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REVIEW ARTICLE

Surgical management of proximal bile duct cancers

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Abstract
Introduction Tumors arising from the proximal biliary tree remain particularly challenging with respect to their evaluation and treatment. Complete resection with negative histologic margins is the most effective treatment modality.
Results However, the majority of patients are not candidates for surgery.
Summary Over the last decades, advances have evolved to improve resectability and morbidity after major liver and bile duct resection. However, these disease processes still pose a management challenge. Herein, we provide an overview of proximal bile duct cancers, hilar cholangiocarcinoma (HCCa) and intrahepatic cholangiocarcinoma (ICCa).

Keywords Hilar cholangiocarcinoma · Intrahepatic cholangiocarcinoma

Introduction

Bile duct adenocarcinoma, or cholangiocarcinoma (CCa), may arise anywhere in the biliary tree from the intrahepatic biliary radicles to the ampulla of Vater. Tumors arising from the proximal biliary tree remain particularly challenging with respect to their evaluation and treatment. While complete resection with negative histologic margins is the most effective treatment modality, the majority of patients present with unresectable tumors. Over the last decades, advances in imaging technology, understanding of tumor biology and perioperative interventions including preoperative portal vein embolization (PVE) and biliary decompression have evolved to improve resectability and morbidity after major liver and bile duct resection. Herein, we provide an overview of proximal bile duct cancers, hilar cholangiocarcinoma (HCCa) and intrahepatic cholangiocarcinoma (ICCa) including discussions of the clinical presentation, workup and surgical management of these diseases.

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General considerations

Classification

CCa are classified as either extrahepatic or intrahepatic, based on their location in the biliary system and the technique required for resection. Extrahepatic CCa are further subclassified into distal or proximal, or HCCa. HCCa are the most common and comprise 60% of cases. Tumors involving the distal bile duct or the intrahepatic biliary system are less common, contributing 20 to 30% and 10% of cases, respectively [1–11]. ICCa is an uncommon disease, although recent epidemiological evidence has shown a clear increase in incidence [7, 12].

Demographics and risk factors

Malignant lesions of the biliary tract are rare and account for about 15% of hepatobiliary neoplasms worldwide. CCa accounts for 40% of these cases and represents about 3% of all gastrointestinal cancers. In the United States, approximately 5,000 new cases (excluding gallbladder carcinoma) are diagnosed annually with an incidence of one to two per 100,000 [13–17]. Peak incidence occurs during the eighth decade of life with men being affected 1.5 times more frequently than women [13].

While the majority of patients do not have any identifiable risk factors, several conditions are associated with an increased risk of CCa. In the United States, the most common risk factor is primary sclerosing cholangitis (PSC), an autoimmune disease characterized by periductal inflammation and multifocal intra- and extrahepatic bile duct strictures. The majority of patients with PSC (70–80%) will have ulcerative colitis (UC); however, only a minority of those with UC will have PSC. Due to the variable natural history of the disease, the true incidence of CCa is unknown but does appear to be related to disease duration. A Swedish series of 305 patients with PSC followed for >5 years demonstrated that 8% of patients eventually developed carcinoma; occult carcinoma was reported in 40% of autopsy specimens [18–21]. Unfortunately, CCa in the setting of PSC is frequently unresectable due to advanced parenchymal disease or multifocal malignancy. Additionally, management of UC in patients with PSC does not appear to alter the risk of developing CCa.

Additional risk factors include congenital biliary cystic disease (i.e., choledochal cysts), hepatolithiasis, biliary parasites, and radionuclide and chemical carcinogen exposure. In the setting of choledochal cysts, the presence of an abnormal choledochopancreatic duct junction results in reflux of pancreatic secretions into the biliary tree, with subsequent chronic inflammation and bacterial contamination [22–25]. It is perhaps via a similar mechanism that patients who have had transduodenal sphincteroplasty or endoscopic sphincterotomy are at increased risk for CCa. Hakamada et al. reported a 7.4% incidence over 18 years [26]. In Japan and parts of Southeast Asia, hepatolithiasis as the causative factor contributes to 10% of CCa cases. The subsequent chronic portal bacteremia and portal phlebitis lead to intrahepatic pigment stone formation, obstruction of intrahepatic ducts and recurrent episodes of cholangitis and strictures [27, 28]. Additional contributing factors including biliary parasites (i.e., *Clonorchis sinensis* and *Opisthorchis viverrini*); exposure to radionuclides and chemical carcinogens including thorium, radon, and nitrosamines and more recently appreciated, hepatitis C infection, obesity and nonalcoholic cirrhosis all appear to be associated with the worldwide increase in ICCa incidence [11, 20].

Natural history

The majority of patients with unresectable CCa will die within 6 months of diagnosis, primarily from liver failure or infectious complications related to biliary obstruction [29]. Hilar lesions have long been considered to have a worse prognosis compared to distal bile duct tumors. However, as tumor location itself does not influence disease-specific survival (DSS), the difference in survival is possibly related to the greater difficulty in management and lower resectability rate of proximal lesions [1, 2, 17].

Pathology

Macroscopically, extrahepatic CCa can be classified into three subtypes: sclerosing, nodular and papillary. The former two are often combined into "nodular sclerosing," as features of both types are often seen together [30]. Sclerosing tumors are the most common subtype and are more common at the hilus than in the distal common bile duct (CBD). These tumors are often firm and result in an annular thickening of the bile duct with periductal infiltration and fibrosis. Nodular tumors exhibit a firm, irregular nodule that projects intraluminally. The papillary variant accounts for 10 to 20% of cases, and while previously considered more common in the distal bile duct, they arise from the proximal duct with some regularity. Lesions are often soft and friable, and often exhibit limited transmural invasion. The duct, in this setting, often expands, rather than contracts. While these lesions frequently grow to a large size, they often arise from a discrete stalk and may be associated with little mural invasion, and as such, are often resectable and associated with a more favorable prognosis [20, 29, 31].

Microscopically, more than 90% of extrahepatic CCa are adenocarcinomas. These tumors are often well-differentiated and mucin-producing, and they commonly produce carcinoembryonic antigen (CEA) and CA19-9. While serum levels have little diagnostic value, some have suggested that bile CEA levels might help differentiate benign and malignant strictures.

The molecular basis of CCa remains elusive. While distal bile duct cancers may harbor a *Kras* mutation at codon 12 in up to 100% of specimens, the presence of such a mutation in ICCa appears to be less common (20–50% of tumors). Therefore, such a mutation is likely one of many necessary events in the progression to carcinoma at least in a subset of bile duct cancers [20, 29, 32–35].

The liver is the most common site of metastatic spread. Approximately one-third of patients will have evidence of nodal spread, and direct invasion to the liver and portal vein is seen commonly in the setting of HCCa. CCa demonstrate some special characteristics including neural, perineural and lymphatic involvement [1, 29, 30, 36]. Longitudinal, subepithelial spread along the duct wall and periductal tissues is an important pathologic feature. As there might be substantial submucosal tumor extension (as much as 2 cm proximal and 1 cm distal), the full extent of tumor may be underestimated by radiologic studies and intraoperative palpation [37]. This characteristic feature highlights the need for partial hepatectomy to achieve a complete resection of HCCa and the importance of intraoperative frozen section of the bile duct margin to ensure complete resection. It should be

noted, though, that some recent studies have called into question the utility of intraoperative frozen section [38].

Cholangiocarcinoma (CCa) involving the proximal bile ducts (hilar cholangiocarcinoma (HCCa))

Clinical presentation

Early symptoms of CCa are nonspecific. While abdominal pain, anorexia and weight loss are the most common presenting signs and symptoms, these are only present in one-third of patients. The majority of patients with HCCa will ultimately present with jaundice, which is generally the first and leading symptom of biliary cancer. If bilirubin levels are >10 mg/dl, patients may experience pruritus. Jaundice may not be present in cases of incomplete biliary obstruction or segmental ductal obstruction. Jaundice is usually unremitting and progressive. Still, some patients, particularly those with papillary tumors, may provide a history of a intermittent jaundice, which can result from small volume tumor dislodgement [29].

The total bilirubin level may provide some indication of the etiology. In the setting of obstructive CCa, the serum bilirubin level is usually >10 mg/dl and averages 18 mg/dl. However, in the setting of obstructive jaundice from choledocholithiasis, serum bilirubin is usually 2 to 4 mg/dl and rarely >15 mg/dL [29, 39]. As it is uncommon for choledocholithiasis to cause obstruction at the biliary confluence, it is imperative that an evaluation is performed to evaluate the location of a lesion causing jaundice.

Examination findings are generally nonspecific. Patients will usually have jaundice. Hepatomegaly may be present. In the setting of hilar obstruction, the gallbladder is usually decompressed and nonpalpable; a palpable gallbladder is more consistent with a distal obstruction or alternative diagnosis. Portal hypertension may be present with long-standing biliary obstruction or portal vein involvement.

In the absence of prior instrumentation, cholangitis is uncommon at presentation. However, the presence of infection, overt or subclinical, at the time of resection leads to increased morbidity and mortality [29]. In an analysis of 71 patients who underwent curative resection or palliative biliary bypass for proximal CCa, 62% of patients stented percutaneously and all patients stented endoscopically had bacterobilia. Postoperative infectious complications were doubled in those patients stented preoperatively. Noninfectious complications were equivalent. Intraoperative bile cultures most commonly revealed *Enterococcus*, *Klebsiella*, *Streptococcus viridians* and *Enterobacter aerogenes*. Bile should be cultured intraoperatively as this data can help direct postoperative antibiotic use [40].

Differential diagnoses

A diagnosis other than CCa may be present in up to 20% of patients [41]. The most common alternatives are gallbladder carcinoma, Mirizzi syndrome and idiopathic benign focal stenosis. Gallbladder carcinoma may be associated with a thickened gallbladder that infiltrates segments IV and V, with selective involvement of the right portal pedicle or obstruction of the common hepatic duct and occlusion of the cystic duct [29, 42]. Reliance on biopsy or cytology alone may be misleading [43, 44]. Ultimately, a definitive diagnosis sometimes cannot be made without resection. In the setting of vascular invasion and atrophy, the diagnostic likelihood of HCCa significantly increases [41]. The absence of these findings should raise the suspicion that an alternate diagnosis is present. Therefore, in the clear absence of contraindications, exploration is indicated in all patients with suspicious hilar lesions.

Preoperative evaluation

Imaging evaluation

Patients will generally be referred after some initial studies including a computed tomography (CT) scan or an evaluation of the biliary system with cholangiography. High quality CT scan allows for evaluation of the level of obstruction, vascular involvement and liver atrophy. Duplex ultrasound (US) is operator-dependent, but when performed by a reliable operator, may delineate tumor extent including level of biliary obstruction and extent of ductal and periductal involvement with great accuracy. In a series of 39 patients with HCCa, duplex Doppler US was equivalent to CT angiography in diagnosing lobar atrophy, parenchymal involvement, venous invasion and level of biliary obstruction [45]. A series of 63 patients demonstrated that duplex US predicted portal vein involvement in 93% of cases with a specificity of 99% and positive predictive value of 97% [46].

Cholangiography allows for determination of the tumor location and biliary extent of disease. More recently, magnetic resonance cholangiopancreatography (MRCP) has essentially replaced percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) in the preoperative assessment of proximal CCa. MRCP has the added utility of revealing obstructed and isolated ducts, patency of vascular structures, presence of lobar atrophy or presence of regional or distant metastasis, which were not appreciated with more invasive modalities (Fig. 1).

Determining resectability

The goal of the preoperative evaluation is to identify patients who are candidates for a potentially curative operation. The evaluation must address four critical determinants

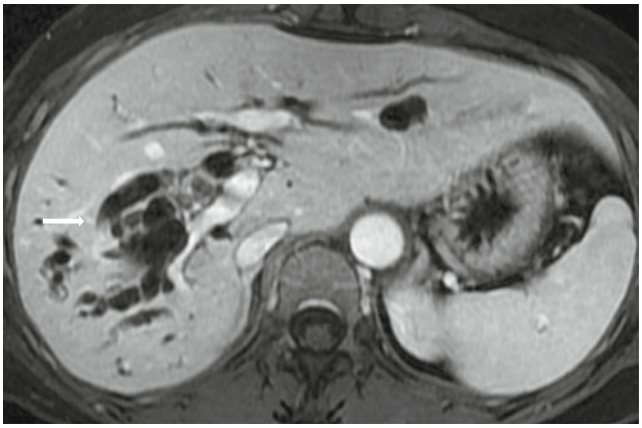

Fig. 1 MRCP of patient with hilar cholangiocarcinoma demonstrating atrophy of the right liver with associated dilatation and crowding of the right biliary tree (*arrowhead*) and marked hypertrophy of the left liver. Liver size and mass is maintained by portal venous and bile flow. The findings in this MRCP suggest probable long-standing bile duct obstruction

of resectability: 1) extent of tumor within the biliary tree, 2) vascular invasion, 3) hepatic lobe atrophy and 4) presence of metastatic disease. Criteria for irresectability include 1) presence of distant metastases, 2) bilateral hepatic duct involvement to the second-order biliary radicles, 3) unreconstructable vascular involvement and 4) atrophy of one hepatic lobe with encasement of the contralateral portal vein, or atrophy of one hepatic lobe with involvement of contralateral secondary biliary radicles (Table 1).

Atrophy is often overlooked but is of the utmost importance in determining resectability. If portal or biliary occlusion occurs, as in HCCa, segmental or lobar atrophy occurs. While long-standing biliary obstruction results in moderate atrophy, a concomitant portal compromise will result in rapid, severe atrophy of the affected segments. Atrophy, defined as a small, often hypoperfused lobe with crowding of the dilated intrahepatic ducts (Fig. 1), can be appreciated on preoperative imaging and, consequently, affect management decisions [29, 47]. The presence of atrophy compels the surgeon to remove this portion of the liver en bloc with the bile duct, if resectable [48]. Atrophy is also an important factor when considering palliative biliary drainage, since placement of biliary catheters into an atrophic portion of liver will not influence the serum bilirubin level. Ipsilateral atrophy and/or ipsilateral portal vein or ipsilateral second-order biliary radicle involvement does not necessarily preclude resection. Liver size and mass are maintained by portal venous and bile flow.

Table 1 Criteria for cholangiocarcinoma irresectability

Presence of distant metastases (e.g., peritoneum, liver and lung)
Bilateral hepatic duct involvement to the second-order biliary radicles
Unreconstructable vascular involvement
Atrophy of one hepatic lobe with • Encasement of contralateral portal vein, or • Involvement of contralateral second-order biliary radicles

In an attempt to improve perioperative outcomes, centers have advocated preoperative, ipsilateral PVE and biliary drainage to improve the function of the future liver remnant (FLR). While data regarding preoperative biliary drainage in the setting of periampullary malignancy demonstrated no benefit, there are no randomized trials regarding its use in the setting of HCCa. Cherqui et al. performed a retrospective review of patients undergoing major liver resection without preoperative biliary drainage and found no difference in mortality or recovery of hepatic synthetic function [49]. It should be noted that many patients will present with lobar atrophy at the outset, and the value of PVE in that setting is likely to be questionable at best and probably nil. Rather, it is likely that the volume of the FLR that dictates whether PVE and biliary drainage are necessary. In a study of 60 patients undergoing hepatic resection for HCCa, FLR <30% was associated with an increased risk of hepatic failure and mortality. For patients in whom FLR was <30%, but not FLR ≥30%, preoperative biliary drainage improved outcomes [50].

Prospective trials have demonstrated that PVE can be performed safely [51, 52]. There is currently no definitive evidence to support routine use in the setting of HCCa. However, its use should be considered in patients with compromised liver function with an anticipated FLR <40%, or normal liver function with a FLR <20% [53].

Staging

Vascular involvement and extent of spread along the bile ducts play a critical role in intraoperative decision making as complete resection might not be possible without partial hepatectomy. At this writing, there is no clinical staging system that stratifies patients into subgroups based on potential for resection. The modified Bismuth-Corlette classification system stratifies patients based on the extent of bile duct involvement [54]. Unfortunately, this does not correlate to survival or resectability. The current AJCC staging system, based largely on pathologic criteria, likewise has little applicability to preoperative staging (Table 2) [55].

The Blumgart classification system has been proposed as a means of accurately predicting resectability, need for partial hepatectomy and survival. This system takes into account biliary involvement, vascular involvement and lobar atrophy (Fig. 2). In a series of 87 patients comparing the Blumgart system to the AJCC system, there was no correlation between stage and resectability or median survival with the AJCC system. However, using the Blumgart

Table 2 Summary of the American Joint Committee on Cancer Staging for perihilar cholangiocarcinoma, seventh edition

T stage			
T1	Confined to bile duct		
T2a	Invades beyond bile duct wall		
T2b	Invades adjacent hepatic parenchyma		
T3	Invades unilateral portal vein or hepatic artery		
T4	Invades main portal vein or branches bilaterally, or common hepatic artery, or bilateral second-order biliary radicles, or ipsilateral second-order biliary radicles and contralateral portal vein or hepatic artery		
N stage			
N0	No regional lymph node metastases		
N1	+ Metastases to cystic duct, common bile duct, hepatic artery or portal vein lymph nodes		
N2	+ Metastases to periaortic, pericaval, superior mesenteric or celiac artery lymph nodes		
M stage			
M0	No distant metastases		
M1	+ Distant metastases		
Stage	T	N	M
I	1	0	0
II	2a-b	0	0
IIIA	3	0	0
IIIB	1-3	1	0
IVA	4	0-1	0
IVB	Any T	N2	M0
	Any T	Any N	M1

system, resectability was greater in the T1 group and progressively decreased with increasing T stage. The system also predicted the need for hepatectomy, which increased with increasing T stage [1]. A recent report demonstrated that classification by the Blumgart system not only predicted resectability but also the likelihood of obtaining an R0 resection (Table 3) [56].

Treatment

Surgical management

The goals of therapy for HCCa include 1) complete, potentially curative resection with negative margins and 2) restoration of bilioenteric continuity. For patients who undergo resection, laparoscopy is generally performed to exclude radiologically occult metastases. Contrary to prior belief, the presence of distant disease is relatively common. In a series from MSKCC, 160 patients were taken for potentially curative resection. Eighty patients were found to have disease that precluded resection, most commonly with distant metastatic disease, followed by disease to distant nodal basins, liver, peritoneum or multiple sites [57].

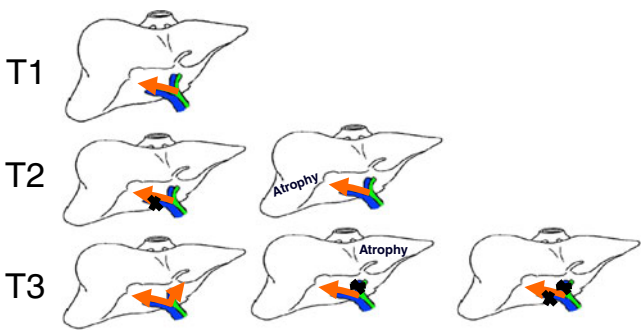

Fig. 2 Blumgart clinical staging system

If laparoscopy does not reveal abnormal findings, laparotomy via an extended right subcostal or bilateral subcostal incision with proximal extension to the xyphoid, when necessary, is performed. Bimanual palpation of the liver and a Kocher maneuver to evaluate the retropancreatic lymph nodes are performed. Multicentric liver disease, intrahepatic liver metastases and spread to distant sites or N2 lymph nodes preclude resection. If these are identified, palliative bilioenteric bypass should be considered at the time of exploration.

There is overwhelming evidence to support the use of concomitant partial hepatectomy, often including the caudate lobe, as part of the resectional procedure. Recurrence and survival rates are markedly lower when bile duct resection alone is performed; the surgeon must, therefore, be prepared to perform a partial hepatectomy in all patients with potentially resectable HCCa. The authors' general approach has been published previously and is similar to that used for all major hepatic resections including use of

Table 3 Resectability based on Blumgart preoperative staging system (2001–2008)

T stage	Number	Operative exploration, *n* (%)	Resected, *n* (%)	R0, *n* (%)	Hepatic resection, *n* (%)	Median survival (months)
1	48	44 (92)	34 (71)	26 (54)	30 (62)	23.0
2	41	38 (90)	25 (61)	21 (51)	24 (59)	22.4
3	29	24 (83)	1 (3)	1 (3)	1 (3)	9.9
Total	118	105 (89)	60 (51)	48 (41)	55 (47)	18.3

low central venous pressure (<5 mmHg), anesthetic management to minimize blood loss during the retrohepatic dissection, dissection of the hepatic veins and parenchymal transection. The patient is positioned in 15° of Trendelenburg to avoid air embolism [29, 58, 59].

If resection is deemed feasible, the distal bile duct should be divided above the duodenum. Next, the hilus is exposed by taking down the gallbladder and lowering the hilar plate by incising Glisson's capsule at the base of segment IV. At this point, the tumor may be palpated to assess extent of disease. The left hepatic duct may be exposed by dividing the bridge of liver tissue between segments III and IV. The dissection, inclusive of the subhilar lymphatics, is carried toward the hilus where vascular involvement and resectability can be assessed. Dissection between the tumor and portal vein is carried cephalad by lifting the bile duct up and skeletonizing the portal vein and hepatic artery.

At this point, the proximal extent of tumor should be determined via palpation. Frozen section of the uninvolved bile duct should be performed to confirm a negative margin. If tumor extends to ipsilateral second-order biliary radicles or if ipsilateral portal vein branch involvement is present, partial hepatectomy should be performed, particularly as en bloc partial hepatectomy as well as R0 resection have been found to be independent predictors of favorable outcomes [31]. Inflow and outflow control must be obtained prior to parenchymal transection.

For all cases with presumed or suspected tumor extension into the caudate, centrally located tumors or tumors extending into the left hepatic duct, caudate resection should be performed [60]. Occasionally, preoperative imaging will reveal a dilated caudate lobe duct suggesting caudate involvement. Additionally, Neuhaus et al. recently reported on the "no touch" radical resection of HCCa involving en bloc resection of the extrahepatic bile ducts, portal vein bifurcation, right hepatic artery and liver segments 1 and 4 through 8. One-, 3- and, 5-year survival rates after en bloc resection were significantly higher (87%, 70% and 58%, respectively) than after conventional major hepatectomy (79%, 40% and 29%, respectively) [61].

Biliary continuity is reestablished with a hepaticojejunostomy to a 70-cm, retrocolic Roux-en-Y jejunal loop. Anastomosis is carried out in an end-to-side fashion using a single layer of 4-0 interrupted absorbable sutures [29, 62]. Removal of the tumor will occasionally result in discontinuity of one or more of the caudate ducts or discontinuity between right anterior and posterior sectoral ducts. In cases of multiple exposed ducts, it is often possible to suture ducts together to create a situation in which no more than two to three separate ducts are to be anastomosed. Hilar biliary anastomosis can be exceedingly difficult to perform, and sequential anastomoses may be impossible in this location. The safest and most reliable method is to view multiple disconnected ducts as a single duct. The entire anterior row of suture may be placed, followed by a separately placed posterior row of duct-to-jejunum. The posterior layer of sutures is tied first. The anterior sutures are then passed sequentially through the anterior jejunal wall to complete the anastomosis.

Orthotopic liver transplantation (OLT) has been proposed as a surgical alternative for selected patients with both unresectable CCa and resectable CCa in the setting of underlying parenchymal disease. The Mayo Clinic has reported on the use of preoperative external beam radiation with bolus 5-FU, followed by brachytherapy with iridium and concomitant, infusional 5-FU for patients with unresectable CCa or CCa arising in the setting of PSC. Patients without metastatic disease were evaluated for OLT. In the initial report by De Vreedes et al., 11 of 918 patients (1.2%) with CCa underwent OLT, with a 5-year recurrence-free survival of 91%. More recently, Rea et al. reported updated results of the protocol with 38 patients ultimately undergoing OLT. When compared to those who underwent resection, the authors reported a lower recurrence rate and a significant improvement in 1-, 3- and 5-year survival with OLT (92%, 82% and 82% after OLT compared to 82%, 48% and 21% after resection, respectively) [63, 64]. Resection, usually with en bloc partial hepatectomy, remains the most effective therapy. However, OLT may also play a role in very carefully selected patients with limited disease and in the setting of underlying parenchymal disease such as PSC.

Adjuvant and palliative chemotherapy

There is only limited data evaluating the effectiveness of adjuvant therapy for HCCa. Results to date are mixed and represent small, heterogeneous populations. Takada et al. conducted a phase III trial of 508 patients, evaluating the

role of adjuvant chemotherapy in patients with resected pancreatobiliary malignancies. Patients were randomized to either surgery alone or surgery with adjuvant mitomycin C and infusional 5-FU followed by oral 5-FU. Adjuvant chemotherapy did not significantly improve 5-year survival, but similar to the retrospective studies, only 139 patients (27%) had CCa [65].

In the phase II–III ABC trial of 410 patients with locally advanced or metastatic CCa, gallbladder cancer or ampullary cancer, patients were randomized to either cisplatin and gemcitabine or gemcitabine alone. Compared to gemcitabine alone, the use of cisplatin with gemcitabine was associated with a significant improvement in overall survival (11.7 months versus 8.1 monts) without additional substantial toxicity [66]. These data are promising and indicate that biliary tract cancers might be more responsive to chemotherapy than previously appreciated.

Palliative interventions

The majority of patients with HCCa are ultimately found to have unresectable disease. Diagnosis should be confirmed with a biopsy. Palliative management may include biliary decompression or supportive care (particularly in patients who are elderly or who have significant comorbid conditions). Indications for biliary decompression include patients who are deemed unresectable with 1) intractable pruritus, 2) cholangitis, 3) need for intraluminal radiology or 4) need for parenchymal recovery in patients receiving chemotherapy.

If found to be unresectable at the time of exploration, palliative bilioenteric bypass should be considered and can be performed with low morbidity [67]. Segment III duct is generally the most accessible and is the preferred approach. In the MSKCC experience of 55 consecutive bypasses in the setting of malignant hilar obstruction, segment III bypass in patients with HCCa yielded the best results with a 1-year bypass patency of 80%. Alternative options include bypass to the right anterior or posterior sectoral ducts, but this approach is technically much more demanding [68]. A bilioenteric bypass to segment III hepatic duct is much less prone to occlusion by tumor than is a self-expandable metallic stent (Wallstent), as the anastomosis may be placed some distance away from the tumor [69]. Jaundice may be alleviated if at least one-third of functioning parenchyma is adequately drained. Communication between right and left hepatic ducts is not mandatory as long as the undrained lobe has not been previously accessed or contaminated.

In patients who do not undergo exploration, decompression may be achieved either by endoscopic stent placement or percutaneous transhepatic puncture. While endoscopic stenting is the preferred means of decompression for patient comfort, hilar tumors are often difficult to effectively stent endoscopically. Additionally, endoscopic stenting is associated with a high rate of failure and subsequent cholangitis [70].

Percutaneous transhepatic biliary drainage and placement of a Wallstent serves as an alternative means of biliary decompression. Even in the hands of experienced interventional radiologists, satisfactory results are difficult to achieve. Hilar tumors frequently isolate all three major hilar ducts, and two or more stents are often required [71]. Moreover, jaundice resulting from portal vein involvement will not resolve with stenting. Percutaneous drainage via the atrophic lobe should be avoided as it does not relieve jaundice.

Median patency of a metallic endoprosthesis at the hilus is approximately 6 months, significantly lower than in the setting of distal bile duct lesions. In our experience, periprocedural mortality was 14% at 30 days with 24% of patients requiring reintervention due to stent occlusion [72].

Outcomes

Long-term survival can be achieved with acceptable morbidity and mortality in specialized centers. In recent series, morbidity ranges from 30 to50% and mortality is <10% [33, 54, 57, 73–78]. Hepatic resection is associated with increased perioperative mortality compared to hepatic resections for other disorders, which is likely related to an increased rate of infectious complications. Isolated hepatic failure as the cause of postoperative death, in the absence of confounding conditions, is less common [57].

Five-year overall survival rates after resection range from 9 to 28% with median survivals from 19 to 35 months [73]. Margin status remains the most important determinant of survival, and several studies have demonstrated that patients with negative histologic margins have improved survival compared to those with involved margins. Reported 5-year survival ranges from 0 to 15% with margin-positive resections, and 24 to 43% with margin-negative resections. In an MSKCC experience of 90 patients, median DSS was significantly greater (56 months) with wide margins, compared to 38 months with narrow margins and 32 mo nthswith positive margins (Fig. 3)

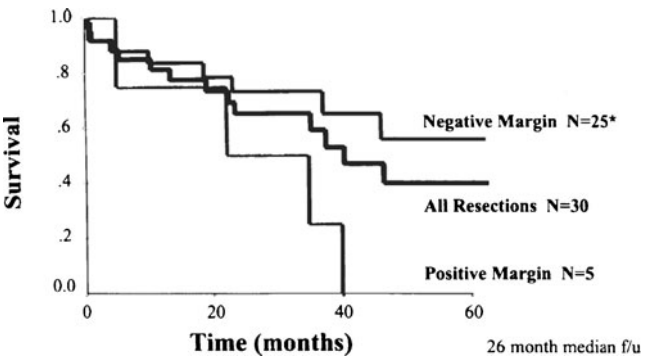

Fig. 3 Actuarial survival curves after resection for hilar cholangiocarcinoma, stratified by histologic margin status

[1]. In a more recent report of 105 patients undergoing exploration for HCCa at MSKCC, patients with an R0 resection had the highest DSS (74 months), followed by those with an R1 resection (24 months) and unresected disease (13 months) [56].

Cholangiocarcinoma (CCa) involving the intrahepatic bile ducts

Clinical presentation

Unlike extrahepatic CCa, in which the patient often presents with jaundice, in ICCa, the patient often presents with an incidental liver mass detected on imaging studies. Less commonly, the patient may present with right upper quadrant pain or constitutional symptoms.

Preoperative evaluation

The workup of an incidentally discovered liver mass commonly involves biopsy, which will often reveal adenocarcinoma. Careful pathologic review and immunohistochemical stains will help elucidate the primary site. Occasionally, the exact source of the tumor remains unknown. As most liver tumors represent metastatic disease, particularly adenocarcinomas, additional workup is per physician's discretion but may include (particularly in the setting of adenocarcinoma) upper and lower endoscopy and CT of the chest, abdomen and pelvis. Mammogram or pelvic US may be indicated.

In addition to routine laboratory tests, tumor marker levels including α-fetoprotein (AFP), CA19-9 and CEA should be obtained. The overall accuracy and utility of these tumor markers remains unclear. In a study of 74 patients undergoing resection for ICCa, preoperative CA19-9 levels >100 U/ml were independently associated with recurrence-free survival [79].

ICCa may be classified into three distinct morphologic subtypes, proposed by the Liver Cancer Study Group of Japan (LCSGJ): mass-forming, periductal-infiltrating and intraductal growth [80]. Similar to HCCa, CT and MR are useful in the preoperative evaluation of ICCa. ICCa subtypes may exhibit characteristic findings. Mass-forming ICCa is the most common subtype (>85%). On imaging, it appears as a low attenuating, homogeneous mass with irregular peripheral enhancement, capsular retraction, satellite nodules, peripheral intrahepatic ductal dilation and sometimes, invasion into the hepatic and portal vasculature. Periductal-infiltrating tumors demonstrate growth, diffuse periductal thickening and enhancement along a dilated or narrowed bile duct without mass formation. Intraductal growth lesions can present with variable findings but may be have strictures with proximal dilation, intraductal castlike lesions or diffuse duct ectasia with or without an intraductal mass [80–83].

A number of staging systems for ICCa have been proposed, both by the Japanese and the AJCC. Analyses from the SEER database by Nathan et al. found that a new staging system, reflected in the recent seventh edition of the AJCC staging system, has superior discriminatory ability compared to previous versions of the AJCC and the Japanese systems (Table 4).

Treatment

Surgical management

Similar to HCCa, laparoscopy maybe performed to rule out radiologically occult metastatic disease. Weber et al. reported on 22 patients with ICCa and found that 27% had previously undetected intrahepatic or peritoneal metastases [84]. However, data on the benefits of staging laparoscopy remain limited, and the use of this modality is controversial.

Also, similar to HCCa, resection offers the only potential for cure. Resection may require extensive surgery including extended hepatectomy and/or resection of adjacent structures including the vena cava, diaphragm, extrahepatic biliary system or bowel. To achieve an R0 resection, Sotiropoulos et al. reported that 78% of cases required an extended hepatectomy; Endo et al. reported that 49% of patients required extended hepatectomy with 21% requiring concomitant biliary reconstruction [7, 85].

Palliative therapies

Locoregional therapies to address unresectable ICC include radiation therapy, transarterial chemoembolization (TACE)

Table 4 Summary of the American Joint Committee on Cancer Staging for intrahepatic cholangiocarcinoma, seventh edition

T stage			
T1	Solitary tumor, − vascular invasion		
T2a	Solitary tumor, + vascular invasion		
T2b	Multiple tumors, ± vascular invasion		
T3	Invades visceral peritoneum or local extrahepatic structures		
T4	Periductal invasion		
N stage			
N0	No regional lymph node metastases		
N1	+ Regional lymph node metastases		
M stage			
M0	No distant metastases		
M1	+ Distant metastases		
Stage	T	N	M
I	1	0	0
II	2	0	0
III	3	0	0
IVA	4 Any T	0 N1	0 0
IVB	Any T	Any N	M1

and hepatic artery infusion (HAI). The role of radiation for unresectable ICCa is unknown. In a study of 45 patients with unresectable ICCa, external beam radiation therapy was associated with 1- and 2-year survivals of 36% and 19%, respectively [86].

Data on TACE in the setting of unresectable ICCa is likewise limited. In a study of 42 patients with unresectable CCa, TACE was found to be well tolerated with limited morbidity and no mortality [87]. Burger et al. reported on 17 patients with unresectable CCa and found that TACE was well tolerated in 82% of patients. Two patients ultimately underwent resection [88].

HAI has been proposed for unresectable hepatocellular carcinoma and ICCa as it delivers high dose, continuous chemotherapy directly to the hepatic arterial system with limited systemic toxicity. A phase II trial evaluating the use of HAI-FUDR for unresectable, histologically confirmed HCC (N=8) or ICCa (N=26) confined to the liver demonstrated that in patients with ICCa, HAI was safe and effective, with a DSS of 31 months and a partial response rate of 53.8%. One patient responded sufficiently to undergo resection [89].

Results

Unfortunately, only about 40% of ICCa are amenable to resection [90]. Five-year survival ranges from 14 to 40% after resection [7, 79, 81, 91–101]. Recurrence remains frequent with a rate of 62% after a median follow-up of 26 months. Recurrence is most common in the liver remnant with or without involvement of extrahepatic sites [7]. DeOliveira et al. reported on a series of 564 patients with CCa. While the number of patients with ICCa was limited, 5-year survival in patients undergoing resection after 1995 was improved compared to resection in the prior time period [97]. Endo et al. reported a similar finding with improved DSS in patients with ICCa treated from 2001 to 2006 (22 months) versus those treated from 1990 to 2000 (12 months). The improvement was particularly evident in those with unresectable disease [7].

Unlike HCCa, data regarding predictors of outcomes is conflicted for ICCa. Various reports have suggested that tumor size, tumor number, regional lymph node involvement and the presence of vascular invasion represent major predictors of outcomes [7, 98]. A recent evaluation of an international, multi-institutional database of 449 patients undergoing surgery for ICCa failed to demonstrate tumor size as a significant prognostic factor. Positive margins, multiple lesions and vascular invasion were associated with an adverse prognosis. However, in patients with N1 disease, these factors failed to discriminate patients into discrete prognostic groups [102].

Summary

In spite of advances in diagnostic imaging, surgical management and perioperative care, CCa of the proximal bile ducts continues to have an overall poor prognosis. The majority of patients' disease remains unresectable at the time of diagnosis, and 5-year survival rates remain poor. Curative resection with negative margins, commonly requiring a partial hepatectomy, remains the only potential option for cure.

Conflicts of interest None.

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