30 Liver Transplantation for Malignant and Benign Tumors

Eloísa Amate[1], Pablo Ramírez[1], Silvio Marcio Pegoraro Balzan[2], Pascual Parrilla[1]

[1] Department of Surgery, Liver Transplantation Unit, Virgen de la Arrixaca University Hospital, Murcia, SPAIN
[2] Department of Surgery, Hospital Moinhos de Vento, Porto Alegre, and Universidade de Santa Cruz do Sul (UNISC), Santa Cruz do Sul, BRAZIL.

- *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).

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

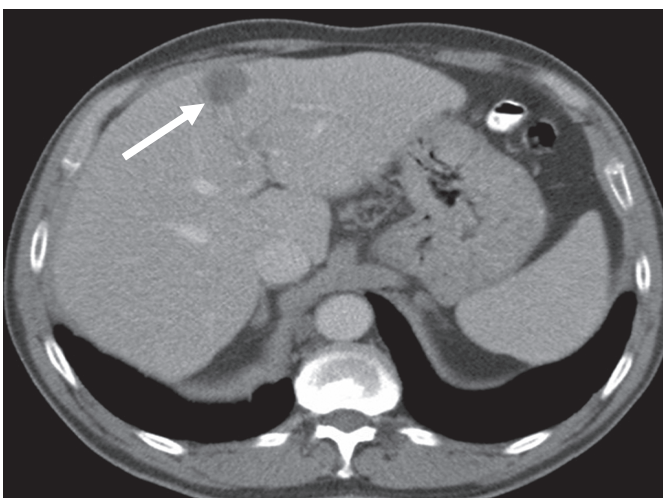

Figure 1. Small and peripheral Hepatocellular Carcinoma in a cirrhotic patient (Child-Pugh A). The most accepted treatment is liver resection.

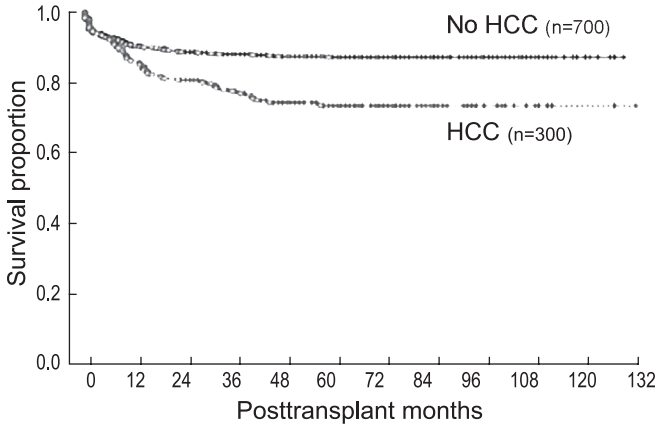

Figure 2. Overall patient survival after living donor liver transplantation for hepatocellular carcinoma and non-hepatocellular carcinoma indications. (Adapted from Hwang et al.[19])

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

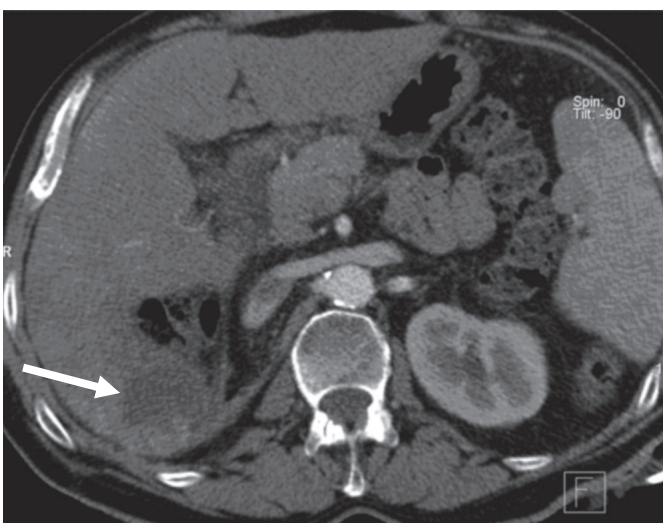

Figure 3. Cirrhotic Child-Pugh C patient with a HCC in segment 6 who underwent chemoembolization while on the waiting list for liver transplantation.

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

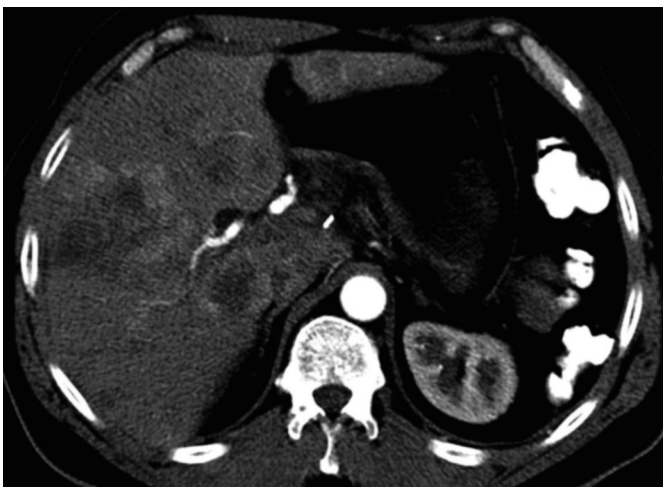

Figure 4. Multiple and bilobar metastases of a neuroendocrine tumour.

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

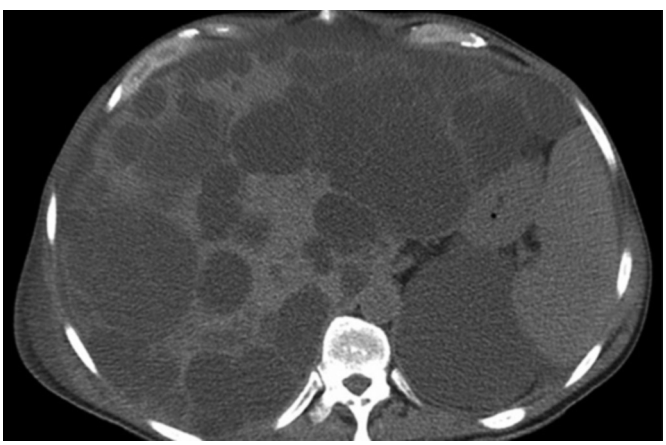

Figure 5. Patient with hepato-renal polycystosis who underwent a double kidney-liver transplantation.

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

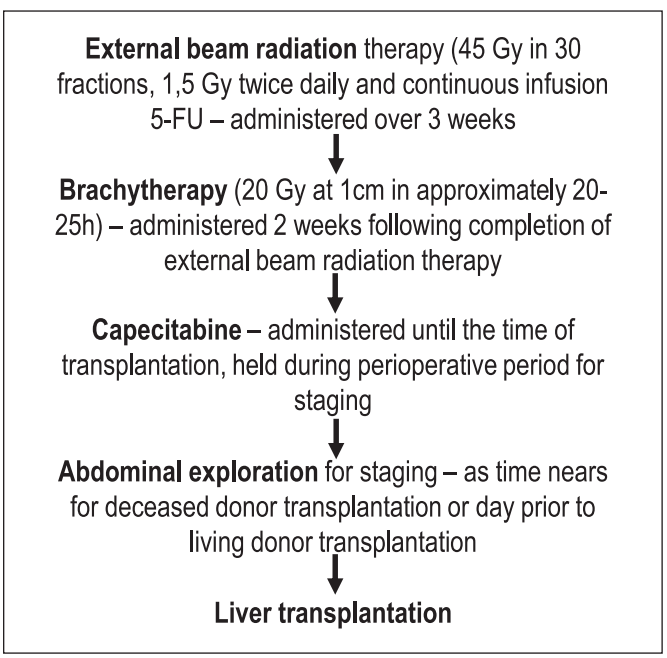

Figure 6. Mayo Clinic neoadjuvant therapy and liver transplantation protocol. (Adapted from De Vreede et al.[132])

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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