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Proximal Biliary Malignancy

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Malignant strictures involving the proximal bile ducts present diagnostic and therapeutic challenges to all specialties involved in its management. They can result from metastatic spread of nonbiliary tumors (eg, pancreas, gallbladder, stomach, colon and rectum, lymphoma) to the hepatic hilum or from primary biliary cancer (cholangiocarcinoma). Cholangiocarcinoma comprises less than 10% of primary hepatic malignancies and can arise from the intrahepatic or extrahepatic bile ducts [1]. Although these tumors can occur at any level of the biliary tree, 67% occur at the bifurcation of the bile duct (hilar cholangiocarcinoma) [2], where they are often referred to as Klatskin tumors [3]. These tumors often invade major branches of the portal vein and the hepatic artery, making resection difficult.

Surgical resection with negative margins carries the only hope for long-term survival. Recently, innovative aggressive techniques combining hepatic resection and hilar vascular resection have increased the number of patients in whom resection with negative margins is achieved [4–7]. A protocol combining neoadjuvant therapy with liver transplantation is currently undergoing evaluation at several transplant centers. Patients with unresectable hilar tumors are candidates for palliative biliary drainage to prevent the development of cholangitis and hepatic failure. Without treatment, death from liver failure generally occurs within 3 to 6 months from initial clinical presentation.

Incidence

Extrahepatic bile duct cancers are relatively rare tumors with an incidence of 0.01% to 0.2% in large autopsy series [8]. The reported incidence

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in the United States is about 1 to 2 cases per 100,000 patients [9]. The disease is more frequently diagnosed in the fifth and sixth decade of life, and there is a slight male predominance [10].

Etiology

Although the etiology of cholangiocarcinoma is obscure, it has been suggested that chronic inflammation of the biliary system or exposure to toxic agents concentrated in bile might result in DNA damage in the biliary epithelial cells leading to malignant transformation. In a recent report, 94% of resected specimens from patients with cholangiocarcinoma stained positive for the tumor suppressor p53 gene, and 100% stained positive for proliferating cell nuclear antigen (PCNA) [11]. Moreover, K-*ras* proto-oncogene mutations were found in 75% of specimens from patients with cholangiocarcinoma [12].

Certain disorders have been associated with an increased incidence of cholangiocarcinoma. Primary sclerosing cholangitis (PSC), an autoimmune disease characterized by multifocal strictures of the intrahepatic and extrahepatic bile ducts, is known to be associated with an increased incidence of cholangiocarcinoma. Unlike most cases of sporadic cholangiocarcinoma of the extrahepatic biliary tree, patients who have PSC are at an increased risk of multifocal disease that may not be amenable to resection. The incidence of cholangiocarcinoma in patients with PSC is unknown, but incidental cholangiocarcinoma was found in 4% to 8.6% of liver explants of patients who underwent liver transplantation for PSC [13,14]. Choledochal cysts and Caroli's disease are congenital disorders that carry an increased risk of cholangiocarcinoma. The risk of malignant degeneration increases to 15% to 20% for patients not treated until adulthood. The reason for the increased risk of cholangiocarcinoma in patients with congenital biliary cysts is not clear but is thought to be related to the abnormal entry of the pancreatic duct into the bile duct, resulting in reflux of pancreatic juice into the biliary tree. The resulting chronic inflammation may predispose to the development of cholangiocarcinoma. Bile stasis and chronic inflammation within the cyst may also be a predisposing factor [15–17].

Cholangiocarcinoma is more prevalent in Southeast Asia than anywhere else in the world. This prevalence is thought to be related to parasitic infection with the liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini*. These liver flukes gain entry to the host through the duodenum and reside in the bile ducts. The resulting chronic biliary obstruction leading to stricture formation and chronic inflammation is thought to predispose to cancer [18]. Oriental cholangiohepatitis, which is prevalent in Japan and parts of Southeast Asia, is characterized by chronic portal bacteremia leading to sepsis and pigment stone formation. Chronic cholangitis and stricture formation have been thought to be predisposing factors for cholangiocarcinoma, which is present in 10% of patients with oriental cholangiohepatitis [19].

Associations with some chemical carcinogens or drugs have been reported, such as oral contraceptives [20], methyldopa [21], isoniazid [22], and asbestos [23].

Pathology

Three distinct macroscopic subtypes of cholangiocarcinoma have been described: sclerosing, nodular, and papillary [24]. The sclerosing variety is the most common and causes annular thickening of the bile duct with infiltration and fibrosis of adjacent tissues. These tumors are locally invasive and tend to invade periductal neural tissues as well as major vascular structures of the hilum. The nodular variety is characterized by irregular intraluminal nodules. When both features are present, the tumor is described as nodular-sclerosing. The papillary variant, which accounts for 10% of cases, is a soft and often friable tumor. These tumors are less likely to cause periductal fibrosis or invade adjacent structures, and they have a more favorable outcome than other variants.

Microscopically, more than 95% of tumors are adenocarcinomas ranging from well to poorly differentiated varieties [9,25]. Cholangiocarcinomas are mucin-secreting adenocarcinomas, and intracellular mucin can often be demonstrated. Immunohistochemical staining for epithelial membrane antigen and tissue polypeptide antigen may be useful in confirming the diagnosis of cholangiocarcinoma. Submucosal tumor spread is an important feature of cholangiocarcinoma. This subepithelial spread beyond the obvious tumor emphasizes the importance of wider resections and confirmation of negative margins by frozen section during the resection operation. Other histologic types such as squamous, leiomyosarcoma, rhabdomyosarcoma, and cystadenocarcinoma are rare.

Hilar cholangiocarcinoma is often slow growing; however, rapid progression has been seen in some patients. Spread by direct invasion to periductal hilar tissues with invasion of portal vein branches as well as hepatic arterial branches is a common feature of hilar cholangiocarcinoma. Direct invasion of adjacent liver tissue is also common. Regional lymph node involvement is present in 30% to 50% of cases, whereas blood-borne metastasis to the lungs, kidneys, bones, or brain is rare [24].

Clinical presentation

The clinical presentation of hilar cholangiocarcinoma varies with the site of origin but most commonly begins with painless jaundice. Intense generalized pruritus may develop months before the onset of jaundice when the site of tumor origin is in the main left or right hepatic duct. It has long been recognized that unilateral obstruction of the bile ducts results in atrophy of the corresponding lobe and compensatory hypertrophy of the contralateral lobe (Fig. 1) [26]. The ability of the contralateral lobe of the liver to

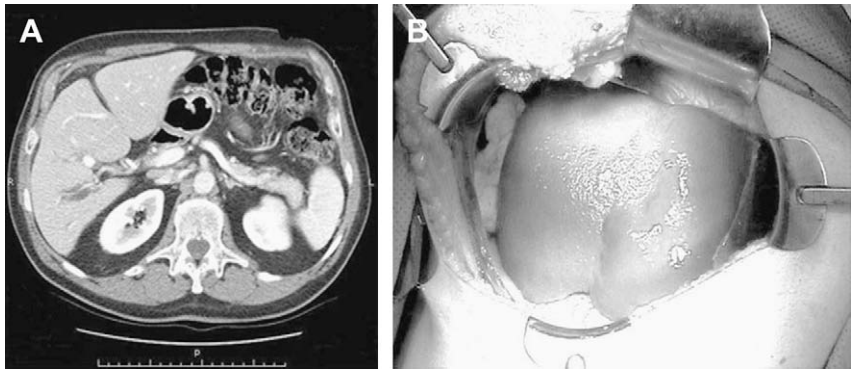

Fig. 1. (*A*) CT scan of a patient with hilar cholangiocarcinoma and long-standing right ductal obstruction resulting in atrophy of the right lobe and compensatory hypertrophy of the left lobe. (*B*) Findings at exploration showing sharply demarcated atrophic right lobe.

hypertrophy in the presence of complete biliary obstruction often delays the development of symptoms. Anorexia and fatigue are nonspecific symptoms that develop in the majority of patients; constant pain is an ominous sign that often (but not always) portends metastatic spread to surrounding tissues. Fever is unusual in the absence of instrumentation of an intact biliary tree despite a 30% incidence of bacterobilia [27]. Most patients have few symptoms and come to attention when they become jaundiced or when they are found to have abnormal liver function tests. Apart from jaundice and skin excoriation in patients with pruritus, physical examination is generally unremarkable.

Total serum bilirubin is elevated in most patients with hilar cholangiocarcinoma at presentation and is usually greater than 10 mg/dL. Alanine aminotransferase and aspartate aminotransferase are usually mildly elevated. Serum alkaline phosphatase and gammaglutamyl transferase are elevated in 90% of patients with cholangiocarcinoma even in the absence of hyperbilirubinemia [28]. In contrast to hepatocellular carcinoma, alphafetoprotein is rarely elevated in patients with cholangiocarcinoma. The level of carcinoembryonic antigen (CEA) is elevated in 40% to 60% of patients and carbohydrate antigen 19-9 in 80% [29].

Radiologic evaluation

Once a patient is diagnosed with obstructive jaundice based on clinical and laboratory data, the initial radiologic modalities are abdominal ultrasonography and abdominal CT scan. Ultrasonography is useful in differentiating hilar obstruction from other causes of obstructive jaundice, such as carcinoma of the head of the pancreas, ampullary tumors, gallbladder carcinoma, and choledocholithiasis. In patients with hilar cholangiocarcinoma, ultrasound often demonstrates a dilated intrahepatic biliary tree and a collapsed

common bile duct and gallbladder. The gallbladder may be distended if the lesion extends distally to occlude the cystic duct orifice. In specialized centers, ultrasonography can identify with reasonable accuracy the presence of a mass and can delineate the extent of the tumor. It can also assess hepatic artery and portal vein patency through Doppler flow imaging [30].

Corporal imaging by CT or MRI scanning is essential in further evaluation of the patient and ideally should be performed before endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). The modality used is dependant on the quality of imaging available at a particular institution. In many centers, magnetic resonant cholangiopancreatography (MRCP) (Fig. 2) has become an invaluable tool in preoperative assessment of patients with hilar cholangiocarcinoma and has almost replaced endoscopic and percutaneous cholangiography [31,32]. MRCP is helpful in staging cholangiocarcinoma and determining resectability by providing information regarding tumor size, the extent of bile duct involvement, vascular invasion, extrahepatic extension, nodal or distant metastases, and the presence of lobar atrophy. The accuracy of MRCP for the assessment of tumor status, periductal infiltration, and lymph node metastases is 90%, 87%, and 66%, respectively [33]. The triphasic CT scan performed in a high-speed scanner is currently the authors' preferred modality for hepatic imaging (Fig. 3). When properly timed, this study can give accurate imaging of hilar vascular anatomy in conjunction with changes in subsegmental hepatic anatomy. Such images can be enhanced to provide three-dimensional mapping of projected surgical planes by providing accurate information about the relationship between the tumor and the adjacent vascular structures (Fig. 4) [34].

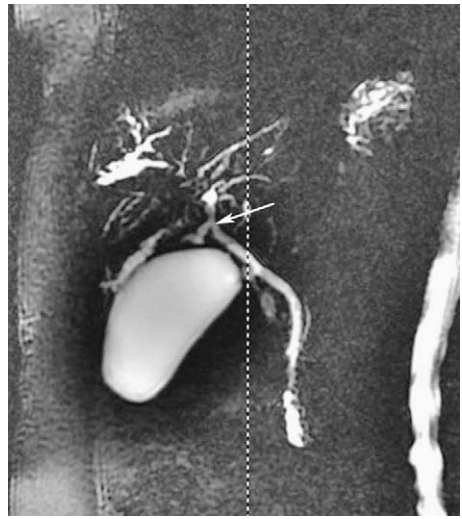

Fig. 2. MRCP of a patient with malignant hilar stricture (*arrow*).

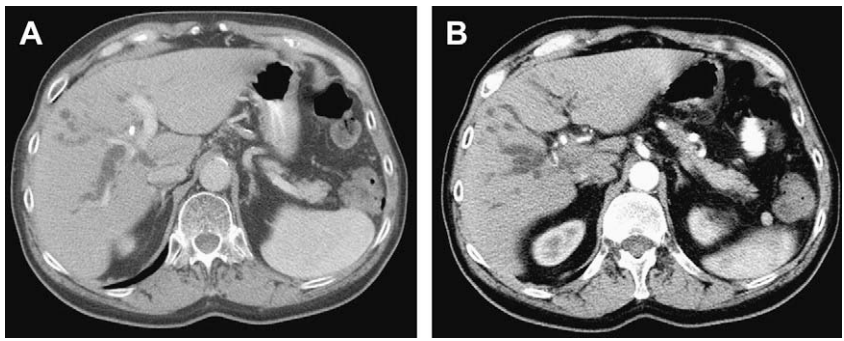

Fig. 3. Triphasic CT scan of a patient with hilar cholangiocarcinoma showing dilatation of the intrahepatic biliary tree. (*A*) Arterial phase. (*B*) Portal venous phase.

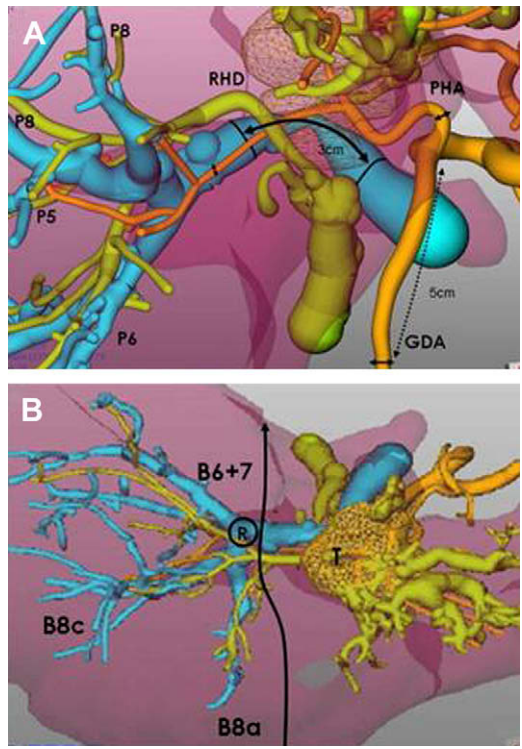

Fig. 4. (*A*) Three-dimensional image reveals narrowing of the portal vein. Resection of a 3-cm segment is required (*long thick line*). The right hepatic artery is also involved by tumor. The lines of transection of the proper hepatic artery and right hepatic artery are planned (*small arrows*). (*B*) Three-dimensional image in the cranial projection. Arrowed line indicates the planned line of resection, just to the left side of the R-point. (*From* Endo I, Shimada H, Sugita M, et al. Role of three-dimensional imaging in operative planning for hilar cholangiocarcinoma. Surgery 2007;142(5):672; with permission.)

Despite the emergence of newer imaging modalities as tools for the evaluation of proximal biliary strictures, cholangiography remains an important diagnostic modality after corporal imaging in many centers. It demonstrates the location and extent of the tumor and delineates the segmental biliary anatomy, which is helpful in planning the hepatic resection. Cholangiography allows both identification and drainage of obstructed ducts. Both ERCP (Fig. 5) and PTC (Fig. 6) have been used with success for preoperative tumor assessment as well as biliary drainage. In operable patients, the authors prefer ERCP with drainage of the uninvolved lobe. ERCP can be difficult to perform in patients with hilar cholangiocarcinoma and carries the risk of cholangitis and post procedure pancreatitis; however, in specialized large-volume centers, ERCP can be performed with a high success rate and low morbidity [35,36]. Despite the tightly obstructing nature of proximal hilar tumors, an experienced endoscopist can often demonstrate the proximal biliary anatomy and establish biliary drainage of the obstructed lobe or lobes. Close communication between the endoscopist and surgeon is vital to adequately delineate the tumor extent and to establish appropriate drainage of the obstructed segments. If endoscopic drainage is not successful or if jaundice persists despite adequate drainage, the authors perform unilateral or bilateral PTC to establish drainage to obstructed segments.

The 18F-fluorodeoxyglucose positron emission tomography (PET) scan is currently being used with increasing frequency to assist with the diagnosis of hilar cholangiocarcinoma [37]. Currently, the PET scan is not used routinely to diagnose hilar cholangiocarcinoma but has been used in patients with PSC, in whom it can be extremely difficult to identify a malignant

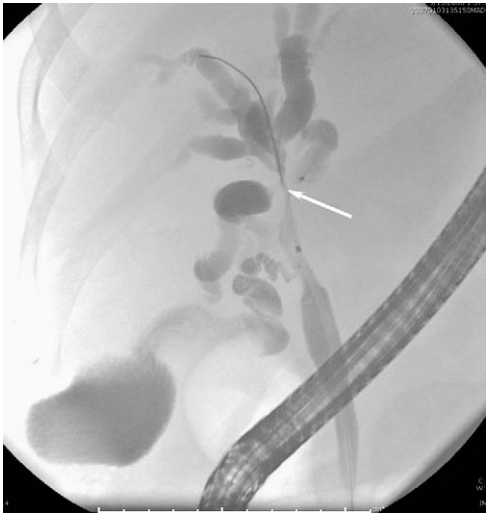

Fig. 5. ERCP of a patient with hilar cholangiocarcinoma showing dilatation of the intrahepatic bile ducts. The arrow points to the stricture.

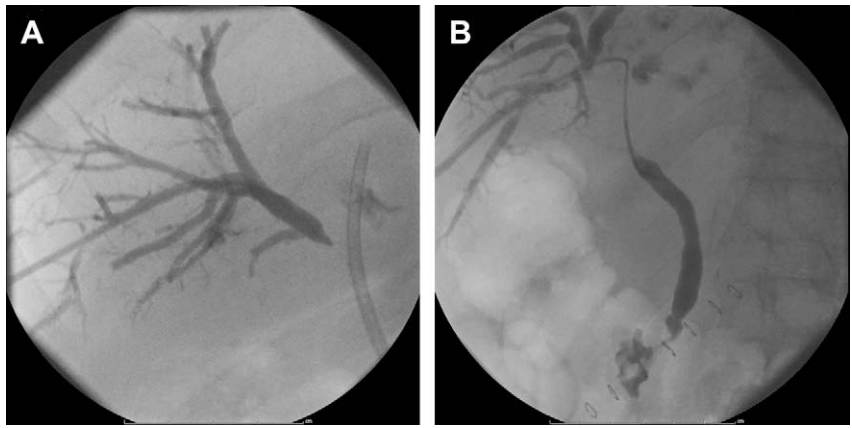

Fig. 6. (*A*) PTC in a patient with hilar cholangiocarcinoma and jaundice not relieved by ERCP stenting of the left hepatic duct. (*B*) The guidewire is passed through the stricture into the common bile duct.

stricture in the background of chronic widespread intrahepatic biliary strictures [38]. It is also being used to confirm recurrent cancer after resection. In a recent study evaluating the use of the PET scan in patients with biliary cancer, it identified occult metastatic disease and changed management in 24% of patients [39].

If patients are surgical candidates, efforts to establish preoperative tissue diagnosis by examining bile cytology, brush cytology, or endoscopic ultrasound–guided fine-needle aspiration are not essential. The sensitivity of bile cytology is only 24% and that of brush cytology 59% [40]. A negative cytology report in the presence of a hilar stricture should never dissuade the clinician from treating the stricture as a malignancy in the appropriate clinical setting. Endoscopic biliary brushings for cytology are only important when the patient is not a surgical candidate.

Preoperative biliary drainage

The value of preoperative biliary drainage for malignant obstructive jaundice remains controversial. Several prospective randomized studies have found no benefit from preoperative biliary drainage in malignant obstructive jaundice from all causes [41–43]. Moreover, a recent meta-analysis found that preoperative biliary drainage did not reduce operative morbidity or mortality in patients with malignant obstructive jaundice [44]; however, most of these studies lacked uniformity and included predominantly patients with distal bile duct obstruction from pancreatic cancer, ampullary tumors, or distal cholangiocarcinoma. In these studies, patients with proximal bile duct malignancy comprised only 12.1%. To date there are no prospective

randomized studies examining the efficacy of preoperative biliary drainage in patients with proximal bile duct tumors; however, several retrospective reports support its use [45–47]. Proximal bile duct tumors comprise a different group because, unlike for distal malignant bile duct obstruction, major hepatic resection constitutes a major component of the resection operation. Extended hepatic resection in patients with complete obstructive jaundice and cholangitis carries a risk of bleeding, sepsis, and severe postoperative hepatic failure [48,49]. Preoperative drainage of obstructed yet salvageable hepatic segments allows resolution of the induration and cholestasis of the involved hepatic parenchyma with more prompt bile excretion in the postoperative period. Results of Japanese series show that preoperative biliary drainage increases resectability and tolerance after major hepatectomy [7,50].

The authors routinely perform preoperative percutaneous or endoscopic biliary drainage of the obstructed lobes or segments if they are anticipated to be important salvageable segments of hepatic parenchyma. To reduce the risk of postoperative hepatic failure, surgery is usually delayed until the total bilirubin levels fall below 2.5 to 3.0 mg/dL.

Patient selection and assessment of resectability

Preoperative staging and assessment of resectability are accomplished by radiologic studies with the goal of identifying potential candidates for surgery and planning the extent of resection. The currently widely used Bismuth-Corlette classification allows comparative stratification of tumor spread along the bile ducts but does not address portal vein or hepatic artery involvement. The classification is useful in operative planning but does not predict resectability or survival [51]. Many patients with types I and II spread may achieve better outcomes with wider resections including hepatectomy [4–7,45,46]. A new preoperative staging system developed by Burke and colleagues [52] stratifies patients according to the degree of biliary involvement, hepatic lobar atrophy, and ipsilateral or bilateral portal vein involvement (Table 1). This staging system has been reported to have better correlation with resectability than the Bismuth classification. Findings of bilobar peripheral hepatic metastasis or extrahepatic disease preclude resection, as does bilateral duct involvement up to the secondary biliary radicals. Unilateral involvement of the portal vein or hepatic artery is treated by ipsilateral hepatic lobectomy and is not a contraindication to resection. More advanced tumors with bilateral vascular involvement need careful preoperative assessment and planning because they may require more advanced vascular techniques with portal vein and hepatic arterial reconstruction and represent relative contraindications.

The overall general medical condition and fitness of the patient for operation, which usually includes major hepatectomy, should be carefully evaluated. Preoperative assessment should include evaluation of the cardiac risk,

Table 1
Proposed T stage criteria for hilar cholangiocarcinoma

Stage	Criteria
T1	Tumor confined to confluence and/or right or left hepatic duct without portal vein involvement or liver atrophy
T2	Tumor confined to confluence and/or right or left hepatic duct with ipsilateral liver atrophy No portal vein involvement demonstrated
T3	Tumor confined to confluence and/or right or left hepatic duct with ipsilateral portal venous branch involvement with/without associated ipsilateral lobar liver atrophy. No main portal vein involvement (occlusion, invasion, or encasement)
T4	Any of the following: (1) tumor involving both right and left hepatic ducts up to the secondary radicals bilaterally, or (2) main portal vein encasement

From Burke EC, Jarnagin WR, et al. Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg 1998;228(3):385–94; with permission.

pulmonary status, and liver and renal function. Nutritional status is generally assessed and nutritional support initiated as indicated. Coagulopathy should be corrected with the administration of vitamin K. Cholangitis should promptly be controlled with the appropriate antibiotics.

Treatment

Resection of hilar malignancies remains one of the most difficult operations in surgery and is heavily dependent on the experience and expertise of the operating surgeon. Nevertheless, surgical resection represents the only successful treatment for cure or significant prolongation of life. The nature of the surgery is determined by the proximal and distal extent of the tumor as defined by preoperative imaging and the anatomic characteristics of the neighboring vascular inflow. The surgical goal is resection of all regional nodal tissue and the common bile duct (and gallbladder) en bloc with the requisite portion of liver to achieve negative microscopic margins.

The authors perform diagnostic laparoscopy at the initiation of the surgical procedure to exclude patients with unrecognized metastases from major laparotomy. A right subcostal incision is used with upward midline extension to the xiphoid to provide exposure for resection. The peritoneal cavity is again inspected for evidence of regional or distant metastasis, and the liver is examined for evidence of metastasis not recognized by preoperative radiologic studies. The duodenum is kocherized to begin resection of the lymphoid tissue lateral and posterior to the common bile duct. We begin dissecting the lymphatic and neural tissue at the level of the celiac artery and proceed to skeletonize the common hepatic artery and its branches. The common bile duct is transected at the superior edge of the pancreas, and all lymphatic and neural tissue lateral and posterior to the bile duct is mobilized en block, skeletonizing the proper hepatic artery as well as the portal vein (Fig. 7). Dissection is carried cephalad including

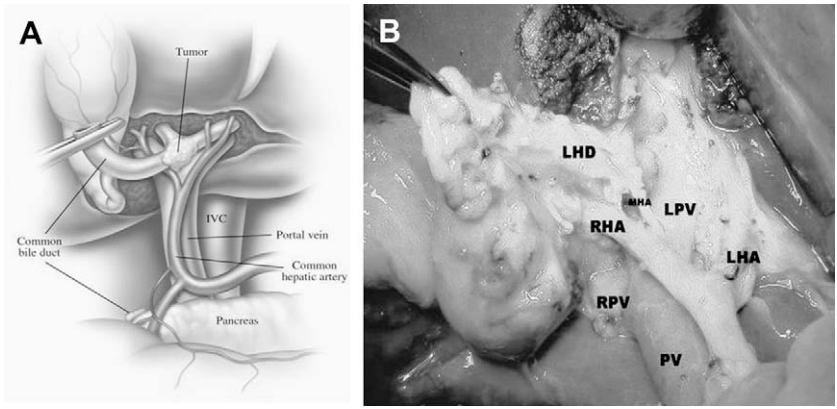

Fig. 7. (*A, B*) Skeletonization of the portal vein and hepatic artery. IVC, inferior vena cava; LHA, left hepatic artery; LHD, left hepatic duct; MHA, segment IV artery; PV, portal vein; RHA, right hepatic artery; RPV, right portal vein.

the gallbladder in the specimen. As more proximal mobilization of the bile duct continues, assessment of involvement of the hepatic artery and portal vein branches allows the operator to determine the need for vascular resection and reconstruction. The bile ducts are eventually divided at the secondary biliary radicals on the hepatic segments to be retained. This maneuver usually entails dividing the duct above the juncture of the right anterior and posterior branches on the right for left side dominant tumors or the segmental branches on the left for right side dominant tumors. The inflow and outflow vasculature of the hepatic lobe to be removed with the specimen is then divided, and the parenchyma transaction is performed using a combination of finger and instrument fracture. The resected liver lobe is removed in continuity with the specimen.

Extended right or left hepatectomies are sometimes necessary to achieve negative margins [4–7,45,46,52–54]. Biliary branches from the caudate lobe can represent an unsuspected repository of residual tumor after bile duct resection for cancer; therefore, most authorities advocate en bloc resection of the caudate lobe with bile duct tumors [45,55,56].

Because of the proximity of the tumor to the major vascular structures in the hilum of the liver, vascular invasion is common. Unilateral involvement is treated by ipsilateral hepatic lobectomy. More advanced vascular techniques with portal vein and hepatic arterial reconstruction are required to resect more advanced tumors with bilateral vascular involvement. The authors' approach to these complex advanced tumors is to completely excise the tumor and re-establish vascular inflow (portal vein and hepatic artery) to the remaining hepatic lobe. This task sometimes requires resection of the portal vein at the bifurcation and anastomosis of the main portal vein to the right or left portal vein. Similarly, arterial reconstruction might be required using microvascular techniques (Figs. 8, 9). Many of these more

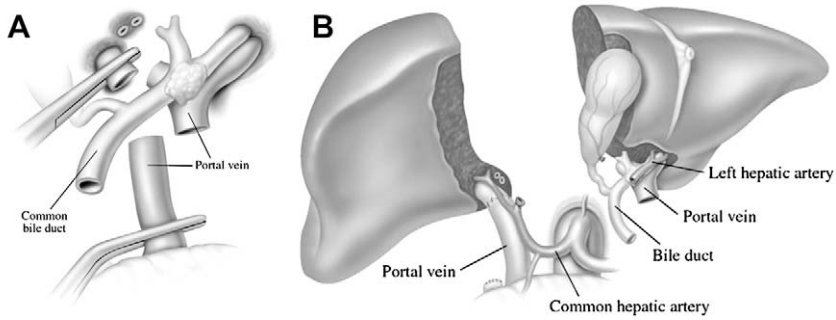

Fig. 8. (*A*) Hilar cholangiocarcinoma involving the portal vein bifurcation requiring resection of the portal vein. (*B*) Blood flow to the remnant lobe is re-established by anastomosing the main portal vein to the right portal vein.

advanced techniques have evolved directly as a result of our growing experience with living donor liver transplantation. Many reports have shown that this aggressive surgical approach increases the number of patients in whom complete excision of the tumor with negative margins can be achieved with acceptable morbidity and mortality [50,57–59].

Reconstruction of the biliary tree with a Roux-en-Y limb of jejunum completes the procedure. Frequently, with high resection into the secondary biliary radicals, multiple bile ducts require proper drainage after removal of the specimen. This drainage can be simplified by converting two or three neighboring ducts into a single orifice by dividing the septum between them and suturing the adjacent walls together. The anastomosis is performed using 5-0 polydioxanone sutures by laying the posterior layer first and completing the anterior layer over a pediatric feeding tube passed through the proximal end of the roux as a biliary stent. The biliary stents allow easy access for postoperative radiologic confirmation of biliary

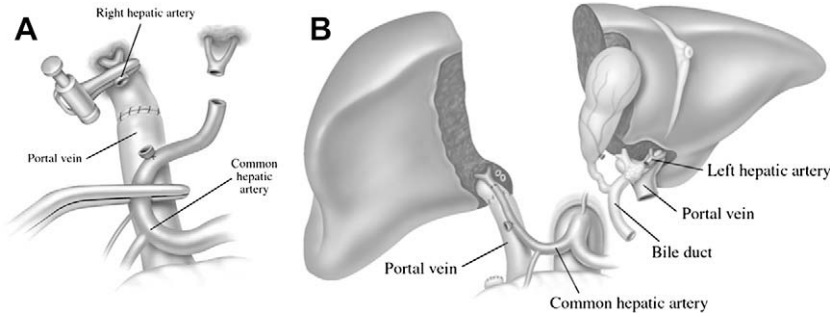

Fig. 9. (*A*) Bilateral involvement of the hepatic artery and portal vein requiring resection of the portal vein bifurcation and both right and left hepatic arteries involved with tumor. (*B*) Flow to the remnant lobe is established by sewing the main portal vein to the right portal vein and the proper hepatic artery to the right hepatic artery using microvascular techniques.

anatomy and are removed 3 to 4 weeks after discharge. Closed suction drainage is routinely performed.

Adjuvant therapy

Currently, there are no data supporting the routine use of adjuvant or neoadjuvant therapy in patients with hilar cholangiocarcinoma. Radiotherapy using external beam radiation delivering doses of up to 60 Gy with duodenal protection has been used as an adjunct to surgical resection in patients with positive surgical margins. In a prospective study, Pitt and colleagues [60] found that adjuvant radiotherapy had no effect on overall survival. Percutaneous and endoscopic endoluminal radiation techniques as well as radioimmunotherapy with ^{131}I-anti-CEA have also been used in combination with systemic chemotherapy in patients with cholangiocarcinoma with little benefit. Nevertheless, some retrospective studies have shown some survival advantage with adjuvant radiotherapy [61,62]. These studies were nonrandomized and included a heterogeneous group of patients. Moreover, many multivariate analyses looking at neoadjuvant therapy among other factors have identified resection with negative histologic margins as the only factor associated with prolonged survival [4–6,45]. Similarly, single agent or combination chemotherapy has failed to show efficacy. Drugs such as 5-fluorouracil (5-FU), methansulfon, cisplatin, mitomycin C, paclitaxel, and gemcitabine have shown little efficacy, with response rates ranging from 0% to 9% and median survivals between 2 and 12 months [63]. A prospective randomized trial comparing oral 5-FU with oral 5-FU plus streptozotocin and oral 5-FU plus methyl-CCNU in patients with unresectable cholangiocarcinoma demonstrated a response rate of only 9% [64]. Presently, there are no data to support the routine use of adjuvant chemoradiation, except in controlled trials. Despite the lack of evidence, adjuvant chemoradiation is used at the many centers around the world. The authors reserve the use of adjuvant chemoradiation for patients with positive nodal status or microscopically positive bile duct margins.

Results

Long-term survival can be achieved with acceptable morbidity and mortality. The perioperative mortality rate ranges from 1.3% to 11%, and morbidity rates range from 35% to 50% [4–7,45,46,65–67]. The presence or absence of positive histologic margins in the resected specimen is an important determinant of disease recurrence and patient survival [4–6,46,68,69]. The early experience with local hilar resection was associated with a high incidence of positive margins and poor long-term survival [2]. With growing experience in the management of hilar cholangiocarcinoma, the number of patients undergoing hepatic resection has increased steadily. Moreover, the addition of sophisticated vascular reconstructions to the

surgical armamentarium has led to an increase in the number of patients undergoing R0 resection. This aggressive surgical approach has increased the number of patients undergoing curative resections and has been associated with improved patient survival. Five-year survival rates as high as 59% have been reported [70]; however, the 5-year survival rates in most recent reports range from 20% to 45% [4–7,45,46,65–67,71,72].

Combining hepatic resection with portal vein resection for locally advanced tumors has increased the resectability rate with acceptable morbidity and mortality. These complex vascular resections are technically difficult and may increase the risk of the procedure. Some authorities have reported worse 5-year survival in patients who undergo portal vein resection [50], whereas others have reported a similar outcome to those without portal vein resection [57,73].

The Lahey Clinic experience

The authors' program started in 1985 at the former New England Deaconess Hospital and moved to the Lahey Clinic in 1999. From 1985 to 2007, 124 patients with hilar cholangiocarcinoma underwent resection with curative intent. As our experience evolved, we adopted a more radical aggressive surgical approach with the addition of hepatectomy and complex vascular reconstruction to achieve negative surgical margins. When comparing our earlier experience between 1985 and 1999 (period 1) [74] with that between 1999 and 2007 (period 2) (Mohamed Akoad, MD, FACS, unpublished data, 2008), local and hepatic resection was performed in 75.9% of patients in period 2 as compared with 48.6% in period 1. Combined vascular resection was performed in 17 patients (3 in period 1 and 14 in period 2). Portal vein resection only was performed in 13 patients, hepatic artery resection only in 2, and both hepatic artery and portal vein resection in 2. Negative margins were achieved in 86.8% in period 2 compared with 50% in period 1($P < .05$). The perioperative mortality rate was 6% in period 1 and 5% in period 2. The 1-, 3-, and 5-year survival rates in period 1 were 83.1%, 56.1%, and 13.6%, respectively, as compared with 89.1%, 56%, and 32.5%, respectively, in period 2 ($P = .007$). The overall 1-, 3-, and 5-year survival rates in patients with R0 resection were 92.9%, 67.5%, and 38.3%, respectively, compared with 72%, 3.5%, and 0%, respectively, for R1 resections. Clearly, the improvement in survival is a result of the application of wider resections with the addition of partial hepatectomy and vascular resections.

Palliation

Extensive surgical resection should only be carried out with the goal of achieving complete tumor removal and negative histologic margins. In patients who are not candidates for surgical resection due to bilateral

extensive biliary involvement, bilateral vascular invasion not amenable to reconstruction, or extensive regional spread, management options include adequate biliary drainage and preventing infectious complications.

The relief of jaundice can be achieved by surgical or nonsurgical means. To date, randomized studies comparing surgical palliation with nonoperative biliary drainage have demonstrated no difference in survival time, complication rates, or the relief of jaundice; therefore, surgical bypass should only be considered in patients who are found to be unresectable at operation. Because most of these patients have preoperative biliary drainage, surgical bypass is rarely indicated [75–77]. If surgical bypass is considered, we prefer to perform hepaticojejunostomy to bile ducts far away from the upper extent of the tumor to prevent obstruction from rapid tumor growth. Only one lobe of the liver needs to be bypassed to maintain adequate function. Traditionally, anastomosis to the segment III bile duct at the base of the round ligament has been the most common drainage option. Bypass of an atrophic lobe or a lobe heavily involved with tumor is generally ineffective.

Nonoperative biliary drainage can be accomplished by an endoscopic or percutaneous approach. In patients with advanced tumor, the endoscopic approach has a high failure rate. Percutaneous biliary drainage and subsequent placement of biliary stents can be performed in most patients with hilar cholangiocarcinoma. The self-expandable metallic wall stents provide a more durable option (Fig. 10) [78,79]. Regardless of whether an endoscopic or percutaneous approach is used, the presence of an atrophic lobe is an important factor to be considered before the drainage procedure. Drainage of an atrophic lobe does not provide relief of jaundice and should be avoided. Sometimes multiple stents may be required to adequately drain the obstructed segments and provide palliation. Recurrent jaundice after

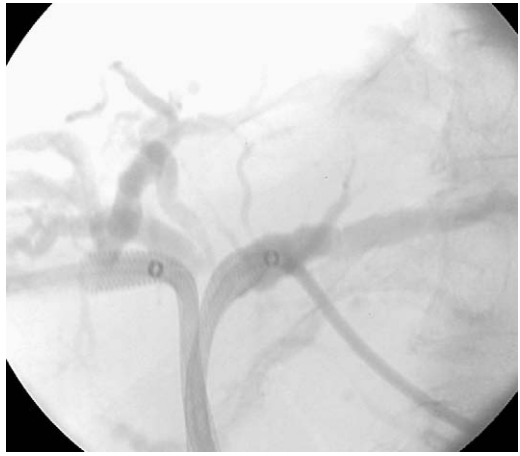

Fig. 10. Metal wall stents placed percutaneously in a patient with unresectable hilar cholangiocarcinoma.

wall stent placement occurs in approximately 18% to 28% of patients because of tumor growth through the mesh of the wall stent or beyond the proximal or distal margins of the stent [79,80]. Biliary drainage can be re-established by adding a longer stent place inside the existing stent. Jaundice that fails to subside after adequately draining all of the segments is likely due to hepatic dysfunction from prolonged obstruction or vascular compromise from tumor invasion and is not likely to be corrected with drainage procedures.

Liver transplantation

Logic would suggest that total hepatectomy and liver transplantation would be the best treatment option because adequate margins are more easily obtained; however, the initial experience with liver transplantation for hilar cholangiocarcinoma has been plagued by early mortality, high recurrence rates, and poor survival. The Cincinnati Transplant Tumor Registry reported a 5-year survival rate of 28% with a 51% tumor recurrence rate [81]. Most patients who underwent liver transplantation for cholangiocarcinoma died within 1 to 2 years due to rapid aggressive disease recurrence [82,83]. More aggressive regional resections, including bile duct resection and pancreaticodudenectomy to eradicate the entire biliary tree and achieve a wide margin, followed by liver replacement and upper abdominal exenteration with subsequent cluster transplantation (liver, pancreas, duodenum, and variable amounts of jejunum) have not demonstrated any added benefit, with few long-term survivors [84,85]. These results have led many centers to abandon liver transplantation for cholangiocarcinoma to avoid wasting the scarce donor organ, and cholangiocarcinoma has become an exclusion criterion for liver transplant.

Recently, a protocol combining radiotherapy, chemosensitization, and liver transplantation has resulted in a dramatic improvement in outcome, with 1-, 3-, and 5-year survival rates of 92%, 82%, and 82%, respectively [86–88]. These results were significantly better than those of resection alone; however, comparing the results between these two groups was difficult, because the medical selection criteria were more stringent for the transplant group, and patients were significantly younger and with higher incidences of PSC than the resection group. Nevertheless, this approach provides the most promising and encouraging treatment strategy for hilar cholangiocarcinoma and is worth further evaluation.

Summary

Hilar cholangiocarcinoma is a rare malignancy that occurs at the bifurcation of the bile ducts. Complete surgical excision with negative histologic margins remains the only hope for cure or long-term survival. Because of its location and proximity to the vascular inflow of the liver, surgical

resection is technically difficult and may require advanced vascular reconstructions to achieve complete excision. Despite advances in surgical techniques, the 5-year survival rate in most recent reports ranges from 20% to 45%. The role of neoadjuvant therapy and liver transplantation in the management of hilar cholangiocarcinoma remains to be defined in light of recent promising results. Patients with advanced unresectable tumors and patients who are not candidates for surgical resection because of other comorbidities are candidates for palliative biliary drainage.

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