Advances in the management of cholangiocarcinoma

Andreas G Zori, Dennis Yang, Peter V Draganov, Roniel Cabrera

ORCID number: Andreas G Zori 0000-0002-4262-2401; Dennis Yang 0000-0003-3038-4669; Peter V Draganov 0000-0002-3922-0882; Roniel Cabrera 0000-0002-1863-0073.

Author contributions: Zori AG, Yang D, Draganov PV, and Cabrera R contributed to conception and design of the paper; Draganov PV and Cabrera R revised paper critically for important intellectual content; Zori AG, Yang D wrote majority of the draft;

Conflict-of-interest statement: Zori AG, Draganov PV, and Cabrera R have no conflicts of interest; Yang D is a consultant for Lumendi and Boston Scientific.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Andreas G Zori, Dennis Yang, Peter V Draganov, Roniel Cabrera, Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, FL 32608, United States

Corresponding author: Andreas G Zori, MD, Assistant Professor, Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, 1329 SW 16th St Suite 5251, Gainesville, FL 32608, United States. andreas.zori@medicine.ufl.edu

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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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.
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). 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 capcitabine 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 capcitabine to observation[29]. This demonstrated improved overall survival of 51 mo in the capcitabine 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
 Advances in the management of cholangiocarcinoma

Zori AG et al.

either radiofrequency or microwave induced thermal ablation with an image guided approach has been explored. A recent study reported a median overall survival of 12.3 mo in patients without extrahepatic disease, with 1-year overall survival of 60% [31]. This provides strong evidence for targeted therapy and molecular profiling in CCA.

TACE (transarterial chemoembolization) is a standard of care treatment demonstrated median overall survival of 11 mo (95% CI 8.8-14.9) in a phase II trial of 115 patients with unresectable iCCA treated with TARE in addition 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. Although the immune micro environment of iCCA is quite variable, it often displays features associated with responsiveness to immune checkpoint inhibitors (ICIs) [32]. 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 [41]. 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 with advanced biliary tract cancer without MSI demonstrated an objective response rate of 23% [45] 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 intraarterial 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 [38].

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 approach.
Table 1 Targetable genomic alterations in cholangiocarcinoma under investigation

| Alterations                        | iCCA          | pCCA/dCCA     | Products under investigation                               |
|------------------------------------|---------------|---------------|-----------------------------------------------------------|
| FGFR fusion                        | 15%-20%       | < 5%          | Pemigatinib, Derantinib (ARQ-087), Infigrantinib (BGJ398), Erdafitinib, TAS-120, ADZ4547 |
| IDH1/2 mutation                    | 20%           | < 5%          | Ivosidenib, Enasidenib (AG-221), BAY 1436032, IDH305     |
| ErbB2 (HER-2) amplification        | < 5%          | 10%-15%       | Trastuzumab, lapatinib, 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)                     |

1FDA approved.

iCCA: Intrahepatic cholangiocarcinoma; pCCA: Perihilar cholangiocarcinoma; dCCA: Distal cholangiocarcinoma; FGFR: Fibroblast 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 demonstrated promising results in phase II studies of patients with unresectable iCCA. Of the 38 patients who were treated with intra-arterial infusion of fluoridine 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 69.5%[54].

Radiation therapy is also increasingly being evaluated for patients with unresectable iCCA as technologic advances has improved 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)[38]. 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 resectability 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 intrahepatic 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 |
|----------------|---------|----------------------|------------------|-------------------|
| 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)[83].

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 minimal 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 also confer some additional benefits when compared to SEMS in 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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[30]}. However, survival for patients with advanced unresectable biliary tract cancers treated with gemcitabine/cisplatin is approximately 11 mo\textsuperscript{[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\textsuperscript{[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\textsuperscript{[107,108]}. Several studies have evaluated outcomes between uncovered vs covered metal stents for distal MBO\textsuperscript{[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%\textsuperscript{[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%)\textsuperscript{[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.

**REFERENCES**

1. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014; 60: 1268-1289 [PMID: 24681130 DOI: 10.1016/j.jhep.2014.01.021]
2. Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. HPB (Oxford) 2008; 10: 77-82 [PMID: 18773060 DOI: 10.1080/13651820801992641]
3. Rizvi S, Khan SA, Hallemeyer CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts
and therapeutic strategies. *Nat Rev Clin Oncol* 2018; 15: 95-111 [PMID: 28094423DOI: 10.1038/nrclinonc.2017.157]

4 Banales JM, Marin JG, Llanarca A, Rodrigues PM, Khan SA, Roberts LR, Cardinale V, Carpio G, Andersen JB, Braconi C, Calvisi DF, Perugorria MJ, Fabris L, Boulter L, Macias RIR, Gasdio E, Alvaro D, Gradilone SA, Strazzabosco M, Marzioni M, Coulouarn C, Fouassier L, Raggi C, Ishizawarizzi P, Mertens JC; Monsec A, Rizvi S, Heimbach J, Koerkamp BG, Brux J, Forner J, Arnera A, Bridgewater I, Valle JW, Gores GI. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020; 17: 557-588 [PMID: 32606456DOI: 10.1038/s41575-020-0310-z]

5 Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniwicz BS J, Youssef BA M, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001; 234: 507-517 [PMID: 11573044DOI: 10.1097/00000658-200110000-00010]

6 Bertuccio P, Malvezzi M, Carioti G, Hashim D, Boffetta P, El-Serag HB, La Vecchia C, Negri E. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol* 2019; 71: 104-114 [PMID: 30910538DOI: 10.1016/j.jhep.2019.03.013]

7 AJCC Cancer Staging Handbook - From the AJCC Cancer Staging Manual. 7th ed. New York: Springer-Verlag, 2010

8 Weber SM, Riberio D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 2015; 17: 669-680 [PMID: 26172134DOI: 10.1111/hpb.12441]

9 Amini N, Ejaz A, Spolverato G, Kim Y, Herman JM, Pawlik TM. Temporal trends in liver-directed therapy of patients with intrahepatic cholangiocarcinoma in the United States: a population-based analysis. *J Surg Oncol* 2014; 110: 163-170 [PMID: 24676600DOI: 10.1002/jso.23605]

10 DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, Choti MA, Yeo CJ, Schick RD. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007; 245: 755-762 [PMID: 17457168DOI: 10.1097/01.sla.0000251666.62632.d3]

11 Si A, Li J, Yang Z, Xia Y, Yang T, Lei Z, Cheng Z, Pawlik TM, Lau WY, Shen F. Impact of Anatomical Versus Non-anatomical Liver Resection on Short- and Long-Term Outcomes for Patients with Intrahepatic Cholangiocarcinoma. *Ann Surg Oncol* 2019; 26: 1841-1850 [PMID: 30843164DOI: 10.1245/s10434-019-07260-8]

12 Chapelle T, Op de Beeck B, Roeyen G, Bracke B, Hartman V, De Greef K, Huyghe I, Van der Zijden T, Morrison S, Franque S, Ysebaert D. Measuring future liver remnant function prior to hepatectomy may guide the indication for portal vein occlusion and avoid posthepatectomy liver failure: a prospective intervention study. *HPB (Oxford)* 2017; 19: 108-117 [PMID: 27936027DOI: 10.1016/j.hpb.2016.11.005]

13 Ebata T, Yokoyama Y, Iguni T, Sugawara G, Takahashi Y, Nagino M. Portal vein embolization before extended hepatectomy for biliary cancer: current technique and review of 494 consecutive embolizations. *Dig Surg* 2012; 29: 23-29 [PMID: 22441616DOI: 10.1159/000335718]

14 Liu R, Wakabayashi G, Kim HJ, Choi GH, Yiengpruksawan A, Fong Y, He J, Boggii U, Troisi RI, Efano M, Azoulay D, Panaro F, Pessoa P, Wang XY, Zhu JY, Zhang SG, Sun CD, Wu Z, Tao KS, Yang KH, Fan J, Chou XP. Expert consensus statement. *Ann Surg Oncol* 2018; 25: 1432-1444 [PMID: 30948907DOI: 10.1089/wjo.v25.i12.1432]

15 Sahara K, Tsiliimiras DJ, Merath K, Bagante F, Guglielmi A, Aldrighetti L, Weiss M, Bauer TW, Alexandrescu S, Poultsides GA, Mathkel SK, Marques HF, Martel G, Pulitano C, Shen F, Soubrane O, Koerkamp BG, Matsuyama R, Endo I, Pawlik TM. Therapeutic Index Associated with Lymphadenectomy Among Patients with Intrahepatic Cholangiocarcinoma: Which Patients Benefit the Most from Nodal Evaluation? *Ann Surg Oncol* 2019; 26: 2959-2968 [PMID: 31152272DOI: 10.1245/s10434-019-07463-9]

16 Mazzaferro V, Gorgon A, Roayaie S, Droz Dit Busset M, Sapisochin G. Liver resection and transplantation for intransigent cholangiocarcinoma. *J Hepatol* 2020, 72: 364-377 [PMID: 31954498DOI: 10.1016/j.jhep.2019.11.020]

17 Wright GP, Perkins S, Jones H, Zureikat AH, Marsh JW, Holtzman MP, Zeh HH 3rd, Bartlett DL, Pingpank JF Jr. Surgical Resection Does Not Improve Survival in Multifocal Intrahepatic Cholangiocarcinoma: A Comparison of Surgical Resection with Intra-Arterial Therapies. *Ann Surg Oncol* 2018; 25: 83-90 [PMID: 29063296DOI: 10.1245/s10434-017-6110-1]

18 Tan JC, Coburn NG, Baxter NN, Kiss A, Law CH. Surgical management of intransigent cholangiocarcinoma--a population-based study. *Ann Surg Oncol* 2008; 15: 600-605 [PMID: 17987347DOI: 10.1245/s10434-007-9627-x]

19 Chan KM, Tsai CY, Yeh CN, Yeh TS, Lee WC, Jan YY, Chen MF. Characterization of intransigent cholangiocarcinoma after curative resection: outcome, prognostic factor, and recurrence. *BMC Gastroenterol* 2018; 18: 180 [PMID: 30514231DOI: 10.1186/s12876-018-0912-x]

20 Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology* 2001; 33: 1353-1357 [PMID: 11391522DOI: 10.1053/jhep.2001.25087]

21 Hyder O, Marques H, Pulitano C, Marsh JW, Alexandrescu S, Bauer TW, Gambill TC, Sotropoulos GC, Paul A, Barroso E, Clary BM, Aldrighetti L, Ferrone CR, Zhu AX, Popsescu I, Gigot JF, Menthia G, Feng S, Pawlik TM. A nomogram to predict long-term survival after resection
for intrahepatic cholangiocarcinoma: an Eastern and Western experience. *JAMA Surg* 2014; 149: 432-438 [PMID: 24599477 DOI: 10.1001/jamasurg.2013.5168]

22 **Mavros MN**, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma: Systematic Review and Meta-analysis. *JAMA Surg* 2014; 149: 565-574 [PMID: 24718873 DOI: 10.1001/jamasurg.2013.5137]

23 **Spolivaro G**, Kim Y, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L, Clark Gamblin T, Maithekl SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Tran TB, Wallis Marsh J, Pawlik TM. Management and Outcomes of Patients with Recurrent Intrahepatic Cholangiocarcinoma Following Previous Curative-Intent Surgical Resection. *Ann Surg Oncol* 2016; 23: 235-243 [PMID: 26059651 DOI: 10.1007/s10434-015-4642-9]

24 **Goldstein RM**, Stone M, Tillery GW, Senzer N, Levy M, Husberg BS, Gonwa T, Klintmalm G. Is liver transplantation indicated for intrahepatic cholangiocarcinoma? *Am J Surg Pathol* 1993; 16: 768-771 [PMID: 8273866 DOIP: 10.1002/hep.28747]

25 **Sapischin G**, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, Vibert E, Cherqui D, Grant DR, Hernandez-Alejandro R, Dale CH, Cucetti A, Pinna A, Hwang S, Lee SG, Apogian VG, Busuttil RW, Rizvi S, Heinbach JK, Montenovo M, Reyes J, Cesaretti M, Sobrane O, Reichman T, Seal J, Kim PT, Klintmalm G, Sposito C, Mazzaferrr V, Dutkowski P, Clavien PA, Tosco C, Majno P, Keteman N, Saunders C, Bruix J; iCCA International Consortium. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. *Hepatology* 2016; 64: 1178-1188 [PMID: 27481548 DOI: 10.1002/hep.28747]

26 **De Martin E**, Rayar M, Golse N, Dupeux M, Gelli M, Gneemi V, Allard MA, Cherqui D, Sa Cunha A, Adam R, Coilly A, Antonini TM, Guettier C, Samuel D, Boudjema K, Boleslawski E, Vibert E. Analysis of Liver Resection Versus Liver Transplantation on Outcome of Small Intrahepatic Cholangiocarcinoma and Combined Hepatocellular-Cholangiocarcinoma in the Setting of Cirrhosis. *Liver Transpl* 2020; 26: 785-798 [PMID: 32090444 DOI: 10.1002/lt.25377]

27 **Lunsford KE**, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, Mobiley CM, Saharia A, Victor DW, Nguyen DT, Graiviss EA, Kaseb AO, McFadden RS, Aloia TA, Conrad C, Li XC, Monsour HP, Gaber AO, Vauthen JN, Gobriel RM; Methodists-MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC). Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol* 2018; 3: 337-348 [PMID: 29548617 DOI: 10.1016/S2468-1381(18)30045-1]

28 **Shroff RT**, Kennedy EB, Bachini M, Bekaii-Saab T, Crane C, Edeline J, El-Khoueiry A, Feng M, Katz MHG, Primrose J, Soares HP, Valle JW. Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline. *J Clin Oncol* 2019; 37: 1015-1027 [PMID: 30856044 DOI: 10.1200/JCO.18.02178]

29 **Primrose JN**, Fox R, Palmer DH, Prasad R, Mirza D, Anthoncy DA, Corrie P, Falk S, Wasan HS, Ross PJ, Wall LR, Wadsley J, Evans TRJ, Stocken D, Praseedom R, Cunningham D, Garden OJ, Stubbs C, Valle JW, Bridgewater JA. Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study. *J Clin Oncol* 2017; 35: 4006 [DOI: 10.1200/JCO.2017.35.15_suppl.4006]

30 **Valle J**, Wasan H, Palmer DH, Cunningham D, Anthoncy A, Aravayayas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *Lancet* 2020; 395: 1273-1281 [PMID: 32054040 DOI: 10.1016/NEJMoa0908721]

31 **Lamarca A**, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillimore R, Wadsley J, Patel K, Anthoncy A, Maraveyas A, Waters JS, Hobbs C, Barber S, Ryder D, Ramage J, Davies LM, Bridgewater JA, Valle JW. ABC-06 [A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+iFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy]. *J Clin Oncol* 2019; 37: 4003 [DOI: 10.1200/JCO.2019.37.15_suppl.4003]

32 **Kelley RK**, Bridgewater J, Gores GJ, Zhu AX. Systemic therapies for intrahepatic cholangiocarcinoma. *J Hepatol* 2020; 72: 353-363 [PMID: 31954497 DOI: 10.1016/j.jhep.2019.10.009]

33 **Lee J**, Park SH, Chang HM, Kim JS, Choi HI, Lee MA, Jang JS, Jeung HK, Kang JH, Lee HW, Shin DB, Kang HK, Sun JM, Park JO, Park YS, Kang WK, Lim HY. Gemicitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2012; 13: 181-188 [PMID: 22192731 DOI: 10.1016/S1470-2045(11)70301-1]

34 **Kipp BR**, Yous JS, Kerr SE, Barr Frichter EG, Graham RP, Zhang L, Highsmith WE, Zhang J, Roberts LR, Gores GJ, Halling KC. Isocitrate dehydrogenase 1 and 2 mutations in cholangiocarcinoma. *Hum Pathol* 2012; 43: 1552-1558 [PMID: 22503487 DOI: 10.1016/j.humpath.2011.12.007]

35 **Abou-Alfa GK**, Macarulla T, Javle MM, Kelley RK, Luhner SJ, Adeva J, Cleeay JM, Catennacci DV, Borad MJ, Bridgewater J, Harris WP, Murphy AG, Oh DY, Whisenant MA, Goyal L, Shroff RT, El-Khoueiry AB, Fan B, Wu B, Chamberlain CX, Jiang L, Glicer C, Pandya SS, Valle JW, Zhu AX. Iosibenin in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; 21.
Zori AG et al. Advances in the management of cholangiocarcinoma

796-807 [PMID: 32416072 DOI: 10.1016/S1470-2045(20)30157-1]

36 Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. Nat Rev Cancer 2017; 17: 318-332 [PMID: 28303906 DOI: 10.1038/nrc.2017.8]

37 Graham RP, Barr Frichter EG, Pestova E, Schulz J, Staitio LA, Vasmatzis G, Murphy SJ, McWilliams RR, Hart SN, Hailing KC, Roberts LR, Gores GJ, Couch FJ, Zhang L, Borad MJ, Kipp BR. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. Hum Pathol 2014; 45: 1630-1638 [PMID: 24837095 DOI: 10.1016/j.humpath.2014.03.014]

38 Dia S, Losic B, Moeini A, Cabellos L, Hao K, Revill K, Bonal D, Miltiadous O, Zhang Z, Hoshida Y, Cornella H, Castillo-Martin M, Pinyol R, Kasai Y, Rouayie S, Thung SN, Fuster J, Schwartz ME, Waxman S, Cordon-Cardo C, Schad J, Mazzaferrro V, Llovet JM. Massive parallel sequencing uncovers actionable FGFR2-PPHLN1 fusion and ARAF mutations in intrahepatic cholangiocarcinoma. Nat Commun 2015; 6: 6087 [PMID: 25608663 DOI: 10.1038/ncomms7087]

39 Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, Borad MJ, Gallinson D, Murphy AG, Oh DY, Dotan E, Catenacci DV, Van Cutsem E, Ji Ti, Lihou CF, Zhen H, Feliz L, Vogel A. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020; 21: 671-684 [PMID: 32203698 DOI: 10.1016/S1470-2045(20)30109-1]

40 Jave M, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, Ramanathan RK, Goyal L, Sadeghi S, Macarulla T, El-Khoueiry A, Kelley RK, Borbath I, Choo SP, Oh DY, Philip PA, Chen L, Reungwetwattana T, Van Cutsem E, Yeh KH, Ciombor K, Finn RS, Patel A, Sen S, Porter D, Isaac A, Zhu AX, Abou-Alfa GK, Bekaii-Saab T. Phase II Study of BQJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. J Clin Oncol 2018; 36: 276-282 [PMID: 29182496 DOI: 10.1200/JCO.2017.75.5009]

41 Goyal L, Shi L, Liu LY, Fece de la Cruz F, Lennerz JK, Raghavan S, Leschinger I, Elagina L, Siravegna G, Ng RWS, Pu P, Patha KC, Saha SK, Upton RN, Arellano R, Reyes S, Sagara T, Otuski S, Nadres H, Shahrzade HA, Dey-Guha I, Fudenberg JD, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van Cutsem E, Ji, T, Liu LY, Donadon M, Ofman J, Bach RE, Denekamp J, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crowenzi TS, Lee JJ, Duffy SM, Le DT, Swanton C, Alexander SP, Stroobants S, Van E
Mahvash A, IJzermans JNM, Weiss MJ, Lamarc A, Bell JK, Valle JW, Hagendoorn J, Koerkamp BG, Sze DY, Lam MG EH. Yttrium-90 Radioembolization in Intrahepatic Cholangiocarcinoma: A Multicenter Retrospective Analysis. J Vasc Interv Radiol 2020; 31: 1035-1043 [PMID: 32473575 DOI: 10.1016/j.jvir.2020.02.008]

Kiefer MV, Albert M, McNally M, Robertson M, Sun W, Franer D, Olthoff K, Christians K, Pappas S, Rilling W, Soulen MC. Chemoembolization of intrahepatic cholangiocarcinoma with cisplatinum, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol: a 2-center study. Cancer 2011; 117: 1498-1505 [PMID: 21425151 DOI: 10.1002/cncr.25625]

Han K, Ko HK, Kim KW, Won HJ, Shin YM, Kim PN. Radiofrequency ablation in the treatment of unresectable intrahepatic cholangiocarcinoma: systematic review and meta-analysis. J Vasc Interv Radiol 2015; 26: 943-948 [PMID: 25899049 DOI: 10.1016/j.jvir.2015.02.024]

Koay EJ, Odisso BC, Javle M, Vauthney JN, Crane CH. Management of unresectable intrahepatic cholangiocarcinoma: how do we decide among the various liver-directed treatments? Hepatobiliary Surg Nutr 2017; 6: 105-116 [PMID: 28503558 DOI: 10.21037/hbsn.2017.01.16]

Wu ZF, Zhang HB, Yang N, Zhao WC, Fu Y, Yang GS. Postoperative adjuvant transcutaneous arterial chemoembolisation improves survival of intrahepatic cholangiocarcinoma patients with poor prognostic factors: results of a large monocentric series. Eur J Oncol 2012; 38: 602-610 [PMID: 22447004 DOI: 10.1016/j.ejso.2012.02.185]

Kim JH, Won HJ, Shin YM, Kim PN, Lee SG, Hwang S. Radiofrequency ablation for recurrent intrahepatic cholangiocarcinoma after curative resection. Eur J Radiol 2011; 80: e221-e225 [PMID: 20950977 DOI: 10.1016/j.ejrad.2010.09.019]

Cercek A, Boerner T, Tan BR, Chou JF, Gönen M, Boucher TM, Hauser HF, Do RKG, Lowery MA, Harding JI, Varghese AM, Reidy-Lagunes D, Saltz L, Schulz N, Kingham TP, D’Angelica MI, DeMatteo RP, Drebin JA, Allen PJ, Balachandran VP, Lim KH, Sanchez-Vega F, Vachharajani N, Majella Doyle MB, Fields RC, Hawkins WG, Strasberg SM, Chapman WC, Diaz LA Jr, Kemeny NE, Jarragin WR. Assessment of Hepatic Arterial Infusion of Mitomycin C: Multiinstitutional Phase II Study of Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. J Clin Oncol 2016; 34: 460-466 [PMID: 26668346 DOI: 10.1200/JCO.2015.64.2710]

Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, Sherman M, Dawson LA. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008; 26: 657-666 [PMID: 18172187 DOI: 10.1200/JCO.2007.14.3529]

Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, Kaseb AO, Bishop AJ, Swanick CW, Koay EJ, Thames HD, Hong TS, Das P, Crane CH. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 2016; 34: 219-226 [PMID: 26503201 DOI: 10.1200/JCO.2015.63.1778]

Weismüller TJ, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, Swink CW, Koay EJ, Thames HD, Hong TS, Das P, Crane CH. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 2016; 34: 219-226 [PMID: 26503201 DOI: 10.1200/JCO.2015.63.1778]

E221-e225 [PMID: 20950977 DOI: 10.1016/j.ejrad.2010.09.019]

Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, Sherman M, Dawson LA. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008; 26: 657-666 [PMID: 18172187 DOI: 10.1200/JCO.2007.14.3529]

Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, Kaseb AO, Bishop AJ, Swanick CW, Koay EJ, Thames HD, Hong TS, Das P, Crane CH. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 2016; 34: 219-226 [PMID: 26503201 DOI: 10.1200/JCO.2015.63.1778]

Weismüller TJ, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, Swink CW, Koay EJ, Thames HD, Hong TS, Das P, Crane CH. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 2016; 34: 219-226 [PMID: 26503201 DOI: 10.1200/JCO.2015.63.1778]

E221-e225 [PMID: 20950977 DOI: 10.1016/j.ejrad.2010.09.019]

Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, Sherman M, Dawson LA. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008; 26: 657-666 [PMID: 18172187 DOI: 10.1200/JCO.2007.14.3529]

Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, Kaseb AO, Bishop AJ, Swanick CW, Koay EJ, Thames HD, Hong TS, Das P, Crane CH. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 2016; 34: 219-226 [PMID: 26503201 DOI: 10.1200/JCO.2015.63.1778]

Weismüller TJ, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, Swink CW, Koay EJ, Thames HD, Hong TS, Das P, Crane CH. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 2016; 34: 219-226 [PMID: 26503201 DOI: 10.1200/JCO.2015.63.1778]

E221-e225 [PMID: 20950977 DOI: 10.1016/j.ejrad.2010.09.019]

Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, Sherman M, Dawson LA. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008; 26: 657-666 [PMID: 18172187 DOI: 10.1200/JCO.2007.14.3529]

Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, Kaseb AO, Bishop AJ, Swanick CW, Koay EJ, Thames HD, Hong TS, Das P, Crane CH. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 2016; 34: 219-226 [PMID: 26503201 DOI: 10.1200/JCO.2015.63.1778]

Weismüller TJ, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, Swink CW, Koay EJ, Thames HD, Hong TS, Das P, Crane CH. Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis. J Clin Oncol 2016; 34: 219-226 [PMID: 26503201 DOI: 10.1200/JCO.2015.63.1778]
Clinical diagnosis and management of perihilar cholangiocarcinoma. *Clin Liver Dis* (Hoboken) 2014; 3: 60-64 [PMID: 30992887 DOI: 10.1016/j.clld.2013.238]

Bird N, Elmasry M, Jones R, Elnief M, Kelly P, Palmer D, Fenwick S, Poston G, Malik H. Role of staging laparoscopy in the stratification of patients with perihilar cholangiocarcinoma. *Br J Surg* 2017; 104: 418-425 [PMID: 27861766 DOI: 10.1002/bjs.10399]

Groot Koerkamp B, Wiggers JK, Allen PJ, Besseling MG, Blumgart LH, Busch OR, Coelen RJ, D'Angelica MI, DeMatteo RP, Gouma DJ, Kingham TP, Jarnagin WR, van Gulik TM. Recurrence Rate and Pattern of Perihilar Cholangiocarcinoma after Curative Intent Resection. *J Am Coll Surg* 2015; 221: 1041-1049 [PMID: 26454735 DOI: 10.1016/j.jamcollsurg.2015.09.005]

Ebata T, Mizuno T, Yokoyama Y, Igame T, Sugawara G, Nagino M. Surgical resection for Bismuth type IV perihilar cholangiocarcinoma. *Br J Surg* 2018; 105: 829-838 [PMID: 28488733 DOI: 10.1002/bjs.10556]

Neuhaus P, Jonas S, Bechstein WO, Lohmann R, Radke C, Kling N, Wex C, Lobeck H, Hintze R. Extended resections for hilar cholangiocarcinoma. *Ann Surg* 1999; 230: 808-818 [PMID: 10619536 DOI: 10.1097/00000658-199912000-00010]

van Vugt JLA, Gasparz MP, Coelen RJS, Vugts J, Labeur TA, de Jonge J, Polak WG, Busch ORC, Besselink MG, Uzermans JNM, Nio CY, van Gulik TM, Willemsen FEJA, Groot Koerkamp B. The prognostic value of portal vein and hepatic artery involvement in patients with perihilar cholangiocarcinoma. *HPB (Oxford)* 2018; 20: 83-92 [PMID: 28958483 DOI: 10.1016/j.hljp.2017.08.025]

Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. *Transpl Int* 2010; 23: 692-697 [PMID: 20497401 DOI: 10.1111/j.1432-2277.2010.01008.x]

Meyer CG, Penn J, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000; 69: 1633-1637 [PMID: 10836374 DOI: 10.1097/00007098-200004270-00019]

Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, Both JF, Mezrich JD, Chapman WC, Schwartz JJ, Hong JC, Emond JC, Jeon H, Rosen CB, Gores GJ, Heimbach JK. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012; 143: 88-98 [PMID: 22504095 DOI: 10.1053/j.gastro.2012.04.008]

Elthun CG, Lopez-Aguir AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, Chapman WC, Krasnick BA, Weber SM, Mezrich JD, Salem A, Pawlik TM, Poulsides G, Tran TB, Idrees K, Isom CA, Martin RCG, Scougals CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Cardona K, Maithel SK. Transplantation Versus Resection for Hilar Cholangiocarcinoma: An Argument for Shifting Treatment Paradigms for Resectable Disease. *Ann Surg* 2018; 267: 797-805 [PMID: 29064885 DOI: 10.1097/SLA.S.0000000000002574]

Frosio F, Mocchegiani F, Conte G, Bona ED, Vecchi A, Nicolini D, Vivarelli M. Neoadjuvant therapy in the treatment of hilar cholangiocarcinoma: Review of the literature. *World J Gastrointest Surg* 2019; 11: 279-286 [PMID: 31367275 DOI: 10.4240/wjgs.v11.i6.279]

Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Pedersen R, Kremers W, Nyberg SL, Ishitani MS, Rosen CB. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. *Transplantation* 2006; 82: 1703-1707 [PMID: 17198263 DOI: 10.1097/01.tp.0000253551.43583.d1]

Hong JC, Jones CM, Duffy JP, Petrowsky H, Farmer DG, French S, Finn R, Durazo FA, Saab S, Tong MJ, Hiatt JR, Busuttil RW. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. *Arch Surg* 2011; 146: 683-689 [PMID: 21690444 DOI: 10.1001archsurg.2011.116]

Valle JW, Funuse J, Jitlal M, Beare S, Mizuno N, Wasan H, Bridgewater J, Okusaka T. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol* 2014; 25: 391-398 [PMID: 24351397 DOI: 10.1093/annonc/mdu150]

Vern-Gross TZ, Shrivani AT, Chen K, Lee CM, Tward JD, MacDonald OK, Crane CH, Talamonti MS, Mannoz LL, Small W Jr. Survival outcomes in resected extrahepatic cholangiocarcinoma: effect of adjuvant radiotherapy in a surveillance, epidemiology, and end results analysis. *Int J Radiat Oncol Biol Phys* 2011; 81: 189-198 [PMID: 20971573 DOI: 10.1016/j.ijrobp.2010.05.001]

Kim YI, Park JW, Kim BH, Woo SM, Kim TH, Koh YH, Lee WJ, Kim CM. Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for advanced-stage unresectable intrahepatic cholangiocarcinoma. *Radiat Oncol* 2013; 8: 292 [PMID: 24359879 DOI: 10.1186/1748-717X-8-292]

Gikka E, Hallauer L, Kirste S, Adebah S, Bartl N, Neeff HP, Fritsch R, Brass V, Nestle U, Grosu AL, Brunner TB. Stereotactic body radiotherapy (SBRT) for locally advanced intrahepatic and extrahepatic cholangiocarcinoma. *BMC Cancer* 2017; 17: 781 [PMID: 29162055 DOI: 10.1186/s12885-017-3788-1]

van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, Gerritsen J,
Greve JW, Gerhards MF, de Hingh IH, Klinkenbijl JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010; 362: 129-137 [PMID: 20071702 DOI: 10.1056/NEJMoa0903230]

82 Qiu YD, Bai JL, Xu FG, Ding YT. Effect of preoperative biliary diversion on malignant obstructive jaundice: a meta-analysis. *World J Gastroenterol* 2011; 17: 391-396 [PMID: 21253401 DOI: 10.3748/wjg.v17.i3.391]

83 Sewnath ME, Karsten TM, Prins MH, Raauws EJ, Obertop H, Gouma DJ. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. *Ann Surg* 2002; 236: 17-27 [PMID: 12131081 DOI: 10.1097/00000658-200207000-00005]

84 Lee SH, Park JK, Yoon WJ, Lee JK, Ryu JK, Yoon YB, Kim YT. Optimal biliary drainage for inoperable Klatskin's tumor based on Bismuth type. *World J Gastroenterol* 2007; 13: 3948-3955 [PMID: 17663508 DOI: 10.3748/wjg.v13.i29.3948]

85 Moole H, Dharmapuri S, Duvvuri V, Boddiredy R, Moole V, Yedama P, Bondalapati N, Uppu A, Yerasi C. Endoscopic versus Percutaneous Biliary Drainage in Palliation of Advanced Malignant Hilar Obstruction: A Meta-Analysis and Systematic Review. *Can J Gastroenterol Hepatol* 2016; 4: 4726078 [PMID: 27648439 DOI: 10.1155/2016/4726078]

86 Perdue DG, Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Obervy CS, Ryan ME, Bochna GS, Snady HW, Moore JP; ERCPT Outcome Study ERCOST Group. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. *J Clin Gastroenterol* 2008; 42: 1040-1046 [PMID: 18719507 DOI: 10.1097/MGC.0b013e31815853e0]

87 Peters RA, Williams SG, Lombard M, Karani J, Westaby D. The management of high-grade hilar strictures by endoscopic insertion of self-expanding metal endoprostheses. *Endoscopy* 1997; 29: 10-16 [PMID: 9083730 DOI: 10.1055/s-2007-1004054]

88 Sangchan A, Kongkasame W, Pugkhem K, Jenwitheesuk K, Mairiang P. Efficacy of metal and plastic stents in unresectable complex hilar cholangiocarcinoma: a randomized controlled trial. *Gastrointest Endosc* 2012; 76: 93-99 [PMID: 22595446 DOI: 10.1016/j.gie.2012.02.048]

89 De Palma GD, Galloro G, Siciliano S, Iovino P, Catanzano C. Unilateral versus bilateral hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. *Gastrointest Endosc* 2001; 53: 547-553 [PMID: 11323577 DOI: 10.1067/mge.2001.113381]

90 Lee TH, Kim TH, Moon JH, Lee SH, Choi HJ, Hwangbo Y, Hyun JJ, Choi JH, Jeong S, Kim JH, Park DH, Han JH, Park SH. Bilateral versus unilateral placement of metal stents for inoperable high-grade malignant hilar biliary strictures: a multicenter, prospective, randomized study (with video). *Gastrointest Endosc* 2017; 86: 817-827 [PMID: 28479493 DOI: 10.1016/j.gi.2017.04.037]

91 Xia MX, Cai XB, Pan YL, Wu J, Gao TT, Ye X, Wang TT, Hu B. Optimal stent placement strategy for malignant hilar biliary obstruction: a large multicenter parallel study. *Gastrointest Endosc* 2020; 91: 1117-1128 [PMID: 31881205 DOI: 10.1016/j.gie.2019.12.023]

92 Naitoh I, Hayashi K, Nakazawa T, Okumura F, Miyabe K, Shimizu S, Yoshida M, Yamashita H, Ohara H, Itoh T. Side-by-side versus stent-in-stent deployment in bilateral endoscopic metal stenting for malignant hilar biliary obstruction. *Dig Dis Sci* 2012; 57: 3279-3285 [PMID: 22772832 DOI: 10.1007/s10620-012-2270-9]

93 Liu N, Yang D, Draganoz PV. Endoscopic Stenting for Malignant Hilar Biliary Obstruction: After You Double Down, Are You In or Out? *Dig Dis Sci* 2020; 65: 3428-3430 [PMID: 32290766 DOI: 10.1007/s10620-020-06249-8]

94 Kim KM, Lee KH, Chung YH, Shin JU, Lee JK, Lee KT, Shim SG. A comparison of bilateral stenting methods for malignant hilar biliary obstruction. *Hepatogastroenterology* 2012; 59: 341-346 [PMID: 22353496 DOI: 10.5754/hge11533]

95 Vienne A, Hobeika E, Gouya H, Lapidus N, Fritsch J, Choury AD, Chryssostalis A, Gaudric M, Pelletier G, Buffet C, Chausse S, Prat F. Prediction of drainage effectiveness during endoscopic stenting of malignant hilar strictures: the role of liver volume assessment. *Gastrointest Endosc* 2010; 72: 728-735 [PMID: 20883850 DOI: 10.1016/j.gie.2010.06.040]

96 Buerlein RC, Wang AY. Endoscopic Retrograde Cholangiopancreatography-Guided Ablation for Cholangiocarcinoma. *Gastrointest Endosc Clin N Am* 2019; 29: 351-367 [PMID: 30846158 DOI: 10.1016/j.gice2018.11.006]

97 Alvarez-Sánchez MV, Napoléon B. Review of endoscopic radiofrequency in bilopancreatic tumours with emphasis on clinical benefits, controversies and safety. *World J Gastroenterol* 2016; 22: 8257-8270 [PMID: 27729733 DOI: 10.3748/wjg.v22.i37.8257]

98 Yang J, Wang J, Zhou H, Zhou Y, Wang Y, Jin H, Lou Q, Zhang X. Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. *Endoscopy* 2018; 50: 751-760 [PMID: 29342492 DOI: 10.1055/s-0043-124870]

99 Paik WH, Lee TH, Park DH, Choi HJ, Kim SO, Jang S, Kim DU, Shim JH, Song TJ, Lee SS, Seo DW, Lee SK, Kim MH. EUS-Guided Biliary Drainage Versus ERCP for the Primary Palliation of Malignant Biliary Obstruction: A Multicenter Randomized Clinical Trial. *Am J Gastroenterol* 2018; 113: 987-997 [PMID: 29961772 DOI: 10.10384/s41395-018-0122-8]

100 Bang JY, Navaneethan U, Hasan M, Hawes R, Varadarajulu S. Stent placement by EUS or ERCP for primary biliary decompression in pancreatic cancer: a randomized trial (with videos). *Gastrointest Endosc* 2018; 88: 9-17 [PMID: 29574126 DOI: 10.1016/j.gie.2018.03.012]

101 Park JK, Woo YS, Noh DH, Yang JI, Bae SY, Yun HS, Lee JK, Lee KT, Lee KH. Efficacy of
EUS-guided and ERCP-guided biliary drainage for malignant biliary obstruction: prospective randomized controlled study. *Gastrointest Endosc* 2018; 88: 277-282 [PMID: 29605722 DOI: 10.1016/j.gie.2018.03.013]

102 Sharaïha RZ, Khan MA, Kamal F, Tyberg A, Tombazzi CR, Ali B, Tombazzi C, Kahaleh M. Efficacy and safety of EUS-guided biliary drainage in comparison with percutaneous biliary drainage when ERCP fails: a systematic review and meta-analysis. *Gastrointest Endosc* 2017; 85: 904-914 [PMID: 28063840 DOI: 10.1016/j.gie.2016.12.023]

103 Zhou Y, Liu S, Wu L, Wan T. Survival after surgical resection of distal cholangiocarcinoma: A systematic review and meta-analysis of prognostic factors. *Asian J Surg* 2017; 40: 129-138 [PMID: 26373377 DOI: 10.1016/j.ajsur.2015.07.002]

104 Velanovich V, Kheibek T, Khan M. Relationship of postoperative complications from preoperative biliary stents after pancreaticoduodenectomy. A new cohort analysis and meta-analysis of modern studies. *JOP* 2009; 10: 24-29 [PMID: 19129611]

105 Abraham NS, Barkun JS, Barkun AN. Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life. *Gastrointest Endosc* 2002; 56: 835-841 [PMID: 12447294 DOI: 10.1067/mge.2002.129868]

106 Inamdar S, Slattery E, Bhalla R, Sejpal DV, Trindade AJ. Comparison of Adverse Events for Endoscopic vs Percutaneous Biliary Drainage in the Treatment of Malignant Biliary Tract Obstruction in an Inpatient National Cohort. *JAMA Oncol* 2016; 2: 112-117 [PMID: 26513013 DOI: 10.1001/jamaoncol.2015.3670]

107 Sawas T, Al Halabi S, Parsi MA, Vargo JJ. Self-expandable metal stents versus plastic stents for malignant biliary obstruction: a meta-analysis. *Gastrointest Endosc* 2015; 82: 256-267 [PMID: 25982849 DOI: 10.1016/j.gie.2015.03.1980]

108 Almadi MA, Barkun A, Martel M. Plastic vs. Self-Expandable Metal Stents for Palliation in Malignant Biliary Obstruction: A Series of Meta-Analyses. *Am J Gastroenterol* 2017; 112: 260-273 [PMID: 27845340 DOI: 10.1038/ajg.2016.512]

109 Davids PH, Groen AK, Rauws EA, Tytgat GN, Hrubetz KE. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. *Lancet* 1992; 340: 1488-1492 [PMID: 1281903 DOI: 10.1016/0140-6736(92)92752-2]

110 Kaassis M, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcencerie R, Canard JM, Fritsch J, Rey JF, Burtin P. Plastic or metal stents for malignant stricture of the common bile duct? *Gastrointest Endosc* 2003; 57: 178-182 [PMID: 12556780 DOI: 10.1067/mge.2003.66]

111 Telford JJ, Carr-Locke DL, Baron TH, Poneser JM, Bounds BC, Kelsey PB, Schapiro RH, Huang CS, Lichtenstein DR, Jacobson BC, Saltzman JR, Thompson CC, Forcione DG, Gostout CJ, Brugge WR. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. *Gastrointest Endosc* 2010; 72: 907-914 [PMID: 21034891 DOI: 10.1016/j.gie.2010.08.021]

112 Kullman E, Frozanpor F, Söderlund C, Linder S, Sandström P, Lindhoff-Larssen A, Toth E, Lindell G, Jonas E, Freedman J, Ljungman M, Rudberg C, Ohlin B, Zacharias R, Leijonmarck CE, Teder K, Ringman A, Persson G, Gözün M, Eriksson O. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. *Gastrointest Endosc* 2010; 72: 915-923 [PMID: 21034892 DOI: 10.1016/j.gie.2010.07.036]
