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REVIEW ARTICLE – HEPATOBILIARY TUMORS

Cholangiocarcinoma of the Middle Bile Duct: A Narrative Review

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ABSTRACT Resectable cholangiocarcinoma (CCA) arising from the middle of the extrahepatic biliary tree has historically been classified as perihilar or distal CCA, depending on the operation contemplated or performed, namely the associated hepatectomy or pancreaticoduodenectomy, respectively. Segmental bile duct resection is a less invasive alternative for select patients harboring true middle extrahepatic CCA (MCC). A small, yet growing body of literature has emerged detailing institutional experiences with bile duct resection versus pancreaticoduodenectomy or concomitant hepatectomy for MCC. Herein, we provide a brief overview of the epidemiology, preoperative evaluation, and emerging systemic therapies for MCC, and narratively review the existing work comparing segmental resection with pancreaticoduodenectomy or less commonly, hepatectomy, for MCC, with emphasis on the surgical management and oncologic implications of the approach used.

Keywords Cholangiocarcinoma · Segmental bile duct resection · Pancreaticoduodenectomy · Hepatectomy

Cholangiocarcinomas (CCA) are rare epithelial neoplasms arising from the biliary tree. Broad classifications of CCAs stem from the site of tumor origin, either intrahepatic (ICC) or extrahepatic (ECC), each possessing a unique tumor biology and molecular profile.[1,2] ECCs can be further classified as perihilar or Klatskin tumors arising near or at the confluence of the right and left biliary ducts to the insertion of the cystic duct (perihilar ECC distal margin) or distal in which tumors can arise anywhere along the common bile duct (CBD) from the insertion of the cystic duct to the ampulla of Vater.[3] However, CCAs of the middle of the biliary tract (MCC), typically defined as tumors distal to the cystic duct insertion (proximal margin) and proximal to the junction of the bile duct and pancreatic neck (i.e., above the upper pancreatic neck border; distal margin) have gained acceptance as a separate anatomic subtype of distal ECC with implications for surgical management.[4] Despite recent investigations demonstrating different molecular and genetic phenotypes of perihilar and distal CCAs, MCCs have yet to be distinguished from the conventional ECC variants.[5]

Surgical resection remains the mainstay of treatment for distal ECCs as well as those of the middle biliary tract. Conventionally, such tumors are managed with pancreaticoduodenectomy (PD) given the anatomic relationships between the distal CBD and the more distal CHD and pancreas. Bile duct segmental resection (BDSR) has been proposed as a less morbid and potentially comparable oncologic procedure in lieu of PD in select patients.[4,6,7] As aging populations and the burden of comorbidities grow, hepatobiliary surgeons may be more often confronted with the dilemma of which procedure to perform for MCC lesions, PD, or BDSR, considering the balance of oncologic outcomes and perioperative risk. This narrative review analyzed relevant studies in a summative fashion and detail the major elements of MCC, including epidemiology, presentation/workup/diagnostic approach, surgical management/principles and associated outcomes, role of systemic and locoregional therapies, and prognostic indicators for risk assessment and preoperative

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planning. We close with potential future directions concerning the care of middle CCA.

INCIDENCE, EPIDEMIOLOGY, AND CLASSIFICATION

The age-adjusted incidence of CCA varies considerably depending on geographical location with particularly high incidence in Eastern countries and Thailand, which can be attributed to differences in local risk factors and genetic predisposition.[8–11] Importantly, the global mortality due to CCA has increased over the past decades and is higher in Asian countries than in the West and in men than in women.[8,12] Within the United States, the most significant increases in mortality were noted in the African American population followed by the Asian population.[13]

Several risk factors have been implicated in the development of CCA (Table 1).[8,11] The common denominator of all these risk factors is their association with bile stasis and inflammation of the bile ducts.[8,11] The factors most strongly associated with the development of ECC include choledochal cysts, Caroli disease, primary sclerosing cholangitis, cholelithiasis and choledocholithiasis, cirrhosis, liver parasites (*Opisthorchis verrini, Clonorchis sinesis*), and environmental toxins (Thorotrast and 1,2- Dichloropropane).[8,11] Nevertheless, the majority of CCA cases still develop sporadically without the presence of any clear underlying risk factor.

Historically, CCA have been classified as ICC (10–20%), perihilar (50–60%), and distal ECC (20–30%).[8] ICC can arise throughout the intrahepatic biliary tree from bile ductules to the second-order bile ducts (segmental bile ducts), perihilar CCA can emerge near either the left or right hepatic duct and/or near their junction, while distal ECC can involve any part of the common bile duct.[8] That traditional classification has led to MCC been previously grouped either with the perihilar CCA if the patient required hilar resection or hepatectomy and bile duct reconstruction or with the distal ECC if the patient required PD.[1] When MCC is appropriately classified as a separate entity (Fig. 1), then 50–75% of ECC cases are in the perihilar area, 10–25% in the middle third, and 10–20% in the distal third of the common bile duct.[3]

TABLE 1 Risk factors for the development of cholangiocarcinoma

Risk factors for cholangiocarcinoma
Choledochal cyst/Caroli disease
Choledocholithiasis
Cholelithiasis
Primary sclerosing cholangitis
Inflammatory bowel disease
Cirrhosis
Chronic hepatitis B or C infection
Liver parasites (*Opisthorchis viverrini, Clonorchis sinensis*)
Hemochromatosis
Wilson's disease
Chronic pancreatitis
Peptic ulcer disease
Alcohol use
Nonalcoholic fatty liver disease
Obesity
Hypertension
Smoking
Thorotrast
1,2-Dichloropropane
Asbestos

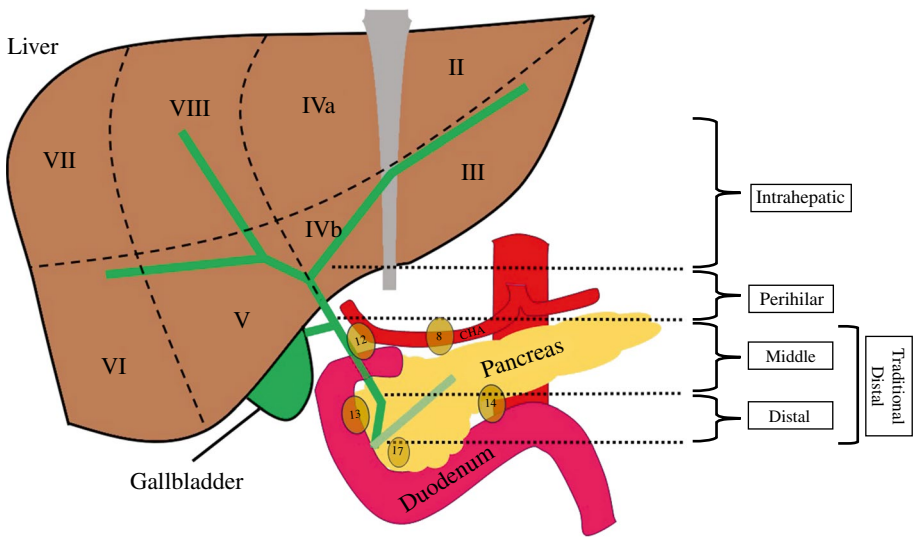

FIG. 1 Schematic representation of pertinent anatomic structures in the hepatopancreatobiliary region with landmarks for cholangiocarcinoma classification. Biliary tree illustrated from ampulla of Vater to right anterior, right posterior, and left hepatic ducts. Pertinent lymph node stations shown (8, common hepatic artery (CHA); 12, hepatoduodenal ligament; 13, 17, peri/retropancreatic; 14, superior mesenteric). Figure created with Microsoft Paint & Microsoft PowerPoint (Redmond, WA)

CLINICAL PRESENTATION AND PREOPERATIVE EVALUATION

The clinical presentation and diagnostic workup of patients with MCC mirror that of ECC. Jaundice, abdominal pain, and nonspecific "constitutional" symptoms, such as fever and weight loss are characteristic.[14] Direct hyperbilirubinemia and transaminitis are objective laboratory measurements associated with obstructive tumors. Collection of serum tumor markers, such as cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), are recommended to establish trends; however, the former should be noted after adequate decompression of the biliary tree to avoid spuriously elevated values. Once malignancy is suspected, multiphasic contrasted computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis are recommended as first-line cross-sectional imaging modalities for staging and evaluation of lesion resectability in relation to surrounding vasculature; CT of the thoracic cavity completes staging workup. Magnetic resonance cholangiopancreatography (MRCP) may be helpful to delineate the biliary anatomy in addition to being able to give information about the hepatic parenchyma and thickening within the bile duct walls. Endoscopic retrograde cholangiopancreatography (ERCP) with stent placement is commonly performed in the workup of these patients and to relieve symptoms while diagnosis and staging are underway, as well as to obtain brush cytology or clam shell biopsy.[15]

According to the most recent consensus guidelines, routine biopsy of MCC/ECC is not mandatory in the setting of a high suspicion for malignancy in the absence of meeting unresectability criteria (unresectable vascular involvement, metastatic disease) given that the neoadjuvant approach has not been established as standard practice.[16] Cases in which chemotherapy is planned without resection, tissue biopsy via brush cytology, core needle biopsy (CNB), or forceps should be obtained either via ERCP, endoscopic ultrasound (EUS), or cholangioscopy before treatment. The modality utilized is variable and dependent on institution and provider practices as well as anatomic accessibility; lesions more distal in the CBD may be more amenable to brush cytology via ERCP or CNB via EUS, whereas more proximal lesions can be assessed via transhepatic cholangioscopy. Data support CNB as the most accurate biopsy technique with sensitivity, specificity, and diagnostic accuracy of 74%, 100%, and 80%, respectively for mass-forming lesions.[17] Brush cytology may be more appropriate in the presence of a biliary stricture without a definitive lesion on cross-sectional imaging; a diagnostic accuracy of 30–60% is attributed to diagnosis of a malignant biliary stricture via brush cytology.[18] Taken together, while biopsy of MCC may be forgone in the setting of a potentially resectable lesion, several diagnostic approaches are available that can aid decision making in a multidisciplinary setting.

The practice of routine preoperative biliary drainage has been controversial. Several randomized control trials demonstrate no difference in intra- and postoperative outcomes compared with no drainage; select studies advocate against routine drainage citing higher infectious postoperative complications.[19–21] Consensus guidelines currently recommend biliary drainage (endoscopic or percutaneous transhepatic) in the setting of clinical jaundice and/or receipt of systemic therapy before surgery or in the palliative setting as no definitive serum bilirubin level thresholds necessitating drainage have been established.[16,22,23] Additionally, if major hepatectomy is a real possibility after preoperative staging, then drainage should be performed in patients with clinically relevant hyperbilirubinemia causing jaundice, pruritus, or coagulopathy or until total bilirubin <3 mg/dl has been achieved as suggested by some authors.[16,24] For obstructive MCCs in which biliary drainage is pursued, the decision to drain either via percutaneous transhepatic or endoscopic approaches should consider the relative position of the lesion in the CBD to the ampulla and the risks of retrograde biliary contamination via sphincterotomy. Endoscopic biliary stenting should be performed after MRCP as a stent can potentially distort visualization of the bile ducts.[22]

SURGICAL MANAGEMENT AND CONSIDERATIONS

Surgical resection remains the mainstay to achieving a cure in ECC. The median survival of those who undergo curative-intent resection, which accounts for 20% of all patients with ECC, has been reported to be three times longer than with palliative systemic therapy.[8,25–27] PD has been the conventional operation for distal CCAs, including MCCs with the following oncologic principles: achievement of microscopically negative resection margins confirmed with the use of intraoperative frozen section pathologic analysis and dedicated regional lymphadenectomy.[28,29] A handful of reports predominantly from Asia have suggested BDSR with reconstructive Roux-en-Y hepaticojejunostomy can be a safe and effective alternative to PD by offering several appealing features, namely a significantly less invasive procedure with less postoperative morbidity and mortality and similar oncologic results.[4,6,7,30,31] The following subsections will review the existing literature describing experience with BDSR versus PD for MCC, focusing on the preoperative risk status and clinicopathologic characteristics of included patients/tumors, the intra- and perioperative outcomes following these procedures, and the pathologic and long-term oncologic outcomes achieved with either procedure (Tables 2, 3 and 4).

TABLE 2 Prognostic factors for survival and recurrence after resection for middle bile duct cholangiocarcinoma

Prognostic factor	Survival	Recurrence
T stage	X	
N stage	X	X
# of lymph nodes harvested/positive lymph node ratio	X	X
Margin status	X	X
Perineural invasion	X	
Tumor differentiation grade	X	
Tumor biology	X	X

Patient Comorbid Status and Tumor Pathologic Characteristics

Among the select studies that report their experience with BDSR and/or PD for MCC, those who underwent BDSR were more likely to be older with more preoperative comorbidities without differences in clinical presentation (jaundice, cholangitis, serum markers) compared with those who underwent PD.[6,31] Patients who received BDSR were predominantly more likely to have earlier T-stage tumors but otherwise exhibited no substantial differences in the pathologic features, including nodal status.[6,7,30] None were reported to have received neoadjuvant therapy.

Regarding intraoperative differences, patients who underwent BDSR unsurprisingly had shorter operative times and less intraoperative blood loss. Morbidity in the form of postoperative complications were significantly decreased post-BDSR compared with PD. Patients with ECC are known to typically have soft pancreatic gland texture with small pancreatic ducts, thus increasing the risk for postoperative pancreatic fistula (POPF) after pancreatic resection.[32,33] Studies have affirmed this as rates of POPF were upwards of 40–50% in PD groups compared with 0–10% in BDSR cohorts.[30,31] Overall postoperative complication rates after PD are reported to be double that of BDSR (41–46% vs. 10–20%).[4,6,30] Furthermore, length of stay in patients recovering from BDSR was significantly shorter compared with PD (11–20 vs. 28–40 days).[4,6,30] Perioperative mortality also was higher after PD, where one study reported 90-day mortality rate of 5% after PD versus no deaths following

TABLE 3 Characteristics of lymph node harvest, margin status, and recurrence location from selected studies of middle bile duct extrahepatic cholangiocarcinoma

Study	Operation (no. patients)		# nodes harvested median (range)		Margin status & recurrence *n* (% of total patients in cohort)							
					BDSR				*PD*			
	BDSR	*PD*	*BDSR*	*PD*	R0	>R0	Local	Distant	R0	>R0	Local	Distant
Lee *et al.* (2009)	45	149	–	–	–	–	–	–	–	–	–	–
Schreuder *et al.* (2019)	22	38	5 (3–7)	9 (7–14)	13 (59)	9 (41)	11 (50)	6 (27)	22 (58)	16 (42)	13 (34)	14 (37)
Hayashi *et al.* (2020)	245	418	8	17	136 (56)	109 (44)	(34)	(36)	286 (68)	132 (32)	(14)	(33)
Akita *et al.* (2020)	21	84	8 (3–12)	13 (9–21)	8 (38)	13 (62)	5 (33)	11 (66)	67 (80)	17 (20)	14 (33)	37 (66)
Jikei *et al.* (2021)	38	54	9 (0–22)	20 (7–39)	28 (74)	10 (26)	17 (45)	10 (26)	51 (94)	3 (6)	15 (28)	12 (22)

BDSR bile duct segmental resection; *PD* pancreaticoduodenectomy

TABLE 4 Oncologic outcomes of bile duct segmental resection compared with pancreaticoduodenectomy

Study	Median follow-up Months (range)	Disease-free survival Months or 5-yr %			Overall survival Months or 5-yr %		
		BDSR	*PD*	*p-value*	*BDSR*	*PD*	*p-value*
Lee *et al.* (2009)	22 (0–109)	NR	NR	NR	37%	38%	0.09
Schreuder *et al.* (2019)	67 (23–106)	30 40%	13 25%	0.968	46 39%	19 55%	0.394
Hayashi *et al.* (2020)	–	25	34	0.018*	41	59	0.0019*
Akita *et al.* (2020)	26 (1–160)	38%	40%	0.99	44%	51%	0.72
Jikei *et al.* (2021)	>8 years	48	74	0.018*	43	65	0.035*

Disease-free survival and overall survival are represented by median survival times or 5-year rates (%)

NR not reported

*Statistical significance ($p < 0.05$) reached

BDSR.[4] Taken together, patients receiving BDSR, although older, experience less postoperative morbidity and mortality compared with PD patients.

Resection Margins and Lymph Node Harvest

Among the most crucial surgical aspects determining oncologic outcomes for patients with MCC are the ability to achieve negative surgical margins and performance of adequate lymphadenectomy. Consideration of three resection margins for MCC are tracked: the proximal, distal, and radial bile duct margins. In PD, the proximal bile duct margin is the most common site of residual disease as the distal margin is resected *en bloc* with the surgical specimen.[31] In contrast, all three margins are at risk when performing BDSR, which naturally leads to an increased likelihood of positive margin status. Furthermore, it is hypothesized that ECC has a propensity to spread longitudinally along the lymphatics spanning the length of the bile duct, thus compounding the challenge of obtaining definitively negative proximal and distal margins.[34] Intraoperative frozen pathology analysis is standard practice and nearly always performed in BDSR and PD alike; however, it is an inherently incomplete modality to assess surgical specimens thus prone to false-negative results.[35–37] Studies comparing BDSR and PD have confirmed that the former generally results in higher rates of non-R0 margins ranging from 26–62% versus 6–42% in BDSR and PD, respectively (Table 3).[4,6,30,31] Consistently, the radial margin, which is often challenging to assess, is reported positive in roughly 15–20% of BDSR cases.[6,30,31] The radial margin also is more difficult to define and prone to misinterpretation.

The nodal status of patients with MCC has been demonstrated to be an independent risk factor determining overall survival (OS).[31,38,39] One method to ensure accurate nodal staging is a thorough lymphadenectomy at the time of resection. The harvest of at least 10 to 12 nodes during resection for ECC has been recommended to increase the sensitivity of nodal staging; however, this particular harvest threshold remains controversial because of the limited studies examining the topic and the variability in cutoffs for which authors suggest.[40–42] The number of retrieved lymph nodes after BDSR range from five to nine nodes compared with up to 20 with PD, yields that have been corroborated by a systematic review and meta-analysis comparing BDSR with PD for MCC and distal ECC.[4,6,30,31,43] This discrepancy stems from a difference in operations, as BDSR typically addresses nodes only from the hepatoduodenal ligament (station 12), common hepatic artery (station 8), and retropancreatic nodes (station 13), whereas PD also performs more extensive lymphadenectomy of additional peripancreatic nodes (station 17) and those surrounding the superior mesenteric artery (SMA, station 14).[6] Although studies cite the most common location of positive nodes in MCC and distal ECCs are within the HDL, Akita et al. reported a third of patients who underwent PD had positive nodes around the pancreatic head, suggesting that without PD, these nodes would not normally be retrieved.[6,34] Of note, it is technically possible to remove at least some of the peripancreatic lymph nodes around the head of the pancreas, at least the more accessible ones during BDSR. Both resection margin positivity and lymph node status have been demonstrated to be significant prognosticators for survival on multivariate analysis of patients with ECC undergoing resection, however, which is more relevant to long-term oncologic outcomes is subject to ongoing investigation.[30,31]

Oncologic Outcomes: Survival and Recurrence

Historically, 5-year OS following curative-intent resection of ECC ranges from 20 to 50% with PD.[26,44] With a heterogeneity of follow-up times ranging from 2 years to upwards of eight, and biases inherent to nonrandomized retrospective reviews, studies reporting outcomes of MCC treated with BDSR or PD report 5-year OS rates of 37–44% for BDSR compared to 25–55% for PD (Table 4).[4,6,30,31]

Various studies report that survival in MCC undergoing BDSR or PD may be dependent on pathologic tumor stage. Akita et al. reported on their experience of more than 100 cases of BDSR or PD and observed no statistical difference in 5-year OS in T1-2 stage tumors.[6] Likewise, in subgroup analysis of overall stage Ia lesions, Lee et al. cited 100% 3- and 5-year survival rate in patients undergoing BDSR compared with 77% and 68% in PD group but deteriorated to 5-year survival rate of 33% and 59% for BDSR and PD in stage Ib tumors, respectively.[7] Other studies cite contrasting findings: Hayashi et al. in a multicenter review of MCC reported a significant survival advantage for PD at every T1-3 stage and regardless of nodal or resection margin status (for T1-2 and N0 tumors).[30] Jikei et al. also observed that patients with Tis-T2 MCCs receiving PD had significantly improved OS compared with BDSR with an absolute difference in median survival time of nearly 2 years.[31] These discrepancies may be secondary to variations in receipt of adjuvant systemic therapy (Akita et al. 68% BDSR vs. 38% PD), the benefit of which will be discussed in subsequent sections, in conjunction with the known prognostic significance of margin and nodal status.[6] Reports of a long-term survival advantage with PD is supported by a recent systematic review demonstrating significantly worse 5-year OS following BDSR compared with PD for middle and distal cholangiocarcinomas (odds ratio [OR] 0.75; 95% confidence interval [CI] 0.65–0.85; $p < 0.01$).[43] However, these results should be interpretated with the consideration that distal ECCs are not only different anatomic entities but potentially distinct biologic ones compared with MCC. Overall,

the impact of BDSR on survival remains ill-defined; at best, in select cases, there is low-level evidence suggestive that BDSR for early-stage tumors may achieve comparable survival to PD.

Locoregional and distant recurrence remain major barriers to cure in ECC and likewise in MCC. Although specific recurrence patterns in MCC have not been previously documented, local rather than distant recurrence seems to be the main driver of relapse occurring in one to two thirds of the overall study population.[4,31] Local recurrence rates unsurprisingly correlate with the rate of positive surgical margins, which are more common after BDSR compared to PD as discussed above.[4,30,31] However, Hayashi et al. found that even in R0 resections among early-stage tumors, median disease-free survival (DFS) after PD was significantly improved compared to BDSR by nearly 2.5 years, largely driven by significantly increased local rather than distant recurrence (Table 3).[30] In contrast, Akita et al. report that a significantly higher R1 resection rate in BDSR compared with PD did not result in a difference in local or distant recurrence between the two groups.[6] These two opposing results highlight additional factors apart from margin status including individual tumor biological heterogeneity, nodal status, and/or technical aspects of pathologic margin analysis that further obscure our understanding of tumor recurrence in MCC. As such, whether BDSR can consistently achieve comparable DFS as PD is unclear from the limited evidence available.

In summary, based on the few studies examining oncologic outcomes after BDSR and PD, resection margin status and lymph node positivity may be factors among many that drive survival and disease recurrence in MCC (Table 2). In the context of complex tumor biology and limited study population sizes, studies suggest that BDSR may be indicated for comorbid patients with early-stage tumors amenable to negative ductal margins.

Improving Outcomes in Bile Duct Segmental Resection

Lessened intraoperative demand and mitigated postoperative morbidity of BDSR compared with PD make local resection an appealing option for patients with early-stage tumors who may have a harder time tolerating an extensive pancreaticobiliary procedure. Additionally, a few studies have suggested intraoperative technical aspects that may improve the outcomes following BDSR for MCC, among which are tumor-free duct margin length and tumor size. Park et al. in an analysis of 130 BDSR for MCC found that tumor free ductal margins >5 mm were significantly associated with improved survival.[45] Extending this concept further, Jikei et al. in their experience of 90 patients undergoing BDSR/PD advocate for obtaining ≥10 mm proximal and ductal margins in patients with tumors ≤15mm.[31] The presence of one or both features achieved equivalent survival as PD counterparts (55–63% 5-year) compared with the absence of both (7% 5-year). The removal of residual disease is paramount to achieving lasting oncologic results, yet broad consensus regarding the optimal length of negative margins among other intraoperative assessments has yet to be reached.

Going the Distance: Extended Bile Duct Resections

On rare occasions, organ-sparing bile duct resections of either the intrapancreatic or very proximal portions of the CBD may be indicated for patients with MCCs with significant comorbid disease who harbor extensive bile duct involvement. For limited intrapancreatic CBD disease, a technique termed extended bile duct resection (EBDR) pioneered by the University of Nagoya has been shown proof-of-concept.[46] EBDR consists of careful excavation of the intrapancreatic portion of the CBD creating a funnel within the pancreatic parenchyma to assess the distal bile duct. In a small series of patients, 3- and 5-year survival rates (60% and 30%, respectively) were comparable to historic controls. Occurrence of POPFs was low (18%), and all were managed conservatively.

Similarly, the same group from Nagoya has pioneered the extended hilar plate resection (HPR) for patients lacking adequate functional liver remnant with perihilar CCAs that involve the biliary tree proximal to the confluence or distal/middle ECCs with proximal spread.[47] Briefly, the procedure entails bile duct resection up to and proximal to the hilar plate. Transection of the bile ducts can typically be performed proximal to the bifurcation of the anterior and posterior right bile ducts and at the base of the umbilical fissure followed by a cholangiojejunostomy with average of five bile duct reconstructions as reported in their institutional experience. The hepatic parenchyma also can be taken where possible around these structures but is limited by preservation of the hepatic arterial and portal venous vasculature. Additionally, isolated resection of the caudate should be considered because of multiple branches draining near the bifurcation of the right and left hepatic ducts. In proof-of-concepts study, there was less intraoperative blood loss, decreased postoperative complications, and no difference in OS compared with conventional major hepatectomy.

Taken together, these niche biliary operations can be performed safely with comparable oncologic outcomes in expert hands. These techniques and subsequent results could potentially be extrapolated to those with advanced MCC in effort to avoid major solid organ resections.

SYSTEMIC AND LOCOREGIONAL THERAPIES

The use of systemic cytotoxic chemotherapy and radiation therapy (RT), either in the adjuvant or neoadjuvant setting, for distal ECCs including MCC has not been clearly defined. As a result of disease rarity and resultant need to combine the spectrum of biliary tract tumors (ICC, ECC, and GBC) in clinical trials despite documented differences in tumor biology, execution of high-powered, practice changing clinical trials has been limited. Nonetheless, a growing body of evidence supports the use of adjuvant chemotherapy or chemoradiation therapy (CRT) for resected ECCs that can be extended to MCCs.

(Neo)adjuvant Systemic Therapy

The evidence supporting the use of adjuvant chemotherapy after curative-intent resection for ECCs stems from four randomized phase III clinical trials, all of which compare either single or dual-agent chemotherapy against observation alone across the spectrum of CCAs. Two of these studies, BILCAP (2022) and ASCOT-1 (2015), which included a third of patients with ECCs, both demonstrate significant OS benefit with administration of single fluoropyrimidine agent (capecitabine in BILCAP; S-1 in ASCOT-1) in the adjuvant setting.[48,49] In contrast, BCAT (2018) and PRODIGE-12-ACCORD-18 (2019) trials, which tested single-agent gemcitabine or gemcitabine plus oxaliplatin, observed no statistically significant differences in overall nor DFS between groups.[50,51] The discrepancy in outcomes between these studies may be a reflection of the ineffectiveness of gemcitabine-based therapies in resectable CCAs (in contrast to advanced or metastatic CCA as included in the ABC-02 trial) or the tumor location (ICC vs. ECC vs. GCC) dependent heterogeneity of response to chemotherapeutics.[27] Interestingly, in subgroup analyses conducted within the PRODIGE-12 trial, distal ECCs in the treatment arm demonstrated favorable OS and DFS, although not statistically significant. Based on these results, the consensus guidelines currently recommends adjuvant capecitabine as first-line treatment for resected ECC.[16,52] The use of adjuvant chemotherapy may be further supported by low-level evidence from a retrospective cohort review of patients undergoing BDSR or PD for MCC in which nearly 70% of patients undergoing BDSR received adjuvant chemotherapy compared with 40% following PD with comparable 5-year OS following the two operations.[6]

The neoadjuvant approach for resectable biliary tract cancers has not been critically investigated; current evidence is limited to a few, small retrospective series. Nearly 30 years ago, McMasters et al. reported the use of preoperative CRT with concomitant 5-FU in nine patients with perihilar and distal ECC; 33% achieved pathologic complete response and all patients who received neoadjuvant CRT had negative margins compared with approximately half of those who underwent upfront surgery.[53] A 2009 report by Nelson et al., including 12 patients who underwent neoadjuvant CRT followed by PD, achieved negative surgical margins in 91% of patients and 5-year survival rate of 53% compared with 23% in those with did not receive preoperative therapy.[54] More recently, experience from MD Anderson Cancer Center did not find any survival benefit in patients with distal ECC undergoing preoperative therapy (combinations of chemotherapy with or without RT); however, those who did undergo neoadjuvant approach harbored more clinically advanced disease and were poorer surgical candidates.[55] Currently, there are several ongoing clinical trials in East Asia and one in the United States examining the neoadjuvant approach for resectable ICCs but none for distal ECCs. While consensus criteria have not been established, current indications for a neoadjuvant approach outside a protocol-based setting may include tumor downstaging in attempt of BDSR in medically compromised patients or in the setting of delays to timely surgery such as cholangitis necessitating drainage and resolution of infection.

In summary, studies support the administration of adjuvant chemotherapy in patients who have undergone curative resection for distal ECCs. The use of neoadjuvant therapy for ECCs continues to be investigated with no definitive, high-quality evidence of its benefit and at this time should be reserved for the clinical trial setting.

Locoregional Therapy

Considering the prominent locoregional failure rates in MCC and ECC at-large, CRT has emerged as a potential avenue to mitigate local recurrence. Results from retrospective studies predominantly, including patients with distal ECC undergoing PD, have largely found survival and recurrence trends after concomitant CRT comparable or better than standard of care. A nearly 10-year experience from the Johns Hopkins Hospital demonstrated that patients with periampullary CCA who underwent adjuvant CRT had significantly improved OS compared with historical controls regardless of nodal status.[56] Although survival was improved, distant recurrence still occurred in 75% of the treated patients, highlighting systemic limitations of CRT. Similarly, Duke University reported their experience in 30 patients who achieved comparable median OS of 34 months following adjuvant CRT.[54] An extension of adjuvant therapy principle, Lim et al. reported a nonrandomized, single-center study comparing patients receiving either concomitant CRT alone compared with CRT followed by maintenance chemotherapy following resection of ECC.[57] The latter group experienced significantly improved OS and DFS despite R1 margin status and higher T-stage tumors. Finally, in a phase II clinical trial

of nearly 80 patients, 68% of whom had resected ECC, adjuvant dual-agent capecitabine, and gemcitabine followed by CRT achieved 2-year OS of 68% with a local recurrence rate of 13%. Notably, the DFS at 2 years was similar between R0 and R1 margin status tumors, which suggests a potentially beneficial role of adjuvant RT in achieving clinically relevant local control. Currently, the National Comprehensive Cancer Network (NCCN) only recommends CRT in setting of R0 resection with negative regional nodes.[16]

Collectively, the small body of evidence concerning the use of adjuvant CRT for resected distal ECC suggests that this modality may be effective in resected MCC in improving local control, thus potentially impactful for long-term outcomes. However, distant disease undeniably contributes to poor outcomes in CCAs at-large and remains a clinical challenge that CRT may not address. Theoretically, there may be more of a rationale for the use of CRT after BDSR as it appears margin status may be more of an issue.

Immunotherapy Considerations

Although in-depth discussion is beyond the scope of this review, a brief comment is reserved for the emerging role of immunotherapy for the treatment of bile duct cancers, including those arising from the mid-biliary tree. Accumulating evidence suggests that like other epithelial carcinomas, those of the biliary system harbor immunosuppressive microenvironments characterized by upregulation of immune checkpoints, such as programmed death-ligand 1 (PD-L1).[58] Recently, a phase III clinical trial (TOPAZ-I, 2022) established combination PD-L1 inhibitor (durvalumab) with dual-agent gemcitabine and cisplatin as standard of care over chemotherapy alone for metastatic/advanced biliary tract disease as 2-year OS was significantly improved by a margin of 15 months with combination therapy.[59] Notably, this advantage was observed regardless of PD-L1 expression, suggesting pleiotropic effects of immune checkpoint inhibition on the tumor milieu. In subgroup analysis of ECC, DFS but not OS was significantly improved with combination immuno-/chemotherapy. These promising results may implicate their use in the perioperative setting.

Future Perspectives and Conclusions

Cholangiocarcinoma of the middle bile duct is a rare clinical entity, and its true incidence is subject to interpretation of its anatomical boundaries. As the incidence of ECC at-large steadily increases, even in the Western world, and as populations age with improved health measures and standard of living, the role of bile duct segmental resection may expand. Currently, low-level evidence from retrospective studies supports the use of segmental resection for MCCs in a select subset of patients and appear to have the best chance of oncologic results with negative resection margins and thorough regional lymphadenectomy. Continued investigation into which patients and disease-specific features are most suitable for BDSR is warranted. Advances in regional, systemic, and targeted/immunotherapies have the potential to revolutionize the perioperative care of even resectable ECCs in the coming years; thus, the role of a less morbid procedure in BDSR may become more prominent. Although PD currently remains the standard of care curative operation for MCC, BDSR should not be completely abandoned. In the end, proper judgement must be used in considering the advantages of lower morbidity and mortality compared with disadvantages of a seemingly higher chance of local recurrence.

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