. **A**) Intraoperative view showing atrophy of the right posterior sector (S6 and S7). **B**) Intraoperative view showing atrophy of the left lateral sector (arrow). S5, S6, S7, and S8: hepatic segments 5, 6, 7, and 8, respectively.

plete removal of intrahepatic stones and intrahepatic biliary strictures simultaneously.[5,55,56] Liver resection seems to result in more effective stone clearance (83% to 100%)[16,39] than percutaneous or intraoperative lithotripsy without hepatectomy (20% to 64%).[4,39,50,57–60] Moreover, hepatectomy results in lower rates of stone recurrence (5.7% to 13.9%) than more conservative treatments (31.5% to 52%).[9,46,61–63]

Liver resections in patients with PIL have been frequently reported by Eastern centers with a high prevalence of the disease (**Table 2**), while fewer instances of patients undergoing liver resections have been reported by Western centers (**Table 3**). This is related mainly to the lower incidence of intrahepatic lithiasis in the Western world. However, relative unawareness of this disease, along with the risks associated with hepatectomy for this condition, has further limited the Western data set.

Well-established indications for hepatic resection of PIL include: i) lithiasis limited to one lobe, sector, or segment; ii) parenchymal hypo-atrophy; iii) presence of liver abscess; iv) failure of previous treatments; and v) suspected cholangiocarcinoma. Indication of hepatectomy in patients with incidental finding of PIL is controversial; however, for young patients with low surgical risk, liver resection - especially in localized forms of PIL - should be encouraged to minimize the early and long-term complication risks of PIL.

Table 1. Rate of cholangiocarcinoma in patients with primary intrahepatic lithiasis.

Author	Synchronous cholangiocarcinoma (%)	Unexpected cholangiocarcinoma (%)	Metachronous cholangiocarcinoma (%)
Chen [16]	9.7	60	3.3
Kim [56]	11.1	82	2.1
Lee [65]	3.2	100	1.6
Uenishi [90]	11.6	70	2.7
Lee [9]	7.8	60	-
Kassahun [73]	9.7	33	-
Catena [14]	11.7	100	-
Bockhorn [44]	25.0	100	-
Vetrone [60]	5.3	100	-
Mabrut [31]	7.4	-	-
Clemente [67]	12.2	66	-
Yang [8]	-	-	3.7
Jarufe [41]	-	-	0

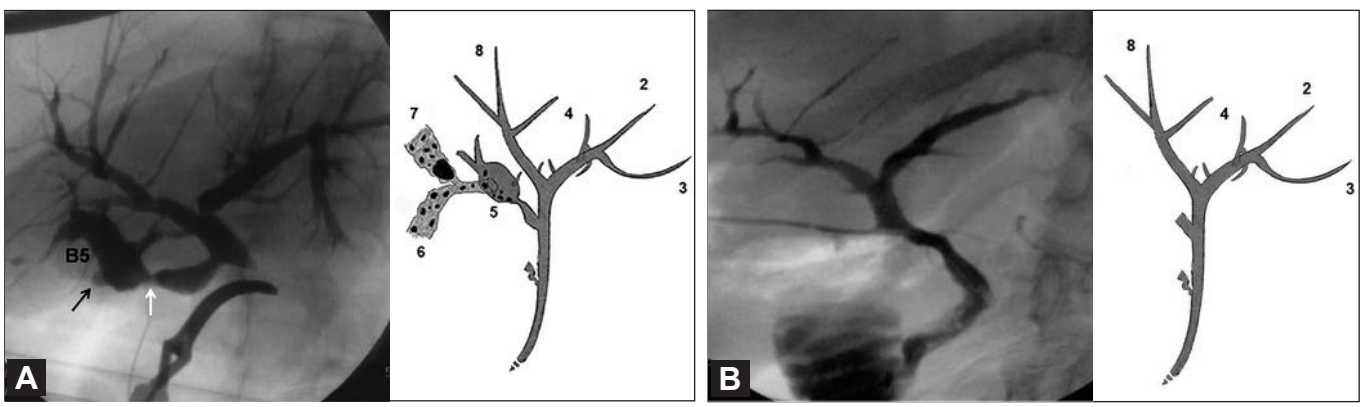


Figure 14. Primary intrahepatic lithiasis (PIL) involving hepatic segments 5,6 and 7, associated with biliary anomaly and treated by anatomic segmental hepatectomy. **A**) Intraoperative direct cholangiography through the stump of cystic duct before resection and schematic representation on the right side. Biliary branches from right posterior sector (black arrow) join the bile duct from segment 5 (B5). Bile duct from segment 5 is dilated proximally to a stricture (white arrow). Bile ducts from segments 5, 6, and 7 were filled with contrast only after choledochal clamping (Bulldog) and cholangiography under higher pressure, but were visible on intraoperative ultrasound (IOUS). **B**) Intraoperative direct cholangiography after resection of segments 5, 6, and 7 through the stump of the bile duct of segment 5. Schematic representation of the right side.

Perioperative **mortality** after hepatectomy for hepatolithiasis in recent Western studies is nil (**Table 3**). Studies with Eastern populations have also shown low postoperative mortality, despite involving more complex cases than those reported in Western studies (as represented, for example, by higher rates of bilateral intrahepatic lithiasis and cirrhosis).

Postoperative **morbidity** rates in Eastern and Western studies have ranged from 7.4% to 58.8% (**Tables 2 and 3**) and are mainly represented by septic complications. Diagnosis and surgical treatment of hepatolithiasis at an early stage are key factors in performing liver resections with low operative risk.[31] Preoperative recurrent cholangitis, due to the disease itself or related to preoperative endoscopic or percutaneous procedures, increases the risk of infectious complications. In fact, preoperative or intraoperative bile culture present positively in most cases, and multi-drug resistant bacteria colonization can occur after multiple endoscopic and/or percutaneous procedures or recurrent episodes of cholangitis. Therefore, preoperative direct cholangiography should be avoided and preferably limited to therapeutic percutaneous or endoscopic procedures (such as PTBD), or in case non-invasive methods (such as CT and/or MRI and/or MRC) do not provide enough information to properly define the best treatment approach. Likewise, sampling bile from intrahepatic ducts for microbiological studies is mandatory during surgical procedures; it is also recommended to irrigate the whole biliary tree with saline solution during surgery. Appropriate prophylactic antibiotics are given empirically and/or according to bacteriological studies.

When liver resection is being considered, operative planning should be decided according to the following issues: location of stones, biliary strictures, and/or dilations; number of involved liver segments; presence of extrahepatic stones; presence of choledochal cysts; presence of anatomical variation; presence of cirrhosis; and suspicion of malignancy. Furthermore, the need for other associated procedures should be accurately evaluated and planned.

In case of **unilateral disease** (up to 61% of cases), partial hepatectomy represents the treatment of choice that can radically resolve recurrent cholangitis and stone formation, and prevent the risk of cholangiocarcinoma. Again, the left liver is affected more commonly (58% to 86%) than the right liver.[14,16,31,42–45,64,65] Left hepatic resections

Table 2. Mortality and morbidity rates after liver resection for primary intrahepatic lithiasis (Eastern studies).

Author, year	Patients (n)	Mortality (%)	Morbidity (%)
Chen, 2004 [16]	103	2.0	28.0
Kim, 2006 [56]	128	0	25.7
Li, 2007 [64]	312	0.3	>19
Lee, 2007 [65]	123	1.6	33.3
Huang, 2008 [89]	245	0.4	16.3
Uenishi, 2009 [90]	86	3.5	-
Lee, 2009 [9]	64	0	42.2
Yang, 2010 [8]	136	2.2	46.3
Jiang, 2010 [63]	106	0	29

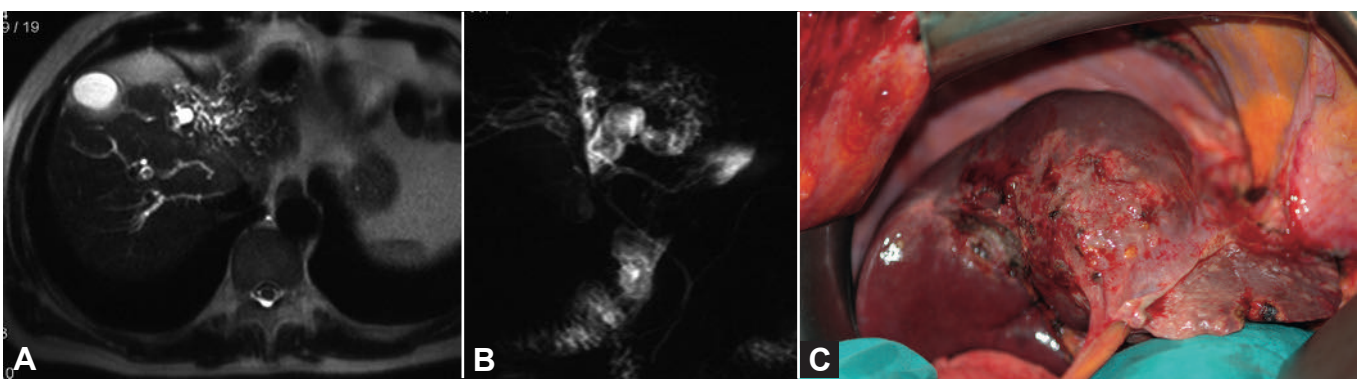


Figure 15. Unexpected cholangiocarcinoma found intraoperatively in a 66-year-old male with intrahepatic lithiasis. **A**) Preoperative magnetic resonance imaging. **B**) Preoperative magnetic resonance cholangiography. Left bile duct dilations and stones are apparent, as well as left lateral sector atrophy. No signs of possible cholangiocarcinoma are present. **C**) Intraoperative view, showing unresectable cholangiocarcinoma. Diagnosis confirmed by anatomopathological study of frozen sections.

are associated with lower morbidity rates than right hepatic resections for unilateral PIL, and represent the most frequent type of hepatectomy (**Figure 16**). The extension of left resections (i.e. left hepatectomy or left lateral sectionectomy) is controversial, but could be based on a precise evaluation of extension of the disease in order to reduce the risk of postoperative biliary fistula or stone recurrence. Sun et al.[66], in a retrospective analysis of 128 patients with left-sided PIL, showed that left hepatectomy was more effective than left lateral sectionectomy, with a significantly lower rate of residual stones (4% vs. 22%; P<0.01). Conversely, Lee et al. [5] showed that there were no significant differences in stone recurrence and complications between left hepatectomy and left lateral sectionectomy for treatment of left-sided PIL. Actually, accurate evaluation of the presence and precise location of bile duct strictures, as well the biliary anatomy (especially the site of junction of ducts from segment 4), should be used to define the extension of left liver resections. The involvement of biliary ducts of the caudate lobe should also be considered. Indeed, the caudate lobe can be affected in up to 21% of cases of PIL,[67] and in this case it should be resected in order to prevent postoperative biliary fistula and late stone recurrence (**Figure 16**).

Intraoperative cholangiography during hepatectomy should be performed when preoperative cholangiography is not complete, with the extension of resection not clearly

Table 3. Mortality and morbidity rates after liver resection for primary intrahepatic lithiasis (Western studies).

Author, year	Patients (n)	Mortality (%)	Morbidity (%)
Di Carlo, 2000 [42]	12	0	16.6
Kassahun, 2005 [73]	27	7.4	58.8*
Herman, 2006 [43]	27	0	7.4
Catena, 2006 [14]	17	0	29.4
Bockhorn, 2006 [44]	9	0	-
Vetrone, 2006 [60]	22	0	27.3**
Mabrut, 2007 [31]	27	0	44.4
Ulrich, 2008 [74]	33	0	37.5
Nuzzo, 2008 [10]	34	0	20
Clemente, 2010 [67]	47	0	24.5
Jarufe, 2012 [41]	52	0	30.8

* including liver transplantation. ** including hepaticojejunostomy

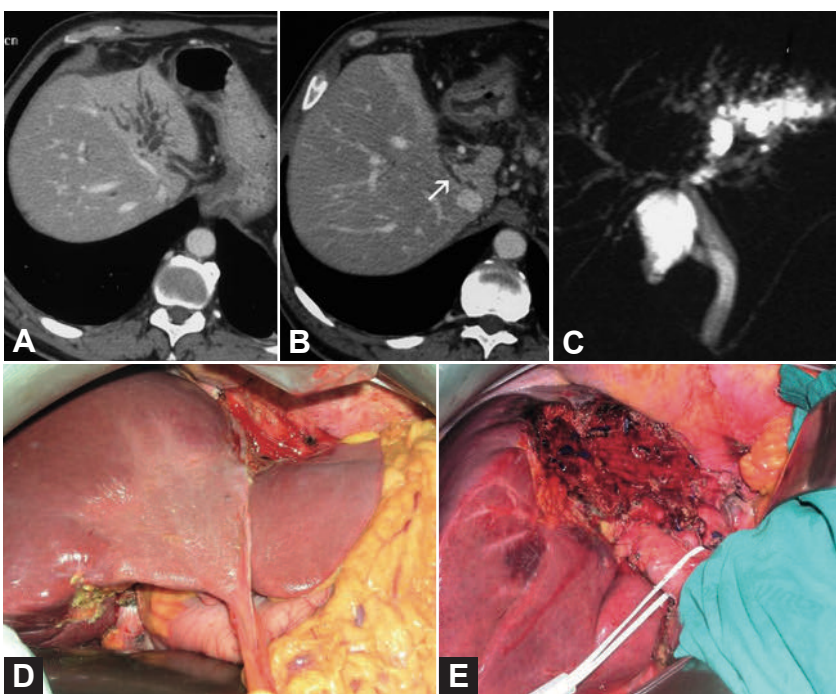


Figure 16. Left-sided primary intrahepatic lithiasis (PIL) associated with parenchymal atrophy treated by liver resection. **A**) Computed tomography (CT) revealing dilated left bile ducts associated with parenchymal atrophy. **B**) Dilated bile ducts from caudate lobe (arrow) are also identified on CT. **C**) Magnetic resonance cholangiography confirming unilateral involvement of PIL. **D**) Intraoperative view confirming parenchymal atrophy, especially of segment 4. **E**) Intraoperative aspect after left hepatectomy extended to the caudate lobe.

defined, and in case of imprecise delineation or doubt of the intrahepatic biliary anatomy (**Figure 15**). Also, intraoperative cholangioscopy is an important tool for further evaluation of extent of the disease (strictures and stones), lithotripsy (such as hydroelectrolitic or by laser) and removal of stones, and eventual biopsy of suspicious strictures. Intraoperative ultrasonography (IOUS) is extremely useful to visualize bile ducts filled with stones (including those not visualized on cholangiography) and to guide anatomical segmental hepatic resections (**Figures 17**). However, artifacts due to pneumobilia can complicate its use.

After liver resection, rates of stone clearance (83% to 100%), late stone recurrence (3.7% to 15.4%) and recurrent cholangitis (0% to 24%) are satisfactory (**Table 4**). The highest rate of stone clearance can be obtained with the addition of intraoperative and postoperative treatments (such as stone extraction by cholangioscopy, percutaneous or through a hepaticocutaneous jejunostomy or T-tube). Immediate and late results depend on extent and severity of disease, presence and site of biliary strictures, time interval between onset of symptoms and treatment, and duration of preoperative treatments. Anatomic segmental hepatectomy seems to be associated with better results than non-anatomic resection, resulting in lower rates of residual stones, bile leakage and recurrence.[63]

Recently laparoscopic liver resection for PIL have been reported with good results, suggesting that laparoscopic hepatectomy could be an effective therapeutic option for these patients, in particular, for those with left sided disease, which is the most frequent.[68–70] Recent series of laparoscopic left hepatic resections for PIL report a morbidity of 11% to 21%, rate of stone clearance of 100%, and no recurrence.[70,71] It is of note that laparoscopic liver resection for PIL should be performed by surgeons with experience in both open and laparoscopic hepatobiliary surgery. In fact, liver resections for PIL are frequently more technically demanding than those for tumors due to severe perihepatic adhesions, parenchyma fibrosis, deformed intrahepatic biliary anatomy, and atrophic changes.

The optimal management of patients with **bilateral PIL** remains a very complex and challenging task, especially because of the difficulty inherent to obtaining complete stone clearance. Several treatment options have been proposed, including: i) bilateral limited liver resections (**Figure 10**); ii) partial hepatectomy of the most affected side, combined with contralateral stone extraction by intraoperative cholangioscopy or by other perioperative non-surgical procedure; iii) partial hepatectomy and hepaticojejunostomy (**Figure 18**) or hepaticocutaneous jejunostomy (**Figure 19**) or common bile duct exploration with T-tube insertion for further biliary access; and iv) liver transplantation.

Table 4. Early and long-term results after liver resection for primary intrahepatic lithiasis.

Author	Patients (n)	Final stone clearance (%)	Median follow-up (months)	Stone recurrence (%)	Cholangitis recurrence (%)	Good results (%)
Chen [16]	103	98.0	56.0	8.8	5.5	91.2
Kim [56]	128	99.0	25.6	4.2	8.3	89.6
Lee [65]	123	96.0	40.3	5.7	-	94.3
Uenishi [90]	86	95.0	75.0	10.1	24.0	76.0
Lee [9]	64	-	42.7	7.8	9.4	-
Di Carlo [42]	12	-	42*	8.3	8.3	83.3
Kassahun [73]	27	-	44.0	-	-	92.5
Herman [43]	27	-	41.2	3.7	7.4	83.3
Catena [14]	17	-	50*	6.2	6.2	87.5
Bockhorn [44]	9	-	31	-	-	100
Vetrone [60]	22	-	67*	-	0	100
Mabrut [31]	27	95	80	15.4	-	84.6
Ulrich [74]	33	-	86.5	-	12.5	87.5
Clemente [67]	47	-	58*	-	19.4	80.6
Jiang [63]	106	86	40.3	11.3	-	-
Yang [8]	136	83	50.7	29.3	25.7	-
Jarufe [41]	52	90.4	63.7	5.8	-	-

♯ Free of symptoms and no recurrent stones. * Mean follow-up.

When partial hepatectomy of the most involved side is planned, complete clearance of the contralateral bile ducts should be obtained. For this, the use of tools such as intraoperative cholangiography, ultrasonography, and cholangioscopy is useful. Recently, Yang et al.[8] compared bilateral hepatectomy (54 patients) with unilateral hepatectomy (82 patients), combined with stone extraction in the treatment of biliary strictures and bilateral hepatolithiasis. Operative mortality was 5.6% after bilateral and 0% after unilateral liver resections. Postoperative residual stones and stone recurrence rate were higher after unilateral hepatectomy. In addition, cholangiocarcinoma developed in 4.9% of patients after unilateral resections and in only 2% after bilateral resections. Therefore, bilateral resection seems more effective, but is possibly associated with higher mortality. These results confirm the complexity of the management of bilateral intrahepatic stones. Risks of extended resection, based on the evaluation of remnant liver, should be weighed against the efficacy of other perioperative techniques to obtain complete removal of

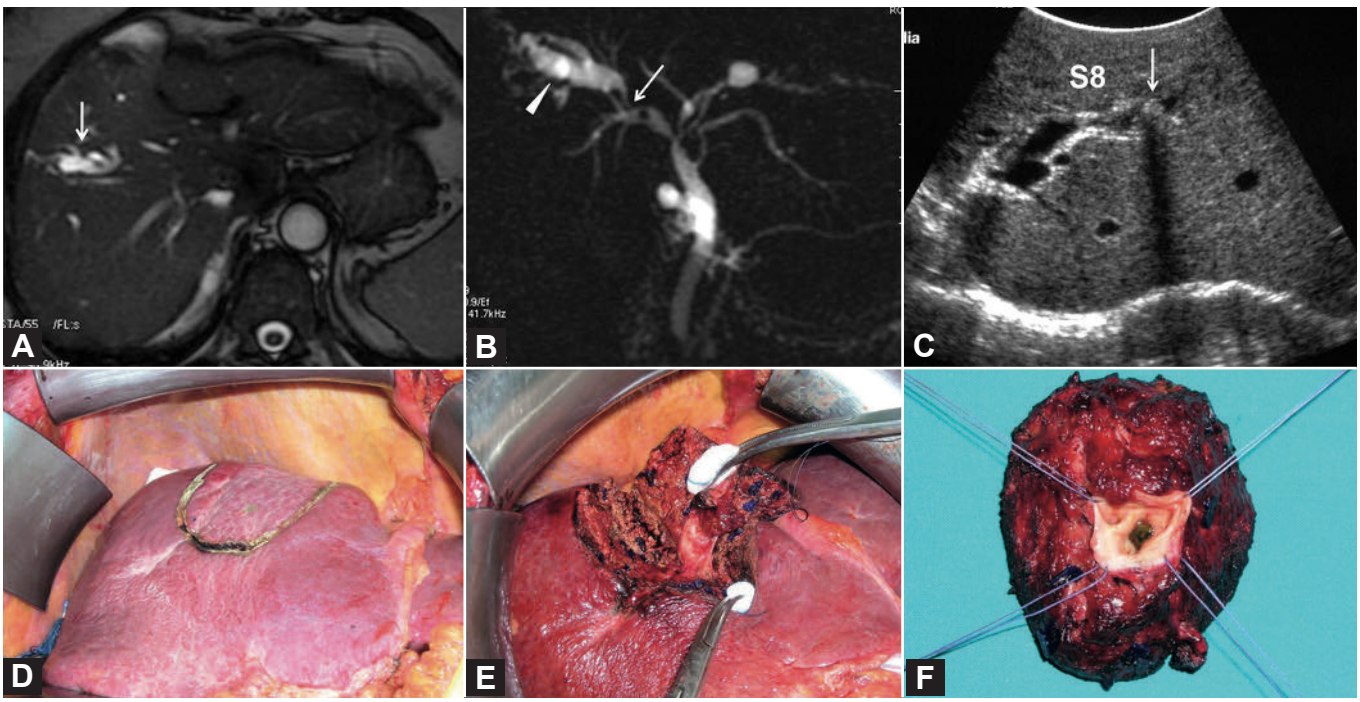


Figure 17. Primary intrahepatic lithiasis of segment 8 treated by anatomical hepatic resection. **A**) Magnetic resonance imaging: dilated bile duct of segment 8 (arrow). **B**) Magnetic resonance cholangiography: Stricture of bile duct of segment 8 with proximal dilatation (arrow head). **C**) Intraoperative ultrasound (IOUS): stone (arrow) in dilated bile duct near the stenosis. **D**) Intraoperative view: demarcation of limits of resection guided by IOUS. **E**) Intraoperative view during parenchymal transection; dilated bile duct of segment 8 is evident at the deeper plane of section. **F**) Surgical specimen after anatomical segmental resection; stones are seen in dilated bile ducts.



Figure 18. Diffuse bilateral primary intrahepatic lithiasis in a 36-year-old female. **A**) Magnetic resonance cholangiography (MRC) showing multiple bilateral intrahepatic stones. **B**) A choledochal cyst filled with stones is also seen on MRC. **C**) Intraoperative direct cholangiography after left lateral sectionectomy, contralateral cholangiocopic extraction of stones, resection of choledochal cyst, and hepaticojejunostomy (arrow).

the stones.

Liver transplantation should be considered in patients with bilateral PIL complicated with liver fibrosis or cirrhosis.[31,44,72–75] Liver transplantation for PIL is rarely reported and represents only 0.2% of the total liver transplants reported in the European Liver Transplant Registry (ELTR).[31]

In summary, early and late outcomes after hepatectomy for PIL are usually favorable.[16] Depite the high rates of postoperative complications (20% to 44%), mortality rates are typically low (0% to 3.8%), and the rate of stone clearance is high (83% to 100%). Also, the long-term results of liver resection for PIL are encouraging and include low rates of stone and/or cholangitis recurrence. Despite the real incidence of cholangiocarcinoma after liver resection for PIL not being clear, some researchers suggest a lower risk of malignancy after hepatectomy than following other treatments. Therefore, liver resection represents the treatment of choice for hepatolithiasis located in one segment or lobe, associated with biliary stenosis or atrophy. Hepatectomy should also be considered the best treatment for bilateral hepatolithiasis when all affected segments can be safely resected and/or if cholangiocarcinoma is suspected.

ROLE OF HEPATICOJEJUNOSTOMY.

Historically, biliary-enteric anastomosis (choledochoduodenostomy and Roux-en-Y hepaticojejunostomy) was one of the most common procedures performed for PIL in order to facilitate postoperative spontaneous discharge of intrahepatic stones into the jejunum. More recently, the role of hepaticojenunostomy (HJ) in the treatment of PIL has been deeply reconsidered.[76,77] In fact, according to the results reported in recent papers, hepaticojejunostomy is not effective for drainage of residual and recurrent stones and increases the long-term risk of cholangitis. Li et al.[76] reported on a retrospective study of 314 patients who underwent HJ for PIL without biliary stricture or cystic dilation, and concluded that the results of HJ were not satisfactory due to the high rates of residual stones and postoperative cholangitis. Indeed, in patients with biliary-enteric anastomosis, reflux of intestinal contents into the bile duct may occur and cause cholangitis. In another retrospective study, Herman et al.[77] reported a higher rate of late complications when HJ was associated with liver resection.

Furthermore, HJ eliminates the continuity of the common bile duct and precludes further endoscopic procedures for removal of recurrent stones. For this reason, in patients with a high risk of recurrence, such as those with complex bilateral lithiasis, techniques that allow an easy access (percutaneous/endoscopic) to intrahepatic bile ducts have been proposed, including hepaticocutaneous jejunostomy;[78–80] hepatoduodenal anastomosis with an interposed jejunal loop;[42] and latero-lateral anastomosis between the jejunal loop of the HJ and duodenum.[81] However, in a large long-term study, Tocchi et al.[82] found that the biliary tract may have a tendency to develop malignancy following biliary-enteric bypass procedures for benign biliary disease (choledocholithiasis, sphincter of Oddi stenosis and postoperative benign stricture). This indicates that bile duct cancer may be a long-term complication of biliary-enteric anastomosis, probably due to the chronic inflammation of the bile duct. For all of these reasons, HJ is not recommended as a routine treatment for PIL. However, the concomitant presence of choledochal cysts or of extrahepatic bile duct strictures can indicate a need for biliary-enteric anastomosis (**Figure 18**).

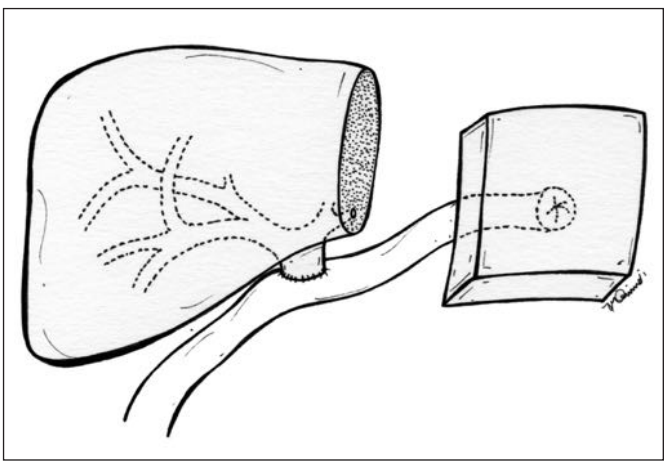


Figure 19. Schematic representation of hepatic resection of left lateral sector associated with hepaticocutaneous jejunostomy (Roux-en-Y) to provide postoperative access for cholangioscopy and residual stone extraction.

NON-SURGICAL APPROACH FOR PIL

Percutaneous and/or endoscopic procedures for hepatolithiasis are useful with patients at high surgical risk and those that refuse surgery. Also, patients that have previously undergone biliary surgery and/or those with diffuse hepatolithiasis can benefit from non-surgical methods. Moreover, initial approach to treat acute cholangitis is use of antibiotics, associated or not with biliary drainage, mainly percutaneous.

Both percutaneous and endoscopic procedures on the treatment of PIL have been widely described in the literature. They are effective for the clearance of bile ducts, but the choice between one of the two accesses depends on location of stones and strictures, presence of associated common bile duct stones, and local expertise.

The role of **endoscopic procedures** in the treatment of hepatolithiasis seems to be more limited than that

of percutaneous ones. The treatment of PIL via the transpapillary route may be difficult in many circumstances, particularly in case of tightening strictures, peripheral stone impaction, or acute ductal angulation.[2,6] Okugawa et al.[83] followed, for an average of 93 months, 36 consecutive patients who underwent peroral cholangioscopic lithotomy for PIL. Complete stone removal rate was 64% and stone recurrence rate was 21.7%. Two patients in this study (5.5%) developed intrahepatic cholangiocarcinoma during follow-up. In patients with associated extrahepatic bile duct stones and that will undergo liver resection, ERC can be performed preoperatively to extract stones from the extrahepatic bile ducts. Furthermore, endoscopic approach is the first choice for common bile duct recurrent stones in patients with previous hepatectomy for PIL (**Figure 20**).

Percutaneous approach in the treatment of PIL, by PTBD and PTCS, has been supported since 1981 by Nimura et al.[84] and represents the most effective non-surgical treatment for hepatolithiasis.[85] The possibility of performing selective cannulation of multiple segmental bile ducts has been clearly shown to obtain precise intrahepatic biliary anatomy and complete removal of stones. The size of extractable stones was initially the limiting factor of this approach, but the development and refinement of electrohydraulic and laser lithotripsy has overcome this limitation. Percutaneous transhepatic cholangioscopic lithotomy (PTCSL) is the mainstay for the treatment of recurrent intrahepatic stones.[51]

The presence of **intrahepatic biliary strictures** represents the most debated issue in non-surgical treatment, because it is usually associated with failure in stone clearance and with intrahepatic stone recurrence. Biliary strictures were classified on the basis of feasibility of choledochoscopic removal of stones as: i) no stricture (grade 0); ii) ductal diameter of the strictured site >5 mm (grade 1, mild); iii) ductal diameter of the strictured site between 2 and 5 mm (grade 2, moderate); and iv) ductal diameter of the strictured site <2 mm (grade 3, severe).[86] Biliary strictures can be treated by dilation with balloons, stent placement, or biliary catheter (exchanging the catheter for a bigger one, step by step). Even after dilation and/or stenting of the biliary strictures, the rate of incomplete clearance in patients with intrahepatic duct strictures is higher than in those without strictures. Indeed, Lee et al.[50] performed a follow-up study with 92 patients that underwent percutaneous treatment for PIL and reported a rate of complete stone clearance rate of 58% in patients with bile duct stricture, versus 100% in those without strictures (P<0.001). Moreover, rate of stone recurrence in patients with severe strictures was 100%. Similar results were observed by Cheung et al.[87]

Another major concern with non-surgical approaches is the risk of misdiagnosis and inadequate treatment of an eventual associated **cholangiocarcinoma**. Severe biliary stricture should be carefully examined by PTC, and a biopsy is mandatory to exclude a possible association with cholangiocarcinoma. Despite the real incidence of cholangiocarcinoma after non-surgical therapies for PIL beingunclear, it is not negligible in either Eastern or Western countries.[8,10,31,42,53] Cheon et al.[39] reported an incidence of cholangiocarcinoma of 4.9% after non-surgical therapy, reaching 9% if residual stones remain after initial treatment. In a retrospective comparative study, Jan et al.[58] followed up with 427 patients for 4 to 10 years after surgical treatment (n = 380) or PTC treatment (n = 47), and patients who underwent hepatectomy had a significantly lower incidence of cholangiocarcinoma. It has also been reported that resection of cholangiocarcinoma with associated intrahepatic stones has a significantly poorer prognosis than cholangiocarcinoma alone, probably related to delayed diagnosis, lower diagnostic rate, and less radical resection.[54,88] Therefore, in all patients treated for PIL, after surgical or non-surgical treatments, regular follow-up with US and MRI is recommended for early detection of cholangiocarcinoma.

Residual and recurrent stones are the most troublesome problems after non-surgical treatment for hepatolithiasis. Cheon et al.[39] evaluated immediate and long-term results of more than 200 patients who underwent treatment by surgical therapy, PTCS, or peroral cholangioscopy. The rates of complete stone clearance were 83.3%, 63.9%, and 57.1%, respectively. In multivariate analysis, non-surgical treatment and intrahepatic bile duct strictures significantly increased the risk of residual stones after treatment. However, following complete stone clearance, similar rates of intrahepatic stone recurrence and/or cholangitis occurred after hepatectomy with postoperative cholangioscopy, after PTC with lithotripsy,

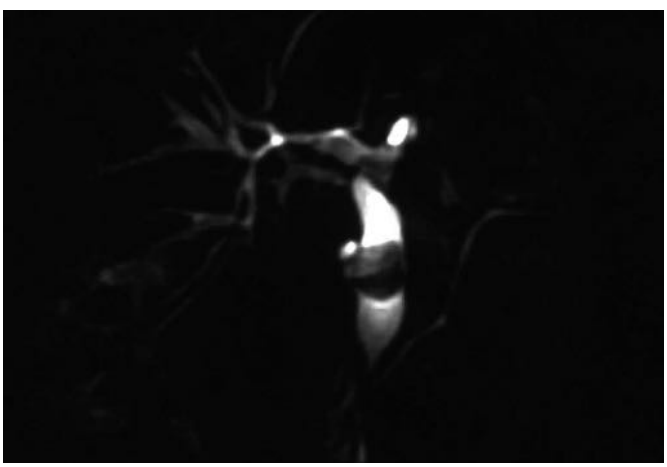


Figure 20. Magnetic resonance cholangiography showing recurrent common bile duct stone two years after a left hepatectomy extended to caudate lobe for primary intrahepatic lithiasis. The stone was removed by endoscopic retrograde cholangiography access.

and after peroral cholangioscopy (18%, 21%, and 25%, respectively).

Extracorporeal shock wave lithotripsy is particularly useful for cholesterol stones, and the use of holmium (Ho) YAG laser for calcium bilirubinate hepatolithiasis has been described with favorable results.[59]

Endoscopic and/or percutaneous approaches should be considered mainly in patients with a poor performance status and in patients with postoperative residual or recurrent hepatolithiasis after surgery.

FINAL CONSIDERATIONS

In summary, the best treatment for primary intrahepatic lithiasis is hepatic resection of the affected segments. Well-defined indications for hepatectomy are unilateral stones associated with strictures and parenchymal atrophy, or suspicion of malignancy. However, localized bilateral disease also seems to be adequately managed by liver resections. Approaching diffuse bilateral disease is challenging, and must be individualized with acceptable therapeutic options, including a combination of the following procedures: hepatic resection of the most affected side, perioperative stone extraction by cholangioscopy, hepaticojejunostomy, hepaticocutaneous jejunostomy, common bile duct T-tube insertion, stricture dilation with balloon or stent or surgical strictureplasty, or even liver transplantation. Regular follow-up is advisable regardless of the approach (surgical or non-surgical) in an attempt to detect an eventual cholangiocarcinoma at an early stage.

SUGGESTED READING

Yang, T. *et al.* Hepatectomy for bilateral primary hepatolithiasis: a cohort study. *Ann. Surg.* **251**, 84–90 (2010).

This large retrospective cohort study compares results of bilateral and unilateral hepatectomy for the treatment of bilateral primary intrahepatic lithiasis and biliary strictures. Long-term results were favorable for bilateral hepatectomy.

Chen, D.-W., Tung-Ping Poon, R., Liu, C.-L., Fan, S.-T. & Wong, J. Immediate and long-term outcomes of hepatectomy for hepatolithiasis. *Surgery* **135**, 386–393 (2004).

A large study including 103 patients with hepatolithiasis who underwent liver resection. Details of early and long-term outcomes are reported and discussed. The presence of cholangiocarcinoma is found as the main factor compromising survival.

Cheon, Y. K., Cho, Y. D., Moon, J. H., Lee, J. S. & Shim, C. S. Evaluation of long-term results and recurrent factors after operative and nonoperative treatment for hepatolithiasis. *Surgery* **146**, 843–853 (2009).

This large retrospective study including 311 patients compares long-term results of surgical, percutaneous, or peroral treatment for hepatolithiasis. Results are favorable to surgical treatment (hepatectomy).

Jarufe, N. *et al.* Anatomic hepatectomy as a definitive treatment for hepatolithiasis: a cohort study. *HPB (Oxford).* **14**, 604–610 (2012).

One of the largest western studies of liver resection for hepatolithiasis (52 patients).

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22 General Technical Aspects of Liver Resections

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- *Knowledge of hepatic segmentation is crucial for safe liver resection. Remnant liver parenchyma should have adequate vascular inflow, vascular outflow, and biliary drainage.*
- *Different methods of vascular control are available and useful to reduce bleeding during hepatectomy. Inflow occlusion is the easiest and best tolerated option. Total vascular exclusion of the liver is required in some cases of tumors close to the debouchment of the hepatic veins and inferior vena cava.*
- *The two main approaches to selective inflow hepatic control are intrafascial and extrafascial (or Glissonean). The first is required for tumors close to the hepatic hilum.*
- *Anterior approach, mainly using the hanging maneuver, seems to reduce blood loss, facilitates "no touch" resection, and reduces the risk of liver damage for mechanical compression of the remnant liver during surgery.*

CONCEPTS OF SEGMENTAL HEPATIC ANATOMY

Segment-oriented liver resections were developed with the goal of preserving the maximum amount of liver parenchyma while maintaining adequate vascular inflow, vascular outflow, and biliary drainage. Two main concepts regarding hepatic segmentation are used for liver resections.

The anatomical description of Couinaud[1] (**Figure 1**) is the most frequently used in hepatic surgery. Couinaud demonstrated that eight hepatic segments are anatomically individualized and can be separately resected. The three main hepatic veins (right, middle, and left) divide the liver into four sectors. Cantlie's line (main portal scissura) divides the liver into two hemilivers: right and left. The right hemiliver comprises the right posterior (segments 6 and 7) and right anterior (segments 5 and 8) sectors. The right portal scissura (where the right hepatic vein runs) separates these two sectors. The left hemiliver comprises segment 2 (left lateral sector), and segments 3 and 4 (medial left sector). These sectors are separated by the left portal scissura (where the left hepatic vein runs). Couinaud's segments 2 and 3 correspond to Goldsmith and Woodburne's left lobe,[2] and segment 4 represents the quadrate lobe. The caudate lobe is a sector that is embryonically and anatomically independent of the right and the left hemilivers. It makes extensive contact with the inferior vena cava.[3] It is of note that the modern nomenclature of liver anatomy and resections considers segments 2 and 3 (instead of only segment 2) as the left lateral ***section***, and segment 4 (instead of segments 4 and 3) as the left medial ***section***. This terminology is different from the Couinaud sectors, based on portal vein ramification, where the left medial ***sector*** includes segments 4 and 3, and the left lateral ***sector*** is represented by segment 2 alone (see *Terminology of Hepatic Resections* below).

The other frequently used anatomical segmental description is called the "Glissonean approach" in liver resections, as described by Takasaki[4] (**Figure 1**). In Takasaki's description, the liver is divided into three segments based

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on the distribution of the portal branches. The extrahepatic portion of the Glissonean pedicle corresponds to the portal triads in the hepatoduodenal ligament enclosed by connective tissue and peritoneum. The intrahepatic Glissonean pedicles consist of portal triads enclosed by Glisson's sheath. Three secondary Glissonean branches separately enter the liver at the level of the hepatic hilum, contributing to the right, middle, and left Takasaki's segments. Small branches originating from the primary branch nourish one additional region, the caudate area. The right and middle hepatic veins (the left hepatic vein is here considered a tributary of the middle vein) run among the three segments.

In fact, there is a close correlation between the anatomical concepts of Couinaud and Takasaki, as described in **Table 1**. Couinaud's right posterior sector, right anterior sector, and left hemiliver correspond, respectively, to Takasaki's right, middle, and left segments. The caudate lobe, or caudate area, is a portion of liver parenchyma that receives arterial and portal branches (and has biliary branches) from the right and left pedicles, at the level of the hilum, and its veins drain directly into the retrohepatic vena cava. This area of the liver has the appearance of a pyramid, with its apex at the level of the confluence of the main hepatic veins, a side border with the right posterior sector (or right segment of Takasaki), another side border with segment 4 (or left segment of Takasaki), and the other sides in contact with the vena cava and the minor omentum (**Figure 2**).

Each Couinaud's segment receives one or more Glissonean pedicle branches. According to Takasaki, each tertiary Glissonean branch nourishes a cone of liver parenchyma, the so-called "cone unit". Thus, a Couinaud's segment consists of several cone units. The boundaries of hepatic resections can be guided by either Couinaud's segmentation or by Takasaki's concept of cone units. The resection of one Couinaud's segment implies the section of two or more tertiary Glissonean pedicles. On the other hand, Takasaki suggests that more limited resections can be guided by the identification of the parenchyma area supplied by each tertiary branch, i.e. each cone unit could be individually resected (**Figure 3**).

TERMINOLOGY OF HEPATIC RESECTIONS

In order to standardize the nomenclature of the liver anatomy and resections, the "Brisbane 2000 Nomenclature of Liver Anatomy and Resections" was proposed by the Scientific Committee of the International Hepato-Pancreato-Biliary Association (IHPBA). Despite some criticisms, this terminology is very appropriate and recommended by the editors of this textbook. Indeed, this terminology was applied in all chapters.[5]

The Brisbane 2000 terminology is based on arterial and biliary ramifications. The first order division separates the

Table 1. Relationship between hepatic segmentation according to Couinaud's and Takasaki's concepts.

Couinaud's		Takasaki's
Right posterior sector	Segment 6 Segment 7	Right segment
Right anterior sector	Segment 5 Segment 8	Middle segment
Medial left sector	Segment 4 Segment 3	Left segment
Lateral left sector	Segment 2	

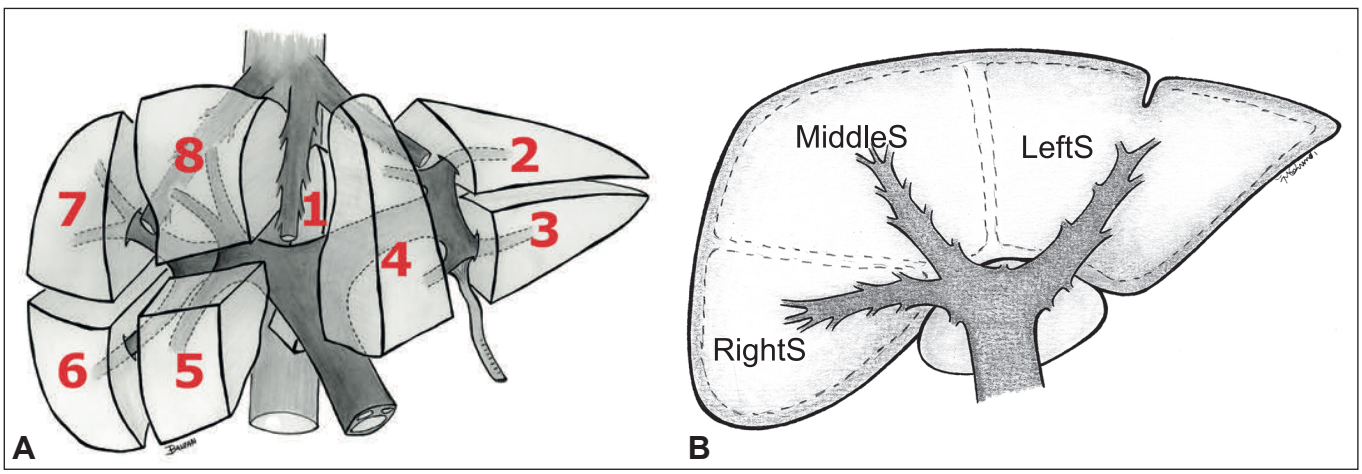


Figure 1. Schematic illustration of hepatic segmentation. **A**) Segmental anatomy according to Couinaud. The middle hepatic vein divides the right hemiliver (segments 5,6,7 and 8) from the left hemiliver (segments 2,3 and 4). **B**) Takasaki's liver segmentation is based on the two major venous trunks (right hepatic vein and middle/left hepatic vein trunk). The right, the middle, and the left segments correspond to Couinaud's segments 6/7, 5/8, and 2/3/4, respectively. The caudate area corresponds to Couinaud's segment 1.

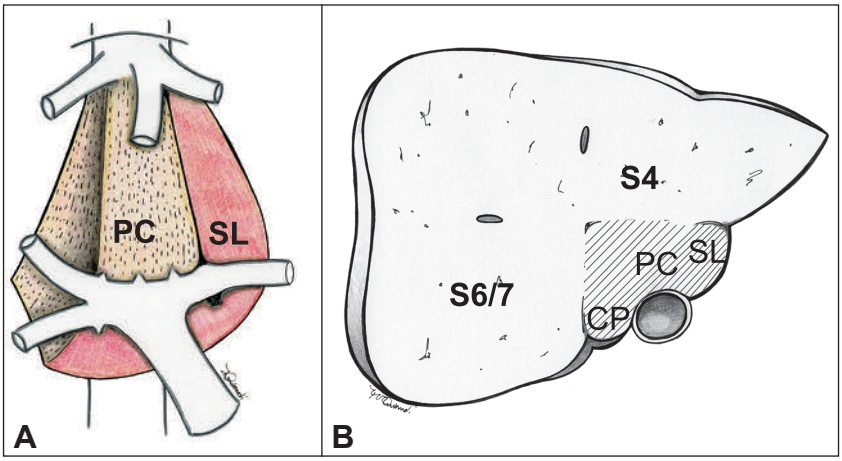


Figure 2. Schematic representation of the caudate lobe (or Segment 1 of Couinaud, or caudate area of Takasaki). This portion of the liver is divided in three parts: Caudate process (CP), Paracaval portion (PC), and Spiegelian lobe (SL). **A**) Anterior view. Hachured area represents the anterior paracaval and the lateral paracaval triangles. **B**) Transversal section demonstrates the depth contact of CP with the right posterior sector (or right segment of Takasaki), and the contact of PC with segment 4. The SL is the bulbous left part of the caudate lobe, seeing through the minor omentum. S4: segment 4; S6/7: segments 6/7.

liver into two hemilivers (right and left) by the "midplane of the liver" (which intersects the gallbladder fossa and the fossa of the inferior vena cava). Two other planes, the left intersectional plane (which passes through the umbilical fissure and the attachment of the falciform ligament) and the right intersectional plane (with no surface marking) are responsible for the second order division, and delimit the four hepatic sections (right posterior and right anterior sections, and left medial and left lateral sections). The delimitation into seven segments (third order division) is done by the association of horizontal intersegmental planes. Segment 1 (**Figure 2**) is a distinct portion of the liver, separate from the right and left hemilivers. It is subdivided into three parts: the Spigelian lobe, the paracaval portion (anterior to the vena cava), and the caudate process (merging indistinctly with the right hemiliver).

In summary, the terminology of anatomy considers two hemilivers (first order division), four sections (second order division), and eight segments (seven derived from the third order division plus segment 1).

It is worth noting that segment 4 is arbitrarily divided into superior (4a) and inferior (4b) parts without an exact anatomical plane of separation. However, there is no individual arterial blood supply for these parts, and the left medial section corresponds to segment 4.

The terminology of hepatic resections is based upon anatomical terminology, as shown in **Figure 4**. Thus, resection of one hemiliver is a hemihepatectomy (right or left hemihepatectomy, also called right hepatectomy or left hepatectomy according to the resected hemiliver), resection of a section is a sectionectomy (right posterior sectionectomy, right anterior sectionectomy, left medial sectionectomy, and left lateral sectionectomy), and resection of a segment is a segmentectomy (for example segmentectomy 1, segmentectomy 5). Resection of three contiguous sections is referred to as a trisectionectomy (right or left trisectionectomy). When segment 1 is resected as part of a procedure, the term "with resection of segment 1", or "extended to segment 1", should be added (for example: "right hepatectomy with resection of segment 1"). Also, the use of the segment number to refer to any resection is correct. For instance, one might describe resection of segments 5-8 (or right hemihepatectomy, or right hepatectomy), resection of segments 2,3 (or left lateral sectionectomy), and resection of segments 5,6 (or bisegmentectomy 5,6). As cited above, note that the left lateral ***section*** (segments 2 and 3) is not the same as the left lateral ***sector*** of Couinaud (segment 2), and similarly, the left medial ***section*** of Brisbane terminology (segment 4) is not the same as the left medial ***sector*** of Couinaud (segments 4 and 3).

MAJOR OR MINOR HEPATECTOMY

The classification of a liver resection as a *major hepatectomy* or a *minor hepatectomy* has some goals such as comparing

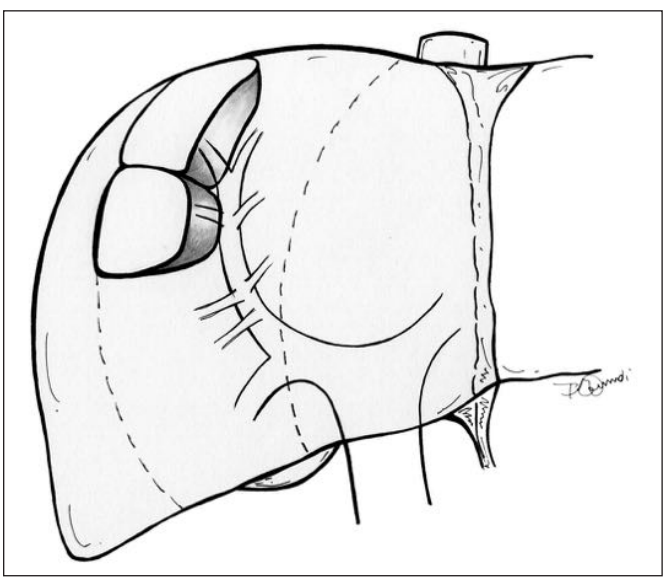


Figure 3. Takasaki's cone unit concept applied to segment 8 of Couinaud. (Adapted from Takasaki.[83])

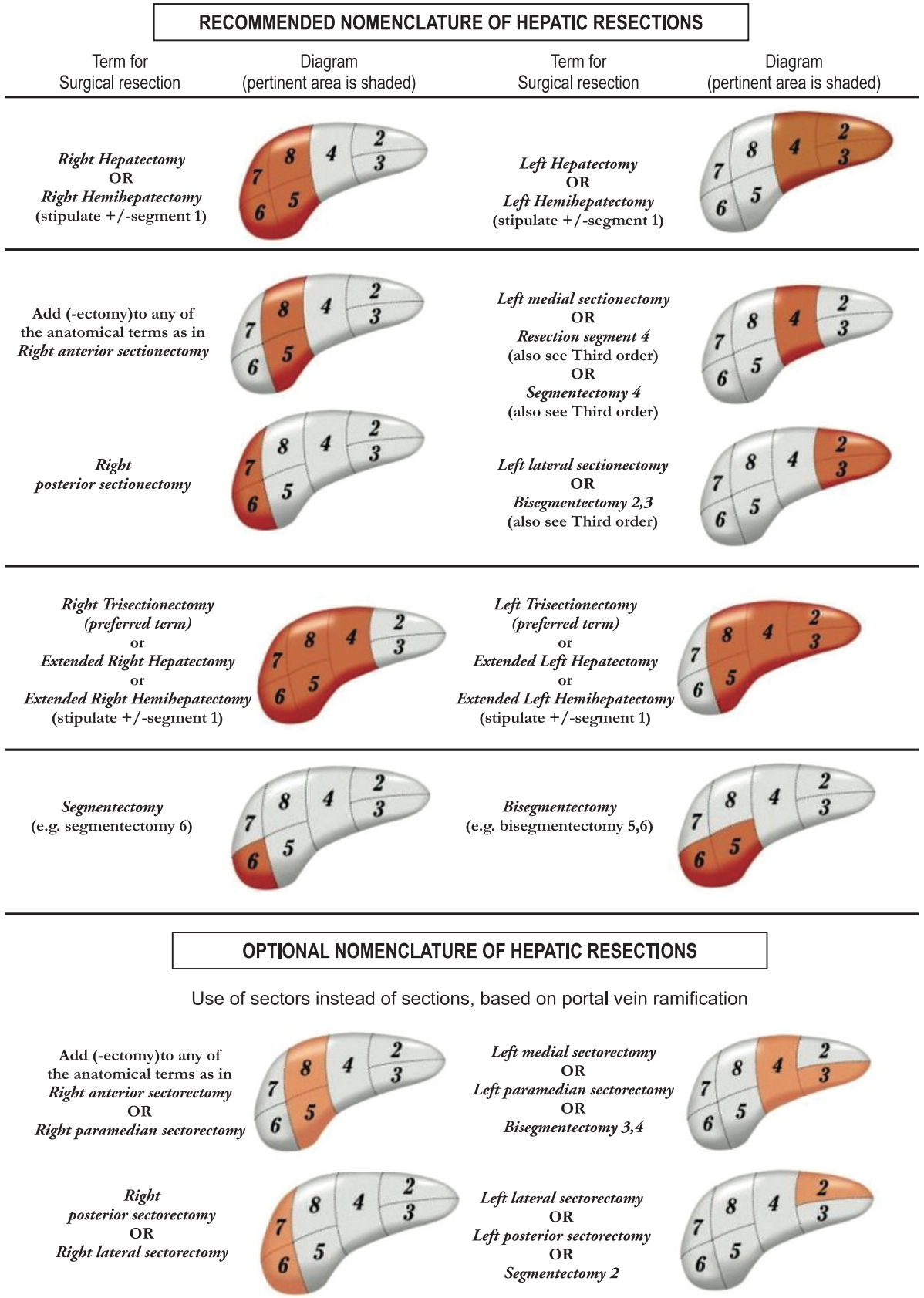


Figure 4. Terminology of hepatic resections. The Arabic numbers represent the respective Couinaud segment. (Adapted from The terminology committee of the IHPBA [5])

results between studies and predicting morbidity and mortality rates. The remnant liver (considering its volume and quality) is the major determinant of complications following a liver resection. The volume of liver resected has a direct relationship with the remnant liver, and classically liver resections have been classified as a **major hepatectomy** when three or more hepatic Couinaud's segments are resected, and a **minor hepatectomy** if up to two Couinaud's segments are resected.

Recently, the cutoff of four or more segments to define a major hepatectomy has been proposed. Based on outcomes after 1,670 consecutive hepatectomies, Reddy et al.[6] found that resection of four or more hepatic segments was associated with poorer outcomes; on the other hand, the outcomes were similar after resection of three or fewer segments.

While the classifications of major or minor hepatectomy based on the number of segments resected are widely used, they are not always indicative of the complexity of the liver resection. For example, a central liver resection of segments 5 and 8 is certainly more complex than a left lateral resection (segments 2 and 3).

INCISION

The majority of hepatic resections are performed through an exclusive abdominal approach. Laparoscopic approach is discussed in **Chapter 27** (Principles of Laparoscopic Liver Resections). For most liver resections, open operative exposure can be achieved through a variety of incisions. The bilateral subcostal incision (with or without a vertical midline extension) can be used to access both hemilivers. However, other accesses have been used to provide adequate exposition with minimal complications. A midline incision from the xiphoid to 2-3 cm above the umbilicus with an oblique or transversal extension to the right flank ("J" or inverted "L" incisions) provides excellent operative exposure and allows for abdominal or thoracic extension if necessary. Another incision, called a "hockey stick" incision, combines a right subcostal incision with a midline extension to the xiphoid (**Figure 5**).

The use of a thoracoabdominal incision (thoraco-phreno-laparotomy) might be useful to approach tumors close to the confluence of the hepatic veins, as it enables an effective retraction of the costal arch. The chest is usually opened through the 9th interspace after division of the costal arch. Frequently used incisions are the J-shaped incision extended laterally to a thoracotomy and median laparotomy extended laterally in the 9th interspace close to the xiphoid (**Figure 5**). The diaphragm can be divided radially from the chest wall to the hiatus, or circumferentially leaving 3 to 4 cm along the chest wall for later approximation. One must be careful to avoid injury to the phrenic nerve. With the combined thoracic approach, the surgeon is able to lift the liver together with the diaphragm, and bleeding from the hepatic veins or inferior vena cava can be easily stopped by digital compression. This exposition allows for resection of tumors invading the diaphragm with proper control of the suprahepatic vena cava and adequate exposition of the hepatic vein confluence (for dissection, resection, and eventual reconstruction). Moreover, in large tumors of the right liver that preclude its mobilization and are not eligible for anterior approach, control of the short hepatic veins can be facilitated by thoracoabdominal incision.

Rarely, resection of small tumors located in the superior hepatic segments can be accomplished exclusively through the chest with the opening of the diaphragm to approach the liver. This strategy is usually reserved for resection of hepatocellular carcinoma in cirrhotic patients to avoid the complications of laparotomy in this subset of patients (i.e., ascites or peritonitis). The difficulty inherent to obtaining vascular inflow control (frequently needed in these patients) and the development of laparoscopic surgery (with fewer complications than laparotomy in cirrhotic patients) have made this approach exceedingly rare.

The selection of the appropriate incision should take into account the hepatic anatomy (especially in cases of repeated hepatectomy and severe atrophy or hypertrophy of certain segments), tumor location and size, and presence of previous incisions (for example, for resection of a primary colorectal tumor). In case exposure of the suprahepatic vena cava and the hepatic veins is needed, it is advisable to choose an incision that allows for adequate thoracic extension.

Adequate exposure is facilitated by the use of appropriate retractors. It is of utmost importance to invest enough time intraoperatively to optimize exposure. Many options of retractors, from various manufacturers, are available. The most useful are those that are fixed to the operating table and allow for cephalad and somewhat anterior retraction of the costal margins.

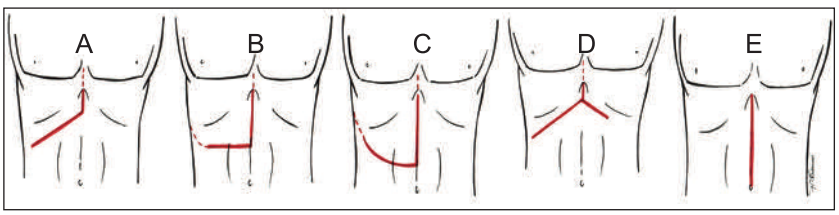


Figure 5. Frequently used incision for open hepatic resections. Dotted lines represent possible extensions. **A**) Hockey Stick Incision; **B**) Inverted L Incision; **C**) J Incision; **D**) Bilateral Subcostal Incision; **E**) Midline Incision.

DRAINAGE

In order to evacuate peritoneal fluid collections, drains can be left in place for diagnostic, prophylactic, or therapeutic purposes.

The potential benefits of prophylactic drainage following liver resection include: i) prevention of possible harmful fluid accumulation (i.e., bile) that can eventually become infected and ii) to detect early postoperative complications (i.e., intra-abdominal bleeding or anastomotic leakage). However, routine prophylactic drainage is not used after hepatic resection due to the risk of secondary infection and the development of interventional radiology to treat occasional deep operative site complications.[7] In general, it is acceptable to drain extensive right resections and procedures with associated biliary reconstruction. In case drainage is performed, the use of a silicone close-suction product (i.e., Jackson-Pratt or Blake) in the resection bed is preferred.

EXPOSITION AND LIVER MOBILIZATION

The extent of liver mobilization depends on the type of hepatectomy to be performed. In most cases, the ligamentum teres and the falciform ligament are divided. The falciform ligament is sectioned in a cephalad direction to the subdiaphragmatic inferior vena cava. Dissection can be continued laterally towards the right and left sides of the inferior vena cava (IVC) in an avascular plane, very close to the liver. The division of the upper part of the falciform ligament enables exposition of the debouchment of hepatic veins into the IVC (**Figure 6**).

If necessary, the left liver is mobilized by sectioning the left triangular ligament. This step can be facilitated by the opening of the ligament close to the IVC and passing an umbilical tape to encircle the left hepatic lobe. A caudal traction on the left lobe facilitates the exposure and section of the left triangular ligament, especially in cases of a large ligament reaching the left abdominal wall laterally. Also, placement of a laparotomy pad under the left triangular ligament between the stomach and the left lobe, and keeping contact with the diaphragm, facilitates the section of the left triangular ligament and avoids injury to the stomach and spleen. The left lobe is pulled upward, and the lesser omentum is divided exposing the Arantius ligament (ligamentum venosum), which is divided near its cephalad insertion (in the left hepatic vein or the common trunk). This maneuver facilitates encircling the common trunk or the left hepatic vein. Care should be taken not to injure the left phrenic vein, which drains into the IVC close to the opening of the hepatic vein common trunk.

Section of the right triangular ligament allows for mobilization of the right liver and access to the right aspect of the retrohepatic vena cava. The liver is pulled downward and the cephalad portion of the right triangular ligament is divided with exposure of the bare area of the right liver (**Figure 7**). Attention should be paid to prevent injury of the right hepatic vein, which is in close proximity to the peritoneum, recovering the transition between the falciform and right triangular ligaments. At this point, blunt dissection making contact with the IVC can help avoid injuries to the diaphragm. After section of the upper portion of the right triangular ligament, the liver is pulled upward and the inferior portion of the ligament is divided. Dissection is performed close to the liver to avoid lesion of the right adrenal. Finally, the liver can be rotated to the left, and the right liver progressively separated from the diaphragm, exposing the entire right bare area of the liver.

Thus, exposition of the retrohepatic vena cava can be obtained after sectioning the falciform, left triangular, and right triangular ligaments. The short retrohepatic veins draining directly from the caudate lobe to the IVC can be divided (**Figure 7**). The upper part of the right side of the retrohepatic vena cava is covered by the vena cava ligament (also called the Makuuchi ligament or caval ligament). This ligament should be divided to complete exposure of the vena cava and the right hepatic vein (**Figure 7**). The vena cava ligament extends behind the vena cava, joining the caudate lobe at the left aspect of the vena cava. This ligament can be avascular, contain vascular and biliary structures, or even be composed of hepatic tissue (creating a ring of parenchyma encircling the vena cava).

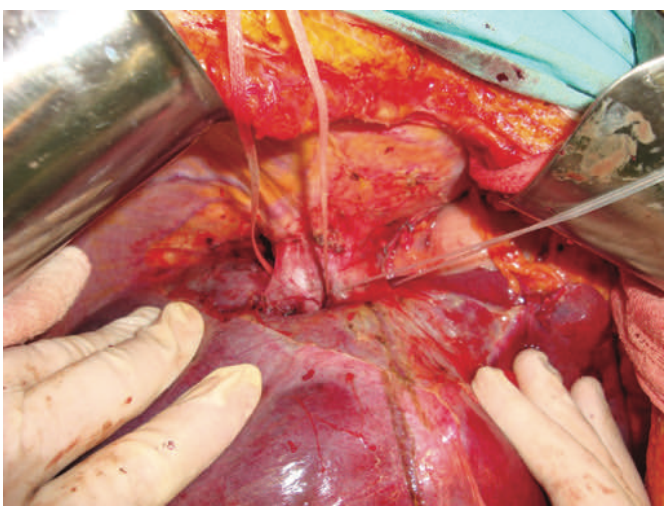


Figure 6. Surgical aspect after section of the falciform, right triangular and left triangular ligaments, and downward traction of the liver. Usually the suprahepatic inferior vena cava is easily identified and dissected (among the arrows). The right hepatic vein and the common trunk (left and middle hepatic veins) can be isolated at this point (umbilical tapes).

The complete mobilization of the liver facilitates adequate intraoperative ultrasound evaluation, as discussed in **Chapter 3** (Intraoperative Assessment of the Liver). In case of tumor attachment to the diaphragm, resection with posterior repair can be performed during liver mobilization. In case of diaphragmatic compromise, the anterior approach might be useful (this topic is discussed later in this chapter).

VASCULAR CONTROL

Blood loss is a major intraoperative complication of liver resections. Blood transfusion is frequently associated with increased operative morbidity and mortality, and poor oncological outcomes (discussed in detail in **Chapter 9** – Morbidity and Mortality after Liver Surgery).[8,9] Vascular occlusion modalities (inflow control or a combination of inflow and outflow control) and techniques of hepatic transection have contributed to minimize blood loss and perioperative blood transfusion. However, the benefit of reduction of bleeding by vascular clamping should be balanced with the resulting liver injury induced by ischemia and reperfusion, especially in patients with a chronic underlying liver disease. Thus, intermittent pedicular clamping (combined with low central venous pressure) has been the preferred vascular clamping method to reduce blood loss with lower morbidity. Safe liver resections with no vascular clamping are possible using low central venous pressure and adequate cross-section methods. Total vascular exclusion of the liver has been limited to tumors involving the major hepatic veins or the IVC close to these veins.[10]

In this chapter, some technical aspects of vascular control are discussed. Complementary reading of **Chapter 23** (Vascular Control and Parenchymal Transection Techniques) is recommended.

INFLOW VASCULAR OCCLUSION

Inflow vascular (arterial and portal) occlusion is an efficient means of reducing bleeding during hepatotomy. Inflow vascular occlusion can be applied to the whole liver or selectively to target areas. Interruption of the inflow to the whole liver is usually obtained by occlusion of the portal vein trunk and the proper hepatic artery. Selective inflow vascular occlusion of the segments to be resected can be performed outside the parenchyma (by intrafascial or Glissonean approaches) or by transection of the relevant vascular structures within the liver substance.

Total inflow vascular occlusion of the whole liver (pedicular control)

Continuous inflow occlusion can be safely applied to a normal liver under normothermic conditions for up to 60 minutes, and for up to 30 minutes in pathological (fatty or cirrhotic) livers.[11] However, longer durations of continuous clamping (90 minutes in normal livers[12–15]) have been reported. Duration of inflow occlusion can be safely prolonged using strategies such as intermittent clamping and hepatic hypothermia, discussed below in this chapter. Intermittent pedicular clamping results in less hepatic ischemia and splanchnic congestion than continuous clamping.

The simplest method of hepatic inflow vascular clamping is the **Pringle maneuver**, described in 1908, which consists of clamping of the hepatoduodenal ligament.[16] Once the lesser omentum is opened, a blunt dissector (or a finger) is passed through the foramen of Winslow and the hepatoduodenal ligament is encircled with an umbilical tape. The entire contents are clamped en masse. Optionally, the structures of the hepatoduodenal ligament can be dissected and the portal vein and hepatic artery occluded individually, avoiding possible bile duct injuries. For both techniques, non-traumatic vascular clamps or tourniquets can be used to perform the Pringle maneuver.[17] Attention should be paid to the identification and clamping of an accessory left hepatic artery originating from the left gastric artery; it generally runs through the lesser omentum and requires individual clamping. Conversely, when present, a right accessory hepatic artery originating from the superior mesenteric artery is clamped in a regular way, as it runs within the hepatoduodenal ligament.

Selective inflow clamping (intrafascial and Glissonean approaches)

Selective inflow vascular occlusion can be used to avoid ischemia of the remnant liver, reduce splanchnic congestion,

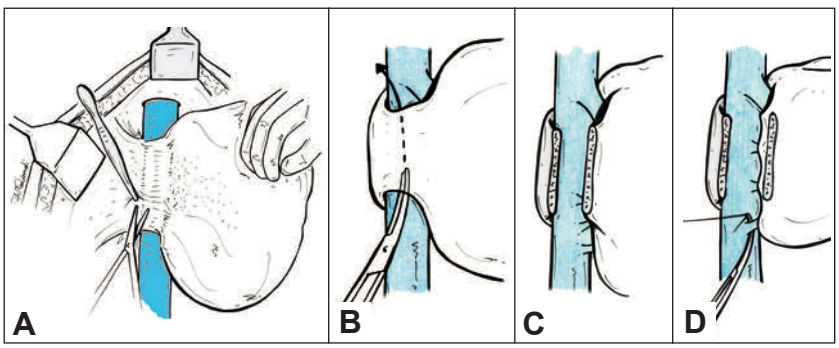


Figure 7. Mobilization of the right hemiliver. **A**) Completion of section of the right triangular ligament. **B**) A tunnel is created by blunt dissection between the vena cava ligament and the vena cava. **C**) Division of the vena cava ligament allows exposition of the right hepatic vein and the right aspect of the retro-hepatic vena cava. **D**) Short retrohepatic veins are sectioned and the retrohepatic vena cava fully exposed.

and to accurately demarcate the limits of the segments to be resected in the hepatic surface by changes in its color. Selective inflow occlusion can be applied to the right or the left hemiliver, or to each hepatic sector (mainly right anterior and right posterior sectors), or even individual segments. Selective inflow occlusion can be definitive (such as by ligature) or temporary (by vascular clamping or tourniquet). Temporary selective occlusion can be useful for resections smaller than the occluded sector. For example, during a wedge resection or a segment hepatic resection of the right liver, a temporary clamping of the right hemiliver can be used to reduce blood loss, preserving the inflow for the left hemiliver. Selective control of the main vascular pedicles can be accomplished by Glissonean approach or by intrafascial hilar dissection. Occlusion of a segmental or subsegmental portal branch can also be performed with vascular balloon insertion into the (sub) segmental portal vein (by intraoperative ultrasound-guided transhepatic puncture[18] or through the superior mesenteric vein[19]) combined with unilateral clamping of the ipsilateral hepatic artery.[18] Segmental or subsegmental portal vein occlusion, aiming to demarcate the area to be resected, can also be accomplished by intraoperative ultrasound-guided finger compression.[20,21] Another technique for segmental demarcation, without portal occlusion, is through the injection of a dye (such as indigo-carmine) by intraoperative-guided puncture in the portal branches of the tumor area to be resected while the hepatic artery at the hilum is clamped.[22]

The two main methods for control of the vascular inflow pedicles are: extrafascial (or Glissonean) and intrafascial approaches. These methods with their variants can be used for most hepatic resections. One exception is tumor compromise of the hilum when combined hepatectomy and resection of the biliary confluence or vascular structures of the hilum preclude the Glissonean approach, which is performed above the hilum. Also, for tumors close to the hepatic hilum (less than 2 cm), the intrafascial approach can help to avoid violation of the tumor margin.

Intrafascial hilar approach (Figure 8)

With the Glissonean approach (intrafascial hilar approach), the portal vein, hepatic artery, and biliary duct are usually dissected in the hilum after opening the peritoneal fascia. To avoid accidental section of structures to be preserved close to the hilum, the vascular structures might be temporarily clamped at this level but sectioned (together with the biliary tract) into the parenchyma, across the section area.

Structures of the right pedicle are more difficult to individualize than those of the left pedicle. The cystic artery is ligated and sectioned and a cholecystectomy is performed. A tube can be placed through the stump of the cystic duct for an eventual further cholangiography or bile leak tests. The peritoneal fascia is generally opened at the right side of the common bile duct and the right hepatic artery identified, usually posteriorly to the common bile duct. The common bile duct, together with the surrounding connective tissue, is pulled to the left and upward. The division of the right hepatic artery facilitates exposition and control of the right portal vein. If the right hepatic artery should not be divided, it can be properly displaced using a Gil-Vernet retractor to facilitate exposure of the right portal vein. The right portal vein is encircled using blunt dissection with a right-angle clamp. Attention should be paid to avoid injury of the inferior and posterior portal branches to the caudate lobe, more precisely those to the paracaval portion of segment 1. If control of the right portal branch is difficult to obtain, the portal vein trunk can be dissected and encircled by the right and posterior aspect of the hepatoduodenal ligament, and a downward traction can enable better exposition of the portal bifurcation. Usually, the right hepatic artery and the portal vein are dissected (and can be sectioned) at the hilum, but the right bile duct is not. The right bile duct is safely sectioned during the parenchymal cross section or at the hilum but without dissection. These strategies avoid direct or ischemic injury of the biliary tract. Structures of the left hepatic pedicle are longer and easier to individualize by intrafascial approach than the right.

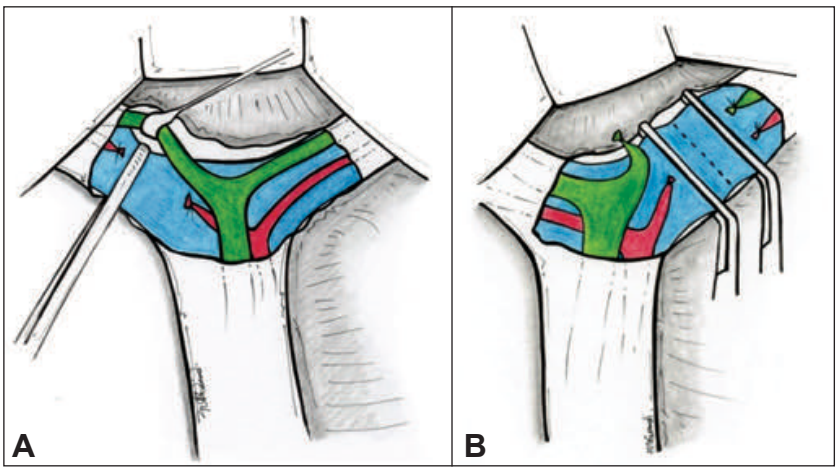


Figure 8. Intrafascial approach to the structures of the right and left hemilivers. **A**) Control of the right portal vein is facilitated by the section of the right hepatic artery (at the right side of the common bile duct). The right hepatic bile duct is pulled upward and to the left by a Gil-Vernet retractor. **B**) Left hemiliver pedicle dissection. The left bile duct is usually long and sectioned to allow easier access to vascular structures.

Optionally, intrafascial approach to the right pedicle can be performed in a posterior to anterior direction; i.e., first dissection and/or section of the right portal vein is achieved and then the right hepatic artery is identified and controlled.

It is important to note that intrafascial dissection is usually performed below the hilar plate, where variations of the hepatic artery and bile duct are frequent. The vascular anatomy should be carefully evaluated by preoperative imaging. The main vascular variations are described in **Chapter 1** and **Chapter 2**.

The standard arterial anatomy occurs in two thirds of patients. The median hepatic artery (to segment 4) has frequent variants, but generally runs anteriorly to or crosses the left hepatic duct. Dissection of the middle hepatic artery from the left hepatic duct is needed for safe section of the left hepatic duct.

Biliary duct variations are also common. In case a variation is suspected, an intraoperative cholangiography should be performed, especially if the bile duct will be sectioned in the hilar plate.

Glissonean approach (extrafascial approach) (Figures 9 and 10)

Glisson's capsule refers to the connective tissue that wraps the hepatic pedicles (hepatic artery, portal vein, and bile duct). With the extrafascial (or Glissonean) approach, the so-called Glissonean pedicles at the hilar plate are detached from the liver parenchyma. Control of the main Glissonean pedicles (left hemiliver, right anterior sector, and right posterior sector from Couinaud's classification; or Takasaki's left, middle, and right segments, respectively) is accomplished extrahepatically at the level of the hepatic hilum following hilar plate lowering.

This approach was initially developed by Launois and Jamieson[23] and enhanced by Takasaki.[4] Since the arterial and biliary variations occur below the hilar plate, this approach does not pose a risk of injury to the elements that supply the remaining liver segments when the pedicles are sectioned above the hilar plate.[24]

The three Takasaki segmental branches (right, middle, and left, corresponding to Couinaud's right posterior sector, right anterior sector, and left hemiliver, respectively) can be encircled separately, and various combinations of pedicle control and section are possible.

The whole right hemiliver pedicles can be encircled by inserting a right-angled clamp in the superior aspect of the hilar plate (after lowering the hilar plate from segment 4), passing posteriorly to the right liver pedicle through an oblique trajectory to reach the transition between segments 7 and 1, at a level on the right of the hepatoduodenal ligament (**Figure 9**). This maneuver can be made more challenging

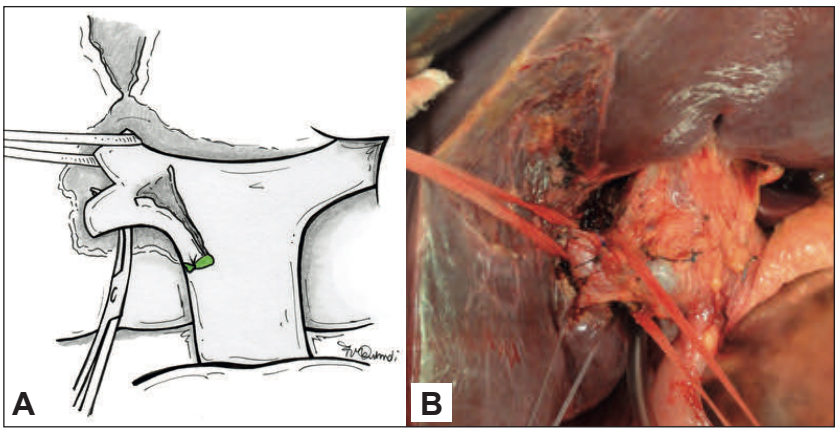


Figure 9. Glissonean approach to right liver pedicles. The hilar plate is lowered and the hepatic parenchyma separated from it. The separation of hepatic parenchyma from the connective tissue is followed until identification of right and middle Takasaki's segment pedicles. **A**) The middle segment pedicle is easily encircled using a blunt clamp. The right Takasaki's segment pedicle is showed being encircled. **B**) Surgical aspect showing the right Takasaki's pedicle encircled by a silicone tube and the middle one encircled by an umbilical tape (pulled upward). The right hemiliver pedicle is encircled by another umbilical tape (pulled downward).

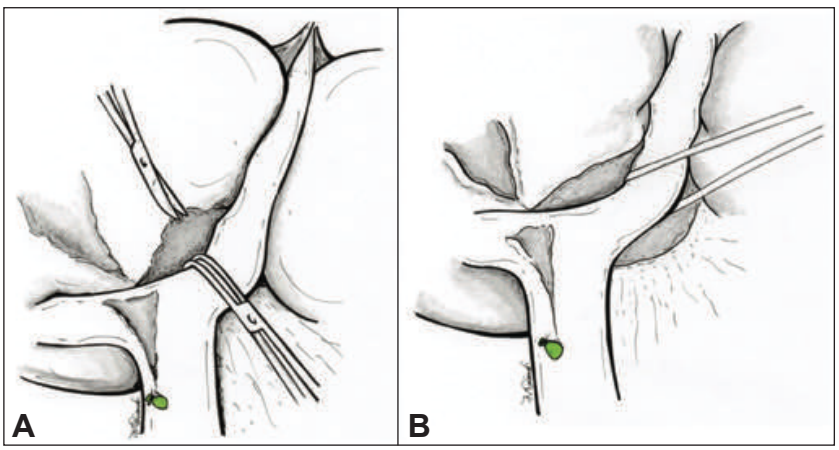


Figure 10. Glissonean approach to left liver. A) The hilar plate is lowered. B) After section of the Arantius's ligament (optional), a blunt clamp is used to dissect the pedicle of the left hemiliver (Left Takasaki's segment).

by the presence of a tertiary order pedicle originating from the posterior aspect of the hepatic hilum.

Control of the right anterior pedicle (Takasaki's middle branch) is possible by introducing a right-angled clamp in the superior aspect of the hilar plate, passing posteriorly to the right anterior pedicle to reach the right side of cystic plate (**Figure 9**). Encircling the right posterior pedicle is more easily performed by a two-step maneuver: First, an umbilical tape is used to encircle the whole right liver pedicles. Second, the right anterior pedicle is encircled from right to left and the end of the umbilical tape is retrieved to exclude the right anterior pedicle from the loop. For a right hepatectomy, both the right anterior and right posterior sectoral branches can be controlled and sectioned together, or they can be sectioned separately to prevent injury to the left branches. Running sutures or vascular staplers can be used. During positioning of clamps or staplers, an umbilical tape is used to retract the hilum away from the section plane.

Both the Glissonean and the intrafascial approaches have also been used for laparoscopic liver resections. Dissection of the three main secondary order Glissonean branches can be performed using the same technique used with open surgery. A simplified method using endovascular stapler and minimal parenchymal dissection was described for right segmental resections, and it is useful for both open and laparoscopic resections. Three small incisions around the hilar plate (one on segment 4, above the hilar plate, another on the right edge of the gallbladder, and another posteriorly on segment 7) are used to introduce vascular staplers including the right and/or middle Takasaki segments (**Figure 11**).[1] A similar method is used for left resections. The Arantius ligament is divided and retracted to facilitate the encircling of left segment pedicle.[25,26]

Couinaud's segment 4, similar to the left lobe (segments 2/3), does not have an individual Glissonean segmental branch. Thus, resection of segment 4, or segments 2/3, usually requires dissection and ligature of multiple branches.

For segmental resections (Takasaki's tertiary branches) of the right and middle Takasaki segments using a Glissonean approach, first the secondary branch (right or middle, respectively) is taped and pulled away from the liver. Then, the pedicle is progressively peeled away from the liver parenchyma and the bases of tertiary branches became visible. Parenchymal incision is required if the secondary branch has a long trunk or is deep. For segmental resections of the left Takasaki segment, the round ligament is pulled upward to expose the left secondary branch (when present, the umbilical bridge of liver parenchyma is sectioned).

OUTFLOW VASCULAR CONTROL

Methods to reduce bleeding through the hepatic venous system (outflow) include non-surgical procedures, such as the use of low central venous pressure (CVP). When a low CVP (<5 mmHg) is not reached by ordinary measures, i.e. pharmacologically or by fluid restriction, clamping (partial or complete) of the infrahepatic inferior vena cava (IVC) is effective in reducing blood loss due to venous backflow during hepatectomy.[27]

Occlusion of the hepatic veins to be resected together with the hepatic specimen is generally the last step of the liver resection. The occlusion and division of the hepatic veins after the parenchymal section allows for the maintenance of adequate outflow during the procedure, and helps to avoid hepatic congestion. Control and occlusion of hepatic veins before parenchymal transection can be used to reduce the bleeding resulting from venous backflow; however, complete blood inflow for the segments drained by the vein to be occluded must also be stopped.

Classical total vascular exclusion (TVE) of the liver is obtained clamping the inflow and outflow by using Pringle maneuver, and suprahepatic and infrahepatic IVC clamping. Also, TVE of the liver can be performed without IVC occlusion, by clamping blood inflow structures (arterial and portal) and the hepatic veins. In this situation, all direct branches from the liver to the IVC should be ligated before TVE. The main technical aspects of vascular outflow control are described below.

Infrahepatic IVC clamping

The infrahepatic IVC is easily encircled above the renal veins. The hepatoduodenal ligament is pulled to the right and the peritoneal reflection between the liver and IVC is sectioned. Careful blunt dissection is performed on each side of the IVC and it is encircled using umbilical tape. Partial or total occlusion can be done by vascular clamp or tourniquet application.

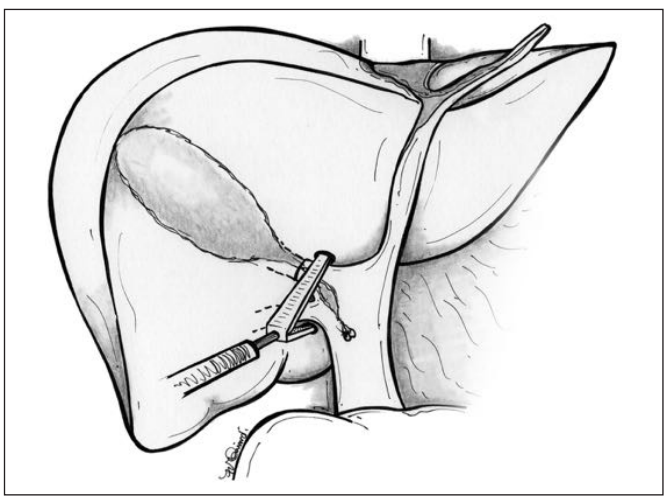


Figure 11. Glissonean approach for right resections using small parenchymal incisions. Vascular stapler is introduced comprising a combination of two incisions according to sections to be resected. (Adapted from Machado et al.[25])

Hepatic vein control

Hepatic veins can be controlled extrahepatically or within the liver during the parenchymal transection. The extrahepatic control of hepatic veins can be necessary, especially in case of tumors close to hepatic veins and the IVC. Central venous pressure should be less than 5 mmHg. The patient is placed in a 15-degree Trendelenburg position to prevent air embolism. Thoracic-abdominal incision allows for the best exposure of the suprahepatic IVC, and hepatic veins and should be used in some cases of large tumors at the junction of the hepatic veins and the vena cava.

Extrahepatic control of the right hepatic vein

After mobilization of the liver by section of the falciform ligament and right and left triangular ligaments, the liver is turned to the left to expose the retrohepatic IVC (**Figure 7**). The filamentous fibrous tissue covering the suprahepatic IVC (between the diaphragm and the liver) is opened, and dissection downward is performed between the right hepatic vein and the common left/middle hepatic veins trunk, making contact with the anterior wall of the IVC. The vena cava ligament (Makuuchi's ligament) is divided to complete exposition of the lateral aspect of the IVC. The short retrohepatic veins are ligated and sectioned (large accessory hepatic veins could need clamping and running sutures) to free the anterior aspect of the IVC (**Figure 7**). A blunt dissector or clamp is then used to carefully encircle the right hepatic vein from below in an upward direction to join the previously dissected space between right and middle hepatic veins. A vascular stapler can be used alternatively to clamping and section followed by running suture for definitive control of the right hepatic vein (**Figure 12**).

Extrahepatic control of the left and middle hepatic veins

The falciform ligament and left triangular ligament are sectioned. Section of the falciform ligament exposes the upper surface of the left and middle hepatic veins. The leaves of the left triangular ligament separate close to the left hepatic vein. The left lobe is then turned anteriorly and to the right. The gastrohepatic ligament (lesser omentum) is sectioned and the ligamentum venosum (Arantius ligament) exposed. It runs between the caudate lobe and segments 2 and 3, from the left portal vein to the left hepatic vein (**Figure 13**). This ligament is sectioned close to its fixation in the left hepatic vein. Subsequently, dissection is performed in contact with the anterior surface of the vena cava, creating a tunnel from the left to the right up to the previously created space between the right and middle hepatic veins. This maneuver results in encircling of the common trunk of middle/left hepatic veins. Sometimes, the section of the left diaphragmatic vein enables better exposure of the extrahepatic portion of the left hepatic vein. More proximal dissection (close to the liver parenchyma) of the common trunk permits control of the left hepatic vein alone. To control only the middle hepatic vein, first a tape is used to encircle the common trunk, and subsequently the left-side end of the tape is retrieved by forceps introduced beneath the left hepatic vein from the right to the left. Occasionally, the left and the middle hepatic veins drain separately into the IVC.

Total vascular exclusion of the liver is discussed in another topic in this chapter.

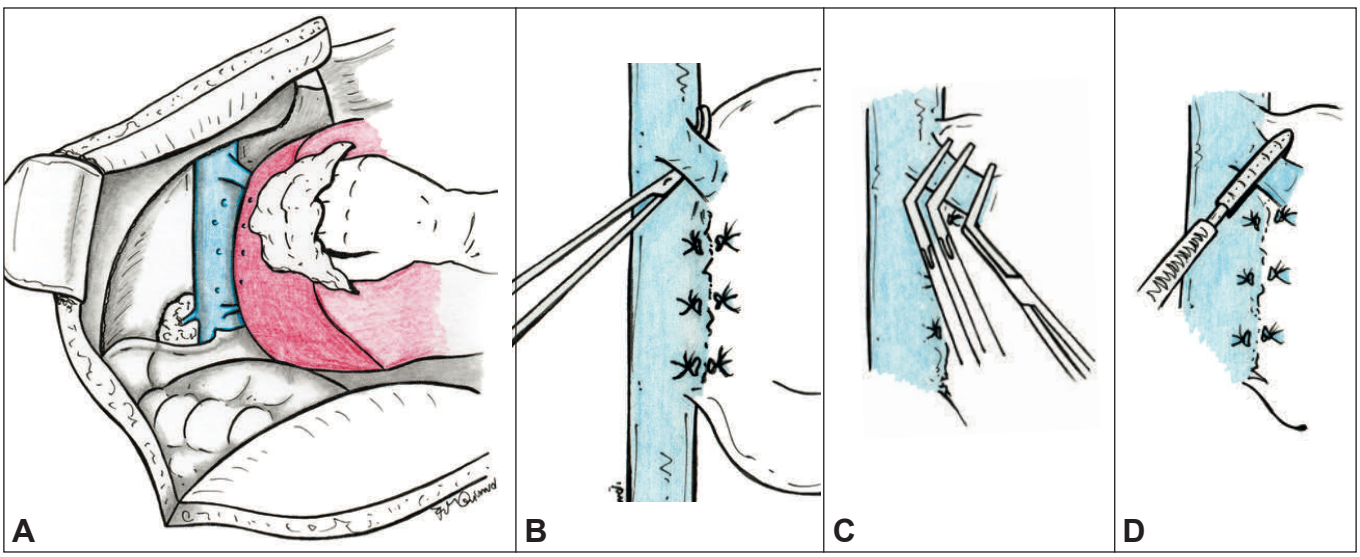


Figure 12. Extrahepatic control of the right hepatic vein. **A** and **B**) After mobilization of the liver and section of the vena cava ligament a clamp is carefully used to progressively create a tunnel beginning on the anterior aspect of IVC below the debouchment of the right hepatic vein and ending in a space previously create between the right hepatic vein and the trunk of middle/left hepatic veins. **C**) extrahepatic clamping before section and suture of right hepatic vein. **D**) Alternatively a vascular stapler can be used to section of right hepatic vein.

PARENCHYMAL TRANSECTION

Since perioperative blood loss and blood transfusion are factors that are predictive of postoperative complications, liver transection is one of the most important steps during hepatectomy. Many different methods have been put forward in order to reduce excessive bleeding during parenchymal transection. This chapter summarizes methods for liver transection and treatment of the cross section. The many options to avoid bleeding and heterologous blood transfusion in hepatic resections are discussed in **Chapter 9** (Morbidity and Mortality after Liver Surgery) and in **Chapter 23** (Vascular Control and Parenchymal Transection Techniques).

METHODS FOR PARENCHYMAL TRANSECTION

The main goal during liver transection is to divide the hepatic parenchyma with minimal bleeding. For this purpose, many techniques and devices have been tested. Frequently, one device is used to divide the parenchyma (such as the clamp-crush technique, ultrasonic dissector, or water jet) and another to accomplish the hemostasis. The visualization of intraparenchymal vessels and their control prior to division leads to a reduction in blood loss. Hemostasis of small vessels (less than 3 mm in diameter) can be achieved by thermocoagulation, ties, or surgical clips. Larger vessels and biliary branches usually require other methods, such as suture ligatures or vascular staplers. Among the several methods available for parenchymal transection, none of them has been demonstrated to be more effective than the others. The combined use of available methods seems to be an adequate option, taking into account the characteristics of each device and the skills and features of the surgeon.[28–30] Detailed description of transection methods can be found in **Chapter 23** (Vascular Control and Parenchymal Transection Techniques).

Knowledge of the intrahepatic anatomy helps the surgeon during hepatic transection (**Figure 14**). Intraoperative ultrasound provides information about the main structures to be sectioned during transection.

In cirrhotic patients, parenchymal transection can be a more challenging step during liver resection. The firmness of the liver substance prevents the destruction of the parenchyma with preservation of the vascular and biliary structures, and the clamp-crush technique may not work adequately. In this case, the use of devices that coagulate while transecting may be useful.

TREATMENT OF THE LIVER CROSS SECTION

Omentoplasty. Apposition of the greater omentum to the liver cross-section area was used in the past for reduce bleeding. However, following the development of modern techniques of anesthesia and parenchymal transection, omentoplasty is no longer recommended with this goal in mind.[31] Some authors suggest using it after left liver resections to avoid gastroparesia due to adhesions between the stomach and the raw surface of the liver.

Topical sealants. A variety of topic sealants have been used over the raw surface of the liver after hepatectomy.

Collagen (the main component of extracellular matrix) has been used in several formulations (sponges, compresses, powder). It is applied on the raw surface of the liver serving as

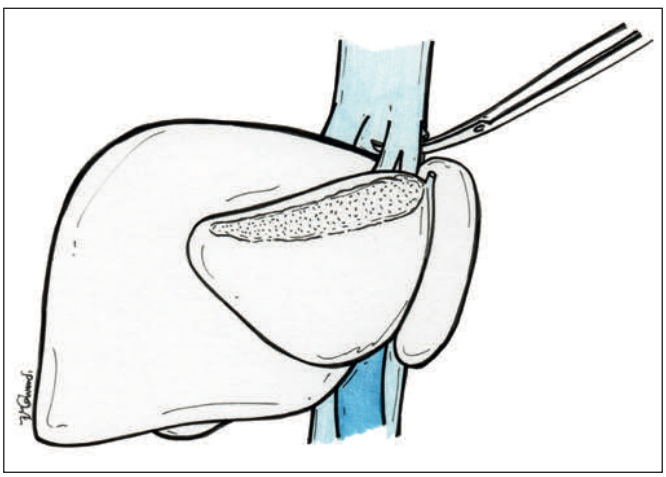


Figure 13. Extrahepatic approach and dissection of the left and middle hepatic veins. The left lobe of the liver is completely mobilized after section of the falciform and left triangular ligaments. The Arantius' ligament is divided allowing the exposure of the window between the IVC and the left hepatic vein. The common trunk (left and middle hepatic veins) or the left hepatic vein can be easily controlled.

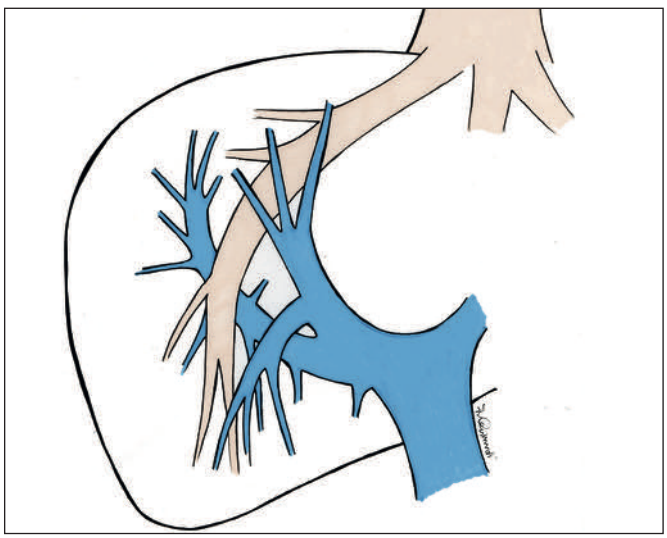


Figure 14. The relative position of the hepatic veins and Glissonean pedicles in the right liver. In the upper part of the liver most of Glissonean pedicle branches intersect those of the hepatic veins, while in the lower part almost all branches run parallel to the hepatic veins.

a matrix for the formation of the platelet clot. Its hemostatic mechanism is based on the mechanical adhesive effect.[32,33]

Products derived from fibrin and fibrinogen have been used as topical hemostatic agents in liver surgery by reproducing hemostatic biological mechanisms. Many products are available with different combinations of composition (such as thrombin, thrombin + fibrinogen, thrombin + collagen, or thrombin + collagen + fibrinogen) and formulation (such as glue, compress, or sponge), but with the same goal: optimal platelet adhesion and clot formation.

Results regarding the use of these products to avoid intraoperative blood loss and/or postoperative complications are controversial.[34–38] The use of fibrin derivative combinations has also been reported to reduce postoperative biliary leak.[39,40]

Biliary control. The incidence of biliary complications after major hepatectomy remains elevated, reaching 10%. Biliostasis of large biliary ducts on the cross-section plane is usually obtained by suture ligation or surgical clips. Ischemia and necrosis on the surface of cross section could be sources of postoperative biliary leakage, resulting in biliary fistulae or biloma. However, the method used for parenchymal transection does not seem to affect the occurrence of bile leakage.

A variety of intraoperative tests have been used to identify and treat bile leaks during liver resections. However, despite their efficacy in identifying intraoperative leakage, the postoperative clinical impact is inconclusive. In fact, most bile leaks originating from the parenchyma surface resolve spontaneously or after non-surgical procedures. Despite that, all bile leaks identified intraoperatively should be treated. Methods for intraoperative detection of bile leakage and biliostasis vary from simple procedures, such as keeping gauze in contact with the section surface for several moments and observing the presence of yellow dyed areas, to more complex procedures demanding specific apparatus, such as indocyanine green fluorescence cholangiography.

Formal intraoperative cholangiography has no impact on the clinical incidence of postoperative biliary leakage; however, it can be useful to verify biliary anatomy and biliary permeability of the remnant liver. Another simple method to verify the continuity between the intrahepatic biliary tree of the remnant liver and the common bile duct is the injection of air through the cystic duct stump during intraoperative hepatic ultrasound. The occurrence of artifacts inside the parenchyma tissue confirms continuity between the main bile duct and intrahepatic biliary tree.

ANTERIOR APPROACH AND HANGING MANEUVER

The anterior approach consists of initial vascular inflow control and parenchymal transection without prior mobilization of the liver.[41,42] The potential advantages of this approach are i) the reduction of intraoperative blood loss and transfusion requirements (more easy liver mobilization after transection), ii) probably diminished tumor cell dissemination (the "no touch" technique), iii) reduction of postoperative liver failure (avoidance of pedicle torsion and mechanical compression of the remnant liver), and iv) reduced risk of bacterial translocation into the bloodstream in case of cholangitis or pyogenic abscesses. However, bleeding control in the deeper parenchymal plane can be difficult.

The "liver hanging maneuver" was initially described as a procedure in which the liver was lifted by a tape passed between the anterior surface of the vena cava and the liver. After the initial description of the hanging maneuver for right hepatectomy, many variants were developed for application in most anatomical hepatic resections. This maneuver provides effective vascular control, making the anterior approach safer and easier.[43,44]

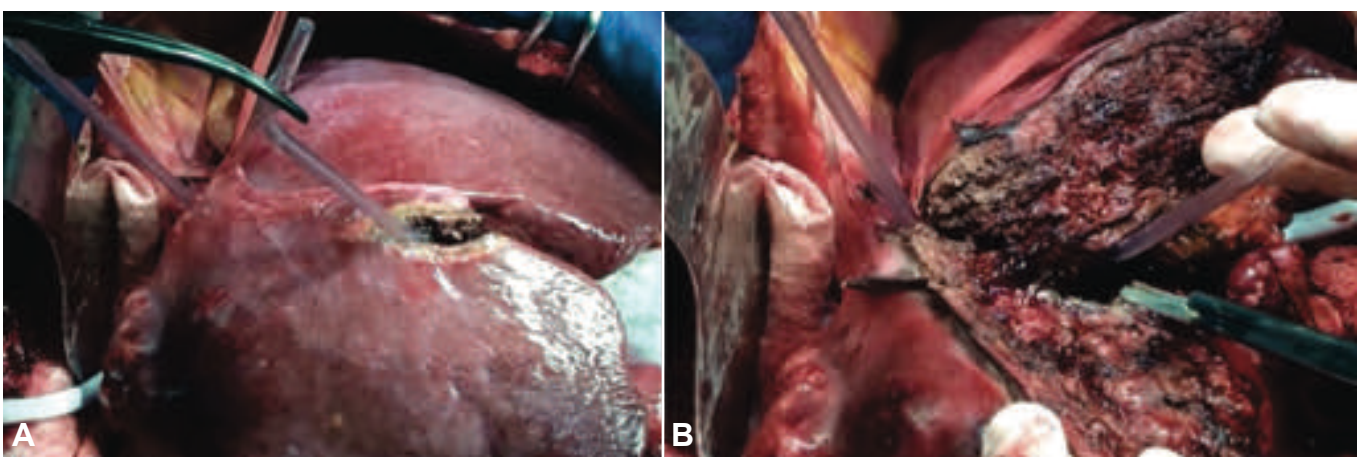


Figure 15. Use of liver-hanging maneuver during a right trisectionectomy. **A**) The nasogastric tube guide the plan of transection and **B**) it is used to upward traction to reduce bleeding and to facilitate the cross section exposition.

For resections in which the parenchymal transection reaches the anterior surface of the IVC, the first step is to create a tunnel between the anterior surface of the IVC and the liver. The hepatoduodenal ligament is retracted to the left, and the inferior aspect of hepatic segment 1 is lifted from the IVC. The anterior aspect of the IVC is dissected and the short hepatic veins are ligated and divided. This dissection is extended upward until it can be performed under direct visualization to minimize the length of the blind dissection of the next steps. Afterward, the anterior aspect of the suprahepatic IVC is exposed and an "up to down" dissection of the space between the right and the middle hepatic veins is performed. This dissection is done for 2-3 cm along a right oblique axis and making contact with the IVC. The next step is usually a blind dissection, where the retrohepatic tunnel between the previously dissected spaces in the infrahepatic and suprahepatic IVC is created. This blind dissection can be performed "down to up" using a blunt curvilinear instrument (such as a Debakey aortic clamp or Kelly forceps), or "up to down" introducing a nasogastric tube that is pushed downward. Alternatively, retrohepatic dissection can be guided by intraoperative ultrasound,[45] or it can even be performed by direct visualization using endoscope or laparoscope.[46] Through the retrohepatic tunnel a nasogastric tube (or an umbilical tape) is placed for continuous upward traction during parenchymal transection.[43] This strategy enables continuous guidance for the correct cross-section plane and provides control of backflow bleeding on the cross section (**Figure 15**).

The liver hanging maneuver can be applied in a variety of anatomical liver resections. Depending on of the type of resection required, the nasogastric tube is positioned along the anterior surface of the IVC or along the ligamentum venosum (Arantius ligament). The upper end of the nasogastric tube can be repositioned between the middle and the left hepatic veins. The lower end can be placed behind one or two of the Glissonean pedicles. However, more than one tube can be used for central resections. The many possible combinations according to the position along the precaval space or along the Arantius ligament, and the placement of the upper and the lower ends of the tube(s), define different planes of parenchymal transection, as illustrated in **Figures 16** and **17**. These planes are used for different anatomical hepatic resections. For central hepatic resections, the combination of two hanging maneuvers can be used to determinate each plane of section. Guidance for caudate lobe resection alone is possible by positioning the tube along the precaval space, the upper end passing behind the common trunk of the middle/left hepatic veins, and finally along the Arantius ligament.

The main limitation factor for the liver hanging maneuver is the presence of adhesions between the IVC and the liver. On the other hand, this is a particular indication for anterior approach (**Figure 18**). Conditions such as cirrhosis; large tumors; direct tumor invasion of major hepatic veins, diaphragm, or retroperitoneum; contact of the tumor with the IVC; and preoperative transarterial chemoembolization and/or portal vein embolization are not contraindications to the liver hanging maneuver.[47,48]

TOTAL VASCULAR EXCLUSION OF THE LIVER and HYPOTHERMIA

Some hepatic tumors are difficult to resect, or demand associated vascular resections and reconstructions. The use of total vascular exclusion, as initially described by Huguet et al.,[49] enables this kind of resection. The technique consists of complete occlusion of vascular inflow (arterial and portal) and outflow (generally controlling the IVC above and below the liver). This technique allows for very effective control of bleeding. However, TVE of the liver is less tolerated than inflow occlusion alone, probably due to the stoppage of blood backflow by the hepatic veins. A liver with no underlying liver disease is capable of tolerating continuous total normothermic ischemia for as long as one hour. Also, temporary occlusion of the IVC can cause hemodynamic instability (reduction of cardiac output coupled with increased systemic vascular resistance), and the release of toxic substances accumulated during ischemia can result

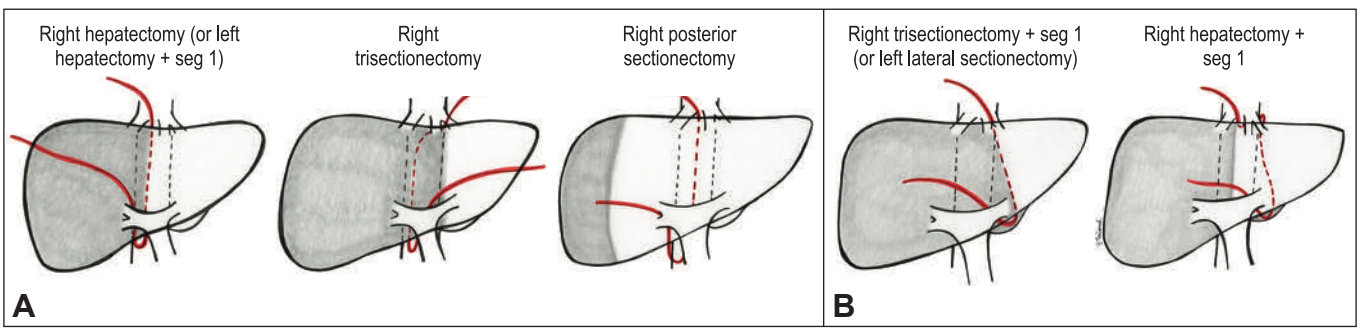


Figure 16. Various techniques for liver resection with hanging maneuver using a single tube. **A**) Tube along the anterior surface of the inferior vena cava. **B**) Tube along the Arantius' ligament. Adapted from Liddo et al.

in severe injury by ischemia-reperfusion syndrome. Thus, TVE is used almost exclusively in cases of hepatectomy associated with hepatic veins or IVC reconstruction. In most other cases, inflow vascular clamping (continuous or intermittent) and low central venous pressure anesthesia are sufficient means of controlling bleeding. Strategies to minimize parenchymal injury during TVE or during inflow control of the liver include preconditioning, hypothermia, and perfusion with cold organ preservation solutions. To overcome hemodynamic instability, a venovenous bypass may be installed to drain the splanchnic blood into the systemic circulation.

Hypothermia may reduce the ischemic injury to the remnant liver, being particularly useful in patients with underlying chronic liver disease. Reduction of the liver temperature is usually obtained by vascular infusion of cool solution (through the portal vein during hepatic vascular exclusion) or by topical hypothermia on the liver surface (with ice pack or ice slush under inflow vascular control or TVE).[50–54]

Inflow control for TVE of the liver is obtained by Pringle maneuver or by separate arterial and portal clamping. It is crucial to identify and control any anomalous arterial branch to the liver, such as an accessory left artery originating from the left gastric artery and running through the hepatogastric ligament. Outflow occlusion is classically obtained by control of the IVC above the hepatic veins (between the diaphragm and the liver) superiorly, and above the renal veins inferiorly. If the IVC is clamped inferiorly below the right adrenal vein, it should be identified and ligated. The persistent entry of blood flow into the liver (resulting from pathological retrohepatic vessels in case of tumor adhesions, or even from inadequate occlusion of clamped vessels) results in progressive congestion of the liver and hemodynamic intolerance.[14]

Alternatively, TVE can be achieved with no IVC occlusion. In this case, outflow occlusion is achieved by clamping the hepatic veins, and all short veins that drain directly to the IVC must be ligated (vascular exclusion with caval flow preservation). This technique is hemodynamically well tolerated.

Also, it is possible to obtain a total caval clamping with total vascular exclusion of the hepatic segments to be resected, but preserving the perfusion of the remnant liver (selective total vascular exclusion).[55] This approach is mainly used for right side hepatectomy combined with vena cava resection; in this case, the inflow and outflow of the remnant liver is preserved by selective hilar clamping and oblique occlusion of the suprahepatic inferior vena cava, keeping the left hepatic vein (or the common trunk) out from the clamping. This method, such as the vascular exclusion with caval flow preservation, avoids the use of venovenous bypass, since the blood flow through the left liver reduce splanchnic congestion and hemodynamic variations.

Venovenous bypass (**Figure 19**) has been used to prevent some of the drawbacks of normothermic total vascular occlusion, such as hemodynamic intolerance and splanchnic congestion, which are at least partially responsible for ischemia-reperfusion syndrome. The safe time limit of liver tolerance to total vascular exclusion with venovenous bypass seems to be up to roughly 120 minutes.[56] Venovenous bypass consists of carrying, by the bio-pump, the blood from the portal vein and inferior vena cava to the superior vena cava system. The internal jugular vein and femoral vein are cannulated percutaneously or by surgical dissection. Another cannula is placed into the superior mesenteric vein, inserted

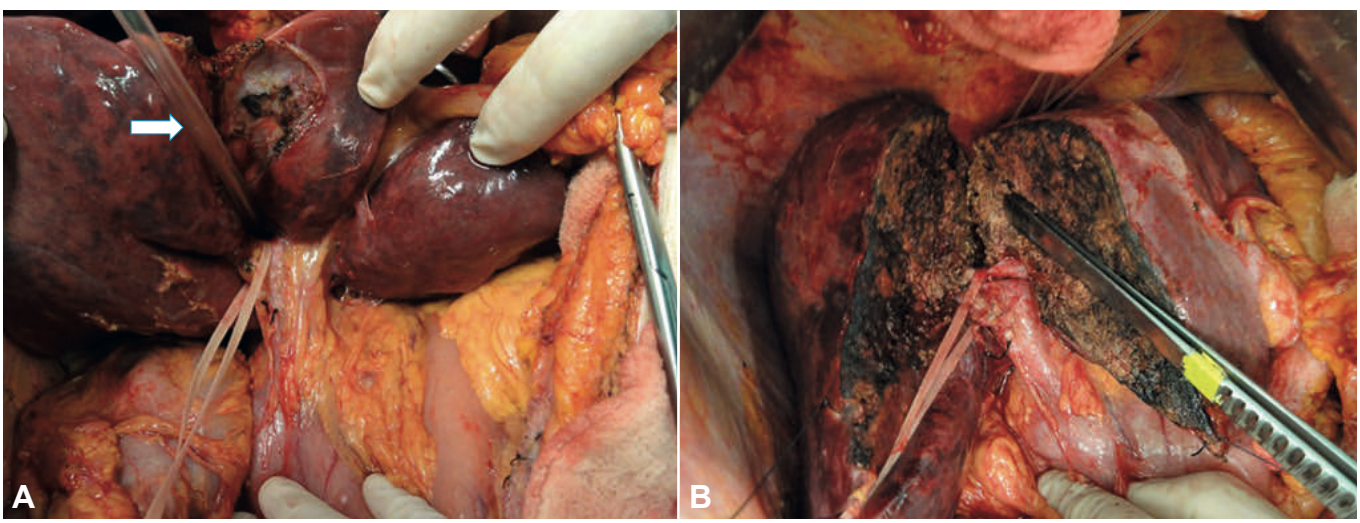


Figure 17. Right hepatectomy using hanging maneuver and Glissonean approach. **A**) After encircling of the right hepatic pedicle (umbilical tape) the tube used for the hanging maneuver (arrow) is repositioned to not include the portal pedicle. **B**) This maneuver facilitates the parenchymal transection before section of portal pedicle.

through the portal vein. Thus, after clamping of the inflow (arterial and portal) and the outflow (infrahepatic IVC and suprahepatic IVC), the bypass is started, gathering blood from the splanchnic system and IVC territories and carrying it to the superior vena cava system.

Hypothermic perfusion and topical hypothermia

Liver resections requiring complex reconstruction of hepatic venous outflow and a long time of total vascular exclusion may benefit from techniques of hypothermic perfusion of the liver and topical hypothermia. With the use of hypothermia and organ preservation solutions, tolerance to the ischemic phase can be extended to four hours, allowing for complex resections and reconstructions by *in situ*, *ante situm*, or even *ex-vivo* (*ex-situ*) procedures. Total vascular exclusion of the liver is a condition to apply hypothermic perfusion.[57]

In situ hypothermic perfusion refers to the cold perfusion of the liver through the portal vein, and the liver resection is performed through standard techniques. ***Ante situm*** liver surgery refers to the division of the suprahepatic IVC and the rotation of the liver forward to allow access to the retrohepatic vena cava and hepatic vein confluence. ***Ex situ*** resection comprises the complete removal of the liver from the body and perfusion with cold preservation solution on a back table.

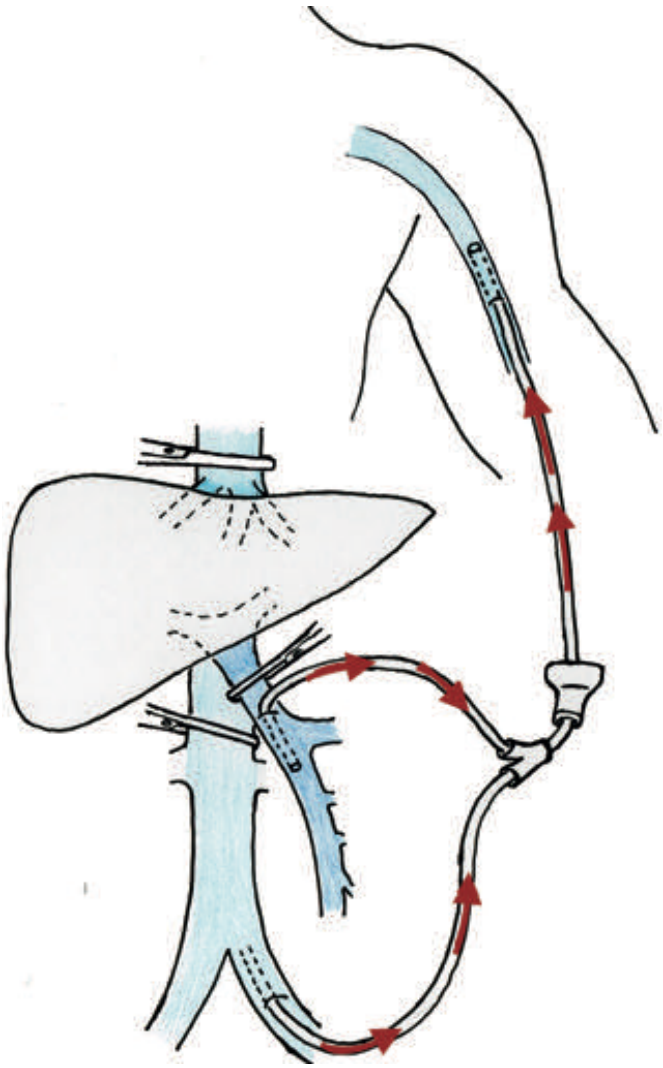


Figure 18. Venovenous bypass. The blood from the portal vein and inferior vena cava is carry, by the bio-pump, to the superior vena cava system.

Usually, the perfusion of cold preservation solution is through a cannula placed into the portal vein of the side to be resected and directed into the contralateral portal vein (side to be preserved) to avoid subsequently portal vein repair, or optionally into the main portal vein. Cold (4° C) standard organ preservation solutions, such as University of Wisconsin (UW) solution or histidine-tryptophan-ketoglutarate (HTK), can be used. The resection is completed in a bloodless field. Before vascular anastomotic completion, the liver is flushed with 5% albumin or ringer lactate solution, and then the blood inflow and outflow are reestablished.

In situ and ***ante situm*** hypothermic perfusion techniques have been associated with acceptable mortality rates of less than 10% in many centers. *In situ* perfusion requires standard liver mobilization and total vascular exclusion techniques. A cannula into the portal vein is used to perfusion of cold solution and a cava venotomy made to discharge. Optionally, the liver can be cooled by superficial application of ice. This technique can be used additionally to cold perfusion or eventually alone. For the *ante situm* technique the division of the suprahepatic IVC is added to allow mobilization of the liver, which remains connected by the hepatic pedicle. The advantage is a generous access to hepatic veins confluence and retrohepatic IVC with the necessity of only one vascular anastomosis (cavo-caval anastomosis).

In situ hypothermic perfusion can be used when a single hepatic vein or the IVC requires reconstruction. In general, most parenchymal transections can be performed before the total vascular occlusion and the hypothermic perfusion applied only during vascular resection and reconstruction.

Ante situm liver resections (*in vivo* hypothermic perfusion and venovenous bypass) were first described by Hannoun et al.,[58] and this method is useful for patients with large liver tumors that invade all three hepatic veins at the hepatic venous confluence, and reconstruction of hepatic veins is necessary.[58–60]

Ex situ liver resection with hypothermic perfusion is a high mortality surgery (up to 30%).[53] This procedure was developed by Pichlmayr et al.[61] and a venovenous bypass is required. The portal vein is dissected and sectioned below its bifurcation; the proper hepatic artery is divided at the level of its origin (in the junction with the gastroduodenal artery). The suprahepatic and infrahepatic IVC are clamped and transected, and the liver removed. Optionally the liver can be removed with preservation of the IVC, in cases of

involvement of all hepatic veins but with no involvement of the IVC. In this case a temporary portocaval shunt is used to prevent splanchnic congestion.

Topical hypothermia requires inflow vascular control. The temperature of the remnant liver is decreased to 20-28° Celsius by application of ice packs or slush on the liver surface.

LYMPHADENECTOMY AND BILIARY RESECTION

The role and extent of a **lymphadenectomy** concurrently with a hepatectomy for malignant tumors of the liver are controversial. Most superficial and deep lymphatics of the liver drain into lymph nodes at the hepatic hilum and gastrohepatic omentum, and then enter the abdominal/retroperitoneal lymphatic system. Only superficial lymphatics from the convex surface of the liver run along the hepato-caval confluence, reaching the mediastinal lymphatic system.[62] Lymphadenectomy could be limited to hepatoduodenal ligament (more frequent site of lymph node metastases) and pancreaticoduodenal region, or it can be extended up to celiac axis or para-aortic lymph nodes.[63–66] Extended lymphadenectomy seems useful in selected cases of hilar cholangiocarcinoma. Regional lymphadenectomy for some primary and metastatic liver tumors could provide prognostic data, assist selection of patients for adjuvant therapy, and even improve survival in patients with limited nodal involvement. Detailed indications for and extension of lymphadenectomy are discussed in the pertinent chapters.

Extended **biliary resection** is part of the curative surgical treatment of hilar cholangiocarcinoma and some cases of gallbladder cancer. Habitually, resection of caudate lobe is added due to the early tumoral extension to bile ducts from this segment.

Lymphadenectomy combined with biliary resection

The distal common bile duct is dissected and sectioned close to the upper margin of the head pancreas. If a more extended resection of the distal bile duct is indicated, the posterior superior pancreatoduodenal artery should be divided to allow the pursuit and section of the bile duct into the head of the pancreas. The skeletonization of the hepatoduodenal ligament begins with the dissection of the lymph nodes behind the portal vein. The main portal vein is encircled in the lower portion of the hepatoduodenal ligament and the common hepatic artery is also identified and encircled at this level. The vascular skeletonization is then advanced up to the hepatic hilum. All structures and tissues except the portal vein and hepatic artery are resected. The upper limit of resection depends of the type of liver resection to be performed (**Figure 20**). Biliary reconstruction is usually by hepaticojejunal anastomosis with Roux-en-Y limb.

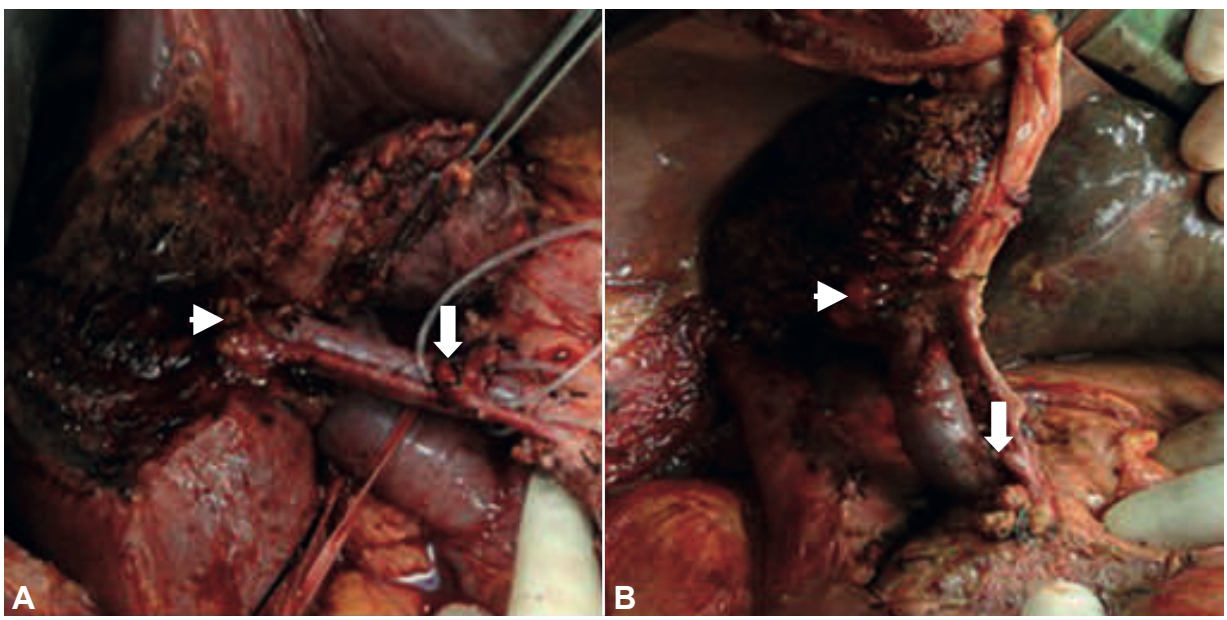


Figure 19. Surgical aspect of hilar vascular skeletonization. **A**) During an anterior hepatectomy for cholangiocarcinoma. Arrow shows the stump of the sectioned left hepatic artery. Arrowhead indicates the opened right posterior bile duct. Note the inferior vena cava encircled by an umbilical tape posteriorly. **B**) During a right extended trisectionectomy for hilar cholangiocarcinoma. Arrow shows right hepatic artery sectioned close its origin. Arrowhead indicates the opened left bile duct. Note the round ligament pulled upward and the complete resection of segment 1.

VASCULAR RESECTION AND RECONSTRUCTION

Resection of **major vessels** during hepatectomy can represent a valuable therapeutic option in selected cases. Surgical techniques in hepatobiliary surgery have evolved and the reconstruction of hepatic vessels can be performed with acceptable morbidity and mortality. Malignant involvement of major vessels is associated with poor prognosis; however, an aggressive surgical approach can represent the only potential of long-term survival. Thus, major vascular resection to achieve a R0 resection can expand the role of liver resection in selected cases of primary and metastatic liver tumors, and hilar cholangiocarcinoma.[55,67–74]

ARTERIAL RESECTION AND RECONSTRUCTION

If arterial resection is needed, reconstruction can be performed before the complete tumor resection, to avoid long hepatic ischemia of the remnant parenchyma. The hepatic artery to be revascularizated (left or right hepatic artery) should be dissected distally to the tumor level and encircled. If the length between the two stumps to be anastomosed is short a primary direct anastomosis is possible. The resected segment can also be replaced by an arterial or venous homologous graft, or by a synthetic graft. Also, arterial supply can be obtained by the displacement of arterial branches, such as the use of the splenic artery (after distal section) to anastomose with right or left hepatic artery.

In some rare situations, when an arterial reconstruction is not possible, an arterioportal shunt (portal arterialization) could help to avoid biliary ischemia by increasing the oxygenation of the portal vein. This procedure can be accomplished by an anastomosis between an arterial branch (such as splenic artery or proper hepatic artery) and the portal vein. However, an excessive arterial flow into the portal circulation can lead to portal hypertension. Thus, various techniques of portal arterialization have been reported to avoid excessive portal hypertension, such as mesenteric arterial branch (up to 3 mm in diameter) anastomosis with mesenteric venous branch.

HEPATIC VEINS AND IVC RESECTION AND RECONSTRUCTION

Minor tumor extension compromising the IVC (narrowing of less than 30%, length less than 2 cm) can be resected by using a laterally positioned vascular clamp, while maintaining or not maintaining a partial flow through the IVC (**Figure 21**). For more extensive compromising of the IVC, a total flow occlusion is needed. Partial IVC resection can be followed by *primary repair* (if it results in a narrowing of no more than 50% of the IVC diameter). If the defect is larger than can be repaired primarily, a *patch* (of autologous veins, bovine pericardium, parietal peritoneum, or Gore-Tex) can be used. After resection of a segment of IVC, a primary end-to-end can be performed or the resected segment can be replaced using an *interposition graft* (Gore-Tex or autologous grafts) (**Figure 22**).

Large tumors or those compromising a high segment of the IVC (near the debouchment of the hepatic veins) usually require total vascular exclusion of the liver. If the tumor spares the debouchment of at least one of the hepatic veins it is possible place the clamps on the IVC preserving the flow of the hepatic vein to be preserved. Thus, resection

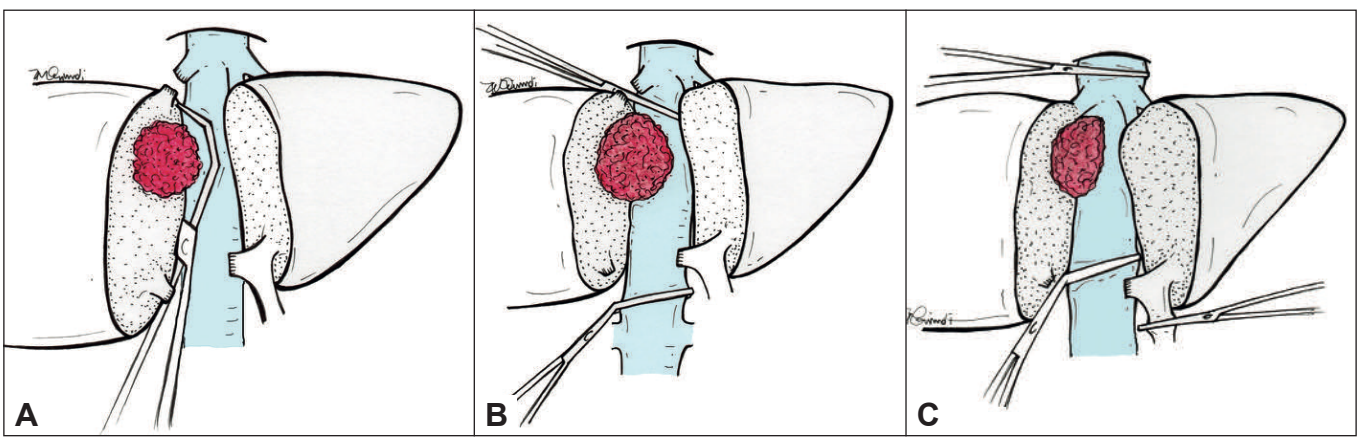


Figure 20. Hepatectomy combined to inferior vena cava (IVC) resection. **A**) Lateral clamping of the IVC after right portal pedicle and right hepatic vein section and parenchymal transection. Useful for tumors compromising up to 30% of the IVC. **B**) Total clamping of the suprahepatic IVC, but keeping the flow through the common trunk (left/middle hepatic veins), and the infrahepatic IVC. Useful for tumors close to the debouchment of the right hepatic vein. Figure shows the right portal pedicle sectioned and the parenchyma partially transected. Note that the blood flow through the remnant liver is kept. **C**) Total vascular exclusion of the liver; the suprahepatic and infrahepatic IVC is clamped together with the portal pedicle. Useful for tumors compromising the debouchment of the right hepatic vein.

can be performed with continued perfusion of the liver and reduced hepatic ischemic time.

Hepatic vein reconstruction

Hepatic vein reconstruction is usually indicated in extended resection with compromise of the third hepatic vein, or when the best outflow possible is required to optimize remnant liver function (**Figure 23**).

The technique for vascular reconstruction depends on the extent of vascular resection. Hepatic veins transected close to the IVC can be directly reimplanted. When multiple hepatic vein orifices are present a variety of reconstruction techniques are possible, including use of grafts and/or transformation of various orifices in only one to be reimplanted. The IVC can be replaced by artificial graft or by an autologous graft made from other veins or peritoneum. If the hepatic veins cannot be anastomosed to the native vena cava, they can be implanted on triangle aperture on the graft.

In cases of resection of segments 7 and/or 8 requiring resection of the right hepatic vein, the short hepatic veins draining directly to the IVC should be preserved to prevent congestion of the remnant segments.

Generally, the hepatic veins can be controlled extrahepatically. For reconstruction of the right hepatic vein, its distal extremity should be skeletonized for a distance of 1 cm to achieve enough space to the placement of a vascular clamp in the caval side. The proximal side of the right vein is identified, controlled and divided intrahepatically during the parenchymal division. Resection and reconstruction of left hepatic vein is similar. In cases where resection of all the three hepatic veins is necessary, the liver is usually completely mobilized off of the vena cava.

The reconstruction after resection of a hepatic vein segment can be by primary anastomosis (if the proximal stump is close to the distal stump) or by graft interposition. In the primary reconstruction the implantation of the proximal stump of the hepatic vein can be done on the distal stump or it can be reimplanted lower down on the IVC (or on a prosthetic replaced vena cava in case of caval resection). If the primary reconstruction is not possible, autologous graft can be used. Autologous venous grafts can be harvested from a variety of vessels, such as the internal jugular vein, left renal vein, extern iliac vein, superficial femoral vein, inferior mesenteric vein, or the portal vein of the resected specimen. Customized venous grafts can be created from lesser veins, such as the saphenous vein or ovarian vein, to avoid deficiency or complications associated with sacrificing intrinsic thicker veins. When more than one tributary vein must be reconstructed, the cited options can be used individually for each tributary or "Y" grafts used. For the creation of a customized graft from veins with a diameter lesser than that need, two or more pieces of vein can be opened longitudinally and sutured side-by-side around a drain tube to obtain a cylindrical graft with the adequate diameter. A similar procedure is used for graft creation from parietal peritoneum.

PORTAL VEIN RESECTION AND RECONSTRUCTION

Portal vein bifurcation is often involved in hilar cholangiocarcinoma, gallbladder carcinoma, and intrahepatic cholangiocarcinoma. Hepatectomy with en-bloc portal vein resection is a demanding procedure but may represent the

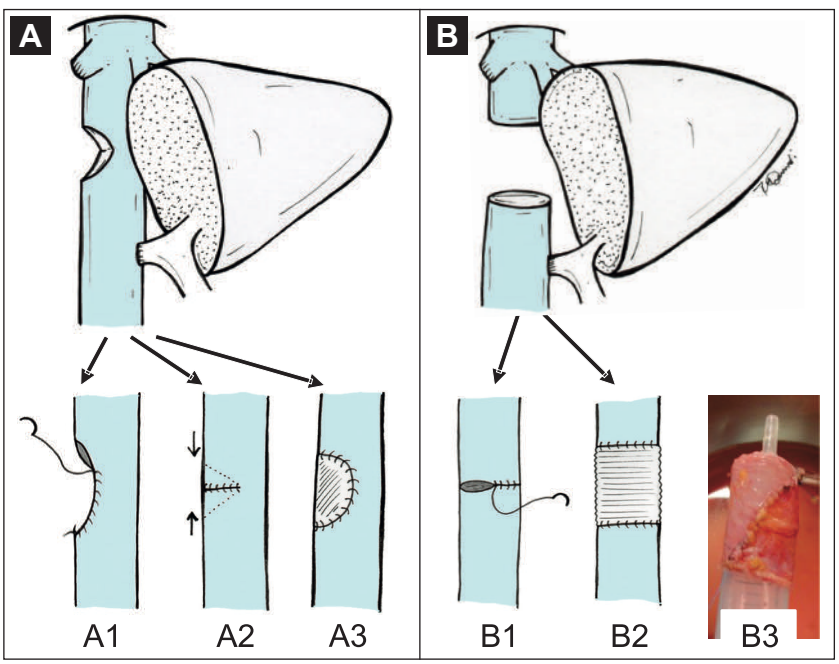


Figure 21. Options of inferior vena cava (IVC) reconstruction. **A**) After lateral partial resection of IVC options for reconstruction include primary repair (A1) (if suture results in narrow of less than 50% of the IVC diameter), transversal suture (A2) (to avoid narrowing of IVC) if defect allow adequate approximation of edges, and replacement of the defect (A3) with a patch. **B**) After resection of a complete segment of IVC, it can be reconstructed by a direct end-to-end anastomosis (B1) if approximation of edges is possible, or by replacement of the resected segment (B2) with an interposition graft. B3) surgical aspect of a tube of peritoneum molded to replace a segment of IVC.

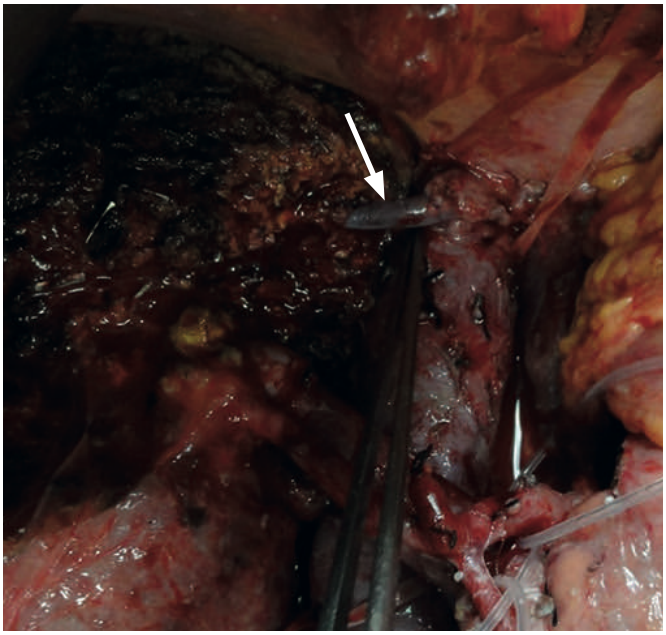


Figure 22. Reconstruction of hepatic vein draining segment 7 using a graft from the inferior mesenteric vein (arrow) after an anterior hepatectomy.

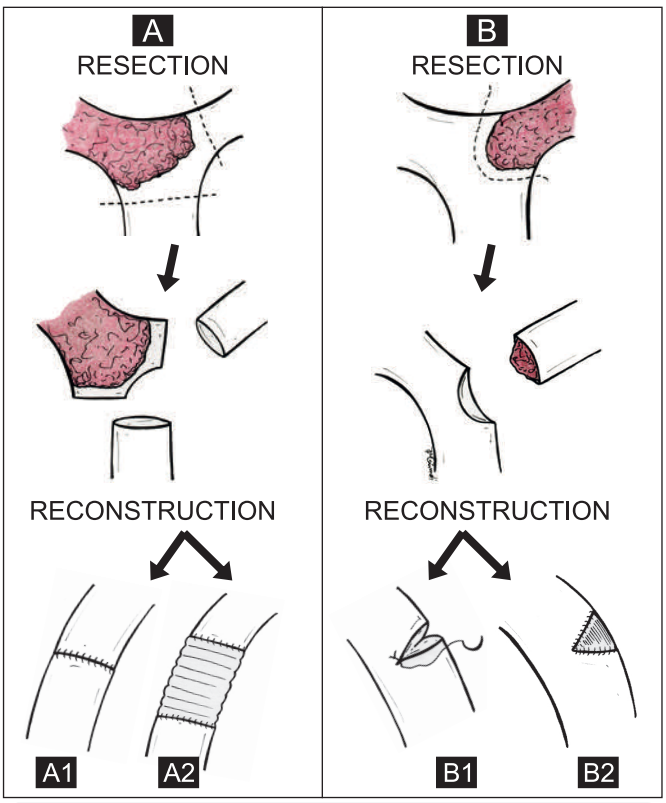


Figure 23. Resection of portal vein bifurcation (PVB) and portal reconstruction. **A**) Resection of PVB and right portal vein. Reconstruction by end-to-end anastomosis without (A1) or with (A2) graft interposition. **B**) Resection of PVB (wedge resection) and left portal vein. Reconstruction with primary repair (B1) or graft patch (B2), according to extend of the defect.

only curative treatment in many cases. Also, resection of hepatocellular carcinoma with tumor thrombi extending to portal bifurcation or main trunk can improve survival. Extent of portal vein resection depends of the tumor involvement and the type of liver resection to be performed.

Portal resection usually starts with dissection and taping of the main portal trunk and the portal vein to the lobe to be preserved. The bile duct and hepatic artery to the lobe to be resected are divided. After clamping of the portal trunk and the portal vein to the remnant liver, the portal trunk is opened and resection of portal vein performed according to the tumor involvement. Reconstruction after partial resection of the portal bifurcation can be by direct closing, as shown in **Figure 24**. When a segment of the portal bifurcation is resected, reconstruction can be performed with end-to-end anastomosis or the defect can be covered with a patch graft (**Figure 24**). Similar to reconstruction of hepatic arteries, portal vein reconstruction can be prior to hepatic dissection.[75–77]

EVALUATION OF THE REMNANT LIVER

Conceptually, for a safe hepatic resection the remnant liver should have a sufficient volume of parenchyma (larger volumes required for diseased parenchyma), which must have adequate inflow, outflow and biliary drainage. The precise evaluation of parenchymal function is a challenging topic discussed in other chapters of this textbook.

The minimal amount of functional remnant liver is also something controversial and it is depending not only from the parenchyma condition, but it also depends on the complexity of the anticipated resection, simultaneous procedures, and patient comorbidities.

The safe limit of the liver remnant volume can be assessed by different methods: i) rate of liver remnant volume and total liver volume (LRV/TLV), ii) rate of liver remnant volume and body weight (LRV/BW), and iii) liver remnant volume and body surface area (LRV/BSA).

Accepted remnant liver volume in the absence of underlying liver disease is 20% of the total functional liver (LRV/TLV), or 0.5% of the body weight (LRV/BW). In patients with underlying liver disease (cirrhosis or hepatitis), a LRV/TLV of 40% is suggested, and in patients with chemotherapy-associated liver injury or severe steatosis the threshold LRV/TLV is 30%.

The total liver volume (TLV) can be obtained in two ways: i) calculation of standardized total liver volume (or total estimated liver volume – TELV) utilizing body surface area or body weight and ii) actual liver volume calculated with imaging techniques. Note that tumor volumes are considered nonfunctional liver parenchyma and should be subtracted from TLV. In patients with multiple tumors, the calculation

of the actual liver volume by imaging can be inaccurate. Also, areas of non-functioning liver for biliary or vascular obstruction are not properly estimated. On the other hand, the calculation of standardized total liver volume related to the body surface area is a precise method that prevents the error variability associated with each measurement. The formula TELV = - 794 + 1267 x BSA (BSA = body surface area) is an example to calculate the total liver volume. Body surface area can be calculated by various formulas, such as [BSA (m^2) = 0.20247 x Height(m)$^{0.725}$ x Weight(kg)$^{0.425}$].

OPTIMIZATION OF THE REMNANT LIVER

Patients that are initially poor candidates for liver resection because of an insufficient future remnant liver can benefit from multiple advances to improve resectability rates. These advances include strategies of: i) shrinkage of liver tumors (allowing parenchymal sparing liver resection techniques), ii) minimizing injury of the future remnant liver (optimizing its functioning), and iii) increasing of the remnant liver (allowing more extensive resections). Systemic and/or regional chemotherapy induces tumor size reduction in a variety of hepatic malignancies, and it is discussed in the pertinent chapters in this textbook. Preconditioning is a useful technique to prevent injury from ischemia-reperfusion syndrome in selected cases. Ischemic preconditioning consists of a short period of liver ischemia to "prepare" the liver for a long period of clamping.[78–80] Techniques to increase the future remnant liver include portal vein embolization or ligation and two-stage resections.

Portal vein embolization and portal vein ligation. Occlusion of the portal supply of certain hepatic segments induces the hypertrophy of the other ones. Percutaneous right portal vein embolization prior an extended right trisectionectomy is the main use of the method. Additional embolization of portal branches to segment 4 increases the hypertrophy of future remnant segments 2 and 3. Portal vein embolization has been shown to be more effective than portal vein ligation to induce contralateral hypertrophy. This topic is detailed in **Chapter 7** (Portal Vein Embolization, Transarterial Chemoembolization, and Radiofrequency Ablation).

Two-stage hepatectomy. The first description of two-stage hepatectomy was for the treatment of bilateral liver metastases. Most commonly, the first operation is to clear one hemiliver from all macroscopic disease, usually by either resection or ablation. Combined intraoperative portal vein ligation or postoperative portal vein embolization of the hemi-liver to be resected is performed. After four to six weeks, the second operation is performed to complete the disease resection.

Variations of the method include: i) associating liver partition and portal vein ligation (ALPPS), and ii) first major hepatic resection followed by minor resection of the remnant liver. With the ALPPS procedure, in addition to clearance of the future remnant liver and contra-lateral portal vein occlusion, a hepatotomy (total or partial) is associated. This procedure seems to increase the hypertrophy rate of the future remnant liver; however, it is associated with high morbidity.[81] In cases of very small future remnant liver, a technique of major liver resection as the first step allows for a greater rate of hypertrophy of the remnant liver.[82]

SUGGESTED READING

Takasaki, K. Glissonean pedicle transection method for hepatic resection: a new concept of liver segmentation. *J. Hepatobiliary Pancreat. Surg.* **5**, 286–291 (1998).

This paper summarizes the hepatic segmentation and the method of hepatic resection based on the distribution of Glissonean pedicles. Each of the three hepatic segments is nourished by a secondary branch that can be isolated outside the liver during the so-called "Glissonean approach" for hepatic resections.

Abdalla, E. K., Noun, R. & Belghiti, J. Hepatic vascular occlusion: which technique? *Surg. Clin. North Am.* **84**, 563–585 (2004).

A review including the anatomic basis and methods for vascular occlusion, in addition to the indications, hemodynamic responses and limitations of different techniques.

Liddo, G. *et al.* The liver hanging manoeuvre. *HPB (Oxford).* **11**, 296–305 (2009).

The liver hanging maneuver was first described by Belghiti et al. in 2001 as a safe approach to anterior approach on right hepatectomy. Since this first report, the maneuver has been used for a variety of liver resections. This paper summarizes main technical aspects and applications of the hanging maneuver.

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23 Vascular Control and Parenchymal Transection Techniques

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- *Excessive intraoperative blood loss and the potential need for blood transfusion are major problems in hepatic resection for liver tumors.*
- *Decrease in blood loss is a goal in liver surgery, and several technical developments have been introduced for this purpose, such as the ultrasonic dissector, the water jet, the harmonic scalpel, the Ligasure®, and the tissuelink dissecting sealer.*
- *Other advances in operative techniques have also contributed to reducing blood loss during liver transection: better determination of the liver transection plane with the use of intraoperative ultrasound, and better hepatic vein flow control (inflow and outflow) as well as strict central venous pressure control. This chapter aims to outline and overview the surgical techniques currently used in liver surgery.*

INTRODUCTION

Hepatic resection has been considered a challenging procedure due to the risk of bleeding during liver transection. Before the 1980s, hepatic resection was associated with a high operative mortality rate ranging from 10-20%, often related to intraoperative bleeding.[1] Currently, the in-hospital mortality rate after liver resection has decreased to less than 5%.[2–4] These favorable results can be explained by the improvement of surgical techniques, better patient selection, improved preoperative evaluation of the future remnant liver (FRL) volume, adequate perioperative management, and reduced intraoperative blood loss with less perioperative transfusion.[4] Several studies have strongly suggested that intraoperative blood loss during liver surgery is associated with higher rates of early postoperative morbi-mortality and poor long-term outcome with decreased rates of both disease-free and overall survival, particularly in patients operated on for hepatocellular carcinoma and colorectal liver metastases.[3,5–7] Over the past 20 years, several technological advances have led to the development of specific devices used for liver transection, such as the ultrasonic dissector, the water jet, the harmonic scalpel, the Ligasure®, and the tissuelink dissecting sealer. Other advances in operative techniques have also contributed to reducing blood loss during liver transection: better determination of the liver transection plane with the use of intraoperative ultrasound, and better hepatic vein flow control (inflow and outflow), as well as strict central venous pressure control. This chapter aims to outline and overview the surgical techniques currently used in liver surgery.

DELINEATION OF THE OPTIMAL TRANSECTION PLANE

The delineation of an optimal transection plane enables resection with an adequate tumor-free margin, and also avoids inadvertent injuries to hepatic pedicles. The delineation

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of the transection plane starts with a critical appraisal of the preoperative contrast three-dimensional computed tomography (CT) scan and/or magnetic resonance imaging (MRI) to initially define the relationship between the tumor and the intrahepatic vessels or bile duct pedicles, and can be further evaluated during laparotomy by intraoperative ultrasound (IOUS). A preoperative evaluation of the future remnant liver (FRL) is mandatory in order to avoid postoperative liver failure. In patients with a large tumor, IOUS enables evaluation of the relationship between the tumor and the middle hepatic vein, and helps the surgeon to decide whether or not extended hepatic resection is needed in order to achieve complete tumor clearance (R_0 resection). IOUS also plays a particularly important role in segmental resection of the liver. Moreover, IOUS allows for localization of the segmental portal pedicles, and some surgeons use dye injection into the segmental portal vein to stain the liver segments which will be completely resected.[8] Recently, the use of IOUS to guide finger compression in order to achieve anatomical segmentectomy or subsegmental liver resection for hepatocellular carcinoma has been shown to be a safe, effective, and simpler alternative to the techniques previously proposed.[9] Finally, in patients undergoing surgery for colorectal liver metastases (CRLM), contrast-enhanced IOUS improves the sensitivity of IOUS in cases of small, hypoechoic lesions, reducing the risk of down-staging the disease and enhancing the rate of curative intent treatment.[10]

Better understanding of the segmental anatomy of the liver has led to wider use of segmental resection, which sacrifices less liver parenchyma compared to formal right or left hepatectomy, while improving the chance of tumor clearance compared to non-anatomical wedge resection.[11] Hemiliver pedicles and intrahepatic Glissonean clamping are other techniques useful in delineation of the transection plane for segmental resection.[12] The "Resection Map", a new intraoperative three-dimensional (3D) visualization system, has been described.[13] It supports the surgeon during the hepatectomy procedure and provides accurate cartography of the liver. Surgeons can therefore anticipate risks, increase their confidence, improve their orientation and achieve safer liver resection. The "Resection Map" may, in the future, constitute a pragmatic solution to enhance orientation and surgeon confidence, and further studies should be conducted to demonstrate improvement in patient safety.

INTRAOPERATIVE BLOOD LOSS DURING LIVER TRANSECTION

Blood transfusions are an independent risk factor for adverse outcomes after hepatectomy. In-hospital transfusions are still reported in one third of patients, and factors influencing blood transfusions after liver resection are limited. In a large series, multivariate analysis showed that female gender, preoperative hematocrit <30%, platelet count <100,000/mm^3, simultaneous resection of other organs, major liver resection, use of the Pringle maneuver, and tumors >10 cm significantly increased the need for red cell transfusion.[14] Interestingly, the parenchymal transection technique was an independent risk factor for perioperative red cell transfusion requirement. The use of a combination of saline-linked cautery and ultrasonic dissection technique was significantly associated with a lower transfusion rate than other techniques, including ultrasonic dissection alone, finger fracture, and stapling. These results emphasize the important role of the surgeon in determining outcomes after liver resection, since most factors that affect red cell transfusion rate after liver resection are patient- or tumor-related, with parenchymal transection technique being under the surgeon's control.

Control of bleeding remains crucial in liver surgery. Hemorrhage during liver resection occurs mainly from the liver cut surface during liver transection, but may also occur during liver mobilization, dissection of the tumor from the surrounding organs and from additional procedures. Intraoperative blood loss and the need for transfusion also depend on the presence of an underlying liver disease or injured liver parenchyma (jaundice or chemotherapy), extent of liver resection, type of liver resection, and associated procedures. Several innovative techniques, strategies, materials, and devices have been proposed to decrease the amount of intraoperative blood loss and transfusion, such as: preoperative blood auto-donation with or without use of erythropoietin; intraoperative hemodilution before liver parenchymal transection; and the use of cell savers, conventional finger fracture, clamp-crushing techniques, and various tools for liver transection, including an ultrasonic aspiration apparatus, microwave tissue coagulator, water jet device, and radiofrequency coagulator. Moreover, several strategies with hepatic vessel occlusion techniques and a policy of low central venous pressure were preferentially used compared to some devices (Lin's liver clamp, tourniquets, needles) adopted to compress liver parenchyma in order to reduce operative bleeding. Finally, before closing the abdomen and after removal of the specimen, the bleeding area on the liver transection plane needs to be completely controlled by suturing bleeding points on the parenchymal cross section and by using some tools and coagulation materials, such as an argon beam coagulator (**Figure 1**), fibrin glue, or Tachosil® to facilitate and improve hemostasis on the liver transection edge. The benefits and drawbacks of each of these technical strategies, materials, and devices have been recently analyzed.[15,16] There is little data available comparing segmental and wedge resection in terms of intraoperative bleeding or tumor clearance. DeMatteo et al. described a large series of 267 patients who underwent liver resection for

CRLM and who had either a wedge (n=119) or a segmental (n=148) resection.[17] They demonstrated that anatomic segmental resection was associated with similar blood loss, operative time, and complication rate as those observed after a wedge resection. However, segmental resection had a significantly lower rate of positive margins (2% vs. 16%) compared to wedge resection, and resulted in longer survival (median 53 months versus 38 months). Moreover, Zorzi et al.[18] described another series of 253 consecutive patients and observed no difference in positive surgical margins (8.3%), in overall recurrence rates, or in patterns of recurrence between patients treated with wedge or with anatomical resections. Recently, Torzilli et al.[19] reported that IOUS-guided liver resection in highly selected patients with multiple bilobar CLM allows for a one-stage operative treatment, decreasing the need for a two-stage hepatectomy and avoiding the disadvantages of a two-stage hepatectomy approach. However, the conclusion of this study should be regarded with caution, particularly from an oncological point of view, as the recurrence rate after a one-stage procedure was as high as 53.8% and the failure rate was 10.3% (3 out of 29 patients). During the last decade, the impact of the size of the resection margin on long-term outcome after hepatic resection has been debated. The reported studies provide evidence that margin width of >1 cm is optimal and that sub-centimeter resections are also associated with favorable outcomes, and should not preclude patients from undergoing resection.[20,21] However, occurrence of micrometastases, proven histologically, around the main CLM is not common and most are confined to the immediate vicinity of the tumor border.[22] A surgical margin of 2 mm is a clinically acceptable minimal requirement, which carries approximately a 6% risk of margin-related recurrence.[22] In this series, it should be underlined that the overall and disease-free survival curves were quite scattered (even if there was no statistical difference) in relation to the number of subgroups analyzed (four groups).[22] However, these issues need to be further analyzed in the future by randomized trials.

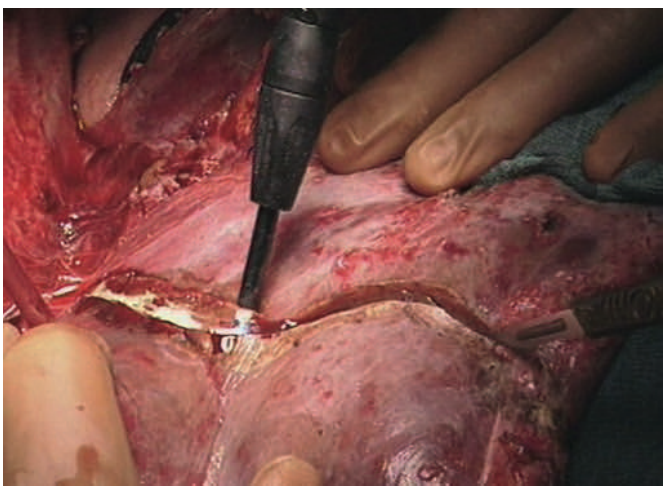


Figure 1. Argon beam coagulator leading to superficial coagulation and hemostasis along the liver transection area.

TECHNIQUES OF LIVER TRANSECTION

Outcomes after liver resection have obviously improved by reducing blood loss as far as possible.[2,4,23] The most effective means of controlling intraoperative bleeding include several techniques for liver transection and various types of vascular clamping, which are used by a growing number of surgical teams. Several anesthetic measures have also contributed to reduced blood loss. They include hypoventilation, normovolemic hemodilution and autotransfusion, control of central venous pressure, which should remain under 5 mmHg, and intraoperative serum perfusion restriction.

In brief, under positive pressure ventilation, lung inflation directly compresses the heart and increases central venous pressure, which induces subsequent bleeding from the hepatic veins. Therefore, reducing respiratory tidal volume by 30-40% may have a benefit by reducing the intrathoracic pressure. However, a randomized trial showed no benefit of hypoventilation on bleeding during liver transection.[24]

Two main blood conservation strategies have evolved and are routinely used in liver surgery. One of them is preoperative autologous blood donation, which requires donating one or more units of blood in the weeks preceding liver surgery. However, this approach can be expensive, is contraindicated in the case of malignant disease, and requires a time delay to replace the lost red cell mass before the surgical procedure. This delay may be prolonged particularly in patients treated preoperatively by neoadjuvant chemotherapy. The second strategy is acute normovolemic hemodilution.[25] Acute normovolemic hemodilution, a technique successfully used in cardiac, orthopedic, and urologic surgery, which consists of removing blood immediately before surgery while maintaining normovolemia status, has the advantage of being less expensive and eliminates the need to postpone liver surgery. A recent prospective randomized study showed that acute normovolemic hemodilution is safe, effective, and reduces the need for transfusions after major hepatic resection (1.6% versus 10.4% for patients receiving standard anesthetic management).[25] However, its routine use should be considered only in patients with significant risk of intraoperative bleeding exceeding 800 ml.[26]

Bleeding from openings made in major hepatic veins cannot easily be controlled with the new devices. Such bleeding can be increased in the presence of high central venous pressure. Therefore, one of the most important advances in liver resection in recent years has been the practice of low central venous pressure anesthesia, achieved by a combination of posture change, fluid restriction, diuretics,

vasodilators, and anesthetic agents, such as isoflurane, which produce vasodilatation. Increased central venous pressure raises the pressure within the hepatic veins leading to higher risk of blood loss during liver parenchyma transection, even under inflow occlusion. Therefore, central venous pressure should be lowered to <5 mmHg in order to achieve a safe liver resection. This condition is a prerequisite that requires a close collaboration between the surgeon and the anesthesiologist. Several studies have demonstrated that low central venous pressure anesthesia is well tolerated by most patients and is effective in reducing blood loss, with results superior to that of total vascular exclusion.[27,28] A recent randomized controlled trial (n=50) showed that the use of low central venous pressure during liver transection leads to significantly reduced blood loss and shortens the length of hospital stay.[29] However, low central venous pressure also has several drawbacks, including risk of air embolism during liver parenchyma transection, reduction of retrograde venous liver perfusion, insufficient left ventricular preload, and inadequate end-organ perfusion. The currently used cardiopulmonary interventions to decrease blood loss and allogeneic blood transfusion requirements in patients undergoing liver resections have been reviewed.[30] Indeed, in liver resection surgery, none of the cardiopulmonary interventions seems to decrease perioperative morbidity or offer any long-term survival benefit, but hemodilution shows promising results in the reduction of blood transfusion requirements. However, these conclusions should be regarded cautiously because of the few trials included, the small sample size in each trial, and the high risk of bias and errors (type I and II).

The above mentioned anesthetic measures associated with an early intraoperative fluid restriction help to control and stabilize the central venous pressure below 5 mmHg in order to reduce the venous bleeding during liver transection. It is recommended to limit the intraoperative fluid administration flow to less than 4.5 to 5.0 mL/Kg/hour for patients with liver cirrhosis, while this flow can be raised to 5.0 to 7.0 mL/Kg/hour for patients with a normal liver.[2,31]

FINGER FRACTURE / CLAMP CRUSHING

The finger fracture technique **(Figure 2)** under inflow occlusion in order to isolate vessels and bile ducts was introduced by Lin et al. in 1958,[32] and followed by Ton That Tung et al.[33] This technique was subsequently improved by the use of a Kelly clamp for blunt dissection (clamp crushing).[34] Nowadays, the clamp-crushing technique is still one of the most widely used techniques for liver transection.[35,36] However, it almost always requires, and should be combined with a Pringle maneuver (total inflow occlusion). Typically, it is more advisable to dissect and isolate the extrahepatic bile duct from the remaining structures of the hepatic pedicle (hepatic artery and portal vein) in order to avoid ischemia and subsequent stenosis of the extrahepatic bile duct. A recent meta-analysis compared the clamp-crushing method to all subsequently introduced transection techniques.[37] This meta-analysis showed no benefit of any alternative transection technique on patients' perioperative outcomes compared with the clamp-crushing method, which still remains the reference technique for transection of the parenchyma in elective hepatic resection.[37]

ULTRASONIC DISSECTION

Ultrasonic dissection **(Figure 3)** using the Cavitron Ultrasonic Surgical Aspirator (CUSA, Tyco Healthcare, Mansfield, MA, USA) has become the standard technique of liver transection in many centers. The liver parenchyma tissue is fragmented by ultrasonic energy (the range of the vibration is about 100 microns) and aspirated, exposing vascular and ductal structures that can be ligated. The tip of the handpiece is constantly irrigated. A suction line is connected to the hollow tip and aspirates irrigant, blood, and

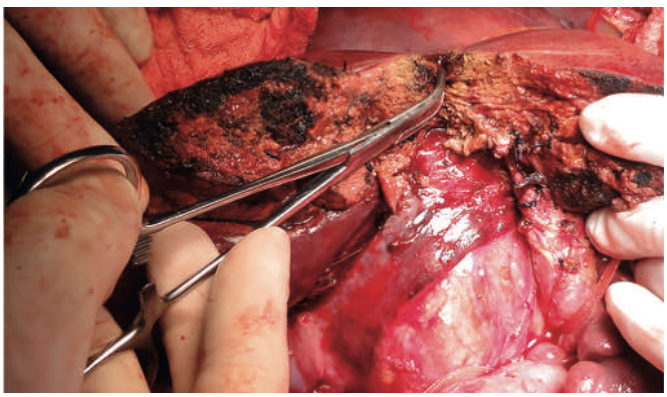


Figure 2. The clamp-crushing method for liver transection. (*courtesy of Silvio M P Balzan*)

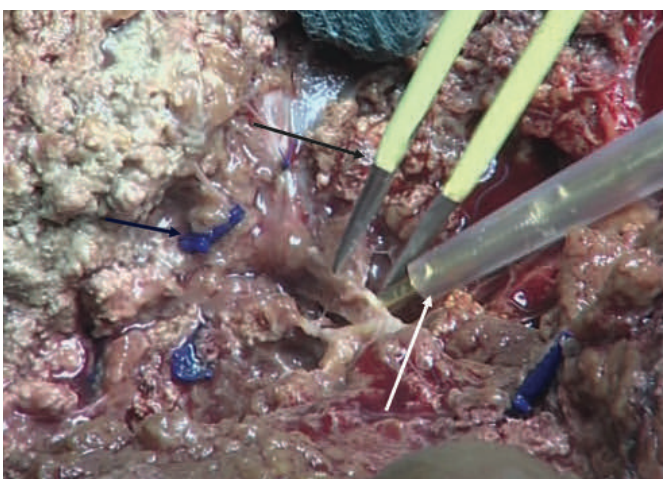


Figure 3. Techniques of liver transection routinely used. Ultrasound dissecting device, absorbable clips (blue clips) and irrigated bipolar coagulation.

tissue fragments. The principle of action of the ultrasonic dissector is based on the higher water content of the liver parenchyma cells as compared with the vascular and bile duct structures, which have a higher content of collagen and elastin. As a result, the ultrasonic vibrations selectively destroy the liver parenchyma cells. The cell detritus thus produced is removed by the interaction of the irrigant and suction. Correctly used and adjusted, even the smallest vessels and bile ducts remain intact when cutting parenchyma, and can be selectively closed. The ultrasonic dissector itself possesses no hemostatic properties. The vibration setting, the negative suction pressure, and the supply of irrigant can be adjusted. Dissection of cirrhotic liver parenchyma requires a higher frequency of vibration. Furthermore, ultrasonic dissection results in a larger tumor-free margin because of a more precise transection plane. The main advantage of the ultrasonic dissector is that it preserves large anatomical structures (branches of the hepatic artery, the portal vein, the hepatic veins, and the bile ducts), thus making them accessible to careful surgical management. However, in a randomized controlled trial comparing clamp crushing and ultrasonic dissection conducted by a Japanese group, no significant difference in blood loss, transection speed, tumor infiltration of the surgical margin, or postoperative morbidity were observed.[35] This device has also been developed to allow transection of liver parenchyma during minimally invasive, laparoscopic, and robotic liver surgery.

WATER JET

The water jet dissector uses a pressurized jet of water to fragment the liver parenchyma and to expose the vascular and bile duct pedicles. The jet-cutting technique uses a high-pressure pump, which imparts potential energy to a liquid. Via a high-pressure line the liquid is conducted to a nozzle, from which it issues as a fine high-pressure jet. By adjusting the pressure and nozzle parameters appropriately, it is possible to use such an instrument for selective cutting. Anatomical structures such as veins, arteries, and bile ducts can be avoided while the parenchyma, which is far softer and less resistant, is fragmented. The only available prospective randomized trial comparing water jet transection (n=31) and liver resection using CUSA (n=30), showed that water jet transection reduced blood loss, blood transfusion, and transection time compared with CUSA.[38] Both CUSA and water jet techniques are quite good for dissecting major hepatic veins close to the tumors.

HARMONIC SCALPEL

New technologies that allow sealing of vessels during transection of liver parenchyma are now available. These technologies can be used alone for transection of the liver parenchyma, or in combination with clamp crushing or CUSA. One of these technologies is ultrasonic shear (Harmonic Scalpel, Ethicon Endo-Surgery, Cincinnati, OH, USA), which uses ultrasonically activated shears to seal small vessels.[39] Electrical impulses are transmitted from the microprocessor-controlled generator via shielded coaxial cable to the handpiece. Crystals are able to transform alternating current into mechanical oscillations (piezoelectric effect). In this manner the handpiece transmits harmonic vibrations of 55,000 Hz, which are amplified and conducted to the surgical working device by an aluminum rod. The surgical instrument itself vibrates exclusively in a longitudinal direction at a frequency of 55,000 Hz. The vibration cannot be perceived by the surgeon at the handpiece. Via a feedback system, the generator reacts to any changes in frequency and resistance by sounding an alarm, thus enabling defects of the scalpel or too-high temperatures to be recognized at once. The coagulation effect is caused by protein denaturation. The local temperature rises as a result of the friction of the blade against the tissue to a maximum of 80°C, but the denaturation of tissue occurs by the splitting of hydrogen compounds in the cell affected by the high-frequency longitudinal vibration of the blade. This instrument has been used for liver transection in both open and minimally invasive laparoscopic or robotic liver resections. A non-randomized study comparing the Harmonic Scalpel with the conventional clamp-crushing method showed that the use of the Harmonic Scalpel was associated with a significantly increased rate of postoperative bile leaks.[40] This device may also have a limitation in dissecting the liver parenchyma around the main trunk of hepatic veins, since it is difficult to achieve sufficient control of bleeding from large vessels using the Harmonic Scalpel alone. However, when combined with ultrasonic dissection, the Harmonic Scalpel may reduce blood loss.[41] This needs to be further evaluated by a prospective randomized trial.

LIGASURE

Ligasure (Valley Lab, Tyco Healthcare, Boulder, CO, USA) is another device designed to seal small vessels by combining a compression pressure and a bipolar electrothermal energy. A feedback mechanism is incorporated into the device that automatically stops the energy delivery when tissue sealing is completed. The product works by obliterating the lumen and denaturing the collagen and elastin in vessel walls to create a bloodless permanent seal. Similar to the Harmonic Scalpel, there is also some concern for its ability to seal bile ducts. This technology can fuse vessels up to and including 7 mm. However, a small series (n=30) showed that the use of Ligasure for liver transection has not been associated with clinical evidence of bile leakage, but its use should be avoided in cirrhotic patients.[42] A randomized controlled

trial demonstrated that the use of Ligasure in combination with a clamp-crushing technique resulted in a lower blood loss and a faster transection speed in minor liver resections compared with the conventional technique of electric cautery or ligature.[43] However, the bile leakage rate with the use of Ligasure was higher (9%) compared to that observed in the conventional technique group (3%) but did not reach statistical significance. Based on these reports, the efficacy of Ligasure in sealing bile duct needs to be further investigated. Recently, a larger randomized controlled trial including a total of 120 patients undergoing liver resection for benign or malignant disease showed that the use of a vessel sealing system was safe, but was not associated with any significant decrease in operation time or blood loss during liver transection in comparison with the conventional clamp-crushing method.[44] In this study, the median liver transection time with Ligasure was similar to that after use of clamp crushing method (57 minutes versus 56 minutes). There was no difference between the two groups in transection speed (1.16 cm/minute versus 1.10 cm/min), the amount of blood loss (median: 315 mL versus 315 mL), and blood loss per transection area (5.04 mL/cm versus 4.36 mL/cm).[44] Recently, a large study including 252 patients evaluated the efficacy of the VIO soft-coagulation system for liver parenchyma transection.[45] The authors noticed a decreased surgical time and bleeding, even for major liver resection, without any rise in bile leakage rate and overall morbidity.[45]

TISSUELINK DISSECTING SEALER

Recent technology using saline-linked radiofrequency (RF) energy (TissueLink Medical, Inc., Dover, NH, USA) has been developed for liver transection (**Figure 4**). The saline runs to the tip of the probe to allow RF energy to achieve coagulation of the liver. The combined use of a Floating Ball coagulator with Ligasure has been shown to reduce blood loss compared with the conventional technique during clamp crushing transection of the liver.[46] In this preliminary report, the median blood loss was 100 mL (range 30–700 mL) and no postoperative bile leak was observed. The effect of using a saline-linked radiofrequency coagulator (dissecting sealer) on the amount of blood loss was also assessed by few randomized clinical trial.[47,48] No significant differences were observed between the dissecting sealer and the clamp-crushing method in terms of blood loss during liver parenchyma transection (median 373 mL versus 535 mL) or of total intraoperative blood loss (665 mL versus 733 mL).[47] Another randomized trial concluded that the monopolar Floating Ball did not offer any significant benefit over bipolar forceps when combined with the standard Pean-clasia technique, while its cost is not negligible.[48] This instrument may also be used in laparoscopic liver resection. Recently, the efficacy and safety of the Cavitron ultrasonic surgical aspirator (CUSA) with bipolar cautery were prospectively evaluated and compared to CUSA with a radiofrequency coagulator (TissueLink) in living donor liver transplantation.[49] Morbidity rates were similar for both groups. However, CUSA with a radiofrequency coagulator seems superior to CUSA with bipolar cautery in terms of blood loss and speed of transection.[49]

RADIOFREQUENCY-ASSISTED LIVER TRANSECTION

Radiofrequency (RF) thermocoagulation or ablation (**Figure 5**) has been proposed as a new modality of treatment for liver tumors,[50] and has contributed to the development of a new technique of liver transection.[51] The goal of RF is to induce thermal injury to the tissue through electromagnetic energy deposition. The patient is part of a closed-loop circuit that includes a radiofrequency generator, an electrode needle, and a large dispersive electrode (ground pads). An

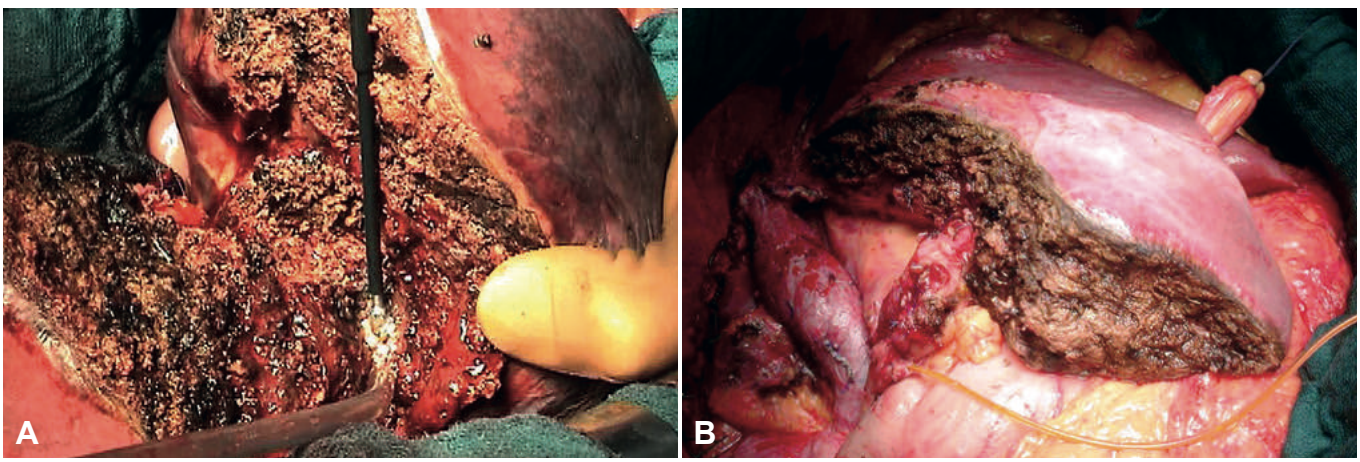


Figure 4. Dissecting sealer device (Tissuelink®). No need for ligatures or clips but should be used cautiously near to the main hepatic pedicles particularly the bile ducts. **A**) right hepatectomy, **B**) right hepatectomy extended to segment 4A and segment 1.

alternating electric field is created within the tissue of the patient. Because of the relatively high electrical resistance of tissue compared with the metal electrodes, there is marked agitation of the ions present in the target tissue that surrounds the electrode, as the tissue ions attempt to follow the changes in direction of alternating electric current. The agitation results in frictional heat around the electrode. The discrepancy between the small surface area of the needle electrode and the large area of the ground pads causes the generated heat to be focused and concentrated around the needle electrode. In this technique, a Cool-tip RF electrode (Radionics Inc., Burlington, MA, USA) is inserted along the transection plane serially 1–2 cm apart, and RF energy is applied for 1–2 min to create overlapping areas of coagulated tissue, followed by transection of the coagulated liver using a simple scalpel. In a preliminary study (n=15) of segmental or wedge resection reported by Weber et al.,[51] mean blood loss was only 307 10 mL, and no complication such as bile leakage was observed. The technique has the advantage of simplicity compared with the transection techniques mentioned before. One potential disadvantage of this technique is the sacrifice of parenchymal tissue in the remnant liver. However, the major concern still remains possible thermal injury to the hilar structures and hepatic veins when using this technique for major liver resection.[52] This technique has been compared with conventional techniques of liver transection.[53] In the RF group, the resection plane was pre-coagulated by multiple insertion of a planar triple-cooled radiofrequency needle, and then the parenchyma was sectioned using a scalpel. The RF-assisted liver transection allowed parenchymal resection in a clean surgical field but was associated with a higher rate of postoperative complications compared to that after use of clamp-crushing technique. In brief, eight patients developed serious postoperative complications including abscess, biliary fistula, and biliary stenosis.[53] Recently, an in-line RF device consisting of multiple parallel RF probes has been specifically developed for liver transection. This device has been shown to reduce bleeding compared with CUSA in a preliminary pilot study,[54] or with total vascular exclusion,[55] and allows to achieve liver resection without the need for an hepatic inflow occlusion,[56] or a laparoscopic liver resection.[57] However, the role of this device in hepatic resection has to be validated in the future.

RADIOFREQUENCY-BASED BIPOLAR HEMOSTATIC SEALER

The bipolar sealer reportedly seals blood vessels in soft tissue and cut bone while keeping the surface temperature at <100°C. This device works by coupling RF energy from a standard electrosurgical generator with saline irrigation to conduct thermal energy. The thermal effect shrinks the collagen in the walls of veins and arteries, effectively stopping bleeding and oozing from the vessels without producing smoke or charring or burning tissue. The saline coupling of the bipolar sealer technology provides an advantage over conventional electrocautery for sealing cancellous tissue. This coupling provides a direct conduit between the electrodes and the embedded vessels, resulting in a rapid energy transfer. Furthermore, the depth of necrosis is minimal (<0.3 mm at 6 weeks and none at 12 weeks), allowing native blood vessels to assist with bone healing. Hemostasis via vessel shrinking occurs without the tissue desiccation, smoking, and charring of conventional electrocautery. A prospective randomized study [58] demonstrated that a radiofrequency-based bipolar sealer with CUSA resulted in decreases in excessive blood loss overall and increased speed in transection time with no increase in morbidity compared with standard bipolar cautery with CUSA during hepatectomy.

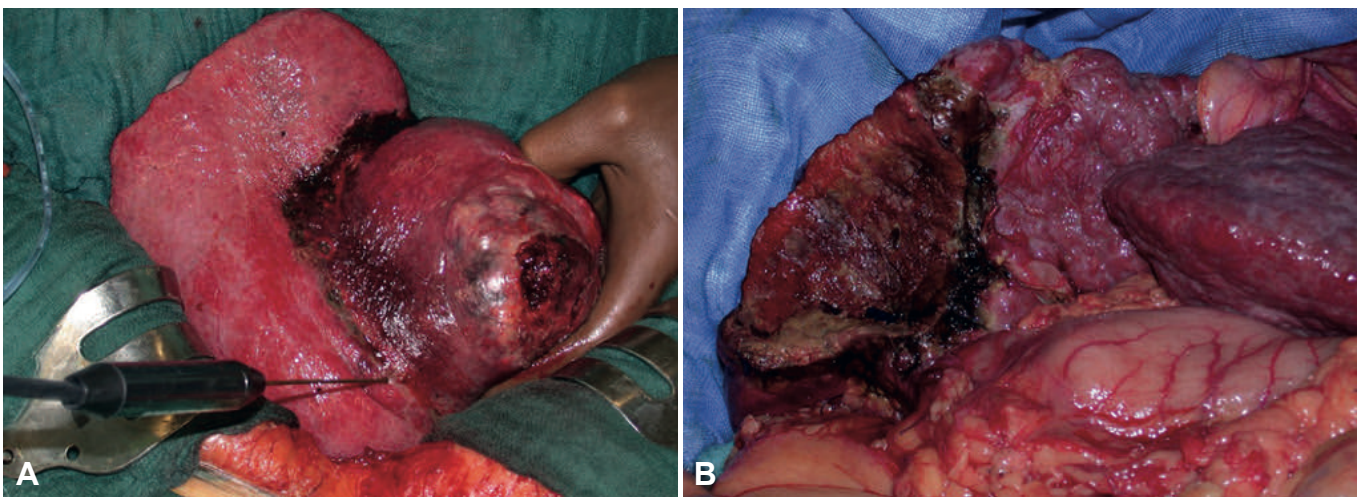


Figure 5. Radiofrequency assisted segmentectomy 6. **A**) The transection plan is treated by radiofrequency; **B**) the transection is performed using a knife to remove the specimen avoiding bleeding from the liver transection area.

COMPARISON OF THE DIFFERENT LIVER TRANSECTION TECHNIQUES

The choice of a transection technique is still a matter of preference of surgeons. It has been shown in small prospective randomized trials that clamp crushing or water jet may be preferable to CUSA in terms of quality of transection or speed of transection.[35,38] However, the results of these trials remain to be validated by larger trials. CUSA dissection is still a widely used technique worldwide. Recently, a randomized trial compared four methods of liver transection, namely clamp crushing, CUSA, Hydrojet, and dissecting sealer (n=25 patients in each group).[59] The authors showed that clamp crushing was associated with the fastest transection speed, lowest blood loss, and lowest blood transfusion requirement. However, in this study, clamp crushing was associated with a Pringle maneuver, whereas the other techniques were performed without a Pringle maneuver, leading to a major bias in favor of clamp crushing. Further randomized trials are needed to compare different liver transection techniques, not only to analyze their efficacy in reducing blood loss and safety, but also to evaluate their relative cost-effectiveness. The benefits and risks of the different techniques of liver parenchymal transection for liver resections has been recently reviewed.[60] This meta-analysis suggested that clamp-crush technique remains the method of choice for liver parenchymal transection whereas the newer methods do not seem to offer any significant benefit in decreasing the morbidity or transfusion requirement.[60]

VASCULAR STAPLES IN HEPATIC RESECTION

Staplers have been used in liver surgery to control major hepatic pedicles and hepatic veins, or to divide liver parenchyma.[61] Vascular staplers to divide the hepatic duct pedicle during the right or left hepatectomy should be used with caution in order to avoid the risk of hepatic duct confluence stenosis, especially in case of a large tumor.[62] In case of minor wedge resection or left lateral segmentectomy, liver parenchyma transection may be stapled when the liver tissue is not too bulky. However, the risk of bile leakage is still a major concern. Indeed, the risk of surgical morbidity has been recently analyzed in a prospective study based on routine use of stapler for liver parenchymal transection in 300 consecutive patients.[63] This study showed the feasibility of a stapler hepatectomy with relatively low mortality (4%) and acceptable morbidity (33%). However, the reduction of the overall operative time observed with the use of a stapler hepatectomy should be regarded cautiously as it is counterbalanced by the relative increased rates of bile leakage and of relaparotomy.[63] Finally, the use of stapling of the portal triad during "Glissonean" approach has been randomly compared to the hilar dissection in patients submitted for major liver resection.[64] This study showed that both techniques are equally effective procedures for treating hilar structures, and were associated with similar rates of biliary fistula (10% for stapling portal triad versus 7.5% for hilar dissection). Although en bloc stapling transection was faster, hilar dissection was less expensive and associated with a shorter pedicular clamping time and reduced postoperative cytolysis.[64]

POST-RADIOFREQUENCY TRANS-METASTASES HEPATECTOMY

Curative trans-metastases liver resection immediately following RF destruction enables to perform a curative intent resection in patients with bilateral, unresectable CRLM, when the only possible resection plane passes through a CRLM. Elias et al. reported the feasibility and efficacy (n=30) of this new approach.[65] The mortality rate was 7.6%, and morbidity was 24%. No local recurrence was observed at the post-RF trans-metastases hepatectomy site after a mean follow-up of 19.4 months.

INFLOW VASCULAR CLAMPING

Inflow occlusion by clamping the hepatic pedicle was first described by Pringle in 1908.[66] He successfully used the hepatic inflow occlusion to control major bleeding following severe liver trauma. Currently, the so-called Pringle maneuver is frequently used to reduce parenchymal bleeding during hepatic transection. Hepatic pedicle clamping is associated with hemodynamic changes. Indeed, the cardiac output drops slightly while the systolic and diastolic arterial pressure rises as a consequence of an increased peripheral vascular resistance.[67] Thereafter, the hemodynamic parameters remain stable under Pringle maneuver and return to their previous values within few minutes after declamping. A randomized clinical trial, assessing the safety and the effectiveness of Pringle maneuver, showed that the use of Pringle maneuver during liver transection resulted in less blood loss and in better preservation of liver function in the early postoperative period owing to a reduced hemodynamic disturbances related to bleeding.[68] However, there is no absolute evidence that routine use of Pringle maneuver offers any benefit in terms of perioperative outcome after liver resection.[69]

Occlusion of both the portal vein and hepatic artery (Pringle maneuver) results in ischemia of the liver and splanchnic congestion. This latest adverse event is exceptionally encountered in humans even after prolonged portal vein clamping owing to the presence of natural porto-systemic collateral circulation, which lessens the severity of

splanchnic blood sequestration. However, ischemic injury of the liver alters the liver regeneration processes and increases the risk of postoperative liver failure. Moreover, bacterial translocation often occurs during and after ischemia reperfusion and liver resection;[70,71] and the occurrence of a sepsis seems associated with an increased postoperative mortality in patients presenting with liver dysfunction after liver resection.[72]

CONTINUOUS OR INTERMITTENT INFLOW OCCLUSION

Whether to clamp hepatic vascular inflow in order to prevent excessive blood loss or to reduce liver ischemic damage and subsequent post-ischemic reperfusion injuries still remains the major concern. As the liver tolerates better ischemia than the patient tolerates blood loss it seems justified to use preferentially hepatic vascular inflow occlusion than to leave bleeding. Several strategies have been described either to reduce ischemia reperfusion injuries or to increase the tolerance of the liver to ischemia. They include pharmacologic interventions (allopurinol, acetylcysteine, adenosine), interventions on the inflammatory cascade (C1 inhibitor, interleukin-10, lipopolysaccharide-blocking agents), ischemic preconditioning of the liver, intermittent vascular inflow occlusion and in situ cooling of the liver under total hepatic vascular exclusion.

The pharmacologic interventions focused on scavenging reactive oxygen species, decreasing apoptosis and inhibiting the inflammatory cascade. Most of them were investigated in experimental studies and the therapeutic options are limited for human use.

Since the 1970s, the evaluation of the biological tolerance of the human liver to prolonged warm ischemia confirmed that the hepatic warm ischemia period may be safely extended beyond the traditional duration of 15 minutes.[73] However, whether clamping should be applied continuously or intermittently is still controversial. Intermittent clamping consists to perform successive sequences of 15 to 30 minutes of ischemia, followed by 5 to 10 minutes of reperfusion. Theoretically, intermittent clamping shortens the ischemic period, improves the hemostasis of the cut surface of the liver during each cycle of reperfusion but increases the amount of bleeding, the periods of reperfusion, the total time required for liver parenchymal transection as well as the liver tolerance for ischemia.[74,75] Belghiti et al.[74] demonstrated in a prospective randomized trial that liver parenchyma tolerance was better after intermittent Pringle maneuver than after continuous Pringle maneuver, especially in patients with chronic liver disease. Another randomized trial, however, showed no significant difference in blood loss after liver resection with or without inflow occlusion.[76] A prospective randomized study has been designed to evaluate the protective pharmacologic effect of synthetic protease inhibitor in mitigating the impact of visceral congestion following portal triad clamping. This study indicated that intermittent application of Pringle maneuver for 30 minutes is as effective and safe as intermittent Pringle maneuver for 15 minutes during hepatectomy in humans, provided that a protease inhibitor is used.[77] However, the 30-minute intermittent Pringle maneuver doubled the serum transaminase levels on postoperative day one compared with the 15-minute intermittent clamping when a protease inhibitor was not used.[77] Similar early postoperative outcomes have also been reported in another randomized study, which confirmed that the extension of intermittent hepatic pedicle clamping to 30 minutes allows for faster liver transection with greater resection area per unit of time, while preserving the remnant liver function.[78] Therefore, there is little advantage for intermittent clamping during liver resection in which parenchymal transection could be achieved within 30 minutes.[78]

HEMIHEPATIC OR SEGMENTAL HEPATIC INFLOW OCCLUSION

To reduce the severity of the visceral congestion and total liver ischemia, vascular occlusion techniques have been developed to suppress the vascular supply either to one hemiliver or to one or two liver segments (**Figures 6 and 7**).[79–82] They include selective hemiliver or supraselective inflow occlusions and may sometimes represent extrahepatic extra-Glissonean approaches. After such clamping, the borders of the area to be resected is demarcated on the liver surface and may be enhanced by ultrasound guided injection of methylene blue into the portal branch.[80] These techniques are particularly useful when performing mesohepatectomies, bisegmentectomies 6/7, 5/8, and 2/3, or when dealing with bilobar resections under hemihepatic clamping, achieving non-stop liver resections while the controlateral hemiliver is reperfused. A randomized study comparing complete or selective hepatic inflow clamping for minor hepatectomies showed that both techniques are equally effective and feasible, with similar amounts of blood loss and postoperative morbidity rates as found in patients presenting with normal liver parenchyma.[83] However, in cirrhotic patients, complete clamping is associated with higher rates of serum transaminase levels on postoperative day one, suggesting an increased ischemic injury. Therefore, selective hemihepatic vascular occlusion technique should be recommended in cirrhotic patients even for minor liver resections.[83]

TOTAL HEPATIC VASCULAR EXCLUSION

Portal triad clamping is often sufficient to control blood loss during liver parenchyma transection. However, it does

not suppress the backflow from the hepatic veins, which may cause major bleeding. In such situations, bleeding can be stopped by applying a total hepatic vascular occlusion in which the suprahepatic and infrahepatic suprarenal caval veins are clamped in addition to the portal vein and hepatic artery (**Figure 8**). Therefore, total hepatic vascular

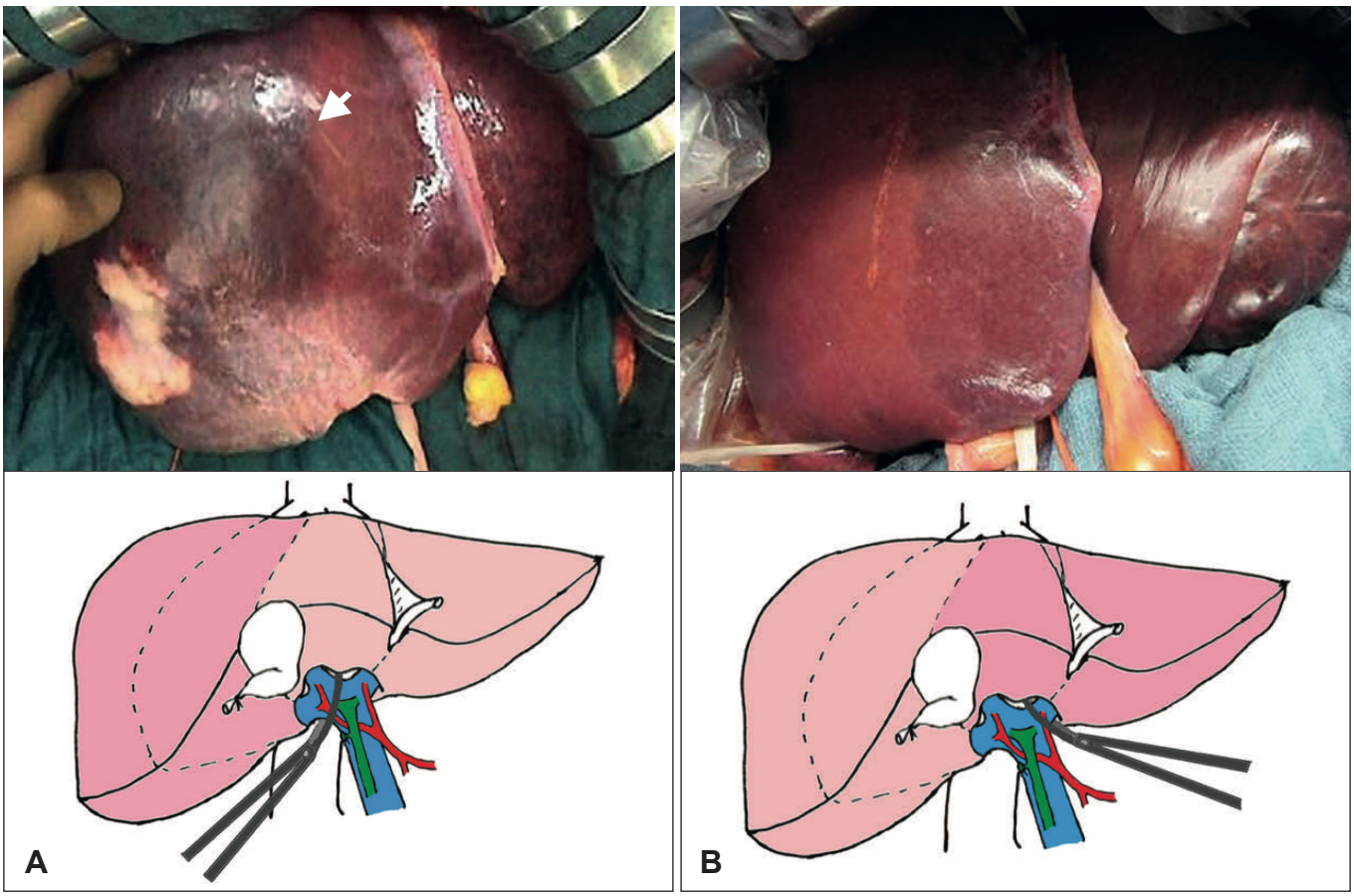


Figure 6. Selective hemi-hepatic inflow clamping. Note a demarcation line between the right and left hemilivers (arrow). **A**) The right hemiliver vascular inflow is clamped and the left hemiliver inflow preserved. **B**) The left hemiliver vascular inflow is clamped and the right hemiliver inflow preserved.

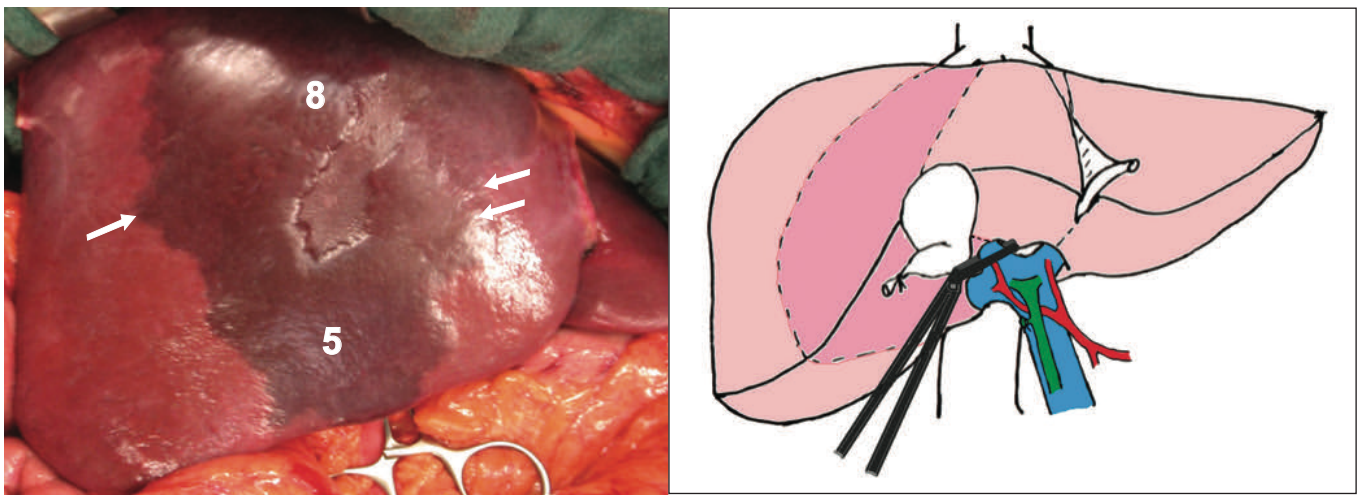


Figure 7. Selective hepatic right anterior sector inflow clamping. Note a demarcation line between the right anterior and right posterior sectors (single arrow) and between the right anterior sector and segment 4 (double arrow). The vascular inflow of the left hemiliver and of the right posterior sector are preserved.

exclusion has been proposed to avoid massive hemorrhage and air embolism through hepatic vein injuries occurring during removal of unfavorably located tumors near to the hepato-caval junction. Vascular exclusion of the liver results provides more marked hemodynamic changes. Clamping of both portal vein and inferior vena cava results in severe hypotension, requiring invasive anesthetic management as the venous return and cardiac output are massively reduced by sequestration of the blood in the splanchnic and inferior vena cava beds, respectively. Total hepatic vascular exclusion can be applied while preserving the inferior vena cava flow. This procedure is applicable when the inferior vena cava is not involved by liver tumors and requires elective control and clamping of the hepatic veins just above their hepatocaval junction. It offers the advantages of a conventional hepatic vascular exclusion without its hemodynamic drawbacks, and it can be applied intermittently or partially. In their experience, Cherqui et al. noticed an excellent hemodynamic tolerance in all patients without the need for therapeutic adjustment. The in-hospital mortality was nil, the morbidity rate was acceptable (17.5%), the hospital stay was not longer, and only 30% of the patients required red blood cell transfusion.[84] A prospective randomized study compared hepatic vascular exclusion and portal triad clamping in non-cirrhotic patients undergoing major liver resection.[85] This study showed that both methods of vascular occlusion are equally effective in reducing intraoperative blood loss while total hepatic vascular exclusion seems associated with unpredictable hemodynamic intolerance with increased postoperative complications and prolonged hospital stay. For these reasons, total hepatic vascular exclusion should be restricted to lesions involving the cavo-hepatic junction.

ISCHEMIC PRECONDITIONING

Ischemic preconditioning has been proposed as an alternative to continuous portal triad clamping in order to avoid liver parenchyma injury due to prolonged ischemia. This hepatoprotective measure consists to apply a brief period (10 minutes) of ischemia by using standard Pringle maneuver followed by 10 minutes of reperfusion, after which liver resection can be performed under prolonged and continuous hepatic inflow occlusion. A landmark article published in Annals of Surgery in 2003 established the protective effect of ischemic preconditioning against hepatic ischemia in humans and have been shown to be particularly effective in young patients requiring a prolonged period of inflow occlusion, and in the presence of steatosis.[86] The same team in a randomized study compared ischemic preconditioning and intermittent clamping of the portal triad in non-cirrhotic patients undergoing major liver resection. They observed similar protective effects against postoperative liver injury. However, ischemic preconditioning confers lower blood loss and shorter transection time.[87] Currently, ischemic preconditioning is still not unanimously accepted by the hepatobiliary surgeons. Recently, preconditioning with volatile anesthetics, which provides protection against cardiac and renal ischemic injury in several animal models, has been evaluated by a randomized trial in patients undergoing liver surgery.[88] The results of this study showed that sevoflurane pharmacologic preconditioning significantly limited the postoperative increase of serum transaminase levels by 30%, particularly in patients presenting steatotic livers and reduced the overall complications rates including severe complications requiring invasive procedure.

A meta-analysis of all methods of vascular occlusion for elective liver resections concluded that hepatic vascular occlusion cannot be recommended over portal triad clamping.[15] Intermittent portal triad or hemihepatic clamping seems to be better than continuous portal triad clamping at least in patients with chronic liver disease.[89,90] There is no evidence to support selective inflow occlusion over portal triad clamping. The optimal method of intermittent portal triad clamping is not clear. There is no evidence for any difference between the ischemic preconditioning followed by vascular occlusion and intermittent vascular occlusion for liver resection in patients with a non-cirrhotic liver.[15] Further randomized trials of low risk of bias are needed to determine the optimal technique of vascular occlusion.

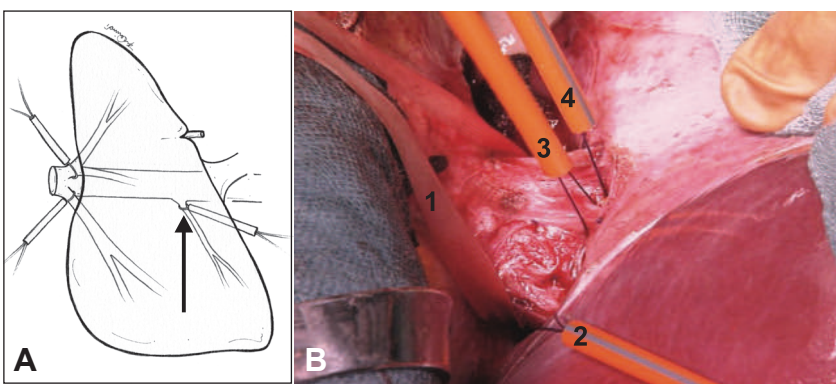


Figure 8. A) Schematic representation of elective outflow clamping without interruption of the flow within the inferior vena cava. Note also the elective control of an inconstant inferior hepatic vein draining the segment 6 (black arrow). **B**) Intraoperative view of outflow control. The inferior vena cava was encircled and taped (1). Elective control of the right (2), middle (3), and left (4) hepatic veins.

LAPAROSCOPIC LIVER RESECTION

The current practice of laparoscopic liver resection was reviewed in meta-analysis.[91–94] Available evidence indicates that laparoscopic liver resection can be performed safely in selected patients with comparable duration of surgery, blood loss, tumor clearance, and mortality to that of open resection.[91] The development of the innovative devices for liver transection has allowed laparoscopic liver surgery to develop. Tumors localized peripherally in the left lateral segments or in anterior segments of the liver seem to be the best indications for laparoscopic resection. Two conferences of consensus described the safety and benefit of laparoscopic liver resection.[95,96]

FINAL CONSIDERATIONS

In conclusion, efficient control of intraoperative blood loss is without doubt the main key to perform safe liver resection. Basically, control of bleeding from the liver transection edge is obtained by vascular inflow occlusion and of hepatic vein backflow preferentially without interruption of the vena cava flow. Maintenance of low central venous pressure remains an important adjunctive measure to reduce blood loss in liver resection, and offers better control of the retrograde hepatic venous flow without affecting the post-ischemic liver reperfusion injuries often encountered after Pringle maneuver. Intermittent clamping is recommended for prolonged period of clamping and for diseased liver parenchyma. However, the role of the Pringle maneuver seems to be decreasing with improved transection techniques and replaced by elective clamping of the pedicles intended for the resected specimen. New instruments such as ultrasonic shears and radiofrequency devices in liver transection have gained acceptance in surgical practice and should be used carefully. Knowledge and regular use of standard techniques of vascular occlusion and innovative surgical devices can result in blood loss reduction and achievement of safe liver surgery.

SUGGESTED READING

Katz, S. C. *et al.* Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann. Surg.* **249**, 617–623 (2009).

Study comprising 192 patients with hepatocellular carcinoma that found intraoperative blood loss as a risk factor of poorer overall and disease-free survival in multivariate analysis taking in account clinicopathologic features.

Rahbari, N. N. *et al.* Meta-analysis of the clamp-crushing technique for transection of the parenchyma in elective hepatic resection: back to where we started? *Ann. Surg. Oncol.* **16**, 630–639 (2009).

Meta-analysis with more than 500 patients that found no clinically important benefits (in terms of blood loss, parenchymal injury, transection time, and hospital stay) of alternative liver transection methods over clamp crushing method.

Clavien, P. A. *et al.* A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. *Ann. Surg.* **238**, 842–843 (2003).

In this randomized study authors found a benefit of ischemic liver preconditioning compared with continuous clamping of at least 30 minutes in younger patients requiring long duration of ischemia and in patients with hepatic steatosis.

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24 Principles of Segment-oriented Liver Resections - Mesohepatectomy, Monosegmentectomies, and Bisegmentectomies

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- *Segment-oriented anatomical hepatic resection has the advantages of achieving tumor-free margin and preservation of sufficient functional liver parenchyma.*
- *In this context, hepatic resection can be performed based on the precise anatomical location of the tumor, according to the segmental anatomy as described by Couinaud.*
- *In the technical aspect, this approach offers the advantage of performing liver transection along avascular planes so as to minimize intraoperative blood loss.*

INTRODUCTION

This chapter describes the principles of segment-oriented liver resections and some details regarding central hepatectomy (or mesohepatectomy), main bisegmentectomies, and monosegmentectomies. Supplemental reading of other chapters of this textbook, as cited throughout the text, is strongly suggested.

Hepatic resection for liver cancer has played an expanding role over the last decade. This is mainly the result of remarkable reduction in operative mortality and the proven value of hepatic tumor removal on prognosis. It is not uncommon for a primary liver tumor to be associated with underlying chronic liver disease (for example, secondary to hepatitis viral infection). In a similar fashion, patients operated on for secondary liver tumors frequently have chemotherapy-associated liver injury (CALI). Therefore, a successful hepatic resection has to strike a balance between effective tumor clearance and postoperative functional liver reserve.

Considering the need to achieve adequate tumor-free margin while preserving sufficient functional liver parenchyma, segment-oriented anatomical hepatic resection frequently offers the best treatment option for patients with malignant liver tumors. In this context, hepatic resection can be performed based on the precise anatomical location of the tumor, according to the segmental anatomy as described by Couinaud.[1] The hepatic segment confined by the tumor-bearing portal tributaries is removed in a standard manner. In the technical aspect, this approach offers the advantage of performing liver transection along avascular planes so as to minimize intraoperative blood loss. Hepatic resection without blood transfusion is considered to be the current standard of liver surgery because perioperative blood transfusion is associated with higher morbidity and recurrence, and poor patient survival (see **Chapter 9** - Morbidity and Mortality After Liver Surgery).

There is additional oncological rationale for anatomical versus non-anatomical hepatic resection based on the

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biological characteristics of liver tumors.

In the management of hepatocellular carcinoma (HCC), there is a high incidence of postoperative recurrence, with a 3-year recurrence rate of up to 60% after curative hepatic resection.[2,3] An important mechanism of HCC recurrence is intrahepatic metastasis via vascular invasion. Pathologically, HCC has a high propensity to invade the portal and hepatic veins. Vascular invasion and subsequent intrahepatic metastasis are the most important risk factors accounting for poor postoperative prognosis after hepatic resection. Hence, eradication of intrahepatic metastases is the most crucial consideration for improving the surgical outcome in HCC. Theoretically, anatomical hepatic resection is effective for eradication of intrahepatic metastases of HCC because all portal pedicle tributaries are removed *en bloc* with the tumor. The potential superiority of such surgical approach has been emphasized in the literature.[4,5] Regimbeau et al.[6] clarified the importance of anatomic versus non-anatomic wedge resection for 64 patients with HCC. Prognostic factors included the type of surgery, vascular invasion, cirrhosis, and the width of resection margin. In this study, the overall and disease-free survival rates were significantly longer in the anatomic resection group when compared with the non-anatomic group. More importantly, the local recurrence rate was lower in the anatomic resection group than the non-anatomic group. Another study by Hasegawa et al.[7] revisited this issue in a larger group of 210 patients. It was shown that anatomic resection yields more favorable results than non-anatomic resection for HCC patients. Both the 5-year overall survival and disease-free survival rates in the anatomic resection group were significantly higher than in the non-anatomic resection group (66% vs. 35% and 34% vs. 16%). Multivariate analysis revealed that anatomic resection was a significantly favorable factor for overall and disease-free survival rates. With this evidence, segment-oriented anatomical hepatic resection should be considered in patients with primary liver tumors. (For further information on HCC, refer to **Chapter 13** – Hepatocellular Carcinoma).

The rationale for performing anatomical resections for primary liver tumors does not apply to metastatic liver disease. In secondary hepatic tumors, achievement of complete malignancy clearance while sparing liver parenchyma should be the goal. In this setting, non-anatomical (wedge) resections are a valuable option. (For further information on colorectal liver metastases refer to **Chapter 10** – Colorectal Liver Metastases).

ANATOMICAL CONSIDERATIONS

Segmental anatomy of the liver forms the basis of segment-oriented anatomical liver resection. According to Couinaud's description, the liver consists of eight segments, which are numbered in a clockwise direction from an anterior viewpoint, starting with the caudate lobe as segment 1 (**Figure 1**). The three main hepatic veins (right, middle, and left) divide the liver into four sectors, each of which receives a portal pedicle of hepatic artery, hepatic duct, and portal vein, in an independent manner. The liver is divided by the main trunk of the middle hepatic vein within the main portal scissura into right and left hemi-livers. This main demarcating line was first described by Cantlie in 1898 and it extends from the gallbladder bed anteroinferiorly to the right side of the inferior vena cava (IVC) posterosuperiorly. The right and left hemilivers are further divided in two sectors each (right anterior and posterior sectors, left medial and lateral sectors, respectively) by right and left hepatic veins, respectively. The major branches of portal pedicle at the liver hilum further separate the sectors in individual liver segments. The right anterior and posterior sectors are divided by the right portal pedicle plane into segments 8 superiorly and 5 inferiorly, and segments 7 superiorly and 6 inferiorly, respectively. The left medial sector is termed segment 4 and the left lateral sector is divided by the left portal pedicle in segments 2 superiorly and 3 inferiorly.

Couinaud's segment 1 (the caudate lobe) is positioned between the hilar branching of the portal triad anteriorly and the IVC posteriorly. The caudate lobe is an independent anatomical segment composed of three distinct parts. The caudate lobe proper (segment 1-l, or Spiegel's lobe) extends to the left of the IVC and under the lesser omentum. The paracaval portion of the caudate lobe lies anterior to the IVC and extends cranially to the roots of the three hepatic veins. The caudate process (segment 1-r) is located between the right portal pedicle and the IVC and fuses mainly with segment 6 of the right liver.

For more details on liver anatomy, refer to **Chapters 1** (Surgical Anatomy of the Liver) and **2** (Radiological Anatomy of the Liver).

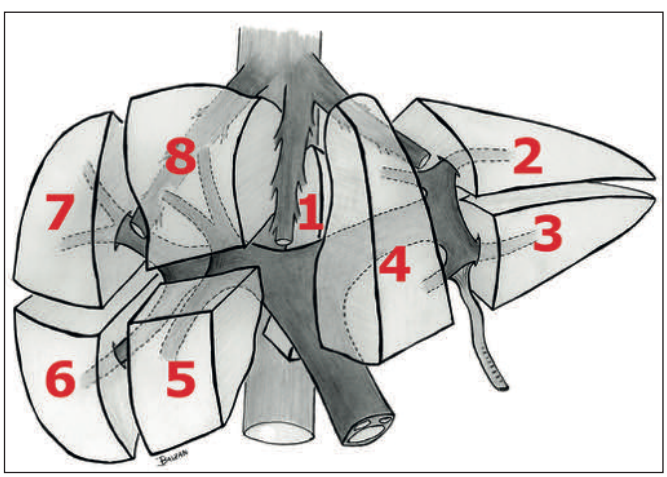


Figure 1. Couinaud's classification of segmental anatomy of liver (Segments 1 – 8).

PREOPERATIVE ASSESSMENT

Multi-detector computed tomography (CT) or magnetic resonance imaging (MRI) is essential in the determination of hepatic tumor resectability. These imaging methods provide the anatomical basis and the volumetric assessment of the future remnant liver (FRL). They can also demonstrate the anatomical relationship of the tumor with the three hepatic veins and the inferior vena cava, as well as the segmental location of the tumor. Further pieces of information on the relationship between the portal pedicle elements (portal vein, hepatic artery, and bile ducts) and the tumor, together with the depiction of distant metastases, are obtained with CT scan and MRI.

The definition of resectability lies with the FRL. The tumor extension is not a contraindication for resection as long as enough functional liver parenchyma is preserved (enough volume with adequate blood inflow and outflow, and biliary drainage). Thus, a hepatic tumor is generally considered to be resectable if there is absence of tumor invasion to the contralateral hepatic vein or portal vein. Nevertheless, major hepatic vessel resection and reconstruction can be performed in selected cases to achieve complete tumor clearance. Tumor invasion into the bile duct is not an absolute contraindication for hepatic resection, because the hepatic duct can always be resected and the biliary tract reconstructed by hepaticojejunostomy.

Adequate FRL volume is particularly important to prevent postoperative liver failure after hepatic resection. In the absence of underlying chronic liver disease, a functional remnant of 30% of the standard liver volume (as estimated by the Urata et al. formula[8]) is considered enough to avoid postoperative liver failure.[9] For patients with chronic liver disease, a minimum of 40% of the estimated standard liver volume is considered to be the safety limit for the FRL. Procedures such as portal vein embolization or staged surgery may be employed to overcome the risks of a small FRL by induction of hypertrophy.

Liver functional status is particularly crucial to cirrhotic patients undergoing hepatic resection. Child-Pugh classification[10] is a simple, reproducible, and reliable method to determine the hepatic functional reserve preoperatively. Child-Pugh class A patients can tolerate major hepatic resection (removal of three or more Couinaud's segments) with low operative mortality. For patients with marginal liver function (Child-Pugh class B), only minor hepatic resection (removal of less than three Couinaud's segments) can be done with acceptable operative risk. Another commonly employed dynamic liver function test is the indocyanine green (ICG) clearance test. It has been demonstrated that ICG retention rate of less than 20% at 15 minutes after intravenous administration is considered safe for performing major hepatic resections. Nonetheless, the value of an ICG clearance test may be high in the case of bile obstruction, and it should not be used in patients with malignant biliary obstruction. This topic is discussed in further detail in **Chapter 5** (Liver Function Assessment Before and After Hepatic Resection).

Medical comorbidities are a major determinant of postoperative complications. Major postoperative complications, such as severe sepsis, often precipitate liver failure in patients with otherwise adequate liver functional reserve. Thus, preoperative medical condition is associated with mortality rate, even in patients that are carefully selected on the basis of high-quality imaging studies and accurate liver functional assessment. Therefore, patients with significant comorbidities (e.g. recent myocardial infarction, uncorrected uremia) should not be subjected to hepatic resection.

INTRAOPERATIVE ULTRASONOGRAPHY

Intraoperative ultrasound (IOUS) was developed initially as a diagnostic tool for detection of tumor nodules and major vascular invasion by tumors. It is currently a useful tool for segmental localization of the tumor, the portal pedicles, and the hepatic veins. IOUS precisely delineates the transection plane allowing segment-oriented anatomical hepatic resections. The use of IOUS ensures an adequate tumor-free margin and prevents both vascular injury and excessive liver parenchymal removal. In some centers, selective dye injection or balloon occlusion of the segmental portal vein under IOUS guidance helps in tattooing the liver segment for hepatic resection.[11] For further details on IOUS, refer to **Chapter 3** (Intraoperative Assessment of the Liver).

PARENCHYMAL TRANSECTION

The main difficulty of anatomical hepatic resections lies in the control of bleeding during transection of the liver. It is particularly challenging in the cirrhotic liver, due to the fibrotic nature of liver tissue. Finger fracture and clamp crushing are the conventional methods employed for liver transection. These methods allow for skeletonization of the biliary and vascular structures. Intrahepatic vessels and bile ducts are progressively exposed and controlled by metal clips or ligatures.

Using a Cavitron ultrasonic surgical aspirator (CUSA®, Tyco Healthcare, Mansfield, USA) is the standard technique of liver transection in many centers (**Figure 2**). With this technology, the liver tissue is fragmented with high-energy

ultrasound and sucked off, thus exposing vascular and biliary structures (greater than 2 mm) that can be ligated or clipped with titanium clips (author's technique). The axially directed effect of oscillatory energy leads to fragmentation of liver parenchyma within a 1-2 mm wide area. The irregular saline spray with simultaneous aspiration allows a constantly clear operative view. Small vessels and bile ducts within the transection plane are not destroyed due to their high collagen and elastin content. These structures are dealt with individually using the methods mentioned above. At the author's center, CUSA has resulted in reduced blood loss compared with the clamp-crushing technique in non-randomized studies, and achieving a wide tumor-free margin has been enabled because of a more precise transection plane among patients with HCC.[2] In the case of resecting large tumors with narrow margins, leaving a complete layer of intact liver parenchyma is crucial to ensure oncological clearance. This can be readily performed by CUSA because there is no lateral tear of liver tissue along the transection plane.

Another method for skeletonization of intrahepatic structures is water-jet dissection (Erbejet 2, Erbe USA Inc, Marietta, USA).

Other techniques for parenchymal transection include tools that achieve destructive control of the parenchyma and crossing structures before division, such as cutting staplers, in-line radiofrequency assisted transection (Habib 4x, Angiodynamics, Queensbury, USA), sealing devices such as Ligasure Vessel Sealing System (Covidien, Mansfield, USA) and Salient Dissecting Sealer (Salient Surgical Technologies, Portsmouth, USA) – formerly called Tissuelink, among other devices.

Data from randomized trials and meta-analyses has failed to demonstrate superior efficacy of one method over others.[12,13]

STRATEGIES TO REDUCE BLOOD LOSS

Reduction in intraoperative blood loss and avoidance of perioperative blood transfusion are important goals of anatomical hepatic resections. Apart from meticulous liver transection, other strategies to reduce intraoperative blood loss include the use of vascular staplers, inflow vascular control, and low central venous pressure anesthesia.

The vascular stapler has been used in liver surgery for control of inflow and outflow vessels. In the author's experience, it is currently a routine practice to use a vascular stapler (endoGIA™) to divide hepatic veins inside or outside of the liver. The use of vascular staplers helps to reduce blood loss, especially when the exposure of the right or the left hepatic veins is rendered by a large tumor, or during control of the middle hepatic vein deep in the transection plane (**Figure 3**). In these circumstances, slipping of the clamp or tearing of a suture can occur and can result in massive blood loss, with the conventional technique of applying a vascular clamp followed by hand suturing. Control of the inflow and biliary ducts (portal pedicles) can also be done using the endoGIA™ stapler. This strategy avoids extra blood loss from the richly arterialized biliary ducts. It is preferable to divide biliary ducts during hepatic transection instead of dividing them extrahepatically. This avoids leaving an ischemic stump and the consequent increase in the risk of biliary fistula. Vascular staplers should be used carefully close to hepatic duct confluence to avoid narrowing the right or left hepatic ducts.

Intermittent or continuous clamping of the portal triad (Pringle maneuver) is commonly employed to reduce bleeding during hepatic transection. Intermittent clamping (alternating 15 minutes of occlusion with five minutes

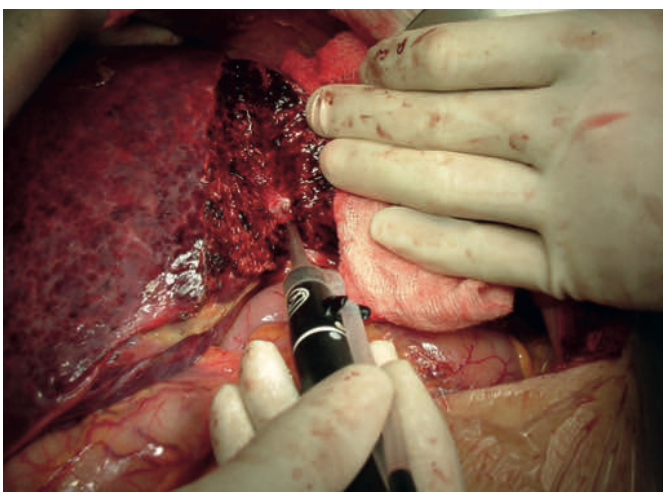


Figure 2. Cavitron ultrasonic aspirator (CUSA) for liver transection.

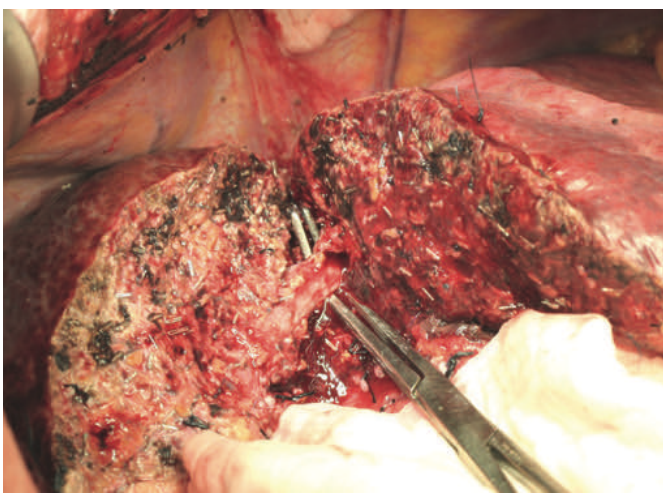


Figure 3. Isolation of the middle hepatic vein along the liver transection line in a patient undergoing extended right hepatectomy.

of re-circulation) allows for a longer total period of vascular occlusion than continuous Pringle maneuver. Nevertheless, even the use of intermittent clamping should be limited to no more than a total of 120 minutes of occlusion to avoid the deleterious effect of ischemia on the liver function. In order to avoid prolonged global liver ischemia due to total inflow occlusion, selective clamping has been proposed. This can be performed at the hilar level by dissection and occlusion of ipsilateral branches of portal vein and hepatic artery using bulldogs or vascular clamps. This approach allows for a longer period of ischemia in a selective area.

Hepatic venous branches can be a main source of bleeding during liver transection. Inflow occlusion has a minor effect on the control of such source and the efforts should be based on the reduction of the central venous pressure.

Central venous pressure should be lowered to less than 5 mmHg, provided that hemodynamic status can be maintained. This low central venous pressure can be obtained with anesthetic techniques based on fluid restriction and morphine infusion if necessary. Also, isoflurane is the preferred anesthetic agent to accomplish a low central venous pressure anesthesia as it induces vasodilatation and results in only minor myocardial depression. Volume replacement can be started once liver transection is completed.

Total hepatic vascular exclusion is also useful to reduce bleeding from hepatic venous branches; however, its use is limited mainly due to major hemodynamic changes.

OPERATIVE TECHNIQUES

INCISION

Bilateral subcostal incision (with or without upward midline extension), or a J-shaped incision, provides adequate exposure for most patients undergoing segment-oriented anatomical hepatic resection. With a self-retaining retractor, the costal arch is pulled up cranially to expose the entire anterior surface of liver. Retraction of the sternum in the cranial direction helps to expose the suprahepatic IVC, which can be viewed perpendicularly.

For a large right lobe tumor, additional thoracotomy incision can be made along the 9th or 10th intercostal space in order to expose the tumor adequately. For a large tumor at the liver dome (segments 7 and 8), a vertical midline and curved thoracoabdominal extension along the 8th, 9th, and 10th intercostal space (J-shaped incision) could be made. Through the thoracic extension, the right liver can be safely mobilized allowing access to the plane in between the paracaval portion of the caudate lobe and IVC without excessive traction and rotation of the right liver.

STEPS

All segment-oriented liver resection usually requires some common steps, summarized in **Table 1**. For further detail on each step, please refer to **Chapter 22** (General Technical Aspects of Liver Resections). Adequate tumor location and

Table 1. Regular steps in segment-oriented hepatic resections.

Steps	Usual options
1- Accurate tumor location	Preoperative imaging Intraoperative ultrasound
2- Delimitation of segments	Intraoperative ultrasound Dye injection
3- Liver mobilization (on demand)	Round and falciform ligaments section Left triangular attachment dissection Right triangular attachment dissection Section of vein branches to retrohepatic IVC
4- Vascular control	Segment portal pedicle clamping Hemiliver inflow clamping Pringle maneuver Total vascular exclusion
5- Parenchymal transection	Crushing technique Ultrasonic dissection Sealing devices Saline-linked radiofrequency sealer Radiofrequency-assisted Other methods

segment boundaries are needed to define the segment(s) that should be included in the resection. These steps may be accomplished with preoperative imaging, use of IOUS, and other techniques such as dye injection. The boundaries of hepatic segments can be defined with the use of IOUS mainly using vascular hallmarks. In some situations, dye injection on the corresponding portal pedicle under ultrasound guidance can help to clearly define the demarcation lines on the liver surface (**Figure 4**).[14] Also, segmentectomy and subsegmentectomy by IOUS-guided finger compression (compression of vascular pedicle feeding the tumor with consequent demarcation area) has been described.[15]

Subsequently, mobilization of the liver is accomplished according to the resection to be performed. Full mobilization of the liver is usually necessary to facilitate parenchymal transection in right liver tumor resection and includes section of the round, falciform, right triangular, and left triangular ligaments, and sometimes section of short hepatic veins draining directly to the inferior vena cava.

Next, vascular control can be obtained using selective segmental clamping or hemiliver clamping to complete inflow clamping (such as the Pringle maneuver), or even total vascular exclusion. Individual segmental portal pedicles should be identified and ligated in a secure manner to prevent bile leakage.

Finally, parenchymal transection is performed. Various methods are available and are discussed in **Chapter 23** (Vascular Control and Parenchymal Transection Techniques). Care should be taken with sectioning, especially in case of major hepatic veins in proximity to the section plane, to avoid vascular damage.

CENTRAL HEPATECTOMY (MESOHEPATECTOMY)

This procedure involves *en bloc* removal of Couinaud's segments 4, 5 and 8 (associated or not to segment 1 resection). This segment-oriented resection is useful for centrally located tumors in patients with marginal liver function, mainly HCC patients with cirrhosis, since it preserves functional liver parenchyma compared to conventional or extended lobectomy (40-60% versus 60-85%).[16,17] The technique involves a combination of complete resection of segment 4 and the right anterior sector (**Figure 5**). It is a technically demanding procedure, requiring two hepatic parenchymal transection planes with a large raw area after resection. The right transection plane runs close the right hepatic vein, which should be preserved. The middle hepatic vein is sectioned close to the common trunk of the middle and the left hepatic veins. Additionally, the portal pedicles supplying the liver remnant on both sides need to be preserved.

Strategies to prevent blood loss would be beneficial in this procedure. Inflow control to the right anterior sector can be obtained by hilar dissection and isolating the right anterior hepatic artery and portal vein individually, or by Glissonean approach. Liver transection starts along the umbilical fissure. Segment 4 inflow pedicles are easily ligated and divided. Care should be taken to preserve the left portal pedicle. The transection plane continues cranially until the origin of the middle hepatic vein, which is isolated and encircled. The demarcation line on the right side, seen after division (or clamping) of the right anterior hepatic artery and portal vein, represents the reference plane for liver transection. On this transection plane, the right hepatic

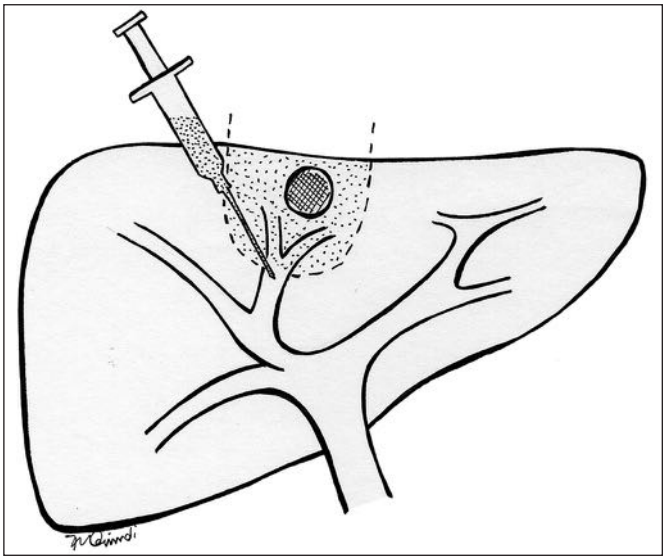


Figure 4. Schematic representation of portal dye injection to staining the segment to be resected. Boundaries of segment supplied by the portal branch are clearly demarcated on the liver surface.

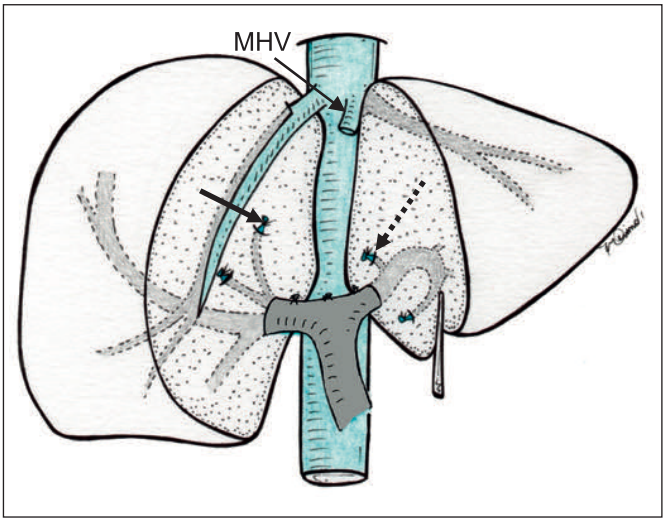


Figure 5. Schematic representation of a central hepatectomy, i.e. resection of Couinaud's segments 4, 5 and 8. On the two transection planes the stumps of segment 4 (dashed arrow) and right anterior pedicles (black arrow) are identified. MHV: middle hepatic vein.

vein is exposed and preserved (**Figure 5**). The left and right transection planes join at the site of biliary section (right anterior duct). The right anterior bile duct is identified by intraoperative cholangiogram and then divided. The middle hepatic vein is finally divided with a vascular stapler. At the completion of the procedure, the anterior surface of the IVC is exposed and the right and left hepatic veins are preserved (**Figure 5**).

Alternatively, inflow control can be obtained by alternating left and right hemiliver clamping with Glissonean approach. In this situation right hemiliver pedicle clamping is used during the right plane transection (between right anterior and right posterior sectors) and left hemiliver pedicle clamping is applied during left plane transection (between segment 4 and left lateral sector). With this approach total inflow occlusion is not performed. Instead, certain surgeons prefer the use of Pringle maneuver and outflow control.[18] However, a prospective trial demonstrated that blood loss during declamping was greater in total inflow occlusion than in hemihepatic inflow occlusion.[19] The middle hepatic vein can be controlled before parenchymal transection, as described in **Chapter 22**.

RIGHT ANTERIOR SECTOR RESECTION

This procedure involves removal of Couinaud's segments 5 and 8. Similar to central hepatectomy, right anterior sector resection requires hilar dissection and isolation of the right anterior hepatic artery and portal vein (or by Glissonean approach of the pedicle to the right anterior sector) and it also requires two liver transection planes. The left transection plane follows exactly the same used for a right hepatectomy. The middle hepatic vein is exposed on its right side and is preserved. The right transection plane follows the demarcation line between the right anterior and posterior sectors (similarly to central hepatectomy). The right hepatic vein is exposed on its left side and preserved (**Figure 6**). The procedure is concluded by joining the two planes of transection at the site of division of the right anterior hepatic duct.

RIGHT POSTERIOR SECTOR RESECTION

This procedure involves removal of Couinaud's segments 6 and 7. Because the right posterior sector is situated deep in the right subphrenic space, complete resection of this sector needs adequate exposure. A J-shaped incision with thoracotomy is the preferred incision. Moreover, complete mobilization of the right liver is necessary until the anterior surface of the IVC is exposed. The right hepatic vein is encircled extrahepatically and protected. Hilar dissection with isolation of the right posterior hepatic artery and portal vein are carri ed out (**Figure 7**). The liver transection plane is similar to the right transection plane of right anterior sector resection, except that the right hepatic vein is exposed on its right side. The transection continues on the inferior surface of the liver toward Rouviere's sulcus and the right posterior hepatic duct is divided. The liver transection is completed and the right side of the IVC is exposed (**Figure 8**).

SEGMENT 1 RESECTION

Isolated resection of segment 1 is challenging because of its deep-seated anatomical location. Segment 1 (caudate lobe) can be approached from the left and/or the right sides. Control of inflow supply is achieved by hilar dissection, exposing the left and right hepatic arteries and portal veins, since blood supply derives from both right and left portal pedicles. Very often, the left inflow branches are prominent,

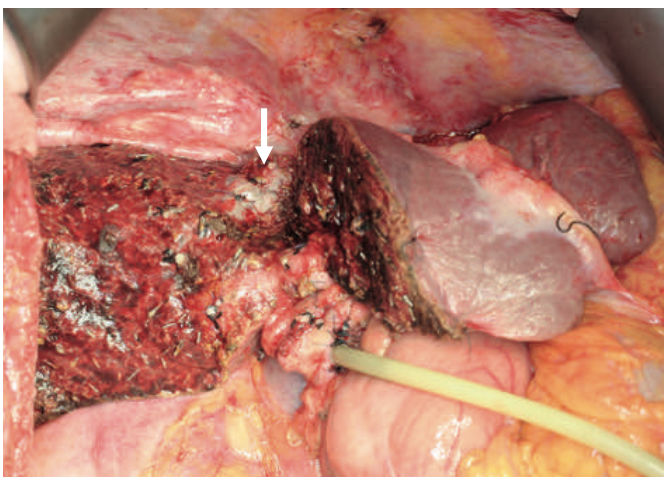


Figure 6. Exposure of the right hepatic vein (white arrow) in right anterior sectionectomy (segments 5 and 8).

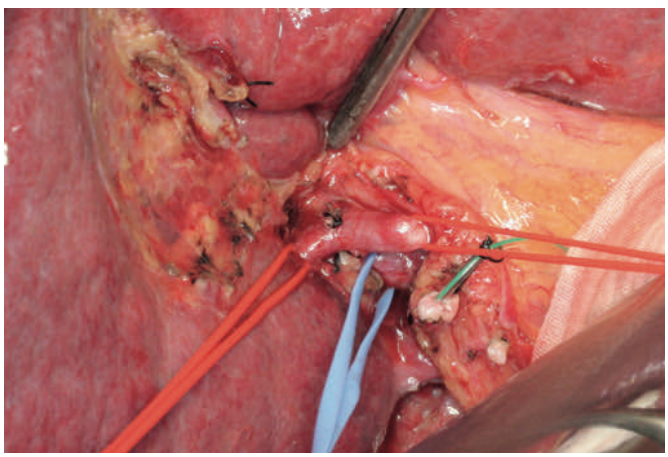


Figure 7. Isolation of the right posterior hepatic artery (red vessel loop) and right posterior portal vein (blue vessel loop) in right posterior sectionectomy.

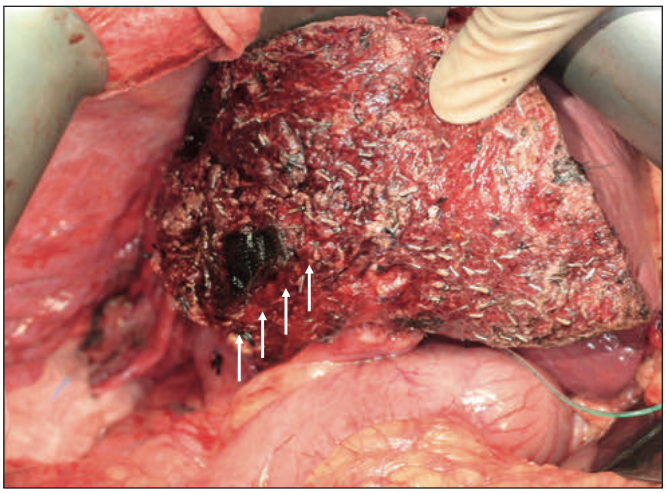


Figure 8. Right posterior sectionectomy with the exposed right hepatic vein on its right side (white arrows).

particularly at the base of the umbilical fissure, supply a greater portion of the lobe, and are easily controlled and sectioned (**Figures 9 and 10**). Section of the left triangular ligament and of the ligamentum venosum exposes the left hepatic vein and allows encircling the common trunk of left and middle hepatic veins.

Veins draining directly to IVC are ligated and sectioned to get outflow control. This step requires detachment of the caudate lobe from the IVC. It is usually performed in a left to right manner, with progressive mobilization and exposition of the posterior aspect of the caudate lobe (**Figure 11**). Occasionally, approach to caudate veins can be from right to left, after mobilization of the right hemiliver (**Figure 11**). At this point, the caudate lobe is devascularized, remaining only its parenchymal attachments to the base of segment 4 and left boundary of segment 7. Transection of these parenchymal attachments may be performed from left and right side, usually with CUSA (**Figure 11B**). Meanwhile, care should be taken to not injure the middle hepatic vein, which is in close proximity. Therefore, isolation of the middle hepatic vein extrahepatically is a valuable step to prevent injury during transection. Also, exposure of the paracaval portion can be obtained by anterior approach, with a split liver technique (parenchymal transection on the Cantlie line) (**Figure 11B**). On some occasions, caudate lobe resection can be combined with right or left hepatectomy to gain adequate tumor-free margins.

SEGMENT 2 AND 3 RESECTION

This procedure was formerly called left lateral segmentectomy, according to Goldsmith and Woodburne in 1957.[20] It involves removal of Couinaud's segments 2 and 3. The left liver is mobilized in the same way as in left hepatectomy. Portal inflow is controlled during liver transection along the left side of the falciform ligament and umbilical fissure. The transection is completed by dividing the left hepatic vein. More details of this resection are discussed in **Chapter 26** (Left Liver Resections).

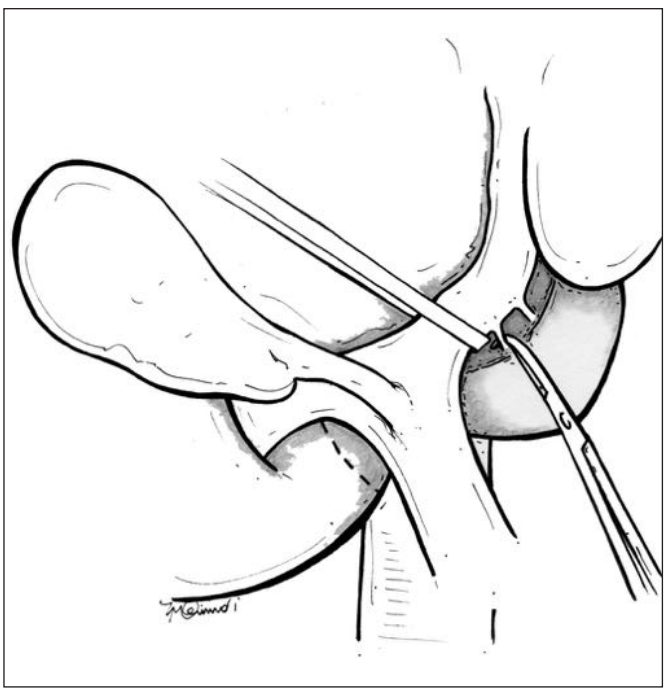


Figure 9. Schematic representation of dissection of inflow branches to caudate lobe originated from the left hepatic pedicle.

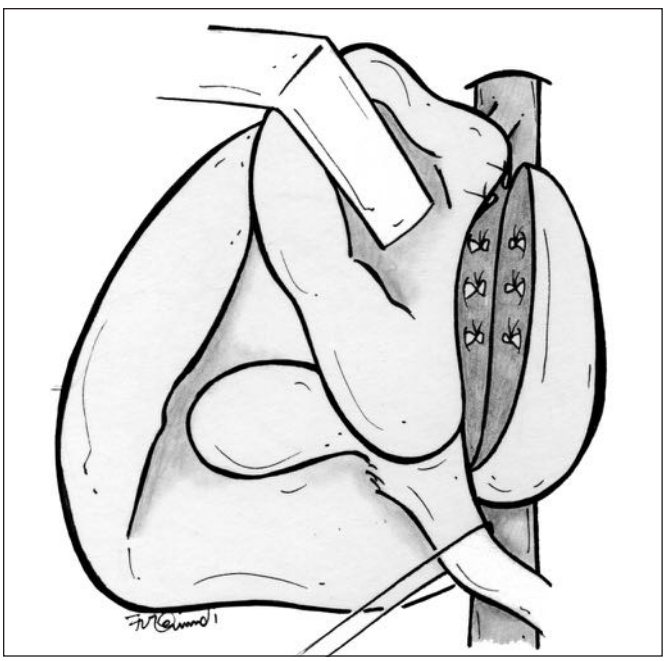


Figure 10. Schematic representation of section between segment 1 and 4. The left lobe is pulled upward and to the right to expose the ligamentum venosum.

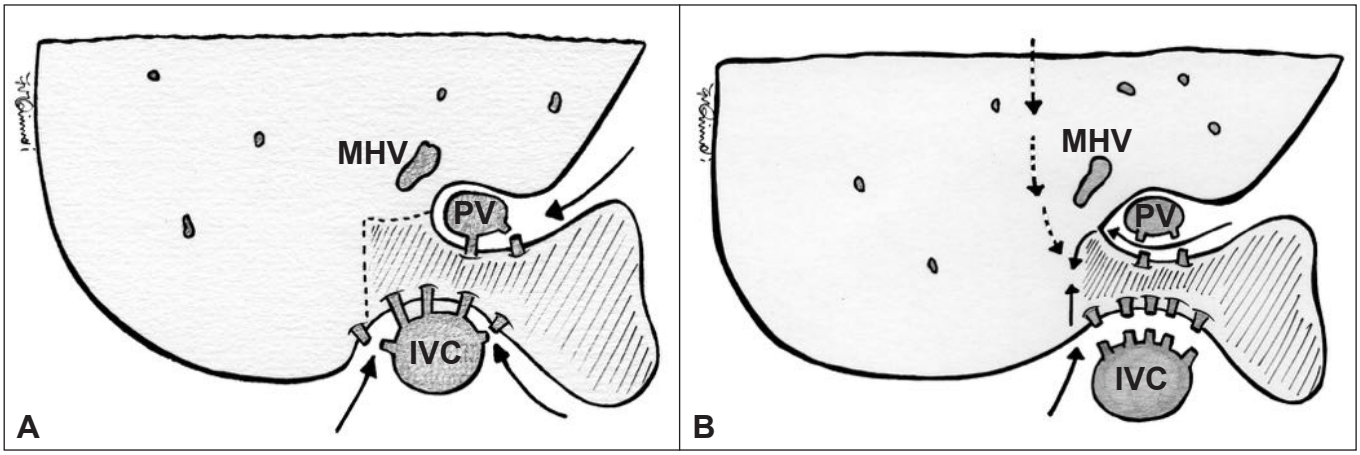


Figure 11. Schematic representation of segment 1 resection, axial view. **A**) Portal branches and short hepatic veins are sectioned in a left to right approach (arrows 1 and 2). Some short hepatic veins are easily approached from right to left (arrow 3). **B**) After division of portal branches and complete separation from the inferior vena cava by section of all short veins, the parenchymal transection is accomplished from left to right and/or right to left (black arrows). Alternatively, the liver is split to access this area (dashed arrows). MHV: middle hepatic vein; PV: portal vein; IVC: inferior vena cava.

SEGMENT 4 RESECTION

Segment 4 resection involves two transection planes. The left transection plane follows the left plane of central hepatectomy, between segment 4 and segments 2 and 3. All portal inflow pedicles to segment 4 are controlled along this plane. The main portal pedicles to segments 4b and 4a can usually be identified and divided extrahepatically after incision of the peritoneal reflection on the right side of the umbilical fissure. The right transection plane follows the plane of left hepatectomy (between segment 4 and segments 5 and 8), where the middle hepatic vein is exposed and preserved. These two planes converge to the junction of the left and middle hepatic veins. Care should be taken not to injure the right and especially the left portal pedicles during liver transection close to the liver hilum. Parenchymal transection close to the hilar plate becomes transverse. Finally, the two planes unite at the junction between middle and left hepatic veins. Venous drainage is predominantly to the middle hepatic vein; the sizable hepatic veins draining into the left and middle hepatic veins are ligated and divided.

Isolated resection of segment 4b is usually performed for small tumors in this segment, contrarily to isolated resection of segment 4a, which is rarely performed. Further, combined resection of segments 4b and 5 is used for some cases of gallbladder carcinoma.

INDIVIDUAL SEGMENT RESECTION IN RIGHT LIVER

Each of the four right side Couinaud's segments (i.e. segments 5, 6, 7, 8) can be resected individually according to the oncological necessity. The principles of resection for each of these segments are similar. First, the boundaries of the segment can be defined with the use of IOUS. In some situations, dye injection to the corresponding portal pedicle under ultrasound guidance can help to define clearly the demarcation lines on the liver surface. Second, full mobilization of the right liver is necessary to facilitate the liver transection. Third, individual portal pedicles should be identified and ligated in a secure manner to prevent bile leakage. Finally, in the case of major hepatic veins in proximity, great care should be taken not to induce collateral damage to the vein.

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25 Right Liver Resections

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- *Anatomical right liver resections include right hepatectomy (segments 5 to 8), right lobectomy (segments 4 to 8), right paramedian setorectomy (segments 5 and 8), and right lateral sectorectomy (segments 6 and 7).*
- *Anatomical segment-oriented liver resections require accurate knowledge of landmarks and precise dissection of the hilar region. Appropriate surgical view, occasionally requiring associated laparotomy and thoracotomy, is crucial for a safe resection.*
- *Right liver mobilization (before or after parenchymal transection) is usually needed, and complete mobilization from the inferior vena cava is required if liver resection includes segment 1.*
- *After right hepatectomy or right lobectomy, fixation of the falciform ligament keeps the remnant liver in anatomical position and allows adequate outflow.*

INTRODUCTION

The liver may be anatomically divided according to the portal system into two hemilivers: the right and the left liver. The middle hepatic vein (MHV) runs between the right liver and left liver on the main portal fissure. The right liver is usually two thirds of the whole liver volume. It consists of two sectors: the right paramedian sector (RPMS) and the right lateral sector (RLS), with the right hepatic vein (RHV) running between the two (on the right portal fissure).

The liver is attached to the abdominal wall in the ventral direction by the falciform ligament at the midline. The right liver is located in the right subphrenic space, and is fixed to the diaphragm and the retroperitoneum by the right coronary, triangular ligaments and the hepato-renal ligament. A part of the dorsal surface of the right liver is attached to the retroperitoneum, which is called the bare area, between the right coronary and the hepato-renal ligaments.

Anatomical right liver resections include right hemihepatectomy, right lobectomy (right liver plus segment 4), right paramedian sectorectomy, and right lateral sectorectomy. The resection planes of each of these procedures are different (**Figure 1**); however, they have some key points in common, such as laparotomy, hilar dissection, mobilization, and parenchymal division.

In this chapter, common techniques of right liver resections are described according to the authors' experience. Other technical aspects are described in other chapters in this section (see Section 4 – Technical Aspects of Liver Resections).

GENERAL STATEMENT

LAPAROTOMY

A J-shaped incision is generally used for right liver resection.[1] First, an upper median incision is made turning to the right

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lateral direction about 3 to 5 cm above the umbilicus entering the 9th intercostal space. The diaphragm is then incised to open the thoracic cavity. Intercostal muscles are divided along the cranial surface of the 10th rib to the midpoint between the vertebra and the posterior axillary line. Better access to the area around the juncture between the inferior vena cava (IVC) and major hepatic veins is gained by entering the right pleural and abdominal cavities. Thoracotomy also facilitates palpation of the lower mediastinum and the upper hepatic portion of the IVC, as well as intraoperative ultrasound examination. Moreover, bleeding from the area between the IVC and retroperitoneum can be controlled from the thoracic cavity by the surgeon's left index finger. Thoracic pressure becomes almost the same as that of the abdominal cavity; thus, inadvertent and unexpected air embolism can be avoided. The xyphoid process is excised for better exposure. The falciform ligament is divided along the anterior abdominal wall, and its continuation into the coronary ligaments is detached from the diaphragm, to expose the bare area. The junction of the RHV and the MHV with the IVC is dissected until it is possible to insert the left index finger between these veins and also behind the RHV, enabling surgeons to control the venous bleeding by compression.

When the tumor is large, an inverted T-shaped incision is made, and the transverse incision reaches the left edge of the left rectus. On the right side, it extends to the 9th intercostal space, as does the J-shaped incision.

DISSECTION OF THE HILAR REGION

In most cases, the second order branch of hepatic arteries and portal veins can be extraparenchymally skeletonized. To expose the hilum, the gallbladder is first removed, leaving the full length of the cystic duct to insert a balloon catheter for intraoperative cholangiography and bile leakage test.

The vessels on the hilar right side are dissected out. The cystic duct with the balloon catheter is retracted to the left side. The connective tissue behind it is incised longitudinally to expose the right hepatic artery, which is encircled. The dissection is continued until it reaches the division into branches to the right paramedian and right lateral sectors. During dissection of the cystic duct and the right hepatic artery, the aberrant right lateral duct should be preserved. Intraoperative cholangiography should be carried out without hesitation upon encountering questionable ducts or bundles of connective tissues. After the connective tissues have been fully divided, the right wall of the portal vein becomes visible. The portal vein is encircled, taped, and dissected along the right branch up to its bifurcation into the branches to the right paramedian and the right lateral sectors.

After skeletonization of the hepatic artery and the portal vein, a clamp test of the vessels to be ligated and divided is carried out (decolorization on the liver surface demarcating the clamped segments). When the area expected to be resected is not obtained as a discolored area, surgeons should consider the possibility of error in the procedure identifying the vascular branches. These vessels should be ligated and divided only after a reliable demarcation area is obtained by the clamp test. The decolorized area can be demarcated at the liver surface using electrocautery.

MOBILIZATION OF THE RIGHT LIVER

When a tumor is large and the area attached to the diaphragm is wide, the right inferior phrenic artery should be ligated.

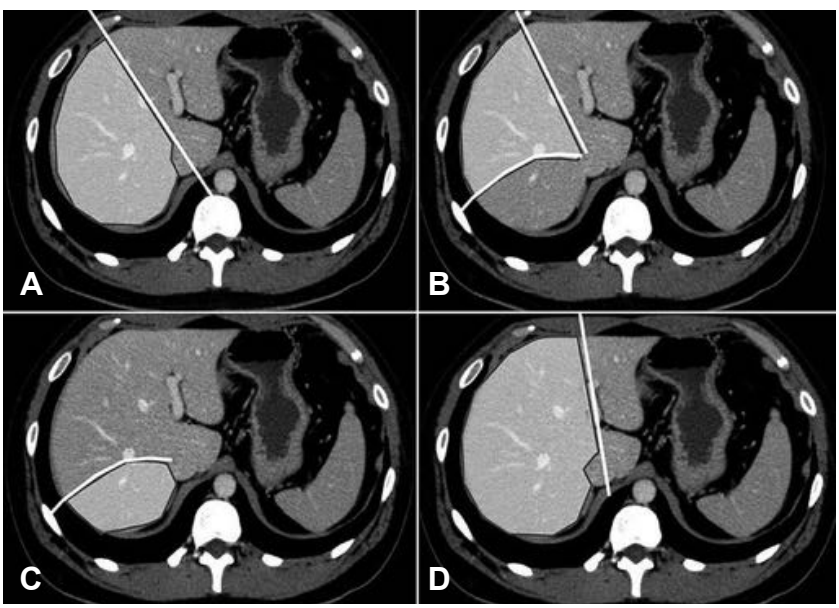


Figure 1. Resection planes of the right liver resections on computed tomography. **A**) Right hemihepatectomy. **B**) Right paramedian sectorectomy. **C**) Right lateral sectorectomy. **D**) Right trisectorectomy.

The right infraphrenic artery originates around the celiac axis and proceeds in a craniolateral direction, running behind the caudate lobe. This artery can be identified after cranial retraction of the caudate lobe and dissection of the fatty tissue between the IVC and the crus of the diaphragm. In thin patients, this artery may be visible without any dissection. Next, the right triangular and coronary ligaments are dissected, and the right hemiliver can now be mobilized, dissecting the bare area. The right adrenal gland is usually an obstacle for liver mobilization, especially for extrahepatic control of the RHV.[2]

Even when the adrenal gland seems tightly attached to the liver, it is only attached by its ventral surface of the right lateral half. Therefore, when the suprarenal grand is found to be tightly attached to the liver during the dissection of the bare area from the retroperitoneum and from the right lateral side, its dissection is halted and the caudal part of the retrohepatic IVC is first dissected. The right lateral side of the IVC is detached from the liver until the anterior surface of the suprarenal gland appears. To avoid damaging the adrenal vein, this dissection must be carried out with great care. The bare area of the liver is then dissected, commencing from the cranial side, proceeding caudally along the IVC. The surgeon's left index finger is then inserted along the IVC from the cranial side, and thumb from the caudal side, so that their tips meet with only a thin loose connective tissue between them. The thumb is replaced by Kelly forceps, penetrating the connective tissue towards the left index finger through the tunnel, along the right side of the IVC. A thick tie is then passed through the tunnel and the adrenal gland is divided from the lateral side towards the IVC by electrocautery. If bleeding occurs from the adrenal gland, it can be controlled by ligating the suprarenal gland itself, using the thick tie that has already been placed. Bleeding from the liver side is stopped by the surgeon's left hand. It can be finally controlled by sutures after controlling the bleeding from the adrenal side. However, if a short hepatic vein is found flowing into the adrenal vein, this vein is ligated at both the liver and adrenal sides before dividing the adrenal gland.

The dissection of the IVC on the right dorsolateral side of the IVC proceeds to the cranial side, and a thick bundle of fibrous tissue appears near its junction with the right hepatic veins above the suprarenal vein, connecting the dorsal edge of the right liver with the left caudate lobe. The thick bundle of fibrous tissue is the IVC ligament.

Identification, ligation and division of the IVC ligament are essential to safely expose the RHV. The IVC is compressed by the ligament when the right liver is lifted up. Since the RHV is in contact with the inner aspect of the IVC ligament, the ligament must be divided before approaching the RHV. After mobilizing the right liver from the retroperitoneum, the short hepatic veins are ligated and divided, proceeding cranially. The right lateral side of the IVC together with the RHV are pulled inward by the IVC ligament when the right liver is lifted up, placing the IVC with its junction with the RHV in close contact with the IVC ligament. The tips of Metzenbaum scissors are inserted between the IVC and the ligament. The right wall of the vein is then pushed gently to the left to separate the ligament from the vein. The ligament may contain a short hepatic vein, and is therefore ligated before division. After the procedure, the root of the RHV is easily dissected; the RHV is clamped with vascular forceps, divided, and then sutured. Dissection of the liver from the IVC continues inward until the trunks of the middle and left hepatic veins are exposed. Dissecting the IVC up to this site is essential for right hemihepatectomy and right lobectomy. When the entire caudate lobe is to be resected, dissection of the IVC is continued until the liver is completely mobilized from the IVC, excluding the trunks of the middle and left hepatic veins.

Right liver mobilization may be also accomplished after parenchymal transection in the so-called anterior approach, with or without hanging maneuver, as described in **Chapter 22** (General Technical Aspects of Liver Resections).

PARENCHYMAL DIVISION

The resection line is marked on the surface of the liver using electrocautery. Generally, the crush-clamping method is used for hepatic parenchymal division. According to the surgeon's preference, surgical tools such as an ultrasonic dissector/aspirator with electrocautery (SONOP 5000, Aloka, Tokyo, Japan), ultrasonic dissector (Cavitron Ultrasonic Surgical Aspirator System 200, Valleylab Inc., Colorado, USA), or saline-linked radiofrequency coagulator (DS 3.0, Tissue Link Medical, New Hampshire, USA), among others, may be employed.

At the outset, the total inflow occlusion technique (Pringle maneuver) or selective hemihepatic inflow occlusion technique[3] is used. Hemihepatic occlusion of the right liver is especially useful during the division of the right portal fissure during right paramedian sectorectomy or right lateral sectorectomy. In these procedures, after the portal and the hepatic arterial inflow to the right paramedian (or right lateral) sector are ligated and divided, hemihepatic inflow occlusion of the left liver is effective in controlling bleeding from the division carried out along the main portal fissure (see details on specific topics below). Inflow occlusion is applied in an intermittent manner, usually with 15 minutes of occlusion alternated with 5 minutes of reperfusion in cases of total liver occlusion, and with 30 minutes of occlusion and 5 minutes of reperfusion for hemihepatic occlusion. During parenchymal transection, the round ligament is pulled ventrally and caudally to better expose the diaphragmatic surface and to decrease the hepatic venous pressure in the transection plane (by optimizing the outflow). Lifting up the

right liver using the surgeon's left hand is also important to decrease the venous pressure and the amount of bleeding from the hepatic veins. In order to maintain the quality of anatomical hepatic resection, exposing the landmark hepatic veins on the raw surface of the liver is essential. During exposure, the small veins draining to major hepatic veins become obstacles for liver transection. Therefore, these small branches should be ligated meticulously. To avoid tearing the forks of the hepatic venous tributaries, a suction probe is moved gently along the hepatic vein away from the IVC, from the cranial to the caudal direction.

To control bleeding from the resection plane, it is helpful to place the operating table in a right anterior oblique position. Also, to decrease thoracic pressure (and backflow bleeding), a sufficient level of anesthesia is maintained, an adequate dose of muscle relaxant is given, and the tidal volume of the ventilation is reduced to 30% to 40% of the standard volume. By using a combination of anesthesia and early intraoperative fluid restriction (7 ml/kg/hour, excluding blood loss), central venous pressure would ideally be controlled below 5 cm H_2O to reduce backflow venous hemorrhage during transection. When these procedures are ineffective, blood sanguination of 7 ml/kg is quite effective in decreasing the amount of bleeding from the hepatic veins. For patients with liver cirrhosis and chronic hepatitis, fresh frozen plasma, either autologous or homologous, is administered at a rate exceeding the amount of blood loss by 10% to 20%.

CLOSURE

After removing the specimen, complete hemostasis should be confirmed. First, the raw surface of the liver is covered by a rubber sheet made from surgical gloves. The internal side of the surgical glove is spread on the raw surface and gauze is added. The gauze is pushed gently for five minutes. If bleeding continues, it is controlled using electrocautery or fine suture ligation.

For detection of bile leakage, intraoperative cholangiography and/or a bile leakage test is carried out. First, saline is slowly injected through the cystic catheter until the biliary tree is filled, which may be assessed by feeling for swelling of the common bile duct with the fingers. If bile leakages are found, the sites are sutured on a point-by-point basis with a non-traumatic needle with absorbable sutures. 24F silicone tubes are left at each cut surface, and are connected to a closed drainage system. A 16F tube is also inserted in the thoracic cavity if it has been opened, and is sucked continuously with negative pressure of 20 to 30 cm H_2O.

After right hemihepatectomy or right lobectomy, the falciform ligament must be fixed at the same former position where it was attached, to avoid outflow blocking and consequent ascites and/or liver dysfunction.

RIGHT HEMIHEPATECTOMY

After thoraco-phreno-laparotomy with a J-shaped incision, the cystic artery and the cystic duct are ligated and divided near the neck of the gallbladder. The gallbladder is freed from the liver bed at the left side of Rex line. Cholecystectomy is not necessarily to be performed.

Right hilar dissection is started by retracting the cystic duct with the balloon catheter to the left ventral side. Any structure at the right side of the common bile duct is ligated and divided without hesitation. The right hepatic artery may now be exposed at the right side of the common bile duct, and is doubly ligated at the proximal side, and then divided after single ligation at the distal side. Optionally, if the bifurcation of the right paramedian and lateral branches is easily found, these branches are independently ligated and the right hepatic artery is divided. Division of the right hepatic artery at the right side of the common bile duct results in safe preservation of the left hepatic artery.

The main trunk of the portal vein can be observed behind the right hepatic artery. The wall of portal vein should be exposed, sharply dissecting the surrounding tissue. The connective tissue behind the extrahepatic bile duct is incised to the caudal side, about 1 cm along the duct. Then, the portal vein is encircled with an umbilical tape. The connective tissue behind the umbilical tape at the right side of the portal vein is divided. After the right anterior wall of portal vein is exposed in the direction toward the bifurcation of right and left portal veins, dissection around the right portal vein is commenced. Near the bifurcation, the small branches to the caudate lobe appear. All of these branches from the right portal vein should be carefully isolated, ligated, and divided. The right portal vein can now be safely encircled and ligated. The proximal side of the right portal vein is doubly ligated and divided, carefully avoiding narrowing down the left portal vein.

If the branching pattern of the portal vein is of a trifurcation type, or an independent branch of the RLS is present, portal veins to the RPMS and RLS can be ligated and divided separately. When the right hepatic artery and the right portal vein are ligated and divided but the demarcation line on the main portal fissure does not appear, a missed, non-ligated RPMS portal vein may be the cause. Ultrasonic examination should be carried out to confirm the existence of this RPMS portal vein.

When the right hepatic duct is located at the ventro-cranial side of the right portal vein, it is divided with a margin of approximately 1 cm left. What remains of the Glissonean sheath of the right liver is then divided. Through this procedure, the inflow blood to the right liver is completely halted. When the right hepatic duct is not clearly seen, it is divided when the parenchymal division reaches

the hepatic hilum, with the assistance of intraoperative cholangiography.

The liver transection plane includes the demarcation line at the liver surface, the right side wall of the MHV and the mid-line of the IVC (**Figure 2**). The liver parenchyma between the right and left caudate lobe is divided before transecting the liver. The demarcation line should also appear along this division line.

The liver parenchyma is divided using the Pringle maneuver along Cantlie's line, commencing from the caudal edge between segment 4 and segment 5. A relatively thick tributary of the MHV, which appears at the division plane, is a helpful leading mark to reach the main trunk of the MHV. The distal end of the MHV tributary should be ligated or clipped to avoid excessive bleeding. Liver transection is continued along the MHV. If the right hepatic duct has not yet been divided, it can be divided at this stage. Intraoperative cholangiography is useful for safe bile duct division. The right wall of the MHV is then exposed to the root, and some thick tributaries from the RPMS are ligated and divided. Beyond the MHV, liver transection is continued to the IVC. At this stage, the surgeon's left index finger, inserted between the liver and the IVC, acts as a helpful guide for safe transection, and is useful in reducing bleeding from the hepatic vein. When the right hemiliver is removed, the MHV is fully exposed at the resection plane (**Figure 3**).

Other techniques can be used as a means of accomplishing the anatomical resections described in this chapter, such as the anterior approach and the hanging maneuver for right hepatectomy. These technical options are described in other chapters of this textbook.

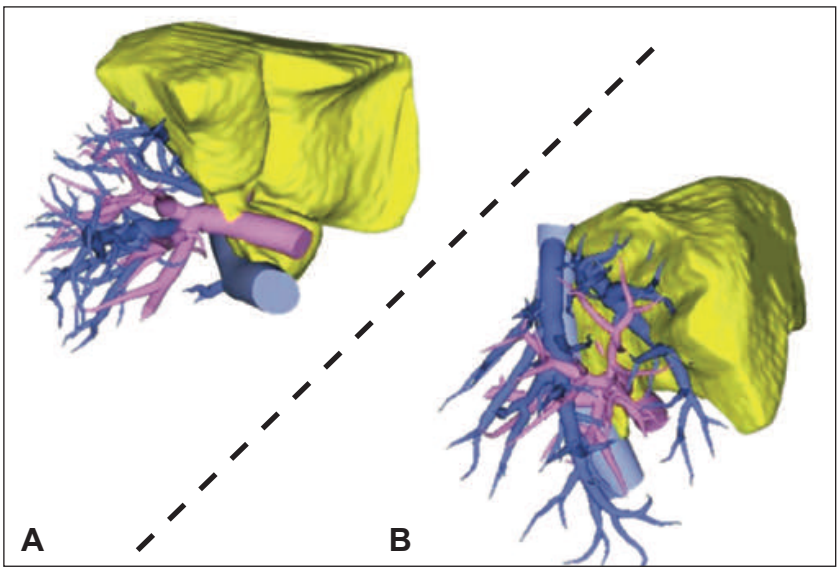


Figure 2. Schematic view images of right hemihepatectomy using 3D liver volumetry. Remnant liver volume is shown in yellow, inferior vena cava is in light blue, hepatic veins are in dark blue, and portal veins are in purple. Resected parenchymal volume was subtracted and major vessels maintained on images. Resection plane passes through the right side wall of the middle hepatic vein to the mid-line of the inferior vena cava. Right portal vein and right hepatic vein are to be resected. **A**) Inferior view. **B**) Right view.

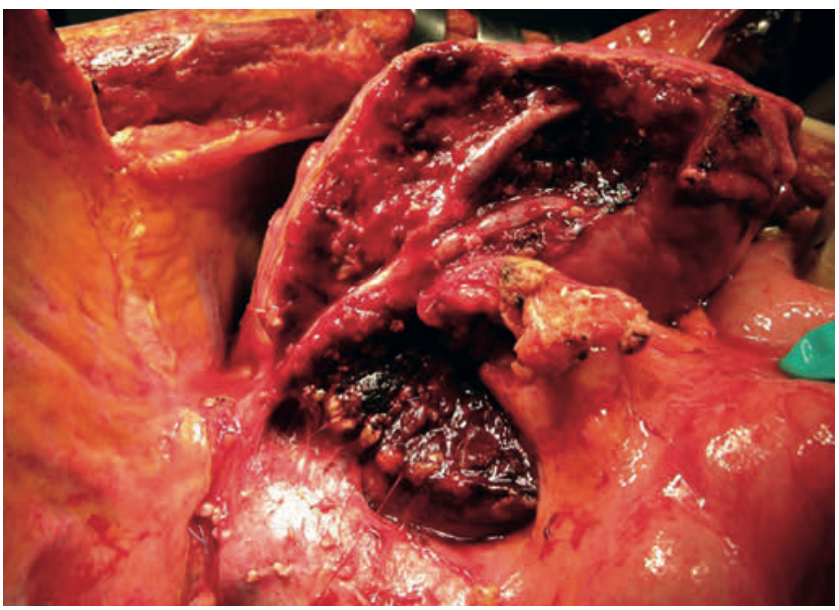


Figure 3. The resection plane after right hemihepatectomy. The middle hepatic vein and its tributaries are exposed on the raw surface of the liver.

RIGHT PARAMEDIAN SECTORECTOMY [4]

After thoraco-phreno-laparotomy is carried out and retractors are fixed, cholecystectomy is performed. Calot's triangle is completely dissected. Further dissection of the right portal pedicle will be hindered if fatty tissue is not completely removed. Hilar dissection starts by the right side. In most cases, second order branches of the hepatic artery and the portal vein may be exposed separately. The hepatic artery and portal vein flowing into the right paramedian sector are encircled and taped. In some cases, there are two arteries flowing into this sector. If the portal branch flowing into the segment 7 (to be preserved) originates from the right portal vein independently, its branching site is carefully avoided using ultrasonic guidance. If the right pedicle bifurcation is found to be deeply located, extrahepatic dissection should be abandoned. At this stage of hilar dissection, clamp tests of the hepatic artery and the portal vein branches should be carried out in order to ensure that these vessels can be ligated and divided (with no compromise of remnant segments).

Next, the vessels on the left side are dissected for hemihepatic vascular occlusion. The common bile duct is retracted to the right side to expose the left portal vein. The left portal vein is then dissected out and taped. The tips of Kelly forceps are passed through above the right hepatic artery on the left side of the common bile duct, in order to lift up the hepatoduodenal ligament below the left portal vein. A vessel loop is caught and pulled out ventrally in order to cut off the arterial supply to the left liver. Exposure of the left and the middle hepatic arteries is unnecessary using this method.

The minor omentum is examined carefully for any accessory of the left hepatic artery originating from the left gastric artery. If present, it is encircled and taped.

In patients with typical vasculature, the portal pedicle of the right paramedian sector runs in a cranio-lateral direction, whereas the right lateral sector branch runs dorsal-laterally. When in doubt, the suspicious pair is temporally occluded, and is observed to determine whether the sector they supply would appear discolored on the liver surface. If discoloration is not observed, a clamp test should be repeated using Doppler ultrasonography to identify the corresponding vessels.

The artery to the right paramedian sector is ligated and divided. Approximately 1 to 1.5 cm of the portal vein to this sector is exposed and divided between double ligatures. The bile duct at the cranio-ventral side of the exposed portal vein becomes now accessible for dissection, ligation, and division at a safe distance from its confluence with the portal pedicle to the right lateral sector, thus avoiding injury to the bile duct. However, ligature is only placed if the portal vein to the right paramedian sector cannot be sufficiently exposed, and it is dealt together with the rest of the portal pedicle when liver transection of the right portal fissure reaches the portal pedicle of the right paramedian sector.

Two resection planes are needed to accomplish a right paramedian sectorectomy, the main portal fissure plane and the right portal fissure plane (**Figure 4**), and the area of resection plane is the widest of all the typical segment oriented hepatic resections.

The blood supply of the left liver is occluded and the liver parenchyma is divided along the Rex line or main portal fissure proceeding from the caudal edge. When the bifurcation of the middle hepatic vein is exposed, the right tributary is ligated and divided. Liver transection is continued

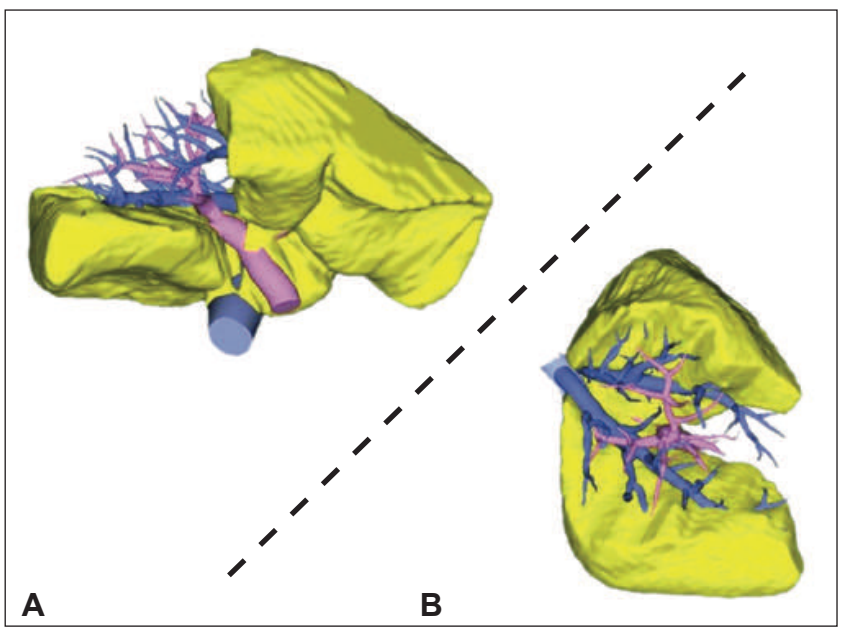


Figure 4. Schematic view images of right paramedian sectorectomy. Remnant liver volume is shown in yellow, inferior vena cava in light blue, hepatic veins in dark blue, and portal veins in purple. Resected parenchymal volume has been subtracted and major vessels maintained on images. Cross section area consists of two resection planes, main portal fissure and right portal fissure. The portal pedicle of the right paramedian sector is to be resected. Major hepatic veins are exposed and preserved. **A**) Inferior view. **B**) Right view.

along the middle hepatic vein. Small tributaries from the right side are all carefully isolated and meticulously ligated. Large tributaries of the middle hepatic vein are found near the confluence with the inferior vena cava. They are carefully ligated and divided. If bleeding is observed, the surgeon's left index finger inserted between the middle and the right hepatic veins is useful to pull up the parenchyma to compress the tributaries on the ventral side and control the bleeding. During the transection, the hemihepatic vascular occlusion is released every 30 minutes to allow for five minutes of perfusion.

Next, the blood supply to the right liver is occluded, and the liver parenchyma is divided between the right paramedian and lateral sectors, proceeding from the caudal edge. Hemihepatic vascular occlusion is particularly suitable because liver transection may be commenced from the center of the ischemic area. When the transection reaches the hilum, the portal pedicle of the right paramedian sector is ligated and divided, if this procedure has not been carried out during the hilar dissection. The main trunk of the right hepatic vein is then exposed, and the transection is continued from this vein toward the cranial surface of the liver. Once the entire hepatic vein is exposed, the right paramedian sector is tilted superiorly to widen the transection plane. As with the middle hepatic vein, a few large tributaries of the right hepatic vein are found just before where it drains into the inferior vena cava. They are carefully freed from the surrounding parenchyma before ligation and division are carried out. Bleeding from the right hepatic vein and its tributaries is controlled by placing the surgeon's left index finger behind the right hepatic vein and compressing it anteriorly. When the right paramedian sector is removed, both the middle and the right hepatic veins are fully exposed (**Figure 5**).

RIGHT LATERAL SECTORECTOMY

In general, a J-shaped incision with thoracotomy in a supine position is placed for right lateral sectorectomy. When the tumor is attached to the IVC, an oblique incision through 8th or 9th intercostal space in a left hemilateral position is useful.

After cholecystectomy, dissection of the right side of the hepatoduodenal ligament is commenced retracting the common bile duct to the left. The right hepatic artery can now be exposed on the right side of the common hepatic duct, and is dissected to the distal. After the right hepatic artery is taped, it is pulled up ventrally and the right portal vein is taped. The bifurcation of the hepatic artery of the right paramedian and the lateral branches is exposed and taped. Under occlusion of the right portal vein, typical demarcation is obtained, and the artery to the RLS is doubly ligated and divided. The branching patterns of the right paramedian and lateral sector vary. Therefore, preoperative evaluation by 3D image reconstruction of the hepatic artery using thin slice multi-detector CT is recommended. During the dissection of the hepatic artery, the main trunk of the portal vein is identified. Dissection of the portal vein is continued along the wall of the portal vein to the distal side. The bifurcation of the RPMS and the RLS can be exposed after encircling the right portal vein. Small branches to the paracaval portion are carefully ligated and divided. The portal vein to the RLS can then be encircled, ligated and divided. If the portal branch to segment 7 originates from the right portal vein independently, its branching site is carefully dissected and taped. When the safety margin cannot be secured, ligation alone is carried out, and the division is left until after the liver transection reaches segment 7 portal pedicle. When the portal vein to the RLS independently

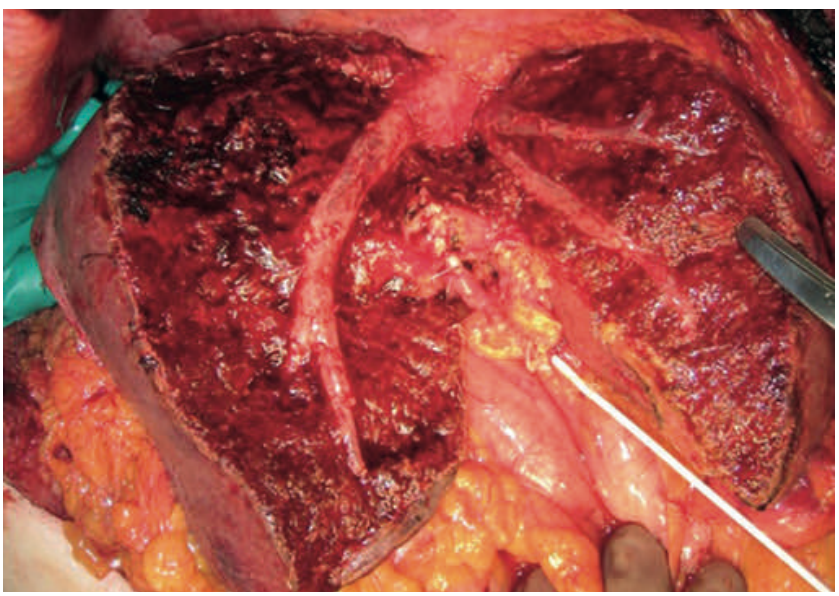


Figure 5. The resection plane after right paramedian sectorectomy. Two resection planes are shown. The middle hepatic vein (MHV) is exposed on the left resection plane, and the right hepatic vein (RHV) is exposed on the right resection plane. The confluence of hepatic veins to the inferior vena cava (IVC) is also exposed.

branches out from the main portal vein, the ligation and division of portal vein is comparatively easy. However, special attention should be paid in case of an anatomically anomalous biliary system. Following the hepatic artery and portal vein is the Glissonean sheath of RLS, including its bile duct. The Glissonean sheath is divided during liver transection. When thick, short hepatic veins - including the inferior right hepatic vein (IRHV) and middle right hepatic vein (MRHV) – are encountered during mobilization of the liver, these veins may be divided.

The liver transection plane includes the demarcation line on the liver surface, the RHV, and the IVC (**Figure 6**). In principle, the main trunk of the RHV is fully preserved.

The liver parenchyma is divided along the demarcation line from the caudal edge, during which 10 minutes of preconditioning and 30 minutes of hemihepatic inflow occlusion of the right liver (with five minutes of reperfusion between), are repeated until the transection is completed. The main trunk of the RHV is located tracing the tributaries, and is then exposed. The main trunk of the RHV does not run on the caudal half of the right portal fissure in patients with thick IRHV. Liver transection is continued exposing the wall of the RHV. Bleeding from the RHV is easily controlled by compressing it to the ventral side with the surgeon's left index finger behind the RHV.

Beyond the RHV, liver transection is continued to the IVC towards the surgeon's left index finger inserted in front of the IVC. The liver parenchyma between the caudate process and the RLS is divided behind the hilar plate.

After the parenchymal division, the Glissonean sheath of the RLS is divided. To avoid injuring the bile duct of the RPMS, the Glissonean sheath should be ligated and divided 1cm away from the portal pedicle of the RPMS.

When the RLS is removed, the RHV is fully exposed at

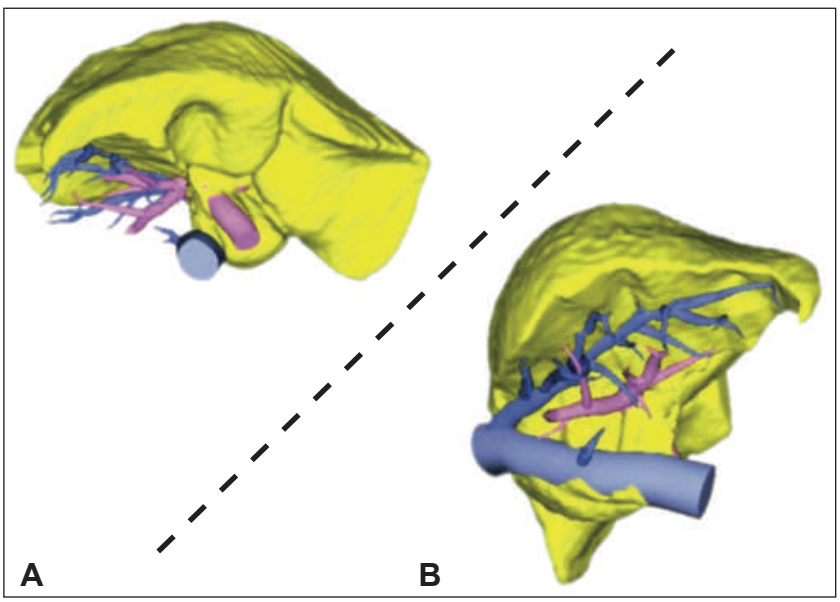


Figure 6. Schematic view images of right lateral sectorectomy. Remnant liver volume is shown in yellow, inferior vena cava in light blue, hepatic veins in dark blue, and portal veins in purple. Resected parenchymal volume has been subtracted and major vessels maintained on images. The resection plane passes through the dorsal wall of the right hepatic vein to the midline of the inferior vena cava. The portal pedicle of right lateral sector is to be resected. RHV is preserved. **A**) Inferior view. **B**) Right view.

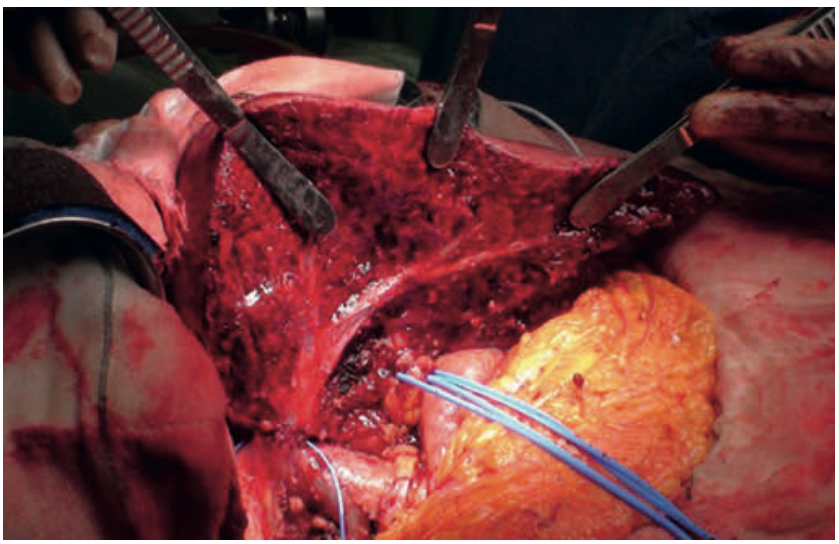


Figure 7. The resection plane after right lateral sectorectomy. The right hepatic vein (RHV) and its tributaries are exposed on the resection plane.

the resection plane (**Figure 7**). However, if a thick IRHV is draining segment 6, the RHV is not used as a landmark for the liver transection of the caudal part, and if a thick MHV tributary is draining segment 6, the tributary is found at the resection plane and should be easily divided.

RIGHT LOBECTOMY

Right lobectomy includes the removal of segments 4 to 8 with or without bile duct resection. For hilar bile duct carcinoma, the removal of Spiegel's lobe is concomitantly performed. Details of hilar dissection, liver mobilization, and parenchymal division differ with each procedure. Most patients who receive this operation have a huge tumor compressing the hilar and umbilical plates and the IVC, except for those with hilar cholangiocarcinoma.

A J-shaped incision is usually employed, and the cystic artery and the cystic duct are ligated and divided near the neck of the gallbladder. A balloon catheter is inserted via the cystic duct for intraoperative cholangiography and bile leakage test. Dissection of the right side of the gallbladder is unnecessary. The common bile duct is encircled with surrounding connective tissue at the root of the cystic duct level.

When the bile duct is to be preserved, right hilar dissection is performed in a similar fashion to right hemihepatectomy. When the right hepatic duct is compressed by a large tumor, it is divided during the parenchymal division. The dissection of the left side of the hilum is unnecessary. The portal pedicles to segment 4 are divided in transparenchymal fashion at the right side of the umbilical portion of the left portal vein during hepatic division, or after dividing the umbilical fissure. All portal and arterial branches to segment 4 are ligated and divided, and discoloration of segment 4 is observed.

Complete mobilization of the right liver is necessary. Extrahepatic division of the RHV should be carried out. Dissection around the root of the LHV and the MHV is important. After the division of the RHV, the right side of the root of the MHV can be safely approached. The short hepatic veins are meticulously ligated and divided until the ventral aspect of the IVC is exposed. The IVC can be easily separated from the tumor in patients with hepatocellular carcinoma. However, the same cannot be expected in patients with metastatic tumor from colorectal cancer or mass-forming intrahepatic cholangiocarcinoma close to the IVC.

The resection line is set along the center of the falciform ligament on the diaphragmatic surface, and along the midline of the umbilical fossa on the visceral surface. Using the inflow occlusion technique, liver transection is commenced from the caudal edge, at the right side of the falciform ligament. The portal pedicles to segment 4 are ligated and divided. Occasionally, the fissural vein is exposed at the resection plane, and if so, it is preserved. The liver parenchyma is divided vertically until the front of the transection reaches the level of hilar plate. When the round ligament is pulled up, the umbilical portion and hilar plate will straighten, and a tumor near the hilum may be carefully separated from the hilar plate avoiding injury of the bile ducts. All small pedicles to the right portal pedicle on the hilar plate are gently isolated and ligated. Ligation of the caudate lobe branch feeding the paracaval portion of the right caudate lobe is particularly important. At the cranial portion, the root of the MHV is exposed. The MHV is carefully divided, avoiding narrowing of the left hepatic vein, which is preserved. Double ligation or running suture should be applied for the division of the MHV. The transection is then continued to the IVC preserving the caudate lobe, and right lobectomy is completed. If the left

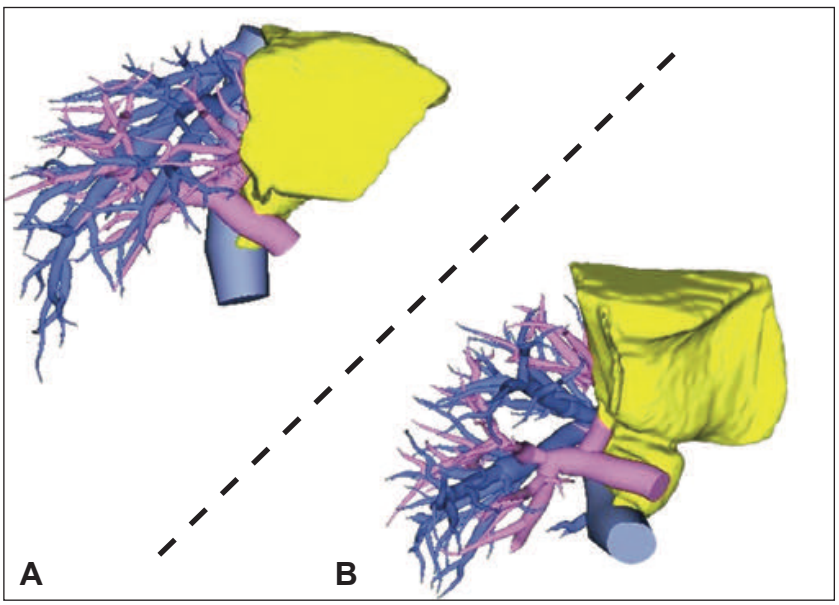


Figure 8. Schematic view images of right lobectomy. Remnant liver volume is shown in yellow, inferior vena cava in light blue, hepatic veins in dark blue, and portal veins in purple. Resected parenchymal volume has been subtracted and major vessels maintained on images. The resection plane passes through the right dorsal wall of the umbilical portion to the mid-line of the IVC. The portal pedicle of segment 4 and right portal vein are to be resected. MHV and RHV are also resected. **A**) Anterior view. **B**) Inferior view.

bile duct is injured, bile duct resection should be carried out without hesitation.

Right lobectomy with biliary and segment 1 resection. If the extrahepatic bile duct is to be resected concomitantly, hilar dissection is commenced at the left part of the hepatoduodenal ligament, exposing the left and proper hepatic arteries. The right hepatic artery may be ligated and divided at its root. The common bile duct is ligated and divided at the cranial side of the pancreas. Lymph node dissection is performed around the common hepatic artery and the pancreas head. The left hepatic artery is exposed to the hilum. If the artery to segment 4 is branching out from the left hepatic artery, this artery may be ligated and divided. Behind the hepatic artery, the main portal vein is taped. All connective tissue, lymph nodes and bile ducts are pulled up to the cranial side and the right portal vein is ligated and divided. The dissection is continued carefully, retracting the taped portal vein to the left. Small portal branches from the transverse portion of the left portal vein are ligated and divided.

The serosa of the umbilical fossa is opened, and the wall of the portal vein is exposed. The portal branches to segment 4 are found on the right side. These branches may be ligated and divided.

The right liver is fully mobilized. The RHV is extrahepatically divided. The short hepatic veins including the IRHV and the MRHV are ligated and divided in order from the right side of the IVC. All short hepatic veins and the principal caudate vein is ligated and divided in order from right to left. Finally, the wall of the IVC is fully exposed, except for the root of the LHV and the MHV. Mobilization of Spiegel's lobe is reliably achieved with approach from the right side.

The resection line for this procedure is the same as in the procedure described for right lobectomy without segment 1 resection. The liver transection is commenced from the caudal edge at the right side of the falciform ligament using the inflow occlusion technique. Spiegel's lobe may be inverted and set aside to the right, while the surgeon's left index finger is inserted along the duct of Arantius. The liver parenchyma should be divided vertically toward the surgeon's left index finger. Upon completion of the liver transection, the left bile duct with surrounding connective tissue is the only part remaining to connect the part of the liver to be resected and the part of the liver to be preserved. The bile duct is then divided, and right lobectomy is completed. Biliary reconstruction is performed by Roux-en-Y fashion.

FINAL CONSIDERATIONS

In this chapter, general techniques and step-by-step detailed description of various types of right liver resection are presented. Accurate dissection of the hilar region with correct anatomical knowledge is important for complete anatomical resection, and full exposure of landmark veins on the resection plane is essential. In addition, a good surgical view obtained by thoracotomy is helpful in carrying out safe and successful hepatic resection.

Alternative approaches and technical options can be used in anatomical liver resections, as described by authors of other chapters in this textbook. Choice of a specific method depends mainly upon surgeon preference and/or experience.

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26 Left Liver Resections

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- *An extrahepatic approach to vascular structures, combined with an intra-parenchymal left bile duct division, is the preferred technique to perform left liver resection. IOUS is an indispensable resource – not only to confirm selective vascular disconnection, but also to identify the appropriate transection plane during parenchyma transection.*
- *The left hepatic vascular pedicle is perpendicular in relation to the right pedicle when the round ligament is held upward during left hepatectomy.*
- *The transection plane of a left hepatectomy is initially vertical until the hilar plate, and becomes horizontal following the Arantius plane after the bile duct section.*
- *A hanging maneuver is also a useful technique for left resection extended to segment 1 or to the middle hepatic vein, since the transection plane is the same as that for a right hepatectomy.*
- *Total vascular exclusion should be performed in case of voluminous tumors that are in close proximity to hepatic veins.*
- *Vascular control of the left middle hepatic trunk is achieved from the left to the right in a strict horizontal plane. Lowering segment 1 and cutting the Arantius ligament are mandatory in order to safely perform this vascular control.*

INTRODUCTION

The terminology recommendations presented by the International Hepato-pancreatic and Biliary Association (IHPBA) committee at its biannual meeting in Australia in 2000, called *The Brisbane 2000*,[1] defined left liver resections as follows: i) *left lateral sectionectomy* or *bisegmentectomy 2,3* (previously called *left lobectomy*) for resections of segments 2 and 3; ii) *left hepatectomy* or *left hemihepatectomy* for resections of segments 2, 3 and 4; and iii) *left trisectionectomy*, also called *extended left hepatectomy* or *extended left hemihepatectomy*, for resections that include segments 2, 3, 4, 5 and 8. For oncological or technical reasons, the caudate lobe (segment 1) can also be removed during these procedures. Currently, laparoscopic approach for left liver resections is a feasible option.[2,3] Moreover, laparoscopic left lateral sectionectomy has become the gold standard approach in expert centers.[4–7] Nevertheless, an open approach for major left liver resections remains the standard for the majority of indications, and is the subject of this chapter (for laparoscopic approach, see **Chapter 27**). Among the different types of left resections, left trisectionectomy remains the most challenging and technically demanding resection. Almost all left liver resections can be performed without vascular clamping; however, left trisectionectomy, especially if indicated for hepatic vein involvement, can require total vascular exclusion.[8–10]

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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GENERAL APPROACH

The left liver is more accessible than the right liver, because of its anterior and medial anatomical presentation. Access can therefore be achieved without difficulties particular to different types of incisions. The authors favour a J-shaped right subcostal incision, which is feasible even in obese patients. However, if the resectable lesion is bulky, we suggest extending to a left subcostal incision to produce a "Mercedes" incision. In case of limited left resection, associated or not with a colorectal procedure, a simple midline incision may be proposed. After opening the abdominal cavity, the round and falciform ligaments are divided. The round ligament is used for further retraction. The subcostal margins are protected by gauze swabs, and bilateral fixed retractors are used for exposure. The left lobe is mobilized by sectioning the left triangular and coronary ligament by bipolar or monopolar electrocautery over a gauze swab, which protects posterior organs like the esophagus, stomach, and spleen. If the left lobe is voluminous and left triangular ligament lies over the upper surface of the spleen, it is safer to commence the dissection by the middle portion of the ligament, in order to avoid accidental lesions of the spleen. The lateral extremity of the left triangular ligament is better divided by lifting the left lobe to expose its posterior surface and downwardly retracting the spleen. At this point, one may pass a tape around the left lobe in order to optimize the exposition. Reaching the midline, the two leaves of the coronary ligament become separated (the so-called bare area of the liver) and the left hepatic vein is in close proximity. The inferior vena cava and the hepatic veins lie within this area. Dissection of the left hepatic vein itself or of the common trunk is a hazardous maneuver that might be reserved only for extended left liver resections or in exceptional situations. In case of extended left resection, right liver ligaments might be divided in order to facilitate exposure of the right medial sector, but their division is not necessary for ordinary left resections. Evaluation of the liver by bimanual palpation and intraoperative ultrasonography (IOUS) is essential to identify lesions that were not seen by preoperative imaging and to confirm its extension and its relationship to vascular structures. After confirmation of resectability, preparation for a Pringle maneuver can be done by opening the hepatogastric ligament and surrounding the main hepatic pedicle by a tape that is passed through a 16F rubber drain used as a tourniquet. At this point, an aberrant left hepatic artery arriving from the left gastric artery should be isolated in order to provide total hepatic inflow clamping. The Pringle maneuver may be useful for intermittent inflow occlusion in case of major resections. In exceptional cases, it may be necessary for limited liver resections (e.g., left lateral sectionectomy).

SURGICAL TECHNIQUES

LEFT LATERAL SECTIONECTOMY

This procedure consists of removing the morphological left lobe of the liver that corresponds to up to 20% of the whole liver mass. Laparoscopic approach is currently the gold standard for left lateral sectionectomy. The left lateral section is anteriorly delimited by the falciform ligament and inferiorly by the umbilical fissure. The caudate lobe (segment 1) is posteriorly separated from these two segments by the lesser omentum and the Arantius ligament. The incision on the liver capsule is performed 5 mm along the left edge of the falciform ligament, reaching the left edge of the left hepatic vein on the top. On the inferior surface, a virtual line passes on the left side of the umbilical fissure.

Liver transection begins at the anterior margin using a combination of ultrasonic dissection and saline-linked bipolar electrocoagulation. At this point, there is no hepatic vein that runs within the transection plane and the parenchyma thickness is about 4-5 cm. The authors favour the so-called "two-surgeon technique" (**Figure 1**) described by Aloia et al.,[11] which is associated with reduced blood loss as well as shorter parenchymal transection times. Pedicle inflow clamping is usually not required for this kind of resection. Exposure of the cutting surface is better achieved by a stay suture of 4-0 Prolene® on the inferior liver margin on the left side, and by holding the round ligament upwards and to the right. Small structures emerging from its left margin

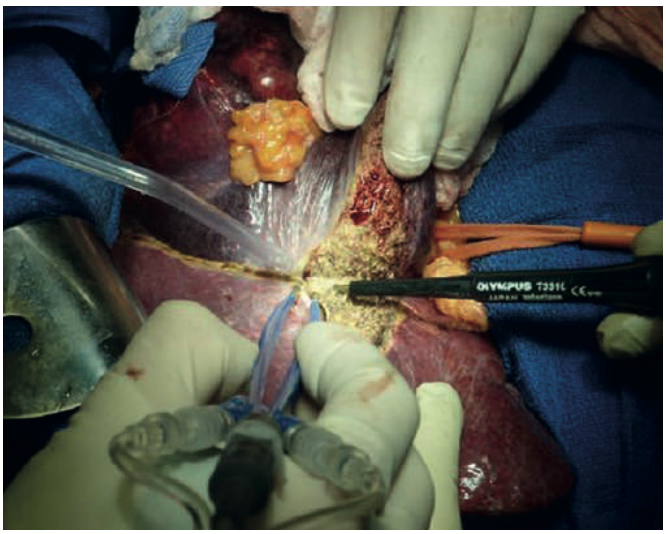


Figure 1. Transection plane performed according to the "two-surgeon technique". The first surgeon dissociates hepatic substance with an ultrasonic dissector, while the second one ensures hemostasis and biliostasis using a double saline-linked bipolar electro-cautery. Both surgeons are placed on the right side of the patient.

are selectively dissected by ultrasonic device and individually ligated or clipped and divided. In this way, within 3-4 cm of the anterior margin of the liver, the first important structure encountered is the Glissonean sheath of segment 3. It should be freed of all surrounding parenchyma before ligature by selective running suture with 4-0 or 3-0 Prolene®. Dissection continues straight in the direction of the second major structure encountered, which is the Glissonean sheath of segment 2, which is controlled and divided in the same way. Reaching the posterior portion of the liver (2-3 cm from the top), the last important vascular structure to be divided is the left hepatic vein. At this point, its section might be performed within the hepatic parenchyma, after fine dissection by an ultrasonic device over 8-10 mm. A tape is passed around the left hepatic vein in order to better place an automatic stapler. For this technique, it is not necessary to perform previous dissection of the left hepatic vein, nor section of the Arantius ligament. After dividing the left hepatic vein, the left lobe is free from all anatomical attachments and vascular structures and can be removed.

LEFT HEPATECTOMY

This procedure (**Figure 2**) consists of removing the part of the liver that is located on the left side of the main fissure (segments 2, 3 and 4). Generally, the volume of parenchyma that is removed corresponds to less than 40% of the whole hepatic volume. So, in non-cirrhotic patients, there is no intrinsic risk of postoperative liver failure. For oncological or technical reasons, resection of the median hepatic vein and segment 1 may be included in this resection.

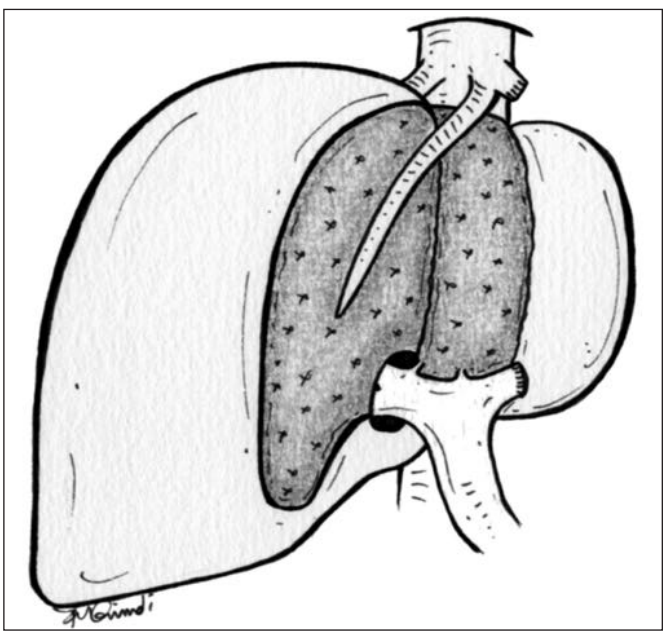


Figure 2. Schematic representation of surgical aspect after a left hepatectomy with preservation of segment 1. Two planes of transection are needed; the middle hepatic vein is seen on the vertical plane and the horizontal plane divides segment 1 from segment 4.

Structures of the left side of the hepatic pedicle may be approached either outside the liver substance (extrahepatic approach) or within the liver (Glissonean approach). Because of frequent anatomical variations (e.g., an aberrant drainage of the right posterior sector into the left biliary duct), the authors prefer a vascular extrahepatic approach combined with an intraparenchymal biliary section.

The left extrahepatic approach was first described by Couinaud, and consists of selective dissection of the left hepatic triad outside the liver, which permits a reliable dissection of the pedicle anatomy by individual identification of vascular pedicle structures. However, the left biliary duct is divided during hepatic transection in order to avoid biliary bifurcation lesion. On the left side, the main Glissonean sheath is often extrahepatic for a variable length at the base of the quadrate lobe. To access the left pedicle structures, the superficial leaf of the hepatoduodenal ligament is opened above the line of the free edge of the lesser omentum, upward to the base of the round ligament. The left hepatic artery is usually identified on the left edge of hepatoduodenal ligament. Overall, while lifting the left lobe, vascular structures of the left pedicle present a vertical disposition. At this point, the left hepatic artery can be dissected, controlled, and taped before its section. Before this maneuver, the artery must be freed of all surrounding nerve and lymphatic tissue. The patency of the right arterial inflow should be assessed by the convincing persistence of the right hepatic artery pulsation after clamping the left artery with a bulldog. Care must be taken to identify the accessory left hepatic artery arriving from the left gastric artery (**Figure 3**). After arterial control, the left portal vein is the next vascular structure to be identified. While dissecting the left portal branch, care must be taken with the

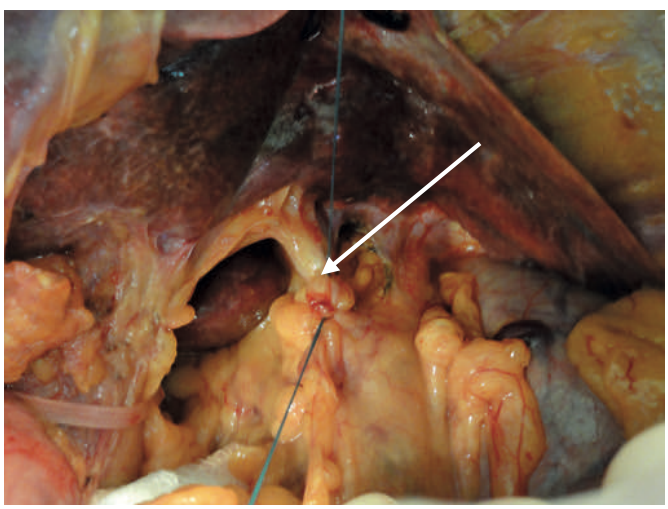


Figure 3. Ligature of an accessory left hepatic artery (arrow) within the lesser omentum. (*Courtesy of Silvio M P Balzan*)

branch to segment 1 on the back left side of the left portal vein. When the left portal vein branch is freed from the adventitial tissue, a silicone tape is passed around, just above the branch to segment 1, in order to facilitate the placement of a vascular clamp. At this point, attention should be paid to ensure placement above portal bifurcation (**Figure 4**). Left pedicle blood inflow is occluded using a vascular clamp for the portal vein and a bulldog clamp for the artery. A Doppler ultrasound is performed to ensure the selective left hemiliver disconnection. As blood supply to the left hemiliver is interrupted, an ischemic demarcation on the liver surface is established along the main portal fissure from the top of the gallbladder back to the confluence of the middle and right hepatic veins (**Figure 5**). Consequently, a cholecystectomy is usually necessary. The middle hepatic vein is routinely identified by Doppler ultrasound. This is used all along the parenchymal transection in order to ensure an adequate transection plane. In case of left hepatectomy extended to the middle hepatic vein, the transection line can pass 5 mm to the right of the ischemic demarcation (middle hepatic vein). In this case, this line ends between the right and middle hepatic vein. At this stage, the left hepatic artery and the left portal vein can be divided. The left hepatic artery is ligated with a 4-0 Prolene® stitch and sectioned. Before section of the left portal vein, care must be taken to place the vascular clamp at least 5 mm above the bifurcation in order to avoid a portal bifurcation stricture. Ligature is better performed by a running suture of 5-0 Prolene®. The inferior and posterior limits are the upper margin of the hilar plate and the insertion of the lesser omentum, respectively. Two stay sutures of 4-0 Prolene® are placed at the inferior margin of the liver – one on each side of the ischemic demarcation, for better exposure. Liver transection is performed according to the two-surgeon technique, as previously described. Contrary to the left

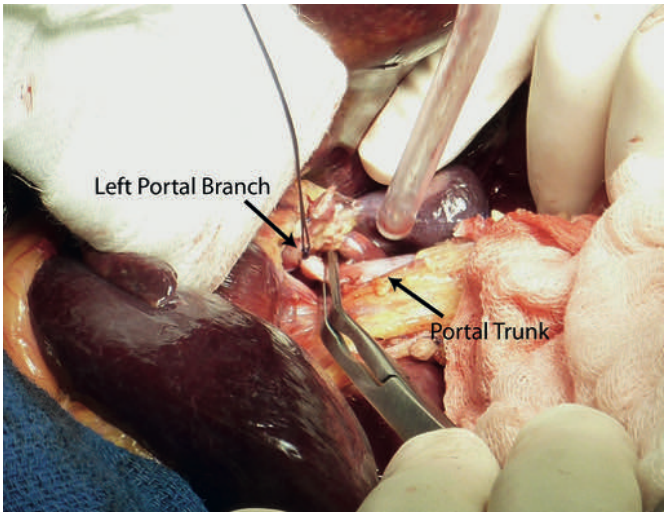


Figure 4. Ligature of the left portal branch over a vascular clamp placed above the portal bifurcation.

lateral sectionectomy, the plane of liver transection is not straightforward. The left hepatectomy transection plane commences perpendicular (i.e., vertical) to the inferior vena cava, and changes its direction when the hilar plate is cut. At this point, transection becomes horizontal, leaving the caudate lobe inferiorly. The Arantius ligament should be followed on its upper edge, in the direction of the left or middle hepatic vein. The left biliary duct is sectioned within the parenchyma, 1 cm to the left of the biliary convergence, in order to avoid aberrant structures entering from the right hemiliver, especially drainage of posterior right sector into the left biliary duct. Hemostasis of this area is performed by selective ligatures using 5-0 Prolene stitches, and coagulation should be avoided in order to protect the biliary convergence from ischemia, preventing delayed biliary leakages or stenosis. Continuing the parenchyma

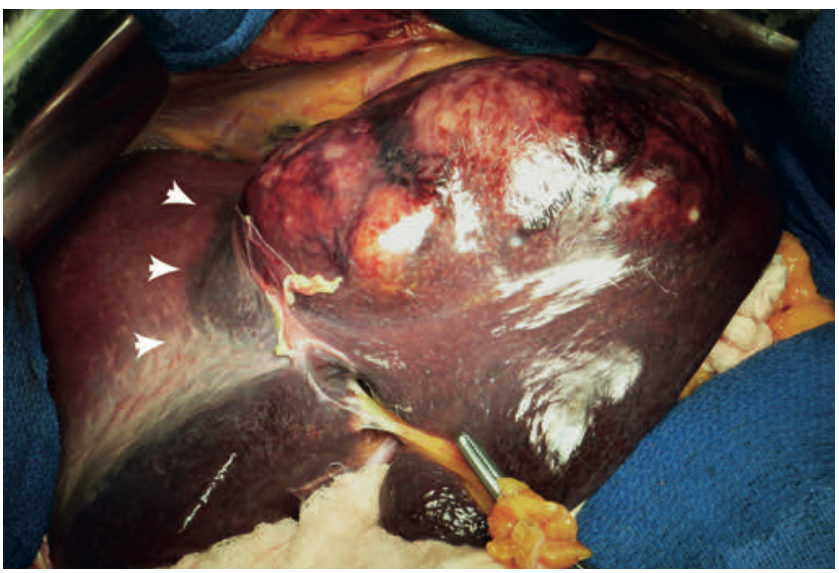


Figure 5. Parenchyma ischemic demarcation after selective left devascularization for left hepatectomy.

dissection upward in a transversal plane, over 2-3 cm from the top of the liver, the last important vascular structure is the left hepatic vein. At this time, the Arantius ligament may be divided and the vein is freed from adventitial tissue by fine dissection. A tape is finally passed around the vein in order to facilitate the placing of an automatic stapler or a vascular clamp. After dividing the left hepatic vein, the left hemihepatectomy is completed.

LEFT HEPATECTOMY EXTENDED TO THE CAUDATE LOBE

This procedure is only performed if the lesion directly involves the caudate lobe or its Glissonean pedicles (e.g., cholangiocarcinoma of the hepatic hilum). The line of hepatic section and the dissection of the liver substance are performed as for any standard left hepatectomy until the section of the left bile duct. Additionally, the caudate lobe should be mobilized from the vena cava. There are two ways to achieve this maneuver. The first is performed from the cut surface to the left, lifting segment 1 upward and dividing the Spigelian veins. The second is performed from the left to the right. At this point, the transection plane is carried out straight into the plane of the inferior vena cava. The key to this procedure is to divide the layer of peritoneum that attaches the left edge of the caudate lobe to the vena cava. Following this, the short veins from the caudate lobe draining into the vena cava are dissected and divided. The dissection of the liver substance continues posteriorly and upward following the anterior face of the vena cava, until the insertion of the Arantius ligament. The left hepatic vein lies behind this ligament and its division is easily performed by a vascular suture or even by an automatic vascular stapler (**Figure 6**).

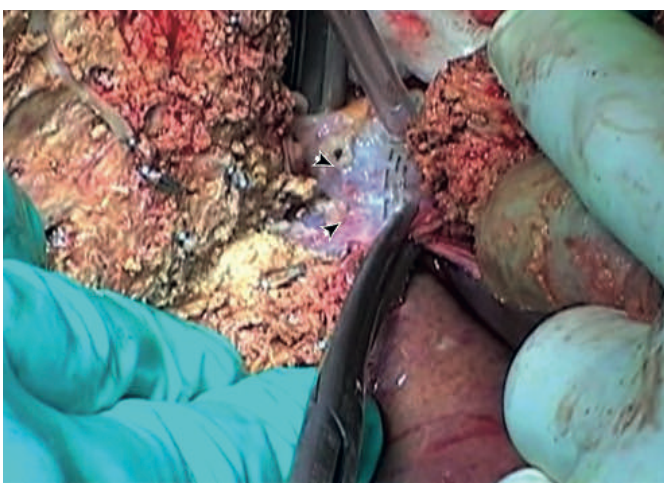


Figure 6. Intra-parenchymal section of the left hepatic vein after ligature with stapler. Note that the left hepatic vein was dissected along 10-15 mm for safe placement of the stapler (arrows).

LEFT TRISECTIONECTOMY

This procedure (**Figure 7**) was first described by Starzl et al.[12] in 1982 as *left hepatic trisegmentectomy*, and is also called *anterior hepatectomy*. In this procedure, the left lateral section (segments 2 and 3) and the left medial section (segments 4a and 4b) are removed, as well as the right anterior section (segments 5 and 8). Concomitant caudate lobe resection may be performed depending on the surgical indication and the remnant liver volume. It is considered one of the most challenging major hepatic resections because of the numerous segments removed and the great variability of anatomy of the right side of the liver, sometimes leading to complex biliary or venous reconstruction. However, preoperative portal vein embolization (PVE) is rarely performed. Three-dimensional imaging systems are emerging tools that contribute to safe operation planning. The authors favour selective ligation of pedicles of segments 5 and 8 prior to parenchyma transection. However, in the case of large tumours involving the portal bifurcation, the intra-parenchymal approach might be preferred. For this procedure, all of the attachments of the right and left sides of the liver should be divided, especially when a total vascular exclusion is anticipated. However, mobilization of the right liver from the inferior vena cava is generally not necessary. Left liver structures are divided as described in the left hepatectomy technique.

Afterwards, the medial sheath (segments 5 and 8) is isolated and clamped. The right margin of the ischemic zone

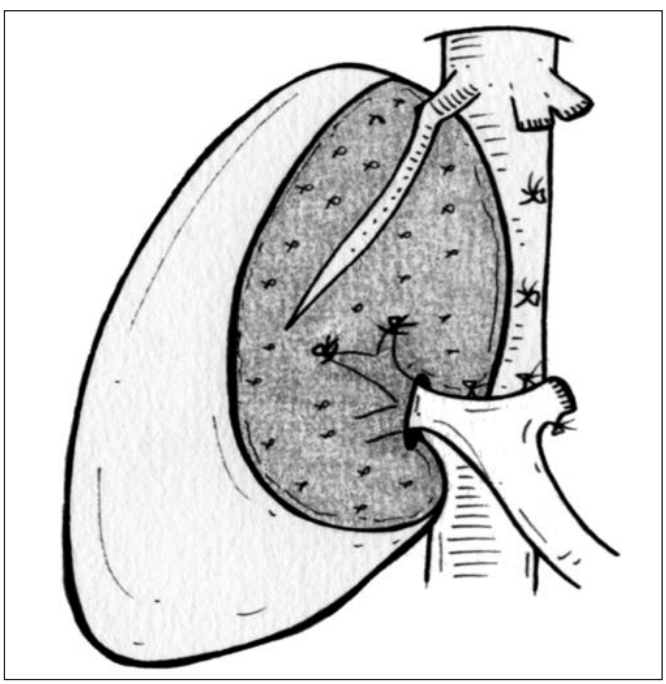


Figure 7. Schematic representation of surgical aspect after a left trisectionectomy extended to segment 1. The transection plane is horizontal and contains the right hepatic vein.

of the liver parenchyma corresponds to the right fissure. Care must be taken with eventual anatomical variations disturbing the correct determination of the right fissure. Intraoperative ultrasound is mandatory in order to determine the position of the right hepatic vein that might be on the right side of the right fissure. The transection plane runs toward the anterior surface of the inferior vena cava on the left side of the right hepatic vein. In order to delimited the common trunk prior to parenchyma dissection, guiding the transection plane, a "modified hanging maneuver" may be performed, as described below.

SPECIAL MANEUVERS

HANGING MANEUVER FOR LEFT TRISECTIONECTOMY

The hanging maneuver is usually performed for right hepatectomies by anterior approach, without mobilization of the right liver.[13] This technique has decreased intraoperative bleeding at the deeper parenchymal plane. Its use has also been described for other procedures such as living donor liver transplantation, where hepatic transection is performed before dividing the graft pedicle. For extended left liver resection, the hanging maneuver might be performed in order to retract the deeper transection plane upward, avoiding possible inadvertent lesions to suprahepatic veins. This maneuver is first prepared by opening the coronary ligament on both sides. The anterior leaf of the coronary ligament is dissected to expose the junction of the right hepatic vein and the common trunk. At this moment, the avascular space between the right hepatic vein and the common trunk is freed from the adventitial tissue by blunt dissection in a downward fashion. Subsequently, the lesser omentum is divided by bipolar electrocautery. The infrahepatic preparation of the vena cava commences right above the origin of the right renal vein. One or two short veins to the caudate lobe should be divided in order to open the space between the liver and the inferior vena cava. The tunnel is now prepared by carefully opening the avascular plane (known as Couinaud's space) between the liver and the anterior surface of the vena cava. This is a 10 mm-wide retrohepatic space located on the right side of the midline of the anterior surface of the inferior vena cava. A long, curved Crawford clamp is inserted behind the caudal edge of the caudate lobe following an 11 o'clock clockwise orientation, relative to the inferior vena cava at 12 o'clock. The clamp is passed cranially in the direction of the previous dissected space between the right and the median hepatic veins (**Figure 8**). This dissection must be performed in a resistance-free fashion, in order to avoid injury to short veins. In case of resistance, the clamp must be withdrawn and the dissection restarted from the beginning. When the tip of the clamp has reached the freed area between the RHV and the MHV, a gastric tube or plastic tape is passed through the tunnel. Retracting the tube upward will serve as a guide during parenchyma transection, facilitating control of bleeding in the deeper plane and protecting the inferior vena cava.

COMMON TRUNK CONTROL

This technique is useful when resecting lesions located between and in close proximity of the middle and the left hepatic veins, in cases of extended left resection or total vascular exclusion with preservation of the vena cava flow. This maneuver is achieved by lifting the left lobe upward and pushing down the caudate lobe. At this point, the Arantius ligament can be divided. This exposure plan has the caudate lobe as the inferior limit, and the confluence of the left hepatic vein and the vena cava as the upper limit. This avascular zone should be opened by blunt dissection following a horizontal plane (**Figure 9**). Care must be taken with the right hepatic vein, which is inserted in the inferior vena cava about 5-10 mm lower than the common trunk. The plane between the right hepatic vein and the common trunk must be previously dissected as described using

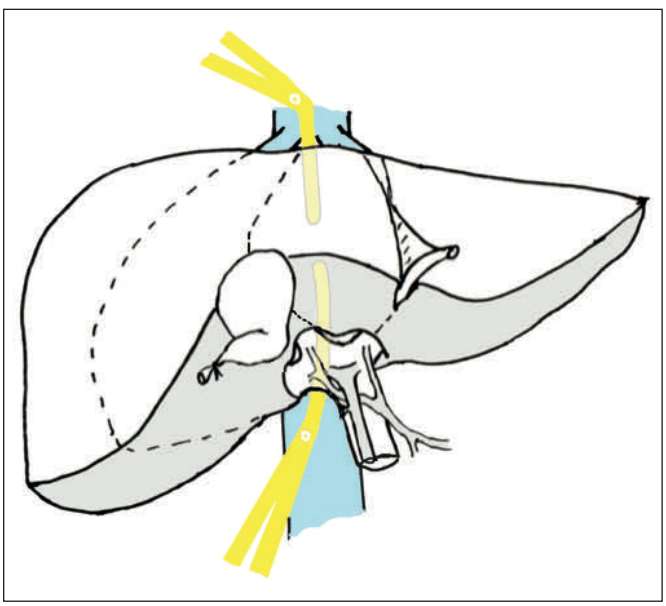


Figure 8. Schematic representation of hanging maneuver for a left hepatectomy. First, the space between the right and the middle hepatic veins is dissected, and a right-angle clamp is directed downward taking contact with anterior face of the inferior vena cava (IVC). After, a curved clamp is inserted inferiorly, between the IVC and segment 1, and directed upward to join the superior space previously created between the hepatic veins. An umbilical tape or nasogastric tube is placed in this retrohepatic tunnel and pulled anteriorly.

the hanging maneuver. A blunt dissector is finally passed horizontally above the inferior vena cava and upwardly between the right and middle hepatic veins. At this point, tape is passed throughout this plane and a tourniquet might be prepared using a rubber tube, as with a Pringle maneuver (**Figure 10**).

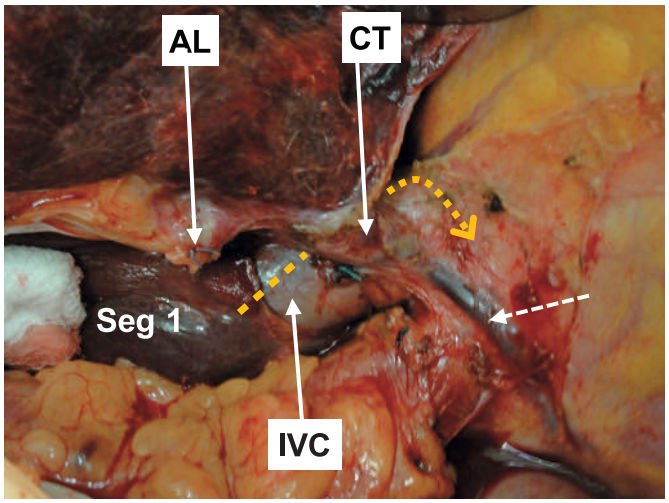


Figure 9. Lateral view showing access to the common trunk (middle and left hepatic veins). The caudate lobe (Seg 1) is retracted caudally to expose the anterior face of the inferior vena cava. Section of the Arantius ligament facilitates access to the common trunk (ties are seen in each side after section). Note a phrenic vein (dashed arrow) debouching at the junction of the common trunk and the inferior vena cava. The yellow dashed arrow indicates the trajectory to isolate the common trunk. AL: Arantius ligament; CT: common trunk; IVC: Inferior vena cava. (*Courtesy of Silvio M P Balzan*)

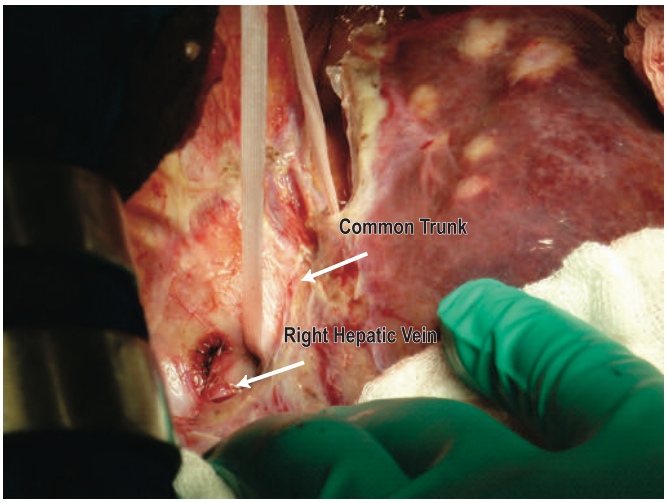


Figure 10. Superior view showing the common trunk (left and middle hepatic veins) controlled.

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27 Principles of Laparoscopic Liver Resections

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- *The laparoscopic liver resection procedure has evolved over the last two decades from a novel segmental operation to an established procedure with proven efficacy and safety in skilled hands.*
- *Adoption of laparoscopic liver resection has been variable among centers from 5-70% of resections. Throughout its evolution, numerous techniques and devices have been introduced into the field since the original description of pure laparoscopic approach. These innovations include stapler hepatectomy, hand-assist devices, single port access, and robotics.*
- *Laparoscopic liver resection was initially applied to the management of peripheral benign tumors and subsequently adapted for the routine management of malignant tumors. Multiple studies have subsequently confirmed the oncological non-inferiority of laparoscopic liver resection.*
- *Laparoscopic liver resection has been accepted as the standard of care for left lateral sectionectomy while major hepatectomy continues to evolve as a standard of care. Laparoscopic live donor hepatectomy and major robotic resections continue to be areas of investigation that have been recommended to proceed in the setting of a prospective study.*

INTRODUCTION

Minimally invasive techniques have revolutionized modern surgery. In the early 1990s, laparoscopic cholecystectomy became the first minimally invasive surgery to be widely performed. Multiple other laparoscopic procedures have subsequently gained acceptance, including hernia, gastric, spleen, kidney, and colon surgery. The first reported cases of laparoscopic liver surgery were wedge resections performed for the staging of hematologic malignancies or isolated peripheral metastases.[1,2] It was not until Cherqui et al.[3] published a paper describing Cherqui's initial series of liver resections, utilizing minimally invasive techniques for the management of peripheral liver tumors, that this procedure gained widespread acceptance.[3] This report was first met with great skepticism, but eventually was replicated by several major centers.

Once other centers embraced the results of Cherqui's original work, several comparative studies confirmed the advantages of a minimally invasive left lateral segmentectomy over the open procedure.[4,5] These studies allowed the laparoscopic approach to gain recognition as the standard of care. Despite considerable acceptance for minor and peripheral resections, most major resections were considered too extensive until O'Rourke reported a successful laparoscopic right hepatic lobectomy.[6] Subsequent to this initial report, multiple groups have described their experiences with both right and left hepatic lobectomy. A recent multicenter study by Dagher confirmed major hepatic lobectomy is a

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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safe and effective operation in high volume centers.[7] Despite these successes and advances, several major concerns about the safety of laparoscopic liver surgery have arisen in the surgical community. The first and foremost has been a concern over air embolism; other risks have included argon gas accumulation and the ability to control intraoperative hemorrhage. This chapter is dedicated to the description of current philosophies, technologies, and management of complications used in laparoscopic liver surgery required to perform a safe and efficacious operation.

PATIENT SELECTION

As with any other surgical procedure, patient selection is critical. Laparoscopic liver surgery is a technically demanding procedure that requires significant expertise in both open hepatobiliary surgery and laparoscopy. Cherqui's work emphasizes this fact multiple times, and has indicated that laparoscopic liver resection should only proceed in institutions with adequate field strength and appropriate resources for this procedure.[3] When evaluating a potential patient for laparoscopic liver resection, there are several clinical concerns that must be considered. These include: body habitus, underlying liver disease, disease distribution, tumor size, and coexisting pathology. As with other laparoscopic surgical procedures, obese patients can often benefit the most from the avoidance of an open procedure. The laparoscopic approach even affords superior visualization of the vena cava and posterior sectors of the liver. The true limitations of laparoscopic liver resection are those with extreme morbid obesity with a BMI in excess of 40, where long instrumentation is mandatory. Underlying liver disease is another critical factor. Fatty liver, fibrosis, and even cirrhosis dictate the approach and often the technique of parenchymal transection. These factors will be discussed later in this chapter. The type of disease as well as its distribution is a critical factor in operative approach. By the nature of benign disease, a limited resection and minimal surgical margins are acceptable. This has led to comfort in tackling larger lesions, often in excess of 10 cm, with a laparoscopic approach. Laparoscopic approach has been used more conservatively with malignancy. All groups agree that attempts must be made to preserve a surgical margin of at least 1 cm or greater. For the management of larger tumors, this has led to the proliferation of laparoscopic lobectomy and central hepatic resections. The last factor that dictates the ability to approach a liver lesion laparoscopically has been the distribution of disease. The complexity of resecting more than four lesions or multiple bilobar lesions by laparoscopy often dictates an open approach. The surgeon must consider patient positioning, access to bilobar disease, and even the length of the procedure required for successful resection. Lastly, concomitant disease involving the stomach, small bowel, or even the colon can be managed concurrently with hepatic disease. However, as Cherqui et al.[3] first described, laparoscopic hepatic surgery has evolved successfully in several advanced centers, where an extensive preliminary experience has made such resections feasible.

PERIPHERAL AND LEFT LATERAL HEPATIC RESECTIONS

The initial experience with hepatic resections was limited to peripheral lesions within the liver. These resections were often small tumors managed with either wedge or segmental resections. It is important to note that these resections avoided centrally located tumors or those in the right posterior sector of the liver. These lesions were avoided due to the lack of experience in laparoscopic mobilization of the liver and ability to control major hemorrhage. The first descriptions of laparoscopic resection emulated traditional hepatic resection techniques including the use of the Pringle maneuver, CUSA dissection, meticulous clip placement, and division of vascular inflow, outflow, and biliary radicles under direct vision. A second philosophy rapidly arose whereby hepatic resection was performed using "en masse" division of the hepatic parenchyma and the vasculobiliary pedicles with endovascular staplers. Stapler hepatectomy introduced laparoscopic resection to a wider group of surgeons. After this technique was described and its use in anterior wedge and segmental resections was perfected, stapler hepatectomy was then employed for left lateral segmentectomy. This operation required experience in mobilization of the left hepatic vein and dissection of the left portal structures.

RIGHT POSTERIOR HEPATIC RESECTION

Continued experience and comfort with hepatic mobilization and control of major vascular structures, particularly the right hepatic vein, led select groups in Europe and Japan to gain extensive experience in right posterior segmental resections. One unique approach to tumors was to employ a transdiaphragmatic approach using a thoracoscope. Eventually the abdominal approach became more widely accepted as the principle approach to lesions located in segments 6 and 7, and the transthoracic approach was abandoned. The abdominal approach involved complex mobilization, hepatic inflow occlusion, and methods for control of major and minor hemorrhage. In our assessment, the most challenging hepatic resection is the right posterior resection, for reasons previously stated. This resection is a critical part of the laparoscopic resectionist's armamentarium because multiple patients present with compromised hepatic parenchyma

from steatosis, fibrosis, cirrhosis, or chemotherapeutic-induced steatofibrosis. The greatest challenge to the posterior resection patient is metachronous hepatic disease. Hence, the risk of recurrent disease and limited hepatic reserve induced by prior major hepatectomy make the posterior hepatic resection a superior option for patients with a small hepatocellular cancer in a fibrotic or cirrhotic liver or a small posterior colorectal metastasis in a patient with prior oxaliplatin therapy.

MAJOR HEPATIC RESECTION

The initial report of a laparoscopic right hepatic resection by O'Rourke and Fielding[6] stimulated a great amount of excitement over laparoscopic hepatic resection. Several subsequent reports by Dagher, Belli, and Koffron confirmed the viability of major hepatic resections.[7,8] Interestingly, most major series reported a predominance of left hepatic lobectomies to right hepatic lobectomies performed laparoscopically. Careful examination of this data indicated right lobar resections were still being performed laparoscopically. This disparity eventually resolved with time and experience. A subsequent multicenter report from Dagher reported a higher incidence of right hepatic resections. The most convincing argument that can be made explaining surgeons' reluctance to perform right hepatic lobectomies is the complexity of the procedure and the need to manage the right hepatic vein. A more disturbing trend has been recently observed in the excessive use of the laparoscopic right hepatic lobectomy. It is important not to perform a right hepatectomy for disease that could be managed by a segmental resection or bisegmentectomy so as not to limit the patient's options for re-hepatectomy in the setting of recurrent disease. The most interesting concept that has been recently put forward is the use of the hybrid resection. This was described by Koffron et al., who advocated a laparoscopic mobilization with parenchymal transection performed through a mini laparotomy incision.[8]

LIVE DONOR HEPATECTOMY

The most challenging hepatic resection, whether open or laparoscopic, has been the living donor hepatectomy. This operation requires a precise division of the hepatic parenchyma with skeletonization of the porta hepatis and the middle hepatic vein. This continues to be an operation in evolution. Several groups have advocated pure laparoscopy, while others prefer the hybrid technique. No one technique for parenchymal transection is predominant, whether it be by CUSA, tissuelink, bipolar, or ligasure. A greater controversy exists over the incidence of complications and the incidence of hepatic artery thrombosis. The complication rate of open live donor hepatectomy is considerable, with rates varying from 30-60% and a mortality ranging from 0.1% to 2%.[9–17] Laparoscopic live donor hepatectomy has a small area of utilization. Perhaps the use of hybrid donor hepatectomy is the most favorable, but continued refinement of the procedure is essential.

PATIENT POSITIONING

Access to the patient is a critical factor in laparoscopic liver resection. Three current techniques for positioning exist today: the French position, supine, and lateral decubitus. The French position is defined by the patient in a supine position with their legs in stirrups and the surgeon positioned between the legs. This position provides the surgeon the ability to operate with two hands, while his assistants retract from either side of the patient. The alternative supine position is where the patient is flat on the operative table with their legs straight on the bed. This position is used to access the left lobe of the liver and the right anterior sectors of the liver. This positioning was also employed by O'Rourke for his right hepatic lobectomy using the "tunnel technique" to access the right hepatic vein, which will be discussed later in this chapter. The last position, defined as the lateral decubitus position, is the placement of the patient on their left side recumbent at 60 degrees. This positioning evolved from the complete supine position, to a full lateral, to the current 60 degrees position. This was felt to be the optimal position to access the posterior sector of the liver as well as the right hepatic vein without the right lobe dependently dropping into the operative field. These last two positions allow the operative surgeon to stand on either side to achieve maximal visualization and access to the liver. Several groups have employed the use of a hand-assist device to improve the mobility of the liver, aid in dissection, and increase the safety of the procedure when others feel less comfortable using it, having more bleeding and a smaller field to dissect the different structures. The use of a hand-assist device has traditionally been in the right upper abdomen, with its height and position based on the region of the liver that must be accessed.

ANESTHESIA AND CRITICAL CARE

Early experience with liver resection was moderate at best. Operative mortality could be as high as 30% from intraoperative hemorrhage and postoperative liver failure. In the 1980s and 1990s, significant improvements in patient

survival were achieved through changes in intraoperative and postoperative patient management including volume dilution, cell saver, and improved comprehension of hepatic anatomy. Laparoscopic liver resection relies on several of these very same tenets. The most important has been the monitoring and management of central venous pressure. All patients have central venous lines placed for monitoring. Central venous pressure is maintained between 2 and 4 mmHg using nitroglycerine, nitrous oxide, and aggressive diuresis. Blood pressure monitoring is performed using arterial lines, with the patient's blood pressure supported with vasoactive drugs to minimize hepatic ischemia. To minimize transfusion-related coagulopathy, cell saver can be used during benign resections. Blood transfusion is performed based on intraoperative blood loss, using either a TEG or 1:4 ratio of fresh frozen plasma to packed red cells.

OPERATIVE APPROACHES

During most forms of laparoscopic surgery, pneumoperitoneum has traditionally been produced with carbon dioxide and maintained between 10 and 12 mmHg. Early experiences with laparoscopic liver surgery involved considerable concern over gas embolism produced by carbon dioxide under pressure being absorbed through open venous vessels. This led to multiple manipulations including low volume pneumoperitoneum, attempts at changing the insufflation gas to an inert gas, and even the introduction of a non-gas expansion of the peritoneum.[18] This resulted in the development of the laparo-lift by surgeons in Asia. This was a scaffold placed in the abdomen to lift the abdominal cavity producing a working space. This was found to be significantly complex and cumbersome, and was eventually abandoned. The effects of gas embolism were minimized by several studies from the Netherlands where animals had significant vascular injuries of the liver induced during hemodynamic and transesophageal monitoring. After significant experience with laparoscopic liver and prostate surgery, we have recognized that carbon dioxide does not lead to gas embolism. In cases of venous "ooze," increasing the pneumoperitoneum to 14 or 16 mmHg can reduce bleeding. The risk of gas embolism does arise from inadvertent introduction of argon gas into the hepatic vein or through major interruption of the hepatic veins.

PURE LAPAROSCOPY

The initial description of laparoscopic liver resection utilized a pure laparoscopic approach for liver transection with bag extraction of the specimen. Pure laparoscopy has been considered the choice of purists. These techniques included the use of traditional resection techniques, such as CUSA and crush and clamp dissection performed with ties and clips. The principle drawback to pure laparoscopy has been the advanced level of laparoscopic skills required to perform these procedures. This may have also attributed to the slow adaptation of laparoscopy to major hepatic resections, particularly right lobectomy. The greatest challenge to the pure laparoscopic approach has been the ability to control major hemorrhage. Despite this, multiple groups have relied on pure laparoscopy as the principal operative approach. O'Rourke reported the first successful laparoscopic right hepatic lobectomy using the pure laparoscopic approach. This operation was performed using the "tunnel" technique, where the liver is mobilized off the vena cava to access the right hepatic vein through this newly created "tunnel". Recent studies have advocated that the anterior approach be performed in all cases of hepatic transection prior to the lobar mobilization. This approach has been suggested to prevent tumor embolization, resulting in a superior oncological procedure.

HAND-ASSISTED LAPAROSCOPY

Hand-assisted laparoscopy has been employed in numerous general surgical procedures. The principal benefits to hand-assisted surgery are tactile feedback, digital control of hemorrhage, and the ability to manipulate the liver. Several reports have indicated that the potential for gas embolism and adverse release of cytokines is lessened with the hand-assisted approach in contrast to a pure laparoscopy. The application of the hand-assist device allowed multiple programs to evolve from smaller peripheral resections to larger and often formal lobar resections. The placement of the hand-assist device has been described in the right upper quadrant, the upper midline, and even through a Pfannenstiel incision.

HYBRID RESECTION

A recent paper by Koffron et al.[8] described the hybrid technique, in which hepatic mobilization is performed through laparoscopic approach and parenchymal transaction is then carried out through a small open incision. The incision can be placed in the midline or in the right upper quadrant, similar to a Kocher incision. Once the incision is placed over the transection line, a plastic obturator from a hand-assist device can be placed into the incision to allow improved retraction and exposure. This technique has been widely described in Asia, but was advocated by Koffron et al. as a method for most surgeons.

ROBOTIC RESECTION

The most recent adaption to laparoscopic hepatic resection has been robotic resection. Current robotic models have three or four arms with high definition visual systems. The multiple arms can be articulated and locked to provide improved exposure. Our group has performed left and right lobar resections using robotic mobilization and stapler hepatectomy using an assistant access port. Robotic liver surgery is feasible and safe in skilled hands. The greatest challenge to robotic liver surgery is the steep learning curve required for robotic placement and the ability to rapidly undock and roll off the robot in cases of emergency. The latest instrumentation introduced for the robot is an ultrasonic dissector and a clip applier. The robot can support a hepatic resection, but as a technology does increase the complexity of the operation and concordantly the time required for the operation.

PARENCHYMAL TRANSECTION TECHNIQUES

Access to and mobilization of the liver are critical to laparoscopic liver resection. However, the most critical factor is the hepatic transection. The entire operation can become futile if transection leads to hemorrhage and conversion. The following are descriptions of hepatic transection techniques.

ELECTROSURGICAL HEPATECTOMY

Techniques of electrosurgical resection of liver parenchyma have been described in several articles.[3,19–21] Different kinds of electrosurgical resection devices are advocated in individual centers, according to surgeons' preferences and patients' conditions. Basically, the instruments and equipment for electrosurgical resection of liver parenchyma should include an ultrasonic dissector (UltraCision Harmonic Scalpel: Ethicon Endosurgery, Cincinnati, OH; or SonoSurg and Thunderbeat: Olympus, Japan) or thermofusion (Ligasure: Tyco Healthcare), bipolar cautery forceps, an electrosurgical generator, laparoscopic scissors with single-use scissors tips, laparoscopic suction tube with blunt tip, appropriate laparoscopic dissectors, atraumatic graspers, and an atraumatic liver retractor. The ultrasonic dissector or the thermofusion device is mainly used for liver parenchyma transection and should be held in the surgeon's dominant hand, while bipolar cautery forceps are mandatory for hemostasis and should be always held in the surgeon's other hand. To accomplish a successful liver resection, surgeons should be able to manipulate the devices in both hands and sometimes activate the devices with both feet simultaneously.

Technique

Before starting the parenchymal division, central venous pressure (CVP) should be decreased to avoid excessive bleeding. Due to pressure modifications associated with pneumoperitoneum, the optimal method to estimate CVP is to inspect the inferior vena cava, which should be "beating" or "breathing" but not distended. The resection line of the liver is designed according to intraoperative ultrasound or the demarcated line after hilar dissection and vascular control of portal vein and hepatic artery.

The incision of Glisson's capsule is initiated with ultrasonic dissector and bipolar electrocautery. Half of the length of the active blade is used as a dissector and is inserted into parenchyma with the device activated, and the non-active blade is positioned outside the capsule (**Figure 1**). The blades are then slowly and gently closed to avoid crushing liver tissue during the activation of the dissector. Any visible bleeding should be managed with bipolar electrocautery immediately.

Deeper liver parenchymal transection is continued after incision of Glisson's capsule. Tissue dissection and hemostasis are mainly performed by ultrasonic dissectors, while the bipolar electrocautery forceps are responsible for retraction and rescue hemostasis. The active blade of the dissector should not be fully introduced into the parenchyma to avoid injuring large vessels, and care should be taken to prevent tearing or crushing small vessels and bile ducts before these structures are adequately sealed off. In some cirrhotic patients, the Ligasure vessel sealing system (Valleylab, Boulder, CO) can be useful in dividing the parenchyma. Larger branches of vessels should be controlled with surgical clips or suture-ligation and trunks of hepatic veins should be divided with linear staplers (white cartridge).



Figure 1. Incision of the Glisson's capsule. Active blade of ultrasonic dissector is introduced into liver with half-length.

Delicate dissection is essential when approaching large branches of vessels by applying the ultrasonic dissector to the liver tissue with the active blade opened only (**Figure 2**), which creates an effect similar to the Cavitron ultrasonic dissector (CUSA: Radionics, Burlington, MA) or by utilization of sharp scissors or suction tube with blunt tip. To ensure the accuracy of resection plane and the detection of adjacent large vessels, repeat ultrasound may be needed during the operation, especially when there is a doubt.

When bleeding occurs, complete hemostasis must be achieved before dissecting any further. Most bleeding can be controlled by bipolar electrocautery. The power of the bipolar electrocautery device is set at 40 watts initially. It is better to decrease the wattage instead of increasing it if the bleeding persists during coagulation. The device should be kept activated until the bipolar tips, partially closed, are fully removed from the coagulated clot. To achieve the optimal coagulation effect, the tips of the bipolar device should always be clean and changed by a scrub nurse frequently on the table when necessary.

Smoking from an ultrasonic dissector can be an annoying problem during the operation. An automatic smoke evacuation system (Olympus) can be useful when it works simultaneously with the ultrasonic dissector, providing a clear surgical field and facilitating the surgical process.

The technique of two-handed-and-two-footed surgery can be difficult for a surgeon without significant experience in laparoscopy. Surgeons need to shift the balance of their body back and forth when controlling the activation of the devices with both feet. Sitting on a high stool is one of the solutions (**Figure 3**), which helps the surgeons with the controlling of the pedals of devices. As the technique of electrosurgical resection requires surgeons to work with two hands synchronously, pure laparoscopy may be preferable to a hand-assisted approach.

STAPLER HEPATECTOMY

Stapler hepatectomy is a concept that has been around for several decades. The first description of its use was by Meyers, who employed the technique for intrahepatic division of the right hepatic pedicle. Recently, Schemmer et al.[22] reported on an extensive study of open hepatic resections employing the stapler technique. Stapler hepatectomy has evolved to allow extensive dissection of the liver parenchyma without the requirement of individual ligation of multiple intrahepatic vessels. As with any surgical technique, there are multiple advocates and even more skeptics. When one evaluates stapler hepatectomy, two clear methods rapidly become evident. The first is the use of the stapler as compression device after dissection with a grasper or formal dissector. The other is the use of the thin firm blade of the stapler as a dissector. Considerable concern was initially raised over the use of the stapler as a dissector due to the nature of the device, leaving a vessel potentially cut and not stapled. However, modern endovascular staplers are designed to staple far past the final cut line. This then becomes relatively safe; however, it does leave little room for error caused by inadvertent manipulation of the remaining liver. The stapler articulates, which is optimal for exposure but can be the root cause of vascular avulsions. When an articulated stapler is fired it must be firmly held in place to avoid a sheering motion against the remaining vessel. Several well-described cases of hepatic vein avulsion have occurred by this mechanism. This makes the use of a hand-assist device extremely attractive during stapler hepatectomy. The intracorporeal hand can provide stapler stabilization and, in the event of hemorrhage, digital control.

Currently, there are several types of staplers available. Two principle designs are the cantilever design and the I-beam design. The older cantilever design is based on pre-compression and secondary staple discharge. This design leads to liver parenchyma tearing and potential bleeding. The I-beam construction relies on staple application during the compression phase, avoiding sheering and improving hemostasis. The principle choice of staple loads must be based on the quality and substance of the liver. A 2.5 mm vascular load has been our principle stapler load employed. However, several groups have advocated a larger stapler breadth with the ability to compress larger segments of liver. Our group has advocated this strategy in division of the right portal triad and in compromised liver substance, principally fibrosis and cirrhosis.

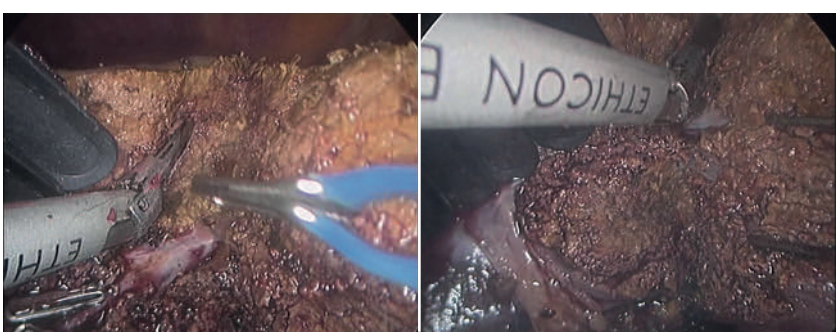


Figure 2. A and **B**) Intraoperative view. Using ultrasonic dissector with only activated blade to dissect during hepatic parenchymal transection.

LAPAROSCOPIC LIVER RESECTION IN CIRRHOTIC PATIENTS

Hepatocellular carcinoma is the most common primary hepatic malignancy, and in 90% of cases occurs in cirrhotic patients.[23] Screening for hepatocellular carcinoma among chronic liver disease patients permits early detection of small and asymptomatic tumors. Technical advances and improvements in postoperative patient management have increased the safety of liver resection as a curative treatment for hepatocellular carcinoma.[24,25]

Therapeutic options with curative intent for small tumors in patients with chronic liver disease include liver transplantation, hepatic resection, and percutaneous treatments such as radiofrequency ablation. Liver transplantation is theoretically the best treatment, because it cures both the tumor and the underlying chronic liver disease, thus preventing the development of new tumoral foci.[23] However, it cannot be offered to all patients because of the continuously increasing prevalence of hepatocellular carcinoma on the one hand and organ shortage on the other. Surgical resection is generally considered an efficient treatment, but its use in the context of chronic liver disease is limited because of significant morbidity, which could be, at least in part, related to the laparotomy itself.[26]

A number of recent studies have suggested that laparoscopic liver resections are associated with less intraoperative bleeding, a lower rate of postoperative general complications, better cosmetic results, less postoperative analgesic drug consumption, and a shorter hospital stay.[5,27–32] The laparoscopic approach may be particularly beneficial for cirrhotic patients over open procedures, by sparing the parietal collateral circulation and the abdominal musculature, and consequently preserving intraabdominal pressure and reducing the increase in portal pressure and postoperative ascites. Until recently, this had been suggested by series with a rather small number of patients. In a three-center European study, Dagher et al.[33] reported the encouraging results of 163 resections for hepatocellular carcinoma in an equal number of patients, 120 (73.6%) of which had a cirrhotic liver parenchyma, presenting thus the largest study of laparoscopic liver surgery for hepatocellular carcinoma to date.

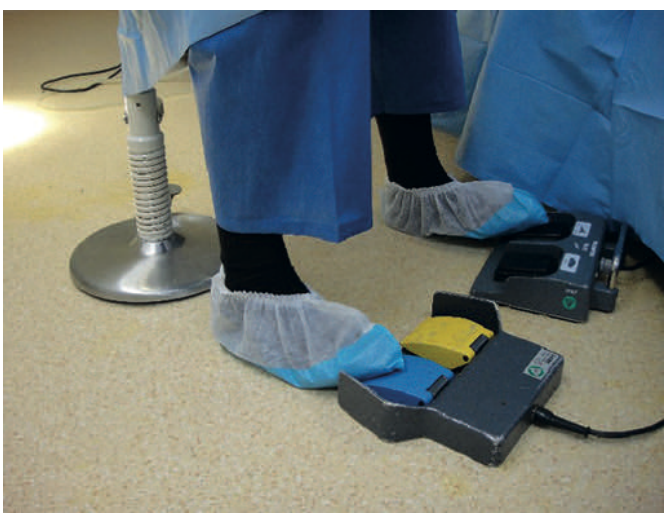


Figure 3. A surgeon sits on a high stool to control the pedals of two different devices with both feet.

The indications for and the type of hepatectomy performed should not be modified by the use of laparoscopy.

Patient selection criteria for laparoscopic resection include liver- and tumor-related criteria. Underlying liver conditions compatible with hepatic resection in cirrhosis are common for both open and laparoscopic approaches, and include compensated cirrhosis (or its absence), esophageal varices grade ≤1 and a platelet count of 80 x 10^9/L or higher. Tumor-related criteria are more specific for laparoscopy and include tumors smaller than 5 cm, well clear from the portal pedicle or hepatic veins, and distant from the transection line.[26]

The above-mentioned three-center European study confirmed the decrease in operative blood loss with the laparoscopic approach, although this series includes a majority of cirrhotic patients (in whom bleeding was more significant than in non-cirrhotic patients) and also a number of anatomic resections (107, or 65.6%) and major liver resections (16, or 10%). A low rate of porta hepatis clamping was used selectively in patients with hemorrhagic parenchymal transection. The pressure of the pneumoperitoneum has been suggested to play an additional hemostatic role. This is very important, as transfusion rates have been identified as independent prognostic factors for disease-free survival,[34] and operative blood loss was recently shown to be associated with recurrence and survival rates after resection for hepatocellular carcinoma.[35]

Some issues concerning the laparoscopic approach for hepatocellular carcinoma are still pending resolution. Lack of palpation during laparoscopic procedures has been feared to compromise the acquisition of adequate surgical margins. The usually accepted surgical margin is 1 cm, but a 2 cm margin has recently been reported to be preferable.[36] Additionally, anatomic resection has been shown to reduce local recurrence and improve survival in patients with hepatocellular carcinoma when compared to atypical wedge resections.[34,37] However, in cirrhotic livers, parenchyma-sparing resections remain important. An adequate surgical margin is thought to be provided by the appropriate preoperative choice of the type of resection. Intraoperative ultrasonography can help to localize the tumor and keep an intended margin in difficult cases.

In some patients, resection may be the initial treatment, enabling salvage transplantation in case of delayed and limited recurrences within the Milan criteria. In this case, performing the initial resection by laparoscopy could facilitate a subsequent liver transplantation. In a recent study by Laurent et al., it was shown that when the initial liver resection was done by laparoscopy, the subsequent salvage transplantation was associated with reduced operative time, blood loss, and transfusion requirement.[38]

The available results of expert centers and data from the existing retrospective comparative studies suggest that laparoscopic resection for hepatocellular carcinoma in cirrhosis is feasible, provides good operative and oncological results, and should be considered in selected patients in centers experienced in liver surgery and advanced laparoscopy. Close monitoring of recurrences is required and improves survival by permitting secondary treatments such as re-hepatectomy, radiofrequency ablation, or even salvage liver transplantation in eligible patients.

MAJOR HEPATIC RESECTION

Although laparoscopic liver surgery has seen an incredible proliferation worldwide,[4,21,39–43] major laparoscopic liver resections have been subject to a considerably restrained dissemination compared with other minimally invasive procedures. This is due to the fact that laparoscopic hemihepatectomies are more technically demanding, and that the common indications for typical major resections, such as large, multiple, and/or ill-located lesions are considered contraindications to a laparoscopic approach.[44] However, significant improvements in technology and accumulation of experience in laparoscopic liver surgery have permitted the application of laparoscopic techniques in major liver resections. Over the last few years, several centers worldwide have reported series that include modest numbers of major hepatectomies with good results.[6,19,27,44,45] In 2009, a multicenter international study by Dagher et al.[7] reported on a series of 210 major liver resections, 114 of which were performed for malignant and 96 for benign tumors, with a conversion rate of 12.4%. The constant evolution of laparoscopic surgical techniques is reflected in the six centers' experience. Some surgeons used hand assistance routinely, while others chose to use it selectively or not at all. Some centers preferred selective vascular control of inflow and outflow before parenchymal division, while others used Pringle's maneuver selectively. Parenchymal transection was performed according to surgeon preference.

With regard to some technical aspects, left hemihepatectomies retain the advantages of a maneuverable left liver and easier access to the longer extrahepatic course of the left pedicle. The left hepatic vein remains difficult to dissect because of the existence of a left-median common trunk. Right hemihepatectomies impose the difficulty of a voluminous and heavy right liver, offer a short portal pedicle, need delicacy in dividing the hepatocaval ligament, and require division of the right hepatic vein in close proximity to the inferior vena cava with either the traditional or the anterior approach. In both cases, the middle hepatic vein runs in the transection line, thus making hemostasis demanding.

Patient selection is paramount. The tumors must be well clear of the transection line on preoperative investigations, and not too close to major vessels. Small (≤5 cm) tumors are preferred, although size alone is not a contraindication to laparoscopy. Localization also plays an important role as, for example, very superficial tumors that risk breaking during mobilization are not considered suitable.

Operative times are longer as compared to open procedures, but are shown to decrease significantly with experience and extremes are observed in the initial experience.

The greatest concern remains bleeding, with the most common source being during parenchymal transection. Surgeons worldwide employ different transection methods and vascular occlusion types. The effect of the pneumoperitoneum probably explains the lower amount of bleeding in laparoscopic hepatectomies.[32,37] Gas embolism can be encountered during hepatic vein dissection. Conversion for bleeding from the hepatic veins can cause air embolism, which is much more dangerous than CO_2 embolism. Clinically significant CO_2 embolism is rarely experienced during minor bleeding. When argon beam coagulation devices are used, special care should be taken to vent the ports and to use preferably small vessels for coagulating, avoiding direct application to large open vessels. Reports of fatal embolism have been associated with misuse of argon.[7]

The final challenge to major liver resections is the issue of credentialing. No surgeon should embark on any major liver resection without extensive experience in minor laparoscopic resections. Surgeons must have a combined experience in both hepatic surgery and advanced laparoscopy. Additionally, they must begin laparoscopic liver surgery with left lateral sectionectomy and minor resections. When performed by expert surgeons, major hepatectomies have been demonstrated to be feasible and safe, and results improve with experience.

REPEAT HEPATIC RESECTION

Despite more and more successful experiences with laparoscopic hepatectomies, including major hepatectomies that have been reported by several specialized centers all around the world,[39,44,46,47] larger series of repeat laparoscopic hepatectomy have not yet been published in the literature.

To date, studies with laparoscopic re-hepatectomies are only available from a series of small reports,[48] individual reported cases,[49,50] and limited cases contained in a larger laparoscopic liver resection series. The rationales for performing liver resection include primary liver cancers and metastatic malignancies. These preliminary results indicate that the possibilities of performing repeat laparoscopic liver resection in patients with previous open or laparoscopic liver surgeries and patients can still benefit similarly from receiving primary laparoscopic hepatectomies. Recently, a large scale study[51] including 74 patients undergoing 76 laparoscopic re-hepatectomies in three experienced hepatobiliary and laparoscopic centers (Institut Mutualiste Montsouris, Paris, France; Rikshospitalet, Oslo University Hospital, Oslo, Norway; and University of Louisville, Louisville, United States) concluded that the operations can be performed safely and efficaciously while patients benefit from decreased blood loss, reduced postoperative pain, fast recovery, and shorter hospital stays, without compromising oncological results.

Technical Issues

Owing to the complexities of surgical procedures, risk of hemorrhage, and fragility of the re-operated liver, the surgeon's experience in laparoscopic liver surgery is critical. Repeat laparoscopic liver resections should only be performed in centers with significant experience in minor and major laparoscopic liver resections. Prior to the surgery, patient safety, feasibility, and the oncological rationale for resection must be evaluated carefully. The most common difficulties encountered in these procedures are extensive adhesions, intraoperative bleeding, inability to approach the tumor location, and multiple tumors. When encountered, these difficulties may lead to conversion.

Equipment Setup and Procedures

The equipment used for repeat laparoscopic liver resection is similar to that used for primary laparoscopic hepatectomies, depending on surgeon preference. Concerning the increased risk of hemorrhage, surgeons are strongly recommended to use bipolar electrocautery along the whole procedure with meticulous hemostasis maintained. Compared to re-operation after previous laparoscopic procedures, increased adhesions may be found in patients with previous open liver resections, which require extensive adhesiolysis. The GelPort device (Applied Medical; California) can be very helpful in these patients. Instead of lysing adhesions completely laparoscopically, a minimal laparotomy wound along the previous laparotomy scar can be created initially for lysis of adhesions around trocar insertion sites and areas of dense adhesion. Then, a GelPort can be put on the laparotomy wound and the adhesiolysis can be continued laparoscopically (**Figures 4 and 5**). Peritoneal carcinomatosis can sometimes be harbored in dense intra-abdominal adhesions, and therefore complete lysis of the suspicious adhesions with frequent frozen sections of these lesions is mandatory. In case of underestimation or overestimation of the number of lesions, intraoperative ultrasonography should be performed repeatedly. The surgical margin should always be measured meticulously.

In the hands of an experienced surgeon, repeated liver resection could be considered via an open or laparoscopic approach. Owing to the clinical benefits from minimally invasive procedures with equal oncological outcomes compared to open surgery, laparoscopic approach may be preferable. However, further large-scale studies are still pending for justification of long-term survival benefits of laparoscopic re-hepatectomies.

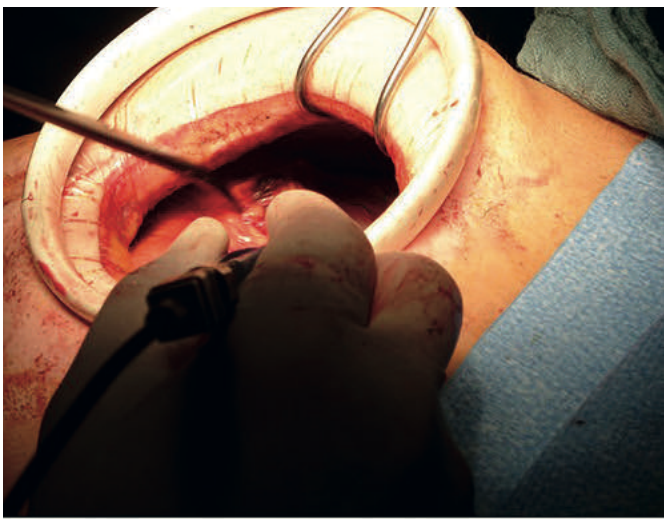


Figure 4. Intraoperative view of a minimal laparotomy wound is created for adhesiolysis.



Figure 5. Intraoperative view. A GelPort is attached to the patient's laparotomy (with previous ureterostomy and colostomy) wound to achieve pneumoperitoneum and the surgery is continued laparoscopically.

SAFETY AND EFFICACY OF LAPAROSCOPIC LIVER RESECTIONS

As in any other area of surgery, several points of controversy persist in the performance of laparoscopic liver resection. Most of these issues surround strong personal opinions and concerns. This section is offered to address these concerns and offer potential remedies.

GAS EMBOLISM

The most controversial of these issues is the occurrence of gas embolism. Since the inception of laparoscopic liver resection, multiple authors have vehemently voiced their concerns over pneumoperitoneum-induced gas embolism. These concerns have led many authors to speculate and even develop numerous alternatives to CO_2-induced pneumoperitoneum. The first of many manipulations was to reduce the pneumoperitoneum working pressure to between 8 and 10 mmHg. Subsequently, several authors experimented with alternative gases including inert gases. The most interesting and complex answer was a scaffold designed to lift the abdomen externally to create a working space. Several experiential solutions led to the demise of these efforts. The first was the observation that cardiac surgeons will often run CO_2 gas into the coronaries to clear them of an air embolism. The second was the use of elevated pneumoperitoneal pressures of 15 mmHg employed by a urologist during laparoscopic prostatectomy to minimize venous bleeding. Lastly, Fors et al.[52,53] performed several studies evaluating the incidence and impact of gas embolism during induced laparoscopic hepatic injuries in a porcine model; this finally demonstrated that the physiological impact of gas embolism through bleeding hepatic vessels was less drastic than previously predicted.

These studies aside, there have been several deaths reported worldwide from gas embolism during laparoscopic hepatic resection. These can be attributed to significant disruption of the hepatic veins at their origin. Additionally, two deaths have been attributed to argon gas embolism by direct argon beam direction into a bleeding hepatic vein. This lends credence to several authors' insistence that argon beam electrocoagulation should never be used. We believe this statement is too extreme. Argon coagulation is a safe and efficacious modality to control mild to moderate hepatic bleeding. The surgeon must be cautious to avoid direct introduction of argon gas into a bleeding major hepatic vein branch. Additionally, when larger resections are performed the use of an intraoperative transesophageal echo can be helpful. Three prior cases of gas embolism were identified early and successfully managed during lobar or trisegmental resection.

HEMORRHAGE

The second most dreaded complication of laparoscopic liver resection is hemorrhage. Bleeding comes from multiple sources, including arterial, portal, hepatic vein, or even caval. There are numerous methods of hemorrhage control. Multiple authors advocate the routine use of portal inflow control. Others authors have long abandoned this technique. All agree that minimization of central venous pressure is critical to a successful resection. This can be carried out through isovolemic hemodilution or administration of nitrates or anesthetic gases.

Hemorrhage can be controlled by a variety of techniques. The simplest of these is the re-application of the endovascular stapler. The stapler can often be replaced against the resection bed and a second staple line placed to close the bleeding vessel. Another frequently used technique is application of 5 or 10 mm endoclips. Unfortunately, through early experiences with laparoscopic donor nephrectomy, it was noted that clips could often cause stapler misfires. This catastrophic event can often led to significant blood loss and event greater vascular injury. The most advanced method for vascular control is the use of Koffron's quick stitch. The quick stitch is a precut 10 cm long silk or prolene suture with two 10 mm vascular clips placed on the tail of the suture. The quick stitch is an alternative to the more cumbersome laparoscopic suturing, which requires hand tying. Once the suture is placed and is hemostatic, additional clips can be placed on the proximal end to effect closure.

Lastly, there is an addition class of agents known as biologics, which aid in hemostasis. The most common agents are sealants including Tisseel, Coseal (Baxter) and Bioglue (Cryolife; Kennesaw, GA). The first two agents are approved for control of mild to moderate bleeding. These agents also have the advantage of decreasing postoperative adhesions. In the setting of metastatic disease or primary malignancy that may be referred for definitive liver transplantation, sealants are often used to decrease subsequent adhesions. Bioglue is a sealant with a physiological burst pressure of 120 mmHg. This agent has a half-life of over 24 months, leading the FDA to categorize it as a device rather than a pharmaceutical. Bioglue is most commonly used during aortic and cardiac surgery to control arterial hemorrhage after anastamosis. During hepatic surgery, Bioglue can be used on the resection bed when repetitive arterial hemorrhage is encountered or after a complex suture repair is required. One note of caution must be made: Bioglue requires a minute to set. Allowing abdominal contents to come into contact with the Bioglue prematurely has led to intestinal obstruction. Despite these detractions, sealants appear to be another excellent approach to hemostasis.

CONVERSION

When surgeons encounter bleeding that is not amenable to laparoscopic repair, or are faced with the inability to progress the operation to completion, conversion should be performed. During the International Consensus on Minimally Invasive Liver Surgery in Louisville in 2008, significant agreement was reached in that pure laparoscopic procedures should be converted to a hand-assisted approach rather than a formal open procedure.[54] This consensus was derived from the belief that open conversion is prolonged and often requires more time to achieve hemostasis than conversion to hand-assisted laparoscopy.

COMPLICATIONS

Aside from gas embolism, complications encountered in laparoscopic liver resection surgery are similar to those of open hepatic resection. The incidence of complications varies between 12% and 18% in reported series. Complication rates vary as well, based on the extent of resection and the underlying hepatic substance. The most difficult complication to manage has been bile leak. The incidence of bile leaks and bilomas associated with laparoscopic liver surgery varies from 3% to 5%. Like other aspects of surgery, there are many methods to manage this complication. These include percutaneous drainage and endoscopic retrograde cholangiopancreatography (ERCP) with stenting.

MORTALITY

The mortality rate for hepatic resection has dramatically dropped over the last four decades. Initial reports of open hepatic resection carried a mortality rate in excess of 25%. Multiple series have recently and consistently reported perioperative mortality rates of 5% or less. Laparoscopic hepatic resection has reported similarly low mortality rates. Reported rates have varied from 0-3%.[55] These low mortality rates may be related to a selection bias. Most groups advocate a highly conservative approach to patient selection. The proportion of resections being performed laparoscopically varies from center to center, with an average of 20-65% at highly aggressive centers. The most troublesome mortalities in laparoscopic hepatic resection have been from gas embolism. These include several documented gases of argon gas embolization from inadvertent use in a bleeding hepatic vein, and from massive disruption of the hepatic vein confluence with the vena cava. The remaining mortalities arise from inadequate hepatic reserve, particularly in end stage liver disease patients.

ONCOLOGICAL INTEGRITY

The role of laparoscopic liver resection in the setting of malignancy has remained controversial, primarily due to concerns over oncological adequacy.[56] Reports of port site recurrences after laparoscopic resection for other malignancies have translated into similar concern for hepatic neoplasms.[57,58] The effects of pneumoperitoneum on tumor growth and recurrence have also been a cause for concern. In animal models, the use of pneumoperitoneum has been found to induce growth of occult hepatic metastases.[59,60] Other practical concerns that have been raised include inadequate staging using laparoscopy[61] and the lack of tactile sensation leading to difficulty in evaluating the appropriate resection margin.[62] The relative paucity of long-term survival and recurrence data has further dampened enthusiasm for the widespread adoption of laparoscopic resection for hepatic malignancies (**Table 1**).

As laparoscopic liver resection has matured, many of these fears are being put to rest. In a 2009 review of the global literature, Nguyen found only one reported case of port site recurrence in 2,804 patients undergoing laparoscopic liver resection. This was in a patient with renal cell carcinoma whose tumor had ruptured prior to surgery.[55] Increased facility with laparoscopic ultrasound has overcome much of the difficulty with evaluating intrahepatic tumor anatomy,[63] while adoption of the hand-assisted technique has allowed the incorporation of tactile feedback to the laparoscopic technique. A few centers have now reported 5-year survival rates for laparoscopic resection of hepatocellular carcinoma that are similar to those seen with traditional open surgery.[33,43,64] Given such advances, a 2008 international consensus conference on laparoscopic liver surgery recommended that laparoscopic resection is an acceptable method for the treatment of hepatic malignancy.[54] What appears to be most important is adherence to sound

Table 1. Selected series of laparoscopic resection for hepatocellular carcinoma and colorectal liver metastases.

Author	Diagnosis	Survival
Dagher et al. [33]	Hepatocellular carcinoma	64.9% at 5 years
Chen et al. [43]	Hepatocellular carcinoma	59.4% at 5 years
Lai et al. [64]	Hepatocellular carcinoma	50% at 5 years
Castaing et al. [46]	Colorectal liver metastases	64% at 5 years
Abu et al. [68]	Colorectal liver metastases	90% with 22 month median follow-up

oncological techniques such as R0 radical resection and gentle handling of the tumor, rather than whether a laparoscopic or open approach is taken. We will focus here on laparoscopic treatment of two of the most common hepatic malignancies: colorectal metastases and hepatocellular carcinoma.

HEPATOCELLULAR CARCINOMA

There are now several published studies comparing laparoscopic versus open resection for hepatocellular carcinoma.[28,65–67] All of these studies have shown that laparoscopic liver resection is non-inferior to open resection in terms of overall and disease-free survival. In addition, laparoscopic approach has been consistently shown to result in less intraoperative blood loss than an open approach. Given the known adverse effects of allogeneic blood transfusion on oncological outcomes, laparoscopic resection may prove to be more attractive to open surgery in experienced hands. Follow-up in the above studies is relatively short, however, limiting the strength of conclusions that can be drawn. Several recently published studies have shown excellent long-term outcomes, however. Lai et al.[64] demonstrated a 5-year overall and disease-free survival of 50% and 36%, respectively. Dagher et al.[33] showed 5-year overall and recurrence-free survival of 64.9% and 32.2% respectively, while Chen et al.[43] demonstrated 59.4% 5-year overall survival following laparoscopic resection of hepatocellular carcinoma. For patients with recurrence within Milan criteria, the reduced formation of intra-abdominal adhesions following laparoscopic resection can facilitate salvage transplantation.[38] Thus, laparoscopic resection for hepatocellular carcinoma appears to be at least non-inferior to open surgery, while offering a number of additional benefits such as decreased postoperative pain and hospitalization, lower blood loss, and decreased adhesion formation. A randomized controlled trial will be needed to firmly establish these benefits, although this may not be feasible given increasing patient preference for minimally invasive approaches.

COLORECTAL METASTASES

Laparoscopic resection has become the standard of care for resection of primary colorectal cancers, so it is natural that the minimally invasive approach would be extended to resection of hepatic colorectal metastases. Several studies have demonstrated the oncological efficacy of laparoscopic resection in this setting.[46,68,69] Castaing et al.[46] was the first to compare long-term outcomes of laparoscopic versus open resection of hepatic colorectal metastases. In the laparoscopic group, 5-year overall and recurrence-free survival were 64% and 35%, respectively. This compared favorably to the 5-year overall and recurrence-free survival of 56% and 27% seen in the open resection group. As with hepatocellular carcinoma, laparoscopic resection of hepatic colorectal metastases appears to be at least non-inferior to open surgery, with the additional benefits of minimally invasive surgery. There are no randomized controlled trials in this area either.

FINAL CONSIDERATIONS

Laparoscopic hepatic resection has evolved rapidly over the last decade, from a limited procedure used for small peripheral resections to a widely accepted procedure applicable to the majority of resections. However, the cautions of Cherqui et al.[3] from his first description of laparoscopic liver resection are still valid. Laparoscopic liver resection should only be pursued with adequate expertise in hepatic resection and laparoscopy.

SUGGESTED READING

Cherqui, D. *et al.* Laparoscopic liver resections: a feasibility study in 30 patients. *Ann. Surg.* **232**, 753–762 (2000).

Prospective study including 30 patients during the initial practice of laparoscopic liver resection. Hepatic segments 2 through 6 were considered safe for laparoscopic resection. Technical aspects, such as portal clamping, are discussed

Dagher, I. *et al.* Laparoscopic major hepatectomy: an evolution in standard of care. *Ann. Surg.* **250**, 856–860 (2009).

A large study on major laparoscopic liver resection: 210 laparoscopic major hepatectomies from 6 international surgical centers. Results demonstrates that major hepatic resection is safe when performed by expert surgeons.

Buell, J. F. *et al.* Experience with more than 500 minimally invasive hepatic procedures. *Ann. Surg.* **248**, 475–486 (2008).

Study with a large number of minimally invasive hepatic procedures, including 306 hepatic resections and 240 laparoscopic rafiofrequency ablations. Recurrence rate and survival are reported.

Castaing, D. *et al.* Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. *Ann. Surg.* **250**, 849–855 (2009).

Comparison of survival rates of patients that underwent open hepatectomy or laparoscopic hepatectomy for colorectal liver metastases. Comparable oncologic results are reported.

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28 Complementary Techniques in Liver Surgery

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- *The most important technical tools that have improved speed and safety of liver resection are: staplers, sealers, and ablation devices.*
- *Staplers now allow reliable and rapid closure of major blood vessels.*
- *Sealers allow secure transection of liver parenchyma, minimizing bleeding and securing small bile ducts.*
- *Ablation instruments allow a parenchymal sparing alternative to resection for deep, small tumors, and can be combined with simultaneous major liver resection to extend possibility of curative therapy.*

INTRODUCTION

The historical development of liver surgery techniques is notable for the struggle against hemorrhage from liver transection. Hepatic resection is a challenging surgical procedure to begin with because of the risk of massive bleeding during transection and the complicated biliary and vascular anatomy in the liver. Before the 1980s, hepatic resection was associated with a mortality rate of 10-20%, with hemorrhage as a common cause of operative mortality.[1] Nowadays, the hospital mortality rates of even major hepatectomies are 5% or lower at many specialized centers.[2–4]

Several factors may account for the reduction of mortality. A better understanding of hepatic anatomically based resections is probably the most important in this regard.[3] In addition, during the last two decades of marked improvement in perioperative outcome, various novel devices for liver transection have been developed and rapidly introduced in the clinical setting. Thus, in addition to conventional clamp-crushing and finger fracture techniques, use of devices such as the ultrasonic dissector, water jet dissector, harmonic scalpel, argon beam coagulator, vascular stapler, LigaSure® system (Covidien; Dublin, Ireland), or, more recently, radiofrequency (RF)-assisted devices, have been extensively employed in order to reduce intraoperative blood loss. In that regard, many reported studies compare various techniques for liver transection with varying claims of superiority of one method over another. But if one examines prospective randomized trials for this purpose, few report such comparisons.[5]

In a meta-analysis of prospective randomized controlled trials addressing this question, Rahbari et al.[6] selected seven studies [7–13] that they felt provided a high-quality design with comparable data. Interestingly, there was no overall increase in liver transection speed, reduction of operative blood loss, or change in any other outcome variable demonstrating improvement between patient group assignments. In fact, the clamp-crush technique was numerically, although not statistically, favored over the newer parenchymal transection

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devices. Similar conclusions were drawn from a recent review of the Cochrane Library.[14] However, the surgeon's technique does not depend only on using a specific "modern device" but on his or her ability to accomplish the whole planned procedure in a controlled fashion that is rather difficult to measure in such studies and is not device dependent. We are confident that this ability to perform liver surgery, taking into account the advantages of any specific modern device adapted to a specific liver resection along with a deep knowledge of the anatomic details involved in the procedure, is critically important for safety and accuracy. Therefore, the aim of this chapter is to review several surgical procedures in liver resection using modern devices currently used by the authors.

STAPLERS IN LIVER RESECTION

Staplers are currently used in a number of procedures among several surgical specialities. Colorectal and esophageal anastomoses are usually performed with staplers in a safe and rapid manner even when surgical exposure is compromised.[15] However, for liver resections, the use of staplers is not routine. In that regard, three main aims can be accomplished in liver surgery with these instruments:

A) Hepatic inflow control.

Control of the inflow blood vessels to the liver has been traditionally achieved by extrahepatic dissection of the portal vein and hepatic artery separately. This approach is usually time-consuming and not always safe, but staplers can be safely used. Nevertheless, what we have found particularly useful is intrahepatic pedicle ligation of the portal pedicles.[16] As described by Launois & Jamieson,[17] Glisson's capsule extends into the liver as sheaths around the hepatic ducts, hepatic arteries, and portal tributaries. Therefore, within the hepatic substance these structures are more easily ligated en masse. These sheaths can be approached either anteriorly (after division of the hepatic parenchyma in the chosen transection line into the liver) or posteriorly from behind the porta hepatis by performing several hepatotomies (to selectively dissect these sheaths).[18] We will describe here the technique of using vascular staplers in dividing the various portal pedicles through an intrahepatic approach (especially by a posterior approach). Use of vascular staplers in this situation allows simultaneous ligation of the portal vein, hepatic artery, and bile ducts, and it greatly simplifies hepatic inflow control in liver resection.

Right pedicle ligation. Firstly, the entire right lobe of the liver must be fully mobilized. Then, the most inferior small hepatic veins or any large accessory right hepatic veins from the back of the liver to the vena cava must be divided to avoid any hemorrhage from tearing these venous branches or laceration of the intraparenchymal hepatic veins. The gallbladder is also removed to allow unimpeded access to the base of the right portal access. A hepatotomy (usually 1 or 2 cm in depth) is then created across the caudate process (**Figure 1**, incision A). A second hepatotomy is created in the gallbladder bed (**Figure 1**, incision B). Lowering of the hilar plate (**Figure 1**, incision C) in the back of segment 4 is also essential to ensure that the hilum of the liver is well mobilized and away from the area of the staple ligation. At all times, the surgeon's thumb and index finger are useful "instruments" to dissect sheaths, allowing tape to be placed around them (**Figure 2**). Clamping of an individual sheath with a vascular clamp allows precise delineation of the segments that the sheath supplies (**Figure 2**). The liver tissue overlying the main right pedicle is transected usually by the TA-30 vascular stapler (United States Surgical Corporation, Norwalk, CT) while constant traction is placed on the umbilical tape to the left (**Figure 3**). The traction on the umbilical tape prevents accidental application of staples too close to the hilus. Similarly, selective right anterior or right posterior pedicle ligation can be achieved with staplers (**Figure 1**).

Left pedicle ligation. Similarly to the right pedicle ligation, lowering of the hilar plate (**Figure 1**, incision C) allows for isolation of the left portal pedicle with minimal potential risk of injuring the hilus. If the caudate lobe is

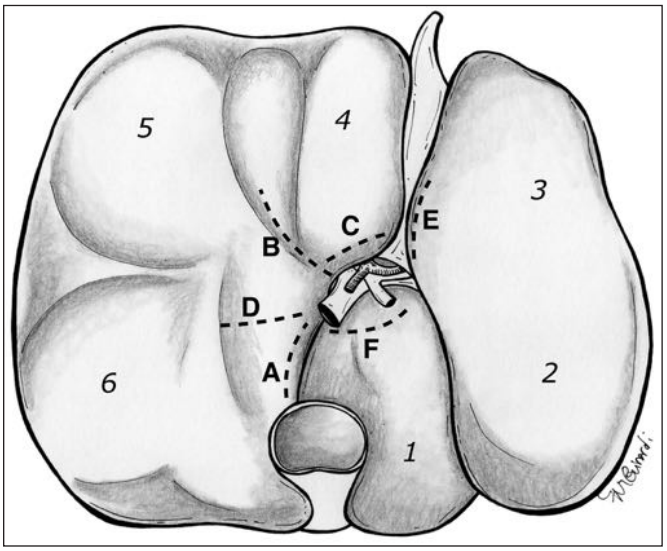


Figure 1. Sites for hepatotomy in portal pedicle ligation by a posterior intrahepatic approach. The undersurface of the liver is illustrated. Incisions at **A** and **B** allow isolation of the right main portal pedicle. Incision at **C** allows lowering of the hilar plate. Incision at sites **A** and **D** allow isolation of the right posterior portal pedicle. Incisions at sites **B** and **D** allow isolation of the right anterior portal pedicle. Incision at sites **C** and E allow isolation of the left main portal pedicle if the caudate process is to be preserved. Incision at sites **C** and **F** allow isolation of the left main portal pedicle if the caudate process is to be removed.

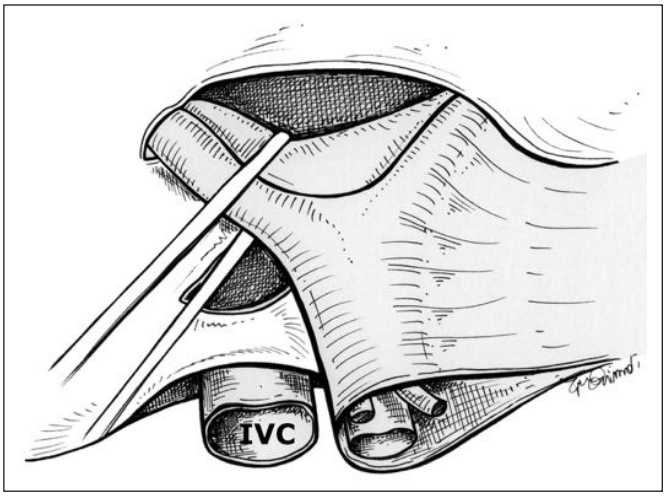


Figure 2. Tape around the right main sheath. IVC: inferior vena cava.

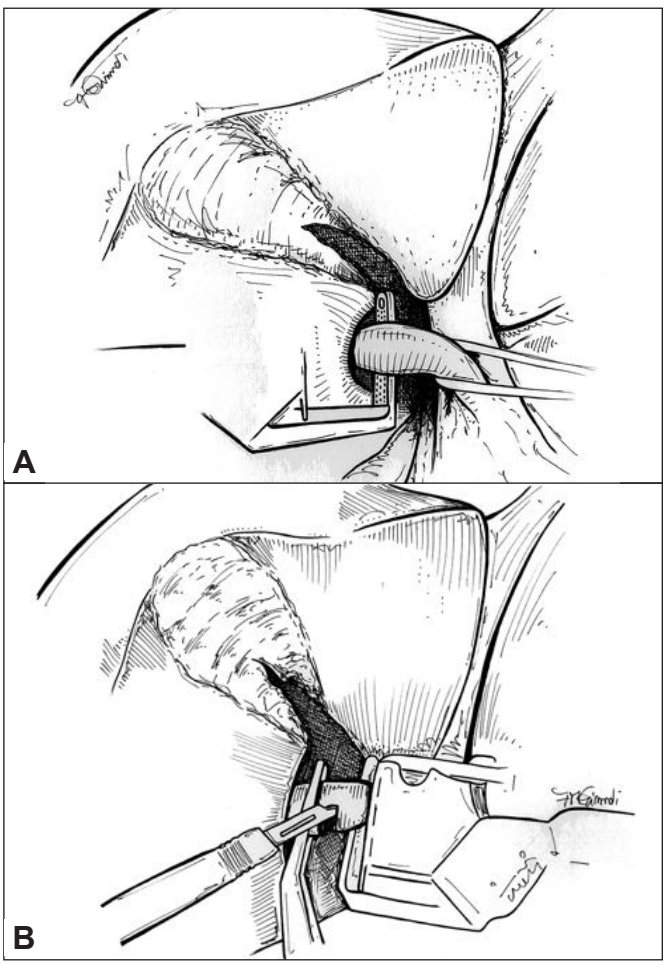


Figure 3. Control of the right portal pedicle by an intrahepatic approach using a stapler. While constant traction is placed on the umbilical tape to the left, a vascular stapler is fired on the main right portal pedicle (**A**). After application of the stapler, a vascular clamp is placed on the specimen side of the portal pedicle. The right portal pedicle is then cut using a scalpel (**B**).

to be preserved, care must be taken to ligate the left portal pedicle distal to the origins of the branches to the caudate probe (**Figure 1**, incision at sites C and E). On the contrary, if the caudate lobe is to be removed these branches are to be ligated as well (**Figure 1**, incision at sites C and F). Similar to the right pedicle ligation, constant traction is placed on the umbilical tape downward, and a vascular clamp is placed on the specimen side of the portal pedicle. The left portal pedicle is then cut using a scalpel (**Figure 4**).

Troubleshooting. There are two important guiding principles that should be followed in deciding on and performing intrahepatic pedicle ligation: 1) an intrahepatic pedicle approach should not be used when a tumor is within 2 cm of the hepatic hilus. In such cases extrahepatic dissection should be performed to avoid violation of the tumor margin; 2) application of the Pringle maneuver reduces bleeding while performing the hepatotomy.

B) Hepatic outflow control.

Control of the hepatic veins may limit blood loss during parenchymal transection. Furthermore, if the location of the tumor to be removed is near the hepatic vein–caval junction, extrahepatic control of the hepatic veins may facilitate excision of the tumor with clearance. However, extrahepatic ligation of the hepatic veins can be technically

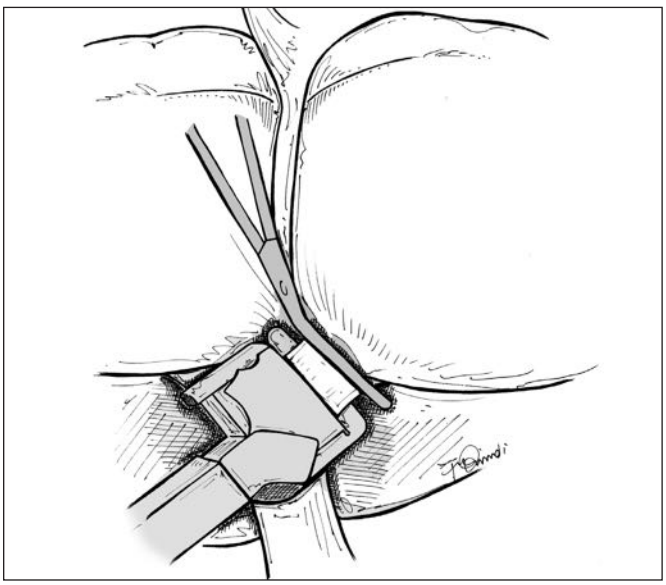


Figure 4. Stapler ligation of the left portal pedicle through an intrahepatic approach with preservation of the caudate lobe after incisions depicted in Figure 1 (incisions C and E). An umbilical tape is placed around the left pedicle for control. While constant traction is placed on the umbilical tape downward, a vascular stapler is applied on the left pedicle. The traction on the umbilical tape prevents accidental application of staples too close to the takeoff point of the caudate process. After firing the stapler, a vascular clamp is placed on the specimen side of the portal pedicle. The left portal pedicle is then cut using a scalpel.

demanding or even hazardous if the tumor is placed in the dome of the liver. Endo-GIA staplers (United States Surgical Corporation; Norwalk, CT), with their low profile and application of staple lines on both sides of the vascular division, can greatly facilitate ligation of any of the major hepatic veins. In that way, the stapling will seal the stump on the vena cava as well as the hepatic stump on the specimen side where sewing is often difficult because of the orientation of the surgical specimen.

Right hepatic vein ligation. After complete mobilization of the right lobe of the liver and ligation of the small perforating branches from the back of the liver to the vena cava, attention is focused on any accessory right hepatic vein. If this accessory is of significant size, it can be stapled after isolation. Stapling of these vessels can be safely achieved using an Endo-GIA 30-mm stapler. In addition, a tongue of liver tissue often passes from the back to the right lobe of the liver to the vena cava. We have found that stapling these pieces of tissue is a rapid and a safe method for obtaining access to the remaining vena cava. After rotation of the liver to the left, the right hepatic vein can be safely dissected and isolated and an Endo-GIA 30-mm vascular stapler more easily introduced parallel to the vena cava and directed from below upward (**Figure 5**). However, we would not recommend using such a staple-ligation technique if visualization of the right hepatic vein is obscured by the size or location of the tumor or when suture repair of the caval side of the right hepatic vein cannot be accomplished if the stapler misfires. To prevent misfiring with staplers, no vascular clips should be near the site of stapler application.

Left hepatic vein ligation. Firstly, mobilization of the lateral segment of the diaphragm by division of the triangular ligament should be achieved. Dissection is performed from above the liver and *from* the area of segments 2 and 3 and the caudate lobe, namely the ligamentum venosum of *Arantius*. It is worthwhile to remember that in approximately 60% of cases, the left and middle hepatic veins join together prior to a common entry point into the vena cava. Therefore, in ligating the left hepatic vein the middle hepatic vein must be protected. After identification of the left hepatic vein the Endo-GIA 30-mm vascular stapler is directed from the top downward (**Figure 6**). If a left hepatectomy is to be performed, middle hepatic vein ligation may be necessary by additional dissection from above the liver and from below (in the region of the ligamentum venosum of with the vascular stapler. This ligation of both middle and left hepatic veins can be accomplished with a single application of the same stapler.

C) Stapler-assisted liver transection.

Stapler hepatectomy can certainly be used as a technique for parenchyma transection for both minor and major resection with low morbidity and mortality, but research on this specific item is limited.[19] Generally, this technique is combined with a clamp-crushing method in order to get a thinner portion of parenchyma to be stapled and to prevent oozing or even massive blood loss from blind placement of the staples.[20,21] However, it can be helpful in laparoscopic fenestration of liver cysts or in liver abscesses by serial application at the junction of the cyst or abscess and the remaining parenchyma.[16,20] The main advantage of the stapler in these settings is that any inadvertently injured bile duct or vasculature is sealed.

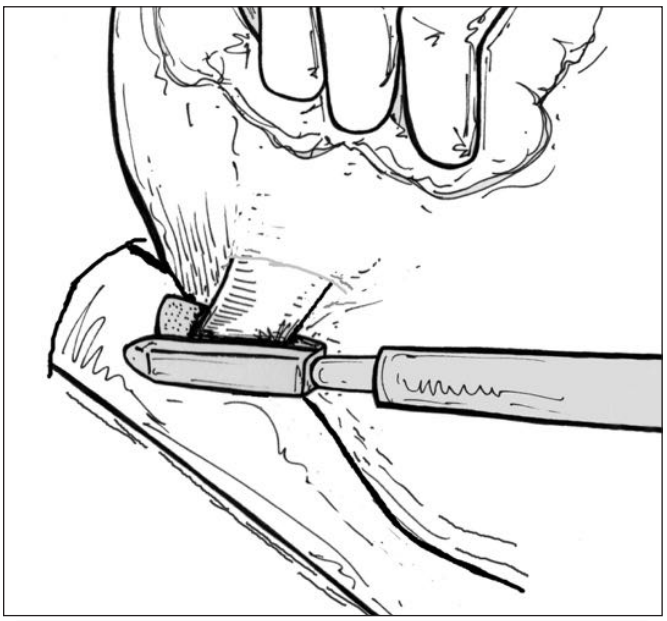


Figure 5. Stapling of the right hepatic vein with an Endo-GIA 30-mm vascular stapler. The safest method for introducing the stapler is to retract the liver to the left, advancing the stapler cephalad in the direction of the vena cava.

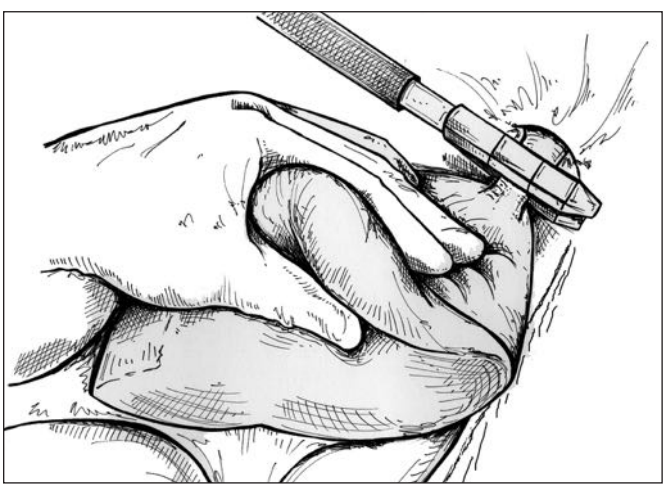


Figure 6. Stapling of the left hepatic vein. The liver is rotated to the right and an Endo-GIA 30-mm vascular stapler is applied at the junction of the left hepatic vein and the vena cava.

THE VESSEL SEALING SYSTEM (LIGASURE) AND OTHER SCISSOR-TYPE COAGULATION DEVICES IN HEPATIC RESECTION

Recently, a vessel ligating system (LigaSure) was developed (**Figure 7**), and has been widely used in the fields of urologic, gynecologic, and gastrointestinal surgery.[22–24] Using bipolar electrothermal energy, this device can seal the vessel wall by denaturing the collagen and elastin in the wall and completely occluding blood vessels as large as 7 mm in diameter.[25] Additionally, this instrument can have a built-in knife to allow rapid and precise division of the sealed vessels (Impact version, **Figure 7**).

The liver is mobilized as usual. Use of the Pringle maneuver and major vascular dissection are undertaken according to surgeon preference.[24,26] It is our preference to perform an intrahepatic anterior approach (see above) to the pedicle under the Pringle maneuver without any extrahepatic dissection of the pedicle if the tumor to be resected is beyond 2 cm of the hepatic hilus. Direct application of the LigaSure system, closing the jaws of the device into the liver tissue, may tear several incompletely sealed vessels and cause oozing from the transection line. In order to avoid this oozing from any torn vessel, the easiest method for liver transection involves combining the use of Kelly clamp dissection and the LigaSure sealing device [24,26] (**Figure 8**). In that way, the Kelly clamp is used to crush the liver in progressive layers, allowing exposure of the underlying vessels. The Kelly clamp is held open with the tip approximately 0.5 to 1.0 cm apart, and pushed into the liver approximately 4 to 5 cm at a time. Three or four layers of crushing will then expose vessels in an area approximately 3 × 5 cm for ligation. The LigaSure is then directed along the same tracts created by the Kelly clamp and the vessels sealed and divided. For efficiency, the Kelly clamp can be operated by the lead surgeon and the LigaSure device by the assistant. Vessels greater than 5 mm in diameter are usually suture ligated, tied, or stapled. It is our preference to staple the intrahepatic pedicle of the specimen to be removed. Although a recent randomized controlled trial [24] failed to confirm the superiority of the vessel sealing system, in terms of either the operation time or the amount of blood loss, to the conventional clamp-crushing method, we feel this system combined with the intrahepatic approach of the pedicle (not employed in this randomized trial) may be useful in reducing the operation time or other complications.

A number of scissor-type devices have been tested in transection of liver parenchyma. The most successful to date are those based on cutting with harmonic energies, which seal tissue with heat generated through vibration of the instruments at high frequencies (over 55,000 per second). These devices include the Harmonic Scalpel (Ethicon Endo-



Figure 7. LigaSure instrument for open surgical ligation of intrahepatic vessels: The Impact instrument is shown. Other instruments (Atlas, Advance) can be used for laparoscopic resection.

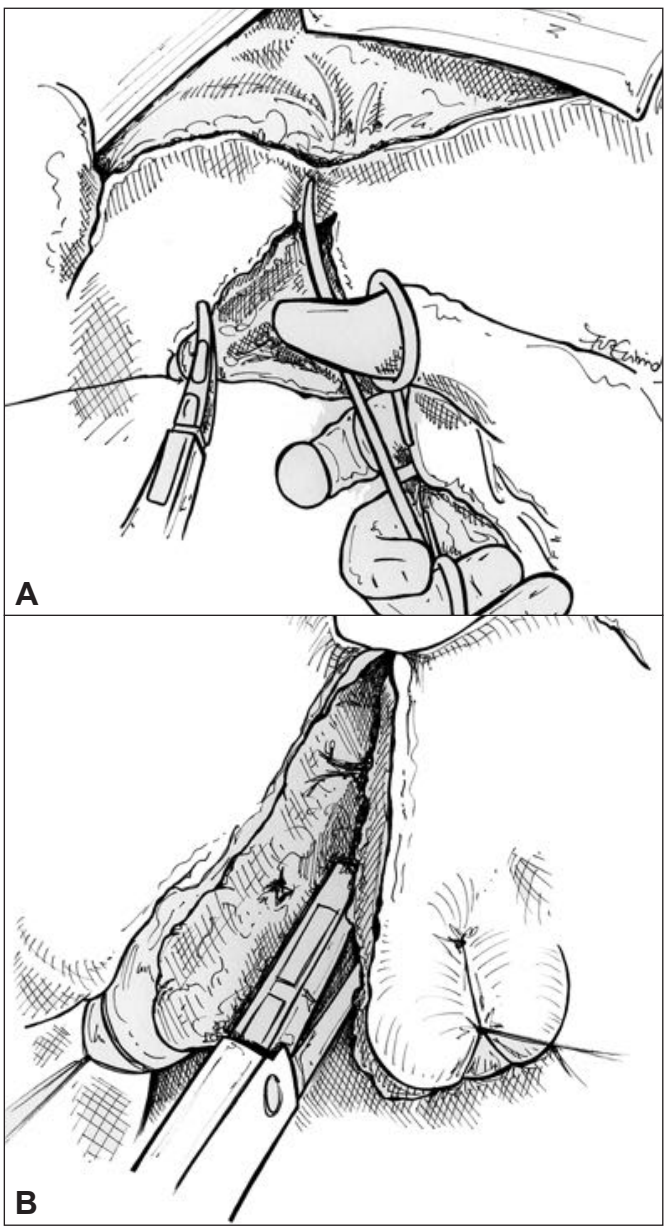


Figure 8. Combined Kelly clamp and Impact transection of the liver (post-coagulation method). The liver parenchyma is crushed as usual to expose the underlying vessels (**A**), which will be transected and sealed by the Impact device (**B**).

Surgery, Inc.; Cincinnati, OH), SonoSurg (Olympus; Center Valley, PA), and Ultracision (Covidien). This instrument has been successfully used for liver transection in open and especially in laparoscopic liver resections in combination with other methods of ligation (mainly stapling of vessels of more than 4 mm in diameter).[27] However, two nonrandomized studies comparing the Harmonic Scalpel with the conventional clamp-crushing method showed that use of the Harmonic Scalpel was associated with a significantly increased rate of postoperative bile leakage.[28,29]

RADIOFREQUENCY-ASSISTED DEVICES IN LIVER RESECTION

Weber et al.[30] pioneered the use of radiofrequency (RF) ablation electrodes to obtain a 1- or 2-cm wide line of coagulation necrosis at the resection line before dividing the line with a scalpel, thereby permitting bloodless liver resection. More specifically, in this technique, a Cool-tip RF electrode (Radionics; Burlington, MA) was inserted along the transection plane serially 1-2 cm apart, and RF energy applied for 1-2 cm to create overlapping cylinders of coagulated liver using a simple scalpel. In this preliminary study of 15 cases of mainly segmental or wedge resections the mean blood loss was only 30 mL and no complications were observed. Further application of this concept has been achieved with more recent devices like the Habib system (AngioDynamics, Queensbury, NY), InLine system (ILRFA; Resect Medical, Freemont, CA), TissueLink (TissueLink Medical, Dover, New Hampshire), or more recently with the CoolInside System (Apieron Medical, Valencia, Spain).

Although these more recent devices are aimed to transect the liver with minimal blood loss, the system of application can be classified according to the RF applicator in use:

A) "Needle" RF-assisted liver resection devices (**Figure 9**).

Several RF-assisted devices (such as the Habib [31] or In-Line system [32]) have recently been tested in an open and laparoscopic approach that may actually achieve bloodless transection usually requiring a limited number of sutures or clips to complete control of the portal or vein branches.[13] These instruments take the form of needles—electrodes that are inserted blindly or under ultrasound guidance 2 or 3 cm into the liver to achieve an area of hepatic ablation. This raises some concerns about possible thermal injuries to the hilar structures or increased risk of bile leaks.[33] For division of the parenchyma, these devices require an additional cutting instrument (usually a scalpel) that is applied to the middle of the supposed ablation area. These shortcomings may explain why their use is mainly restricted to minor resections,[21] even though they have occasionally been employed for anatomic or major resections.[34]biliary leak and postoperative liver function are still the main concerns of surgeons operating on the liver, even though different techniques have been developed to allow safer liver resection. A novel concept for liver resection is described using a radiofrequency energy (RF

B) "Handheld instrument" devices for RF-assisted transection of the liver (**Figure 10**).

These are instruments that are directly applied by the surgeon or the assistant onto the transection line and are not introduced blindly into the liver. This is usually more attractive for the surgeon because the instruments are easier to use and control. So far, two are currently described:

The ***TissueLink system*** (or saline-linked electric cautery) transfers RF energy to the liver through saline dripping at the tip of the device. This device can be used to dissect and achieve hemostasis of small vessels (<5 mm in diameter) [35] in combination with clips or conventional ligatures for larger vessels. However, dissection and cutting

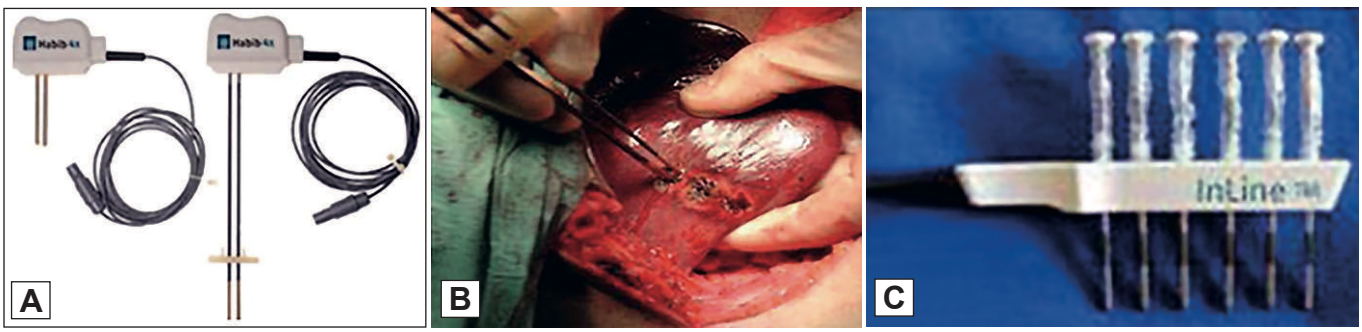


Figure 9. Several "needle" devices for radiofrequency (RF)-assisted transection of the liver: **A**) Habib 4X, a bipolar, disposable RF device for open surgery; **B**) Coagulation effect obtained after several applications with the Habib device in an open approach. After performing a line of coagulation necrosis, the coagulated tissue will be transected by a simple scalpel; **C**) InLine device, a bipolar, disposable RF device for open surgery. This system works in a similar way to the Habib system. Two standard RFA or microwave ablation probes can also be used in a similar fashion.

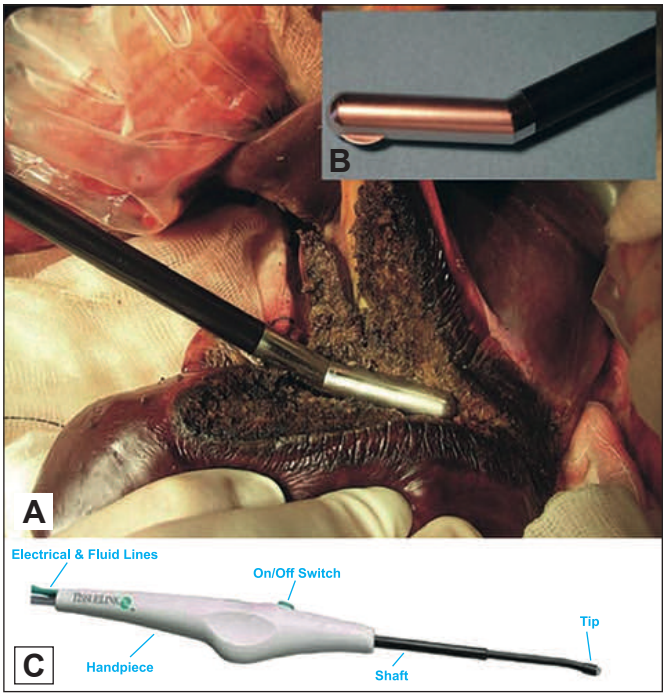


Figure 10. Several "handheld instrument" devices for radiofrequency (RF)-assisted transection of the liver: (**A**, **B**) CoolInside device and its usage in a open procedure without temporary vascular occlusion where no other instruments for cutting, dissection, or hemostasis of the liver; (**C**) TissueLink device.

of the tissue are not easily achieved with this device alone and are usually accomplished in combination with a cavitator ultrasonic surgical aspirator (CUSA) [36–38] and other hemostasis systems (usually clips or ligatures). This technique, where the leading surgeon usually employs the ultrasonic surgical aspirator while the assistant surgeon uses the TissueLink device, is known as the two-surgeon technique.[36–38]

The ***CoolInside system*** is an internally refrigerated RF highly powered instrument that is equipped with a built-in knife that provides in a single device both coagulation and precise cutting of the coagulated tissue simultaneously. Preliminary experimental and clinical data have shown the achievement of anatomic and wedge resections with minimal blood loss without employing any other dissection or hemostasis systems (including sutures or clips) and without employing temporary vascular occlusion.[39–41]

C) Combined Ablation and Resection (CARe).
For many years, surgeons have been using RFA and microwave ablation to attempt to extend the pool of patients who are treatable by physical means for liver cyto-reduction. This combined strategy allowed for the maximum killing of tumor while minimizing amount of functional liver removed. This strategy posits that resection is the best therapy for large tumors, while ablation can effectively kill small tumors. Recent data clearly supports this CARe strategy. In reported clinical series with long enough follow-up, it is clear that for small liver tumors, ablation can be very effective treatment.[42] For tumors 1 cm or smaller, ablation is effective at killing tumor completely in >95% of the time. It is also clear that tumors larger than 5 cm are very unlikely to be completely killed by ablation. Finally, in the largest series of combined resection and ablations published to date, a combined series from the US, from the UK, and from France demonstrated that long-term disease free status can be achieved at a very similar rate to bilateral resections.[43]

FINAL CONSIDERATIONS

The majority of the published randomized studies evaluating modern methods of liver transection have failed to show any relevant superiority over classical methods, mainly the clamp-crushing technique. However, using several "modern" devices may increase the comfort level of the surgeon performing the liver resection, which may be difficult to measure but is critically important for the safe and accurate completion of the procedure. In any case, a deep knowledge of the anatomic details involved in this procedure may be the most relevant factor in a safe liver resection. Tools developed for liver transaction have clearly improve d the comfort level of resections for surgeons, thereby allowing many more surgeons to treat many more patients. As technology evolves, these tools have been adapted to laparoscopic and robotic techniques,[44] allowing an even greater possibility of resecting patients for cure while minimizing morbidity.

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29 Liver Transplantation for Hepatic Failure

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- *Patient and graft survival after liver transplantation (LT) has improved over time. Despite the options available to increase the donor pool, the expansion on indications for LT has surpassed the availability of grafts, exacerbating the scarcity of grafts.*
- *Clinical evaluation of potential recipients is crucial to avoid excessively early LT (with no benefit for patients with a good predicted survival without LT) but also excessively late LT (resulting in poorer outcomes). Timing and methods for organ allocation remain challenging.*
- *Partial liver grafts (including living-donor and splitted grafts) and marginal grafts represent options to increase the graft pool.*
- *Postoperative complications after LT remain significant and are mainly related to graft quality, recipient clinical status, immunosuppression, recurrence of hepatic disease, and technical aspects.*
- *LT in the setting of acute liver failure is uncommon and is accompanied by specific factors related to organ allocation and technical aspects.*

INTRODUCTION

The first human liver transplantation (LT) was performed in 1963 by Thomas Starzl.[1,2] The first liver transplantation with long-term survival (18 months) was performed in 1967.[3] During subsequent years, outcomes after orthotopic liver transplantation (OLT) remained poor, with a 1-year survival rate of 30%.[4] Progress in immunosuppressive therapy and surgical and anesthetic techniques, among other factors, led to improved long-term survival, and by the 1980s LT had become widely accepted as a definitive treatment for end-stage liver disease.[5] Currently, long-term survival prognosis after LT is excellent, with 1-year, 3-year, and 5-year survival rates of approximately 90%, 80%, and 75%, respectively.[6–8]

Liver transplantation became an optimal therapy for patients who have a short estimated life expectancy (less than one year) or a quality of life deemed unacceptable by the patient, due to a variety of liver diseases. Indeed, LT is currently the only definitive treatment for the management of the complications of cirrhosis and liver failure, and it is estimated that 6,000 to 7,000 LT procedures are performed each year worldwide.

The improvement in outcomes after LT has led to an increase in potential recipients. Consequently, the number of cadaveric donors in most countries has become insufficient. Alternatives to increase the donor pool (such as the use of split livers, non-heart-beating donors, and living donors) have alleviated organ scarcity, but globally the number of available organs is not adequate to eliminate the waiting list, and about 5-10% of patients die before receiving a graft.

In summary, indications for liver transplantation include decompensated cirrhosis, acute liver failure, certain malignancies (a subset of patients with hepatocellular carcinoma, cholangiocarcinoma, and metastatic endocrine tumors), and certain types of metabolic derangements. Liver transplantation for malignancies is discussed further in **Chapter 30** (*Liver transplantation for malignant and benign liver tumors*).

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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LIVER TRANSPLANTATION FOR END-STAGE LIVER DISEASE

INDICATIONS

The most common etiologies of chronic end-stage liver disease (ESLD) requiring OLT are cirrhosis from chronic viral hepatitis C or B, and from alcohol abuse. Other chronic liver diseases that may require OLT include primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), non-alcoholic steatohepatitis (NASH), hemochromatosis, alpha-1-antitripsin deficiency, biliary atresia, autoimmune hepatitis, Wilson's disease, hepatic veno-occlusive disease, Budd-Chiari syndrome, and other vascular liver diseases.

Liver transplantation for ESLD is usually indicated when estimated survival is less than one year or quality of life has deteriorated significantly. Predictors of poor survival in cirrhosis include complications such as ascites, gastrointestinal bleeding due to portal hypertensive gastropathy or esophageal varices, synthetic dysfunction, hepatopulmonary syndrome, and portopulmonary hypertension, encephalopathy, and liver cancer.

Thus, specific criteria were determined to select adult patients with chronic liver disease for OLT, as follows:

- Liver cirrhosis classified as Child-Pugh A (**Table 1**), with at least one of the following complications: i) upper gastrointestinal bleeding secondary to portal hypertension, with two or more distinct episodes requiring blood transfusions; ii) hepatopulmonary syndrome with clinical manifestations; and iii) portosystemic encephalopathy.
- Liver cirrhosis classified as Child-Pugh B or C, regardless of complications.
- Primary biliary cirrhosis with a one-year survival prediction of less than 90% according to the mathematical models offered by King's College Hospital or the Mayo Clinic (**Table 2**).
- Primary sclerosing cholangitis, with at least one of the following conditions: i) presence of recurrent cholangitis with more than one episode; ii) prediction of 1-year survival of less than 90% according to the mathem atical models of King's College Hospital or the Mayo Clinic (**Tables 3 and 4**).
- Familial amyloid polyneuropathy (FAP) with disability score grades I, II and III (**Table 5**).

In addition to the Child-Pugh score, the MELD (Model for End-stage Liver Disease) score has been used to assess prognosis for cirrhosis from etiologies other than primary biliary cirrhosis and primary sclerosing cholangitis.

Table 1. Modified Child-Pugh score.

	1 point	2 points	3 points
Ascites	Absent	Controlled	Refractory
Total bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8 – 3.5	< 2.8
INR	<1.7	1.7 – 2.2	> 2.2
Encephalopathy	Absent	Grade 1 or 2	Grade 3 or 4

Sum of parameters 1 to 6 = Child A; 7 to 9 = Child B; 10 to 15 = Child C.
INR: International normalized ratio.

Table 2. Mayo model for predicting prognosis in primary biliary cirrhosis.

R=0.051(age [y]) + 1.209 $\log_e$(bilirubin [mg/dL]) – 3.304 $\log_e$(albumin [g/dL]) + 2.754 $\log_e$ (PT [s]) + 0.675 $\log_e$(edema score)

Edema score: 0 for no edema without diuretics; 0.5 for edema without diuretics or edema resolved with diuretic therapy; 1 for edema despite diuretic therapy.

Table 3. Independent predictors of survival used in mathematical models for primary sclerosing cholangitis.

Mayo model	Revised Mayo model	King's College model
Age	Age	Age
Total bilirubin	Total bilirubin	Hepatomegaly
Histologic stage	Albumin	Histologic stage
Hemoglobin	AST	Splenomegaly
Inflammatory bowel disease	Variceal bleeding	Alkaline phosphatase

AST: aspartate aminotransferase.

Table 4. Mathematical models predictors of survival in primary sclerosing cholangitis.

Mayo model	R = 0.06 (age [y]) + 0.85 $\log_e$ (bilirubin [mg/dL]) - 4.39 $\log_e$ (hemoglobin in [g/dL]) + 0.51 (histological stage) + 1.59 (indicator for inflammatory bowel disease)
Revised Mayo model	R= 0.03 (age [y]) + 0.54 $\log_e$ (bilirubin [mg/dL]) + 0.54 $\log_e$ (aspartate aminotransferase [U/L]) + 1.24 (variceal bleeding [0/1]) – 0.84 (albumin [g/dL])
King's College model	R = 1.81 (hepatomegaly [0/1]) + 0.88 (splenomegaly [0/1]) + 2.66 $\log_e$ (alkaline phosphatase [mg/dL]) + 0.58 (histological stage) + 0.04 (age [y])

The MELD score (**Table 6**) is on a continuous scale from 6 to 40, with estimated three-month survival varying between 90% and 7%, respectively. This score has been used extensively by transplant centers to prioritize grafts to recipients with shorter survival expectancy.

CONTRAINDICATIONS

Contraindications to LT are mainly those conditions leading to poor early or late post-transplantation outcome. Relative contraindications are those correctable prior to transplantation and absolute contraindications are those that are not modifiable, precluding OLT.

Some accepted contraindications to LT are: i) very poor performance status precluding the patient from withstanding surgery; ii) uncontrolled extrahepatic sepsis; iii) alcohol abuse or illicit drug use with less than six months of abstinence; iv) anatomical conditions that rend graft implant technically impossible (such as extensive venous thrombosis); v) extrahepatic malignancy or hepatic malignancies with poor survival prognosis after LT (such as most liver metastases and cholangiocarcinoma, and advanced hepatocellular carcinoma); vi) lack of adequate social support; and vii) acquired immunodeficiency syndrome (AIDS).

Other unsuitable conditions include advanced age, hepatopulmonary syndrome, human immunodeficiency virus (HIV) infection, severe portopulmonary hypertension, and hemodynamic instability. It is important to note that HIV infection and replicative hepatitis B are no longer considered absolute contraindications for LT.

RECIPIENT EVALUATION

Candidates for LT should be investigated extensively in order to establish severity of hepatic disease and comorbidities. Surgical difficulties can be anticipated in recipients with prior abdominal surgery, obesity, and portal vein thrombosis.

Obesity seems to increase surgical risk and to reduce long-term survival following LT.[9–12] Despite a dearth of evidence of reduction in risk with preoperative weight loss, weight reduction should be attempted prior to surgery, and a body mass index of 40 kg/m^2 is a relative contraindication to LT.

Initial cardiac evaluation, including non-invasive stress echocardiography, is performed in all LT candidates to assess perioperative risk and to exclude concomitant cardiopulmonary disorders that preclude surgery or adequate long-term outcome.[13] Coronary artery disease is present in 3-28% of liver transplant candidates.[14,15] Severe coronary artery stenosis (more than 70%) is treated with revascularization before LT. Severe valvular and/or ventricular dysfunction should be improved by medical therapies.[16]

Table 5. Neurological classification of familial amyloid polyneuropathy.

Score degree of disability	
I	Presence of sensory disturbance in the legs and preserved ability to walk
II	Difficulty walking and strolling without orthoses
III A	Patient able to walk only with the aid of a crutch/cane
III B	Need two crutches / walking sticks
IV	Limited to wheelchair or bed

Table 6. Model for End-stage Liver Disease (MELD) score.

MELD = 3.78 ln(serum bilirubin [mg/dL]) + 11.2 ln(INR) + 9.57 ln(serum creatinine [mg/dL]) + 6.43 etiology (0: cholestatic or alcoholic, 1: otherwise)

If the patient has been dialyzed twice within the last seven days, use the value for creatinine as 4.0; any value less than 1 is given a value of 1.

Portopulmonary hypertension (mean pulmonary artery pressure of 25 mmHg or more in the presence of portal hypertension) is detected in 4-8% of LT candidates.[17] Mild and severe pulmonary hypertension (mean pulmonary artery pressure ≥ 25 mmHg and ≥ 50 mmHg, respectively) are associated with 50% and 100% mortality rates, respectively.[18] Vasodilator therapy should reduce the mean pulmonary artery pressure to less than 35 mmHg in order to minimize surgical risk.[19–21]

Hepatopulmonary syndrome (HPS) results from intrapulmonary vascular shunting and is present in 5-32% of LT candidates.[22] Liver transplantation reverses hepatopulmonary syndrome in most patients.[23] Thus, hepatopulmonary syndrome does not preclude LV, despite a high morbidity rate if severe HPS is present.[24–27]

Renal dysfunction in cirrhotic patients also has deleterious effects on early outcomes and should be actively evaluated to determine etiology and prognosis. The most common cause of renal dysfunction prior to LT is hepatorenal syndrome (HRS).[28] Simultaneous liver kidney transplantation may be indicated in selected cases of end-stage renal disease with cirrhosis or end-stage liver failure with chronic kidney disease.

Patients with liver dysfunction are more prone to have infectious diseases, such as spontaneous bacterial peritonitis and urinary and respiratory infection.[29]

These infections should be treated before LT. Additionally, serological tests for viral infections (hepatitis A, B, and C; Epstein-Barr virus; cytomegalovirus; herpes simplex; and HIV), syphilis, tuberculosis, and coccidiodomycosis are required. Treatment or prophylaxis is undertaken according

to results.

Hepatitis C. Cirrhosis due to chronic hepatitis C virus (HCV) infection is the most common indication for LT in most Western countries. Reinfection occurs in most patients after LT, since antiviral therapy is not curative, and 20-30% of patients develop cirrhosis. Liver failure due to recurrent HCV after liver transplantation occurs in 10% of patients within five to 10 years,[30,31] resulting in poorer outcomes than LT for other etiologies. If there is no contraindication to interferon and ribavirin (or other new protocols) therapy, HCV should be treated before LT, especially for more favorable HCV genotypes (II and III).[32]

Hepatitis B. Liver transplantation for cirrhosis due to hepatitis B virus (HBV) infection requires control of the virus prior to LT. Hepatitis B virus immune globulin (HBIG) in association with oral antiviral therapy results in adequate viral control before LT. Five-year graft survival in patients undergoing LT for HBV can reach 85% with this approach. Indeed, the advent of efficacious oral antiviral agents has even reduced the needed for LT due to liver failure associated with HBV infection.[33]

Alcoholic liver disease. Cirrhosis due to alcohol abuse is usually the second most common indication for LT. Alcohol dependence is responsible for a high rate of resumption of alcohol abuse after LT, leading to an incidence of graft failure of 2% by 10 years.[34] Patients should be in abstinence for at least six months prior to LT.

Primary biliary cirrhosis and primary sclerosing cholangitis. Indications for LT in primary biliary cirrhosis (PBC) are similar to those for other causes. Decompensated PBC is the main indication, but also uncontrollable severe pruritus may be an indication for LT. Primary sclerosing cholangitis (PSC) is associated with an increased risk of cholangiocarcinoma and gallbladder carcinoma. Liver transplantation is indicated for decompensated disease. Also, recurrent bacterial cholangitis and cholangiocarcinoma (in selected cases) represent indications for LT. Specific scores to predict survival in PBC and PSC are helpful to define the optimal timing for LT in these diseases (see above).

LISTING AND TIMING

Timing of LT plays a crucial role in outcomes. Excessively early transplantation may not benefit patients with a good predicted survival without liver transplantation, since one-year mortality after orthotopic liver transplantation can reach 10%. On the other hand, transplantation in the sickest and decompensated patients typically has the worst outcomes, and patients should meet minimal conditions to withstand surgery. Finding the ideal timing for transplantation and the most beneficial distribution of grafts available can be challenging. Usually, patients with ESLD are referred for LT when a decompensation occurs, e.g. ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatocellular carcinoma. The American Association for the Study of Liver Diseases (AASLD) guidelines suggest referring patients with a Child-Pugh score ≥7 and/or a MELD score ≥10.[35]

Scarcity of grafts has led to the prioritization of patients with poorer prognosis. Score systems, such as the MELD score, have been validated to predict short-term mortality in patients with ESLD. Besides serum bilirubin, serum creatinine, and INR, all used in the MELD score, other prognosis parameters have been suggested to be included in tools to prioritize liver grafts.[36,37] In addition, some exceptions should be considered, such as in cases of hepatocellular carcinoma, where prognosis is poor even with preserved liver function. Most centers add points to the MELD score in cirrhotic patients with hepatocellular carcinoma, to compensate for more preserved liver function. Other possible exceptions to MELD scoring include certain genetic disorders (primary hyperoxaluria, familial amyloidotic polyneuropathy, and some cases of cystic fibrosis) and other infrequent indications such as metastatic neuroendocrine tumors and hepatopulmonary syndrome.[38]

LIVER GRAFT DONORS

Most liver grafts are whole livers from deceased donors (brain death or, more recently, non-heart-beating donors). Donation after cardiac death is still controversial in some countries, since the results in this setting are poorer than when using brain death donors. Absolute contraindications for deceased organ donation are cancer and uncontrolled infections. However, grafts from donors with HCV can be used for HCV+ recipients, because recurrence and survival rates are similar to the use of HCV- donors. Also, grafts from donors with hepatitis B core antigen positive (anti-HBc+) have been used in association with recipient prophylaxis.[39] Age over 50 years, cardiac arrest or hypotension, high sodium, and liver steatosis have increasingly been accepted in order to increase the pool of donors. However, the use of marginal grafts may result in higher complication rates, such as primary graft non-function, early graft failure, biliary complications, and decreased graft survival. Grafts from donors over 70 years of age or that have more than 60% fat content should not be used, except as a bridge in urgent situations.[39]

Partial liver grafts from living donors or from splitted grafts are used in different proportions worldwide. Living-donor liver transplantation (LDLT) is a well-established method, largely used in Eastern countries. Some recent donor deaths have led to a decline in LDLT in Western countries.[40] Living-donor liver transplantation has the advantages of healthy donors, minimal ischemic time, and optimal timing of transplant. However, the surgery is more demanding than whole-organ transplantation and carries a risk for the donor.

Donor morbidity and mortality rates may reach 30% and 0.8%, respectively.[41,42] A recent meta-analysis including more than 5,000 patients compared surgical outcomes of LDLT and deceased donor LT, and found that biliary and vascular complications, in addition to need for re-transplantation, occurred more frequently after LDLT.[43] Identification of biliary variants and ensuring adequate venous outflow of the graft to the recipient are crucial.

Technical aspects of liver graft procurement for deceased living donors are detailed in **Chapter 32** (Technical aspects of liver transplantation) and summarized as follows. After assessment of macroscopic appearance of the liver and exclusion of contraindications to use it, a Cattel-Kocher maneuver allows for exposition of the retroperitoneum. The infra-renal aorta and portal vein are cannulated (usually by a tube inserted through the superior mesenteric vein). After clamping the thoracic aorta, infusion of cold preservation solution iinto the aorta and portal vein is started. The inferior vena cava is opened for discharge of blood. The liver is resected including the maximum vascular and biliary structures. The celiac trunk is usually resected along with a patch of the aorta. Attention should be paid to identify vascular variations, mainly those relating to arterial liver supply. After resection, the liver is packed in a sterile bag filled with cold conservation solution for transportation. During the back-table procedure, excess tissue attached to the liver and vessels is resected, eventual vascular reconstructions performed, and the graft is ready to be implanted (**Figure 1**).

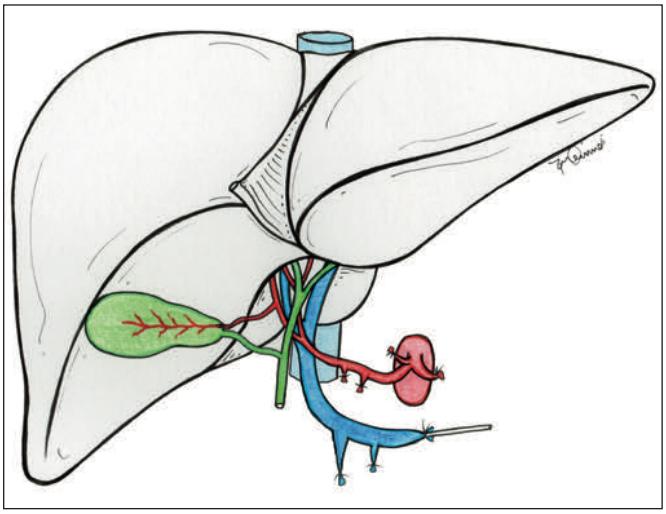


Figure 1. Whole liver graft after back-table preparation.

RECIPIENT SURGERY

Despite some technical variations, the surgical technique for whole liver transplantation has been standardized. Recipient portal hypertension can be a source of bleeding and careful hemostasis is mandatory from the time of incision to the end of procedure.[44]

During the first stage of the recipient operation, i.e. the native liver explantation, two methods are possible: with replacement or with preservation of the inferior vena cava (IVC). Replacement of the IVC requires IVC clamping, and a veno-venous bypass is usually used to prevent hemodynamic alterations and kidney hypoperfusion. The so-called piggyback method preserves the native IVC and only partial clamping is required for caval anastomosis. Results with these two methods are similar.

Technical aspects of recipient surgery can be summarized as follows. After section of all hepatic ligaments, the liver is completely mobilized. The hepatic hilum is dissected and the hepatic artery and bile duct sectioned close to the liver parenchyma. The portal vein is skeletonized along its entire length. A temporary end-to-side portocaval anastomosis may be used to prevent splanchnic congestion during the anhepatic phase, if the native IVC is preserved.[45] This technique reduces hemodynamic instability and could prevent the use of veno-venous bypass. The liver is then progressively dissected from the inferior vena cava and the hepatic veins sectioned to accomplish the native liver resection. Usually, the openings of the three hepatic veins are joined to obtain a sole large orifice. At this point, the suprahepatic IVC of the graft is anastomosed with the piggyback technique. The other vascular anastomoses are then performed. End-to-end portal anastomosis is performed followed by the arterial anastomosis. Less commonly, the arterial anastomosis is performed before the portal one. Finally, the biliary reconstruction is performed, generally with a choledoco-choledocal anastomosis. Additional details can be found in **Chapter 32** (Technical aspects of liver transplantation).

EARLY POSTOPERATIVE COMPLICATIONS

Despite advances in patient care, morbidity and mortality after liver transplantation remain significant. Several factors are implied in the occurrence of postoperative complications, including those related to graft quality, recipient clinical status, immunosuppression, and technical aspects. Most postoperative complications may be classified as: i) technical, ii) related to immunosuppression, iii) related to disease recurrence, and iv) graft dysfunction.

Most common technical complications are biliary (7-29% of cases), including biliary stenosis and/or fistula. Percutaneous treatment with biliary drainage and/or stenting is usually efficacious. In cases of early postoperative stenosis or refractory strictures, reoperation is indicated and choledoco-choledocal anastomosis recreated or a hepatico-jejunal anastomosis performed.[46] Arterial thrombosis is less common (2-10% of cases) and can lead to liver dysfunction, biliary fistula, cholangitis and sepsis. Treatment of hepatic artery thrombosis may be conservative or by reoperation

and arterial reconstruction. Technical complications in other vascular anastomoses are rare. Postoperative bleeding can lead to re-laparotomy in up to 5% of cases.

Infectious complications are the most common cause of death after LT.[47] Infection occurs in up to 80% of organ recipients; bacterial infections are most frequent (70%), followed by viral (20%) and fungal infections (8%). One quarter of deaths in LT recipients is due to infection. Immunosuppression should be individualized and prophylactic antibiotics used to prevent infections. Usually, high levels of immunosuppressive drugs in the early post-LT period are avoided, preventing renal dysfunction, systemic arterial hypertension, neuropsychiatric disturbances, and infections, especially those that are opportunistic. Graft function and patient recovery are initially evaluated by level of consciousness, urine output, and biochemical tests (such as lactate, transaminases, blood gas, blood count, urea, creatinine, bilirubin, gamma glutamil-transferase, prothrombin time and glucose levels).

Graft rejection occurs in approximately 20% of cases after LT. Acute cellular rejection is more common during the first four weeks after transplantation, but it can occur later. Clinical presentation is usually right upper quadrant pain, fever, malaise, and an increase in transaminases. Definitive diagnosis is established by percutaneous liver biopsy. In most cases, pulse administration of steroids and/or increasing immunosuppressant administration is effective. Chronic rejection is uncommon but usually requires re-transplantation. Primary graft non-function is an uncommon (1-7% of cases) but dramatic condition. It leads to multiple organ failure within a few days, and the treatment of choice is re-transplantation.

The length of intensive care unit (ICU) stay after LT has reduced noticeably from a mean of six days in the past to less than 24 hours in many centers nowadays.[48] Early extubation after liver transplantation has been successfully adopted in many centers and validated by a multicenter study.[49] However, preexisting comorbidities and intraoperative or postoperative complications can necessitate longer ICU stays.

LONG-TERM OUTCOMES

Long-term complications after liver transplantation are mostly related to side effects of immunosuppression, acute or chronic graft rejection, biliary complications, malignancies, and recurrence of the primary liver disease.[7,43,46,50–55]

Long-term immunosuppression (see details in **Chapter 31** – Immunosuppression) can be responsible for complications such as systemic arterial hypertension, new-onset diabetes mellitus, and dyslipidemia. New-onset diabetes mellitus occurs in one-quart of recipients after liver transplantation, mainly in the context of deceased donors.[56]

Renal failure is another common long-term complication, occurring in one quarter of recipients. Renal insufficiency is associated with decreased survival, and approximately 25% of patients will need kidney transplantation.[57]

Ischemic cholangiopathy represents a set of disorders characterized by multiple diffuse strictures affecting the graft biliary system in the absence of hepatic artery thrombosis or stenosis. Although its pathogenesis is unclear, it is associated with prolonged warm ischemic time. Biliary complications and ischemic cholangiopathy are more frequent (16-36%) with cardiac death (CD) donor grafts than with brain death (BD) donor grafts (3-17%), and most ischemic cholangiopathy occurs earlier after LT with CD donors (within 30 days) than with BD donors (within 90 days).[58] Treatment of biliary complications includes repeated therapeutic interventions and eventually re-transplantation.[59–62]

Recipients of liver transplant are more likely to develop malignancies. The most common cancers after liver transplantation include non-melanoma skin cancers, lymphoproliferative disease, colorectal cancer, lung cancer, oropharyngeal cancer, and Kaposi sarcoma.[63]

Almost all recipients with HCV infection will experience recurrence after LT, leading to a lower 7- to 10-year survival rate (60%) compared with those transplanted for other causes (75%).[64] Graft failure occurs in 5-8% of recipients during the first 12-18 months due to the development of fibrosing cholestatic HCV, and it is generally fatal.[65] Cirrhosis is found in 30% of recipients by five years after transplant. Antiviral treatment can result in virological clearance, but side effects of treatment can preclude its use.[66,67]

LIVER TRANSPLANTATION FOR ACUTE LIVER FAILURE

INDICATIONS, TIMING, AND RESULTS

Acute liver failure (ALF) is an uncommon (1-10 cases per million persons per year) but life-threatening critical clinical condition that occurs in patients who do not have preexisting liver disease.[68–72] It is characterized by a rapid deterioration of liver function, resulting in coagulopathy and encephalopathy within a few days or weeks after the onset of symptoms, and it is responsible for 4-7% of all liver transplantation.[73,74] Acute liver failure encompasses both fulminant hepatic failure (encephalopathy within eight weeks of the onset of symptoms) and subfulminant hepatic failure (or late-onset hepatic failure, up to 26 weeks after the onset of symptoms) and carries a high morbidity and mortality.

Acute liver failure is usually induced by toxins, drugs (e.g., acetaminophen [paracetamol]), or viral hepatitis (e.g., hepatitis A, B, C, D, or E). Less commonly, fulminant liver failure can be cryptogenic, related to ischemic hepatitis or

pregnancy-related diseases, or due to autoimmune hepatitis or Wilson's disease. The most common causes of ALF vary among countries. In the United States and Europe (particularly in United Kingdom), the most common cause of ALF is acetaminophen overdose (approximately 40-57% of cases), followed by idiosyncratic drug reactions; in Japan, the hepatitis B virus is the most common cause.[68,75,76]

Liver transplantation is the definitive treatment for liver failure, but a significant number of patients survive without transplant. Short-term transplant-free survival can be as high as 68% for patients with acetaminophen-related liver failure, or as low as 17% for patients with ALF from indeterminate cause.[77] It is crucial to rapidly and accurately identify those patients more likely to benefit from emergency LT. Clinical indicators are helpful to predict outcomes. Acute liver failure due to acetaminophen, hepatitis A, ischemic hepatitis, or pregnancy-related disease is less fatal without LT than acute liver failure from other etiologies (mortality 50% vs. 75%, respectively). The degree of hepatic encephalopathy is also predictor of survival without transplant. More severe (Grade III and IV) encephalopathy is associated with poorer spontaneous survival. However, many patients with ALF are not candidates for LT due to very poor clinical status or rapid clinical deterioration. In fact, 15-30% of patients with ALF die before liver transplant from cerebral death, infection, or multiple organ failure.[78,79]

Several prognostic scoring systems have been developed to predict spontaneous survival and then select patients for urgent LT, leading to a 1-year patient survival after orthotopic liver transplant of 60-70%.[80] The most widely applied criteria for LT in cases of ALF are King's College Hospital criteria (KCH criteria) and Clichy's criteria (**Tables 7** and **8**, respectively). These score systems have shown high positive and negative predictive values for mortality or LT.[81–85] However, relying entirely upon these scoring systems as a means of indication for LT is not recommended. It appears that survival in the context of ALF depends on a variety of factors, including etiology, grade of encephalopathy, ability of liver regeneration, and absence of other complications.

Table 8. Clichy criteria for liver transplantation on fulminant hepatic failure.

Presence of hepatic encephalopathy and factor V level:
<30% of normal in patients >30 years of age
<20% of normal in patients <30 years of age

One-year survival after LT for ALF is poorer than LT for chronic end-stage liver disease; however, following the first year, patients who have undergone transplant for ALF have a better long-term survival.[86–88] Most deaths after transplant for ALF occur within the first three months, and are usually due to neurological complications or infection.[68]

Selected patients with acute-on-chronic liver failure – a clinical entity defined recently – and severe alcoholic hepatitis may also represent potential extensions of transplant indication.[89]

TECHNICAL ASPECTS

Patients with ALF are more susceptible to hemodynamic instability during cava or portal clamping, since they usually do not have collateral circulation. Consequently, intracranial hypertension and inappropriate renal perfusion are more frequent than in patients with portosystemic shunts.[90,91] Extracorporeal bypass or the piggyback technique are methods to prevent hemodynamic instability due to clamping of the inferior vena cava. Temporary portocaval anastomosis during liver transplant with the piggyback technique is also useful to prevent hemodynamic changes due to portal clamping (**Figure 2**).[92–95]

Table 7. King's College criteria for liver transplantation on fulminant hepatic failure.

Acetaminophen-induced liver failure
- Arterial lactate >3.0 mmol/L after adequate fluid resuscitation - pH <7.3 - INR >6.5 AND creatinine >3.4 mg/dL in patients with grade 3 or 4 hepatic encephalopathy
Non-acetaminophen-induced liver failure

- INR ≥6.5 (prothrombin time >100 seconds)
- Three of the following:
  - Serum bilirubin ≥17.6 mg/dL (300 mmol/L)
  - non-A non-B hepatitis, idiosyncratic drug reaction
  - age <10 or >40 years
  - duration of jaundice before hepatic encephalopathy >7 days
  - INR >3.5 (prothrombin time >50 seconds)

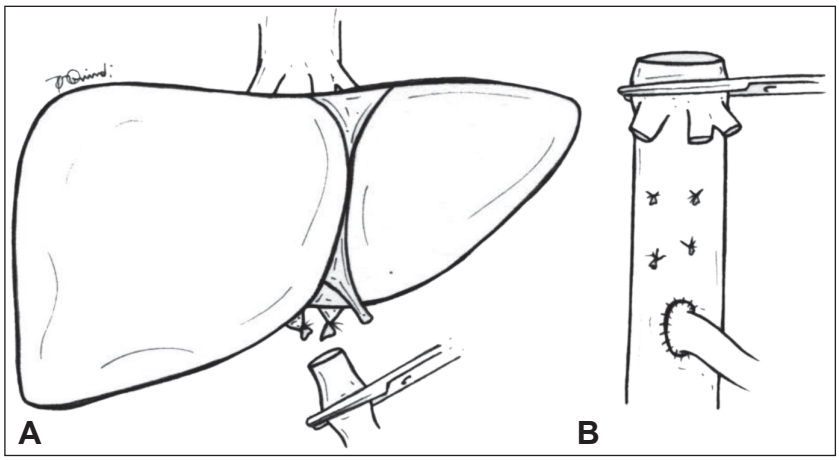


Figure 2. Schematic representation of temporary portacaval shunt during liver transplantation. **A**) Distal section of portal vein. **B**) End-to-side portacaval anastomosis and preservation of native inferior vena cava. This procedure reduces hemodynamic instability during the liver transplantation for acute liver failure.

Living liver donor and auxiliary liver transplantation

In addition to whole-organ LT from deceased donors, living donor liver transplantation (LDLT) has been attempted for ALF. Despite favorable survival following LDLT for ALF (approximately 75% 1-year survival), its use is controversial, mainly due to the need for compressed donor evaluation, which carries a risk of being incomplete, and risk of donor death (estimated at 0.2%).[42,96–98]

Another variant of liver transplant for ALF is auxiliary liver transplant, where the recipient's liver is kept in place and a partial graft (left or right) is implanted. The rationale for this technique is that a significant proportion (approximately 20%) of patients that fulfill criteria for LT are transplanted unnecessarily, because they would survive without liver replacement. Patients with severe ALF and a short interval between jaundice and encephalopathy are more likely to have liver regeneration.[99–101]

Auxiliary liver transplant provides a temporary substitute for metabolic and excretory functioning, allowing for reversion of brain edema and preventing brain damage. The criteria for auxiliary liver transplantation should be the same as that for orthotopic standard liver transplantation. Usually both the recipient and donor livers are size reduced in opposite sites (e.g. resection of the left lobe of a recipient liver and resection of the right lobe of a whole-organ graft) and the graft implanted in the orthotopic position (**Figure 3**). During donor liver reduction, the lobe not used for auxiliary transplant can be discarded or eventually used for another recipient as part of a split-liver transplantation.[102] Grafts from living donors can also be used in auxiliary liver transplantation. The hepatic resection on the recipient is usually facilitates by the liver atrophy in fulminant liver failure. Advantages of positioning a partial graft orthotopically include avoiding increased intra-abdominal pressure (since the graft plus remnant recipient liver result in a volume similar to that of a whole recipient liver) and allowing an adequate portal flow (with hepatotrophic factors) to the graft.[100,103] Conventional immunosuppression is continued until evidence of sufficient regeneration of the native liver appears (on the basis of histological, scintigraphical, and morphological data). After that, immunosuppression is progressively tapered, inducing chronic rejection with subsequent atrophy of the graft. Immunosuppression can be stopped abruptly, which is likely to be followed by severe and symptomatic rejection requiring surgical removal of the graft.[102,104]

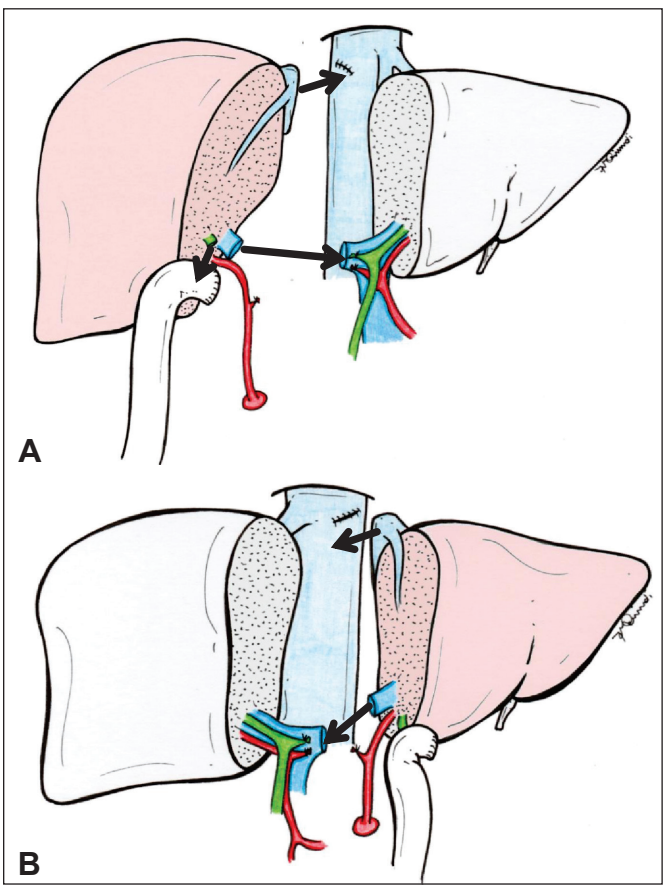


Figure 3. Auxiliary partial liver transplantation. **A**) Right graft implanted after right hepatectomy. **B**) Left graft implanted after left hepatectomy.

SUGGESTED READING

Agopian, V. G. *et al.* The evolution of liver transplantation during 3 decades: analysis of 5347 consecutive liver transplants at a single center. *Ann. Surg.* **258**, 409–421 (2013).

One of the largest series of liver transplantation showing an increase in patient and graft survival rates after implementation of the MELD (Model for end-stage liver disease). Several predictors of survival are identified.

Martin, P., DiMartini, A., Feng, S., Brown, R. & Fallon, M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* **59**, 1144–1165 (2014).

An extensive review of the literature and recommendations about evaluation and indication for liver transplantation.

Petrowsky, H. & Busuttil, R. W. Evolving surgical approaches in liver transplantation. *Semin. Liver Dis.* **29**, 121–133 (2009).

A description of evolving surgical approaches in liver transplantation discussing mainly methods using partial grafts (living donor and splitted grafts).

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A well-structured review on acute liver failure, covering definition and causes as well as therapies and prognosis.

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30 Liver Transplantation for Malignant and Benign Tumors

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- *Results of liver transplantation (LT) for hepatic malignancies have been disappointing and mortality rates nearly prohibitive for benign tumors in initial trials. Clinical and surgical perioperative improvements show satisfactory outcomes in LT for end-stage chronic liver disease, and indications have increased. Currently, malignant and benign tumors are treated using LT; however, the scarcity of donors requires a selection of receptors whose could better profit of grafts.*
- *Liver transplantation should be considered the treatment of choice for selected patients with hepatocellular carcinoma (HCC) who are not candidates for surgical resection, and in whom malignancy is confined to the liver. Best results of LT for HCC are obtained in patients with a single tumor measuring less than 5 cm, or no more than three lesions measuring less than 3 cm each (Milan criteria). However, promising results have been achieved even when these classical criteria are extrapolated. LT for other malignancies primarily includes endocrine metastatic tumors. Cholangiocarcinoma and other malign tumors have controversial indications.*
- *Some benign tumors can represent indications for LT when other treatments, mostly partial hepatic resection, are not anticipated and symptoms or a risk of complication (rupture or malignization) are present.*

INTRODUCTION

Since 1983, liver transplantation (LT) has progressed from an experimental procedure to an accepted clinical definitive treatment for end-stage chronic liver disease. Continuous development, especially in immunosuppressive therapies and technical advances, has allowed for a large expansion in the use of LT and produced very attractive results. Overall survival after LT for end-stage chronic liver disease now reaches 80-90% in the first year and 62-80% at five years.[1–7] These positive outcomes have permitted expanded indications for LT, and the procedure has become an optional or primary treatment for some hepatic tumors, particularly hepatocellular carcinoma (HCC).[8–11] Currently, the most frequent indication for liver transplant (LT) is liver cirrhosis (60-80%), while liver tumors account for 8-15%. Transplant can be indicated in three groups of liver tumors: i) tumors with accepted transplant indications (this group consists of HCC, hepatoblastoma, and metastases of neuroendocrine tumors); ii) liver tumors with uncommon or exceptional LT indications (including liver adenoma, adenomatosis, polycystosis, hemangioma, hepatic epithelioid hemangioendothelioma, focal nodular hyperplasia, inflammatory pseudotumor, hepatic lymphangiomyomatosis, and hepatic hamartoma); and iii) hepatic tumors with controversial LT indication (including metastases from non-neuroendocrine tumors (colorectal cancer) and Klatskin tumors).

Silvio Marcio Pegoraro Balzan and Vinicius Grando Gava (Eds.)
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ACCEPTED INDICATIONS

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is among the six most common malignant diseases in the world. Most develop in patients with an underlying chronic liver disease, mainly cirrhosis from any etiology. It is the most common primary tumor of the liver (90%).

The most frequent clinical scenario in which LT is considered as the best treatment for HCC is when it arises in liver cirrhosis, generally caused by hepatitis C virus and/or alcohol. The choice of the treatment takes into account tumor stage, liver function, and patient functional status.[12,13] Details on diagnosis and treatment options for HCC are discussed in **Chapter 13** (Hepatocellular Carcinoma).

Diagnosis of HCC. Imaging tests, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), play an important role in making a diagnosis of HCCs, due to their specific behaviour in dynamic image studies using contrast. In helicoidal CT, hepatocarcinoma is visualized as a rapid uptake of contrast in the arterial phase and early or late wash-out in the venous phase, leaving a halo-like peritumoural hyperdense area. A diagnostic specificity greater than 99% is achieved when the typical imaging data are associated with alpha fetoprotein values > 200ng/ml.[14]

The EASL (European Association for the Study of the Liver) criteria for the diagnosis of HCC are based on tumor size. In cirrhotic patients, nodules larger than 2 cm can be diagnosed for HCC if typical features are identified using one imaging technique. If the tumor size is between 1-2 cm, it is necessary to carry out two image tests; if these tests have not typical features, a biopsy-proven pathological confirmation is needed. When the size of the suspicious nodule is less than 1 cm, a close patient follow-up is recommended using scheduled ultrasound.

Staging and prognosis. Classically, the prognosis of HCC has been based on tumor stage, according to TNM classification. But owing to the fact that liver function (evaluated by ChildPugh or MELD [Model for End-stage Liver Disease] score) also affects the prognosis, classification systems including different clinical variables, in addition to tumor stage, have been proposed. The Barcelona Clinic Liver Classification (BCLC) is the only staging system that links prognosis with treatment recommendations and is useful for assessing prognosis preoperatively.

Some pathological factors that have prognostic value are evaluated in the explanted liver and include satellite lesions, vascular invasion (macroscopic and microscopic), and lymph node metastases. The TNM system, including pathological examination of the liver, may be used for determining prognosis after transplantation.

Treatment options. Best results for treatment of HCC are obtained by surgical resection. Two modalities of surgical resection are available: partial hepatectomy and total hepatectomy (followed by liver transplantation). **Partial hepatectomy** is recommended when cirrhotic patients have good liver function (Child-Pugh A) (**Figure 1**), and it allows for an impressive five-year disease-free survival of approximately 50% (30% to 90%, according to HCC stage), with reported operative mortality rates of less than 3%.[15–18] The main disadvantage of partial hepatectomy is a high rate of tumor recurrence, since the propice terrain remains. **Total hepatectomy followed by liver transplantation** is indicated in patients with Child-Pugh grade B and C cirrhosis, and has the advantage of treating both the HCC and the underlying chronic liver disease, and of resecting unidentifiable synchronous hepatic tumors. However, the scarcity of grafts is still a challenging concern.

Patient Selection

Early attempts at liver transplantation for HCC resulted in poor post-transplant survival (five-year overall survival between 18% and 40%) and high recurrence rates, which were attributed to suboptimal patient selection. Mazzaferro et al.[17] established the so-called Milan criteria for selection of patients for LT, i.e. radiological evidence of one tumor measuring less than 5 cm or up to three tumors all less than 3 cm, and absence of vascular invasion. The best results from LT in cirrhotic patients have been achieved when Milan criteria are fulfilled, with survival rates similar to those after LT for benign diseases (**Figure 2**), justifying the adoption of this system for allocating grafts by most centers worldwide. According to data from the Spanish Transplant Registry and

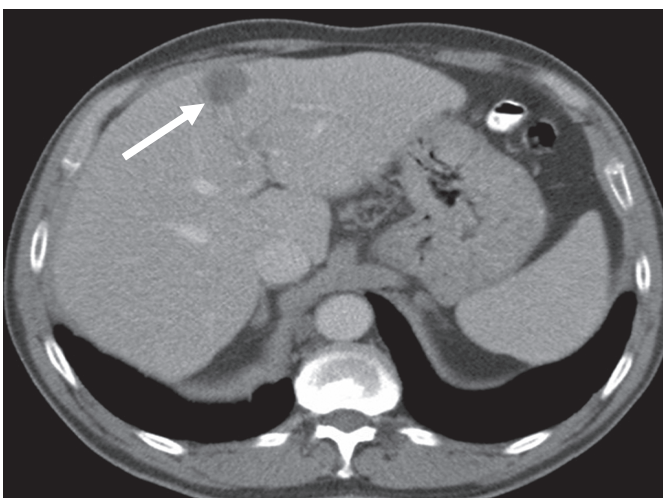


Figure 1. Small and peripheral Hepatocellular Carcinoma in a cirrhotic patient (Child-Pugh A). The most accepted treatment is liver resection.

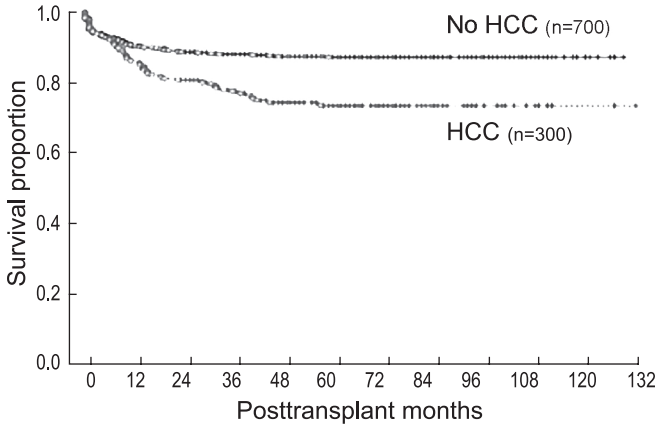


Figure 2. Overall patient survival after living donor liver transplantation for hepatocellular carcinoma and non-hepatocellular carcinoma indications. (Adapted from Hwang et al.[19])

the European Liver Transplant Registry (ELTR), overall survival rates are 82%, 70%, and 60% at one, three, and five years, respectively (www.eltr.org). Similar results of 86%, 70%, and 57%, respectively, are reported by UNOS (www.unos.org). When cirrhosis caused by chronic hepatitis C is present, survival at five years decreases by 10-20%.[14] The Milan group reported a 10-year overall survival rate of more than 70% in 300 liver transplants for HCC that fulfilled the criteria.[12] These results have been validated by other groups.[19,20]

The most important prognostic factor for survival in HCC is determined by TNM classification, but this causes difficulties for pre-transplant evaluation with regard to tumor size, number of lesions, vascular invasion, and localization.[21] UNOS modified this classification in accordance with the Milan criteria, after demonstrating that pTNM at stage I has a good survival prognosis, while at more advanced stages the prognosis becomes more bleak, being affected by vascular invasion, which is in turn affected by tumor size and cellular differentiation (**Table 1**).[22,23] Finally, it has been demonstrated that alpha fetoprotein (AFP) is associated with greater rates of mortality and recurrence when it reaches levels above 300-400 ng/ml.[24–26]

Expanded Criteria

Recently, a possible broadening of the Milan criteria has been discussed, since only a small proportion of patients with HCC fulfill these criteria. A prospective study published by Yao et al.[27] opened up this debate after reporting similar results in transplanted patients who were at a more advanced stage. They used the UCSF (University of California San Francisco) criteria to indicate LT in patients with HCC, as follows: a single tumor measuring up to 6.5 cm, or up to three tumors no greater than 4.5 cm, and the sum of all tumor diameters not being greater than 8 cm. Overall survival of 75% at five years was reached, and the use of these criteria allowed for an increase of 16% of patients with HCC that fulfilled Milan criteria and became candidates for LT.

Since then, other groups have established different criteria for consideration of LT in HCC. Zheng et al.[26], in a study comprising 72 patients meeting Milan criteria and 123 exceeding it, all without macroscopic vascular invasion, identified groups with better prognosis grouped according to total diameter of tumors, AFP levels, and histopathologic grade. The Hangzhou criteria [26] were established as HCCs fulfilling one of the following two criteria: i) total tumor diameter less than or equal to 8 cm; or ii) total tumor diameter greater than 8 cm, with histopathologic grade I or II and preoperative AFP level less than or equal to 400 ng/mL, simultaneously. Five-year survival for patients fulfilling Hangzhou criteria was 71%, similar to that for patients only fulfilling Milan criteria. Using these criteria, an additional 37% of patients with HCC could benefit from LT. Other criteria such as Tokyo criteria[28] (up to five nodules ≤ 5 cm) and Kyoto criteria[29] (up to 10 nodules ≤ 5 cm, and protein induced by vitamin K absence or antagonist-II [PIVKA-II] ≤ 400 mAU/mL), despite favorable five-year survival rates, result in an increase of potential candidates for LT of only 6% and 11%, respectively. Even Milan criteria have been reviewed and new limits established (up to seven tumors and the sum of their sizes up to 7 cm) with a five-year survival of 71% in the absence of micro- or macro-vascular invasion.[30]

Table 1. UNOS Classification of Hepatocellular Carcinoma.

Tumour	Definition
T0	Without a tumour
T1	1 nodule < 1.9cm
T2	1 nodule 2-5cm; 2 or 3 nodules, all <3cm
T3	1 nodule >5cm; 2 or 3 nodules, at least one >3cm
T4A	4 or more nodules of any size
T4B	T2, T3 or T4A plus portal vascular suprahepatic invasion or with computed tomography, magnetic resonance or ultrasound

The expansion of classical criteria for LT in HCC has, however, received some criticism. Tumors can progress during the waiting time for LT, and dropout rates can be high. This could be avoided by shortening waiting times or using an adjuvant treatment during waiting times. Increasing the donor pool using suboptimal livers (elderly or steatosic donors), carriers of the hepatitis C virus, non-heart beating donors, domino transplants, and split or living donor programmes[31] could reduce waiting time. Bridging therapies could avoid tumor growthe and consequent dropout during wait times, as discussed below.

More effective criteria would be necessary to identify tumors with more favorable biology, and consequently satisfactory prognosis after LT, independent of their number or diameter. To this end, alternative scoring systems and molecular tools have been explored to identify patients with better prognosis and that could be transplanted with similar results obtained with the use of Milan criteria. [8,12]

Recent observations suggest that sorafenibe may have a role in the treatment of recurrent hepatocellular carcinoma after LT.[32] Saab et al.[33], in a case-control study following patients with high risk of recurrence (exceeding Milan criteria), reported a lower rate of recurrence in patients that received adjuvant therapy with sorafenibe following LT. Progress in the development of more efficient systemic anti-cancer drugs certainly will result in better survival rates after liver transplant for HCC, but also survival after liver resection should increase and criteria for liver transplantation in HCC could be reevaluated in the next years.

In conclusion, expanded criteria can increase the number of potential candidates for LT; however, it is essential to consider how they might affect the survival of candidates for liver transplantation who do not have HCC. Based on this, liver transplantation should be reserved for HCC patients who have a predicted 5-year survival of 60% or higher.[34]

Prioritizing Allocation of HCC Patients

Patients indicated for LT for HCC may or may not be prioritized when they are added to the LT waiting list. Since 2002 in the USA, UNOS has introduced a criteria for prioritization according to clinical severity based on the MELD system, which is only validated for benign liver disease.[(6;7)35,36] Subsequently, in order to avoid the death of patients with HCC on the waiting list due to disease progression, a proposal of prioritizing these patients was made based on the Milan criteria: for patients with tumors measuring less than 2 cm, 24 points are added to the individual MELD score. For patients with a single tumor of 2 to 5 cm, or two to three nodules all less than 3 cm, an additional 29 points are summed to MELD score. In both cases, MELD score is increased by 10% for each three months on the waiting list. These additional points permit a reduction of time on the waiting list.

"Bridge" Therapies and Downstaging

A variety of neoadjuvant therapies have been proposed as "**bridge therapies**" to avoid cancer progression and dropout of the waiting list. In patients that fulfill Milan criteria for LT, loco-regional therapies (LRT), such as trans-arterial chemoembolization (TACE), trans-arterial radioembolisation (TARE), radiofrequency ablation (RFA), and percutaneous ethanol injection therapy (PEIT), alone or in combination, can be useful to reduce HCC progression and consequently dropout rates in patients awaiting liver transplantation (**Figure 3**). In the same way, partial liver resection can be used as a bridge therapy while waiting for LT.[37–40]

The use of neoadjuvant LRT can also be used to "**downstage**" tumors that initially extrapolate criteria for LT. Patients with more advanced HCC that, after LRT, fulfill criteria for LT, reach similar or even better survival rates than patients that fulfill criteria *ad initium*.[41] Bharat et al.[42] evaluated the use of neoadjuvant therapies before LT for HCC, and observed a tumor downstaging using LRT, together with a better 5-year survival in comparison with no neoadjuvant therapy (82% versus 52%, P<0.01). This benefit was more pronounced for HCC stages II to IV. Additionally, nearly 35% of patients that received LRT, against 0% of untreated patients, had complete tumor necrosis resulting in long-term survival without recurrence.

In a study by Yao et al.,[43] downstaging was obtained in 70% of a group of selected patients with tumors outside Milan criteria. Results after LT in this group were very satisfactory, similar to those obtained in patients that fulfill Milan criteria.

Assessment of successful downstaging is controversial, since the measure of diameter of tumors does not take into account the area of necrosis. Thus, the EASL guidelines

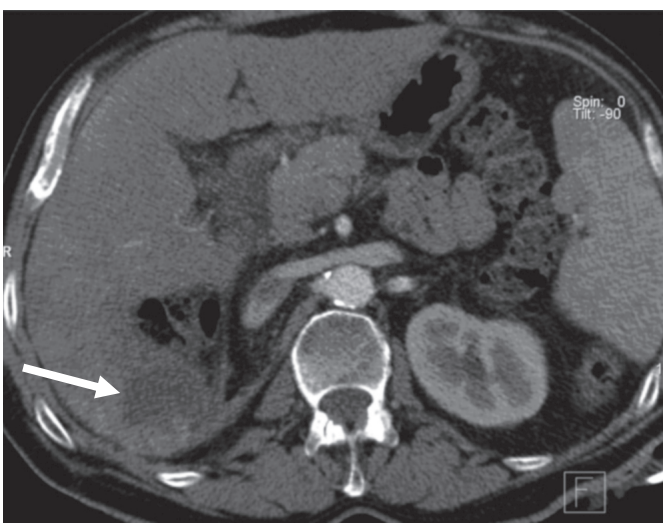


Figure 3. Cirrhotic Child-Pugh C patient with a HCC in segment 6 who underwent chemoembolization while on the waiting list for liver transplantation.

suggest an assessment based on the amount of viable tumor, as differentiated from necrosis by contrast CT or MRI.[44] Also, serum AFP level before and after downstaging may be used additionally to select patients for LT.

The role of pre-transplant HCC loco-regional therapy and tumor downstaging could provide not only a benefit in preventing dropout from the transplant waiting list, but also a definite post-transplant survival advantage.

The choice of the best modality for neoadjuvant therapy is not clear, but some criteria are defined for each one. For instance, TACE should be avoided when portal thrombosis is present; PEIT is more effective for tumors up to 2 cm and RFA for lesions of 2 to 5 cm.

Partial hepatectomy as a bridge therapy before LT in Child-Pugh A patients without severe portal hypertension is a more aggressive treatment but has the advantage of providing precise pathological information and select tumors with unfavorable histology.[43] Liver transplantation following partial hepatectomy may be performed when a graft is available (*de principium*) or as a surgery of salvage after tumor recurrence.

HCC in Non-Cirrhotic Liver

Patients with the fibrolamellar variant of HCC have better prognosis than patients with classic HCC. Most patients with fibrolamellar HCC don't have underlying liver disease and LT is rarely required. However, patients with non-resectable HCC developing in a non-cirrhotic liver may be considered appropriate candidates for LT even outside the Milan criteria, since macroscopic vascular invasion and extrahepatic disease are not present.[45]

HEPATOBLASTOMA

Hepatoblastoma is the most frequent primary hepatic malignant tumor in children. Similar to fibrolamellar HCC, underlying liver disease is not common and liver function is preserved. Also, prognosis is better than classical HCC. LT is suitable for unresectable tumors, independent of size, since extrahepatic disease is not present.[46–53]

HEPATIC METASTASES FROM NEUROENDOCRINE TUMORS

Neuroendocrine tumors are uncommon diseases whose origin is in the digestive tract and pancreas in 85% of cases.[54,55] At the time of diagnosis, up to 40-80% of patients present with metastases, and the liver is the most affected organ, followed by the bones and the lungs.[54,56] Liver metastases from neuroendocrine tumors are the main cause of death for patients with neuroendocrine tumors originating from the intestine and pancreas. Moreover, large liver metastases often cause hormone-related symptoms (carcinoid syndrome) with severe consequences on patient quality of life. The therapeutic options for this type of liver metastasis include chemotherapy[56,57] (with the use of analogues of somatostatin, 5-fluorouracil, or gemcitabine), local ablative techniques, chemoembolization,[58] and finally resection. Partial liver resection provides a five-year survival rate of 46-76%,[59,60] but it can only be completed in 20% of patients because metastases are usually multiple and bilateral (**Figure 4**),[61] and consequently liver transplantation is considered the best option in a significant number of cases, offering excellent survival rates and symptom control.[62–76] Complete surgical treatment is usually performed at two times (two-stage surgery): firstly, primary tumor resection, and secondly, the liver transplant. In this way, patients can benefit from the efficiency of chemotherapy between both resections, thus reducing the surgical risk of transplantation compared to when they are carried out simultaneously.

In order to obtain good results with liver transplantation as a treatment for hepatic metastases for neuroendocrine tumors, it is very important to make an adequate selection of candidates. The Italian National Institute of Tumors uses a system based on the Milan criteria to choose candidates with neuroendocrine tumors who are most appropriate for receiving LT.[77] Histological confirmation of a neuroendocrine tumor at the primary and metastatic sites should be obtained, and well-differentiated tumors are more suitable for LT. The Milan criteria also include two tumor factors as predictors of both response to treatment and tumor recurrence: a) serum levels of chromogranin, which is found at high concentrations in tumor cells;[78] and b) the degree of mitosis, calculated using immunohistochemical techniques.[79] In well-differentiated tumors, it is common to find a Ki-67 proliferation index below 10%, suggesting that this percentage is an ideal level for selecting appropriate candidates for transplant. It is recommended not to carry out the transplant in the first six



Figure 4. Multiple and bilobar metastases of a neuroendocrine tumour.

months after primary tumor resection, in order to be able to rule out tumor persistence. During this time, the patient must undergo systematic chemotherapy (streptozotocin, doxorubicin, 5-FU, etc.) and/or analogues of somatostatin and even I131-MIBG when the tumor has receptors for MIBG (50% of patients).[77]

Liver transplant survival rates at five years in these groups of patients with liver metastases from neuroendocrine tumors range from 52% to 80%,[79–81] with a tumor recurrence rate of approximately 50%. Thus, LT is an acceptable treatment for non-resectable liver metastases from endocrine tumors, but a high frequency of recurrence is expected. Considering the scarcity of cadaveric liver grafts, various centers have considered the use of living liver donors.

UNCOMMON INDICATIONS

HEPATIC ADENOMA

This is an uncommon benign tumor associated with the ingestion of anovulatories and other steroids over a long period of time in young women (for more details, please refer to **Chapter 18**). In males, other conditions can be associated with adenomas, such as glycogen storage disease (glycogenosis type I and III), tyrosinemia, type 1 diabetes mellitus, the ingestion of androgens, or haemosiderosis secondary to β thalassemia.[82] Hepatic adenomas can be single or multiple, and can reach sizes as large as 20-30 cm.

A hepatic adenoma is made up of normal but disorganized hepatocytes, in which the normal lobular architecture cannot be seen. It usually appears as a single lesion and remains asymptomatic for years, showing clinical signs only when there are complications, such as an intratumoral hemorrhage or rupture of the lesion. Malignancy has been reported, but this is a very uncommon occurrence.

Diagnosis from images is carried out mainly by ultrasound and CT scan (where there may be a heterogeneous image if a tumor hemorrhage has occurred, a fact which could otherwise make it difficult to make a differential diagnosis with HCC).[83] In MRI and arteriography, its hypervascular and hypovascular behavior characteristics are shown. These tests are important not only for determining tumor size, but also for revealing intrahepatic vascular relationships.

Cessation of oral contraceptive or anabolic steroid use can allow for partial regression of tumors, but the risk of malignant transformation remains. Surgical treatment is considered when an adenoma is larger than 5 cm or symptoms are present. Tumors larger than 5 cm are at risk for rupture and hemorrhage (intra-tumoral or intra-abdominal) and degeneration to hepatocellular carcinoma. Partial hepatectomy is the definitive treatment in most cases; however, if resection is not technically feasible, liver transplantation should be a treatment option. This can occur more frequently for giant adenomas or multiple tumors, as when associated with glycogenosis type I or IV.

HEPATIC ADENOMATOSIS

The etiology of this entity is unknown (for more details see **Chapter 18**), but it is associated with vascular anomalies or malformations in up to 50% of cases, suggesting a hereditary component. There is no marked gender predominance, and it can also be associated with focal nodular hyperplasia (FNH) and diabetes.[84–86]

Hepatic adenomatosis is defined as the presence of 10 or more adenomas of various sizes in a liver with no underlying chronic disease and in the absence of history of use of oral contraceptives, and in the absence of glycogen storage disease type I. Macroscopically, the liver presents exophytic nodules without cirrhosis. The adenomas can be calcified and, microscopically, extensive areas of hepatocyte proliferation with fatty infiltration in the periphery can be observed. The presence of arterialization of the sinusoids is referred to by Chiche as *adenomatous hyperplasia*.

Hepatic adenomatosis can be classified as: i) *massive*, which is associated with hepatomegaly, and can affect a single hepatic lobe; and ii) *multifocal*, which develops in a normal-sized liver and is usually characterized by a greater adenomas.[85] The multifocal type is more commonly associated with malignancy.[87]

Right hypochondrium chronic pain is the most frequent clinical manifestation (53% of cases), but sudden intense pain can be the first symptom (20% of cases), and occurs due to an intra-tumoral or intra-abdominal hemorrhage. Approximately 25-30% of cases are asymptomatic.

Magnetic resonance imaging with endovenous contrast is useful for diagnosis, and enables differential diagnosis with hemangioma, fatty tissue, and focal nodular hyperplasia. Histopathological study is only mandatory in large or atypical tumors.[84]

Resection is recommended in lesions larger than 5 cm, due to risk of bleeding and association with malignancy. Liver transplantation could be exceptionally indicated in the following situations: massive or progressive forms associated with severe clinical manifestations, giant forms occupying most of the hepatic parenchyma where partial hepatectomy is non-feasible, and when high levels of AFP are detected due to suspicion of malignancy.

HEPATIC POLYCYSTOSIS

Hepatic polycystosis is an inherited disease arising in patients with autosomal dominant polycystic kidney disease (ADPKD) or another mutation resulting in exclusively hepatic cysts,

called polycystic liver disease (PCLD). For details, please refer to **Chapter 19** (Non-parasitic Cystic Diseases of the Liver). It is characterized by the development of multiple biliary epithelial cysts throughout the liver. Cysts commonly affect more than 50% of liver parenchyma. Less frequently, other organs can be affected, such as the pancreas, spleen, ovaries, or lungs. Prevalence varies from 0.08% to 0.5% of the population.[88] Diagnosis is usually in women between 40 and 50 years of age, and size and number of cysts increase with age. Cysts can increase in size secondary to use of hormones and pregnancy.[88,89]

Similarly to simple liver cysts, hepatic polycystosis arise from malformation of the embryonic ductal plate, with formation of von Meyenburg complexes that are lined with functional biliary epithelium, resulting in accumulation of bile in different amounts, from nests of bile ducts and microcysts, to macrocysts that can reach more than 10 cm in diameter.[90] Gigot et al.[91] classified hepatic polycystosis in three types:

Type I: presence of less than ten large-sized cysts.

Type II: presence of multiple hepatic cysts of 5-10cm, but with areas of normal parenchyma between them.

Type III: presence of diffuse liver disease with small and medium-sized cysts, with scarce areas of normal parenchyma (**Figure 5**).

Most patients with hepatic polycystosis are asymptomatic and, despite the impressive findings of multiple cysts, few patients develop an advanced liver disease or complications secondary to hepatomegaly. Symptoms can result from hepatomegaly and/or compression of other organs or structures and include abdominal pain, dyspnea, abdominal distension, early satiety, and symptoms of gastroesophageal reflux. Obstructive jaundice can be present due to compression of biliary ducts, and intracystic hemorrhage can result in anemia. Further, cyst over-infection can lead to liver abscesses; vascular compression can result in Budd-Chiari syndrome; and, exceptionally, hepatic polycystosis can lead to liver failure or malignancy (cystadenocarcinoma).

Diagnosis is carried out using imaging (ultrasound, CT).[92] It is recommended to perform a genetic study in young patients to detect mutations related to kidney polycystosis (ADPKD).[90]

The standard management of asymptomatic patients is limited to clinical observation and therapeutic action is only indicated when symptoms or complications are present. For patients with Gigot type I cysts, percutaneous drainage can be sufficient to resolve symptoms and over-infection.[93] This technique has a low morbidity and mortality rate, but is associated with a high recurrence rate. For patients with type II polycystosis, fenestration is mostly recommended, which can be performed by laparoscopy. However, liver resection is a more effective option, improving symptoms in 95% of patients and with lower rates of recurrence, but with greater morbidity and mortality. Finally, for patients with type III polycystosis, surgical treatment is more complex. If the disease is predominant in one hepatic lobe and sufficient remnant hepatic parenchyma is expected, a partial liver resection can be attempted. However, when predominant small cysts or diffuse disease is present and a low amount of functional hepatic parenchyma will be preserved, the only effective treatment is liver transplantation (**Figure 5**).[88,90,92] When kidney polycystosis associated with chronic kidney failure is present, a combined liver-kidney transplant is indicated, with excellent long term survival rates.[94]

HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA

This is a rare disease of vascular origin that can occur in the liver or in other organs, such as the spleen, bone, brain, meninges, breast, heart, head and neck, soft tissue, stomach, and lymph nodes. Primary malignant hepatic epithelioid hemangioendothelioma has an incidence of less than one per million people, and it is more likely to occur in adults, especially in women (3:2 preponderance). Generally, hepatic epithelioid hemangioendothelioma behaves as a low-grade malignant tumor with a slow progression, with a clinical course intermediate between benign hemangioma and malignant angiosarcoma, as opposed to other vascular tumors such as infantile hemangioendothelioma or angiosarcoma, but its malignant potential is unpredictable. Some reported risk factors are liver trauma, hormones, exposure to vinyl chloride, asbestos, and alcohol.[95] A liver transplant indication is exceptional.[96,97]

Patients can be asymptomatic at the time of diagnosis. When present, clinical manifestations are usually non-specific, generally including upper right quadrant pain, dyspnea, jaundice, and/or weight loss.[95,97] However, some patients may have liver failure, Budd-Chiari syndrome, or portal

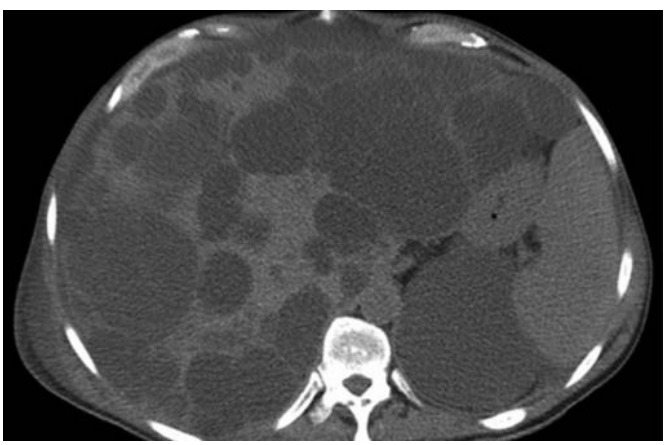


Figure 5. Patient with hepato-renal polycystosis who underwent a double kidney-liver transplantation.

hypertension. Among laboratory tests, it is worthy of note that elevated alkaline phosphatase is present in up to 70% of cases. Carcinoembrionic antigen (CEA) can be elevated, and AFP and antigen 19-9 are normal.

Diagnosis is fundamentally based on image tests, which show characteristic multiple and bilateral lesions, sometimes associated with signs of portal hypertension. The confirmation of diagnosis is carried out using histopathological and immunohistochemical studies, where specific endothelial markers of this tumor, such as factor VIII and antigens CD34 and CD31, are identified.[97]

Prognosis and symptoms are difficult to predict. Published studies have reported metastases in up to 45% of cases (especially of the lung, bones, and spleen) at the time of diagnosis, while other authors have reported spontaneous disease regression in up to 3% of cases.[98]

Many therapeutic options have been attempted, such as hormonotherapy, interferon, radiotherapy, arterial chemoembolization, and surgery.[98] However, surgical resection is the only accepted efficient treatment option, and when it is not feasible, liver transplantation can be the best treatment. In the few published series comprising treatment other than liver transplantation, a recurrence rate of 25-30% is reported with a five-year survival rate of 55%. Series comprising liver transplantation for epithelioid hemangioendothelioma demonstrate better results, with overall survival rates of >70% at five years, and recurrence rates of <25%.[97] Thus, total liver resection followed by liver transplantation is an uncommon but acceptable treatment for this rare disease.[99,100]

HEPATIC HEMANGIOMA

Hemangioma is the most frequent benign liver tumor, and the second most common liver lesion after metastasis, with a prevalence of 0.4-20%.[101] Hemangiomas are more frequent in women, especially between the third and fifth decades of life. In 20% of cases, they are associated with focal nodular hyperplasia (FNH), and in 9% of cases with other liver lesions on a healthy liver.[102] An association between hemangiomas and the use of oral steroids is reported. Indeed, estrogen receptors have been found in cells of some tumors.[103]

It has been demonstrated that at its origin, during the neonatal period, a hemangioma is a neoplasia that grows and eventually regresses during infancy.[104] In adults, hemangioma is considered a vascular malformation (with vascular ectasia) more than a tumor proliferation.[105]

Histologically, hemangioma is an agglomerate of vessels with an endothelium formed by a single layer of cells. Macroscopically, it is usually subcapsular and has a purple color. In most cases, the hemangioma is unique and measures less than 5 cm. Lesions larger than 5 cm are called giant hemangiomas.[106]

Liver hemangiomas are usually asymptomatic, but when they reach larger dimensions they can be a source of abdominal symptoms (25-60% of cases), such as abdominal pain (due to thrombosis of the tumor vessels), or even an acute abdomen due to hemoperitoneum. In 3-4% of patients, Kasabach-Merritt syndrome is present, with disseminated intravascular coagulation and consumption of hematological cells.[107]

Clinical and radiological classification distinguishes three types of hemangiomas:[104] a) focal hemangiomas (usually asymptomatic, having a characteristically solitary ultrasound image); b) multifocal hemangiomas (also generally asymptomatic, but due to arteriovenous communications can cause congestive heart failure); and c) diffuse hemangiomas (which lead to hepatomegaly and can cause such symptoms as compression of inferior vena cava syndrome, respiratory restriction, and even abdominal compartment syndrome). Some large lesions and diffuse forms can also first manifest with Kasabach-Merritt syndrome or with liver failure.[108]

In asymptomatic forms, a "wait and see" attitude is advised. Patients with a single lesion and who are taking hormone treatment should undergo scheduled ultrasound tests, given that these lesions can grow. Hemangioma diagnosis can be strongly suggested by imaging tools, such as ultrasound, in which a hyperechogenic lesion is usually observed. Computed tomography scan and/or MRI with contrast are used to confirm diagnosis. A typical pattern of contrast uptake and washout is present in most cases. Exceptionally, a scintigraphy using isotopic radiomarked red blood cells is used in diagnosis.

Surgical treatment is considered when symptoms are present, when diagnosis is uncertain, or when there is a high risk of tumor rupture. For these reasons, some authors recommend the resection of lesions greater than 10 cm.[105,109,110]

Treatment other than resection has been used in cases of symptomatic giant hemangiomas, such as alpha interferon, radiotherapy, embolization, and ablative radiofrequency, with very poor results.[105,107,111]

Similarly to other benign hepatic tumors, liver transplantation is rarely indicated. Liver transplant is considered for symptomatic giant or diffuse hemangiomas when a partial hepatectomy is not possible, or when terminal liver failure is present. The most frequent indication for transplant is unresectable symptomatic giant hemangioma, generally associated with Kasabach-Merritt syndrome.[108,111,112]

FOCAL NODULAR HYPERPLASIA

Focal Nodular Hyperplasia (FNH) is not a true neoplasia, but rather a reactive proliferation of hepatocytes caused

by congenital vascular malformation. Other pathogenic hypotheses maintain that pluripotent progenitor cells could be the cause. Its incidence in the general population is 0.01%.[113] Occasionally, FNH is associated with taking vincristine, actinomycin, itraconazole, griseofulvin, phenytoin, or antituberculosis agents. FNH has also been described after abdominal trauma.[114]

Image tests can be useful for diagnosis, especially when a central starred scar is present. However, in approximately 20% of patients, a macrobiopsy is needed to confirm the diagnosis.[115]

FNH does not degenerate, and even spontaneous reduction has been reported in up to 50% of cases. Some cases of complete disappearance have also been recorded.[116] Most patients do not require any surgical treatment. Resection can be necessary when symptoms are present or there is doubt about differential diagnosis with adenoma or HCC. Liver transplant has been indicated exceptionally in giant lesions associated with jaundice and irreversible severe liver failure.[117]

HILAR FIBROUS ANGIODYSPLASIA OR INFLAMMATORY PSEUDOTUMOR

This is a very uncommon entity characterized by fibrovascular proliferation in a chronic inflammatory cell infiltrate. It occurs especially in infancy and can affect any liver segment. Manifestations are generally recurrent episodes of cholangitis, which can lead to the development of secondary biliary cirrhosis with portal hypertension. Liver transplant could be indicated in this situation.[118]

LIVER LYMPHANGIOMYOMATOSIS

This entity consists of an uncommon malformation of the lymphatic system that occurs almost exclusively in the lungs, but can affect the liver on very rare occasions.

Liver transplantation is indicated when this tumor reaches a very large size, causing compartment syndrome or irreversible liver failure.[119]

MESENCHYMAL HAMARTOMA

This is a very rare entity, which should not be confused with FNH. It is more frequent in males and, in most cases, first appears as an abdominal mass during the first year of life. It usually appears in the right hepatic lobule, although in 10% of cases it is bilateral. It can reach great dimensions and weigh even more than 5 kg. No case of malignancy or recurrence after resection has been found, so prognosis is very good. Liver transplant is only considered when it causes irreversible liver failure.[120]

CONTROVERSIAL INDICATIONS

LIVER METASTASES FROM COLORECTAL CANCER

Usually, colorectal liver metastases (CLM) is not considered an indication for liver transplantation, due to the low survival rate at five years reported in previous studies and the shortage of available organs. According to ELTR data, survival at five years was only 18% for patients transplanted for CLM during the period from 1977-2004. This rate is significantly lower than that obtained in liver transplants for other causes, such as liver cirrhosis (72%), fulminant liver failure (61%), or even HCC (54%). However, most of these transplants were carried out more than a decade ago, when the experience of these transplant centers was less extensive and the immunosuppression used was less selective than that used currently.

Additionally, nearly half of deaths were related to causes other than tumor recurrence. Recently, some important aspects of this scenario have changed: i) immunosuppression treatment has improved (for instance, sirolimus has an antiproliferative capacity and improves prognosis in terms of tumor recurrence);[32,121] ii) chemotherapy for colorectal cancer has become more effective (the use of chemotherapy drugs such as oxaliplatin, irinotecan, and monoclonal antibodies (cetuximab) directed against tumor growth factors or antiangiogenics (bevacizumab) have significantly increased the survival time of these patients);[122,123] and iii) imaging techniques have substantially improved, including more performant CT and MRI and PET/CT scans, which provide reliable information about number, size, and location of tumors and consequently proper patient selection.

Thus, some authors argue that it is currently possible, in very select cases, to reconsider liver transplantation for patients with CRC liver metastases. Preliminary data from a pilot study of transplantation for CRC liver metastases has shown an overall survival rate of 94% after a median follow-up of 25 months, albeit with a high recurrence rate (63%). In addition, survival rates have also greatly improved after partial hepatectomy, and neoadjuvant therapies have enabled resection in a significant number of previously unresectable patients.[10,124] Liver transplantation could be considered as an option for treatment of CRC metastases; however a five-year survival rate of at least 50% should be anticipated.

CHOLANGIOCARCINOMA

These tumors are classified according to their location in intrahepatic (second-most common primary hepatic

malignancy) and extrahepatic cholangiocarcinoma (CCA). Extrahepatic cholangiocarcinoma includes proximal hilar cholangiocarcinoma, or a Klatskin tumor, situated in the hepatic bile duct confluence (60-70% of all cholangiocarcinomas), and distal hilar cholangiocarcinomas.[125] The International Classification of Disease Codes considers cholangiocarcinoma originating in the small bile ducts being a primary liver tumor, and includes Klatskin tumors in the group of intrahepatic tumors. Extrahepatic CCA can present three different growth patterns: i) periductal infiltrating; ii) papillary or intraductal; and iii) mass forming. Intrahepatic CCA presents generally as an intrahepatic mass.

CCA is characterized by a poor prognosis, with short survival and a scant response to chemotherapy. Primary sclerosing cholangitis (PSC) is an important risk factor for CCA, with an annual incidence of 0.6% to 1.5%, reaching up to 10% in the first 10 years after the diagnosis of PSC. There is no effective medical therapy for CCA and the only curative treatment is complete surgical resection. However, most CCAs are identified at an advanced stage and survival for non-resectable disease is nine to 12 months.

Solitary intrahepatic CCAs are usually managed by partial liver resection. Five-year survival is 22% to 44%, and prognosis is correlated with negative margins, absence of lymph node metastases, and vascular invasion. LT for intrahepatic CCA is associated with poor survival and high rate of recurrence. The presence of PSC associated with advanced liver disease makes partial hepatectomy more challenging, and increases the risk of *de novo* CCA.

Surgical resection is also the mainstay treatment for extrahepatic CCA, with 5-year survival of 20-30%,[126] but resectability of hilar cholangiocarcinomas is frequently discarded due to extensive vascular and/or biliary involvement. Patients with non-resectable hilar cholangiocarcinoma have an expected survival of 12-16 months. For the treatment of locally advanced hilar cholangiocarcinoma, LT may offer the advantage of resection of hilar structures involved by the tumor, including vessels within the hepatoduodenal ligament, all intra- and extrahepatic bile ducts, and whole liver parenchyma. Thus, LT is an attractive treatment for patients requiring a total hepatectomy to achieve a negative margin and those with underlying liver failure precluding partial hepatic resection.[126,127]

Liver transplantation for Klatskin tumor has resulted in a poor 5-year survival rate, less than 30%, in preliminary findings. Despite the poor survival with LT, results are better than other options for non-resectable CCA (null five-year survival). Thus, LT would be an interesting treatment for unresectable tumors; however, the scarcity of liver grafts and frequent later recurrence (56-96%)[128] rends this option problematic, since use of grafts could be optimized by transplanting in diseases with better prognosis. An interesting fact is that even incidental CCA after LT for PSC are associated with poor survival.[129]

Based on the known palliative efficacy of radiotherapy for CCA[130] and the identification of the subgroup of patients that did benefit from LT (negative margins and the absence of regional lymph node metastases), a combined strategy was proposed by the transplant team at the University of Nebraska. They used a neoadjuvant high dose of brachytherapy (by a biliary catheter) and 5-fluoracil chemotherapy followed by liver transplantation. Subsequently, the Mayo Clinic used a similar protocol, combining neoadjuvant external irradiation and 5-fluoracil chemotherapy, followed by brachytherapy with iridium plus 5-fluoracil infusion until LT (**Figure 6**). This protocol was used in strictly selected patients, with unresectable localized hilar CCA (stage I and II), and demonstrated an impressive 80% five-year survival rate after transplant. These results are similar to those obtained after LT for other benign or malignant disease, and better than those obtained after surgical resection. These attractive results could be due in part to an initial strict patient selection (unresectable tumors above the duct cystic, tumor diameter less than 3 cm, absence of intra- and extrahepatic metastases) and also a "biological" selection, since tumors that progress during neoadjuvant therapy will probably be out of criteria at the moment of LT.[131,132]

The benefit of neoadjuvant therapy followed by LT for *de novo* (not associated with PSC), potentially resectable tumors is less pronounced, since results with aggressive surgical resection have improved and 5-year survival of 60% can be achieved.[133]

Therefore, surgical resection remains the mainstay

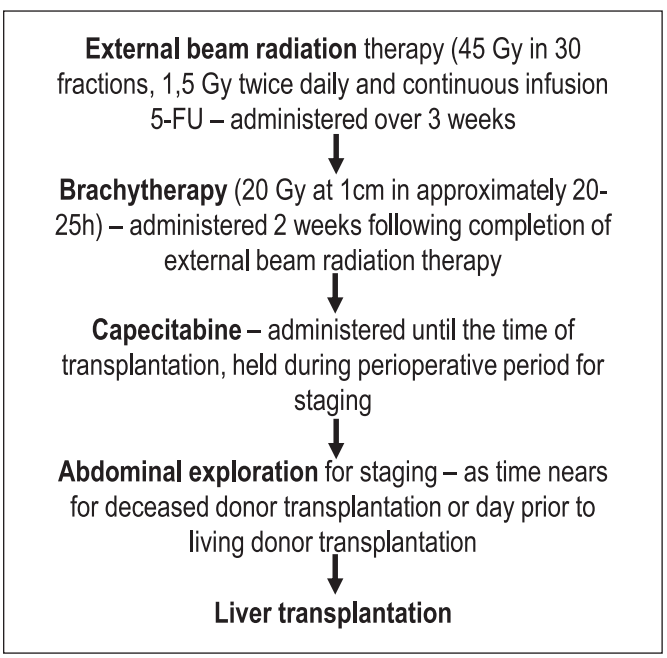


Figure 6. Mayo Clinic neoadjuvant therapy and liver transplantation protocol. (Adapted from De Vreede et al.[132])

treatment for intrahepatic CCA and hilar CCA not associated with PSC. Liver transplantation should be considered in unresectable hilar tumors and those arising in the setting of PSC. Strict selection criteria must be met, and the combination of neoadjuvant therapy and operative staging to rule out regional metastases before LT is essential.[134]

SUGGESTED READING

Mazzaferro, V. *et al.* Liver transplantation for hepatocellular carcinoma. *Ann. Surg. Oncol.* **15**, 1001–1007 (2008).

This is an interesting review covering most controversial topics in liver transplantation for hepatocellular carcinoma. The authors discuss Milan versus expanded criteria for LT, and Eastern and Western experiences with living donor liver transplantation; also, other perspectives for better patient selection are approached.

Majno, P., Mentha, G. & Mazzaferro, V. Resection, transplantation, either, or both? Other pieces of the puzzle. *Liver Transpl.* **11**, 1177–1180 (2005).

This editorial summarizes the milestones on chosing treatment for patients with hepatocellular carcinoma that are candidates either for resection or transplantation. The findings of unfavorable histology after resection could lead to an immediate liver transplantation or, to the contrary, exclude patients for transplant depending on graft availability.

Sutcliffe, R., Maguire, D., Ramage, J., Rela, M. & Heaton, N. Management of neuroendocrine liver metastases. *Am. J. Surg.* **187**, 39–46 (2004).

This review on treatment of neuroendocrine liver metastases attempts to define a logical approach for this heterogeneous disease. Resection is the best curative treatment in most suitable cases, liver transplanttion is indicated for unresectable carcinoid metastases with biologically favorable features and limited tumor volume. Palliative options include systemic chemotherapy, chemoembolization, somatostatin analogues, and local ablation.

Everson, G. T., Taylor, M. R. & Doctor, R. B. Polycystic disease of the liver. *Hepatology* **40**, 774–782 (2004).

This paper shows that options for treatment of polycystic liver disease are essentially radiological or surgical, varying from percutaneous puncture to liver transplantation. The general objective is reducing cyst volume, and a stepwise approach should be used in most cases.

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31 Immunosuppression in Liver Transplantation

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- *Although acute cellular and chronic rejection can lead to graft loss, early acute rejection has no impact on long-term graft function and recipient survival.*
- *Intensive immunosuppression is required in the first months after LT, when the risk of rejection is highest. A combination of immunosuppressive agents (most commonly a combination of steroids, a calcineurin inhibitor, and mycophenolate mofetil) is preferred to avoid high doses and collateral effects of each drug.*
- *Immunosuppression should be minimized after LT for hepatitis C related cirrhosis (due to the effect of increasing viral replication and progression of fibrosis) and for HCC, mainly in cases of recurrence (because immunosuppression accelerates tumor progression). Conversely, the level of immunosuppression should be higher after LT for autoimmune diseases.*
- *Long-term immunosuppression increases the risk of malignancies (skin tumors are the most frequent malignancies) and other collateral effects, such as nephrotoxicity (mainly related to calcineurin inhibitors), diabetes, neurotoxicity, and osteoporosis.*

OBJECTIVES OF IMMUNOSUPPRESSION IN THE CONTEXT OF LIVER TRANSPLANTATION

Independent of lesions related to preservation, transplantation of a solid organ procured from a foreign donor induces a powerful immune response in the recipient of the organ. Immune response is directed to the foreign major histocompatibility complex (MHC) antigens of the donor. It involves several T-cell subtypes, B-cells and antigen-presenting cells. However, acute cellular rejection is basically a T-cell mediated response. In the liver, MHC antigens are mainly expressed by endothelial cells and bile duct epithelium. MHC antigens are expressed to a lesser extent by hepatocytes. As a result, the main targets of acute cellular rejection are the vessels and the bile ducts. This is illustrated by the presence of inflammatory infiltrates within portal tracts, with lymphocytes infiltrating the endothelium and the epithelium of the bile ducts. If untreated (or not prevented), acute cellular rejection would rapidly result in graft loss.

Chronic rejection is a more complex phenomenon involving immune and non-immune mechanisms. Chronic rejection is characterized by a slowly progressive obliteration of hepatic artery branches and, in parallel, a destruction of bile duct epithelium resulting in diffuse cholangitis. If not efficiently prevented and/or if left untreated, chronic rejection would also result in graft loss and patient death, unless re-transplantation is performed.

Effective control of allograft rejection is necessary for transplantation to be successful. In the early ages of transplantation (in the late 1960s and early 1970s), rejection was a major cause of graft failure and patient death. The results of solid organ transplantation improved with the advent of cyclosporine in the early 1980s. Indeed, cyclosporine proved to be more selective and also more effective at preventing rejection. At present, prevention and/or control of acute rejection can be easily achieved

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with new cyclosporine formulations, as well as with other immunosuppressive agents including tacrolimus (an agent with targets close to those of cyclosporine), anti-proliferative agents (mycophenolate mofetil, in particular), m-TOR inhibitors, and specific biological agents. With these agents, the rates of acute and chronic rejection have dramatically decreased. Rejection rates are lower in liver transplant recipients than in kidney or heart transplant recipients. Therefore, at present, the main issue in liver transplantation is not whether more vigorous immunosuppression should be used to better prevent rejection, but rather how to avoid excessive immunosuppression. This objective is supported by two key concepts. First, it has been shown that in contrast to other solid organs, early acute rejection does not have a deleterious impact on long-term graft function and recipient survival.[1] In the vast majority, early acute rejection can be easily treated either by an increase in the dose of maintenance immunosuppressive agents or by steroid boluses. Therefore, complete elimination of acute rejection is not a desirable goal in liver transplantation. Second, over-immunosuppression may have a deleterious impact on the course of recurrent disease following transplantation, especially hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC). Practically speaking, an adequate balance must be obtained between insufficient and excessive immunosuppression, but there is no specific tool to adequately achieve this goal. Adjustments in individual liver transplant recipients are empirical.

In the following sections, immunosuppressive agents used in liver transplantation will be detailed. The most common combinations used in clinical practice will be discussed.

IMMUNOSUPPRESSIVE AGENTS

In theory, a large number of immunosuppressive agents can be used in liver transplantation. In practice, the most commonly used agents are steroids, calcineurin inhibitors, and antimetabolites. Some agents can be used for induction as well as for maintenance immunosuppression. Other agents are only used as induction therapy in specific situations.

AGENTS FOR INDUCTION AND MAINTENANCE IMMUNOSUPPRESSION

Steroids

Corticosteroids were the first agents to be used in solid organ transplantation, more than three decades ago. The effects of corticosteroids on the immune system are especially broad. These effects include an inhibition of lymphocyte activation by decreasing interleukine-1 (IL-1) transcription; suppression of antibody and complement binding; and a reduction in the synthesis of immunomodulating cytokines, such as interferon-γ and interleukin-2 (IL-2). In addition, corticosteroids have potent anti-inflammatory properties (**Table 1**). In general, corticosteroids have broad and non-specific effects on the immune response. They may be effective at preventing rejection but they also have effects on pathways that are not directly involved in the allograft rejection process.

Corticosteroids (prednisone orally or methyl-prednisolone intravenously) can be used either as induction (during the early post-transplant course) or maintenance therapy. A short induction with steroids is frequently used. However, rapid tapering and steroid withdrawal is increasingly recommended due to the numerous side effects related to long-term administration of steroids (**Table 2**). Steroid minimization is especially useful in patients with HCV infection.[2,3] Indeed, steroids have been shown to exacerbate viral replication and fibrosis progression.

Steroid boluses for treating acute rejection episodes can be particularly harmful. Steroid boluses (high dose steroids administered intravenously for two to three consecutive days) remain the reference option in patients who develop early acute rejection despite adequate induction/maintenance therapy. However, it must be kept in mind that transient steroid boluses may have a long-term deleterious impact on disease progression in patients with recurrence of HCV infection.

Table 1. Mechanisms of action of immunosuppressive agents used in liver transplantation.

Agents Maintenance and/or induction	**Mechanisms of action**
Steroids	- Inhibition of IL-1 dependent lymphocyte activation - Suppression of antibody and complement binding - Reduction in the synthesis of interferon-γ and interleukin-2
Cyclosporine	- Inhibition of IL-2 transcription - Blocking calcineurin through cyclophilin
Tacrolimus	- Inhibition of IL-2 transcription - Blocking calcineurin through FK binding protein
Mycophenolate mofetil	- Inhibition of T and B cell proliferation - Blocking inosine-5'-monophosphate dehydrogenase
Sirolimus and everolimus	- Blocking mTOR pathway - Inhibition of T and B cell proliferation

Calcineurin inhibitors

Cyclosporine

Cyclosporine is an inhibitor of calcineurin with potent immunosuppressive properties, which were recognized in 1976. This compound is derived from a soil fungus. Cyclosporine acts by inhibiting IL-2 transcription by T-lymphocytes. The inhibition of IL-2 transcription results from binding to the intracellular receptor cyclophilin and, as a result, the inhibition of calcineurin (**Table 1**).[4] Calcineurin is an intracellular calcium-dependent phosphatase complex that is central in the activation of T-cells. The inhibition of IL-2 transcription blocks T-cell activation. Cyclosporine inhibits gene transcription of other mediators including interferon-γ, IL-3, and IL-4.

Cyclosporine is absorbed in the proximal part of the jejunum and peak serum concentration is observed 2 to 4 hours after ingestion. The absorption of the current micro-emulsified formulation (Neoral®) is better than that of the initial formulation, with less variability. Importantly, the absorption of micro-emulsified cyclosporine is relatively independent of cholestasis and clamping/unclamping of the T-tube. Cyclosporine is metabolized by the liver through cytochrome P450. Interactions may be observed with drugs that either induce (rifampicin, phenobarbital, among others) or inhibit (erythromycin, ketoconazole, among others) the cytochrome P450 system. Drug monitoring is generally based on trough level. It has been suggested that monitoring blood concentration two hours after ingestion (C2 monitoring) could better reflect drug exposure. However, it is somewhat more complex than this.[5] Evidence that C2 monitoring is superior to trough-level monitoring in clinical practice is still lacking.[6] Numerous side effects can be observed with cyclosporine. However, these side effects have to be balanced against the efficacy of the drug at preventing allograft rejection and improving survival. The main side effect of cyclosporine is renal toxicity. Impaired renal function can be observed in the early postoperative course as well as in the long term. While early renal toxicity may be fully or partially reversible, long-term toxicity generally results in an irreversible and progressive deterioration in renal function. Large surveys have shown that the cumulative incidence of chronic renal

Table 2. Main side effects of the immunosuppressive agents independent of the indication for liver transplantation.

Agents Maintenance and/or induction	Main side effects	Frequency	Potential severity
Steroids	Diabetes	+++	+++
	Hypertension	++	++
	Obesity/dyslipidemia	+++	++
	Osteoporosis	+++	+++
	Infection by opportunistic agents	+	++
Cyclosporine and tacrolimus	Renal toxicity	+++	+++
	Neurotoxicity (tremor, headaches, paresthesia, seizures)	++	+
	Diabetes*	++	++
	Hypertension	+	+
	Hyperkalemia	+	+
	Hypertrichosis†	++	±
	Serum lipid change	+	+
	Gingival hyperplasia†	+	±
	Microangiopathy and PRESS‡ syndrome	±	+++
Mycophenolate mofetil and enteric-coated mycophenolate sodium	Diarrhea	++	+
	Leukopenia	+	+
	Thrombocytopenia	+	+
	Anemia	±	±
Sirolimus and everolimus	Anemia	+	±
	Thrombocytopenia	+	+
	Leukopenia	+	±
	Dyslipidemia	++	+
	Diarrhea	+	±
	Oral ulcers	+++	++
	Proteinuria/deterioration of renal function	+	++
	Interstitial pneumonia	±	+++
	Hepatic artery thrombosis	+	+++
	Delayed wound healing	+++	+

failure five years after liver transplantation may be as high as 18%.[7] Renal toxicity related to calcineurin inhibitors is characterized by arterial vasoconstriction followed by glomerular sclerosis and tubulo-interstitial fibrosis. Diabetes and hypertension are also relatively frequent side effects. Other side effects are listed in **Table 2**.

Cyclosporine is an old drug, and generic formulations are now being proposed. These formulations are less costly and are supposed to be bioequivalent in healthy subjects; however, pharmacokinetic differences have been documented in renal transplant recipients. Therefore, substitution to a generic formulation requires careful drug monitoring and repeated liver function tests.

Tacrolimus

Like cyclosporine, tacrolimus (formally called FK506) is a calcineurin inhibitor with potent immunosuppressive properties. It belongs to the family of macrolides. Tacrolimus inhibits IL-2 transcription after binding to the intracellular receptor FK binding protein. Eventually, tacrolimus blocks T-cell activation through pathways comparable to those involved in cyclosporine-induced immunosuppression. For a given dose and a given blood concentration, tacrolimus has more powerful immunosuppressive properties than cyclosporine (about 100 times greater).[8]

After oral administration, tacrolimus is mainly absorbed in the proximal part of the jejunum. Absorption is relatively independent of bile salts and cholestasis. The kinetics of peak concentration is similar to that of cyclosporine. Therefore, oral route can be used in almost all patients and at any time following the procedure, including within the first 48 hours. Tacrolimus can be easily administered through a nasogastric tube. Intravenous administration is highly uncommon with tacrolimus. It is metabolized within the liver, mainly by cytochrome P450 3A.

While the initial formulation (Prograf®) has to be administered twice daily, a recently modified formulation (Advagraf®) with more prolonged release of tacrolimus can be administered only once daily (in the morning) with a similar drug exposure.[9] In the early post-transplant course, slightly higher doses of the delayed released formulation should be given to achieve the same trough levels as standard tacrolimus. In the long term, it is recommended that patients be switched on a 1:1 basis from Prograf® to Advagraf®. However, in patients who are switched from one formulation to another, close monitoring of trough level is recommended. A controlled study has shown similar results in terms of rejection, patient survival, graft survival, and safety with the twice-daily formulation compared to the once-daily formulation.[9]

As both cyclosporine and tacrolimus are calcineurin inhibitors, it is not surprising that their side effects are comparable. However, there are mild differences between the two. Diabetes is less frequent with cyclosporine than with tacrolimus. Hypertrichosis and gingival hyperplasia are only observed with cyclosporine, not with tacrolimus.[10] Randomized studies have shown that, compared to cyclosporine, tacrolimus is associated with a lower risk of acute rejection, steroid resistant acute rejection, and treatment failure for immunological reasons.[10-12]

Antimetabolites

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid that inhibits the proliferation of T- and B-lymphocytes by blocking de novo synthesis of nucleotides.[13] The mechanism of action is based on an inhibition of inosine-5'-monophosphate dehydrogenase, which is critical for the proliferation of lymphocytes, while other cells can utilize other pathways. MMF can be administered either intravenously or orally. After oral administration, MMF is rapidly hydrolyzed into mycophenolic acid by esterases in the stomach, small intestine, and other tissues including the liver. MMF is absorbed throughout the small intestine with a peak serum concentration occurring one to two hours after ingestion. Mycophenolic acid is metabolized by glucuronidation in the gastrointestinal tract, the kidney, and the liver. The metabolites are mainly excreted into bile. There is an enterohepatic recycling, and the concentration time profile often shows two peaks. The second peak in serum concentration occurs four to 12 hours after ingestion. The trough level is poorly correlated to the area under the curve (AUC).

The main side effects of MMF are summarized in **Table 2**. Diarrhea is relatively frequent at initiation but tends to improve over time. The main advantage of MMF is the absence of nephrotoxicity.

Enteric-coated mycophenolate sodium

Enteric-coated mycophenolate sodium is another prodrug of mycophenolic acid. It is a delayed release formulation with absorption in the small intestine. The mechanisms of action are the same as those of MMF. This agent was developed with the aim of reducing gastrointestinal side effects. However, controlled studies have failed to demonstrate fewer side effects with enteric-coated mycophenolate sodium compared to MMF.[14,15] Nonetheless, the efficacy of the two seems to be similar.

Azathioprine

Azathioprine is an old immunosuppressive agent that has been extensively used since the early years of transplantation. Like MMF, azathioprine is an antimetabolite agent that inhibits T- and B-cell proliferation. Azathioprine may induce mild leukopenia and/or thrombocytopenia. Diarrhea and other

gastrointestinal disorders are uncommon with this agent. Azathioprine, which has mild immunosuppressive effects, has been progressively supplanted by MMF and enteric-coated mycophenolate sodium. However, azathioprine is less costly than these agents. Azathioprine is considered a good alternative to MMF.[16]

Mammalian target of rapamycin (mTOR) inhibitors

Inhibitors of mammalian target of rapamycin (mTOR) are potent immunosuppressive agents that inhibit T-cell proliferation between G1 and S phases. The mTOR pathway is involved between signal II and signal III. Two agents have been developed for clinical use (sirolimus and everolimus). Normally, TOR activation, which follows signal II, results in the activation and proliferation of T- and B-cells as well as the proliferation of non-immune cells, including fibroblasts and endothelial cells.[17] mTOR inhibitors block this cascade of events. Importantly, mTOR is a key protein kinase controlling signal transduction from various growth factors, cell proliferation autophagy, and angiogenesis. Therefore, in addition to immunosuppressive properties, mTOR inhibitors have anti-cancer properties.[18]

Sirolimus

Sirolimus, formally called rapamycin, was the first mTOR inhibitor to be developed in solid organ transplantation. Sirolimus belongs to the family of macrolides. After oral ingestion, this drug is rapidly absorbed by the intestine with a maximal blood concentration at one hour. It is metabolized by the liver through cythochrome P-450 enzyme CYP-3A4. Its half-life is long (62 hours). Therefore, sirolimus can be administered once daily. Sirolimus trough concentration is strongly correlated to drug exposure.

The main side effects of sirolimus are listed in **Table 2**. Oral ulcers and gastrointestinal side effects are relatively common and sometimes disabiliting. In theory, sirolimus is non-nephrotoxic. However, sirolimus may increase cyclosporine nephrotoxicity when both drugs are used in combination. In addition, in patients who already have impaired renal function and/or proteinuria, the introduction of sirolimus may increase proteinuria with further deterioration in renal function.[19] An increased incidence of hepatic artery thrombosis in the early post-transplant course has been a limitation in the development of this drug in liver transplantation. In general, it is recommended that sirolimus not be introduced in the first three months postoperatively.

Everolimus

Everolimus, formally called RAD, is another mTOR inhibitor with targets and mechanisms of action similar to those of sirolimus. The half-life of Everolimus is much shorter than that of sirolimus (30 hours), and has to be administered twice daily. The safety profile is comparable to that of sirolimus (**Table 2**). There is no evidence of a lower rate of side effects with everolimus compared to sirolimus.

AGENTS FOR INDUCTION IMMUNOSUPPRESSION

Anti-lymphocyte/anti-thymocyte globulins

Antibodies against lymphocytes and thymocytes have been used since the early days of transplantation. The two currently used antibodies, thymoglobulin and anti-thymocyte globulins, are obtained from immunized rabbits or horses. These polyclonal antibodies target a large number of T-cell surface antigens including CD2, CD3, CD4, CD8, CD28 and the T-cell receptor. Rabbit anti-thymocyte globulins also contain antibodies against natural killer cells (CD16, CD 56) and B-cells (CD20). The administration of anti-thymocyte globulins is followed by a rapid depletion of lymphocytes expressing these surface antigens. Lymphopenia occurs within the first 24 hours and may persist for several weeks or months. These antibodies inhibit the primary alloantigen signaling as well as costimulation.[20] It is generally recommended that anti-thymocyte globulins be administered during the first one to seven days following transplantation as an induction regimen.

The use of xeno-antibodies against lymphocytes and thymocytes is limited by their side effects. Patients may experience a cytokine release syndrome with manifestations ranging from mild flu-like symptoms to a shock-like reaction. Allergy may also occur with fever, rash, pulmonary edema, and anaphylactic reaction. Concomitant use of steroids reduces the incidence of these side effects.

IL-2 receptor antagonists

Since daclizumab is no longer marketed, basiliximab is the only IL-2 receptor antagonist to be used in organ transplantation. Basiliximab is a chimeric monoclonal antibody directed against a subunit (CD25) of the IL-2 receptors at the surface of T-lymphocytes.[21] By blocking IL-2 receptors, this monoclonal antibody inhibits T-cell activation following the binding of foreign antigens from the allograft to antigen-presenting cells. IL-2 receptors are only present on the surface of activated T-cells, not on resting cells.

Basiliximab is a chimeric antibody containing a constant engineered human region and a mouse-derived variable region specific of CD25. The human constant region, which is less immunogenic, mediates antibody-dependent cytotoxicity. After intravenous administration, basiliximab is slowly degraded and eliminated by intracellular proteolysis. As a result, the half-life of basiliximab can be as long as 13 days. Two intravenous administrations at days 0 and 4 postoperatively may induce effective immunosuppression during the first two weeks following transplantation. With basiliximab, IL-2 receptors

are completely saturated on peripheral T-lymphocytes within the first 24 hours after first administration.

The safety profile of basiliximab is excellent. In contrast to anti-lymphocyte/thymocyte globulins, basiliximab does not induce cytokine release syndrome, marked by fever and chills, among other symptoms. Although the variable region is of murine origin, several studies have shown that sensitization is uncommon (less than 2% of treated patients with detectable antibodies).[22] There is no evidence for an increased rate of infection and/or malignancies in recipients of solid organ transplantation receiving basiliximab compared to recipients not receiving this agent.[21]

IMMUNOSUPPRESSIVE REGIMENS: A PRACTICAL APPROACH

In the early post-transplant course, immunosuppressive agents are used in combination in order to obtain a strong immunosuppression level with limited side effects. The risk of rejection is greater during the first one to two months. Thereafter, immunosuppression can be progressively tapered. Most centers use regimens based on calcineurin inhibitors. MMF and enteric-coated mycophenolate are increasingly being used in combination with calcineurin inhibitors, with the aim of using lower doses of these latter agents (and lowering the rate of side effects). Another objective is to discontinue steroids within the first six months as, in most cases, they are not necessary for maintenance immunosuppression and they have many side effects in the long term. There is no consensus as to the usefulness and safety of systematic induction with anti-thymocyte globulins or IL-2 receptor antagonists. Immunosuppression mainly depends on early postoperative renal function, since (a) impaired renal function is common after transplantation and (b) calcineurin inhibitors are nephrotoxic.

IMMUNOSUPPRESSION IN PATIENTS WITHOUT IMPAIRED RENAL FUNCTION IN THE EARLY POST-TRANSPLANT COURSE

In most centers, immunosuppression consists of a combination of steroids, a calcineurin inhibitor (either cyclosporine or tacrolimus), and MMF. Steroids are started during the anhepatic phase while calcineurin inhibitors and MMF are generally started within the first 12 hours following skin closure. This 12-hour interval can be useful to assess postoperative urine output and renal function.

The initial dose of intravenous methylprednisolone may be 5 mg/kg intravenously during the anhepatic phase followed by an additional dose of 5 mg/kg after skin closure. By day 1 post-transplantation, steroid doses may be tapered linearly in order to reach a dose of 20 mg/d on postoperative day 7. Intravenous methylprednisolone may be changed for oral prednisone as soon as the oral route is available. Thereafter, prednisone should be progressively decreased and eventually discontinued in month 4 post-transplant.

Calcineurin-inhibitors (either cyclosporine or tacrolimus) may be started within the first 24 hours post transplant, provided patients have adequate urine output and renal function. The absorption of either microemulsified cyclosporine or tacrolimus is good. Therefore, intravenous administration is not needed in almost all cases. These agents can be administered through nasogastric tube, even within the first 12 hours post-transplantation. Recommended initial doses and target trough levels are shown in **Table 3**. Tacrolimus is a powerful immunosuppressive agent. Adequate immunosuppression can be achieved with very low blood concentration. It must be noted that tacrolimus mainly bonds to red blood cells and circulating proteins. It is virtually impossible to determine the serum-free fraction concentration of tacrolimus. In the long term, it may be recommended to maintain tacrolimus trough levels between 3 and 5 ng/mL. However, some patients do not have evidence of rejection with trough levels below 3 ng/mL. Similarly, effective prevention of rejection may be achieved with a cyclosporine trough level below 100 ng/mL.

The recommended dose of MMF is 1 g twice daily. Intravenous route can be used during the first postoperative days. There are relatively wide inter-individual variations in the metabolism of MMF. Trough levels are poorly representative of drug exposure; therefore, it can be recommended to adjust MMF doses according to a pharmacokinetic profile. Algorithms have been developed to estimate the drug exposure, namely the area under the pharmacokinetic curve (AUC), based on three blood samples (pre-dose, 30 minutes post-dose, and two hours post-dose).[23] A reasonable target AUC is 30-60 mg h/L.

Table 3. Practical use of calcineurin inhibitors in liver transplantation.

Agent	Initial dose	Target trough level post transplant			
		Month 1	Month 3	Months 6	Year 1
Cyclosporine (Neoral®)	5-6 mg/kg/day	200-300 ng/mL	150-250 ng/mL	150-250 ng/mL	100-200 ng/mL
Tacrolimus (Prograf®)	0.15-0.2 mg/kg/day	10-15 ng/mL	8-10 ng/mL	5-8 ng/mL	5 ng/mL
Tacrolimus + MMF	0.15-0.2 mg/kg/day	8-10 ng/mL	5-8 ng/mL	5-8 ng/mL	3-5 ng/mL

IMMUNOSUPPRESSION IN PATIENTS WITH IMPAIRED RENAL FUNCTION IN THE EARLY POST-TRANSPLANT COURSE

Acute renal failure is relatively common in the early post-transplant course. In patients with impaired renal function, delayed introduction of calcineurin inhibitors may be recommended, as these agents are basically nephrotoxic. Indeed, delayed introduction of calcineurin inhibitors may facilitate early recovery of renal function.

In this context, a regimen comprising the administration of the induction agent basiliximab in combination with steroids and MMF, followed by delayed introduction of calcineurin inhibitors, may be recommended. Basiliximab should be administered according to the following protocol: 20 mg intravenously on day 0, followed by an additional dose of 20 mg on day 4 postoperatively. Basiliximab should be combined with steroids and MMF with the same doses as above. Calcineurin inhibitors can be introduced when renal function improves. There is no consensus on an acceptable level of serum creatinine or glomerular filtration rate to start calcineurin inhibitors. It can be proposed to start calcineurin inhibitors within the first 10 days, as soon as the creatinine level is lower than 150 μmol/L. However, if serum creatinine remains above 150 μmol/L on day 10 post-transplantation, or if the patient is on renal replacement therapy, low-dose calcineurin inhibitors should be started with a low target trough level.

IMMUNOSUPPRESSION FOR SPECIFIC DISEASE POPULATIONS

PATIENTS WITH HCV INFECTION

Almost all patients transplanted for HCV-related cirrhosis (decompensated cirrhosis and/or HCC) have evidence of viral replication with positive serum HCV-RNA. As a consequence, almost all patients experience recurrence of HCV infection and chronic hepatitis C involving the allograft after transplantation. Immunosuppression both increases viral replication and accelerates the progression of fibrosis after transplantation. Antiviral therapy, based on a combination of pegylated interferon and ribavirin, is poorly effective and poorly tolerated after transplantation.[24-26]

It is clear that in the long term, due to HCV recurrence, patient and graft survival are significantly lower in patients transplanted for HCV cirrhosis compared to those transplanted for non-HCV cirrhosis.[27]

In the early postoperative period, OKT3 and alemtuzumab (campath) should be avoided since they both increase the severity of hepatitis C recurrence.[28-29] The deleterious effect of anti-thymocyte globulin is less clear. However, it should be used with caution in recipients with HCV infection. Intravenous methylprednisolone pulses used for treatment of acute cellular rejection dramatically increase HCV-RNA levels and are associated with an increase in graft loss.[30-31] In contrast, corticosteroids at a low dose are not worse than a steroid-free immunosuppression regimen in terms of severity of HCV recurrence or graft survival. Finally, it has been suggested that a slow tapering of steroids is less harmful than abrupt discontinuation.[32] The choice of calcineurin inhibitor – tacrolimus or cyclosporine – remains a much-debated issue. In vitro studies have shown that cyclosporine inhibits viral replication; these data have not been confirmed in vivo. Moreover, a meta-analysis of studies comparing the two calcineurin inhibitors has shown that tacrolimus as maintenance immunosuppression is associated with a better outcome (patient and graft survival).[33] Some recent studies have suggested that the rate of sustained virological response to antiviral treatment by pegylated-interferon and ribavirin in recipients with hepatitis C recurrence may be increased with cyclosporine compared to tacrolimus.[34] The impact of MMF on recurrence of HCV seems to be beneficial in terms of long-term outcomes, as concomitant administration of MMF reduces the rate of rejection and the need for steroid pulses.[35] IL2 receptor antagonists do not seem to be harmful to HCV-infected patients. mTOR inhibitors may slow the progression of fibrosis, but this effect has not been clearly documented yet.

PATIENTS WITH HCC

The main limitation of liver transplantation in patients with HCC is the risk of post-transplant tumor recurrence. Even in the absence of detectable extrahepatic metastases on imaging, patients are potentially at risk of intrahepatic or extrahepatic recurrence due to circulating malignant cells. The risk increases with tumor size and number of nodules. The Milan criteria are still widely used to select suitable candidates for transplantation.[36] In patients who are within the Milan criteria (a single nodule smaller than 5 cm, or two to three nodules each smaller than 3 cm), the rate of post-transplant recurrence is generally less than 10%. However, in cases of recurrence, tumor progression is markedly accelerated by immunosuppression. On the one hand, immunosuppression accelerates tumor progression. On the other hand, discontinuing (or drastically reducing) immunosuppression in patients with tumor recurrence may rapidly result in severe rejection and graft loss.

There is no evidence that cyclosporine and tacrolimus-based regimens are associated with different rates of tumor recurrence. The results of studies comparing cyclosporine and tacrolimus in HCC patients are conflicting.[37-38] Similarly, there is no evidence that the use of MMF of IL-2 receptor antagonists increases the risk of recurrence.

On theoretical grounds, mTOR inhibitors represent an attractive option in patients with HCC, as these agents have both immunosuppressive and anticancer properties.[39] Two uncontrolled studies (one case control study and one registry data analysis) suggest that post-transplant outcome may be significantly better in patients receiving mTOR inhibitors compared to patients receiving calcineurin inhibitors.[40-41] In one study, the absence of mTOR inhibitors was an independent risk factor for recurrence, along with other well-known factors including vascular invasion, high alpha-fetoprotein level, and more than four nodules.[40] Controlled studies are currently ongoing to clearly determine whether mTOR inhibitors reduce the rate of recurrence and improve survival.

In patients who have been on calcineurin inhibitors and who have tumor recurrence, switching to mTOR inhibitors, with or without sorafenib, is an option.[42] It must be noted that the administration and doses are different in immunosuppression and oncology. Case reports and small series have been reported with objective tumor response.[43] Unfortunately, the benefits of conversion in terms of survival seem to be limited.

AUTOIMMUNE DISEASES

Autoimmune diseases may recur after liver transplantation, even in patients receiving adequate immunosuppression. In addition, it is generally accepted that the level of immunosuppression in autoimmune diseases (including primary biliary cirrhosis and primary sclerosing cholangitis) should be higher than in other indications. Indeed, several studies have shown that both acute and chronic rejection are more common in these patients, compared with other indications such as alcoholism or virus-associated liver disease.[44]

Autoimmune hepatitis (AIH)

The results of liver transplantation are good, with a 5-year survival rate of about 85%.[45] After liver transplantation, the rate of recurrence of AIH ranges between 20 and 40%.[46] The risk factors for recurrence are still unknown, but it has been suggested that in this condition patients should receive stronger immunosuppressive therapy than in other indications.[47] There is no difference in recurrence rates between recipients of tacrolimus or cyclosporine,[48] and it has been suggested that early steroid withdrawal may be harmful. The superiority of azathioprine over MMF has not been proven. Recurrence is not always associated with abnormal liver function tests and protocol biopsies may be recommended. Generally, recurrent disease can be controlled by an increase in immunosuppression or the addition of corticosteroids.

Primary biliary cirrhosis (PBC)

Liver transplantation offers excellent results in the most severe forms of PBC, with a 5-year survival rate of about 90%.[49] The rate of recurrence of PBC is about 20 to 30%,[49] but graft loss due to recurrence is uncommon. More frequently than in HAI, liver function tests may be normal in case of recurrence, emphasizing the need for liver biopsies. There is no study suggesting that immunosuppression has an impact on the course of the disease after liver transplantation. Maintenance regimens include calcineurin inhibitors and MMF. Documented recurrence of PBC should be treated with ursodeoxycholic acid.

Primary sclerosing cholangitis (PSC)

Although there is good patient survival after transplantation for PSC, recurrent PSC has a major impact on graft survival.[50] The rate of recurrence ranges from 20 to 40%.[51-52] Sometimes, it remains difficult to differentiate recurrence of PSC from ischemic cholangitis or chronic rejection. The risk factors for recurrence include repeated acute cellular rejection episodes and therapy for steroid-resistant acute cellular rejection.[53] There are no published data concerning the optimal immunosuppression therapy. Conventional immunosuppression with tacrolimus and MMF may be recommended. There is no effective therapy for treating recurrent PSC after transplantation, and re-transplantation eventually represents the best option in selected patients.

MANAGEMENT OF ACUTE REJECTION

Acute rejection most often occurs during the first three months following transplantation. With current immunosuppressive regimens, the incidence of acute rejection may be less than 20% in liver transplantation.[54] It is highly recommended to perform a biopsy and to document and grade acute rejection before treatment. The treatment of acute rejection varies according to the baseline immunosuppression status. If acute rejection occurs in a patient with either cyclosporine or tacrolimus trough levels significantly lower than the target levels, acute rejection may be reversed in most cases by increasing the doses of calcineurin inhibitors.[55] In patients with adequate calcineurin inhibitor trough levels, the first-line option is represented by steroid boluses. Steroid boluses consist of the administration of 500 to 1,000 mg methylprednisolone for two to three consecutive days, intravenously. Steroid boluses can be repeated five to seven days after the first series of boluses, in the absence of significant improvement in liver function tests. The administration of steroid boluses should be cautious in patients with HCV infection, as they are associated with a significantly worse outcome.

There is no evidence that anti-thymocyte globulins are superior to steroid boluses at treating acute rejection. Anti-thymocyte globulins may result in more side effects.

MANAGEMENT OF CHRONIC REJECTION

Due to improvements in immunosuppression, the incidence of chronic rejection has dramatically decreased in the last decade. Less than 5% of liver transplant recipients develop chronic rejection. In almost all cases, chronic rejection is preceded by one or more episodes of acute rejection that are often resistant to corticosteroid therapy.[56] The diagnosis is usually based on liver biopsy. In contrast to acute cellular rejection, chronic rejection is difficult to treat. There is no specific immunosuppressive agent or combination of agents that block the progression of the disease. In most cases, chronic rejection leads to graft loss, whatever the changes in immunosuppression. If immunosuppression is based on cyclosporine, a switch to tacrolimus is recommended. If tacrolimus has already been used, the trough level should be increased. There is no evidence that steroids, anti-thymocyte globulins, or other immunosuppressive agents are effective.

SIDE EFFECTS RELATED TO IMMUNOSUPPRESSION AND IMMUNOSUPPRESSIVE AGENTS

CONSEQUENCES OF LONG-TERM IMMUNOSUPPRESSION

Although liver transplant recipients receive potent immunosuppressive agents in the long term, the incidence of common bacterial infections and opportunistic infections is relatively low. Bacterial infections predominate in the early postoperative period.[57] Delayed infections are strongly correlated to biliary complications.

The main complication of long-term immunosuppression is de novo malignancy. Immunosuppression essentially increases the risk of any malignancy. The probability of developing any de novo malignancy at one, five, and 10 years is of about 3%, 10%, and 22%, respectively.[58] Patients transplanted for alcoholic liver disease and primary sclerosing cholangitis are at higher risk. Skin malignancies are the most frequent tumors, representing about 50% of all malignancies.[58] Squamous cell carcinoma is the most frequent tumor, and the prognosis is generally good.[59] The most frequent non-skin cancers are lymphoma, bowel, genito-urinary, head and neck, and lung cancers. Not only does immunosuppression increase the risk of de novo cancer, but it also accelerates tumor progression and reduces the efficacy of anti-cancer therapy. The probability of death after diagnosis of solid organ cancer is 38% and 57% at one and five years, respectively.[58] Overall, mortality related to malignancy more than one year after transplantation (22%) is twice as high as the mortality rate related to infection (11%).[60]

DRUG-RELATED SIDE EFFECTS

The main side effects of immunosuppressive agents have been outlined in previous topics. In liver transplantation, the main drug-related side effects are nephrotoxicity, diabetes, neurotoxicity, and hypertension.

Nephrotoxicity is a major burden in liver transplantation. The cumulated incidence of severe kidney damage is higher in liver transplantation than in heart or lung transplantation, with about 20% patients developing chronic renal failure within five years after transplantation.[7] Calcineurin inhibitors are central in the development of chronic kidney damage. Nephrotoxicity is characterized by arteriolopathy, glomerulosclerosis, and interstitial fibrosis. Renal-sparing interventions should be started early in patients with impaired renal function as, once established, chronic changes are irreversible. Currently, the safest calcineurin-free immunosuppression is based on mTOR inhibitors, which, in theory, are non-nephrotoxic. However, in patients with proteinuria, mTOR inhibitors increase proteinuria with further deterioration in renal function. In addition, the potential advantages of mTOR inhibitors must be balanced by frequent side effects. Calcineurin inhibitor minimization with the adjunction of MMF or mycophenolate sodium is a reference option in patients with impaired renal function.[61]

Diabetes is frequent after liver transplantation, with an incidence that may be as high as 38%.[62] The incidence of new onset diabetes following transplantation is 20%.[63] New onset diabetes generally occurs within the first three months. It is more frequent in patients receiving tacrolimus compared to cyclosporine. Patients with HCV infection are also at higher risk for diabetes.[63]

Mild symptoms related to calcineurin inhibitor-induced neurotoxicity are common, including tremor and neuralgia.[64] These manifestations generally resolve within the first year after dose reduction. Seizures may occur in the early post-transplant course, when patients receive relatively high doses. Long-term administration of anti-convulsants is not warranted. Posterior reversible encephalopathy syndrome (PRESS) is one of the most severe neurological complications of calcineurin inhibitors.[65] It is characterized by rapid changes in mental status, seizures, focal neurological deficits, and visual disturbances in the early post-transplant course. PRESS syndrome may be unrecognized in patients with prolonged mechanical ventilation and sedation after transplantation. Imaging (MRI) is typical, showing posterior subcortical signal changes. Changes may extend to the parietal lobe and deep white matter. Manifestations may be reversible (at least in part) with discontinuation of calcineurin inhibitors. A switch to mTOR inhibitors is generally recommended, although PRESS syndrome has occasionally been observed with these latter agents.

Osteoporosis remains an important issue in liver

transplantation. In the past, osteoporosis continued to progress after transplantation due to long-term administration of steroids. At present, steroids can be withdrawn in the large majority of patients within a few months. Therefore, the objective is to restore bone mass in patients with osteoporosis acquired before transplantation as a consequence of end-stage liver disease.[66]

EMERGING IMMUNOSUPPRESSIVE AGENTS

Several "new generation" immunosuppressive agents with original targets are currently in pre-clinical or clinical development. These agents are either small molecules or biological agents.[67] The targets of the new small molecules are protein kinase-C (AEB071) and JAK3 (CP-690550). There is also a new calcineurin inhibitor (ISA247), which could be more potent than current calcineurin inhibitors with fewer side effects. The targets of the new biological agents are CTLA4-Ig (belatacept, inhibiting costimulation pathway), LFI-1 (elafizumab, inhibiting adhesion molecules), LFA3 (alefacept, inhibiting lymphocyte trafficking) and CD40L (BG9588, inhibiting costimulation pathway) (**Table 4**). The objectives are to develop more specific immunosuppressive agents with a lower impact on "global immunosuppression" and fewer drug-related side effects. Some of these agents could be alternatives to calcineurin inhibitors. Others may be used in combination with calcineurin inhibitors to reduce toxicity.

Controlled studies comparing belatacept to calcineurin inhibitors have been conducted in kidney transplantation.[68-70] It was shown that a belatacept-based regimen was associated with similar patient and graft survival compared to cyclosporine but with better renal function at two years [69]. In another study, the combination of belatacept and MMF was associated with better renal function than a combination of tacrolimus and MMF.[68] Unfortunately, no such results have been obtained yet in liver transplantation. Phase I and II studies are also ongoing with other novel immunosuppressive agents.

Table 4. New immunosuppressive agents in transplantation and their targets.

Agent	Target	Alternative to conventional CNI	Adjunct to CNI
Small molecules			
ISA247	Calcineurin	+++	-
AEB07	Protein kinase-C	-	+
CP690-550	JAK3	+	±
Biological agents			
Belatacept	CD80/86	++	±
Efalizumab	LFA-1	+	±
Alefacept	CD2	+	±

WITHDRAWAL OF IMMUNOSUPPRESSION

Even more attractive than specific immunosuppressive agents is the withdrawal of immunosuppression, which represents a challenging issue in the future. Theoretically, this goal could be achieved, since the liver has a tolerogenic potential. For instance, HLA matching has a minimal impact in liver transplantation. In general, liver transplant recipients need lower doses of immunosuppressive agents than recipients of other solid organs to prevent rejection. They have a lower incidence of acute and chronic rejection. Finally, the liver is immunoprotective to other organs in combined transplantations (liver-kidney or liver-intestine). Withdrawal of immunosuppression has been tested in several prospective series excluding autoimmune or viral diseases, and unfortunately it could only be achieved without rejection in about 20% of patients.[71] However, several reports of successful discontinuation of immunosuppression have been reported in the setting of lymphoproliferative disorders, where immune response should be restored. Other studies have reported successful discontinuation by self-withdrawal. Immunological studies of these patients have shown that some of them may have favourable immunophenotypic profiles of T-cells, leading to spontaneous operational tolerance.[72]

Transplant tolerance was first reported in mouse models more than 50 years ago. The concept was that the injection of allogeneic cells to neonatal mice resulted in tolerance to subsequent skin allograft from the same donor, without any immunosuppressive agents.[73] This strategy is based on the fact that, once all allo-aggressive cells are deleted by central and peripheral tolerance mechanisms, rejection is not possible. However, in clinical transplantation, this strategy needs an aggressive and invasive therapy consisting of lymphocyte depletion, lymphoid irradiation, and donor bone marrow infusion – which is not very realistic. A more reasonable option is the induction of "prope" tolerance, without total myeloablative suppression or donor bone marrow infusion.[74] Although long-term T-cell depletion is sufficient to induce allograft tolerance in animal models, it does not induce tolerance in patients. However, immediate post-transplant T-cell depletion, using lymphocyte depletion agents (alemtuzumab, thymoglobulin), might enable graft acceptance with reduced doses of conventional immunosuppressive therapy. Several successful cases have been reported in kidney and in liver recipients.[75-78] The next step will be to identify potentially tolerant transplant recipients. These patients may have a signature of tolerance that could be used to reduce or stop immunosuppressive therapy. This approach has been investigated analyzing gene expression profiling using blood samples of tolerant and non-tolerant liver recipients.[79] The use of these biomarkers in clinical practice has yet to be defined.

FINAL CONSIDERATIONS AND PERSPECTIVES

The burden of acute and chronic rejection has been reduced in liver transplantation with the advent of calcineurin inhibitors, which are powerful immunosuppressive agents. The more recent advent of adjunctive agents such as MMF has helped reduce calcineurin inhibitor doses and toxicity. However, as life expectancy increases in liver transplant recipients, cumulated toxicity remains a major issue. In the future, a first goal is to develop more specific immunosuppressive agents with fewer side effects. A second goal is to develop reliable markers to determine which minimal level of immunosuppression is needed for a given patient receiving a given allograft. A third goal is to develop protocols of tolerance induction.

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A large study including 762 consecutive liver transplants and determining the incidence, timing, and risk factors for acute rejection.

Watt K, Veldt B, Charlton M. A practical guide to the management of HCV infection following liver transplantation. *Am. J. Transplant*., **9**, 1707-1713 (2009).

A review and guide to manage patients with HCV infection after liver transplant, including the impact of immunosuppression (and other donor and recipient risk factors) on viremia and recurrence and antiviral therapy.

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32 Technical Aspects of Liver Transplantation

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- *The technical evolution and refinement of liver transplantation over the past 50 years has allowed liver replacement to alter the course of end-stage liver disease as a life-ending condition, thereby giving patients a second chance at a full and healthy life.*
- *The execution of donor hepatectomy, back-table preparation, recipient hepatectomy and graft implantation are all essential to the completion of a single liver transplant.*
- *Living donor liver transplantation needs to be carefully considered in select cases while preserving the well-being of the donor to the maximum extent possible.*
- *Early detection and management of vascular and biliary complications provides the best chance for a favorable outcome.*

INTRODUCTION

The technical evolution of liver transplantation since it was first attempted in humans by Thomas E. Starzl in 1963 [1] has been truly dramatic. In fact the unrelenting pioneering work done by Dr. Starzl was paramount in transforming the experimental idea of liver transplantation into the practical lifesaving reality we know today.

The undertaking of a liver transplant involves a series of operations, encompassing donor procurement, back-table preparation, recipient hepatectomy and finally grafting of the donor liver into the recipient. The perfect execution of each of these steps is essential to the overall success of the operation. This chapter will cover the technical details of the cadaveric donor and recipient operations. We will also discuss living donor liver transplantation outlining the advantages, disadvantages, and technical complications associated with both cadaveric and living donors.

HISTORICAL PERSPECTIVE

For about 50 years it had been widely believed that Dr. C. Stuart Welch's report in *Transplantation Bulletin* (the predecessor to the current journal *Transplantation*), out of Albany Medical College in 1955, was the first report of liver transplantation. I This early attempt was in the form of auxiliary liver transplants placed in the right paravertebral gutter of dogs without performing a native hepatectomy.[2] In 1956, Dr. Jack Cannon at UCLA (University of California, Los Angeles) was also thought to be the first to attempt liver replacement in the orthotopic position, again using a dog model.[3] It has recently come to light, however, that Welch and Cannon's attempts were in fact preceded by Dr. Vittorio Staudacher at the University of Milan in 1952.[4] Staudacher reported an orthotopic experimental model in dogs with some significant similarities to the classic technique of liver replacement still used today in liver transplantation. Starzl first attempted liver transplantation in dogs at Northwestern University in 1958.

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These attempts led to the first orthotopic liver transplant in a human by Starzl in 1963 in Denver, Colorado.[1]

First seven orthotopic liver transplantation attempts:

The first seven orthotopic liver transplant attempts in Denver,[5] Boston,[1] and Paris[1] were met with universal early recipient mortality (**Table 1**).[1,5–7]

After these successive patient deaths, a self-imposed worldwide moratorium on liver transplantation went into effect from January 1964 to the summer of 1967. During this period, significant advances were made including the development of antilymphocyte globulin (ALG). Since all donors at the time were only non-heart-beating donors, improved organ preservation with the use of an ex vivo perfusion system was employed in 1966 and 1967.[8] Furthermore, there was a realization that overcorrection of coagulopathy likely increased the patient's disposition to develop thrombotic complications.[9]

These advances resulted in the first successful human liver replacement on July 23, 1967, performed by Starzl on a 19-month-old child with hepatocellular carcinoma.[10] Since that groundbreaking achievement, there have been numerous milestones that have markedly increased the efficacy and decreased the morbidity of liver transplantation.

Milestones in Liver Transplantation:

- 1979 - FDA approves cyclosporine
- 1983 - NIH Consensus Conference declares liver transplantation a valid therapy for ESLD
- 1984 - First reduced-size liver transplant by Bismuth
- 1984 - National Organ Transplant Act passed, prohibiting the sale of human organs and setting up a national transplant network (UNOS 1986)
- 1986 - "Routine request" law passed, requiring hospitals to give families the opportunity to donate organs by asking them in appropriate cases
- 1987 - University of Wisconsin solution for improved organ preservation
- 1988 - Pichlmayr performs first split-liver transplant
- 1990 - First successful living-related liver transplant by Strong in Australia
- 2002 - MELD and PELD scoring systems go into effect

CADAVERIC DONOR PROCUREMENT

The first step in the donor operation is having a complete grasp of the clinical condition of the recipient, in addition to the dimension of their abdominal cavity. This includes knowledge of the recipient's serologies, blood type and MELD score, and history of prior liver transplantation or other abdominal surgery, as well as the potential recipient's cardiopulmonary status. The rationale for this is to assess the quality of the donor liver in light of the recipient condition. This is of particular importance in the case of an extended criteria donor, where the liver may not be most suitable for a severely ill recipient. The cognitive exercise of matching the donor and recipient is of paramount importance to ensure a proper graft-recipient match.

Upon arrival at the donor hospital, careful examination of the donor's chart, prepared by the *Organ Procurement Organization,* is conducted. Attention should be given to the following: i) social history is checked for high-risk behavior including intravenous drug use, multiple sexual partners, recent incarceration, or heavy alcohol consumption,

Table 1. The first seven orthotopic liver transplantation attempts worldwide. (Adapted from Busuttil and Klintmalm[9])

Number	Location	Age (y)	Survival (d)	Indication	Primary Cause of Death
1	*Denver*	3	0	Extrahepatic biliary atresia	Hemorrhage
2	*Denver*	48	22	Hepatocellular cancer	Pulmonary emboli Sepsis
3	*Denver*	68	75	Cholangiocarcinoma	Pulmonary emboli Sepsis
4	*Denver*	52	65	Hepatocellular cancer Cirrhosis	Pulmonary emboli Hepatic failure Pulmonary edema
5	*Boston*	58	11	Metastatic colon carcinoma	Pneumonitis Liver abscesses Hepatic failure
6	*Denver*	29	23	Hepatocellular cancer Cirrhosis	Sepsis Peritonitis Hepatic failure
7	*Paris*	75	0	Metastatic colon carcinoma	Hemorrhage

in addition to history of prior surgery; ii) hemodynamic parameters are inspected for significant episodes of hypotension or hypoxemia as well as down time; iii) laboratory data, particularly liver function tests, coagulation profile, as well as serum sodium are checked; the association between severe hypernatremia and increased incidence of primary non-function warrants using D5W for pre-cool flush as opposed to lactated ringers to decrease hepatic sodium load; and iv) consent for donation must be inspected and verified by the donor team prior to starting surgery.

PREOPERATIVE PREPARATION

The donor procurement operation is often performed in small hospitals that do not possess the infrastructure to support major surgery and do not have specialized surgical equipment. It is therefore essential to put the operating room staff at ease upon arrival to the donor hospital by explaining to them what supplies are needed and to be able to perform the operation without the need for specialized instruments. Expediency and accuracy are essential for successful organ recovery.

HEART-BEATING CADAVERIC DONOR OPERATION

The donor is prepped and draped from cricoid to pubis with the arms tucked to the side. Midline incision is made extending from the xiphoid to the pubis symphysis. Upon entry into the abdominal cavity, the round ligament is ligated and divided, and a full exploration of the abdomen to rule out gross malignancy or occult infection is performed. The liver is also inspected for any significant trauma that may compromise the organ. At this point the assessment of the quality of the liver should include inspecting the liver for any discoloration, congestion, or abnormality in texture. The sharpness of the liver edges and liver size match to the potential recipient are also assessed. The right lobe of the liver is most reflective of the liver quality on gross inspection. It also important to note that most traumatic liver injuries do not preclude use for transplantation. If there is any uncertainty pertaining to the quality of the liver, often the decision to accept or decline the organ should be made after cross-clamping and flushing the liver. A median sternotomy is then utilized to open the chest and a self-retaining sternal retractor is placed. The pericardium is incised and opened along the midline to expose the inferior vena cava at the caval-atrial junction. The pericardium is also incised transversely on the right lateral aspect down to the phrenic nerve, and the right pleural cavity is opened to facilitate generous access to the right hemithorax.

Attention is then redirected to the abdomen where the falciform ligament is taken down using electrocautery. Medial visceral rotation of the right colon and duodenum is then performed to expose the infrahepatic vena cava medially and the left renal vein superiorly. The right colon and small intestine are retracted laterally to the left and superiorly to facilitate exposure of the inferior mesenteric vein close to the ligament of Treitz. The inferior mesenteric vein is then isolated and cannulated. The tip of the cannula should remain in the inferior mesenteric vein to avoid injury to the splenic, superior mesenteric, or portal vein. After successful cannulation of the inferior mesenteric vein, pre-cooling perfusion is started using 5% dextrose in isotonic saline. In cases of donor serum sodium greater than 160 mEq/dL, 5% dextrose is used for pre-cooling instead. Attention is then directed to the segment of abdominal aorta between the iliac bifurcation and the takeoff of the inferior mesenteric artery where the aorta is exposed by incising the overlying peritoneal tissue with electrocautery. Once the aorta is well exposed anteriorly and laterally on both sides it is encircled with umbilical tape, secured inferiorly by a Kelly clamp and superiorly by another umbilical tape, loosely snared using a Rommel tourniquet; these will be used during aortic cannulation. Particular attention should be given to avoid avulsing any lumbar branches while encircling the aorta, as this can result in problematic bleeding. Furthermore, when a severely atherosclerotic aorta is encountered, it is often easier to encircle both common iliacs and prepare to ligate one side and cannulate via the other to avoid manipulating a severely atherosclerotic aorta altogether.

The hepatic left lateral segment is then mobilized and retracted to the right. This facilitates exposure of the gastrohepatic ligament. The clear area of pars flaccida is incised and the gastrohepatic ligament is examined for the presence of a replaced or accessory left hepatic artery arising from the left gastric artery. In 15% to 23% of cases, the replaced or accessory left hepatic artery traverses the gastrohepatic ligament in a transverse manner from the left gastric artery into the umbilical fissure. When present, the gastrohepatic ligament should be incised above and below the replaced left hepatic artery avoiding excessive traction on the artery itself.

Attention is then redirected to the porta hepatis. The duodenum is retracted inferiorly to expose the length of the porta hepatis. The right lateral aspect of the porta hepatis is exposed to visualize the common bile duct as close to the duodenum as possible. The right posterior porta hepatis is palpated to check for the presence of a replaced/accessory right hepatic artery present about 10% to 17% of the time,[11,12] or an early takeoff of the right hepatic artery. The distal common bile duct is then ligated close to the duodenum and then transected. The dome of the gallbladder is incised and flushed using normal saline until the effluent from the transected common bile duct is clear. This maneuver allows for evacuation of bile from the distal biliary tree thus

minimizing bile stasis, and autolysis of biliary epithelium during cold preservation.

Next is exposure of the supraceliac aorta, which will be the site of aortic cross-clamping during retrograde aortic flushing from the infrarenal aorta. The left lateral segment is elevated and retracted laterally. The crus of the diaphragm is then visualized and incised longitudinally. The esophagus is palpated and retracted to the left. This is best facilitated with the presence of a nasogastric tube. The incised crus is then retraced to expose the underlying aorta, which should be easily palpable at this point. The preaortic fascia is sharply divided anteriorly and bilaterally to complete exposure of the aorta. A blunt, large right-angle clamp is then used to encircle the aorta with an umbilical tape. The umbilical tape is secured with a clamp and will aid in elevation and exposure of the aorta at time of cross-clamp. Note that the presence of an accessory/replaced left hepatic artery reduces the available field in which to perform this maneuver and care should be taken to avoid excessive traction on the artery during this procedure.

The final maneuver before cross clamping is cannulation of the abdominal aorta. Prior to this the anesthesiologist is asked to administer 30,000 IU of heparin intravenously. Three minutes after heparin administration the distal umbilical tape around the abdominal aorta is ligated at the aortic bifurcation. The aorta is then occluded using forceps just below the rostral umbilical tape. The aorta is incised transversely immediately above the ligated inferior umbilical tape, and a 22F reinforced cardiac catheter is inserted into the aorta. The Rommel tourniquet is snared down and tightened around the aorta, and the cannula and tourniquet are held together and tied with an umbilical tape to secure them in place (**Figure 1**).

At this point the warm component of the abdominal dissection is complete. The abdominal viscera are returned to their anatomical position in preparation for cold perfusion. The donor surgeon coordinates the timing of cross-clamp with any other recovery teams present as well as the organ procurement agency coordinator.

Once all teams are ready for cold perfusion, the left lateral segment is retracted to the right, and the umbilical tape previously placed around the supraceliac aorta is used to gently lift the aorta anteriorly for better exposure. The esophagus is retracted to the left, and a long straight or slightly curved vascular clamp is used to clamp the supraceliac aorta and cross-clamp time is noted. The inferior vena cava is immediately transected at the caval-atrial junction, evacuating the donor blood volume out of the vascular circuit into the right thorax. Pool suction is employed to maintain adequate suction in the thorax during exsanguination. The aortic cannula is quickly opened to allow cold 4C University of Wisconsin (UW) solution to retrograde perfuse the abdominal viscera. This is done while rapidly and liberally pouring sterile ice slush around and over the liver to provide quick cooling. Aortic perfusate should be flowing easily in a "straight line" and vented through the suprahepatic inferior vena cava. An infusion volume of approximately 3-4 liters of UW solution is typically necessary to obtain an adequate flush of the adult liver. During perfusion the liver is assessed for homogenous asanguinity and softness. Bimanual massage of the liver by placing one hand over the liver anteriorly and the other over the dome of the liver though the right hemithorax can be used to facilitate proper parenchymal venting (**Figure 2**).

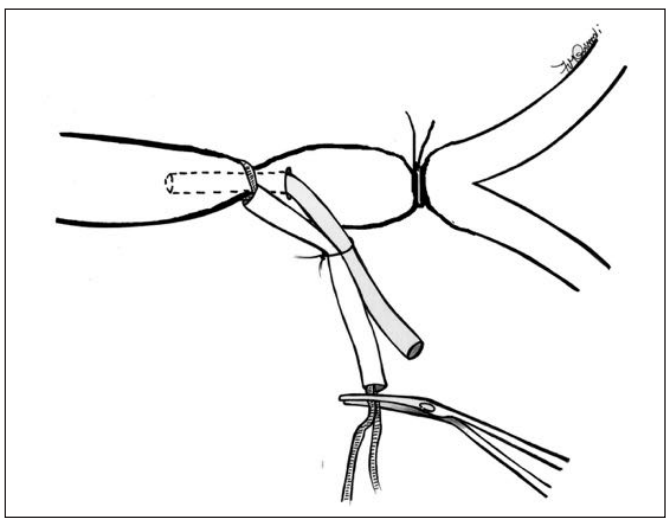


Figure 1. Schematic figure showing aorta cannulated through a transverse incision after distal ligation.

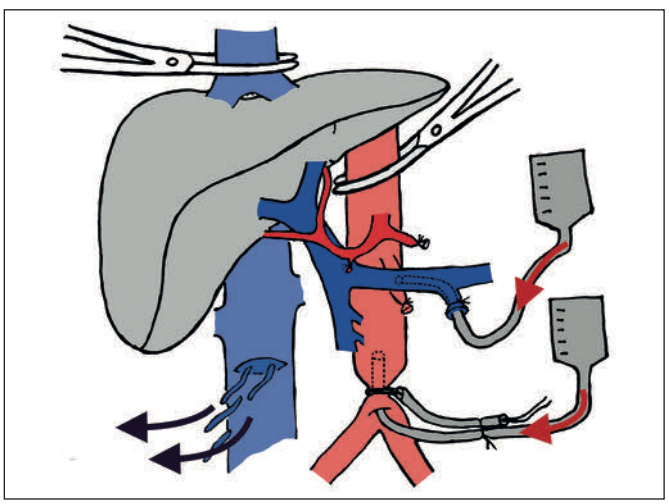


Figure 2. Schematic representation for cadaveric donor procurement. The aorta (between the iliac bifurcation and the inferior mesenteric artery) and the inferior mesenteric vein are cannulated to perfusion with cold preservative solution. The supraceliac aorta is clamped. Evacuation of the donor blood volume is allowed by section of the infrahepatic (as showed in the figure) or the suprahepatic inferior vena cava.

attention is directed to completing the cold dissection component of the donor operation. The diaphragm is divided in an anterior to posterior manner down to the aorta while retracting the esophagus laterally. The right hemidiaphragm is then taken down in a medial to posterolateral fashion over the dome of the liver down to the costodiaphragmatic angle. This allows the liver to be repositioned into the right hemithorax, providing excellent exposure and traction of the porta hepatis. A pool suction tip is placed under the hilum transversely and over the aorta to facilitate exposure**.** The duodenum is retracted inferiorly. Attention is then directed to dissecting the gastroduodenal artery (GDA). Prior to ligating it, the GDA is traced to the common hepatic artery and celiac trunk. This is critical, as failure to do so may result in ligation of an aberrant common/proper hepatic artery arising directly from the aorta or superior mesenteric artery. The splenic artery is subsequently identified, ligated and divided distally from the celiac trunk (**Figure 3**) to allow some length that may be needed for any back-table reconstruction. Medial mobilization of the splenic artery allows better exposure of the celiac trunk as it courses back towards the aorta. All surrounding tissue is divided to expose the celiac trunk at its takeoff. Care must be taken to maintain the plane of dissection at the left inferolateral position to avoid injury to any aberrant left hepatic arteries arising from the left gastric artery, celiac trunk or aorta. The portal vein is identified and divided at the splenic-superior mesenteric vein confluence. In the event of concurrent pancreas procurement, the portal vein is divided at the coronary vein. The common bile duct transection is completed and all remaining posterior tissue in the porta hepatis is dissected and divided, with care being taken to avoid injury to an accessory/replaced or early takeoff right hepatic artery. This is conducted in a lateral to medial fashion down to the aorta, between the superior mesenteric artery (SMA) and celiac trunk. In the absence of a replaced/accessory right hepatic artery arising from the SMA, the aorta is incised between the celiac trunk and SMA origins and extended superiorly on both sides of the celiac to provide an aortic cuff with the celiac trunk (**Figure 3B**). The infrahepatic vena cava is exposed and divided above the takeoff of the right and left renal veins. The tissue between the right kidney and the liver is divided with the plane of transaction going through the adrenal gland. The liver is then elevated and remaining connective tissue and muscle is divided and the liver removed from the abdominal cavity. The biliary system is flushed on the back-table and the liver is placed in UW solution and triple packed and placed in ice for cold storage and transport.

NON-HEART-BEATING DONOR OPERATION

Non-heart-beating donor procurements proceed by sharp dissection. The skin is opened with a knife from the xiphoid to the pubis, with the dissection continued sharply into the peritoneal cavity. The Balfour retractor is positioned and a Cattell-Braasch maneuver performed with Metzenbaum scissors to expose the infrarenal aorta. The abdominal aorta is rapidly cannulated, and cold UW flush is initiated. The suprahepatic inferior vena cava is then transected below the right atrium, the pericardium is opened, and the thoracic aorta is cross-clamped in the left side of the chest. The white line of Toldt is opened along the descending colon to expose the left kidney, and ice is liberally applied around the abdominal organs. The inferior mesenteric vein is identified at the ligament of Treitz and cannulated for portal perfusion. All further dissection is done cold after completion of cold perfusion, as mentioned earlier.

BACK-TABLE PREPARATION

The preparation of the liver on the back-table, typically done at the recipient hospital, is integral in rendering the liver suitable for implantation. First the remnant diaphragm is completely excised, exposing the bare area of the liver and the wall of the suprahepatic inferior vena cava. The phrenic vein orifices are exposed and ligated. The retrohepatic and infrahepatic vena cava is dissected free of attached retroperitoneal tissue. The orifice of the right adrenal vein is

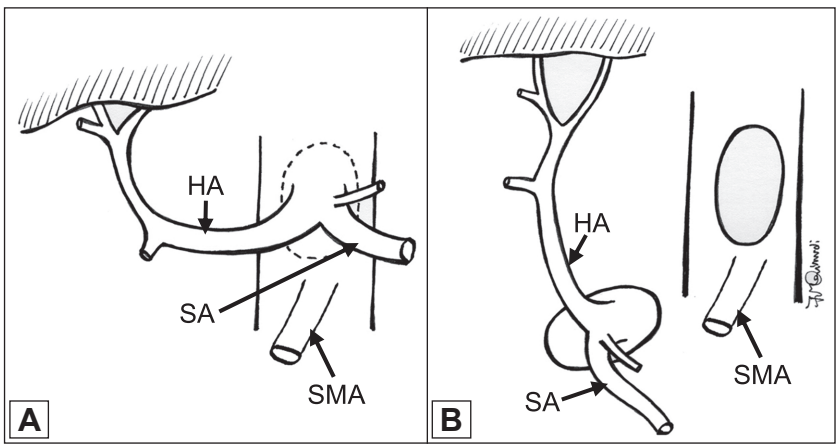


Figure 3. Schematic representation of arterial removal on liver deceased donor. **A**) The gastroduodenal, gastric, and splenic artery are divided. **B**) The celiac trunk is exposed and removed with a aortic patch (Carrel patch). The back-table arterial dissection extends from the aortic cuff to the gastroduodenal artery. GDA: gastroduodenal artery; SA: splenic artery; SMA: superior mesenteric artery; AH: common hepatic artery.

also identified and ligated. The portal vein is then skeletonized down to the bifurcation. All small branches are ligated. The portal vein is then cannulated to allow flushing of the allograft during implantation. The dissection of the artery is then prepared by initially dissecting the vessel free of surrounding adventitial tissue. This is done in a proximal to distal manner from the celiac trunk takeoff from the aortic patch to the GDA takeoff. All branches proximal to the GDA are traced to ascertain that they terminate outside the liver prior to ligation. The proper hepatic artery is not dissected above the GDA takeoff to avoid injury to any branches to the extrahepatic bile duct (**Figure 4**). A suitable cuff is then prepared for the arterial anastomosis. In the case of a replaced/accessory left hepatic artery arising from the left gastric artery, the vessel is dissected free of surrounding tissue with attention being given to ligate the plethora of small branches arising from the left gastric artery. When there is more than a single origin of arterial inflow to the liver, as in the case of a replaced left hepatic artery arising from the celiac trunk or a replaced/accessory right hepatic artery arising from the superior mesenteric artery, reconstruction is performed to establish a single source of inflow to the liver.

RECIPIENT OPERATION

The process of liver replacement has undergone a considerable amount of evolution since its inception. This has been a consequence of improvements in every aspect of the operation including advances in anesthesia and hemodynamic monitoring, resuscitation techniques, and coagulation control.[9] The development of electrocautery markedly assisted in bleeding control and refined the dissection technique.

Modern mechanical retractors have greatly facilitated operative exposure throughout the duration of operations, thereby alleviating the assistant fatigue factor during these long operations. This is better appreciated when one considers that most patients in the past required a right thoracotomy to facilitate access to the suprahepatic vena cava, a procedure that is almost never employed today.

The primary technique for liver replacement developed and used by Starzl and colleagues, now considered the "classic" technique, uses vena cava interposition as opposed to the piggyback technique that retains the native retrohepatic vena cava. Venous outflow reconstruction using the piggyback technique is done between the suprahepatic end of the donor IVC and a common orifice created from the recipient hepatic veins (**Figure 4**). It is critical to insure that the donor hepatic veins are not incorporated into the anastomosis as this can cause outflow obstruction.[9] The infrahepatic cava of the donor liver is ligated. Most notably the piggyback technique is useful in cases with a significant donor-recipient cava size mismatch, wherein the donor cava is much smaller the recipient cava thereby potentially presenting a scenario of postoperative caval stenosis.[9] It is also the preferred technique to use in re-transplant cases, where significant inflammation makes it almost prohibitive to dissect out the native cava.[9]

PORTO-SYSTEMIC VENO-VENOUS BYPASS

Initial attempts using a passive form of bypass from the IVC to the superior vena cava resulted in most cases suffering fatal pulmonary emboli due to clotting in the bypass cannulae.[1,13] In an effort to avert these complications, a partial cardiopulmonary bypass with a pump oxygenator was introduced by Calne et al.[14]

Although this technique provided better hemodynamic stability, the need for systemic heparinization resulted in profound bleeding. In 1983, Griffith et al. introduced a veno-venous bypass (VVB) circuit using a centrifugal pump and heparin-coated cannulae,[13,15] abrogating the need for systemic heparinization. The development of VVB was a significant advance, in that it allowed for: i) better hemodynamic stability during systemic and splanchnic venous clamping, especially in critically ill patients that might otherwise be unable to tolerate the anhepatic phase and the physiological insult of reperfusion; ii) minimization of operative stress to the kidneys by reducing renal congestion during caval clamping; iii) better protection of fulminant liver failure patients with cerebral edema by decreasing the fluid load required to get the patient through the anhepatic phase [16–18]; iv) prevention of splanchnic congestion thereby decreasing intestinal edema, which is useful in patients with a small abdominal domain where intestinal edema will compromise exposure in the operative field; and v) alleviation of portal congestion, which markedly reduces blood loss in cases with severe portal hypertension or history of transjugular intrahepatic

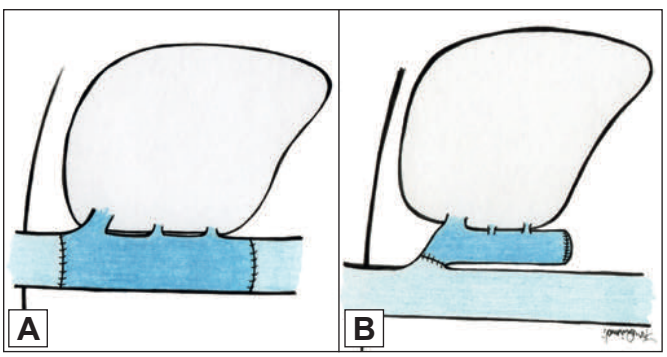


Figure 4. Outflow reconstruction with deceased liver donor. **A**) Classic technique, with native inferior vena cava replaced by graft inferior vena cava. Two caval anastomoses are performed. **B**) Piggyback technique, with native inferior vena cava preserved and a suprahepatic caval anastomosis performed. Note that the donor infrahepatic cava is oversewn.

portosystemic shunt (TIPS). The complication rate of VVB ranges from 10% to 30%.[19] Common complications include infection, hematoma, lymphocoele, deep vein thrombosis, and nerve injuries, particularly at the axillary cannulation site.[19–21] The percutaneous placement of the VVB femoral and axillary cannulae was introduced in 1994.[22] This approach shortens operative time, and is associated with a lower complication rate compared to the open technique.[13,23]

THE CLASSIC TECHNIQUE

The procedure begins with exploration of the abdomen using a bilateral subcostal incision with midline cephalad extension (**Figure 5**). The ligament of Treitz is identified, ligated, and divided. Subxiphoid fatty tissue is then excised and the liver is exposed. Care must be taken while extending the left portion of the incision to avoid injury to the spleen, as most patients have marked splenomegaly at time of surgery. A mechanical retractor is placed for access to the upper abdomen and the perihepatic space. The hepatectomy is begun by taking down the falciform ligament and exposing the hepatic veins anteriorly. The left triangular ligament is taken down with electrocautery but may have some significant collaterals that require ligation. The left lateral segment is retracted anteriorly and to the right, and the left coronary ligament is divided to the level of the left hepatic vein. The gastrohepatic ligament is either divided with electrocautery or doubly ligated and divided depending on the extent of collateral presence within it. The presence of an accessory left hepatic artery also requires ligation within the gastrohepatic ligament. This exposes the caudate lobe and the porta hepatis. Attention is then directed towards dissection of the porta hepatis. The liver is retracted in a cephalad fashion. There is usually a considerable degree of portal hypertension with variceal collaterals traversing along the length of the porta hepatis. These must be ligated in continuity to minimize unnecessary bleeding. The proper hepatic artery is exposed and traced back to the common hepatic artery proximal to the GDA and controlled with an inflow-occluding clamp. This minimizes the likelihood of arterial dissection during the remainder of the case. The GDA is subsequently divided as well as the right, middle, and left hepatic arteries. The cystic duct is then dissected and doubly ligated and divided. The common bile duct is then isolated in the porta hepatis, encircled with a silk tie, doubly ligated, and divided. The bile duct is dissected back towards the duodenum, thus exposing the portal vein and a retroportal right hepatic artery if present. The hepatic artery is dissected back to the level of the inflow occluding clamp, and all the neurolymphatic tissue in this area is divided to complete skeletonization of the hepatic artery. The portal vein is then dissected, and all fibrolymphatic tissue from around the portal vein is dissected free, doubly ligated, and divided from both the right and left sides. This exposes excellent length of the portal vein from the bifurcation to the duodenum.

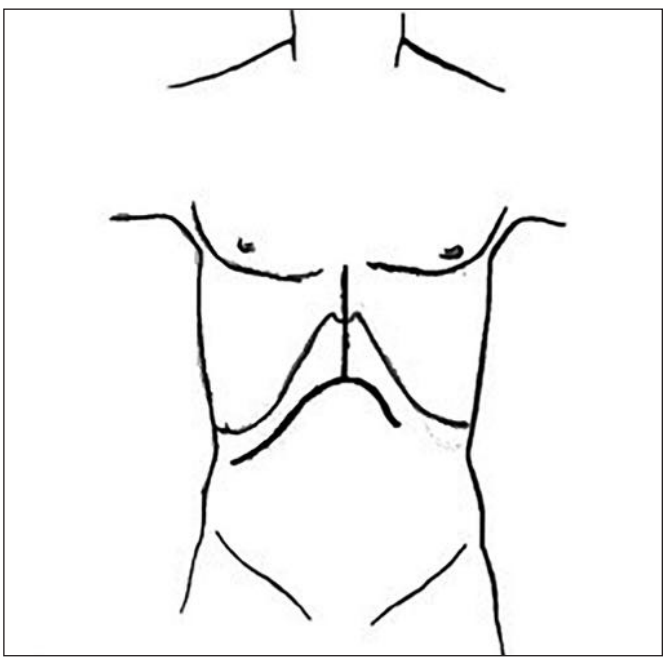


Figure 5. Bilateral subcostal incision with midline extension.

The hepatectomy is continued by skeletonizing the infrahepatic inferior vena cava, and the left-sided vena cava is mobilized from its retroperitoneal position using electrocautery. Attention is then turned towards mobilization of the right lobe of the liver. The right triangular ligament is taken down using electrocautery, and the entirety of the right lobe is mobilized. The coronary ligament is mobilized from the diaphragmatic attachments. The suprahepatic and retrohepatic vena cava are then dissected free from the surrounding tissues on the right side. The right adrenal gland is identified, and the right adrenal vein is doubly ligated and divided. A retroperitoneal window is made posterior to the retrohepatic cava, and therefore complete vascular control of the infrahepatic and suprahepatic vena cava is gained. The retroperitoneal defect along the right side is then repaired using running Prolene® sutures.

If veno-venous bypass is indicated, surgical cut-down to the sapheno-femoral junction in the groin and the axillary vein is performed. Alternatively, percutaneous access to the femoral and internal jugular veins can be obtained prior to abdominal incision.

In order to cannulate the portal vein for bypass, it is ligated as high as possible and encircled with umbilical tape close to the pancreas (**Figure 6A**). A transverse anterior venotomy is made at the distal end of the ligated portal vein while the assistant occludes it proximally. The surgeon's right hand is used to control the portal vein while the cannula is introduced with their left hand (**Figure 6B**). The surgeon holds the cannula in place as the assistant snares down the umbilical tape (**Figures 6B** and **6C**). Transection of the

portal vein is then completed and VVB is initiated (**Figure 7**).

Dense adhesions or injury to the portal vein may be prohibitive to its cannulation for bypass. In those instances, cannulation of the inferior mesenteric vein is preferred.

If VVB is not used, the portal vein is then occluded using a Blalock-Taussig clamp proximally and a tonsil clamp distally. It is sharply divided using Metzenbaum scissors. The infrahepatic vena cava is then occluded using a large Blalock-Taussig clamp, and a large Satinsky clamp is applied to the suprahepatic vena cava. The liver is then sharply excised and removed (**Figures 8** and **9**).

During the hepatectomy, the donor liver is prepared on the back-table as previously described. At the completion of the recipient hepatectomy, the hepatic allograft is then removed from ice, and oriented appropriately. The first anastomosis of implantation is an end-to-end anastomosis of the suprahepatic vena cava using 3-0 Prolene® sutures (**Figure 10**). The second anastomosis is with the infrahepatic vena cava using 4-0 Prolene® sutures (**Figure 11**). Sutures of the infrahepatic vena caval anastomosis are left untied for appropriate flushing maneuvers. During the infrahepatic vena caval anastomosis, 700-900 mL of lactated Ringer solution plus 25 g of albumin is flushed through the portal venous cannula to remove the UW solution. The portal vein anastomosis is then accomplished in an end-to-end manner using running 6-0 Prolene® sutures. These sutures are also

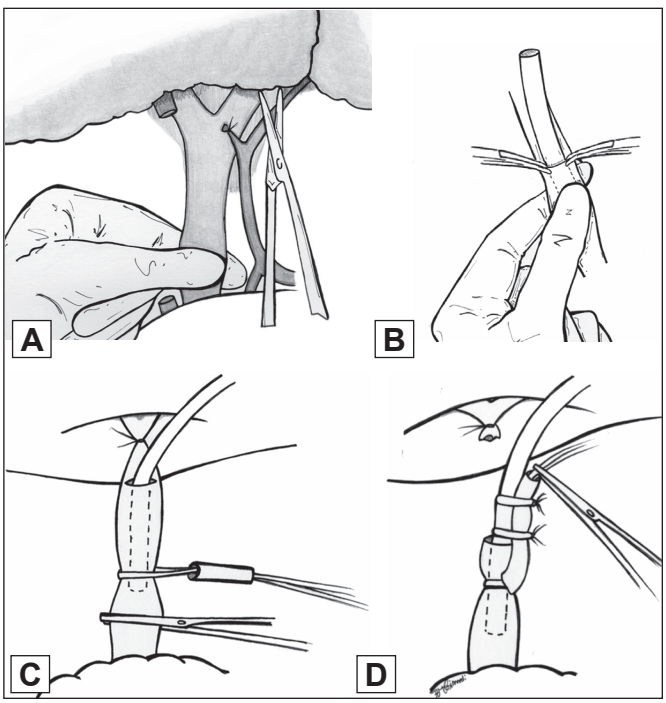


Figure 6. Cannulation of the portal vein for bypass. **A**) Portal vein is dis- sected and ligated close to liver. **B**) Portal vein is cannulated through a transverse venotomy. **C**) The cannula is hold in place by an um- bilical tape encircling the vein. **D**) After cannulated the portal vein is sectioned.

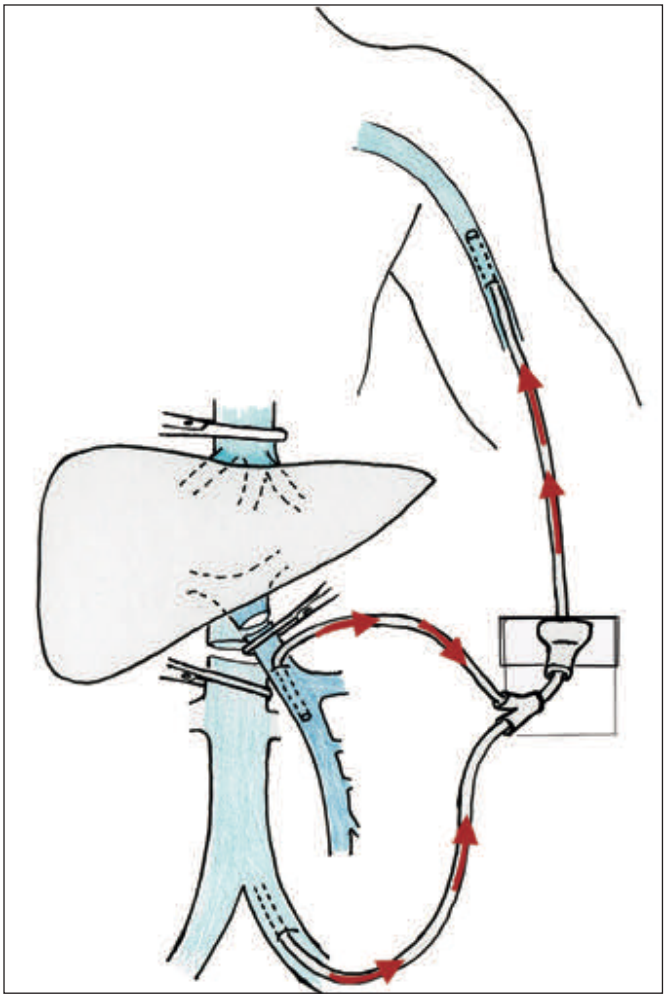


Figure 7. Veno-venous bypass with cannulation of the axillary vein, the left saphenous vein, and the portal vein.

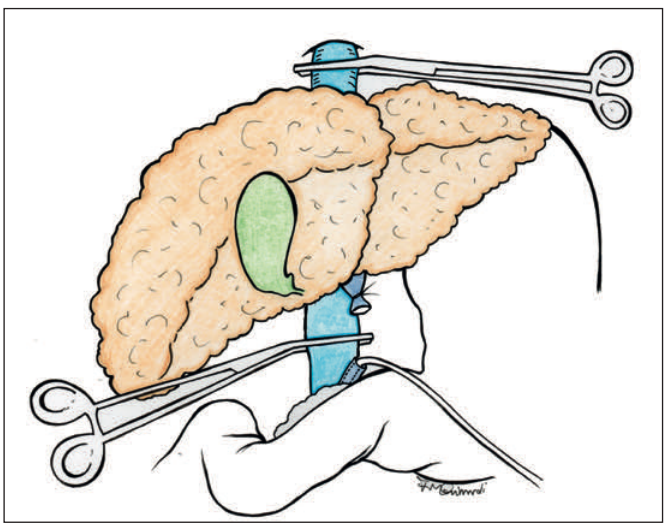


Figure 8. Vascular clamps are place on the infrahepatic vena cava and suprahepatic vena cava; note the portal vein clamped and divided with the bypass cannula in place. (Adapted from Busuttil and Klintmalm.[9])

left untied. The portal vein is then appropriately flushed, and 6-0 Prolene® sutures are then secured to complete the anastomosis (**Figure 12**).

Preventing stenosis of the portal anastomosis is critical in order to avoid portal thrombosis and hypertension.[24] Starzl et al. proposed incorporating a "growth factor", allowing the portal anastomosis to distend to its maximal diameter on reperfusion.[25] This is accomplished by not totally securing the running 6-0 Prolene® sutures, but leaving an "air knot" about half the diameter of the vein.

Portal vein thrombosis. Portal vein thrombosis (PVT) at one point was considered an absolute contraindication for LT.[13] However, with the introduction of formal thromboendovenectomies (**Figure 13**), it became possible to excise the portal vein thrombus with a success rate of 95%.[26–28] When the portal vein is unusable, a "jump-graft" with a donor iliac vein is used between the recipient superior mesenteric vein and the donor PV.[13,29]

In case of extensive thrombosis of the portal system, salvage re-vascularization techniques were introduced. Porto-caval hemitransposition was described by Tzakis et al.,[30] wherein the donor PV is anastamosed to the recipient IVC.[30,31] Arterialization of the portal vein has also been used as a salvage method to establish portal inflow. In this technique, a donor iliac conduit is used to provide portal inflow directly from the aorta.[32] Finally, multivisceral organ transplantation is also an option in such cases with massive portal/mesenteric vein thrombosis.

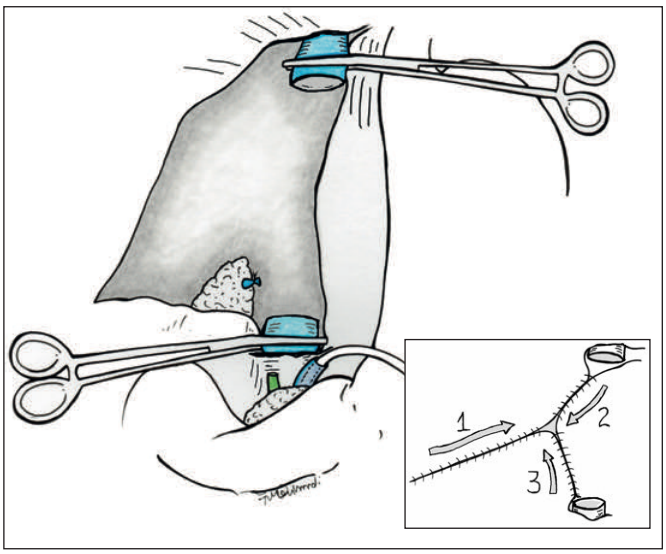


Figure 9. The liver has been excised showing the retrohepatic area with the inset showing the reperitonealized bare area. (Adapted from Busuttil and Klintmalm.[9])

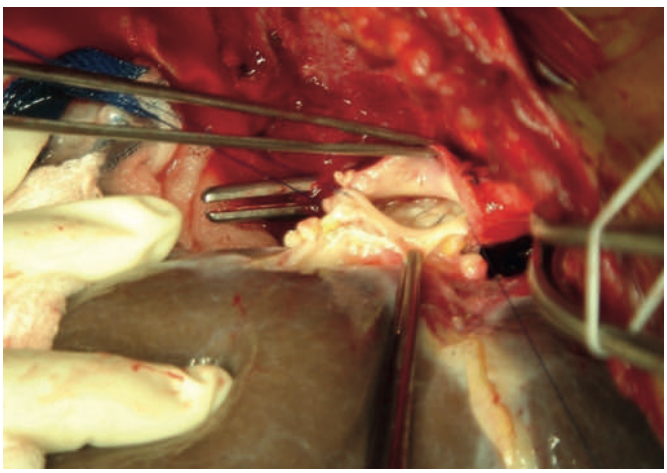


Figure 10. The liver has been excised showing the retrohepatic area with the inset showing the re-peritonealized bare area. (Adapted from Busuttil and Klintmalm [9])

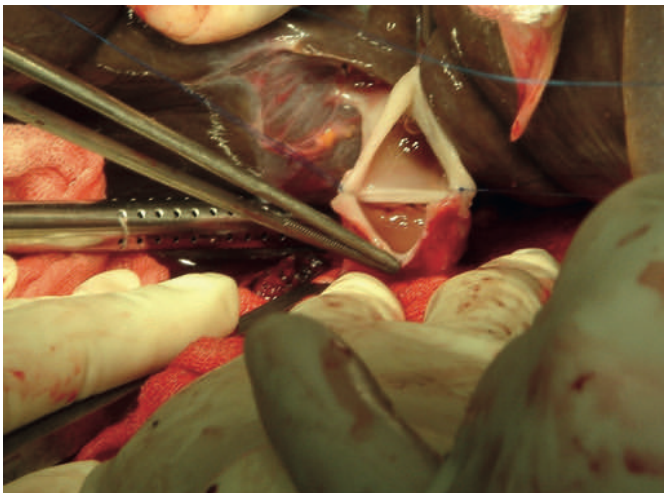


Figure 11. Surgical aspect of infrahepatic vena caval anastomosis in the classic technique.

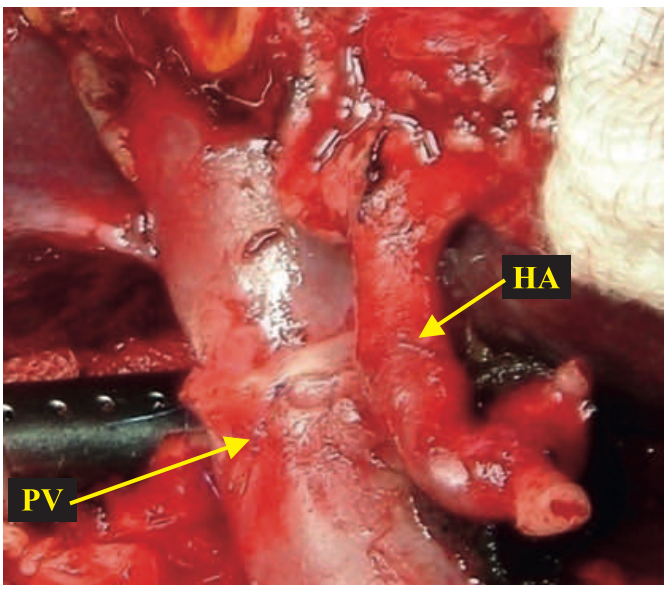


Figure 12. Surgical aspect after completed portal vein and hepatic arterial anastomoses.

After completion of the portal vein anastomosis, appropriate flushing maneuvers are implemented. The portal vein is allowed to vent through the infrahepatic vena caval anastomosis for approximately 15 seconds, and the infrahepatic vena cava is flushed through its anastomosis to confirm absence of any thrombi in the vena cava. The vena cava is then flushed using heparinized saline solution. The sutures of the infrahepatic anastomosis are then tied down to complete the anastomosis. The suprahepatic Satinsky clamp is then removed, followed by the clamp of the infrahepatic vena cava. The Blalock-Taussig clamp is then removed from the portal vein to reperfuse the allograft.

The liver is warmed with warm irrigation solution. Hemostatic surveys are conducted.

Attention is then turned towards arterialization of the liver. The donor artery is oriented appropriately and black vascular clips are applied to the main hepatic branch. The donor artery is then trimmed to appropriate length in preparation for anastomosis. In standard cases, the celiac trunk of the donor artery is anastomosed to the recipient common hepatic artery or a branch patch of the bifurcation between the gastroduodenal and hepatic artery proper in an end-to-end fashion. This is done using 7-0 Prolene® sutures. The sutures are left untied for appropriate arterial flushing maneuvers. The hepatic artery is flushed with heparinized saline solution, and the sutures are tied down to complete the anastomosis with care being taken to allow for a growth factor to prevent anastomotic stricture. The black clip is then removed from the donor artery and the straight vascular clamp is released, thus restoring arterial flow to the liver (**Figure 14**).

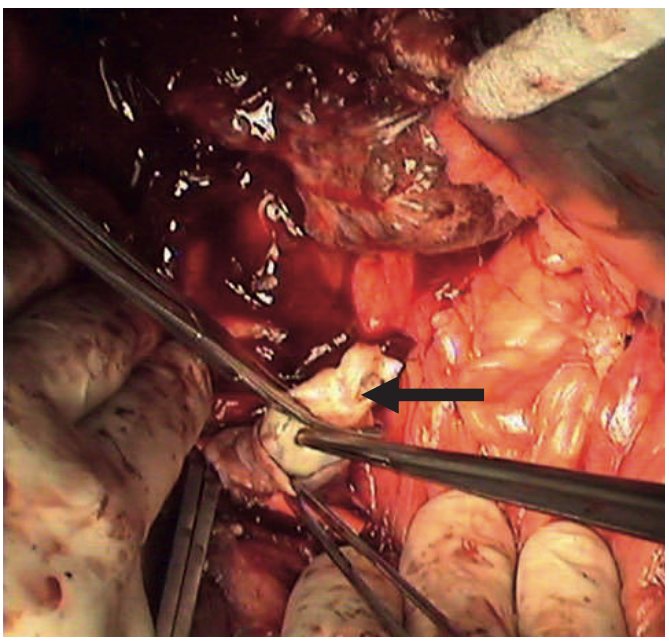


Figure 13. Recipient portal vein thromboendovenectomy. Thrombus (arrow) is being removed.

It is essential to ensure excellent arterial flow at the conclusion of the anastomosis. This may be compromised due to compression of the celiac axis by the arcuate ligament. This can be noted if there is decreased flow with respiratory variation. The presence of median arcuate ligament syndrome necessitates lysis of the median arcuate ligament to improve arterial inflow. Flow should improve and become independent of respiratory variation with successful lysis of the median arcuate ligament. In cases of slightly diminished arterial inflow, ligation of the recipient splenic artery could serve to augment inflow to the common hepatic artery.

In patients with no suitable inflow from the hepatic artery, a conduit is created using donor iliac artery. The infrarenal aorta is exposed above the takeoff of the inferior mesenteric artery. In rare cases the supraceliac aorta is used for inflow via an iliac artery graft. A partially occluding clamp is used on the aorta and an end to side anastomosis is made between the iliac conduit and the aorta. The iliac conduit is the clamped above the anastomosis and the aortic clamp is released. The iliac conduit is then tunneled through the transverse mesocolon anterior to the pancreas and anastamosed in an end-to-end fashion to the donor celiac artery. It is important to note that arterial reconstruction can vary significantly depending on donor anatomy and specific circumstances of the recipient. But the type of reconstruction chosen must allow for excellent arterial inflow to the liver

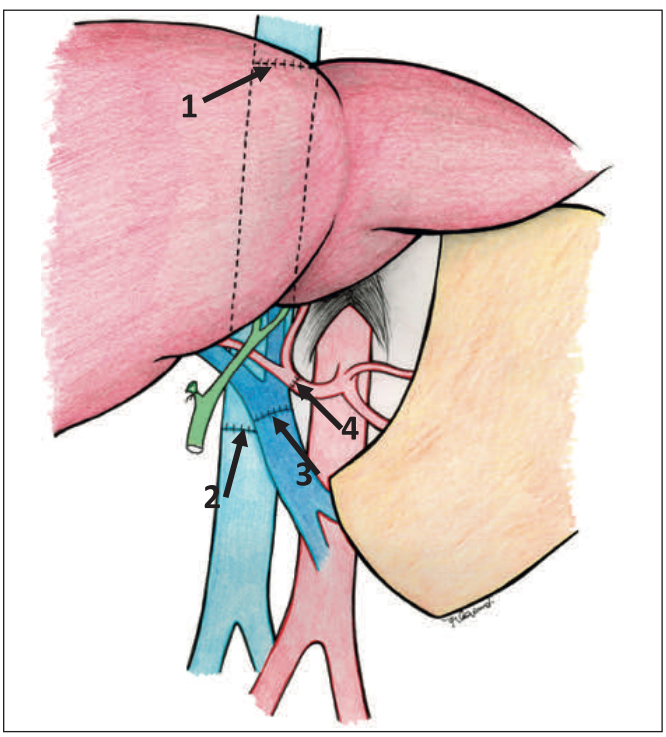


Figure 14. Schematic representation after completed vascular anastomoses using the classic technique: Suprahepatic anastomosis (**1**), infrahepatic anastomosis (**2**), portal vein anastomosis (**3**), and arterial anastomosis (**4**).

to minimize the risk of postoperative arterial and biliary complications.

Biliary tract reconstruction is the last step in the implantation. A retrograde donor allograft cholecystectomy is performed and the donor cystic duct is completely excised. Periductal vascular tissue is then ligated using interrupted 6-0 Prolene® sutures and the donor bile duct is trimmed back to achieve a viable duct. The recipient common bile duct is identified and trimmed to an appropriate length. Periductal vascular tissue is then ligated using 6-0 Prolene® sutures. The recipient duct is then flushed using heparinized saline and solution and is probed using coronary dilators. There should be no resistance to passage into the duodenum. A choledochocholedochostomy is then constructed using interrupted 5-0 PDS® or 5-0 Prolene® sutures. In the case of extended criteria donors, donation after cardiac death donors, or ductoplasty, a T-tube is employed through the anastomosis exiting via the recipient duct. In cases where the recipient duct is unsuitable or too short, as is often the case in re-transplants, a Roux-en-Y choledochojejunostomy is constructed to restore bilio-enteric continuity (**Figure 15**).

TECHNICAL COMPLICATIONS

ARTERIAL COMPLICATIONS

Arterial complications are a significant source of morbidity and mortality in OLT. Most notably, hepatic artery thrombosis (HAT) and hepatic artery stenosis (HAS) are implicated in ischemic biliary complications as well as graft failure. These pathological processes, in addition to hepatic artery pseudoaneurysm and hepatic artery rupture, are a significant impediment to graft and patient survival.

Hepatic artery thrombosis (HAT)

HAT is reported to complicate 2.8% to 15% of OLTs, [33–37] with an incidence in adults between 1.6% and 4%.[38–40] HAT is more prevalent after pediatric liver transplantation, with a reported incidence of 12% to 30%.[41,42] A 50% mortality has been noted in patients with HAT, highlighting its clinical impact .(35) Although this has improved slightly over time, with HAT-related mortality decreasing to 35% in adults and 40% in pediatric recipients, HAT represents one of the major contributors to post-OLT morbidity and mortality.

Risk factors for HAT have been closely examined, with the most significant technical factors being complex hepatic artery reconstruction, aortohepatic interposition graft, history of pre-OLT chemoembolization, and pediatric transplantation (**Table 2**). Medical factors include hypercoagulable state, ABO incompatibility, and previous HAT (**Table 3**).

Clinical manifestations of HAT include elevated transaminases in 75%, biliary complications in 15%, fever and sepsis in 6%, and graft dysfunction or failure in 4% of patients.[38] Treatment options used for HAT include operative revision and thrombectomy, anticoagulation, primary re-transplantation, and catheter-based anticoagulation therapy. These have had varying degrees of success.[38] The most important factor, however, continues to be the need for prompt suspicion and recognition of HAT and initiating treatment as soon as possible to minimize its deleterious clinical sequelae.

Table 2. Multivariate analysis of factors affecting hepatic arterial thrombosis. (Adapted from Duffy et al.[33])

Factor	Odds ratio	P value
Pediatric transplant	4.66	0.001
Aortohepatic graft	2.99	0.001
Transarterial chemoembolization	2.34	0.02
Complex reconstruction	1.99	0.04

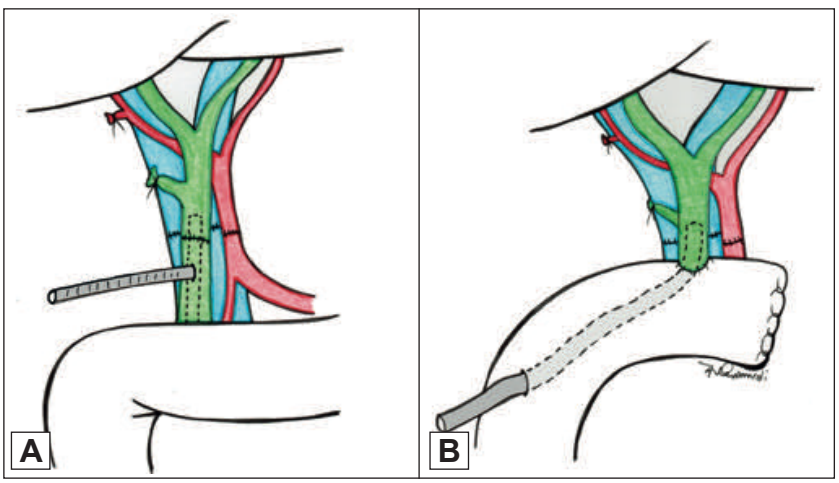


Figure 15. Biliary reconstruction. **A**) Choledochocholedochostomy with T tube in place. **B**) Choledochojejunostomy with internal stent.

Hepatic artery stenosis (HAS)

An anastomotic or non-anastomotic narrowing resulting in increased resistance to arterial blood flow constitutes a stenotic arterial lesion. It is difficult, however, to determine the precise incidence of HAS, since not all cases of HAS are clinically symptomatic. Predisposing factors include technical anastomotic narrowing, rejection, and prolonged cold ischemia time.[43] Significant stenoses require prompt therapy in order to avoid progression of the stenotic segment to a complete occlusion with surgical revision or balloon dilatation.

Hepatic artery pseudoaneurysm / Hepatic artery rupture

Although quite rare, this complication carries a risk of fatal hemorrhage. Most likely causes of this process are either traumatic or infectious etiology.[44] Although there are reports of endovascular treatments for hepatic artery pseudoaneurysms, surgical intervention remains the best method to address both the underlying cause and the arterial complication. Ligation of the hepatic artery can provide an immediate temporizing measure as a bridge to re-transplantation if arterial reconstruction is not feasible.[9]

BILIARY COMPLICATIONS

With the inception of OLT, biliary anastomosis came to be considered the "Achilles heel" of this operation. Biliary and biliary-related complications are the most common source of morbidity and mortality after OLT.[13,45] The reported incidence of biliary complications varies from 6.8-38%.[37,46–49] In early cases of OLT in humans, a loop cholecystojejunostomy with ligation of the donor common bile duct was used.[10,13] The idea of using the gallbladder in restoring bilioenteric continuity expanded to many different types of bilio-digestive anastomoses, such as a Roux-en-Y cholecystojejunostomy and cholecystoduodenostomy.[50–52] The high rate of biliary complications related to leakage, cholangitis, and obstruction of the cystic duct led to the abandonment of these techniques. Initial attempts with choledochocholedochostomy (CDC) were associated with a high incidence of bile leak due to ischemia of the common bile duct.[13] At the time, the role of common bile duct vascularization was yet to be appreciated. A landmark report by Terblanche et al. in 1983 outlined the importance of the vascularization of the common bile duct and its relevance to the biliary anastomosis, thereby substantially improving outcomes of CDC.[53,54]

Currently, the two main techniques of biliary tract reconstruction are CDC and Roux-en-Y hepatico-/choledochojejunostomy. As mentioned earlier, the choice of technique depends mainly on the recipient's common bile duct status. A recent study by Welling et al. in 2008 showed that stenting, use of HTK preservation solution, and prolonged warm ischemia time were all significant variables contributing to the incidence of biliary complications (**Table 4**).[55]

The range and scope of biliary complications also depends on the type of graft used (cadaveric heart-beating, non-heart-beating, split, or living donor) as well as the type of anastomosis used. Duailibi et al.[56] examined several series comparing LDLT and DDLT showing that there is a significantly increased incidence of both bile leaks and bile strictures with LDLT (**Table 5**).[56–61] The majority of biliary complications occur within the first three months of OLT causing significant morbidity and mortality (**Figure 16**).[9,62]

Bile leaks

Occurring in 10-25% of OLTs,[63] their incidence is highest in the first three months postoperatively. The source of the leak can be a result of: i) technical imperfection either at the anastomosis or in sealing the T-tube exit site, if a T-tube is used; and ii) ischemia of the duct, which usually occurs at the anastomosis. It can also originate from a cystic duct stump, or the cut surface of the liver in the case of a split,

Table 3. Factors affecting hepatic artery thrombosis. (Adapted from Busuttil and Klintmalm[9])

Technical	Medical
HA<3mm	Previous HA thrombosis
Recipient<10Kg	Polycythemia/acquired or inherited hypercoagulable state
HA anastomosis other than common HA/branch patch technique	ABO incompatibility
Multiple anastomotic attempts	Multiple ACR episodes
Anomalous HA anatomy (donor recipient) with reconstruction	CMV infection
HA angulation	Hypotension/vasopressor requirement
Intimal flap	Increased CIT
Aggressive HA clamping	Intra-abdominal infection
	Primary nonfunction

HA: hepatic artery; ACR: acute cellular rejection; CMV: cytomegalovirus; CIT: cold ischemia time.

Table 4. Risk factor analysis for anastomotic bile leak. (Adapted from Welling et al.[55])

	No Leak	Bile Leak	P value
Recipient age (years), mean (±SD)	40.8 (11)	50.4 (20)	0.003
Recipient gender (male versus female, %)	62.8	65.1	0.081
MELD, mean (±SD)	22.3 (6)	24.6 (7)	0.021
Donor age (years), mean (±SD)	32 (18)	41.8 (16)	0.003
Donor gender (male versus female, %)	59.2	57.5	0.663
Donor Cr, mean (±SD)	1 (0.8)	1.2 (1.5)	0.365
Preservation (HTK versus UW, %)	56.5	48.9	0.349
Warm ischemia (minutes), mean (±SD)	41.9 (16)	49.1 (23)	0.024
Cold ischemia (minutes), mean (±SD)	522 (154)	488 (98)	0.182
Total ischemia (minutes), mean (±SD)	564 (154)	537 (100)	0.298

SD: standar deviation; MELD: model for end-stage liver disease; Cr; creatinine; HTK: histidine tryptophan ketoglutarate; UW: University of Wisconsin.

living donor, or reduced size graft. In rare cases, diffuse biliary necrosis due to hepatic artery thrombosis or ABO incompatibility can result in sepsis.[9] Those patients will require retransplantation. Late bile leaks are often the result of T-tube removal or accidental dislodgement. Most bile leaks can be diagnosed via T-tube cholangiogram if a T-tube is in place. MRCP/ERCP are of utility in diagnosing a bile leak and potentially treating it in the case of ERCP.[64–67] T-tube insertion site leaks are usually managed conservatively with the T-tube open to drainage, and will seal in a few days[68] if they are small and the patient is asymptomatic. If they persist or the patient develops symptoms, then surgical intervention is indicated. Leaks at the anastomotic site will usually seal spontaneously if small and localized, or they can be amenable to endoscopic stenting. Anastomosis with significant leakage or disruption requires surgical intervention.[69] Leaks at the cut surface of a partial graft can be managed conservatively as long as they are well drained.

Biliary strictures

Strictures can be divided into anastomotic strictures (AS) and non-anastomotic strictures (NAS). AS related to technical error tend to occur earlier than other types of biliary strictures. The majority of strictures, however, occur later in the patient's postoperative course.[70,71]

The incidence of biliary strictures has been reported to range from 5–15% after deceased donor liver transplantation, and 28–32% after LDLT.[70,72]

Table 5. Biliary complications in living versus deceased donor liver transplantation. (Adapted from Duailibi et al.[56])

Author	Year	Country	Transplant modality	n	Biliary complications (%)			P value
					Leaks	Strictures	Overall	
Oliveros et al.[61] *	2005	Spain	LDLT	27	14.8	11.1	25.9	0.021
			DDLT	27	-	-	3	
Maluf et al.[59]	2005	USA	LDLT	69	14.7	10.7	26.1	<0.05
			DDLT	202	4.3	5.3	11.4	
Bourdeaux et al.[60] *	2007	Belgium	LDLT	100	-	-	29	0.451
			DDLT	135	-	-	23	
Tarantino et al.[58]	2008	Italy	LDLT	68	26.4	39.7	64.7	-
			DDLT	193	4.6	31	37.3	
			Average LDLT		18.6	20.5	36.4	
			Average DDLT		4.5	18.2	18.7	

* Pediatric liver transplantation. LDLT: living donor liver transplantation; DDLT: deceased donor liver transplantation.

AS are thought to be a consequence of surgical technique, local ischemic changes, and scarring,[73] and are limited to the anastomotic segment of the bile duct. These strictures are thought to occur with higher frequency with bilioenteric anastomosis compared to choledochocholedochostomy.[9]

Strictures of choledochocholedochostomies should be first approached with ERCP and stenting as the first line of treatment.[74–76] This method is quite successful in up to 70% of cases.[77] Patients that have failed endoscopic stenting require surgical revision with a Roux en-Y choledochojejunostomy.[63,73]

Strictures of choledochojejunostomies may initially be managed with percutaneous transhepatic cholangiography (PTC) and stenting. Failure of PTC requires surgical revision. NAS are usually multiple, longer in length, intrahepatic, or in the extrahepatic donor duct.[70]

NAS can be further classified into macroangiopathic, microangiopathic, and immunogenic causes (**Table 6**). NAS related to ischemic causes usually present within the first year of OLT while immunological NAS usually present later than one year post-transplantation.[78,79] Up to 50% of patients with biliary strictures are found to have hepatic artery thrombosis.[9,63,74] It is therefore critical in the workup of these patients to ascertain the status of hepatic artery patency.

Endoscopic balloon dilation and stenting remain the first line of therapy in NAS, as in AS. The success rate in NAS LDLT is quite poor, with a 25–33% success rate.[80,81] This is primarily due to the complex biliary reconstruction and smaller bile ducts in LDLT.[81] NAS that fail endoscopic treatment can result in lobar atrophy, biliary cirrhosis, and recurrent cholangitis. Up to 50% of patients with NAS will require re-transplantation due to graft loss.[72,82]

The shortage of available organs has resulted in increased use of donation after cardiac death (DCD) donors. Unlike heart beating donor liver transplantation where NAS is usually attributed to ischemic preservation injury or hepatic artery thrombosis/stenosis, NAS in DCD recipients reflects ischemic injury that occurs before organ retrieval in the absence of hepatic artery thrombosis or stenosis.[83] This leads to an ischemic cholangiopathy throughout the liver resulting in biliary abscesses and recurrent cholangitis episodes ultimately requiring retransplantation.

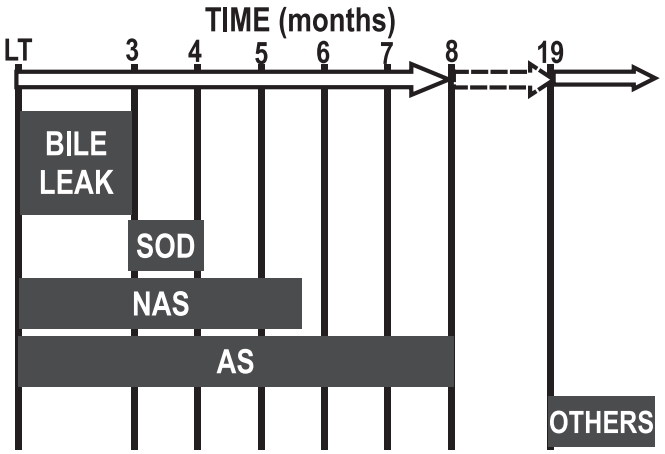


Figure 16. Timeline of biliary complications after orthotopic liver transplantation. SOD: sphincter of Oddi dysfunction; NAS: non-anastomotic stricture; AS: anastomotic stricture; Other: biliary stones, sludge, casts. (Adapted from Ayoub et al.[70])

LIVING DONOR LIVER TRANSPLANTATION

It is important to emphasize that prior to considering healthy individuals as potential donors, other avenues to increase the pool of available organs must be utilized. Hence, the splitting of suitable adult deceased donor grafts was developed.[84] In addition, the reduction of adult grafts has been employed to compensate for the paucity of size-matched pediatric donors. This has, however, deprived adult patients on the waiting list of organs. The shortage of organs thus continues to present a significant problem. To further ameliorate the organ shortage situation for pediatric patients particularly, the option of living-related donation was carefully considered. The first successful LDLT was performed by Strong et al.[85] in 1990, wherein a child's mother donated her left lateral segment to her young child. This ushered in a significant advance, especially in countries in which deceased donors are unavailable due to shortage of donation or cultural beliefs. This is particularly evident in several countries in Asia and the Middle East.[86,87]

ETHICAL CONSIDERATIONS

Living donor liver transplantation (LDLT) is an entirely altruistic endeavor, wrought with a myriad of complex and

Table 6. Stricture Classification of non-anastomotic strictures. (Adapted from Ayoub et al.[70])

Macroangiopathic	Microangiopathic	Immunogenic
Hepatic artery thrombosis	Prolonged cold and warm ischemia times	Chronic rejection
	Donation after cardiac death	ABO incompatibility
	Prolonged use of vasopressors in the donor	Primary sclerosing cholangitis
		Autoimmune hepatitis

controversial ethical issues. The prevalence of LDLT varies globally and is greatly influenced by the particular region's availability of deceased donors. As the concept of brain death is not clearly delineated in some Asian countries, LDLT was readily accepted and incorporated as a practical and valid way to ethically meet patients' needs.[88] Conversely, if deceased donor transplantation is widely accepted and available, it follows that the need for LDLT may not be as pronounced. The ability to present recipients with the possibility of exploring both deceased donor and living donor transplantation is optimal from the viewpoint of the patient and the patient's family, enabling life-saving efforts to be explored to the fullest extent.

The best-case scenario for pediatric LDLT occurs when donor-recipient compatibility is maximized and ethical conflict is minimized. Generally, this role is filled by one of the parents. However, even in these situations, care must be taken to present alternative options to LDLT to the family, in addition to having a thorough discussion of the risks and benefits of LDLT. Family members considering becoming living donors should be counseled regarding the emotional and potential medical complications that may occur as a result of LDLT. It is critical to ensure that living donors act out of a true desire to help the patient, rather than as a result of external pressures or other factors. Additional care should be taken with sibling donor candidates or parents under 18 years of age. In these rare cases, where they may not comprehend the long-term consequences of their decision to donate, their competence to understand the donor process as well as their emotional response should be carefully evaluated. Any donor candidate should undergo extensive evaluation independent of the recipient or other family members to determine suitability for the LDLT process. The informed consent proceedings should include discussion of donor risk as well as the possibility of donor mortality.[89] Thus it is important to make donors aware of all possible risks. The prospect of LDLT may be distressing and induce a number of conflicting emotions. Keeping the patient well informed and providing a thorough explanation of what is to be expected post-transplantation is instrumental in reducing their level of anxiety.

INDICATIONS

Essentially, the indications for LDLT are very similar to those for deceased donor liver transplantation. One significant difference with LDLT is the donated organ is directed to a specific recipient, bypassing the issue of waiting on the transplant list.

TECHNICAL CONSIDERATIONS

The most important technical variables involved in donor recipient matching are size, anatomy, and quality of the graft. If the graft size is too small, it may not be sufficient to support the recipient's metabolic needs, resulting in small-for-size syndrome. Thus, we use the ratio of graft weight to recipient body weight: graft weight (g) / recipient body weight (g) x 100 (%).[90] If this ratio is within 0.8% to 3%, the graft size is acceptable. Conversely, if the graft to recipient body weight ratio is greater than 5%, this may result in poor graft perfusion and function. If the only donor available will yield a left lateral segment that is too large for the recipient (usually a small pediatric recipient), then the graft may need to be further reduced to a monosegment (segment 3) for a better size match.[9]

The highly variable nature of liver anatomy makes it absolutely essential to delineate the hepatic anatomy before any attempted living donor operation. Common variations include an accessory or replaced left hepatic artery originating from the left gastric artery or an accessory or replaced right hepatic artery arising from the superior mesenteric artery. Other common variations in arterial anatomy are illustrated in **Figure 17**. Potential donors with a single artery arising from

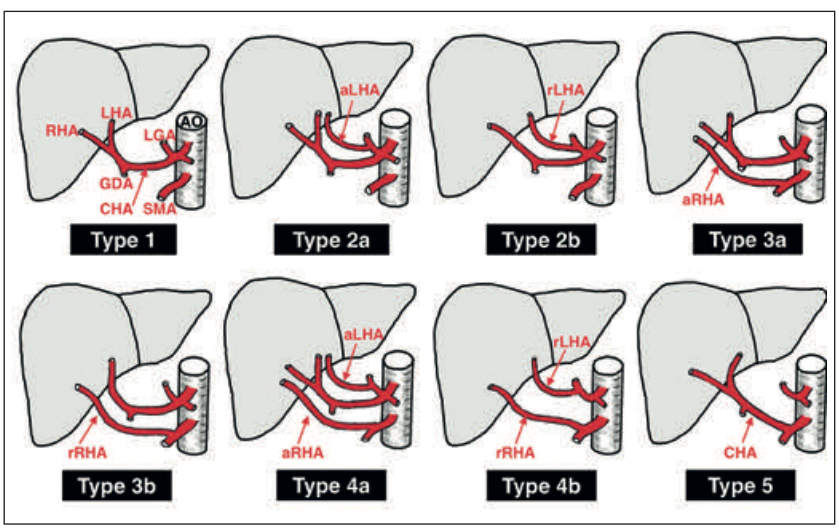


Figure 17. Hepatic artery anatomy variations, **Type 1** – standard presentation; **Type 2** – an accessory or replaced left hepatic artery from left gastric artery; **Type 3** – an accessory or replaced right hepatic artery from superior mesenteric artery (SMA); **Type 4** – both right and left hepatic arteries arising from the superior mesenteric and left gastric arteries, respectively; **Type 5** - common hepatic artery from SMA. **Type 6** (not shown) – common hepatic artery originating directly from the aorta. RHA: right hepatic artery; LHA: left hepatic artery; LGA: left gastric artery; GDA: gastroduodenal artery; CHA: common hepatic artery; SMA: superior mesenteric artery; aLHA: accessory left hepatic artery; rLHA: replaced left hepatic artery; aRHA: accessory right hepatic artery; rRHA: replaced right hepatic artery. (Adapted from Hiatt et al.[11])

the left gastric artery to the whole liver have very complex division patterns and tend to have concomitant portal venous and biliary variations that increase the risk and complexity of the surgery and may contraindicate living donation.

Determining the degree of hepatic steatosis is important when determining donor liver quality. Current imaging modalities allow for determining hepatic steatosis in potential donors.

Living donor hepatectomy

The donor operation for a right or left LDLT is similar to the right or left hemihepatectomy described in earlier sections of this text. There are, however, some critical variations. The health and safety of the donor are the utmost priority. Extreme accuracy and surgical diligence by an expert surgical team are paramount to preventing morbidity and mortality to the donor.

Hepatic mobilization begins by taking down the falciform ligament and exposing the suprahepatic vena cava. The triangular space between the right and middle hepatic veins and the anterior surface of the liver is exposed in right lobe cases. The space between the left and middle hepatic veins is developed in left hepatic cases. Structures on the remnant side should not be dissected leaving tissue planes undisturbed.[9]

Intraoperative ultrasound can aid in tracing the hepatic veins and delineating the line of transection.[91]

Cholecystectomy and cannulation of the cystic duct are performed next. Intraoperative cholangiography allows visualization of biliary anatomy, and appreciation of the donor's precise biliary anatomy.

The decision to include the middle hepatic vein (MHV) with the graft or leave it as part of the donor remnant liver has been quite controversial. This is not as significant an issue in cases of left hemiliver donation where the MHV is almost always included with the graft. In this case, the right posterior sectoral branch is able to compensate for the lack of right anterior sectoral drainage in the donor.[92]

In cases of right hemiliver donation, the exclusion of the MHV from the right liver graft can have a detrimental effect on recipient outcomes, especially in cases where the recipient has significant preexisting portal hypertension. Post-implantation venous congestion in segments 5/8 leading to impaired graft function and regeneration has also been observed.[92–94] In fact, collateralization to the right hepatic vein branches requires up to one week post-implantation, thus leaving the graft quite compromised in the immediate postoperative period. Donor safety and long-term outcomes do not appear to be affected by the inclusion of the MHV with the donated right lobe.[95,96] Reconstruction of segment 5 and 8 hepatic veins using vein conduits are also utilized in cases where the MHV is retained in the donor.

Donor right hepatectomy. Exposure of the right lateral aspect of the retrohepatic vena cava is accomplished by mobilization of the liver from its right lateral attachments allowing the right lobe to be rotated anteriorly and to the left. The left lateral segment and gastrohepatic ligament are retained intact to keep the remnant left side well anchored and prevent torsion. The inferior right hepatic veins and the posterior caval ligament are ligated and divided. This allows better exposure and vascular control of the right hepatic vein (**Figure 18**).

The hilum of the liver is then addressed with the goal of isolating the right hepatic artery, right portal vein and right hepatic duct. This begins by lowering the hilar plate immediately to the left of the gallbladder fossa. The right hepatic artery is identified next and dissected to the right of the common bile duct. Any segment 4 branches encountered during dissection should be preserved. The right portal vein located posterior to the right hepatic artery and to the right of the common bile duct is identified and dissected while clearly identifying the main portal vein and the confluence of the right and left portal veins. Small branches to the caudate lobe are ligated and divided with no impact on the viability of the caudate lobe.[97]

Transection of the bile duct is usually completed before parenchymal transection.

During transection, a 2 to 3 mm margin of the right hepatic duct should be left to allow for over-sewing the stump without narrowing the outflow from the remnant side. Prior to over-sewing the stump, the remnant side is probed to verify that no injury or compromise has resulted to the remnant duct.

The critical element to successful parenchymal tran-

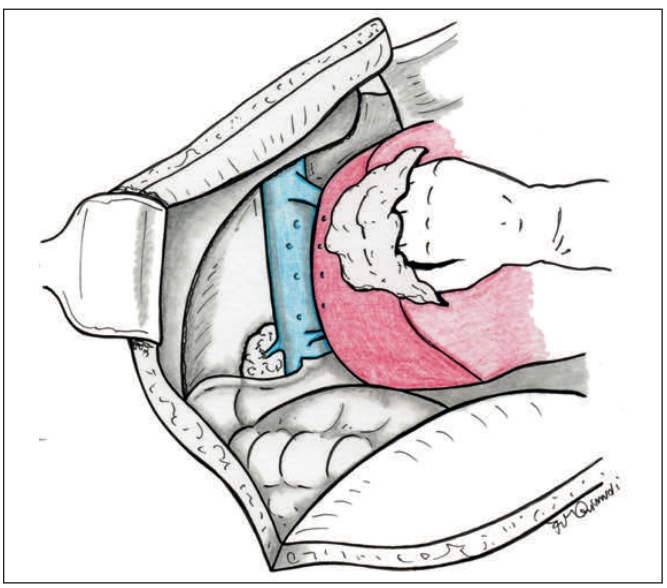


Figure 18. The right lobe is freed from its lateral attachments; direct venous branches are ligated and divided. (Adapted from Busuttil and Klintmalm [9])

section is establishing the correct transection line. A brief occlusion of the right hepatic artery and vein reveals the line of demarcation that is used for transection. Superiorly the transection line is extended just to the right of the middle hepatic vein. An umbilical tape is passed between the right and middle hepatic veins, passed between the right lobe and the vena cava and brought out inferiorly in the hilum behind the hilar plate. This maneuver greatly facilitates parenchymal transection. Transection is performed with Cavitron ultrasonic surgical aspirator (CUSA: TycoHealthcare, Mansfield, MA), or Hydrojet (Erbe, Tubingen, Germany). Small bridging vessels are coagulated, while larger ones and bile ducts are ligated and divided. At the conclusion of the parenchymal transection the right lobe is only attached by the vasculature. The right hepatic vein, artery and portal vein are divided and the right portal vein is used to flush the graft with preservation solution.

Donor left hepatectomy. Left hepatectomy (segments 2 to 4 with or without segment 1) is performed analogous to the right hemihepatectomy with vascular and parenchymal isolation of the left hemiliver.

Donor left lateral sectionectomy. The technique for living donor procurement of the left lateral sector (segments 2/3) most commonly utilized for pediatric patients involves several key points. All arterial and biliary branches to segment 4 are preserved. The parenchymal transection is carried out immediately to the right of the falciform ligament (**Figure 19**). Anomalous left hepatic artery anatomy may constitute a technical contraindication for left lateral sector procurement.

Recipient operation using a living donor graft: technical points

Uniformly, all living donor grafts are implanted using the piggyback technique. Therefore, the recipient hepatectomy in LDLT varies from the technique described earlier for standard recipient hepatectomy in that the entire retrohepatic vena cava is preserved during the hepatectomy in a piggyback fashion (**Figure 20**). Since living donor grafts are procured without the common axis of the hepatic artery and portal

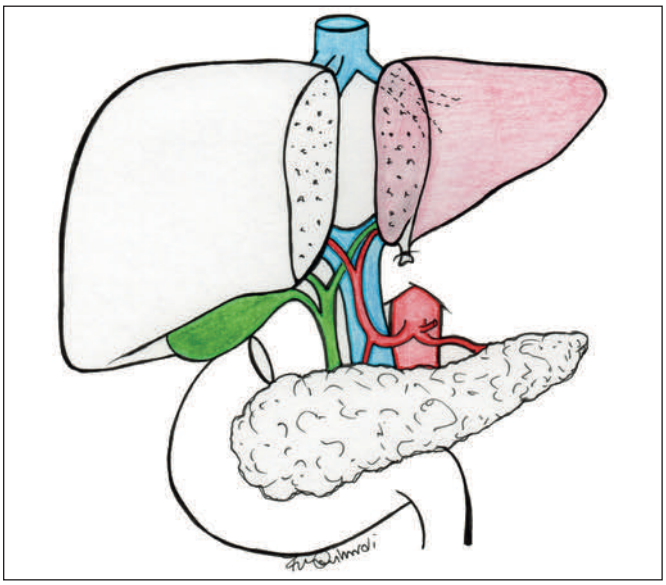


Figure 19. Living donor left lateral segmentectomy. The parenchymal transection is carried out immediately to the right of the falciform ligament.

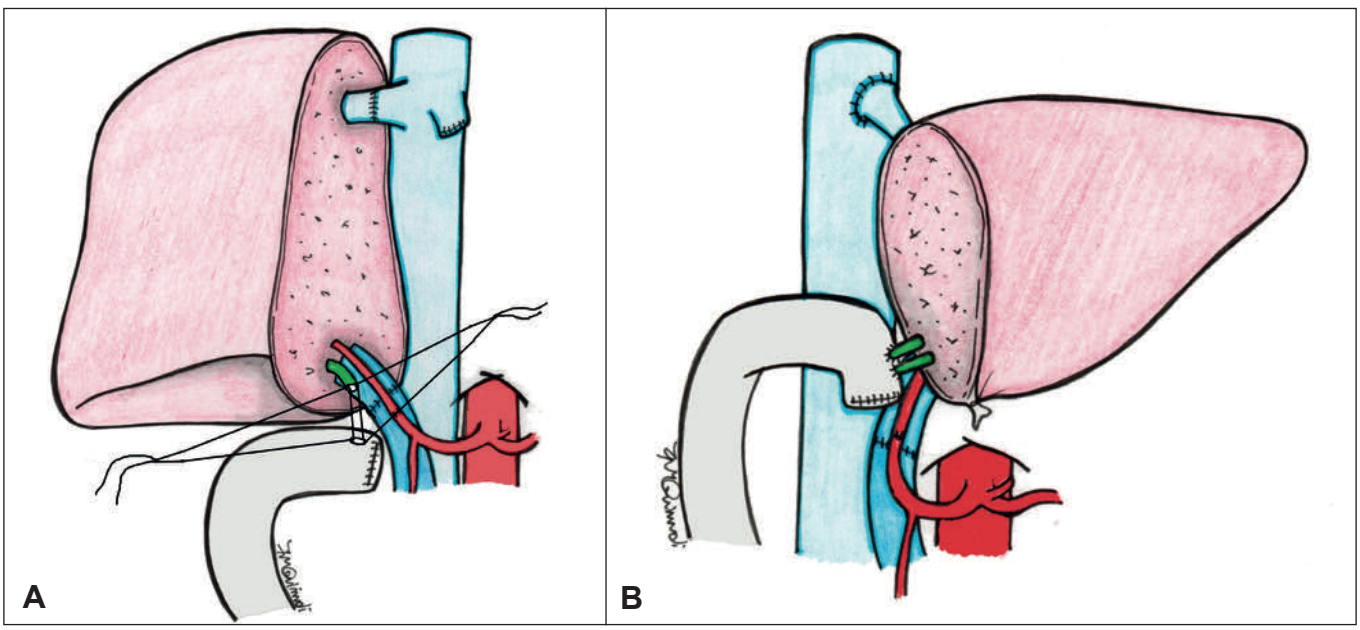


Figure 20. Implantation of a living donor graft. **A**) right living donor graft. **B**) left lateral living donor graft.

vein, it is essential to preserve as much portal vein and hepatic artery length as possible during the recipient hepatectomy.

FINAL CONSIDERATIONS

The development and evolution of liver transplantation as a life-saving modality has been a truly remarkable achievement, which speaks to the perseverance of its pioneers and the desperate need of the patients which it serves. The perfect execution of each component of the operation is essential to its success, beginning with the donor procurement and culminating with implantation. This requires the surgeon to be adept at the operation and capable of dealing with a plethora of potential intraoperative challenges. Refinements in the procedure have increased intraoperative safety and improved outcomes,[37] and allowed for selective modification of the operation based on the recipients' technical and physiological demands. Vascular and biliary complications can be quite detrimental and thus need to be evaluated and managed as effectively and swiftly as possible. The introduction of donation after cardiac death, partial grafting, and living donation have allowed for expansion of the donor pool.

SUGGESTED READING

Polak, W. G., Peeters, P. M. J. G. & Slooff, M. J. H. The evolution of surgical techniques in clinical liver transplantation. A review. *Clin. Transplant.* **23**, 546–564

This paper review the most important technical advancements in liver transplantation, responsible for become it in a safer procedure. Techniques of vascular and biliary reconstruction, evolutions as split liver, domino, and living liver donor liver transplantation are discussed here.

Duffy, J. P. *et al.* Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J. Am. Coll. Surg.* **208**, 896–903 (2009).

The incidence and impact of hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT) are analyzed in a large series of more than 4,000 patients. PVT was responsible for a reduced survival. Re-transplantation was the most effective short-term treatment for PVT. The experience with the use of early atraumatic occlusion of the common hepatic artery during recipient surgery resulted in prevention of HAT.

Bekker, J., Ploem, S. & de Jong, K. P. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am. J. Transplant.* **9**, 746–757 (2009).

This paper consist in a systematic review, including 71 studies and more than 21,000 adult and pediatric patients, concerning early hepatic artery thrombosis (eHAT). The eHAT was identified as a frequent condition (incidence of 4.4%) and it required a re-transplantation in more than half of cases. Mortality occurred in 1/3 of cases. Risk factors and management of eHAT are discussed.

Ayoub, W. S., Esquivel, C. O. & Martin, P. Biliary complications following liver transplantation. *Dig. Dis. Sci.* **55**, 1540–1546 (2010).

An essential problem after liver transplantation are the biliary complications, that include biliary strictures (anastomotic and non-anastomotic), biliary leak, and stones.This paper emphasizes the mechanisms and management of biliary complications, stressing the role of endoscopic and radiological procedures.

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