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Management of perihilar cholangiocarcinoma in the era of multimodal therapy

Vicente Valero III¹, David Cosgrove², Joseph M Herman³, and Timothy M Pawlik^{*,1}

¹Department of Surgery, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Harvey 611, 600 N Wolfe Street, Baltimore, MD 21287, USA

²Division of Surgical Oncology, Department of Medical Oncology, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

³Department of Radiation Oncology, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Perihilar cholangiocarcinoma (CCA) is the second most common primary malignant tumor of the liver. In the USA, there are approximately 3000 cases of CCA diagnosed annually, with approximately 50–70% of these tumors arising at the hilar plate of the biliary tree. Risk factors include advanced age, male gender, primary sclerosing cholangitis, choledochal cysts, cholelithiasis, parasitic infection, inflammatory bowel disease, cirrhosis and chronic pancreatitis. Patients typically present with jaundice, abdominal pain, pruritus and weight loss. The mainstays of treatment include surgery, chemotherapy, radiation therapy and photodynamic therapy. Specific preoperative interventions for patients with perihilar CCA include endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography and portal vein embolization. Surgical resection offers the only chance for curative therapy in perihilar CCA. R0 resection is of utmost importance and has been linked to improved survival. Major hepatic resection is needed to achieve both longitudinal and radial margins negative for tumor. Fractionated stereotactic body radiotherapy has shown promising results in CCA. Perihilar CCA typically presents with advanced disease, and many patients receive systemic therapy; however, the response to current regimens is limited. Orthotopic liver transplantation offers complete resection of locally advanced tumors in select patient groups.

Keywords

cholangiocarcinoma; hilar; multimodality; outcome; perihilar

Cholangiocarcinoma (CCA) is the second most common primary malignant tumor of the liver after hepatocellular carcinoma. Perihilar CCA is a subtype of CCA that stems from aberrant growth of the ductal epithelium in the extrahepatic biliary tree. The anatomical description of this malignancy, as classically chronicled by William Altemeier in 1957 and Gerald Klintskin in 1965, is situated either at the biliary confluence or in the proximal right

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*Author for correspondence: Tel.: +1 410 502 2387, Fax: +1 410 502 2388, tpawlik1@jhmi.edu.

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or left bile duct [1,2]. In the USA, the incidence of this disease is rare with approximately 3000 cases diagnosed annually [3]. Given the high morbidity and mortality associated with this disease as well as the complexity of its treatment, a thorough understanding of the management of perihilar CCA is critical to treat this challenging group of patients.

Epidemiology

Extrahepatic CCAs comprise approximately 80–90% of CCA, with 50–70% situated at the hilar plate of the biliary tree and 20–30% originating in the distal bile ducts [4–6]. The overall incidence of extrahepatic lesions has decreased over the last several decades, whereas the incidence of intrahepatic CCA has risen steadily [7–9]. In the USA, the age-adjusted incidence of extrahepatic CCA has decreased from 1.08 per 100,000 to 0.82 per 100,000 individuals over a 20-year period [10]. In the past, the International Classification of Diseases coding system of Klatskin tumors versus intrahepatic CCA may have contributed to misclassification of these tumors [11]. This misclassification may have led to up to a 13% overestimation of intrahepatic CCAs; however, even in light of possible misclassification bias, the age-adjusted annual incidence of intrahepatic CCA has increased by nearly 4% [12]. At the same time, the worldwide incidence of extrahepatic CCAs has reduced [9,13].

Risk factors

A wide range of risk factors have been identified among patients with perihilar CCA including advanced age, male gender, primary sclerosing cholangitis (PSC), choledochal cysts, cholelithiasis, cholecystitis, parasitic infection, inflammatory bowel disease, alcoholic cirrhosis, nonalcoholic cirrhosis and chronic pancreatitis [14–16]. One of the most influential and well-established risk factors is PSC [14,17]. Patients with PSC have a lifetime risk for CCA as high as 20% and present with early-onset disease with a median age of diagnosis in the 5th decade of life [17–20]. At autopsy, CCA has been identified in as many as 40% of patients with PSC [19]. Cholelithiasis is also a known risk factor for both intrahepatic CCA and extrahepatic CCA. In a recent large retrospective review, patients with gallstones who did not have a cholecystectomy performed had a twofold increased incidence of CCA [21]. This increased risk subsides to the equivalent of the normal population 10 years after cholecystectomy [21]. Choledochal cysts in which cystic dilatation of the biliary tree is present have been shown to be associated with extrahepatic CCA (odds ratio of 47.1 and a lifetime risk of CCA peaking at 30%) [14,22,23]. In Eastern countries, infection with the liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini* have long been known to induce hyperplasia and metaplasia of the biliary epithelial cells that may contribute to malignant transformation into CCA [24,25]. A study from Thailand demonstrated that opisthorchiasis was associated with a fivefold increased risk of CCA and an annual incidence of 87 per 100,000 [16,26].

Presentation

Patients with perihilar CCA typically present with jaundice; however, nonspecific signs such as abdominal pain, pruritus and weight loss can be present before frank jaundice is recognized. The vast majority of patients with a perihilar stricture and jaundice are presumed to have CCA until proven otherwise. Despite this, up to 10% of cases prove to be either benign strictures or another process causing obstruction of the hepatic duct confluence [27,28]. The differential diagnosis of a patient presenting with a perihilar stricture or perihilar bile duct obstruction includes PSC, postoperative biliary stricture, choledocholithiasis, gall bladder carcinoma and metastatic disease to the perihilar nodal basin. Every patient must have a comprehensive history and physical with specific importance being placed on assessment of the risk factors for CCA. Blood tests should

include a complete liver panel and tumor markers carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen. Patients with perihilar CCA classically display an elevation in alkaline phosphatase and serum bilirubin. While CA 19-9 is not specific to CCA as it is elevated in other malignancies such as pancreatic adenocarcinoma and gastric adenocarcinoma, it can help guide the clinician when benign versus malignant stricture is in question. The sensitivity and specificity of CA 19-9 is reported to be 76 and 92%, respectively, in differentiating between a benign versus malignant stricture [29]. It should also be noted that elevated levels of CA 19-9 and carcinoembryonic have been shown to correlate with tumor stage, unresectability and overall survival (OS) [30]. In patients with PSC, 37% of patients with elevated CA 19-9 do not have CCA; and thus, other diagnostic modalities must be employed to further delineate and ensure the diagnosis of CCA [31]. Concomitant elevation of carcinoembryonic increases the likelihood of CCA diagnosis in patients with elevated CA 19-9 [32].

Diagnostic imaging

Computed tomography

Preoperative imaging can help to differentiate benign and malignant strictures, as well as assess resectability of malignant disease including the identification of tumor invasion of adjacent vascular structures and distant metastatic disease. High-quality cross-sectional imaging via multidetector, contrast-enhanced helical computed tomography (multidetector computed tomography [MDCT]) is an important imaging modality for the diagnosis and surgical planning of CCA. If possible, it is usually very helpful to acquire imaging before decompression of the biliary tree, as biliary intubation may compromise the complete assessment of the lesion and cause artifact in the study.

MDCT images should be reconstructed in 1–5-mm slices in the axial, coronal and sagittal planes, as these will aid the surgeon in reconstructing the mass in 3D and assist in assessing the anatomic relationship between the tumor and the major perihilar vascular structures. The accuracy of CCA diagnosis with MDCT is markedly improved when images are obtained with thin collimation in the arterial, portal venous and delayed phases [33]. Perihilar CCA often appears as a heterogeneous, hypervascular lesion in the delayed-phase images. MDCT has been shown to be accurate for the assessment of tumor invasion and was 80% accurate in assessing horizontal tumoral spread and 100% accurate in detecting vertical tumor extension [34]. Involvement of the portal vein or the hepatic artery must be characterized in order to accurately tailor treatment in patients with perihilar CCA. A study reported MDCT to have a 96% accuracy in portal venous involvement and 93% accuracy in hepatic artery involvement [35]. Despite these reported results, the finding of unanticipated involvement of perihilar vascular structures is not uncommon at the time of surgery.

MRI

MRI and magnetic resonance cholangiopancreatography (MRCP) are other important preoperative imaging techniques for perihilar CCA. Images obtained via MRI have high quality spatial resolution; and thus, MRI is considered by many to be the imaging modality of choice for patients with CCA because of its ability to delineate the entire biliary tree and the extension of the lesion [36].

When viewing CCA on MRI, the lesion often appears hypointense compared with the liver parenchyma on T1-weighted images and hyperintense on T2-weighted images (Figure 1). The quality of MRCP-generated images has been compared directly to endoscopic retrograde cholangiopancreatography (ERCP), and studies have shown equivalent sensitivity between the two modalities [37–39]. MRCP advocates point to the noninvasive nature of MRCP and the potential, albeit low, risks being associated with direct biliary tree

manipulation. A big advantage of ERCP is that it can be both diagnostic, as well as therapeutic for patients who are in need of biliary drainage. Percutaneous transhepatic cholangiography (PTC) is another approach that may be useful to visualize the complete bile duct system, especially when the perihilar lesion is occlusive and ERCP is not feasible for drainage. MRCP can be particularly useful in the evaluation of patients with early disease, with a prospective study showing a sensitivity of 90% in detecting extrahepatic CCA [40]. The accuracy of MRI to diagnose CCA has been reported to range from 80% to as high as 95% [39,41]. Of note, diffusion-weighted imaging has a reported sensitivity of 94 versus 74% for MRCP in the diagnosis of extrahepatic CCA [42].

PET

The role of PET in CCA workup and staging currently remains in evolution. Most CCA lesions are fluorodeoxyglucose-avid and the sensitivity and specificity of PET approaches 90% [43,44]. However, PET is vulnerable to misdiagnosis when biliary stents are present, as well as in the setting of PSC, both of which are common in CCA patients. The histopathology of the tumor must be considered, as PET has significant accuracy in diagnosing nodular tumor subtypes but may be less sensitive in infiltrative subtypes [45,46]. Further limitations on PET include the increased cost as compared with other imaging modalities. MDCT has been shown to be equivalent to PET in its accuracy in diagnosing CCA, and therefore some have argued that PET is not warranted [45]. The main role of PET is the identification of distant metastases. As such, in those situations in which metastatic disease is questioned, PET may prove to be helpful. However, currently, the routine use of PET is not warranted for patients with resectable disease.

Direct biliary interventions

ERCP & PTC

As noted, ERCP or PTC or both provide a means to assess and drain the intrahepatic biliary system. These direct methods for examining the biliary system not only allow for characterization of the biliary tree anatomy but also allow for diagnostic biopsies and therapeutic decompression in cases of obstructive jaundice (Figure 2). ERCP has been shown to be equivalent to MRCP in the diagnosis of perihilar CCA with a sensitivity of 74% and a specificity of 70% [47]. PTC is favored by some surgeons because it may have a higher success in biliary decompression, allow for improved visualization of the proximal biliary tree and assist intraoperatively with the biliary anastomosis [48]. Controversy remains, however, as to the best approach and either ERCP or PTC are reasonable alternatives.

At the time of ERCP or PTC, tissue can also be obtained to assist in making a definitive diagnosis. The sensitivity of biliary biopsy ranges from 40 to 80%; and thus, a negative biopsy cannot be considered evidence of no malignancy [49-52]. The appearance of the lesion plays a key role in the number of biopsies needed to achieve a high sensitivity in the diagnosis of malignant disease. A study has shown that polypoid lesions required less biopsy samples than nodular appearing masses [53]. Biopsy yield may also be higher with 'clam-shell' biopsies rather than simply brush biopsies.

Unlike patients with hyperbilirubinemia in the setting of a distal CCA, all patients with an elevated bilirubin level (e.g., >6–7 ng/dl) should undergo preoperative biliary drainage. Despite a higher incidence of postoperative infection with stenting [54], patients undergoing an anticipated major liver resection need biliary drainage as hyperbilirubinemia may impair hepatic regeneration and hypertrophy.

Cholangioscopy

Cholangioscopy was first developed in the 1960s, although it was sparingly used in subsequent decades, given its requirement of two operators and lamentable visibility. However, with the improvement in fiber optics, the visualization of the ducts has improved tremendously, and with the advent of the SpyGlass® System, only a single operator is required [55]. The cholangioscope is advanced through the duodenoscope, and direct cannulation of the biliary tree provides the advantage of directly characterizing the mucosal patterns that are associated with malignant disease. A study showed that when cholangioscopy was added as an adjunct to ERCP, diagnostic accuracy was increased from 78 to 93% and sensitivity from 58 to 100% [56]. In a small series of patients at high risk for CCA (n = 29 patients), who had a malignant appearing stricture, direct cholangioscopy was able to accurately determine a subset of patients in whom the stricture was actually of a benign etiology [57].

Classification & staging of perihilar cholangiocarcinoma

Bismuth–Corlette anatomic classification system

The Bismuth–Corlette classification system provides an anatomic description of the tumor location and longitudinal extension in the biliary tree (Figure 3). It is limited due to its failure to characterize the radial extension of the cancerous lesion. However, it provides a practical manner for surgical oncologists to describe the lesion and in turn, the anticipated extent of liver that may need to be resected to achieve complete extirpation of the malignancy. Type I lesions involve the common hepatic duct (CHD) immediately below the confluence; type II tumors involve the CHD and extend to the confluence but not beyond; type IIIa masses involve the CHD to the confluence and extend into the main right hepatic duct; type IIIb lesions involve the CHD to the confluence and extend into the main left hepatic duct and type IV tumors involve the CHD and extend past the confluence involving both the right and left hepatic ducts [58].

Pathologic subtypes

There are three unique gross pathologic subtypes of CCA: sclerosing, nodular and papillary. As the name describes, sclerosing tumors are fibrous and constitute the majority of cases worldwide. They often manifest as a concentric thickening of the bile duct, coupled with infiltration of the periductal tissues. By contrast, nodular lesions project directly into the lumen of the bile duct. The papillary subtype is the rarest form of perihilar CCA, and these lesions are typically friable and do not invade through the ductal epithelium. As such, papillary lesions may have a more favorable prognosis compared with the other two subtypes.

Memorial Sloan–Kettering Cancer Center clinical staging system

A clinical staging system devised by the hepatobiliary surgeons at the Memorial Sloan–Kettering Cancer Center accounts for longitudinal extension of the tumor and incorporates the radial extension of the mass to more accurately reflect the resectability of the lesion (Table 1) [59]. Specifically, the clinical T-stage is comprised of the local tumor involvement, portal vein involvement and hepatic lobar atrophy. This staging system accurately predicts resectability, the probability of metastatic disease and long-term survival. This system is used to stratify preoperatively patients in regards to the likelihood of resectability and can be used to counsel patients on the potential for a R0 resection. The Memorial Sloan–Kettering Cancer Center staging system for perihilar CCA has since been externally validated [60].

American Joint Committee on Cancer TNM staging system

Most carcinomas are staged via the classic TNM staging, and this is no different for CCA (Box 1 & Table 2). The new edition of the American Joint Committee on Cancer staging system now differentiates extrahepatic CCA into perihilar and distal CCAs, each with its own distinct staging criteria [61]. Studies have shown that the biology of these tumors necessitates individualized treatment paradigms for these discrete lesions [5,6]. One of the major setbacks of the TNM system is its inability to provide the surgeon with any preoperative stratification in regards to degree of resectability. More recently, the American Joint Committee on Cancer staging system has come into question regarding its failure to incorporate tumor depth as part of its histopathologic criteria used in the determination of the T classification. The current T classification in the new TNM system remains unchanged, and it relies on whether the lesion is confined to the bile duct. de Jong *et al.* have recently demonstrated that using tumor depth more accurately stratifies patients and is a better predictor of long-term outcome in patients with perihilar CCA [62]. In this study, tumor depth invasion of more than 5 mm bile resulted in a median survival of 18 months, whereas bile duct invasion of less than 5 mm exhibited a median survival of 30 months (Figure 4). The authors argue that tumor depth is exceedingly important in predicting patient prognosis, as the bile duct is not uniformly concentric along its length [62]. This study suggests further refinements to the TNM staging system for CCA may be needed in future editions of the manual.

International Cholangiocarcinoma Group staging system

A group of international experts has recently proposed a new staging system for perihilar CCA [63]. The thought behind the new staging scheme is to consolidate the current staging systems by taking the important features of every system. It brings the anatomic, pathologic and surgical characteristics of perihilar CCA together. The system provides information about the anatomical location of the tumor along the bile duct, which is labeled B, the involvement of the portal vein denoted as PV, the involvement of the hepatic artery indicated as HA, the volume of the future liver remnant labeled as V, the lymph node status designated as N, metastases status as M, tumor size as T, the tumor pathologic form as F and any underlying liver disease labeled as D (Table 3). If accepted by the international community, this staging system could alleviate many of the current problems with perihilar CCA data comparison across different institutions.

Portal vein embolization

Locally advanced perihilar plate lesions frequently require an extended hepatectomy to ensure negative surgical margins. Up to 70–80% of the liver can be safely removed with a major hepatic resection; however, if the future liver remnant (FLR) is less than 20–40%, the risk of prolonged hospital stay as well as morbidity and mortality are increased [64–67]. Preoperative portal vein embolization (PVE) can be employed to augment the synthetic function and overall volume of the FLR prior to an extended hepatectomy [64,68, 69]. Most groups agree that an FLR of 20–25% is needed to ensure adequate hepatic function postoperatively, and an FLR of 40% is necessary in patients with compromised liver function/fibrosis/cirrhosis [70].

To perform PVE, interventional radiologists gain access to the portal venous system and occlude the ipsilateral portal vein with either polyvinyl alcohol particles, coils or other embolic materials to achieve near stasis in the selected segmental branches. At the cellular level, various mitogens are released including HGF and EGF in response to PVE and hepatocytes regenerate leading to hypertrophy of the contralateral hemiliver [71]. Patients with diabetes may have decreased rates of hypertrophy following PVE, as insulin has been

shown to be a comitogenic factor for HGF [72]. Liver regeneration usually peaks within the first 2 weeks and typically the FLR is reassessed approximately 4 weeks after the PVE. If the FLR has hypertrophied appropriately, the resection can be performed at that time.

Surgery

Resectability

Surgical resection offers the only chance for potential curative therapy in perihilar CCA. The total number of resections, even at major centers, is limited by the unfortunate reality that many patients presenting with perihilar CCA are too locally advanced to undergo curative resection. Even after a patient is taken to the operating theatre, resection is found to be not feasible intraoperatively in a subset of patients. Specifically, resectability rates range from 35 to 94%, and this variability may reflect the differences in preoperative imaging modalities, surgeon expertise and the long inclusion dates on these retrospective series [6,59,73-80]. Among patients who undergo curative intent resection of perihilar CCA, the reported incidence of a margin negative resection ranges from 14 to 78% depending on the particular institution; and thus, the chance for curative resection is highly variable [6,59,73-80].

R0 resection is of utmost importance and has been linked to improved survival [3,4,59,81,82]. It is now universally accepted that perihilar CCA necessitates a major hepatic resection to achieve both longitudinal and radial margins negative for tumor. Case series with low rates of hepatic resections have concomitant reduced rates of margin negative resections ranging from 10 to 30% [77,79,83], while those centers with major hepatic resections have achieved margin negative resections in 68–95% of patients [84-86]. R0 resection is important for OS; and due to the extent of resection required, this can be achieved more readily at specialized hepatobiliary centers [87]. Whether the extent of hepatic resection should routinely include the caudate lobe has been a topic of some discussion. The caudate ductal system empties into both the right and left hepatic ducts, although its primary drainage is into the left biliary tree [86]. While the data are limited, retrospective analysis has shown that caudate lobe resection is associated with a decrease in local recurrence and an increase in 5-year survival [88,89]. A recent examination of 127 patients showed that patients who underwent caudate lobectomy had an OS of 64 versus 34.7 months compared with those without a caudate lobectomy [90]. Whether complete resection of the caudate is routinely necessary is unclear. However, when performing a right hepatectomy, the caudate process should be removed; the paracaval process and Spiegel's lobe of the caudate should be resected for tumors extending into the left hepatic duct (Bismuth–Corlette type IIIb) that necessitate a left hepatectomy.

Routine *en bloc* lymphadenectomy of the perihilar and pericholedochal nodal basins should be performed in all patients with perihilar CCA. Metastasis to regional lymph nodes is relatively common among patients with perihilar CCA ranging from 30 to 50%. Patients with lymph node metastasis have a decreased 5-year survival ranging from 30 to 15 % [82,91].

Due to the anatomical relationship at the hepatic hilum, it is not uncommon to have abutment or frank involvement of the tumor with the portal vein. Some investigators have advocated the routine use of portal vein resection (so-called 'no touch technique') in order to adhere to more strict oncologic principles for *en bloc* eradication of disease [81]. These investigators have reported a higher rate of R0 resections when portal vein resections were employed. When curative resection was achieved, the authors noted a 5-year survival of 65% in the portal vein resection cohort versus 28% among patients who did not have portal vein reconstruction [81]. However, the mortality associated with portal vein resection was

not trivial with a reported 60-day mortality of 17 versus 5% for those patients who did not undergo portal vein resection [81]. Other groups have not been able to replicate the improved 5-year survival following portal vein resection [92-94]. As such, routine portal vein resection is not performed at most major hepatobiliary centers. While routine portal vein resection may not be warranted, patients with actual focal involvement of the portal vein should be strongly considered for segmental portal vein resection and reconstruction to facilitate complete extirpation of all disease.

Morbidity & mortality

Despite advances over the last few decades, resection of perihilar CCA continues to have perioperative risks and a high rate of morbidity. The incidence of morbidities following surgery for perihilar CCA have been reported to range from 14 to 66% [6,59,73-80,95]. Complications following surgery can include bleeding, liver failure, biliary fistulas, hemobilia and infectious complications (wound infection, cholangitis, intra-abdominal abscess, pneumonia and hepatic abscess) [6,59,73-80,95]. Infectious complications are typically the most common and account for 50–80% of all complications. Due to the complex nature of the perioperative period and the difficulties in managing these morbidities, it is strongly preferable that resection of perihilar CCA be undertaken only at specialized hepatobiliary centers. The mortality rates associated with resection of perihilar CCA range from 0 to 19% and can be due to fulminant hepatic failure or uncontrolled sepsis [6,59,73-80,95]. It should be kept in mind that the morbidity and mortality following resection of perihilar CCA may be higher than the general outcome results often reported for other types of hepatic resection.

Long-term outcomes & recurrence

Modest 5-year survival rates and tumor recurrence remain unfortunate realities among patients with perihilar CCA. The outcomes following surgical resection are notable for 5-year survival rates that range from 11 to 40% [6,59,73-80]. Tumor recurrence rates can be as high as 50–65%, and the median time to recurrence has been reported to be 12–43 months [82,88,96,97]. The most common sites for tumor recurrence include local recurrence, the peritoneum, the liver and the lung [6,82,88,96]. A wide array of clinical variables has been identified to be independent predictors of long-term survival and recurrence. Factors associated with a worse outcome include positive margins, higher T stage, metastatic lymph node spread, perineural and perivascular invasion, nonpapillary tumor subtypes and poor tumor differentiation. Of these parameters, the only variable in which the surgeon plays a major role is the margin negative resection, and emphasis needs to be placed on the ability of the surgeon to achieve an R0 resection. The value of an R1 resection has recently been shown to improve long-term survival as compared with foregoing surgical therapy, and thus, some cancer centers have become more aggressive in their pursuit of borderline resectable perihilar lesions [98].

Chemotherapy

Due to the late presentation of CCA and its aggressive biology, many patients may have unresectable disease or potentially benefit from adjuvant chemotherapy following surgery. While different therapeutic regimens have been investigated, the overall response to systemic therapy has been poor. Data on chemotherapy for CCA are limited by the small number of patients accrued to the trials as well as the inclusion of different biliary tree malignancies (extrahepatic, perihilar and gall bladder) in the same cohort for some studies.

Among patients with good performance status, chemotherapeutic regimens should be employed for unresectable lesions. Data have shown an improvement in quality of life and

OS with systemic chemotherapy versus best supportive care for unresectable disease [99]. The most highly studied agents are gemcitabine and 5-fluorouracil, sometimes used in combination with mitomycin C, capecitabine, cisplatin, epirubicin and oxaliplatin. A pooled analysis of all the available clinical trials on CCA has been conducted and these data suggest that gemcitabine with cisplatin or oxaliplatin were the most effective regimens [100]. A recent prospective, randomized trial of 400 patients with unresectable CCA showed an OS of 11.7 months among patients who received gemcitabine plus cisplatin versus 8.3 months for patients receiving gemcitabine alone (Figure 5) [101]. This trial also demonstrated an improvement in median progression-free survival of 8.4 versus 6.5 months. Thus, gemcitabine plus cisplatin (or oxaliplatin) has become the standard of care for systemic therapy. The question of adjuvant therapy still remains controversial in perihilar CCA. A small retrospective study found that patients who received adjuvant gemcitabine therapy had an improved 5-year survival of 57 versus 23% for those treated with surgery alone [102]. Prospective studies are ongoing to address this issue.

Targeted therapy for perihilar CCA has also been investigated on a limited basis. Specifically, therapy with the EGF receptor antibody cetuximab in combination with chemotherapy has shown some promise. In a recent Phase II study, cetuximab plus gemcitabine plus oxaliplatin noted a complete response among 10% of patients and a partial response among 63% of patients [103]. In this trial, 33% of patients who were previously deemed unresectable underwent potentially curative operations after they responded to the chemotherapeutic regimen. Bevacizumab, a VEGF antibody, has also been investigated in combination with chemotherapy in advanced biliary tree malignancies. Data from a small Phase II study showed a median progression-free survival of 7 months and an OS of 12.7 months [104]. Targeted therapy with sorafenib, an inhibitor of tyrosine and Raf protein kinases has recently been investigated in patients with CCA. A recent intention-to-treat analysis showed a progression-free survival of 2.3 months and a median survival of 4.4 months in patients with advanced biliary tree carcinoma [105]. The drug proved safe to use in patients with minimal side effects; however, the efficacy of this regimen as compared with current therapy is limited. Future studies will be needed to examine the role of targeted agents in the treatment of perihilar CCA completely and to identify patients most likely to benefit from abrogation of these pathways.

Radiotherapy

The role of locoregional therapy with external beam radiation remains ill defined for perihilar CCA. In the adjuvant setting, several groups have reported no survival benefit with radiotherapy following curative intent operations [106-109]. By contrast, other small studies have shown an increased survival benefit with adjuvant radiotherapy. One such study in Japan demonstrated an increase in 5-year survival from 13 to 34% among patients receiving adjuvant radiotherapy [110]. Cheng *et al.* reported a 10% increase in the 5-year survival among patients receiving adjuvant external beam radiation, noting that radiotherapy was a significant independent predictor of outcomes [111]. A study from The Netherlands comparing 112 patients who did not receive adjuvant radiation had a median survival of 8 versus 24 months for patients who did undergo radiotherapy [112]. In this same study, patients who received adjuvant external beam radiation plus intraluminal brachytherapy showed an increase in complications (e.g., pain and cholangitis) without any additional survival benefit associated with brachytherapy [112]. The use of adjuvant radiotherapy may be particularly warranted in patients with positive surgical margins. Stein *et al.* demonstrated that adjuvant radiation increased OS among patients who had undergone an R1 resection such that it was comparable with the outcomes of patients who had an R0 resection [113].

Radiation therapy in the setting of unresectable perihilar CCA may have a palliative role. Palliative radiotherapy has been shown to improve pain control, maintain biliary patency and increase OS [106,114]. Some studies have even suggested that radiotherapy alone, when used early enough, can maintain adequate decompression of the biliary tree and mitigate the need for drainage while improving patient quality of life [114]. However, even with radiotherapy, most patients with unresectable perihilar CCA will require biliary decompression. Patients treated with biliary tree decompression and concomitant radiotherapy have been reported to have a median survival of 14 months and a relatively satisfactory quality of life [115]. While conventional fractionated radiation therapy can be effective, it takes 5–6 weeks to deliver the treatment and requires concurrent chemotherapy. Recent advances in radiotherapy, such as fractionated stereotactic body radiotherapy (SBRT), uses multiple beams to deliver high doses of radiation to the perihilar tumor plus a small margin [116]. SBRT is typically delivered over 3–5 days, it does not require concurrent chemotherapy and limits dose to adjacent normal tissues. SBRT, therefore, typically has fewer treatment-related toxicities than standard chemoradiation. A study by Momm *et al.* reported the results of 13 patients with Klatskin tumors who received 32–56 Gy [117]. An impressive median survival of 33.5 (6.6–60.4) months was reached with SBRT after diagnosis. Patients experienced nausea and recurrent cholangitis, but otherwise SBRT was well tolerated. Although encouraging, prospective data are needed to validate the role of SBRT in CCA. Radiation, however, while associated with palliative benefits can also be associated with some morbidity including cholangitis, duodenitis and increased cost as compared with more conservative, supportive measures of palliation [118].

Photodynamic therapy

Photodynamic therapy (PDT) involves the intravenous administration of photosensitizing agents that accumulate within the malignant cells of interest. Following uptake of the agent, specific wavelengths of light are delivered that activate the photosensitive agent inducing tumor necrosis by excitation of the phototoxic molecules [119]. The typical extent of tissue destruction is approximately 5 mm, thereby obviating collateral damage; however, the relatively limited penetration also makes this therapy less effective for advanced lesions [120]. Several studies have observed PDT in patients with inoperable perihilar CCA and have reported increased survival, improved quality of life and increased patency of the biliary tree [121–124]. Ortnier *et al.* designed a small randomized controlled trial looking at patients with unresectable perihilar lesions [124]. One cohort was comprised of palliative biliary stent placement while the other arm had concomitant PDT following stent placement. The trial was stopped as the PDT arm showed a marked improvement in overall median survival (16 vs 3 months) while also demonstrating improved quality of life and biliary patency [124]. Cheon *et al.* demonstrated increased survival for unresectable patients who underwent stenting plus PDT as compared with patients who underwent stenting alone [125]. PDT as a neoadjuvant modality has not been extensively studied. In a small trial, neoadjuvant PDT in seven patients led to 100% R0 resections and a 1-year survival of 83% [126]. Due to the small sample size, further investigation is warranted before routine use of neoadjuvant PDT can be recommended. Cutaneous phototoxicity is the major side effect occurring in 30% of recipients; and thus, patients are instructed to avoid direct sunlight for 4 weeks after treatment [127].

Orthotopic liver transplantation

Complete resection of locally advanced perihilar CCA can also be achieved by orthotopic liver transplantation (OLT) in judiciously selected patients. Given the importance of complete extirpation of all disease, OLT is another surgical modality to be considered. Early trials of OLT in patients with CCA were disappointing as recurrence rates were high and 5-

year survival was reported to be only 10% [128]. For example, the Cincinnati Transplant Tumor Registry reported a recurrence rate of 50% and a 5-year survival of 28% [129]. Further analysis of these data showed that patients who had small tumors, no contiguous organ involvement and negative lymphatic basins had a better long-term survival [130]. This led to the pursuit of aggressive neoadjuvant protocols coupled with OLT developed at both the University of Nebraska (NE, USA) and the Mayo Clinic. The Mayo protocol consists of external beam radiation to 45 Gy with continuous infusional 5-fluorouracil followed by intrabiliary radiation and oral capecitabine until the time of OLT. A staging laparotomy is performed on all patients before OLT to rule out metastatic disease. The results have been promising with the Mayo group reporting a 5-year survival of 73% in these highly selected patients [131]. The Mayo group found that predictors of recurrence following OLT were elevated CA 19-9 >500 U/ml (Hazard ratio [HR] of 1.8), portal vein encasement (HR: 3.3) and residual tumor on explant (HR: 9.8) [132]. More recently, a retrospective review looking at locally advanced CCA compared with traditional resection with OLT demonstrated that neoadjuvant chemotherapy and OLT was superior to radical resection and adjuvant therapy [133,134]. Some have questioned the applicability or generalizability of these data, noting the extremely stringent inclusion and exclusion criteria, as well as possible selection bias inherent in some of these studies. While OLT is a reasonable option for certain patients with perihilar CCA, patient selection and the indications for OLT relative to resection are still emerging.

Expert commentary & five-year view

Perihilar CCA remains difficult to diagnose and treat in many patients. Diagnosis of perihilar CCA needs to include state-of-the-art cross-sectional imaging often with MRI or MRCP. Biliary drainage can be achieved either endoscopically or percutaneously and should be employed in patients with hyperbilirubinemia who need a major hepatic resection. Surgery for perihilar CCA should routinely include hepatic resection to ensure a higher likelihood of an R0 resection. Routine portal vein resection is not warranted and should be undertaken only when necessary to completely extirpate all disease. While progress has been made in the treatment of patients with perihilar CCA, further advancements over the subsequent 5 years – especially in the area of systemic therapies – are needed to improve the long-term survival outcome of patients with this challenging disease. Research should focus on the development of targeted therapies to directly alter the metabolic and signaling pathways specific to CCA tumor cell growth and distant organ metastasis. Furthermore, the role of adjuvant systemic and radiation therapy has been poorly established in patients with biliary tree tumors, and these questions should be addressed in formal prospective multicenter trials. Finally, OLT for perihilar CCA has been explored; however, its role should be further elucidated in locally advanced patients. Specifically, the current data should be reproduced by other centers, and trials should be performed in a prospective fashion. Specific criteria on the eligibility for OLT should be clearly defined by hepatobiliary surgeons and the transplant surgery community, in order to expose patients to the full range of treatment options.

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- of interest
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Box 1**TNM staging for hilar cholangiocarcinoma****Primary tumor (T)**

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma *in situ*
- T1: Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
- T2a: Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
- T2b: Tumor invades adjacent hepatic parenchyma
- T3: Tumor invades unilateral branches of the portal vein or hepatic artery
- T4: Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery and portal vein)
- N2: Metastasis to periaortic, pericaval, superior mesenteric artery and/or celiac artery lymph nodes

Distant metastasis (M)

- M0: No distant metastasis

The new edition of the American Joint Committee on Cancer staging system now differentiates extrahepatic cholangiocarcinoma into perihilar and distal cholangiocarcinomas, each with its own distinct staging criteria.

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Key issues

- Perihilar cholangiocarcinoma (CCA) is a complex disease best approached by a multimodal treatment regimen.
- The incidence of CCA is approximately 3000 patients in the USA. Previous data had leaned towards an increased incidence of intrahepatic CCAs worldwide; however, this has been proved to be secondary to a misclassification of Klatskin's tumors as intrahepatic CCAs.
- Both multidetector computed tomography and MRI/magnetic resonance cholangiopancreatography have been shown to be highly sensitive in the detection of perihilar CCAs. Either imaging modality is appropriate prior to operative resection in order to clearly delineate the arterial, venous and biliary anatomy in relation to the tumor.
- R0 resection is of utmost importance and has been linked to improved survival. It is now universally accepted that these lesions necessitate a major hepatic resection to achieve both longitudinal and radial margins negative for tumors.
- Recent advances in radiotherapy, such as stereotactic body radiotherapy, have shown impressive results as adjuvant therapy improving overall median survival while minimizing collateral damage to surrounding organ systems.
- Orthotopic liver transplantation has proven to be of benefit in a subgroup of patients who are not resectable at the time of diagnosis with perihilar CCA, and this therapeutic option should be held in the clinician's armamentarium.

Figure 1. Magnetic resonance cholangiopancreatography of hilar cholangiocarcinoma (A) Magnetic resonance cholangiopancreatography and (B) MRI revealing a 1.9×1.6 cm hyperintense T2 lesion (arrow) that demonstrates delayed enhancement in the region of the porta hepatis. The mass causes moderate intrahepatic biliary ductal dilation and is a concern for Klatskin tumor.

Figure 2. Placement of left-sided percutaneous transhepatic cholangiography for preoperative biliary drainage (long arrow)

Note the stricture/obstruction at the level of the hilum (short arrow).

Figure 3. The Bismuth–Corlette classification system provides an anatomic description of the tumor location and longitudinal extension in the biliary tree

(A) Locations of cholangiocarcinoma in the biliary tree. (B) Morphological subtypes of cholangiocarcinoma. (C) Bismuth–Corlette classification of hilar cholangiocarcinoma. Reproduced with permission from [135].

Figure 4. Tumor depth may more accurately stratify patients with regard to long-term outcome in patients with perihilar cholangiocarcinoma
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Figure 5. Outcome of patients treated with systemic chemotherapy for cholangiocarcinoma
 A randomized trial of 400 patients with unresectable cholangiocarcinoma showed an improvement in both overall **(A)** and disease-free **(B)** survival among patients who received gemcitabine plus cisplatin versus gemcitabine alone. **(A)** Hazard ratio for death: 0.64 (95% CI: 0.52–0.80); $p < 0.001$. **(B)** Hazard ratio for disease progression: 0.63 (95% CI: 0.51–0.77); $p < 0.001$. Reproduced with permission from [101].

Table 1

Proposed T-stage criteria for hilar cholangiocarcinoma.

Stage	Criteria
T1	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles
T2	Tumor involving biliary confluence ± unilateral extension to second-order biliary and ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + bilateral extension to second-order biliary radicles; or unilateral extension to second-order biliary radicles with contralateral hepatic lobar atrophy; or main or bilateral portal venous involvement

A clinical staging system devised by the hepatobiliary surgeons at the Memorial Sloan–Kettering Cancer Center accounts not only for longitudinal extension of the tumor, but also incorporates the radial extension of the mass to more accurately reflect the resectability of the lesion. Reproduced with permission from [59] © Lippincott Williams and Wilkins (2001).

Table 2

TNM staging for hilar cholangiocarcinoma: anatomic stage/prognostic groups.

Stage	Primary tumor	Regional lymph nodes	Distant metastasis
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a–b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1–3	N1	M0
Stage IVA	T4	N0–1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

For definitions of the different stages please see Box 1.
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Table 3

Proposed classification system for perihilar cholangiocarcinoma.

Label	Side/location	Description
<i>Bile duct[†] (B)</i>		
B1		Common bile duct
B2		Hepatic duct confluence
B3	Right	Right hepatic duct
B3	Left	Left hepatic duct
B4		Right and left hepatic duct
<i>Tumor size (T)</i>		
T1		<1 cm
T2		1–3 cm
T3		3 cm
Sclerosing		Sclerosing (or periductal)
Mass		Mass forming (or nodular)
Mixed		Sclerosing and mass forming
Polypoid		Polypoid (or intraductal)
<i>Involvement (>180°) of the PV</i>		
PV0		No portal involvement
PV1		Main PV
PV2		PV bifurcation
PV3	Right	Right PV
PV3	Left	Left PV
PV4		Right and left PV
<i>Involvement (>180°) of the HA</i>		
HA0		No arterial involvement
HA1		Proper HA
HA2		HA bifurcation
HA3	Right	Right HA
HA3	Left	Left HA
HA4		Right and left HA
<i>Liver remnant volume (V)</i>		
V0		No information on the volume needed (liver resection not foreseen)
V%	Indicate segments	Percentage of the total volume of a putative remnant liver after resection
<i>Underlying liver disease (D)</i>		
		Fibrosis
		Nonalcoholic steatohepatitis
		Primary sclerosing cholangitis
<i>Lymph nodes (N)[‡]</i>		

Label	Side/location	Description
N0		No lymph node involvement
N1		Hilar and/or HA lymph node involvement
N2		Periaortic lymph node involvement
<i>Metastases (M)[§]</i>		
M0		No distant metastases
M1		Distant metastases (including liver and peritoneal metastases)

[†]Based on Bismuth–Corlette classification [19,20].

[‡]Based on the Japanese Society of Biliary Surgery Classification [48].

[§]Based on the TNM classification [21].

HA: Hepatic artery; PV: Portal vein.