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,

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

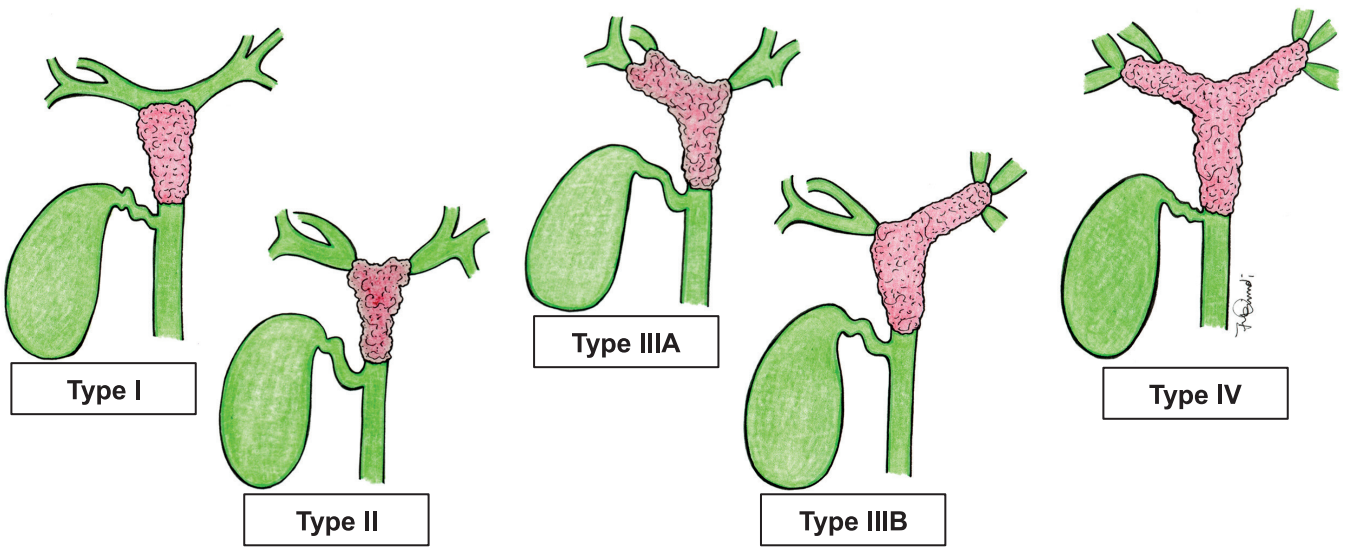

Figure 1. Schematic representation of Bismuth-Corlette classification. Type I: the biliary confluence is reached but not interrupted. Type II: interruption of the biliary confluence. Type III: obstruction of the right (a) or left (b) secondary confluence. Type IV: obstruction of both the right and the left secondary bile ducts.

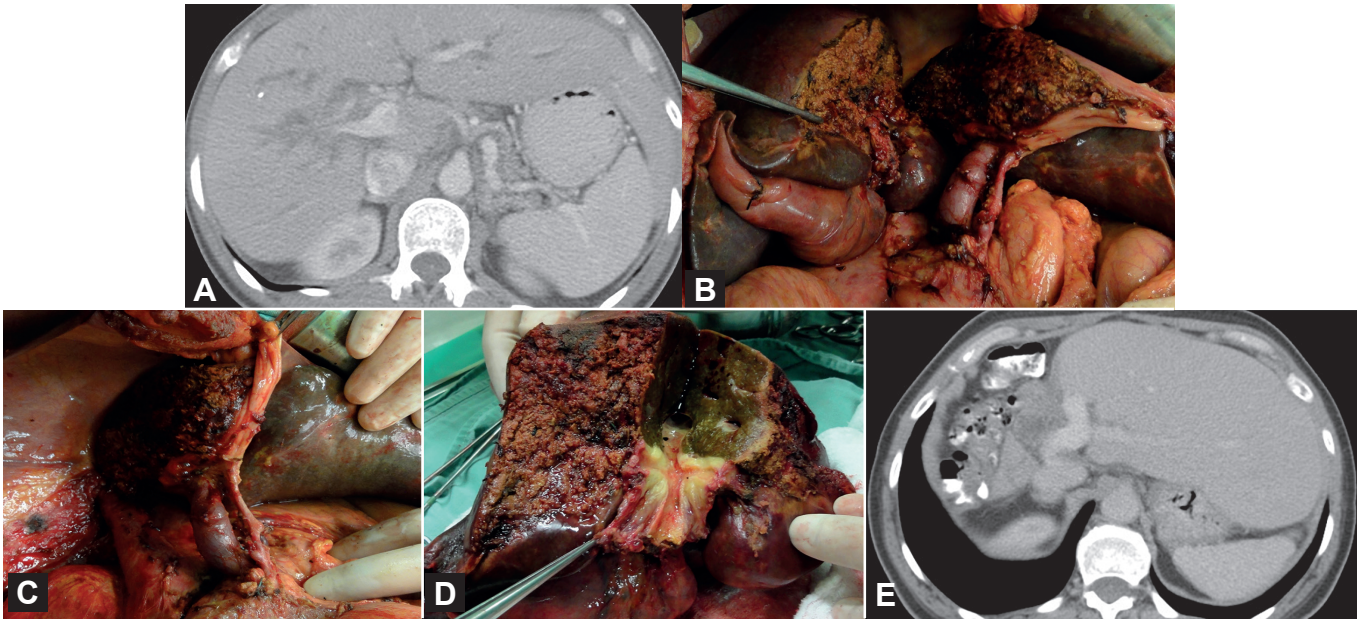

Figure 2. Illustrative case of a hilar cholangiocarcinoma Bismuth-Corlette type IIIa without vascular invasion showing a standard resection for hilar cholanciocarcinoma. **A**) Preoperative computed tomography (CT) showing a predominant extension for secondary right biliary radicles. **B**) Intraoperative 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

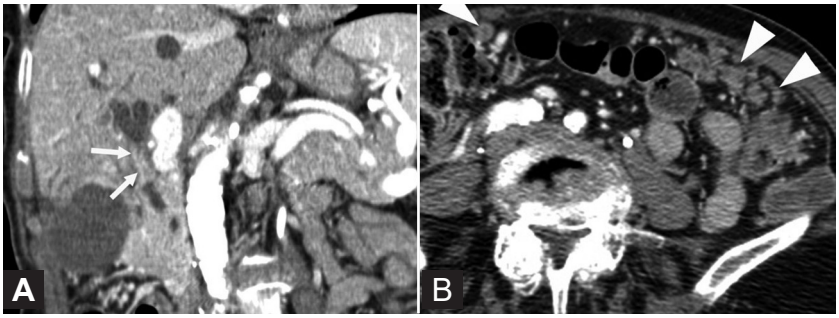

Figure 3. Hilar cholangiocarcinoma Bismuth-Corlette type I. Computed tomography (CT) on portal phase showing stenosis of the proximal bile duct. **A**) Coronal reformation showing thickening of the bile duct wall with contrast enhancement (arrows). **B**) Axial image showing nodules of carcinomatosis (arrowheads).

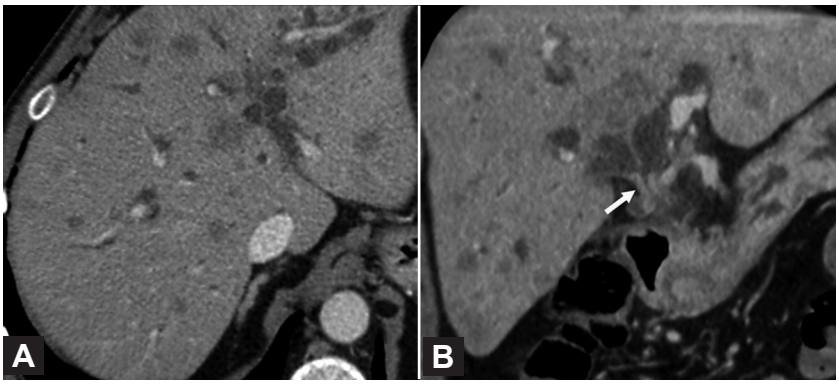

Figure 4. Hilar cholangiocarcinoma Bismuth-Corlette type II. Computed tomography (CT) on portal phase showing biliary stenosis and tumor extension to the biliary confluence (arrow). **A**) Axial image. **B**) Coronal reformation. Note the multiple hypodense hepatic lesions (metastases).

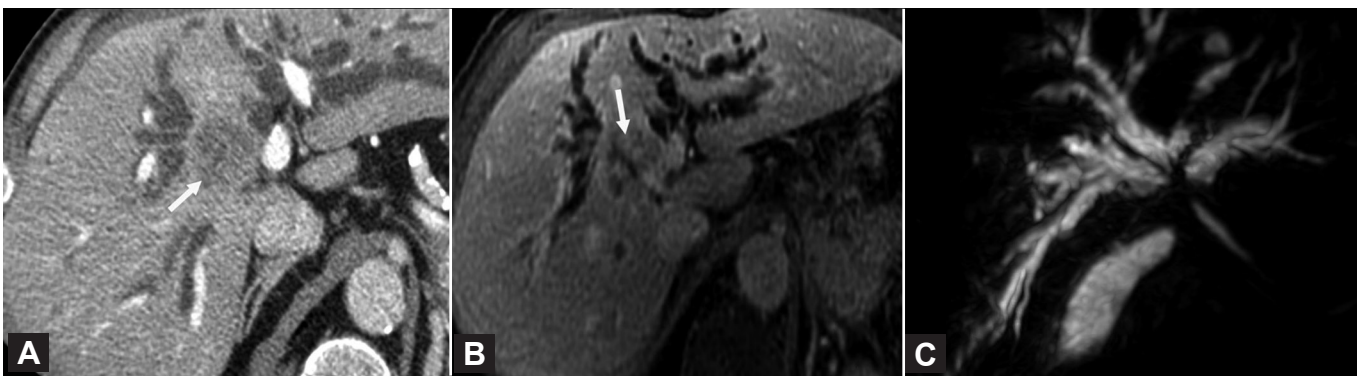

Figure 5. Hilar cholangiocarcinoma Bismuth-Corlette type IIIa. **A**) Axial computed tomography (CT) on portal phase showing a hypodense tumor extended to segment 4 and the right hepatic duct, responsible for intrahepatic bile duct dilatation. **B**) Axial T1-weighted magnetic resonance imaging (MRI) after injection of gadolium in the late phase. **C**) 3D MRI-cholangiography of the same patient.

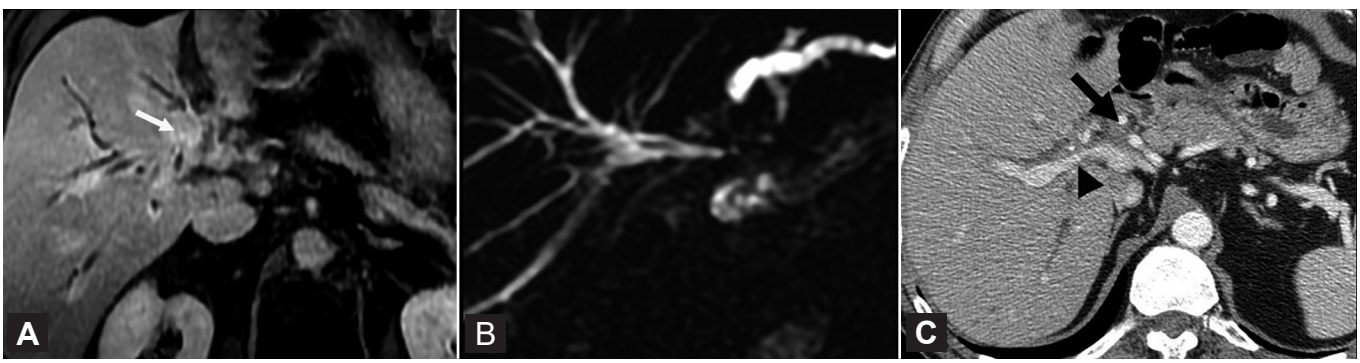

Figure 6. Hilar cholangiocarcinoma Bismuth-Corlette type IIIb. **A**) Magnetic resonance imaging (MRI) in axial T1-weighted after gadolinium in the late phase showing hilar tumor (arrow) extended to the intrahepatic left bile ducts with ipsilateral parenchyma atrophy. **B**) 3D MRI-cholangiography showing 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.

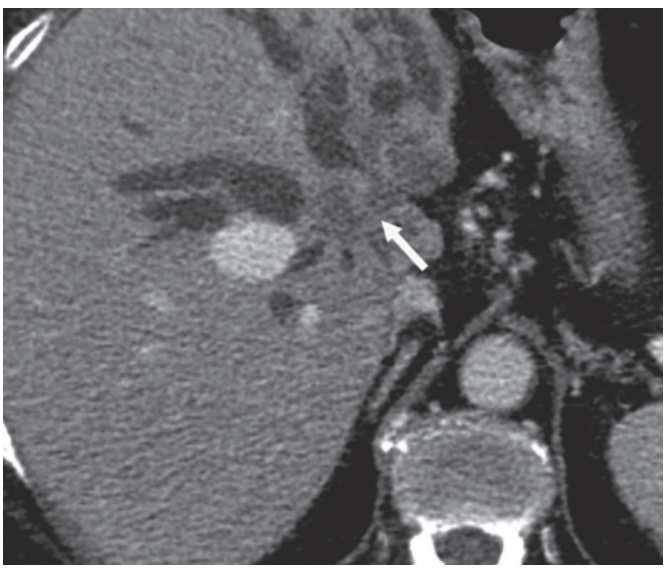

Figure 7. Hilar cholangiocarcinoma Bismuth-Corlette type IV. Axial computed tomography (CT) in portal phase projection MinIP. Hilar tumor extended to segment 4 (arrow) invading the right and the left hepatic ducts. Bilateral intrahepatic bile duct dilatation.

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,

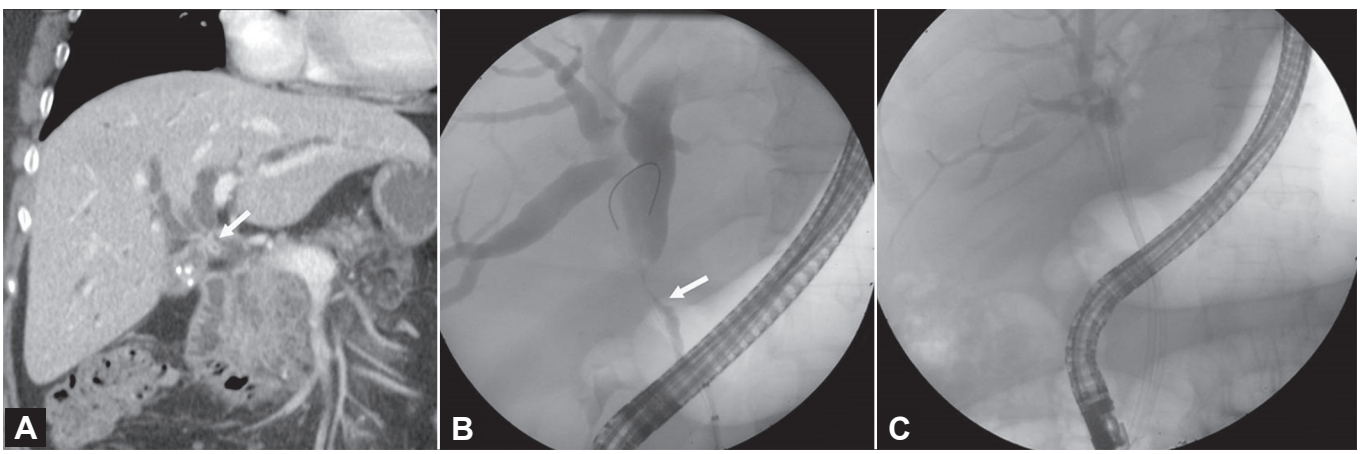

Figure 8. Endoscopic biopsy and drainage of a hilar cholangiocarcinoma Bismuth-Corlette type II. **A**) Coronal computed tomography on portal phase showing the tumor at the biliary confluence (arrow). **B**) Endoscopic retrograde cholangiography (ERC) showing a tight and irregular narrowing of the proximal 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.

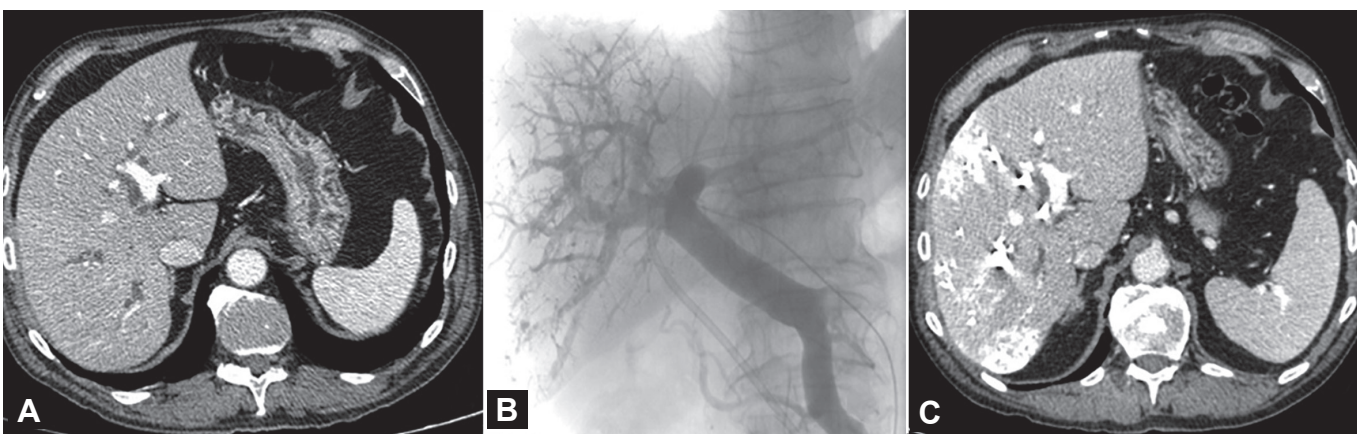

Figure 9. Preoperative right portal vein embolization (PVE). **A**) Axial computed tomography (CT) at portal phase before portal vein embolization. **B**) Portography after placement of a portal catheter. **C**) CT four weeks after right PVE showing hypertrophy of left hemiliver, however insufficient 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,

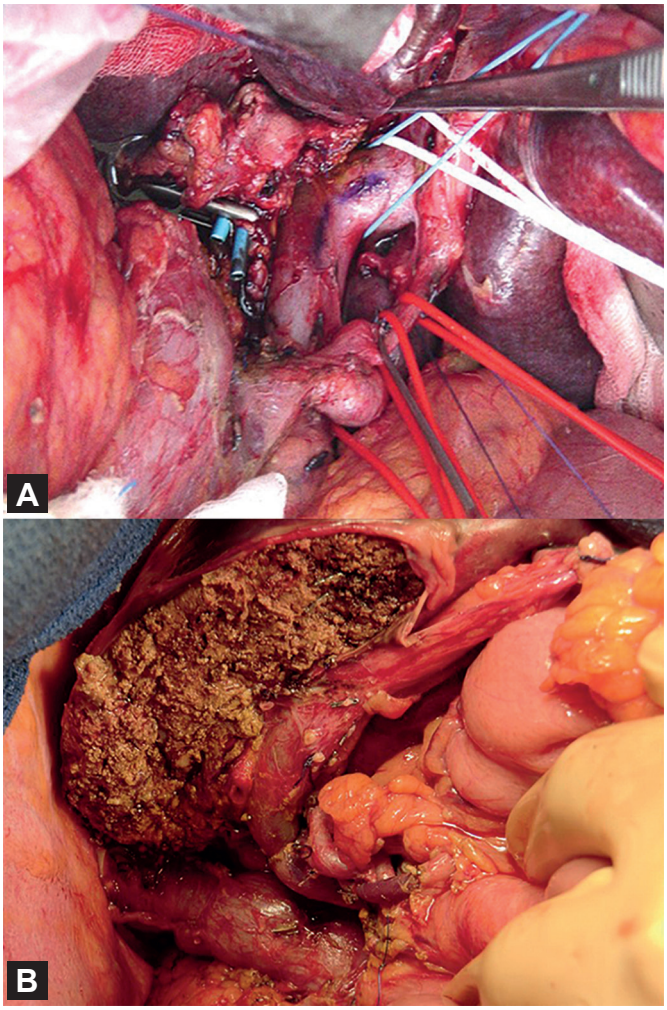

Figure 10. Intraoperative aspect of a right trisectionectomy for hilar cholangiocarcinoma using the "no-touch" concept. **A**) The left portal vein (blue lac) and main portal vein are encircled before en-bloc resection of the portal bifurcation. **B**) Surgical view after resection and end-to-end anastomosis 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

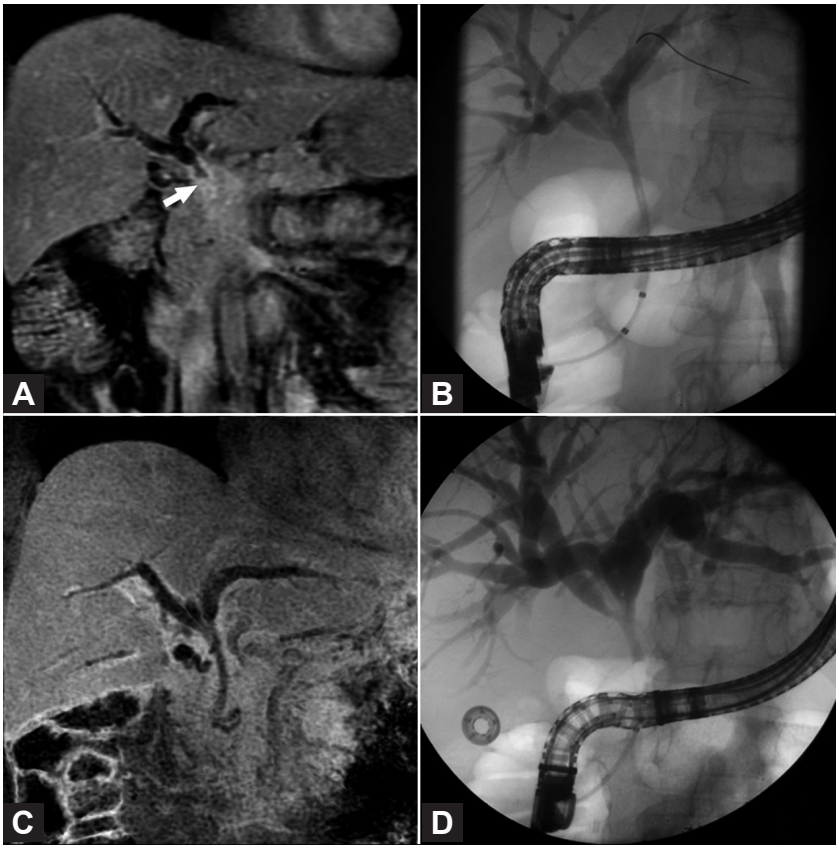

Figure 11. Photodynamic therapy (PDT) for a hilar cholangiocarcinoma. **A**) Magnetic resonance imaging (MRI) with gadolinium in the late phase showing hilar biliary stenosis (arrow). **B**) Endoscopic retrograde cholangiography (ERC) of the same patient before therapy. **C**) MRI after 9 months of the 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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