

Current Management of Perihilar Cholangiocarcinoma and Future Perspectives

Heather L. Lewis¹, Amir A. Rahnama-Azar², Mary Dillhoff¹, Carl R. Schmidt¹, Timothy M. Pawlik¹

¹Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH

²Department of Surgery, University of Washington Medical Center, Seattle, WA

Corresponding author:

Timothy M. Pawlik, MD, MPH, PhD
Professor and Chair
The Urban Meyer III and Shelley
Meyer Chair for Cancer Research
Department of Surgery
Wexner Medical Center,
Ohio State University
395 W. 12th Ave., Suite 670,
Columbus, OH
Email: Tim.Pawlik@osumc.edu

Rezumat

Managementul actual al colangiocarcinomului perihilar și perspective

Colangiocarcinomul perihilar este cel mai des întâlnit tip de cancer al căilor biliare, asociat cu o mortalitate ridicată din cauza întârzierii prezentării la medic. Pentru stabilirea diagnosticului și planificarea preoperatorie este nevoie de modalități imagistice cu secțiuni transversale de înaltă rezoluție. Deși rezecția chirurgicală cu margini de rezecție negative dă speranța vindecării, doar un mic procent al pacienților pot beneficia de intervenție chirurgicală la momentul diagnosticului. Embolizarea venei porte și decompresia căilor biliare au prioritate în cazul unor pacienți, înainte de intervenția chirurgicală. Transplantul hepatic combinat cu tratamentul neoadjuvant a avut rezultate foarte bune la pacienți selectați cu afecțiuni inoperabile, cu o rată de supraviețuire de 5 ani fără recidivă. Gemcitabina plus cisplatin constituie tratamentul chimioterapeutic de bază la pacienții cu colangiocarcinom perihilar metastatic inoperabil. Progresele recente în înțelegerea patogenezei moleculare a colangiocarcinomului au generat un interes ridicat în identificarea de tratamente inovatoare care au ca obiectiv căi moleculare cu rol cheie. În cele de față, prezentăm o trecere în revistă a principiilor actuale de management al pacienților cu colangiocarcinom perihilar.

Cuvinte cheie: cancerul căilor biliare, Klatskin, colangiocarcinom, colangiocarcinom extra-hepatic, management, colangiocarcinom perihilar, chirurgie

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Abstract

Perihilar cholangiocarcinoma is the most common type of biliary tract cancer and is associated with a high mortality, usually due to late presentation. High-resolution cross-sectional imaging modalities are necessary for diagnosis and preoperative planning. Although surgical resection with negative margins offers the only hope for cure, only a small subset of patients are amenable for surgery at the time of diagnosis. Portal vein embolization and biliary tract decompression are important in some patients prior to surgical resection. Liver transplantation in combination with neoadjuvant therapy has resulted in excellent 5-year recurrence-free survival rates in highly selected patients with inoperable disease. Gemcitabine plus cisplatin constitute the backbone of chemotherapy in patients with inoperable metastatic perihilar cholangiocarcinoma. Recent advances in understanding the molecular pathogenesis of CCA have created a growing interest in identifying novel therapies targeting key molecular pathways. Herein, we provide an overview of the most current principles of management of patients with perihilar cholangiocarcinoma.

Key words: biliary tract cancer, Klatskin, cholangiocarcinoma, extra-hepatic cholangiocarcinoma, management, perihilar cholangiocarcinoma, surgery

Introduction

Cholangiocarcinoma (CCA) is a diverse group of rare gastrointestinal malignancies arising from the biliary tract epithelium (1). CCA encompasses three distinct anatomic categories, namely intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) cholangiocarcinoma, all of which demonstrate different clinical, morphologic and epidemiologic features (*Fig. 1 A, B*) (2). The perihilar variant (pCCA) is the most common subtype (50-60%) which arises from malignant proliferation of epithelial cells located between the second-degree bile ducts and the insertion of cystic duct into the common bile duct (3,4). In 1957, Dr. William Altemeier described the first series of three patients with hilar cholangiocarcinoma (5). However, Gerald Klatskin is more broadly recognized for his description of the unique features of CCA which occurs at the confluence of the left and right hepatic ducts (6). Hilar cholangiocarcinoma has since borne the moniker of “*Klatskin tumor*”.

Although surgical resection with negative margins remains the only potentially curative therapy, most patients do not have disease amenable to this treatment strategy at the time of diagnosis. More recently, advances in the understanding of the genetic landscape of CCA have introduced the potential for superior

systemic therapeutic agents which may improve patient outcome. In this review, we provide an overview of the most current principles of management of patients with pCCA and how the understanding of the genetics of cholangiocarcinoma may influence future treatment algorithms.

Epidemiology and Risk Factors

Globally, CCA accounts for approximately three percent of all gastrointestinal malignancies (7,8). The incidence and mortality rates of extrahepatic CCA are declining worldwide, while those of iCCA are rising. Like most cancers, the risk of CCA increases with age and the typically age of presentation is 60-70 years. There is a wide geographic disparity in incidence rate of CCA, perhaps related to variation in exposure to risk factors. Although the annual incidence rate of CCA in the United States is reported to be 1-2 cases per 100,000, this rate is notably higher in eastern Asian countries (8). For instance, Northeast Thailand has reported rates of 85/100,000, most likely attributable to the high infection rates with the liver flukes *Clonorchis sinensis* (*C. sinensis*) and *Opisthorchis viverrini* (*O. viverrini*). Similar trends have been observed in China and Korea (9). Europe, as with other Western

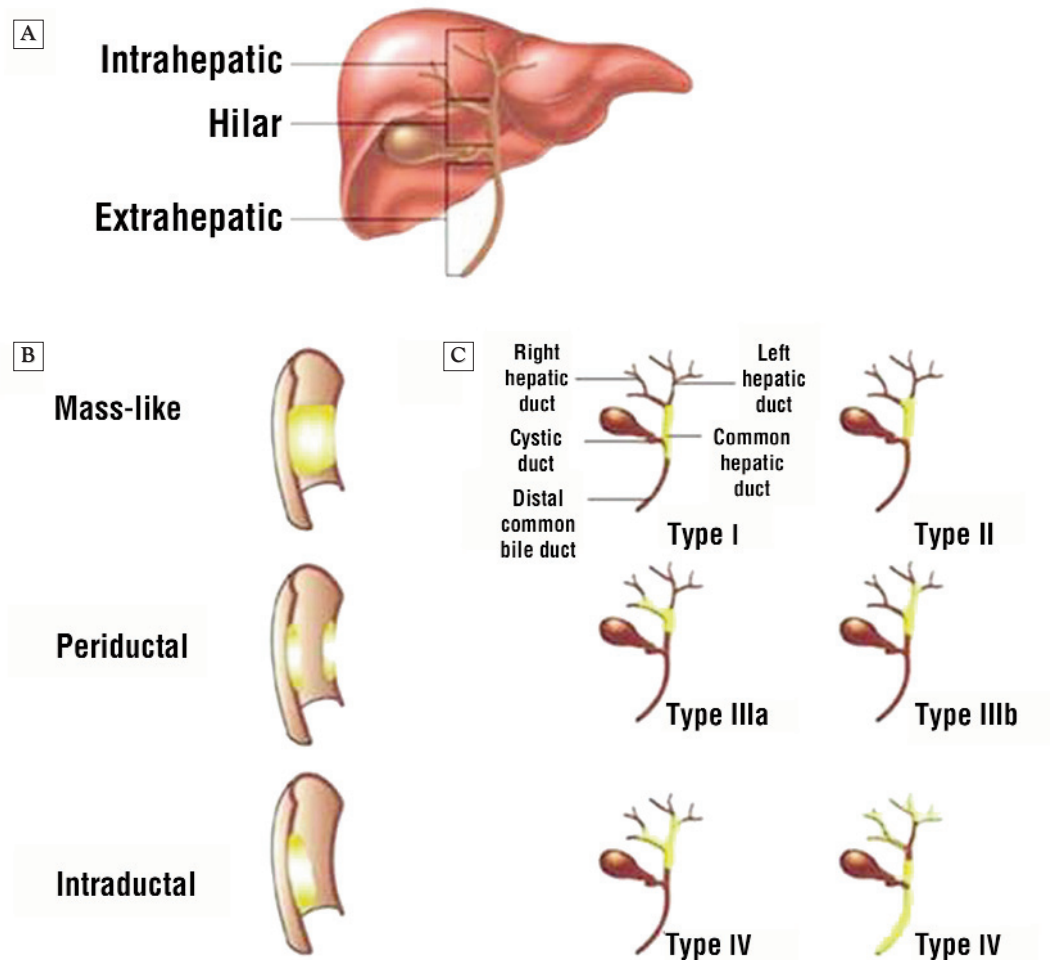


Figure 1. Classification of cholangiocarcinoma. **(A)** The classification of cholangiocarcinoma can be based on anatomic location: intrahepatic, hilar or extrahepatic; **(B)** Lesions can be further characterized as mass-like, periductal or intraductal; **(C)** Bismuth classification for hilar lesions (Bismuth and Corlette, 1975). Type I: Involvement of hepatic duct below the bifurcation, Type II: Involvement of bifurcation without invasion of second order ducts, Type IIIa: Involvement of right sided ducts into second order, but with sparing of left second order ducts, Type IIIb: Involvement of left sided ducts into second order, but with sparing of right second order ducts, Type IV: Involvement of bilateral second order ducts and/or skip lesions

countries, report overall lower incidence rates, although there is some heterogeneity to these trends (10).

Although most cases of CCA occur sporadically, chronic inflammatory processes of the biliary tract, such as primary sclerosing cholangitis (PSC), hepatolithiasis, choledochocyst, Caroli's disease, and parasitic infestation with liver flukes are well-established risk factors. In Western countries, PSC is the most common predisposing condition, especially for pCCA (11). The lifetime risk of developing CCA in patients

with PSC ranges between 5-40%, with a possible association with duration of the disease (12-14). In contrast, infestation with the hepatobiliary flukes *O. viverrini* and *C. sinensis* the most commonly reported risk factor in Asian countries, especially in Southeast Asia as these parasites are endemic in these areas (15,16). Both *O. viverrini* and *C. sinensis* have been deemed by the International Agency for Research on Cancer as carcinogenic to humans based on their ability to increase the risk of CCA development (12). Other chronic liver infections,

such as Hepatitis B (HBV) and Hepatitis C (HCV), have been studied in conjunction with the diagnosis of CCA in Asia, Europe, and the United States. However, no association with extrahepatic CCA and these infections has been well established, although in some studies intrahepatic CCA has been associated with HCV as well as with cirrhosis (9,17-20). Choledochal cysts and Caroli's disease are rare congenital disorders reported to be associated with a 15-20% risk of development of malignant changes after the second decade of life (21,22). Hence, the recommendation for surgical resection within the first decade of life is made for this patient population in order to diminish the risk of malignancy, although the risk does not ever return to that of the general population (23).

Histopathology and Molecular Pathogenesis

The vast majority of pCCAs are adenocarcinomas (>90%) with rare occurrence of other histologic subtypes such as squamous cell carcinoma and signet-ring carcinoma (24-26). Further differentiation of pCCA can be made based on three subtypes, sclerosing (>70%), nodular (20%) and papillary (5-10%) (26,27). A dense desmoplastic reaction is characteristic of the sclerosing subtype, which may complicate the success of preoperative diagnosis by tissue sampling and cytology as malignant cells may be found in clumps mixed within the inflammatory milieu of cells, potentiating the risk for false negative results (28). Immunohistochemical (IHC) staining is most frequently done for cytokeratins (CK7 and CK19), carcinoembryonic antigen, and mucins, although no pathognomonic stain is available for malignancies of biliary tract origin (28). Systematic reviews and meta-analyses of IHC performed in resected CCA has demonstrated an association of the patients' postoperative survival with markers for fascin, VEGF-A, c-erbB-2, EGFR, MUC1, MUC4, p38delta and p27. Marker expression may also vary between iCCA and extrahepatic CCA, which further confirms the biologically distinct behavior of these lesions (29-31).

While nodal metastasis typically occurs via

perineural and periductal lymphatic channels and distal metastasis occur via the hematogenous route, local progression of pCCA usually occurs through intrahepatic ductal extension. Regional (hilar, cystic duct, choledochal, portal, hepatic artery) lymphadenopathy is common and may be considered a relative contraindication for aggressive surgical therapy because of poor prognosis (3,32,33). Lymph node involvement distal to the hepatoduodenal ligament is considered distant disease.

The cellular origin of pCCA is postulated to be in the biliary epithelium and peribiliary glands. Recent studies have demonstrated that gene expression and IHC profiles of mucin-producing pCCAs are similar to the cholangiocytes lining perihilar and large bile ducts (34). The chronic inflammatory state which is thought to contribute to tumor development works through the release of inflammatory cytokines that induce oxidative stress with resultant DNA damage. These cytokines may also create an immune-suppressive environment that promotes tumor cell survival and proliferation by blockade of the apoptosis normally induced by DNA damage (35). Epidermal growth factor receptor (EGFR), along with ERBB2, has also been implicated in cholangiocarcinogenesis. The overexpression of these receptors is associated with activation and up-regulation of growth signals. Additionally, bile acids have been demonstrated to further activate EGFR and increase the expression of oxidative agents (34).

The role of chromosomal aberrations in cholangiocarcinogenesis has been most well studied in the setting of iCCA. Patterns of genomic change appear to be related to the differences in etiology and ethnicity (36). Gains and losses in chromosomal regions containing oncogenes and tumor suppressor genes (e.g. EGFR, ERBB2, MAP2K2/MEK) have been correlated with the development of CCA (37, 38). Most somatic mutations occur at a low frequency. IDH 1/2 mutations, one of the most frequently detected mutations in CCA pathogenesis, are more common in iCCA compared with extrahepatic CCA (22% vs. 7%, respectively; $p = 0.03$) (39,40). Notably, the somatic

mutations found in patients with *O. viverrini* related CCA (e.g. MLL3, ROBO2, RNF43, PEG3, and GNAS) were significantly different than non-infectious CCA (e.g. BAP1, IDH1 and IDH2) (30,31). TP53 and KRAS mutations are frequently seen in CCA patients from all geographic regions including Asia, Europe and the United States. Multiple pathways and genomic alterations are known to be aberrant in CCA include wnt signaling, cytokine signaling, TGF-beta signaling, MAPK signaling, AKT/PI3K signaling, genomic stability, cell cycle control and epigenetic regulation (37).

Clinical Manifestation and Diagnosis

The clinical features of pCCA depend on stage and location of tumor (4,41). The majority of patients present at advanced stage with obstructive jaundice (41). However, in patients with incomplete obstruction of the right or left hepatic duct or segmental ducts, jaundice may not be the presenting feature. Early symptoms are nonspecific and may include abdominal pain, weight loss and pruritus. Some patients develop a hypertrophy-atrophy complex secondary to ipsilateral vascular encasement, which manifests as the palpable prominence of one hepatic lobe (42,43). In the case of intra-ductal papillary tumors, intermittent jaundice

may be a presenting feature (41).

Initial work-up of obstructive jaundice is comprised of serum laboratory values which usually lack a high specificity. While elevated serum alkaline phosphatase (ALP) and bilirubin (Bil) levels are commonly observed in pCCA patients, incomplete obstruction of the right or left hepatic ducts may lead to isolated elevation of ALP (41,44,45). Derangement of liver transaminases and prothrombin time/international normalized ratio (PT/INR) usually occurs in the setting of longstanding biliary obstruction and/or cholestatic hepatocellular injury (45). Serum carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) levels may be elevated as well but also lack specificity. Of note, current United Network for Organ Sharing (UNOS) policy in patients being considered for transplantation uses a cutoff value of CA 19-9 ≥ 100 U/ML for surveillance of CCA in patients with PSC to suspect recurrence, although higher values of CA 19-9 ≥ 129 U/ML have been used by some investigators to increase specificity (46,47).

High quality cross sectional imaging plays a key role in the diagnosis and pre-operative work-up of pCCA (Table 1). High-resolution contrast-enhanced multidetector computed tomography (MDCT) and magnetic resonance imaging / magnetic resonance cholangio-

Table 1. Imaging modalities for diagnosis/staging of cholangiocarcinoma

| Modality | Benefits | Drawbacks | Special Information |
|----------|---|--|---|
| US | <ul style="list-style-type: none"> - No need for IV contrast - Good visualization of bile ducts - Can be tailored to answer specific questions | <ul style="list-style-type: none"> - Operator dependent - Not specific for diagnosis of tumors - May be limited in obese patients | <ul style="list-style-type: none"> - Doppler US can demonstrate flow in vessels and possibly trouble shoot questions regarding vascular involvement |
| CT | <ul style="list-style-type: none"> - Highly reproducible from center-to-center - High spatial resolution for anatomic delineation - Fast and available - Can perform whole body staging | <ul style="list-style-type: none"> - Not as specific as MRI for liver lesion diagnosis - Not as helpful for delineating bile duct anatomy | <ul style="list-style-type: none"> - CT contrast is nephrotoxic and should be avoided in patients with renal failure or acute renal dysfunction |
| MRI/MRCP | <ul style="list-style-type: none"> - Best non-invasive modality for bile duct - Most sensitive/specific modality for diagnosis of CC - Most specific for liver lesion characterization | <ul style="list-style-type: none"> - Motion dependent, poor images in patients who cannot follow breath-hold commands - variable image quality from center-to-center | <ul style="list-style-type: none"> - There are some contraindications to MRI (certain implanted devices, claustrophobia) - Gadolinium contrast is not nephrotoxic but should be avoided in patients with severe renal dysfunction |

pancreatography (MRI/MRCP) are widely accepted as the most accurate modalities for diagnosis of pCCA, assessment of tumor ductal extension and involvement of adjacent vital structures (*Fig. 2*) (48,49). When both are well performed, the accuracy of MRI and CT in predicting resectability exceeds 75% (49). Of note, imaging studies should be obtained prior to any biliary tract intervention as the diagnostic and staging accuracy of both modalities significantly diminish after biliary stent placement. Endoscopic methods such as endoscopic ultrasound scan (EUS), intra-ductal ultrasound (IDUS), and cholangioscopy are used selectively in diagnosing and staging of pCCA.

Tissue diagnosis prior to surgical resection

or liver transplantation is not required in patients with high clinical suspicion for pCCA (49). Some studies have demonstrated that clinical evaluation accurately predicted the presence of malignancy in approximately 90% of the patients (49). However, pathologic confirmation is preferred before treatment with chemo- or radio- therapy, or when it is felt that the patient may benefit from neoadjuvant treatment (e.g. presence of suspicious regional lymphadenopathy). When considering a tissue diagnosis via brush cytology, both endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) have similar sensitivity and specificity. Despite the high specificity of ERCP

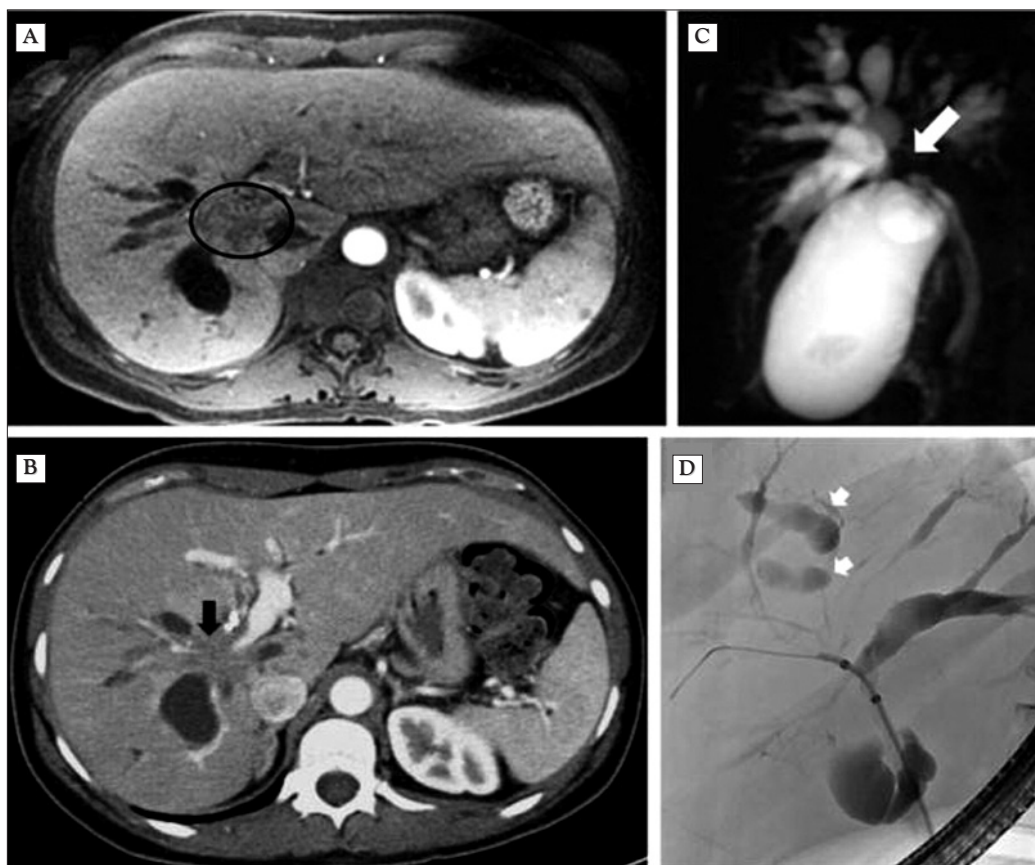


Figure 2. Diagnostic modalities used for cholangiocarcinoma. **(A)** MRI image of a pCCA mass (outlined in circle). **(B)** CT image of a pCCA mass with right portal vein encasement (indicated by black arrow). **(C)** MRCP image of common hepatic duct involvement by tumor (indicated by white arrow). **(D)** ERC image depicting excluded segmental ducts (white arrows) in a patient with a hilar biliary stricture extending into the right main hepatic duct. CT, computed tomography; ERC, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; pCCA, perihilar cholangiocarcinoma

with brush cytology for the diagnosis of CCA, especially dCCA, its sensitivity is much lower (18% - 60%), mainly due to low cellularity and concomitant desmoplastic reaction. New cytological techniques such as DIA (digital image analysis) and FISH (fluorescence in-situ hybridization) can be applied to increase the diagnostic yield of ERCP and brush cytology (50-52). EUS with fine needle aspiration is useful in detection of suspicious regional lymph node involvement (53).

Classification/Staging

Classification of tumors provides a framework within which prognostic and strategic algorithms may be constructed. Several classification systems have been introduced in an effort to aid this process in patients with pCCA (32, 54-56).

A. Bismuth-Corlette Classification

One of the initial steps in the evaluation of pCCA is defining anatomic location and ductal extent of the tumor, essential elements for operative planning. The Bismuth-Corlette classification is perhaps the most widely adopted system, which places lesions into one of four categories based on the relationship to the confluence of the right and left hepatic ducts (*Fig. 1C*) (54). The descriptive classification can then be correlated with the resection method

which may be required for complete extirpation of the tumor and establishment of biliary tract continuity (*Table 2*).

B. American Joint Committee on Cancer (AJCC) Classification

In 2010, considering the distinct biologic and clinical behavior of CCA subtypes, the 7th edition of the AJCC provided a separate TNM classification for pCCA (32). In this system, the primary tumor (T) was assessed based on its relationship to surrounding structures. Specifically, T1: confined to the bile duct, T2a/ T2b: invading surrounding adipose tissue beyond the duct or into the hepatic parenchyma, T3: invading unilateral vascular structures (portal vein or hepatic artery), or T4: invading more distal vascular structures (portal vein, hepatic artery) and/or biliary radicals. Because the bile duct lacks discrete boundaries, T-classification criteria present some challenges, and some authors have suggested that tumor depth might be a more accurate predictor of long-term outcome (57). Nodal assessment is based on regional nodal involvement versus more distant. Notably, number of lymph nodes with metastasis may be a more important prognostic factor, as opposed to the location from which they are retrieved (33,58,59). Metastasis is assessed according to the absence or presence of distant disease. While simple, the utility of the

Table 2. The Bismuth-Corlette classification system is widely utilized for hilar cholangiocarcinoma, and provides categorization of lesions based on anatomic location as it pertains to the confluence of the right and left hepatic ducts. Surgical intervention may be guided by categorization

| Bismuth-Corlette Classification | Surgical Intervention |
|--|--|
| Type I: hilar CCA which is found at the level of the cystic duct, but below the confluence of the right and left hepatic ducts | Extrahepatic biliary duct resection, cholecystectomy, regional lymphadenectomy, biliary reconstruction, +/- pancreaticoduodenectomy depending on distal extent |
| Type II: hilar CCA which is found at the bifurcation of right and left hepatic ducts | If proximal extent is permissive, procedure as annotated for type I |
| Type IIIa: hilar CCA which is found at the bifurcation with extension into the right hepatic duct | Right hepatectomy and regional lymphadenectomy |
| Type IIIb: hilar CCA which is found at the bifurcation with extension into the left hepatic duct | Left hepatectomy and regional lymphadenectomy |
| Type IV: hilar CCA which is found extending into both the right and left hepatic ducts, or, multicentric disease | Limited |

TNM staging system is most relevant in the post-operative setting, after surgical extirpation and for final pathologic determination, and may have lower prognostic implications.

C. Memorial Sloan-Kettering Cancer Center (MSKCC) Classification

The MSKCC classification attempted to create a system which was able to accurately predict resectability and subsequent outcomes. Jarnagin et al. evaluated 225 patients with pCCA who were seen and followed over a nine-year period of time. Through this experience, they introduced a discrete staging system in which the tumor involvement was assessed based on local extension of the tumor, location of bile duct involvement, and the presence of portal vein invasion and hepatic lobar atrophy (55). Further analysis comparing different staging systems has demonstrated good correlation of the MSKCC classification with overall survival of patients undergoing surgical resection (60,61). Recently, prognostic nomograms have been developed to aid with prediction of disease specific survival following curative-intent surgery, although their clinical application requires further validation (62,63).

D. International Guidelines

More recently, an expert consensus proposed a new classification system in an effort to achieve an internationally accepted staging system which was simple, reproducible, and easily applicable. Deoliveira et al. introduced criteria in which the bile duct, portal vein and hepatic artery are assigned a label based on the anatomic involvement of the tumor. The tumor is then additionally classified by the size and histologic subtype. Lymph node involvement and distant metastasis staging is similar to TNM classification. Additionally, the liver remnant volume and underlying hepatic parenchymal integrity are also taken into consideration (56). Further study of these guidelines through multi-center review is needed for optimal validation.

Surgical Resection

A. Criteria to Determine Resectability

Surgical resection is planned based on the ability to achieve R0 resection (resection with negative microscopic margins), while maintaining adequate liver remnant, vascular inflow/ outflow, and biliary drainage. Determination of surgical resectability pre-operatively continues to be a challenge and requires multidisciplinary and multimodality evaluation. Generally, the presence of severe underlying medical comorbidities, distant metastasis, involvement of major vascular structures not amenable to reconstruction, bilateral segmental ductal involvement, unilateral segmental ductal extension with contralateral vascular inflow involvement, and inadequate calculated future liver remnant (FLR) are generally considered contraindications to surgical resection (49).

B. Surgical Resection Technique

Surgical resection with negative margins offers the only chance for potential cure (*Fig. 3*). However, only a small subset of patients will be eligible for surgical resection at the time of diagnosis. Furthermore, 20–50% of patients thought to benefit from surgical resection based on preoperative work-up are found to have unresectable disease at the time of exploration (55,60,64). Therefore, several studies have suggested the potential benefit of staging laparoscopy as a means of identifying locally advanced or metastatic disease not amenable for surgical resection (65,66). However, a more recent study of almost two hundred patients with pCCA demonstrated a decreased overall diagnostic yield and accuracy of staging laparoscopy, mainly due to improved imaging techniques (67). Overall, surgical resectability rates range from 35–94% in large series, with a wide range of margin negativity (14–78%), suggesting wide variation in surgeon and institutional approach (4,55,68,69). In tumors with extension into the caudate lobe, central location, or involvement of the left hepatic duct, caudate resection is recommended (70,71).

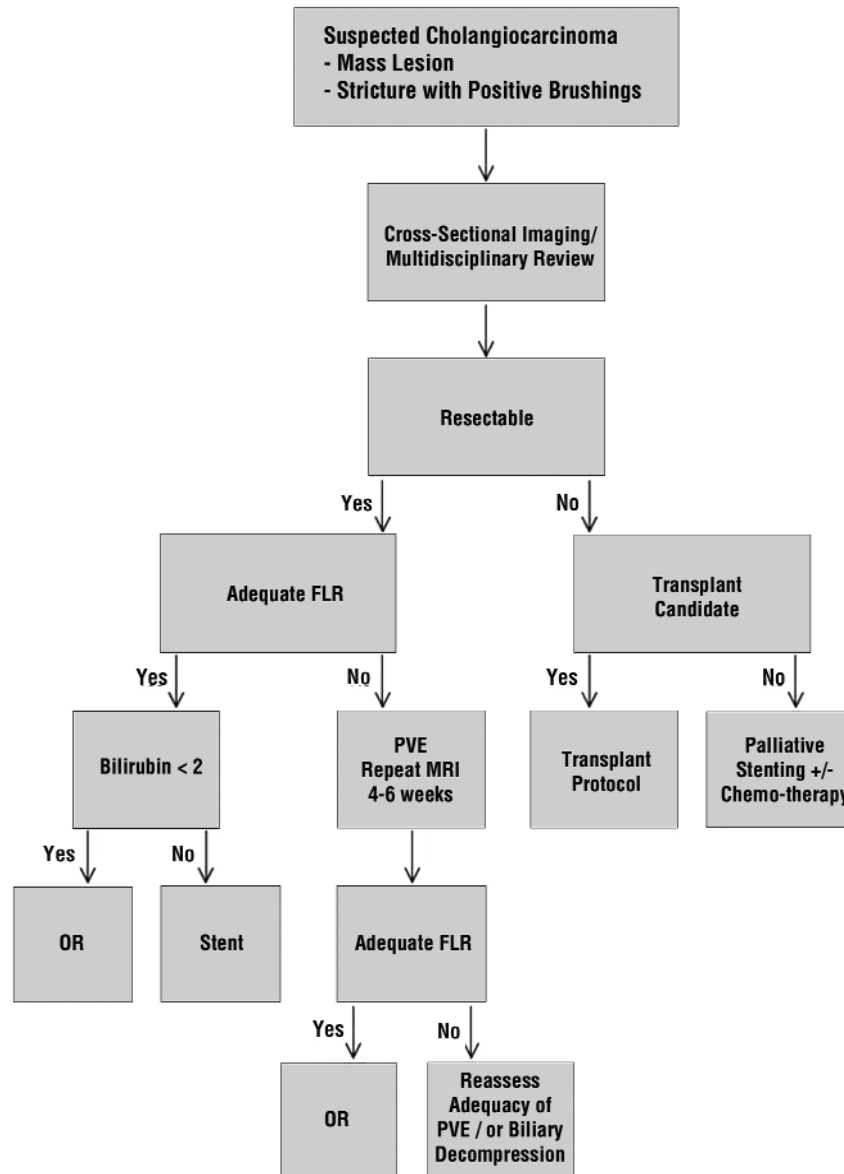


Figure 3. Perihilar cholangiocarcinoma management algorithm

Although controversial, the role of vascular resection and reconstruction (e.g. portal vein and/or hepatic artery) has been advocated by an increasing number of surgeons. Review of patients undergoing curative-intent resection for pCCA identified from a large international, multi-institutional database demonstrated that portal vein resection was not associated with worse outcome and should be undertaken when necessary to achieve an R0 resection (72). However, the decision for vascular resection must be made on an individual patient basis

(73). Patients who successfully undergo an R0 surgical resection have a median survival of which ranges from 27 to 58 months with a 5-year survival rate of 27% to 45%. These numbers drop significantly to 12-21 months and 0-23% in patients with positive resection margins (55,74-76). R0 resection, well-defined histology, concomitant hepatic resection, and absence of lymph node metastasis are the primary factors associated with long-term survival (3,33,77-79).

C. Pre-operative Optimization

Portal Vein Embolization (PVE)

Many patients with pCCA will present with advanced disease and large tumors that require major hepatic resection. A patient with a normal underlying liver requires at least a 20% FLR to prevent postoperative liver failure. The percentage increases to 30% for patients who have steatosis or steatohepatitis and further ascends to 40% in patients with underlying cirrhosis (80,81). For patients with pCCA who do not meet FLR requirements, additional pre-operative procedures to induce hypertrophy of the FLR such PVE may be of benefit (80-82). Postoperative morbidity and mortality for patients who undergo PVE is comparable to those patients who had an adequate FLR prior to surgery (83).

Biliary Decompression

The role and route of preoperative biliary drainage in jaundiced patients remains controversial. Biliary drainage is indicated in septic patients with suspected cholangitis, patients undergoing PVE, or patients with planned pre-operative anti-neoplastic therapy. Biliary decompression may also help to improve coagulopathy, ameliorate renal insufficiency associated with hepatic failure, or provide symptomatic relief (e.g., pruritus) (84). Proponents of preoperative biliary drainage advocate that it provides improved hepatic function, optimization of nutritional parameters, and reduces the risk of cholangitis and post-operative liver failure (85, 86). However, in a recent multicenter retrospective study, preoperative biliary drainage was not associated with improved postoperative outcomes (87). In contrast, opponents believe that biliary drainage increases the risk of drain track tumor seeding, cholangitis, pancreatitis, peri-operative infections, and also may lengthen post-operative hospital stay (88). In general, biliary drainage should be strongly considered for any patient with a bilirubin > 6-7 mg/dl – especially in patients with an anticipated small liver remnant.

Due to a reported 1.4-5% risk of tumor seeding of the drain track with percutaneous

biliary drainage, endoscopic retrograde cholangiopancreatography (ERCP) is advocated by some as the preferred method for stent placement. However, endoscopic stent occlusion rates have been reported as high as 60%. Additionally, unsuccessful attempts with endoscopic decompression place patients at risk for contamination of undrained areas due to retrograde injection of contrast. Furthermore, percutaneous trans-hepatic cholangiography (PTC) can provide much better delineation of the extent of biliary tract involvement for preoperative planning (49). Alternate preoperative drainage methods such as nasobiliary drainage are under ongoing investigation (89).

D. Neoadjuvant Therapy

The role of neoadjuvant therapy in the management of pCCA is not well defined. A relative paucity of large prospective studies confounds the ability to make a well informed conclusion. The current data in the setting of surgical resection is limited to a few small case series and retrospective studies with inconsistent success rates in achieving R0 resection (90). However, the role of neoadjuvant chemoradiation in combination with liver transplantation is better studied (91-93). Although regimens may have some variation among institutions, typically 4000-4500 cGy of external-beam radiation is given in conjunction with 5-fluorouracil chemosensitization, followed by endoluminal brachytherapy with iridium wires. Maintenance capecitabine is administered while patients await transplantation. Up to one-third of patients who initiate neoadjuvant treatment are unable to complete therapy due to toxicity. Additionally, if evidence of disease progression or distant metastasis develops while the patient is receiving neoadjuvant treatment, these factors preclude liver transplantation (91,94).

E. Adjuvant Therapy

High rates of loco-regional recurrence or distant metastases following resection of pCCA provide the main rationale for adjuvant therapies. Due to rarity of the tumor, data on

adjuvant therapy for pCCA are mainly derived from studies that examine a broad category of patients with advanced biliary tract cancers. Takada et al. evaluated the role of post-operative chemotherapy with 5-FU, doxorubicin, and mitomycin in 508 patients with resected pancreatobiliary malignancy and failed to show any statistically significant survival benefit (95). Five year survival rates were similar when the data was stratified to study the subgroup of 118 patients with bile duct cancer (26.7% vs 24.1%, treatment group vs. control group; $p=NS$). In the European Study Group of Pancreatic Cancer trial (ESPAC)-3, the use of adjuvant therapy was not associated with a survival advantage in all patients with peri-ampullary malignancies or in the subset of patients with bile duct cancer (96). However, a meta-analysis of data including 6712 patients with biliary tract cancer who underwent curative-intent surgery revealed that chemo- and chemoradio-therapy are associated with better survival than radiation therapy alone ($p=0.02$). Furthermore, patients with node-positive and margin-positive disease appeared to derive the clearest survival benefit from adjuvant therapy (97).

According to National Comprehensive Cancer Network (NCCN) guidelines for extra-hepatic CCA, adjuvant treatment with fluoropyrimidine-based chemoradiotherapy followed by additional fluoropyrimidine or gemcitabine chemotherapy should be considered for patients after resection with gross residual disease (R2), positive microscopic margins (R1) or regional lymph node involvement. For patients with negative nodes and margins after resection or with carcinoma in-situ at the margin, observation is reasonable however NCCN guidelines also support adjuvant therapy for these patients.

Transplantation

Despite initially disappointing results, the introduction of a more rigorous pre-transplant protocol by the Mayo clinic, including improved patient selection criteria, and the addition of neoadjuvant therapy, has now resulted in excellent 5-year recurrence-free survival rates

of 65–70% (91-93) after transplant for pCCA. The Mayo Clinic selection criteria for pCCA includes: 1) diagnosis via positive biliary biopsy /cytology for adenocarcinoma or malignant appearing stricture with CA 19-9 >100 U/mL without bacterial cholangitis, 2) tumor size < 3 cm, 3) absence of distant metastasis on imaging, and 4) negative EUS-FNA or regional lymph nodes and negative staging laparotomy/hand-assisted laparoscopy with biopsy of regional lymph nodes (93). Patients are excluded if they have mass lesion > 3 cm radial diameter, any evidence of extrahepatic disease or regional lymph node involvement, history of previous malignancy (excluding skin or cervical cancer), prior abdominal radiotherapy, uncontrolled infection, previous attempt at surgical resection with violation of tumor plane, or a medical condition that otherwise precludes transplant (92,93,98).

Management of Metastatic Disease

Data on systemic therapy for pCCA are scarce and are typically derived from studies that examine “all comer” advanced biliary tract cancers. The utility of gemcitabine in the treatment for hepato-pancreatico-biliary tumors has been increasingly recognized. In 2010, Valle et al. demonstrated in a phase III (ABC-02) study of 410 patients with locally advanced or metastatic biliary tract cancers (241 CCA) that treatment with gemcitabine plus cisplatin was associated with a survival advantage over gemcitabine alone group (11.7 months vs. 8.1 months, respectively; $p<0.001$) without additional toxicity (99). Progression-free survival (PFS) also was improved (median OS 8.0 mo vs. 5.0 mo, combination therapy group vs gemcitabine-only, $p<0.001$). Follow up studies utilizing the same regimen have validated these results (100,101).

Recent advances in understanding molecular pathogenesis of CCA have created a growing interest in identifying novel therapies targeting key molecular pathways (38). Considering the role of EGFR in the pathogenesis of CCA, EGFR inhibitors have been proposed as potential chemotherapeutic agents. However, despite initial favorable results, subsequent randomized

trials have failed to confirm the clinical benefit of EGFR inhibitors (102,103). Similarly, combination chemotherapy with panitumumab, another drug in the anti-EGFR antibody class, was not associated with a survival benefit (105). In a phase III study, Lee et al. reported that patients with advanced biliary tract cancers who were treated with erlotinib plus gemcitabine and oxaliplatin had a higher objective response rate compared to patients treated with chemotherapy alone ($p=0.005$) (106). However, there was no difference in median PFS (5.8 months in combination therapy vs. 4.2 in chemotherapy alone; $p=0.087$) or median OS (9.5 months for each arm). In a subgroup analysis of 84 patients with CCA, the addition of erlotinib to chemotherapy was associated with a prolonged median PFS of 5.9 months versus 3 months in chemotherapy alone group ($p=0.049$) (106). In a randomized study of 122 patients with advanced biliary tract cancers who were stratified by KRAS status, the combination of gemcitabine plus oxaliplatin (GEMOX) and cetuximab was associated with improved median progression-free-survival (PFS) (6.7 months) compared with chemotherapy only (4.1 months, $p=0.05$) (102), an improvement which was independent of KRAS mutation status. Median OS was, however, similar between the two groups (10.6 months vs. 9.8 months; $p=0.91$) (102). The addition of cetuximab to the combination regimen of gemcitabine, capecitabine and oxaliplatin did not improve PFS or OS (104). The phase II study ABC-03 investigating the clinical benefit of adding a VEGF inhibitor (cediranib) to cisplatin and gemcitabine was discouraging, with a median PFS in the cediranib group of 8.0 months vs 7.4 months in the placebo arm (HR 0.93; $p=0.72$) (107).

The MAPK/ERK pathway and its different substrates are frequently deregulated in CCA and other biliary tract cancers, making them attractive targets for molecular therapy. The efficacy of MEK inhibition has been investigated in management of patients with advanced biliary tract cancers. In a phase II trial of 28 patients with metastatic biliary tract cancers, selumetinib, a MEK1/2 inhibitor, produced an objective response in 3 participants and maintained stable disease in an additional 17

patients (108). In this cohort, only one patient experienced grade 4 toxicity and the median PFS and OS were 3.7 months and 9.8 months, respectively. Bridgewater et al. recently released the results of the ABC-04 study, a phase Ib trial that added selumetinib to cisplatin and gemcitabine (109). Of the 8 patients who were assessable for objective response, 1 had a complete response, 1 had a partial response and 6 maintained stable diseases. The median PFS was 6.4 months and grade 3/4 selumetinib-associated toxicities occurred in 25% of patients. Currently, trametinib is being studied in an ongoing National Cancer Institute phase II trial evaluating the role of this single agent MEK inhibitor versus 5-FU or capecitabine for non-resectable advanced biliary cancers (ClinicalTrials.gov identifiers: NCT02042443).

AG-120 (IDH 1 inhibitor) and AG-221 (IDH 2 inhibitor) are two agents under investigation in phase I trials for patients with advanced solid tumors including CCA (ClinicalTrials.gov identifiers: NCT02073994 and NCT02273739, respectively). The FGFR2 signaling pathway may have therapeutic implications for CCA as well (78,79). Pazopanib, a pan-FGFR inhibitor, is currently being evaluated in the setting of unresectable or metastatic biliary tract cancers in a phase II trial (ClinicalTrials.gov identifiers: NCT01855724).

Ongoing phase III trials may impact current practice patterns. The ABC-06 trial in the United Kingdom seeks to assess the efficacy of mFOLFOX (modified 5-FU, oxaliplatin, folinic acid) with active symptom control versus active symptom control alone in patients with metastatic disease who have failed first line therapy with gemcitabine and cisplatin (NCT01926236). Several other trials in Europe also are evaluating the use of adjuvant gemcitabine plus oxaliplatin or cisplatin (Germany, ACTOCCA-1, NCT02170090 and France, NCT01313377), as well as the role of concurrent chemoradiotherapy with adjuvant chemotherapy alone (NCT02798510). Additionally, the role of capecitabine in the adjuvant setting is being evaluated in the United Kingdom (NCT00363584).

Conclusion

pCCA is a rare group of gastrointestinal malignancies with high fatality. The diagnosis and treatment of pCCA is often challenging and the majority of patients typically present at advanced stage when surgery is not recommended. Therefore, there is an urgent need for identification of novel diagnostic biomarkers that help in early diagnosis as well as screening of high-risk patients. Furthermore, conventional chemotherapy has demonstrated limited benefit in the management of unresectable or metastatic pCCA. New advances in genomic profiling have contributed to a better understanding of the landscape of molecular alterations in CCA and offer hope for the development of novel targeted therapies. Future studies should continue to focus on targeting deregulated signaling pathways with the goal of personalizing treatment for patients with pCCA.

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