Advances in the management of cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA) is a primary malignancy of the bile ducts with three anatomically and molecularly distinct entities: Intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA. As a result of phenotypic and anatomic differences they differ significantly with respect to management. For each type of CCA there have been significant changes in management over the last several years which will be discussed in this review. Although resection remains the standard of care for all types of CCA, liver transplantation has been established as curative treatment for selected patients with pCCA and is being evaluated for iCCA with early success. With respect to systemic therapy capecitabine is now first line adjuvant therapy for all biliary tract malignancies after curative intent resection. Progress in exploiting the pathologic mutations and molecular abnormalities has also yielded regulatory approval of targeted therapy for CCA in patients with acquired alterations in the fibroblast growth factor receptor. There is also increased consensus in managing malignant biliary obstruction associated with CCA where pre-operative biliary stenting is not beneficial while self-expanding metal stents have been shown to be superior to plastic stents in patients who are not surgical candidates.

Key Words: Cholangiocarcinoma; Intrahepatic cholangiocarcinoma; Perihilar cholangiocarcinoma; Liver transplantation; Chemotherapy

Core Tip: This review presents recent advances in the management of cholangiocarcinoma with particular focus on the expanding role for liver transplantation, updated guidelines in the use of chemotherapy, novel applications of individualized therapy targeting the specific mutation profile of tumors, and management of malignant biliary obstruction.

INTRODUCTION

Cholangiocarcinoma (CCA) is an epithelial cell malignancy of the biliary tree and is the second most common primary hepatic malignancy[1,2]. The management of CCA depends largely on anatomic location and stage of disease. Anatomic location is significant not only because it dictates if a tumor can be resected, but also because different anatomic locations are associated with distinct molecular and biological characteristics which are increasingly important in determining optimal systemic therapy[3]. Intrahepatic CCA (iCCA) arises from the second order bile ducts within the liver and account for 10%-20% of CCAs, perihilar CCA (pCCA) originates between first order bile ducts and the cystic duct accounting for 50%-60% of CCA, and distal CCA (dCCA) arises distal to the cystic duct and account for 20%-30% of CCA[4]. Resection remains the best curative option for all types of CCA but is only possible in about 35% because symptoms occur late, the tumor progresses rapidly, and CCA is difficult to definitively diagnose[1,5]. Despite a historically low 5 year survival of 7%-20% and median survival of unresectable CCA of less than a year there has been significant progress in the management of CCA primarily in the use of liver transplantation and systemic therapy including targeted molecular therapy show promise to improve outcomes in the future[4,6].

iCCA

iCCA generally presents at later stages than other types of CCA because tumor growth is often intrahepatic and causes obstructive jaundice less frequently. When iCCA is diagnosed at early stages, it is often as an incidental finding or in patients with cirrhosis found during routine screening for hepatocellular carcinoma (HCC)[4]. Staging of iCCA should be done in accordance with the American Joint Committee on Cancer/International Union Against Cancer 7th edition staging manual as it has been validated and correlates with prognosis[7].

Surgical resection

Liver resection is the only widely accepted curative treatment for iCCA. Staging laparoscopy is recommended prior to resection in patients with high risk features such as multicentric disease, high CA19-9, questionable vascular invasion, or suspicion for peritoneal disease, because peritoneal or extrahepatic metastases are identified in 27-38% of patients[8]. However, because iCCA presents in advanced stages, only approximately 15% of patients with iCCA are candidates for liver resection[9]. The aim of surgical resection is complete removal of the tumor both grossly and microscopically, termed R0 resection. Resections which have microscopically positive margins are denoted R1 and if all gross tumor cannot be removed R2[10].

In planning liver resection, the location of the tumor in relation to biliary and vascular structure as well as the quality and size of the remaining liver parenchyma after resection are critically important[11]. In patients with inadequate future liver remnant, portal vein embolization can be attempted to allow for hypertrophy of the liver remnant[12]. However, this is associated with significant dropout of 20%-30% due to tumor progression and lack of adequate liver regeneration[13]. In smaller lesions and peripheral lesions anatomic resection is associated with lower recurrence and improved survival compared to non-anatomic resections[11]. Open and minimally invasive resection are associated with similar outcomes and both are endorsed by international consensus[14]. Hilar lymphadenectomy of at least 6 lymph nodes is recommended for accurate staging because imaging has low sensitivity for detecting nodal disease and because a recent multicenter retrospective review demonstrated removal of > 3 Lymph nodes is associated with improved survival compared to those where 1-2 lymph nodes were removed[1,15,16]. In patients with multifocal iCCA, the risk of recurrence is high and resection does not improve overall or recurrence free survival compared to locoregional therapy (LRT)[17].

Although most patients are not candidates for surgical resection, the frequency of liver resection for iCCA is increasing[18]. The 5 year survival after curative intent liver resection is 25%-40% with a median survival of 40 mo[19-21]. However, recurrence remains high at 50%-70%[22]. Tumor recurs most frequently in the remnant liver and can be often be treated with repeat resection which is associated with improved survival of 26.1 mo compared to 9.6 in patients treated with chemotherapy and 18.6 in patients treated with LRT[23].

Liver transplantation

Liver transplantation for iCCA was initially associated with survival as low as 53% at 1 year[24]. As a result liver transplantation was not recommended for the treatment of iCCA and remains a contraindication for liver transplant except as part of research protocols[1]. Subsequently a multicenter series of patients who underwent liver transplantation for presumed HCC but explant pathology showed iCCA demonstrated 1-year, 3-year, and 5-year actuarial survival rates of 93%, 84%, and 65% respectively in patients with tumor < 2 cm[25]. More recently a retrospective series from France demonstrated lower recurrence (18% *vs* 46%, *P* = 0.01) and improved recurrence free survival (75% *vs* 36%, *P* = 0.004) in cirrhotic patients with iCCA who underwent liver transplantation compared to resection[26]. A trend toward reduced recurrence was maintained in patients with tumors 2-5 cm (21% *vs* 48%, *P* = 0.06). Data such as this as well as improved survival after liver transplantation for pCCA prompted a re-examination of the role of liver transplantation for iCCA.

There is currently very limited prospective data for liver transplantation in patients with iCCA. A prospective series of 6 patients with iCCA treated with gemcitabine based neoadjuvant chemotherapy demonstrated excellent post-transplant survival: 100% at 1 year, 83.3% at 3 years, and 83.3% at 5 years[27]. It should be noted that median time from diagnosis to transplantation was 26 mo, which speaks to the value of assessing response to chemotherapy and tumor biology during an initial waiting period before liver transplantation. There are currently ongoing clinical trials to more thoroughly define the role for liver transplantation for iCCA. However, because iCCA is not accepted as an indication for liver transplantation and patients do not receive MELD exception points, organ allocation remains an obstacle and relies largely on marginal donor grafts.

Systemic therapy

The performance status of the patient and disease distribution are the primary determinants of candidacy for systemic therapy. In patients where iCCA is resected with curative intent, neoadjuvant therapy is not recommended but 6 mo of capecitabine should be offered to patients with R0 or R1 resections as adjuvant chemotherapy[28]. This recommendation is based largely on the BILCAP study which included 447 patients with biliary tract cancer including iCCA (19%), pCCA (28%), dCCA (35%), and muscle invasive gallbladder cancer (18%) and compared capecitabine to observation[29]. This demonstrated improved overall survival of 51 mo in the capecitabine group compared to 36 in the observation group. Because this data was not available when the National Comprehensive Cancer Network guidelines were published in 2019, the American Society of Clinical Oncology convened an expert panel who recommended capcitabine for all biliary tract cancers after R0 or R1 resection[28].

In patients who have acceptable performance status but are not candidates for resection, gemcitabine-cisplatin based palliative chemotherapy is recommended as first line[1]. This recommendation is supported by trials such as ABC-02 which included 410 patients where gemcitabine-cisplatin demonstrated improved overall compared to gemcitabine alone (11.7 mo *vs* 8.1 mo)[30]. Recent data from the phase III ABC-06 trial has established FOLFOX (leucovorin, Fluorouracil, and Oxaliplatin) as the preferred second line chemotherapeutic regimen[31]. This trial included 162 patients with advanced biliary tract cancer who progressed on a gemcitabine-cisplatin regimen. The one-year survival of patients randomized to FOLFOX was 25% compared to 11% in patients treated with supportive care. The similar benefit was maintained in the iCCA subgroup but did not achieve statistical significance.

Improved understanding of the molecular pathogenesis of iCCA has allowed for development of targeted therapies. Targeted and immunotherapy is a rapidly developing field with multiple agents under investigation therefore agents which are furthest along in the development/approval process will be reviewed here. Early attempts to use targeted therapy aimed at epidermal growth factor receptor (EGFR) and vascular epidermal growth factor (VEGF) pathways were unsuccessful. Cediranib, bevacizumab, sunitinib and vandetanib which target VEGF and VEGF receptor and

the EGFR inhibitor erlotinib have not shown survival benefit[32,33].

Point Mutations in the isocitrate dehydrogenase (IDH) 1 and 2 genes, present in 28% of iCCA and 7% of pCCA, result in increased production of the oncometabolite hydroxyglutarate[3,34]. Ivosidenib, a small molecule inhibitor of mutant IDH-1, was compared to placebo in patients with advanced IDH-1 positive CCA who progressed on first line therapy. Patients treated with ivosidenib had improved progression free survival compared to placebo (2.7 mo *vs* 1.4 mo $P ≤ 0.0001$) and progression free survival at 6 mo was 32% in the ivosidenib group compared to 0 in the placebo group [35]. This provides strong evidence for targeted therapy and benefit of molecular profiling in CCA and led to approval of ivosidenib in the United States by the Food and Drug Administration (FDA) for treatment of IDH-1 positive CCA.

Acquired alterations in the fibroblast growth factor receptor (FGFR) gene are associated with tumorigenesis through a variety of mechanisms including angio-genesis and enhancing cellular proliferation, migration, survival and invasion[36]. FGFR2 fusions and rearrangements are present in up to 45% of patients with iCCA but are rarely seen in pCCA and dCCA[37,38]. Of the several agents under investigation targeting this pathway pemigatinib, a FGFR 1-3 inhibitor, is the first to receive FDA approval for the treatment of CCA with FGF/FGFR alterations based on results showing 35% objective response in patients with locally advanced or metastatic CCA [39,40]. There is some concern that tumors could acquire resistance to FGFR inhibitors due to mutations in the FGFR kinase domain to early FGFR inhibitors such as infigratinib, but more recently developed irreversible FGFR inhibitor TAS-120 with high specificity for FGFR 1-4 has shown efficacy in patients with treatment failure due to FGFR kinase domain mutations[41,42]. This also suggests that these agents could be intentionally sequenced in order to prolong duration of response.

Immunotherapy has shown efficacy in an increasing number of malignancies and in some has become standard of care. Although the immune micro environment of iCCA is quite variable, it often displays features associated with responsiveness to immune checkpoint inhibitors (ICI)[43]. Although there are several ongoing phase 2 and 3 trials of ICIs in CCA, the review of which is beyond the scope of this review, published data remains limited to multi-tumor basket trials and single arm studies[32]. There is promise in patients with microsatellite instability (MSI) where 40% objective response was seen in tumors, including CCA, with MSI treated with pembrolizumab[44]. Targeting these mutations may have limited application as only 5-10% of biliary tract tumors have these mutations[45]. However, more recently combined anti- PD-1/CTLA-4 blockade with Nivolumab and Ipilimumab showed efficacy in a phase II trial of patients of patients with advanced biliary tract cancer without MSI demonstrated an objective response rate of 23% and disease control in 44%[46]. Interestingly, all of the responders had either gallbladder or intrahepatic tumors again emphasizing that intra and extrahepatic malignancies are phenotypically distinct tumors.

To allow for improved individualization next generation sequencing should be performed early in order to identify targetable aberrations since mutational profiles can already yield actionable mutations in > 40% of biliary tract tumors (Table 1)[47]. Because of the rapidly changing landscape of treatment and increasing number of mutational targets for therapy the importance of early testing, dedicated centers and a multidisciplinary approach is increasing.

Tumor directed therapies

In patients with unresectable tumors liver directed therapies are a possible adjunct to systemic therapy and have demonstrated efficacy in multicenter retrospective and phase II prospective experiences. Although there is increasing interest in these modalities for treatment of iCCA they have not yet become standard of care. Liver directed therapies include trans-arterial radioembolization (TARE), trans-arterial chemoembolization (TACE), thermal ablation, external beam radiation, and intra-arterial pump chemotherapy. TARE delivers a high dose of localized radiation to the target tumor *via* yttrium-90 coated microspheres. A multicenter retrospective review including 115 patients with unresectable iCCA treated with TARE in addition to standard of care treatment demonstrated median overall after treatment was 11 mo and 1-year overall survival was 44%, which compares favorably to historical data[48]. Treatment with TACE involves intraarterial injection of embolic beads impregnated with a chemotherapeutic agent resulting in embolic tumor kill augmented by high dose localized chemotherapy. TACE use in CCA has been limited but have generally shown that TACE is well tolerated and is associated with median overall survival of up to 15 mo in patients without extra-hepatic disease[49]. Thermal therapy involves either radiofrequency or microwave induced thermal ablation with an image guided

Table 1 Targetable genomic alterations in cholagiocarcinoma under investigation

Alterations	iCCA	pCCA/dCCA	Products under investigation
FGFR fusion	15%-20%	< 5%	Pemigatinib[1], Derantinib (ARQ-087), Infigrantinib[1] (BGJ398), Erdafitinib, TAS-120, ADZ4547
IDH1/2 mutation	20%	< 5%	Ivosidenib1, Enasidenib (AG-221), BAY 1436032, IDH305
ErbB2 (HER-2) amplification	< 5%	10%-15%	Trastuzumab, iapatinib, TAS0728, A166, PRS-343, ZW25
BRAF mutation	5%	< 5%	Dabrafenib + trametinib
DNA damage repair gene mutation (*ARID1A*, BRCA1/2)	25%	10%-15%	PARP inhibitors (olaparib, rucaparib)

[1]FDA approved.

iCCA: Intrahepatic cholangiocarcinoma; pCCA: Perihilar cholangiocarcinoma; dCCA: Distal cholangiocarcinoma; FGRR: Fibrobast growth factor receptor; IDH: Isocitrate dehydrogenase; ERBB (HER-2): A subtype of epidermal growth factor receptor tyrosine kinase; *BRAF*: Gene for serine/threonine-protein kinase B-Raf; *ARID1A*: Gene encoding a swItch/sucrose non-fermentable ATP-dependent chromatin remodeling complex; *BRCA*: Breast cancer gene.

probe percutaneously. Although data is limited, a systematic review of observational studies evaluating 84 patients with unresectable CCA treated with radiofrequency ablation showed pooled 1 year, 3 year, and 5 year survival of 82%, 47%, and 24% respectively[50]. Thermal ablation is therefore an option in patients with smaller (less than 4 cm) more peripheral tumors who are ineligible for surgery[51]. Both intraarterial and ablative treatment have also been reported as effective in patients with recurrence after resection[52,53]. Hepatic arterial infusion of high dose chemotherapy has demon-strated promising results in phase II studies of patients with unresectable iCCA. Of the 38 patients who were treated with intra-arterial infusion of floxuridine in addition to gemcitabine and oxaliplatin 58% achieved partial radiographic response with progression free survival of 11.8 mo, overall survival 25 mo, and 1 year survival of 89.5%[54].

Radiation therapy is also increasingly being evaluated for patients with unresectable iCCA as technologic advances has improved to the ability to specifically target malignant tissue while sparing non-malignant tissue. In a phase II trial high dose hypofractonated proton beam therapy was used to treat 37 patients with localized unresectable iCCA and demonstrated progression free survival of 8.4 mo, median overall survival of 22.5 mo and 1 year overall survival of 69.7%[55]. Evaluation of stereotactic body radiotherapy has similarly demonstrated safety and improved survival when compared to historical controls and is currently an area of investigation in phase III clinical trials (NCT02200042)[56,57].

PCCA

pCCA is the most common subset of CCA accounting for approximately 50% of CCA. The most common risk factor for pCCA is primary sclerosing cholangitis (PSC)[58]. Due to the risk of peritoneal seeding, percutaneous or fine-needle aspiration during endoscopic ultrasound is not recommended. Tissue diagnosis is most commonly obtained *via* cytology from endoscopic retrograde cholangiopancreatography (ERCP). Despite good specificity (97%), sensitivity of this is relatively low (43%)[59]. However, the addition of fluorescence in situ hybridization to conventional cytology can increase the sensitivity significantly to 65% while maintaining 100% specificity[60]. There is also interest in combining cytology with other methods to detect molecular or genetic signatures of CCA to aid in diagnosis, but these methods require further study before they are widely adopted[61-63].

Surgical resection

Although both liver transplantation and surgical resection for pCCA can offer cure, resection has historically been the preferred option[64]. Contraindications to resection include underlying PSC (because of high rates of multifocal disease) and presence of metastatic disease. Staging laparoscopy or laparotomy is recommended because occult metastatic disease or vascular involvement prior to surgical resection[65]. Despite this, recurrence is common with estimates based on long term follow up of 306 patients

who underwent curative intent surgery is 76%[66]. Patients with tumors involving both right and left intrahepatic ducts (Bismuth type IV) were previously not considered for resection however successful resection of these tumors has been described, primarily from centers in Asia. In one series from Japan 216 patients with Bismuth IV tumors treated with resection had 5 years survival of 32.8% and 53% in those who were negative for nodal and metastatic disease compared to 1.5% in those with unresected tumors[67]. Survival in Bismuth IV stage disease in this series was similar to earlier stage disease from other centers and suggests that presence of ductal invasion should not necessarily determine respectability if there is a high degree of local expertise[68]. Similarly advances in vascular reconstruction has allowed for resection of tumors with some degree of vascular involvement. While unilateral portal vein involvement does not impact overall survival in patients undergoing resection, there is decreased survival in patients with bilateral/main portal vein involvement or any hepatic artery involvement[69].

Liver transplantation

Although resection has been considered the standard of care for pCCA, only 20% of patients are candidates for surgical resection and of those who undergo surgical resection only 60%-80% achieve free margins (R0). Because survival after R0 resection is 20%-40% at 5 years and approaches 0% in those without R0 resection, there is significant interest in the use of liver transplantation for pCCA[70]. However, early experience with liver transplantation for pCCA resulted in recurrence rates of approximately 50% and poor long term survival[71]. Subsequently incorporating neoadjuvant chemoradiation prior to liver transplantation demonstrated favorable survival with multi-center experience from the United states showing 5-year disease free survival of 65% at 5 years following liver transplantation[72]. Based on this and other similar data, pCCA has been accepted by the United Network for Organ Sharing in the United States as an indication for liver transplantation and receives standard MELD exception points. In order to qualify, patients must have unresectable disease based on technical considerations or underlying liver disease, meet diagnostic criteria for pCCA less than 3 cm in size, be treated with neoadjuvant therapy, undergo operative staging to rule out intraperitoneal/lymph node metastases after neoadjuvant therapy, and be otherwise a candidate for liver transplantation. This approach has been criticized because a pathologic diagnosis is not required to qualify and residual tumor is found in only 52% of explants, therefore patients may undergo transplant without truly having CCA[72]. It has been argued that lack of pathologic evidence of CCA on explant may also be due to effective pre-transplant neoadjuvant therapy. There are no prospective comparisons of liver transplantation and surgical resection, however a multicenter retrospective comparison of curative intent resection (R0, R1) and transplantation for unresectable disease showed an improved overall survival of 77.4 mo compared to 17.1 mo ($P ≤ 0.001$) and five year overall survival was 53% compared to 17%[73]. Survival advantage was maintained when limiting resections to only tumors < 3 cm with negative lymph nodes ($P = 0.002$) and non-PSC patients ($P = 0.049$). It should be noted that in this comparison, all patients had pathologically confirmed CCA. This data raises the possibility that liver transplantation will have an increasing role in the management of pCCA, but further study of this topic is required.

Systemic therapy

There is currently very little data regarding the use of neoadjuvant chemotherapy for pCCA prior to resection and reported experiences are from single centers and with small sample sizes[74]. However, these experiences suggest that there may be a role for neoadjuvant therapy in patients with initially unresectable disease. Neoadjuvant therapy with 5-FU and radiation therapy prior to liver transplantation for pCCA has become standard of care since initial positive experiences were reported[75]. Based on the BILCAP study which was previously described, adjuvant therapy with capecitabine is recommended for 6 mo following curative intent resection regardless of R0 or R1 status[28]. Adjuvant therapy after liver transplantation is not recommended. Reports of adjuvant therapy is primarily from prior to wide application of neoadjuvant therapy or small series where patients had significantly more or more advanced disease than suspected pre-transplant[76]. First and second line systemic therapy for patients with advanced pCCA who are not candidates for liver transplantation or resection are the same as for iCCA, gemcitabine/cisplatin and FOLFOX respectively [31,77] (Table 2).

Table 2 Role of treatment modalities in the management of cholangiocarcinoma

| Tumor location | Surgery | Liver transplantation | Systemic therapy | | | Radiation therapy |
			NeoAdjuvant	Adjuvant	Palliative	
Intrahepatic	Liver resection is first line management, anatomic resection is preferred	Clinical trials and select centers only	Not indicated	Capecitabine	Gemcitabine/Cisplatin; FOLFOX or evaluate for targetable mutations	External beam radiation reduces recurrence in R1 resection
Perihilar	Liver resection is first line management	Consider if not resection candidate, PSC	Only prior to liver transplant	Capecitabine	Gemcitabine/Cisplatin; FOLFOX	External beam radiation required pre liver transplant
Distal	Pancreaticoduodenectomy is first line management	Not indicated	Not indicated	Capecitabine	Gemcitabine/Cisplatin; FOLFOX	No defined role

PSC: Primary sclerosing cholangitis; FOLFOX: Leucovorin, fluorouracil, and oxaliplatin.

Tumor directed therapy

In patients who are candidates for surgical resection, neo adjuvant radiation therapy is not recommended while the role for radiation therapy is well established in prior to liver transplantation for pCCA. Although there are no randomized trials evaluating adjuvant radiation therapy in patients with complete resection of extrahepatic CCA, it has not been shown to improve survival in review of the SEER database[78]. In patients with incomplete surgical resection adjuvant radiation therapy is recommended and was found to reduce post resection local recurrence in retrospective series [64]. Data specific to patients with locally advanced unresectable pCCA is limited however based on small series of patients including pCCA and evidence of benefit of radiation and chemotherapy (capecitabine plus cisplatin) compared to chemotherapy alone (overall survival 9.3 mo *vs* 6.3 mo) in iCCA, radiation therapy is often used in patients with unresectable pCCA[79,80]. There is even less data for TARE and other intra-arterial therapies for pCCA, but based on experience in iCCA, this can also be used in selected patients.

Management of biliary obstruction

Biliary obstruction is a common complication of CCA given the presence of advance disease at the time of diagnosis. Proximal malignant biliary obstruction (MBO) secondary to pCCA accounts for roughly 60% of all MBO, whereas distal MBO is caused by dCCA and account for 20%-30% of cases[3]. Although endoscopic stenting is the mainstream endoscopic approach for MBO, numerous clinical studies have failed to show any benefits of routine pre-operative endoscopic stenting[81-83]. However, since most patients are not candidates for curative surgical resection, endoscopy provides a minimally invasive, cost-effective, and safe intervention for palliative biliary drainage (BD) with the aim of improving the patient's quality of life (QOL)[81].

The optimal approach for proximal MBO remains controversial with conflicting results on whether percutaneous transhepatic biliary drainage (PTHD) or ERCP with biliary stenting is superior[84,85]. The choice between these two strategies depends on multiple factors, including local expertise availability. When available, the potential advantage of an endoscopic approach may include minimally invasiveness, lower risk for leakage and higher patient satisfaction when compared to PTHD[85].

Several randomized clinical trials on patients with hilar MBO support the use of self-expanding metal stents (SEMS) over plastic stents (PS). SEMS are associated with higher stent patency, lower rate of adverse events, and improved survival[86-88]. SEMS can be broadly divided into two types: uncovered (USEMS) or fully-covered (FCSEMS). USEMS are routinely used, as FCSEMS pose the risk of iatrogenic biliary obstruction of the contralateral and/or branch ducts.

The choice between unilateral *vs* bilateral drainage remains a point of debate given the conflicting data. When compared to bilateral stenting, De Palma *et al*[89] demonstrated that unilateral stenting was associated with a higher technical success rate (88.6% *vs* 76.9%; *P* = 0.04) and less adverse events (18.9% *vs* 26.9%; *P* = 0.03). However, recent randomized studies from Asia suggest that bilateral stenting, particularly in patients with Bismuth type III-V strictures, result in fewer interventions,

improved stent patency and BD[90,91]. There are currently two main strategies for bilateral endoscopic drainage: The stent-in-stent (SIS) or stent-by-stent (SBS) techniques. With SIS, a USEMS is placed through the mesh of the first indwelling USEMS into the contralateral hepatic duct. This method requires the use of large cell-sized SEMS to facilitate the introduction of the second stent in the SIS fashion. This type of stents is commonly available in Asia but not in the United States. As opposed to the SIS technique, with SBS, both stents are inserted and deployed simultaneously into two opposite lobes of the liver. Both techniques appear to be associated with similar rates of technical success, adverse events and stent occlusion[92-94]. In clinical practice, the choice between these two techniques is often based on endoscopist's preference and device availability.

In all, the optimal treatment strategy will vary and should be individualized. From a broad perspective, the goal is to drain at least 50% of the total liver volume, as this is associated with improved clinical outcomes and survival[95]. Considering the high degree of technical difficulty of ERCP in this patient population, referral to high-volume centers is recommended. High quality cross-sectional imaging are crucial for pre-procedural planning to determine the extent of the liver volume involved by the strictures and whether BD of those segments is indicated.

Several studies have reported a possible role for endobiliary ablation with different modalities (*i.e.*, radiofrequency ablation, cryoablation, photodynamic therapy, intraluminal brachytherapy) as a primary palliative treatment for CCA or as and adjunct therapy for SEMS occlusion[96]. Several studies suggest that endobiliary ablation combined with palliative stenting may improve stent patency and prolong patient survival without an increase in adverse events[97,98]. Ablative therapies may be of particular benefit for patients with comorbidities who are not surgical candidates. Nonetheless, few prospective comparative trials are available and high-quality studies evaluating endobiliary ablation with standard palliative treatments with QOL and survival endpoints are necessary to better define their role in the management of these patients.

Endoscopic ultrasound guided BD (EUS-BD) has recently emerged as an alternate endoscopic option for the primary palliation of MBO or as rescue therapy in those who have failed conventional ERCP with transpapillary BD[99-101]. The various EUS-BD approaches (*i.e.*, choledochoduodenostomy, hepaticogastrostomy, antegrade biliary stenting and rendezvous procedure) are beyond the scope of this review. Overall, the route of approach and site of BD are largely dependent on local expertise and the level of the obstruction (*i.e.*, distal *vs* proximal MBO). A recent systematic review and meta-analysis of nine studies and 483 patients demonstrated similar technical success between EUS-BD and PTHD, albeit the former was associated with lower rate of adverse events and fewer interventions[102]. Furthermore, EUS-BD obviates the need for an external drain as in PTHD thereby enhancing patient's QOL[102]. EUS-BD may also confer some additional benefits when compared to ERCP. Unlike ERCP, EUS-BD does not require transpapillary access, which increases the likelihood of procedural success when concomitant duodenal obstruction is present and reduces the risk of iatrogenic pancreatitis. Furthermore, EUS-BD can be achieved without strictly placing a SEMS across the MBO, which potentially reduces stent issues associated with tumor overgrowth/ingrowth. Noteworthy, EUS-BD is a technically demanding procedure and should be limited to centers with adequate advanced endoscopy expertise.

DISTAL CCA

Although dCCA and pCCA are similar with respect to the pathologic mutations and cells of origin, they differ significantly in their surgical management largely because of their distinct anatomic location[4]. Lesions suspicious for dCCA are evaluated similarly to pCCA with EUS, ERCP, computed tomography, and magnetic resonance imaging for definitive diagnosis, staging, and determining resectability. In evaluations of radiation therapy for CCA, dCCA and pCCA are generally referred to as extrahepatic CCA. This data was reviewed above, therefore will not be repeated in this section.

Surgical management

As with other types of CCA, the treatment of choice for dCCA is surgical resection. However, patients with dCCA are typically treated with pancreaticoduodenectomy rather than liver resection. Complete R0 resection is more common in patients with dCCA and is achieved in approximately 78% of patients[10]. The five-year survival of

patients who have curative intent surgery remains relatively poor at 37% with median survival of 33 mo[103]. Because the tumor does not involve the liver or require biliary reconstruction, liver transplant is not necessary or beneficial in the management of distal CCA.

Systemic therapy

Patients who undergo curative intent resection should be treated with capcitabine which has been shown to improve survival compared to observation[29]. In patients who are not candidates for resection and have good performance status, first line systemic therapy gemcitabine and cisplatin. Data regarding survival in patients with advanced unresectable dCCA treated with this regimen is difficult interpret due to pCCA and dCCA often being classified together and one trial in which the 95% confidence interval of the hazard radio for death crossed 1 in patients with extrahepatic CCA[30]. However, survival for patients with advanced unresectable biliary tract cancers treated with gemcitabine/cisplatin is approximately 11 mo[77]. Because of the limited data for survival benefit specific to patients with dCCA treated with gemcitabine/cisplatin consideration should be given to enroll patients in clinical trials and evaluate for targetable mutations, when available.

Management of biliary obstruction

ERCP with biliary stenting is the preferred approach for the management of patients with distal MBO. When compared to PTHD, ERCP is associated with less adverse events (8.6% *vs* 12.3%), lower cost and shorter hospitalization, and improved QOL[82, 83,104-106].

Recent data support the use of SEMS over PS for the management of distal MBO, although it largely includes patients with .biliary obstruction secondary to pancreatic malignancy. Overall, there is no significant difference in terms of technical success between the two approaches; however, SEMS are associated with longer stent patency, fewer adverse events, and less reinterventions[107,108].

Several studies have evaluated outcomes between uncovered *vs* covered metal stents for distal MBO[109-112]. In a randomized trial of 129 patients with distal MBO, there was no difference in stent patency or survival rates between uncovered *vs* partially covered SEMS; albeit the latter were associated with a higher rate of stent migration (0% *vs* 12%)[111]. Similarly, in another randomized trial of 400 patients, USEMS and FCSEMS had similar stent failure rates and time to re-occlusion, with no differences in survival time. Notably, stent migration was also more frequent with FCSEMS *vs* USEMS (3% *vs* 0%)[112]. Since MBO secondary to CCA is primarily a consequence of tumor growth within the bile duct lumen, placement of a FCSEMS may be preferable as to reduce the risk of tumor ingrowth.

CONCLUSION

Over the past several years there has been significant progress in the management of CCA. The role of liver transplantation has been clearly established for the management of pCCA and in some series rivaling the success of surgical resection. Transplantation is also being evaluated for iCCA with encouraging early results. Capecitabine has become first line adjuvant chemotherapy for all patients with curative intent resections of biliary tumors. With increasing understanding of mutational pathogenesis of the CCA, targeted therapies are showing significant promise and has led to the first FDA approved therapy for CCA targeting a specific mutation, pemigatinib. The use of SEMS has also improved management of obstructive symptoms over PS and advanced biliary stent design, endobiliary ablation, and EUS guided BD are avenues of investigation that may further improve management.

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