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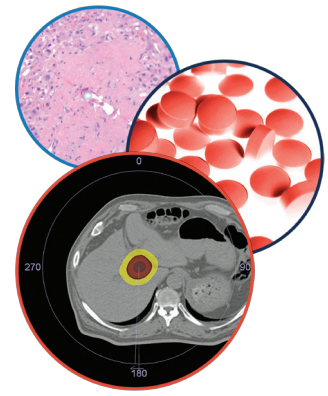

Hepatic Oncology

Liver transplantation in the management of perihilar cholangiocarcinoma

Aliya F Gulamhusein[1] & William Sanchez*[,1]

Practice points

Mayo Clinic protocol

- Structured protocol consisting of neoadjuvant external beam radiation, chemotherapy and brachytherapy followed by liver transplantation.

Pretransplant considerations

- Eligible patients have unresectable perihilar cholangiocarcinoma (pCCA) or pCCA associated with PSC.
- Diagnosis made with pathological confirmation from biopsy or cytology odds ratio (OR) malignant appearing stricture with suspicious cytology and FISH polysomy OR a mass lesion on cross-sectional imaging OR a malignant appearing stricture with CA-19-9 >100 U/ml in the absence of bacterial cholangitis.

Peritransplant challenges

- Wait list drop out is commonly due to progressive disease and occurs in about 30%.
- Predictors of drop out include CA-19-9 level ≥ 500 U/ml, mass ≥ 3 cm, malignant brushing or biopsy and MELD ≥ 20.

Surgical considerations & postoperative complications

- Post-transplantation vascular complications can occur in up to 40% of patients and are likely a result of neoadjuvant chemoradiotherapy.

Outcomes

- Local, national and international experience suggests that 2-year overall survival ranges from 65 to 70% and 5-year recurrence-free survival ranges from 47 to 68%.
- Patients with PSC-associated CCA have improved post-transplant survival compared with patients with *de novo* CCA.
- Predictors of post-transplant recurrence include elevated CA-19-9, portal vein encasement, and residual tumor on explant pathology.

Conclusion

- Neoadjuvant chemoradiotherapy followed by liver transplantation affords prolonged survival in a highly selected group of patients with pCCA managed under a structured protocol.
- Liver transplantation in the management of iCCA is under study, and for the time being remains controversial.

[1]Division of Gastroenterology & Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA
*Author for correspondence: sanchez.william@mayo.edu

Future Medicine part of fsg

Cholangiocarcinoma (CCA) is the second most common primary hepatic neoplasm and accounts for 10–20% of hepatobiliary cancer-related deaths. The prognosis of patients with CCA is poor with 5-year survival rates of 10%, partially due to the limited effective treatment options that exist for this disease. In this review, we discuss the evolving role of liver transplantation in the management of patients with perihilar CCA (pCCA). We specifically discuss the Mayo Clinic protocol of neoadjuvant chemoradiation followed by liver transplantation in selected patients with pCCA and describe pretransplant, peritransplant, and post-transplant considerations and challenges with this approach. Finally, we review local, national and international outcomes and discuss future directions in optimizing this treatment strategy for patients who otherwise have few therapeutic options and limited survival.

KEYWORDS
• cholangiocarcinoma • intrahepatic cholangiocarcinoma • liver transplantation • neoadjuvant therapy • perihilar cholangiocarcinoma • primary sclerosing cholangitis

Cholangiocarcinoma (CCA) is the second most common primary hepatic neoplasm after hepatocellular carcinoma (HCC) and is reported to be rising in incidence worldwide [1]. It is estimated that there are approximately 3000–4000 new cases of CCA per year in the USA [2], with the incidence being particularly high in patients with primary sclerosing cholangitis (PSC) at up to 10% within 10 years of diagnosis [3]. The mean age of diagnosis is at 50 years and is uncommon before age 40 – except in the presence of PSC where CCA can occur earlier [4]. Unfortunately, the prognosis of patients with CCA remains dismal with only approximately 10% of patients surviving 5 years after diagnosis [5].

CCA is a highly aggressive malignant neoplasm with features of biliary epithelial differentiation [4]. It is classified by anatomic location with different sites corresponding to different tumor biology and mandating specific treatment approaches. Intrahepatic CCAs (iCCAs) are located within the hepatic parenchyma and are anatomically separated from extrahepatic CCA by the second order bile ducts [6]. Extrahepatic CCA consists of perihilar CCA (pCCA) and distal CCA (dCCA) with the anatomic distinction between these subtypes occurring at the level of the cystic duct [6]. pCCA is the most common subtype accounting for about 50% of cases, followed by dCCA in about 40%, and iCCA in approximately 10% [7]. As will be discussed, most of the literature has focused on liver transplantation in the management of perihilar CCA and as such for the purposes of this review we will focus on this indication. Currently, the role of transplantation in the management of iCCA remains investigational and not widely accepted.

Liver transplantation in patients with pCCA

The rationale for considering liver transplantation as a management option for patients with pCCA arises from features characteristic of this tumor. pCCA occurs in the perihilar bile ducts and typically presents with signs of biliary obstruction such as jaundice, and less commonly, cholangitis [8] allowing it to clinically manifest early in its course. In addition, distant metastases occur uncommonly and thus, disease often remains confined to the liver. Furthermore, surgical resection for localized disease is often limited by bilateral liver involvement, vascular encasement, perineural and lymphatic invasion, and functional hepatic reserve [9]. Resectability rates vary widely in the literature from 28 to 80% leaving a significant proportion of patients with little hope for cure [10–13]. Survival in patients with unresectable CCA is estimated at just 12–16 months after the onset of symptoms [14]; yet, even among patients who do undergo curative R0 resection, 5-year survival rates range between 20 and 40% [10,15–26]. Patients with PSC who have a lifetime risk of CCA on the order of 10–15% are particularly challenging to manage with resection given their underlying parenchymal liver disease, the presence of skip lesions, and the diffuse oncogenic field defect that exists in the biliary tree [4]. Clearly, alternative and effective treatment options for these patients are desperately needed.

Liver transplantation was considered to be the ideal operation for CCA given its ability to provide radical resection, achieve wide surgical margins, circumvent limitations imposed by residual liver volume and function and treat underlying disease in the case of PSC. Unfortunately, the early experience with liver transplantation alone failed to confirm these desired expectations. The Cincinnati Transplant Tumor Registry reported 5-year survival estimates of just 23% with 51% of patients developing tumor recurrence, usually within 2 years of transplantation. Half of the recurrences occurred in the allograft and survival after recurrence was rarely longer than 1 year [27].

Other series from Scandinavia [28], Spain [29] and Canada [30] reported similar results with 3 and 5-year survival rates of about 30%. Even more aggressive approaches with cluster abdominal transplantation failed to improve outcomes – a series from the University of Pittsburgh reported a 20% 3-year survival with this approach [31]. This knowledge combined with scarcity of the donor pool caused most transplant programs to abandon liver transplantation for CCA **(Figure 1)**.

Though overall outcomes were suboptimal, selected patients with negative surgical margins and absence of regional lymph node metastasis did benefit from transplantation and achieved prolonged survival [33]. Furthermore, adjuvant approaches using radiation with and without chemotherapy also resulted in improved outcomes in a proportion of patients. In a small cohort of patients treated at Mayo Clinic, 22% 5-year survival was achieved in patients with unresectable extrahepatic CCA treated with external beam radiation therapy (EBRT) plus concomitant chemotherapy with infusional 5-FU followed by intraluminal brachytherapy [34]. A similar trimodal approach at the Thomas Jefferson University Hospital demonstrated 2-year survival rates of 30% [35]. Armed with knowledge of potential benefit of chemoradiotherapy and the high rate of locoregional recurrence after surgery, the University of Nebraska [36] and then Mayo Clinic established structured protocols using neoadjuvant chemoradiation therapy followed by liver transplantation in the management of selected patients with pCCA.

Mayo Clinic protocol

In 1993, Mayo Clinic developed a protocol using EBRT plus concomitant infusional 5-FU followed by brachytherapy, prolonged chemotherapy and subsequent liver transplantation for selected patients with early stage pCCA. As of 18 March 2015, 168 patients have been transplanted using this protocol at our center. Eligible patients undergo EBRT at a dose of 1.5 Gy twice daily over 3 weeks for a total of 45 Gy in 30 fractions. 5-FU is administered by continuous venous infusion during radiation therapy at a dose of 225 mg/m^2/day [37]. Two weeks after the completion of EBRT intraluminal brachytherapy is administered by transcatheter irradiation with iridium-192 beads delivered endoluminally through an endoscopically (or rarely, percutaneously) placed biliary tube at a target dose of 16 Gy in four fractions at a 1-cm radius over 2 days [37]. If brachytherapy is not possible, an extra boost of EBRT dosed at 1000–1500 cGy is administered [38]. Since 2001, prolonged chemotherapy with oral capecitabine 2000 mg/m^2/day in two divided doses 2 out of every 3 weeks is then given until the time of transplantation whereas prior to this infusional 5-FU was used and delivered through an ambulatory infusion pump [39]. After listing and prior to transplantation a staging abdominal exploration is performed to ensure disease remains localized. In

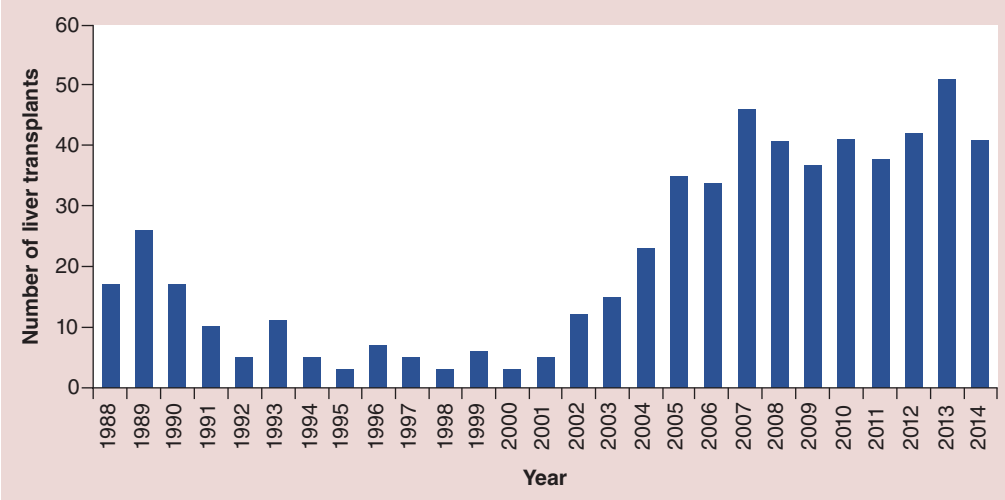

Figure 1. Number of liver transplants done between 1988 and 2014 with an indication of cholangiocarcinoma as per the United Network for Organ Sharing database.
Data taken with permission from [32].

the case of deceased donor transplant recipients this is performed as patients approach the top of the waiting list, and for living donor transplant recipients exploration is performed the day before transplantation. During the staging procedure (now done using a hand assisted laparoscopic approach in patients with no prior abdominal operations) a thorough abdominal exploration is performed [39]. At least one lymph node along the hepatic artery proper and common bile duct is excised and examined for metastasis even if it appears grossly normal. Suspicious lymph nodes or nodules are removed and examined pathologically for tumor. The liver is carefully palpated for evidence of intrahepatic metastasis that has gone undetected by imaging. Identification of regional lymph node metastasis, peritoneal metastasis, or locally extensive disease precludes transplantation. During transplantation, a caval sparing approach is used unless there is suspected caudate involvement or atrophy that would threaten the resection margin. A frozen section of the bile duct margin is also obtained and pancreaticoduodenectomy performed if there is microscopic involvement [40]. Standard immunosuppressive regimens are used post transplantation and currently include short-term mycophenolate mofetil and prednisone taper with long-term tacrolimus monotherapy.

Pretransplant considerations: diagnosis & eligibility

• CCA diagnosis

In its early stages, pCCA can be difficult to diagnose, partly owing to its desmoplastic nature [41] and its initial growth pattern along bile ducts rather than away from them, making both histologic confirmation and imaging detection difficult [42]. This tropism for bile often leads to stricturing and biliary obstruction, which most commonly manifests as painless jaundice [8]. Approximately half of patients have nonspecific or systemic symptoms including abdominal discomfort, generalized malaise, nausea and weight loss [43]. On physical examination, occasionally a palpable liver lobe is detected which usually reflects compensatory hypertrophy of the unaffected lobe due to atrophy of the contralateral affected lobe as a result of vascular encasement by tumor – the so called 'atrophy-hypertrophy complex' (Figure 2). Laboratory studies often include nonspecific elevations in serum alkaline phosphatase, bilirubin and CA19–9. While helpful when used in combination with other diagnostic tests, isolated elevations of CA19-9 can be found in benign hepatobiliary disease such as cholangitis or PSC. Using a cutoff of 129 U/ml in patients with PSC, the sensitivity and specificity of an elevated CA19–9 in CCA is 79 and 98%, respectively [44]. That said, the positive predictive value is about 56% [45] and two-thirds of PSC patients with elevations above this cutoff do not seem to develop CCA [46]. In patients with *de novo* CCA, a CA19–9 level >100 U/ml has a sensitivity of 75% and a specificity of 92% when compared with patients with benign biliary strictures [6,47]. Furthermore, CA19-9 levels >1000 U/ml in the absence of cholangitis are associated with unresectable disease and poorer prognosis compared with lower serum levels [48] and should raise suspicion for metastatic disease.

Imaging modalities including CT, MRI, endoscopic retrograde cholangiography (ERC) and endoscopic ultrasound (EUS) are important in the diagnosis and staging of pCCA. CT has a sensitivity of approximately 85% in identifying vascular involvement by pCCA and an overall accuracy of 86% in determining ductal extent of tumor [49]; however, its ability to reliably detect regional lymphadenopathy is limited. Magnetic resonance cholangiography (MRC) is the modality of choice for pCCA as it has an accuracy of up to 95% in assessing locoregional disease extent and resectability, though its assessment of vascular involvement is suboptimal [6,50–53]. MRI and MRC also perform well in patients with PSC with a sensitivity of 89% and accuracy of 76% in detecting CCA [44]; and in fact, its diagnostic accuracy is comparable to that of ERC.

ERC is critical in the diagnosis and management of pCCA as it allows for direct visualization of dominant strictures and ductal abnormalities, sampling of biliary epithelial cells for cytological analysis, and can provide therapeutic relief of biliary obstruction with dilation and/or stenting [8]. Though conventional cytology can confirm the diagnosis, obtaining adequate tissue endoscopically (or percutaneously) is challenging, and often limited by acellular specimens, sampling errors and difficulty with interpretation, particularly in the setting of PSC or cholangitis where inflammation can mimic malignant cytologic changes [54]. Specimens analyzed by conventional cytology can be classified as negative, atypical, suspicious, or diagnostic of malignancy; when only diagnostic specimens are considered, the sensitivity of this technique is

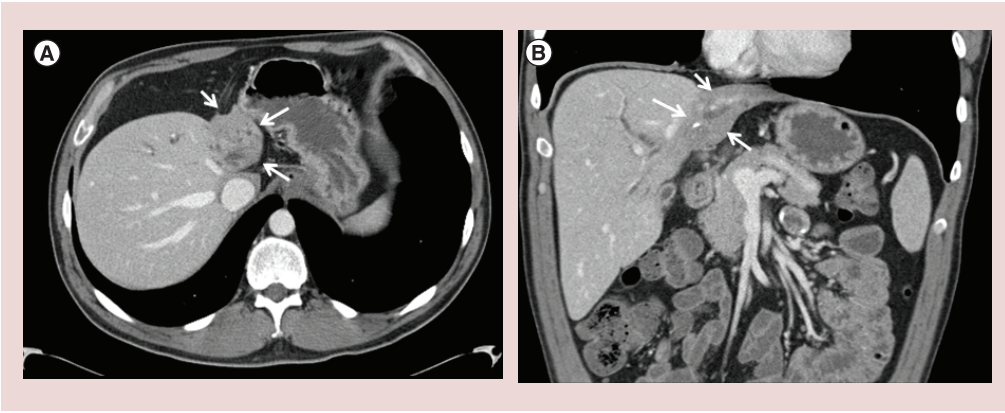

Figure 2. Axial and coronal CT images demonstrating the 'atrophy-hypertrophy complex' in a patient with perihilar cholangiocarcinoma. (A) Axial section demonstrating marked left lobe atrophy as highlighted by the arrows. **(B)** Coronal section demonstrating atrophy of the left lobe due to vascular involvement by tumor and compensatory hypertrophy of the unaffected right lobe.

just 15% with only slight improvement to 48% when diagnostic or suspicious interpretations are considered for cancer diagnosis [54]. Because of the low sensitivity, many centers now use fluorescence *in situ* hybridization (FISH) to aid in the diagnosis of CCA. This technique employs fluorescently labeled DNA probes to identify structural chromosomal changes in chromosomes 3, 7, 17, and the 9p21 locus within cells. Compared with conventional cytology, FISH polysomy increases sensitivity for diagnosis of pCCA to 38–58% [55,56] while maintaining specificity. Polysomy is observed in up to 77% of CCA cases [6,57], and at our center, polysomy in the presence of a malignant appearing stricture is sufficient for the diagnosis of pCCA, particularly if this is confirmed over time [58]. Polysomy as detected by FISH can also predict pCCA development in a subset of patients with PSC. A recent study demonstrated that among patients with PSC with no detectable mass by imaging, equivocal cytology (atypical or suspicious), a CA19–9 >129 U/ml and polysomy all went on to develop CCA, frequently within 2 years [59].

EUS is a particularly valuable imaging modality in the evaluation of unresectable pCCA prior to transplantation [60]. It is able to detect tumors at a rate of 94% in patients with CCA, with distal tumors more readily identified than proximal tumors (100 vs 83%) [61]. While EUS-guided fine needle aspiration of the primary tumor does carry a diagnostic sensitivity 73% [61], this practice is strongly discouraged due to a high risk of tumor seeding. In a study of 191 patients evaluated for liver transplantation for CCA at our center, 16 patients underwent EUS-guided fine needle aspiration (FNA) of their primary tumor and malignancy was detected in 6 patients [62]. Peritoneal metastasis was detected at operative staging in 83% of patients in whom malignancy was detected on EUS-FNA compared with 0% of patients without malignancy. Moreover, only 8% (14/175) of patients who did not undergo transperitoneal FNA had peritoneal metastasis detected emphasizing the high risk of seeding associated with this procedure. Due to this risk, at our center transperitoneal FNA of the primary tumor is an absolute contraindication for proceeding with transplantation. EUS is especially valuable in staging of locoregional lymph node involvement prior to transplantation [60]. In a study of 47 patients with unresectable pCCA, EUS identified lymph nodes in all patients and FNA of identified nodes detected metastasis in 17% of patients, thus precluding transplantation and avoiding operative staging. In addition, 91% of lymph nodes identified as histologically benign by EUS-FNA were confirmed as such during operative staging [63].

Given its associated challenges, at our center eligibility for liver transplantation in the setting of pCCA is not limited by a requirement for histologic confirmation. CCA is diagnosed if any of the criteria in **Box 1** are met. In a study of 215 patients who received neoadjuvant therapy as part of the liver transplant protocol for pCCA, 98 patients did not have pretreatment pathological confirmation, yet 53% of these patients subsequently had pathologically proven disease

either at staging, in the explant, or developed disease recurrence [64]. Thus, though pathological confirmation is ideal, its absence should not be considered an exclusion for transplantation if other criteria are met. As will be discussed later, in this cohort, the survival benefit demonstrated with liver transplantation both in patients with PSC and *de novo* pCCA remained similar even after excluding all patients without pretreatment pathological confirmation [64].

• Eligibility

Eligible patients include those with unresectable pCCA as determined by an experienced hepatobiliary surgeon or pCCA in the setting of PSC [40]. Diagnosis is established as described above. Tumors must have a radial diameter of ≤3 cm though there are no longitudinal limits for bile duct involvement given the difficulty in assessment of this parameter. Clearly, eligible candidates must also otherwise be suitable for neoadjuvant chemoradiotherapy and liver transplantation. All patients undergo staging to assess for intra- and/or extra-hepatic disease using chest CT, abdominal MRI with MRC and bone scan. Whereas detection of distant or metastatic intrahepatic disease precludes transplantation, vascular encasement is not a contraindication. All patients subsequently undergo EUS-FNA of celiac and perihilar nodes and those with negative staging proceed with neoadjuvant therapy, operative staging and, subsequently, transplantation. Exclusion criteria are listed in **Box 2** [40].

Peritransplant challenges

Once eligibility is established, a unique set of challenges ensue related to tolerability of neoadjuvant treatment, risk of progressive disease and wait list drop out, and recipient prioritization. Complications associated with preoperative chemoradiation therapy are variable and range from mild nausea or vomiting to radiation-associated GI ulceration with hemorrhage, venothromboembolic disease and dose limiting bone marrow suppression. Infectious complications are also of concern and in one series, problems related to cholangitis, hepatic abscess or sepsis related to indwelling biliary stents occurred in 20% of patients [65]. Such infections are often treatable with prompt antibiotic therapy; however, in the aforementioned series 1 of 19 included patients died of biliary sepsis [65]. Furthermore, repeated use of broad-spectrum antibiotics may put these patients at increased risk of infection with antibiotic resistant isolates. Patients with PSC have been shown to have altered biliary bacteriology, with a significantly higher rate of infection with gram positive bacteria compared with those without PSC, potentially increasing the risk of complicated infections in this subgroup of patients [66].

The most important factor leading to wait list drop out in patients with pCCA initially eligible for transplantation is progressive disease. In a recent study of 199 patients at Mayo Clinic, 62 (31%) dropped out of the protocol after a median of 4.7 months with 89% of these patients becoming ineligible due to progressive disease [38]. On multivariable analysis, independent predictors of protocol dropout included a CA19–9 level ≥ 500 U/ml (HR = 2.3; 95% CI: 1.2–4.3), tumor mass ≥ 3 cm (HR = 2.2; 95% CI: 1.2–4.0), malignant brushing or biopsy (HR = 3.6; 95% CI: 1.7–7.9) and MELD score ≥ 20 (HR = 3.5; 95% CI: 1.5–8.3) [38]. The outcome of patients who become ineligible for transplantation is poor and comparable with those with advanced and metastatic CCA [37]. In another study using the same cohort, the median overall survival of patients who fell out of the protocol was 12.3 months (95% CI: 10.7–13.5) with median survival after fallout being just 6.8 months (95% CI: 5.1–8.5) [37].

In 2002 the MELD system was implemented, which allowed prioritization for liver transplant candidates based on their risk of dying on the waiting list within 3 months. Selected patients are granted MELD exception points based on regional agreements and since January 2010, all patients with pCCA that meet highly specified criteria are granted standardized MELD exception scores starting at 22 with a 10% increase

Box 1. Diagnostic criteria for eligibility in the liver transplantation for perihilar cholangiocarcinoma protocol at the Mayo Clinic.

Any of

- Biopsy or conventional cytology positive for adenocarcinoma
- Malignant appearing stricture with suspicious cytology for adenocarcinoma plus FISH polysomy
- Mass lesion on cross-sectional imaging
- Malignant appearing stricture with CA-19-9 >100 U/ml in absence of bacterial cholangitis

Box 2. Exclusion criteria for liver transplantation for perihilar cholangiocarcinoma protocol at the Mayo Clinic.

Tumor characteristics

- Intrahepatic cholangiocarcinoma
- Intrahepatic metastasis
- Extrahepatic disease
- Gall bladder involvement

Prior therapies or interventions

- Prior radiation or chemotherapy
- Prior biliary resection or attempted resection
- Transperitoneal biopsy including percutaneous and endoscopic ultrasound guided fine needle aspiration of primary tumor

Patient characteristics

- Comorbid medical condition that renders patient unsuitable for transplantation

every 3 months, corresponding to a 10% waitlist mortality at 3-month intervals [67]. This approach was supported by a recent multicenter study in the USA where 71 of 287 eligible patients (25%) dropped out of the protocol after a median of 4.6 months, corresponding to a dropout rate that increased by 11.5% every 3 months [68].

Surgical considerations & postoperative complications

Liver transplantation for pCCA at our center is most commonly performed with caval sparing hepatectomy. Hilar dissection is avoided to prevent disease spread [69]. The distal bile duct margin is assessed histologically by frozen section and pancreaticoduodenectomy performed if microscopic involvement is detected. After neoadjuvant radiation therapy, the native hepatic artery is damaged and thus an arterial interposition graft using a segment of donor iliac artery is used during deceased donor liver transplant (DDLT) [39]. During live donor liver transplant (LDLT), the native hepatic artery is used for reconstruction. A portal vein interposition graft between the donor right or left portal vein and recipient portal vein is also used in living donor transplantation. Biliary anastomosis is done using a Roux-en-Y choledochojejunostomy [64].

As a result of neoadjuvant therapy, vascular complications are encountered more frequently. In a study of 68 patients who underwent neoadjuvant therapy and subsequent liver transplantation, 40% of patients overall developed vascular problems, with arterial complications occurring in 21% and portal venous complications in 22% [70]. Of the patients who developed arterial complications, 50% occurred within 1 month of transplantation. There was no difference in early or late arterial complications between patients who underwent DDLT for CCA compared with DDLT for other indications; however, there was an increased rate of late hepatic artery complications in patients undergoing LDLT for CCA (18%, 2/11 patients) compared with patients with LDLT for other indications (0%, 0/38 patients). Late portal vein complications including stenosis with or without thrombosis occurred more commonly in in patients with CCA who had either DDLT (18%) or LDLT (27%) compared with patients transplanted for other indications (1% for DDLT and 0% for LDLT) [70]. As a result of these findings, at our center we use low dose aspirin indefinitely after both LDLT and DDLT in patients with pCCA. When they occur, hepatic artery and portal venous stenosis can be effectively managed with transluminal angioplasty and stenting. In the Mayo Clinic experience, no grafts have been lost due to late vascular stenoses [40].

Outcomes

Experience accumulated thus far at the local, national and international level with protocols utilizing neoadjuvant therapy in combination with liver transplantation have demonstrated favorable results as summarized in Table 1. The largest experience comes from Mayo Clinic in Rochester, which enrolled 215 patients into their protocol between 1993 and 2011. Intent to treat survival after the initiation of therapy at 1-, 3- and 5-years was 81% (95% CI: 78–84), 62% (95% CI: 58–66), and 56% (95% CI: 52–60), respectively. In 136 patients who proceeded to transplantation enrolled over the same time period, 1-, 3- and 5-year survival after transplantation was 92% (95% CI: 90–94), 81% (95% CI: 77–85), and 74% (95% CI: 70–78), respectively. Five-year

survival post transplantation was better in patients with PSC associated pCCA at 81% (95% CI: 77–85) compared with those with *de novo* pCCA at 58% (95% CI: 51–65), which may speak to earlier detection in these patients who may be closely clinically monitored. Comparable outcomes have been seen elsewhere. In a large retrospective multicenter review of 287 patients from 12 centers across the USA, overall survival from time of presentation at 2 years was 68% (95% CI: 62–74), at 5 years was 53% (95% CI: 46–60), and at 10 years was 42% (95% CI: 33–51). Recurrence-free survival post transplantation at 2, 5 and 10 years was 78% (95% CI: 72–84), 65% (95% CI: 57–73) and 59% (95% CI: 49–69), respectively. Though 193 patients in this study came from one center, 94 patients were from other transplant programs across the country and no significant differences were identified in intent-to-treat or recurrence free survival between the center that contributed the majority of patients and all other centers combined [68]. Recently, a small series from Ireland that reviewed their experience with neoadjuvant chemoradiotherapy followed by liver transplantation in patients with pCCA reported 1-, 2-, 3- and 4-year post-transplant survival of 94, 73, 73 and 61%, respectively, after excluding operative mortality [71]. Another Scanadanvian series reported a 5-year post-transplant survival of 58% among selected patients transplanted after 1995, with a TNM stage ≤2 and a CA 19–9 <100, though importantly patients did not receive neoadjuvant therapy [72].

Absence of histological confirmation does not significantly affect outcomes. In the multicenter US study described above [68], 30% (n = 87) of patients did not have pretransplant pathological confirmation, though 83% (n = 72) of these patients did have either pathological confirmation on explant or a visible tumor mass on imaging and/or CA-19-9 > 100 U/ml in the absence of biliary obstruction. After exclusion of the 15 patients (5% of the entire cohort) without objective evidence of malignancy despite extensive investigations, 5-year intent to treat survival and recurrence free survival was similar to that of the entire cohort at 50 and 62%, respectively. Furthermore, a study from Mayo Clinic, Rochester compared outcomes of patients with and without pretreatment pathological confirmation [64]. In patients with

Table 1. Outcomes of patients with perihilar cholangiocarcinoma undergoing neoadjuvant chemoradiation followed by liver transplantation by location.

	n	1 YS (%)	2 YS (%)	3 YS (%)	4 YS (%)	5 YS (%)	10 YS (%)	Notes
Mayo Clinic, Rochester, MN, USA								
Survival from presentation (95% CI)	193	–	65% (58–72)	–	–	53% (45–61)	42% (32–52)	
Recurrence-free survival (95% CI)	193	–	80% (73–87)	–	–	68% (59–77)	66% (56–78)	
Survival post-transplant (95% CI)	136	92% (90–94)		81% (77–85)		74% (70–78)		
USA – 12 centers								
Survival from presentation (95% CI)	287	–	68% (62–74)	–	–	53% (46–60)	42% (33–51)	
Recurrence-free survival (95% CI)	287	–	78% (72–84)	–	–	65% (57–73)	59% (49–69)	
Ireland								
Post LT survival	20	94%	73%	73%	61%	–	–	Operative mortality excluded
Mayo Clinic, FL, USA								
Overall survival (95% CI)	22	90% (69–98)	70% (47–87)	63% (40–81)	–	–	–	
University of California, Los Angeles, CA, USA								
Recurrence-free survival	11	–	88%	75%	–	47%	–	iCCA and pCCA

iCCA: Intrahepatic cholangiocarcinoma; LT: Liver transplant; pCCA: Perihilar cholangiocarcinoma; YS: Year survival.

de novo CCA, there was no significant difference in 5-year survival after start of therapy (39% in those with confirmed pathology vs 48% in those without, p = 0.37), survival after transplantation (63 vs 65%, p = 0.77), or recurrence after transplantation (46 vs 34%, p = 0.27). In contrast to those with *de novo* cancer, outcomes were worse in patients with PSC who had confirmed pathology prior to treatment. Five-year intent to treat survival in PSC patients with pathologic confirmation was 50% compared with 80% in those without confirmed histology (p < 0.01) and 5-year post-transplantation survival was also worse in those with confirmed histology (66 vs 92%, p = 0.01). Interestingly, there was no difference in CCA recurrence in PSC patients with and without pre-treatment pathological confirmation (15 vs 14%, p = 0.53). These data suggest that though there is improved survival after liver transplantation in PSC-associated and *de novo* CCA with and without pathologic confirmation, one should be cautious of the diagnosis of CCA in patients with PSC in the absence of pathologic confirmation.

Recurrent CCA post transplantation is clearly a concern and rigorous selection of patients is essential to avoid this dreaded outcome. In the multicenter US study, 20% of patients developed recurrence and those transplanted outside current UNOS criteria for MELD exception points had a threefold worse recurrence-free survival compared with those transplanted within criteria [68]. An analysis of the Mayo Clinic cohort demonstrated that independent predictors of post-transplant recurrence included an elevated CA19–9 (HR 1.8; 95% CI: 1.1–2.8), portal vein encasement (HR 3.3; 95% CI: 1.4–7.9), and most importantly residual tumor on explant pathology (HR 9.8; 95% CI: 2.9–32.8) [38]. In a time of scarcity of organs, careful selection of patients and compliance with a structured protocol is of utmost importance. That said, for the optimally selected patient, such a regimen offers an option for prolonged survival far superior to the alternative.

Future perspective

The data presented suggest that neoadjuvant therapy followed by liver transplantation affords prolonged survival in a highly selected group of patients with pCCA. However, those eligible make up only a small proportion of patients with CCA leaving a significant proportion of patients with few options. Currently, the role of liver transplantation in patients with iCCA remains controversial. Similar to the initial experience with pCCA early reports of liver transplant for iCCA were disappointing with 5-year patient survival rates of 0–42% [73]. Such results caused many centers to abandon this treatment approach and to date, most transplant centers still consider iCCA a contraindication to OLT.

Recently, however, there has been renewed interest in identifying select patients with iCCA that may benefit from liver transplantation. A Spanish multicenter retrospective study assessed outcomes in 42 cirrhotic patients who underwent liver transplant for presumed HCC within Milan criteria which was subsequently pathologically confirmed to be either mixed HCC-CCA or iCCA on explant compared with 84 matched patients with histologically confirmed HCC. The 1-, 3- and 5-year cumulative risk of recurrence was higher in the subset of patients with iCCA compared with their HCC matched controls (12, 25 and 36% compared with 0, 2 and 2%) though no significant survival difference was seen between the HCC-CC subgroup compared with their HCC matched controls, suggesting a potential benefit with transplantation in patients with HCC-CCA for whom transplantation has historically been contraindicated [74]. Similarly, 1-, 3- and 5-year survival was also lower in the iCCA subgroup but no difference was identified in patients with HCC-CCA. Interestingly, when the analysis was limited to patients with uninodular tumors ≤2 cm no significant difference in tumor recurrence or survival was seen among patients with HCC-CCA or iCCA compared with their HCC matched controls [74], suggesting a potential benefit to transplantation in these 'very early' iCCA cases. Another study using the same multicenter Spanish cohort identified risk factors associated with tumor recurrence in patients with iCCA and found that in the small subset of patients with iCCA ≤2 cm, none of the patients presented with disease recurrence after a median follow up of 36.4 months and the 1-, 3- and 5-year actuarial survival of this subset was 100, 73 and 73%, respectively [75]. That said, it is important to note that compared with pCCA which can present early with biliary obstruction, patients with iCCA are much less likely to be symptomatic; thus, unless engaged in a screening program such as in the setting of cirrhosis, few patients with iCCA are likely to be diagnosed with disease at such an early stage.

With the added benefit of neoadjuvant therapy prior to liver transplantation seen in selected patients with pCCA, investigators at the UCLA

reported outcomes in 25 patients who had liver transplantation for locally advanced iCCA, 9 of whom received neoadjuvant therapy. Though survival rate for these patients was not reported, disease-free survival was significantly higher in patients who received neoadjuvant therapy compared with those who did not and independent predictors of decreased survival included perineural invasion and multifocal tumors. Interestingly, tumor size (≥5 cm iCCA) was not a predictor of patient survival [76]. This group has since proposed a protocol for liver transplantation in patients with iCCA after neoadjuvant therapy [77]. Inclusion criteria include unresectable iCCA ≤ 8 cm, disease confined to the operative field for total hepatectomy and regional lymphadenectomy for liver transplantation, and absence of distant metastasis. Patients undergo preoperative risk stratification with biopsy of the mass to classify tumors into low, intermediate and high risk of poor postoperative outcomes based on tumor characteristics. Neoadjuvant treatment consists of stereotactic body radiation therapy (SBRT) for tumors <6 cm and transarterial chemoembolization (TACE) for tumors between 6 and 8 cm followed by 5-FU or capecitabine-based chemotherapy until the time of transplantation. Patients in the low and intermediate risk groups subsequently undergo liver transplantation after staging laparotomy and those initially at high risk are rebiopsied to assess for response. In an analysis of 40 patients by risk score (65% of whom had iCCA), 5-year tumor recurrence free survival was 78% in the low-risk group compared with 19% in the intermediate risk and 0% in the high-risk group [78]. Thus, though evidence from small series are emerging that have demonstrated potential benefit of liver transplantation for iCCA in selected patients, further validation and large-scale studies are needed to confirm these findings. Though this holds promise for the future in terms of expanding indications for liver transplantation for hepatobiliary malignancy and improving patient outcomes, for the time being, this approach remains controversial.

Finally, locoregional therapy in the form of EBRT is an important part of the neoadjuvant protocol for pCCA but interest in alternative forms of locoregional control including TACE [79] for iCCA, and SBRT and photodynamic therapy (PDT) for pCCA has also emerged. Recently, Cosgrove *et al.* reported that ERC directed PDT was reasonably well tolerated and safe in maintaining locoregional control in patients with pCCA awaiting liver transplantation [32]. Another pilot study demonstrated acceptable tolerability with neoadjuvant SBRT followed by chemotherapy in patients with pCCA prior to liver transplantation. As data accumulate, the role that these alternative locoregional options will play in the perioperative management of patients with pCCA will be more clearly defined [80].

In summary, when combined with preoperative neoadjuvant therapy and staging, liver transplantation is an important treatment option for selected patients with pCCA and offers improved survival far beyond what would be expected with nonsurgical therapeutic approaches. However, adherence to strict selection criteria is essential for optimal outcomes. While patients with *de novo* CCA should be treated with surgical resection when possible, those with unresectable pCCA or pCCA with associated PSC should be considered for liver transplantation.

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