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GASTROINTESTINAL CANCERS (J MEYER, SECTION EDITOR)

Liver Transplantation for Cholangiocarcinoma: Insights into the Prognosis and the Evolving Indications

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Abstract

Purpose of Review Cholangiocarcinoma (CCA) is a rare malignancy of the biliary ducts that can be classified as intrahepatic, perihilar, or distal based on anatomic location. Although surgical resection can be curative, complete excision with negative margins is often difficult to achieve. In patients with unresectable disease, long-term survival is rarely seen with medical therapy alone. A multimodal treatment approach, including liver transplantation (LT) for select patients with unresectable CCA, should be considered.

Recent Findings While currently only an approved indication for early, liver-limited, perihilar cholangiocarcinoma, promising results have been achieved for LT in localized intrahepatic disease. The absolute indication for transplant for intrahepatic tumors is currently the subject of multiple investigations. Continued advances in neoadjuvant/adjuvant therapy and better understanding of tumor biology may further augment the number of candidates for surgical therapies, with liver transplant acting as a promising tool to improve patient outcomes.

Summary Thorough consideration for any expansion in the indication for liver transplant in malignancy is necessary in order to balance patient outcomes with utilization of the scarce donor organ resources.

Keywords Cholangiocarcinoma · Liver transplant · Intrahepatic cholangiocarcinoma · Perihilar cholangiocarcinoma · Mixed tumor cholangiocarcinoma

Introduction

Cholangiocarcinoma (CCA) is a malignancy arising from biliary epithelium and is currently the second most common primary liver cancer, following hepatocellular carcinoma (HCC) [1]. It comprises 10–15% of all hepatobiliary tumors in the USA, and the national and world-wide incidence of the disease is on the rise [2, 3]. Although rare, the tumor carries significant mortality as patients are often diagnosed in advanced stages of disease, and long-term survival is poor due to a paucity of effective medical and locoregional therapies [4]. Symptoms at presentation are typically related to biliary obstruction; therefore, tumors at or below the hepatic bifurcation are diagnosed at an earlier stage versus intrahepatic disease [5].

Cholangiocarcinoma is classically divided into types based on the anatomic location of the tumor. Perihilar (hCCA) and intrahepatic lesions (iCCA) are further stratified as proximal, while tumors involving the periampullary region as distal (Fig. 1) [5–8]. Distal disease will not be discussed in this review. There are further subtypes of iCCA based on growth pattern, such as mass-forming (MF-iCCA, most common), periductal infiltrating (PI-iCCA), and intraductal growing (IG-iCCA). Perihilar cholangiocarcinoma can grow in PI-hCCA and IG-hCCA patterns, but may also display nodular plus periductal infiltrating growth, which is most common. Adding another layer of complexity, the tumors vary by histologic subtypes, which can affect response to treatment and clinical outcomes [8]. The heterogeneity of cholangiocarcinoma at presentation presents challenges in diagnosis, staging, and management of this cancer [9]. Furthermore, due to its low incidence, the majority of outcomes and clinical trials data for hCCA and iCCA are presented in conjunction with data

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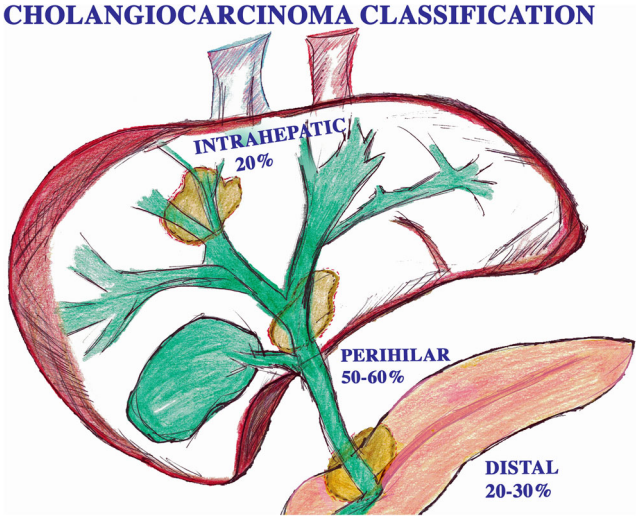

Fig. 1 Cholangiocarcinoma anatomic classification. Lesions are classified as intrahepatic, perihilar, or distal. Approximate incidence of each subtype is shown as a percentage [5, 8]

from distal cholangiocarcinoma and gallbladder carcinoma due to their common origin from biliary tract epithelium. As a result, specific evaluation and data interpretation is difficult despite increasing evidence of biologic diversity among these tumors.

Various systemic and local treatments for cholangiocarcinoma are currently under investigation. In the era of advanced molecular profiling, our understanding of the genetic basis for these tumors is expanding, and possibilities for targeted therapy against tumor mutations are rapidly evolving. Despite ongoing innovations in medical and locoregional interventional therapies, resection remains the only widely accepted curative treatment. A median overall survival (OS) of 80 months (iCCA) and 30 months (hCCA) has been reported with R0 resection in some series [6]. Despite this, the cumulative 5-year survival for patients undergoing resection for cholangiocarcinoma is only 25% [10]. Approximately 53–79% of patients expire as a result of tumor recurrence [11–15], with 83% of recurrences occurring locally in the first 2 years following resection [16]. The technical challenges of surgery due to the infiltrative nature of this cancer often yield inadequate local tumor control, especially in the setting of advanced disease. In the absence of surgical therapy, data from the multicenter phase III ABC-02 trial for treatment of advanced biliary tract cancers demonstrates a median overall patient survival of 9.6 months, despite best medical therapy with gemcitabine and cisplatin [17]. This offers little survival advantage in comparison with the median OS of 7.6 months for patients receiving supportive care. Therapies such as radiation therapy offer additional options for local control of unresectable disease, and can provide meaningful improvement (median OS of 22.5 months); however, the majority of patients ultimately develop progressive disease [18]. Thus, patients with unresectable disease often expire within 6–12 months of diagnosis with few available curative treatment alternatives [17, 18].

The unsatisfactory outcomes achieved with either medical therapy (both local and systemic) or surgical resection have given rise to investigation of novel approaches for achieving tumor-free margins and long-term recurrence-free survival for patients with cholangiocarcinoma. Liver transplantation (LT) offers the advantage of a wider surgical margin without concern for the size of the future liver remnant, thereby providing an alternative, potentially curative, therapy for the treatment of this malignancy. The initial experiences with LT for cholangiocarcinoma were rather dismal with overall and recurrence-free survival of 18–25% after 5 years [19•, 20–22], most likely due to the aggressive biology of this cancer. Improved patient selection and incorporation of neoadjuvant therapies into the pre-transplant treatment algorithm have resulted in improved outcomes, and therefore a re-evaluation of LT as a therapeutic alternative for selected patients with unresectable disease.

Currently, the Organ Procurement and Transplantation Network (OPTN) guidelines only recognize early hCCA as an indication for liver transplantation at a center with an approved protocol, and only patients who meet strict selection criteria may qualify for transplant consideration [23]. In contrast, iCCA has historically been a contraindication to liver transplantation, but more recent data suggest that this may need to be reconsidered as an option in certain patients with liver-limited iCCA. In this review, we discuss the current data on liver transplantation for hCCA and iCCA as well as for mixed hepatocholangiocarcinoma, the combination therapies which have shown superior patient outcomes, and the future directions of research in this area.

Liver Transplantation for Perihilar Cholangiocarcinoma

Perihilar cholangiocarcinoma (hCCA) represents the most common subtype of CCA [24]. Surgical resection can be curative, but due to the infiltrative growth pattern and its location adjacent to critical vascular structures, negative oncologic margins are difficult to achieve. As a result, the postoperative 5-year survival, even in highly selected patients, is only 20–40% [25, 26]. Due to these difficulties, liver transplantation has become an attractive alternative. Unfortunately, early studies evaluating LT for hCCA demonstrated poor survival and high recurrence rates [27, 28], even with the addition of systemic therapy [1]. The majority of patients (47%) recurred in the allograft, with lung being the second most common site of recurrence [29]. However, these studies were small, retrospective, and without protocolized neoadjuvant/

adjuvant regimens [1]. As a result, several centers sought to re-evaluate a more standardized approach to patient selection and pre-transplant therapy to improve outcomes.

In 2000, the team at the Mayo Clinic, Rochester, was among the first to report favorable outcomes for liver transplant in hCCA [30]. The Mayo protocol limited selection of patients to those with early hCCA (< 3 cm in radial diameter) who were unresectable due to underlying liver disease or mass location and were without evidence of lymph node metastases. Patients required diagnosis based on malignant cells on biopsy or cytology, positive aneuploidy on FISH, or Ca 19-9 > 100 in the setting of a malignant appearing mass or stricture. Of note, the protocol excluded any patient receiving a transperitoneal or surgical biopsy of the tumor in order to avoid peritoneal seeding of disease prior to transplant [31]. Patients satisfying these criteria then underwent aggressive neoadjuvant therapy with external beam radiation (4500 cGy in 30 fractions) and intra-biliary brachytherapy (2000–3000 cGy) plus 5-FU chemotherapy. Following completion of chemoradiation, candidates underwent staging surgery with perihilar lymph node biopsy to rule out peritoneal or perihilar metastases. Patients satisfying these criteria were then placed on neoadjuvant oral capecitabine until a donor organ became available for transplantation [3, 28]. Initial outcomes from the Mayo clinic series demonstrated a 5-year actuarial survival of 82% from the time of transplant for patients who completed neoadjuvant chemoradiation and underwent liver transplant, with 26 of 56 patients enrolled receiving transplant [3]. This led to subsequent United Network of Organ Sharing (UNOS)/OPTN acceptance of hCCA as an indication for liver transplant exception points [30].

The results of the initial Mayo series renewed interest in the potential of liver transplant for hCCA; however, the outcomes were not without criticism. First, the involved and prolonged nature of the pre-treatment strategy resulted in a patient drop-out rate of 30–50% due to disease progression, therapy intolerance, and death [32, 33••]. Second, the perihilar radiation treatment resulted in a high initial rate of hepatic artery thrombosis, necessitating a pre-emptive aortic conduit in patients transplanted later in the series [34]. Third, explant pathology from patients transplanted under the Mayo protocol demonstrated that 43% had no evidence of residual disease [27]. While this may have been due to the neoadjuvant chemoradiation, the enrollment protocol did not require a true tissue diagnosis and necessitated early stage of disease. Thus, critics argued that survival outcomes were skewed by transplants performed in patients who did not actually have cancer prior to intervention.

Subsequent multicenter retrospective analysis of patients from 12 US transplant centers treated within Mayo protocol demonstrated 5-year recurrence-free survival of only 69% from the time of transplant compared with the 82% survival initially reported by Mayo. Of patients included in the analysis, 25% (71 of 287 eligible patients) dropped out prior to receiving transplant. Although these results were not as impressive, recurrence-free survival for patients transplanted within Mayo criteria remain significantly better than the 32% 5-year recurrence-free survival observed for recipients transplanted for tumors outside of Mayo criteria (> 3 cm) [35]. While these outcomes exceed that which can be achieved through medical or locoregional therapy alone, it does not meet the threshold of 50–60% 5-year survival necessary for transplantation to be considered a good utilization of resources in the era of organ shortage.

Subsequent multivariate analyses demonstrated that overall prognosis is adversely impacted by older age at transplant, larger mass size, prolonged waiting time, prior cholecystectomy, and CA 19-9 > 100 [36]. Regional lymph node status has also been identified as an independent prognostic factor for survival [37•]. The disparities in OS among the different studies may have been impacted by the underlying liver disease biology associated with patients developing hCCA in the setting of primary sclerosing cholangitis (PSC) versus those with de novo malignancy. Patients transplanted at the Mayo Clinic with PSC-associated cholangiocarcinoma demonstrate a 5-year survival of 77% ($n = 113$) compared with 56% for patients with de novo cholangiocarcinoma ($n = 68$) [28]. However, patients with PSC-associated hCCA tend to be younger, diagnosed at an earlier stage, and are less likely to have pathologic confirmation of their diagnosis. In contrast, de novo hCCA tends to occur at older ages and patients are often diagnosed at later stages of disease.

Given the impressive outcomes of liver transplantation for hCCA, some proponents have argued that LT may offer benefit over surgical resection for patients with resectable hCCA. In fact, subsequent retrospective studies comparing patients treated with similar neoadjuvant therapy protocols undergoing liver transplantation versus surgical resection demonstrated superior survival and lower recurrence rates for patients undergoing LT (5-year survival of 82% vs 21%) [27]. A recent meta-analysis also shows survival benefit for LT in comparison with resection, which is more pronounced at long duration of follow-up [38]. These results are likely skewed by the inclusion of patients with PSC-associated hCCA, a patient subset who are rarely candidates for liver resection by virtue of their underlying liver disease. Outcomes for patients with R0 surgical resection are similar to those observed for patients with de novo hCCA undergoing transplant [28]. Thus, present protocols advocate liver transplantation only when surgical resection is not an option.

Currently, liver transplant for hCCA is only considered for patient with early stage (< 3 cm) hCCA, resulting in the majority of patients being excluded from transplant consideration at diagnosis. With the clear success of neoadjuvant chemoradiation therapy for small perihilar cholangiocarcinoma, many have questioned whether aggressive neoadjuvant treatment

may expand transplant indications to include larger unresectable tumors. Both UCLA and Medical College of Wisconsin have demonstrated successful liver transplant outcomes for hCCA tumors outside of Mayo criteria. Wong et al. reported an 80% 1-year OS and 60% RFS following liver transplant for CCA treated with neoadjuvant chemoradiation therapy, with 2 of 5 patients transplanted having hCCA outside Mayo criteria due to PET positive lymphadenopathy prior to treatment [19•]. These data are difficult to interpret given the combination of outcomes for patients with hCCA and iCCA, the small sample size, and the short duration of follow-up. The Methodist-MD Anderson group also recently re-evaluated liver transplantation for hCCA outside of Mayo criteria in a series of 5 patients. These data demonstrate 3-year OS of 20% for patients with hCCA outside of Mayo criteria despite aggressive pre-transplant neoadjuvant therapy [39]. In the case of surgical resection, neoadjuvant therapy has been shown to downstage unresectable perihilar cholangiocarcinoma to allow for R0 resection in select cases of locally advanced hCCA [40]. Thus, while more aggressive selection criteria for hCCA in transplantation may be warranted in some patients, additional phase II studies are needed to delineate when such an approach is reasonable.

Taking the present literature into consideration, liver transplant for hCCA should only be considered for patients falling within UNOS/OPTN guidelines (unresectable hCCA treated with Mayo protocol neoadjuvant therapy, without regional lymph node or extrahepatic disease, with radial diameter less than 3 cm, who have not undergone transperitoneal aspiration or biopsy) [23]. In this setting, liver transplant is a viable option, and referral to a specialized transplant center should occur early after diagnosis. Transplant referral is also appropriate in the absence of a true "tissue" diagnosis given the diagnostic criteria for transplant do not necessarily require this. Care must be taken to avoid transperitoneal biopsy which could exclude the patient from transplant consideration. Table 1 lists all relevant studies and results discussed in this section.

Liver Transplantation for Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (iCCA) originates from intrahepatic biliary epithelium and accounts for approximately 10–20% of CCA [28]. While rare, the overall incidence for iCCA has increased substantially over the last decade [42]. Similar to hCCA, iCCA is an aggressive tumor with poor response to neoadjuvant therapy. Despite treatment, long-term survival is only 10–40% among patients with favorable tumor characteristics, with outcomes being best among patients with small or solitary nodules, well-differentiated tumors, and tumors without lymphovascular invasion [28, 42, 43]. Intrahepatic cholangiocarcinoma may occur in the setting of cirrhosis or underlying liver disease, in which case, screening protocols for HCC can yield early detection. More commonly, however, iCCA occurs de novo in patients without underlying liver disease, and early detection is uncommon due to the lack of underlying symptoms at early stages, often resulting in large tumors at the time of diagnosis.

Given the aggressive nature of the disease, optimized treatment modalities are needed. Similar to hCCA, surgical resection represents the gold standard for treatment and the only potential therapy offering a definitive cure. Resectability may be limited by the tumor location, size, multifocality, or extension outside of the liver. Especially in cases of central or bilobar tumors, resection is often not possible. For unresectable tumors, medical therapy offers the best option for tumor control, with the gold standard being gemcitabine and cisplatin. Analysis of patients with iCCA from the ABC-01, -02, and -03 trials demonstrates that iCCA exhibits improved OS with systemic therapy when compared with other biliary tract cancers. Patients who completed 6 months of gemcitabine and cisplatin therapy with liver-limited iCCA exhibited an OS of 18.9 months and progression-free survival (PFS) of 11.1 months from initiation of therapy compared with OS of 11.7 months and PFS of 7.8 months for patients with non-iCCA biliary tract cancers [44].

Locoregional therapies (LRT), such as trans-arterial chemoembolization (TACE) and radiation, are also becoming a critical part of the treatment paradigm. These treatments may be utilized as definitive therapy for unresectable disease or adjuncts to medical or surgical therapy. In addition, LRT may be helpful in controlling disease recurrence following resection, as that can be as high as 70% [42]. However, studies evaluating TACE or radiation alone fail to demonstrate a definitive survival benefit. The addition of radiation to chemotherapy as a combined modality treatment for non-metastatic intrahepatic cholangiocarcinoma is associated with improved OS [45]. Overall, intrahepatic CCA appears to be less responsive to LRT than other malignancies, such as HCC or colorectal liver metastases [42, 46]. Proton beam therapy for local control (LC) has also been under recent investigation. In a multi-institutional phase II study from Massachusetts General Hospital, Hong and colleagues investigated high-dose hypofractionated proton beam therapy in patients with unresectable, biopsy-proved HCC or iCCA, showing comparable rates of LC. The median PFS was 8.4 months for iCCA vs 13.9 months for the HCC cohort; the median OS was 22.5 months (iCCA) vs 49.9 months (HCC) [18]. Newer therapies such as trans-arterial radioembolization (TARE) with yttrium-90 or direct hepatic artery infusion of chemotherapy have also demonstrated some survival benefit in unresectable iCCA. These therapies may hold promising avenues for future combination or downstaging protocols, allowing LT for definitive management [47]. Although hCCA has become an accepted indication for liver transplantation over the last decade, as of 2014, the International Liver Cancer Association (ILCA) reported that

Table 1 Liver transplantation outcomes for perihilar cholangiocarcinoma

Reference	Outside Mayo criteria	*N*	Median follow-up (years)	Overall survival (OS)			Recurrence-free survival (RFS)		Overall recurrence	
				1 year (%)	3 years (%)	5 years (%)	1 year (%)	3 years (%)	5 years (%)	rate (%)
DeVreede et al., 2000 [30]	No	19	1	100	–	–	–	–	–	5.2
Heimbach et al., 2004 [3]	No	28	3.6	88	–	82	–	–	85	14
Rea et al., 2005 [27]	No	38	5	92	82	82	0	5	12	13
Panjala et al., 2012 [31]	No	16	1.6	90	70	63	–	–	–	27
	Yes	6		88	52	–	–	–	–	
Darwish Murad et al., 2012 [35]	No	166	2.5	–	68 (2 years)	53	–	85 (2 years)	72	20
	Yes	48					–	56 (2 years)	40	
Croome et al., 2015 [33••]	No	54	3.6	90	71	59	87	64	54	2
Mantel et al., 2016 [37•]	No	28	4.1	–	–	59	–	–	–	46
	Yes	77		–	–	21	–	–	–	79
Loveday et al., 2017 [32]	No	6	1.5	83.3	55.6 (2 years)	–	100	66.6 (2 years)	–	16
Ethun et al., 2018 [41]	No	41	4.8	93	72	64	–	–	–	24
Lunsford et al., 2019 *Abstract* [39]	No	10	5	79	49	49	79	49	49	10
	Yes	5		80	20	20	60	0	0	80

"Liver transplantation is ***not recommended*** for Intrahepatic cholangiocarcinoma or hepatocholangiocarcinoma because results are well below those published for standard indications [48]." Specifically, early studies evaluating liver transplant outcomes in iCCA demonstrated OS and RFS of 18–25% after 5 years [20–22]. More recent retrospective and prospective data may ultimately result in a paradigm shift for liver transplant for iCCA similar to what has previously occurred for hCCA.

As iCCA is considered to be a formal contraindication to transplantation, the majority of outcome data has come from retrospective analyses of incidentally discovered iCCA on explants from patients transplanted for other indications. In the Spanish multicenter analysis of 42 patients with iCCA or mixed HCC-CCA, Sapisochin et al. observed 5-year OS of 62% with a 16.7% risk of recurrence for a single solitary iCCA which was either untreated or treated with LRT prior to transplant [49]. This cohort was subsequently expanded to include data from 17 major international transplant centers from 2000 to 2013. Based on explant pathology, patients with "very early" iCCA (a single lesion ≤ 2 cm) demonstrated statistically significant improvements in tumor recurrence, cumulative recurrence risks, and actuarial survival, with a 5-year OS of 65% [50•]. Dr. Lee and colleagues from Mayo Jacksonville subsequently provided analysis of 618 patients with primary liver cancer, 17 of which were identified as iCCA on explant pathology. Similar to the prior multicenter outcomes, OS survival was comparable between early iCCA and HCC, although recurrence rates were slightly higher for the former [46]. These data have led many to question whether liver transplantation is appropriate to consider for cirrhotic patients with very early (≤ 2 cm) iCCA.

One concern raised with the prior data is that identification of patients with iCCA ≤ 2 cm is difficult. The patients in the aforementioned studies were diagnosed incorrectly or tumors were not recognized prior to transplant; thus, identifying patients with very early iCCA for liver transplant may be difficult. In an attempt to determine whether this threshold could be increased, three French hepatobiliary centers retrospectively compared their outcomes for liver resection versus transplant for iCCA. As in other studies, transplant recipients were either misdiagnosed with HCC or had an incidental finding of iCCA on explant pathology. The group identified 75 patients who underwent LT and 26 patients who received resection. Patients undergoing liver transplant with iCCA tumors ≤ 2 cm trended toward improved OS and demonstrated significantly higher RFS at 1, 3, and 5 years compared with those who underwent resection. Larger tumor diameter on explant and absence of pre-operative treatment were associated with tumor recurrence. The group further evaluated patients with incidental iCCA or mixed tumor types between 2 and 5 cm in diameter ($n = 45$). Importantly, this cohort demonstrated a similar RFS of 74% at 5 years, suggesting that a 2-cm threshold may be too conservative for transplant [51•]. However, none of these studies evaluated effects of neoadjuvant chemotherapy on patient outcomes in transplantation for iCCA, especially in cases of tumors larger than 2 cm. Hong and

colleagues from the University of California, Los Angeles, were perhaps the first to demonstrate the benefits of neoadjuvant chemotherapy when combined with surgery in the management of iCCA. The group combined outcomes for locally advanced intrahepatic and hilar cholangiocarcinoma. Patients receiving LT in combination with adjuvant or neoadjuvant therapy had improved survival compared with no therapy or adjuvant therapy alone [52].

Most recently, the group from Houston Methodist and MD Anderson Cancer Center published the first prospective single center case series evaluating prolonged pre-transplant neoadjuvant chemotherapy for the treatment of iCCA [53••]. In this study, Drs. Lunsford and colleagues performed liver transplant on six patients with unresectable, locally advanced intrahepatic cholangiocarcinoma. Patient selection was based on sustained radiographic stability or response to neoadjuvant gemcitabine- and cisplatin-based chemotherapy for >6 months prior to liver transplant. Unlike patients transplanted under the Mayo hCCA protocol, the Methodist-MD Anderson protocol requires pre-transplant diagnostic confirmation with a tissue biopsy. This protocol offers few limits on the size of the tumor but, instead, relies primarily on the chemotherapeutic response to select patients with favorable disease biology. Inclusion criteria for the protocol include solitary tumors > 2 cm or multifocal disease confined to the liver, and no radiological evidence of extrahepatic, macro- vascular, or lymph node involvement. Patients must exhibit sustained biologic stability or response on a single chemotherapy regimen for 6 months prior to listing, and the tumor must remain at least radiographically stable until transplant. In addition, PET CT screening is employed to monitor tumor activity and development of extrahepatic disease. Following transplant, patients with active disease on explant receive adjuvant chemotherapy. Data from the initial six patients demonstrate an OS of 83.3% and RFS of 50% at 5 years [53••]. A recent update by the group in 2019 reported transplant of three additional patients with persistence of the earlier survival outcomes [54]. Most notable is that the Methodist-MD Anderson group did not exclude patients based on tumor size, and the median tumor diameter on explant pathology was 14.2 cm with no tumors < 5 cm [53••]. Data from this pilot series suggest that tumor biology rather than tumor size may be the more important predictor of recurrence following liver transplantation for iCCA. While limited by patient number, this study showcases feasibility and underscores the need for more prospective evaluation of neoadjuvant and multimodal pre-transplant therapies in the setting of this malignancy, as well as more careful pre-transplant evaluation of tumor characteristics.

The promising outcomes observed in the Methodist-MD Anderson series give rise to new potential avenues for transplant in patients who would otherwise risk certain mortality from iCCA. Combinations of systemic chemotherapy and LRT may improve local and systemic disease control prior to transplant. For example, the combination of TARE (Y-90) and systemic therapy has provided improved local tumor control and downstaging prior to liver resection for iCCA [55]. Advances in chemotherapy may also provide new avenues for controlling and downstaging tumor burden. Triple therapy with nanoparticle albumin-bound (nab)-paclitaxel combined with gemcitabine-cisplatin (i.e., GAP therapy) has been shown to be superior to gemcitabine-cisplatin for both tumor control and patient OS in phase II clinical trials [56]. Phase III trials, as well as evaluation of the regimen for tumor downstaging prior to surgery, are currently underway. The role of liver transplantation in this subset of patients will require further evaluation. In addition, as advances in comprehensive genetic profiling (CGP) expanded our knowledge of genetic mutations common to iCCA, pre-transplant genetic profiling may identify favorable biology for transplant and patients with a lower likelihood of recurrence. For example, KRAS and BAP1 mutations in iCCA have been associated with an aggressive phenotype [57]. In contrast, FGFR-2 mutations exhibit relatively indolent courses [58], and the mutation is commonly observed among recipients of liver transplant [53••]. Furthermore, mutations such as IDH1, FGFR2, and BRCA somatic mutation offer potential therapeutic targets which may aid in tumor control in a neoadjuvant or adjuvant setting.

Despite the promising results of retrospective reviews, multicenter prospective clinical trials are needed to validate liver transplant as treatment for iCCA. As evidenced by the experience with hCCA, the aggressive nature of this disease likely necessitates a multimodal approach to minimize disease recurrence following surgery or transplantation. In patients with underlying liver disease, the toxicity of systemic and liver-directed therapies must be balanced with the patient's physiologic liver reserve to minimize potential morbidity that might preclude definitive therapy. Furthermore, identifying suitable candidates for transplant is a necessity. While size may be an important factor, especially in the absence of systemic therapy, a cutoff of less than 2 cm makes diagnosis difficult. Cumulative retrospective and prospective analyses suggest that successful liver transplant for iCCA is possible for larger tumors; however, additional carefully collected data is necessary to identify patients with biologically favorable disease who will be amenable to transplant. Table 2 lists all relevant studies and results discussed in this section.

Liver Transplantation for Hepatocholangiocarcinoma

Mixed hepatocellular/cholangiocarcinoma (HCC/CCA) is another pathologic subgroup of primary liver malignancy, which lies between pure HCC and iCCA from a tumor biology standpoint. HCC/CCA tumors are thought to arise from hepatic progenitor cells and tend to occur in the presence of

Table 2 Liver transplantation outcomes for intrahepatic cholangiocarcinoma

Reference	Cumulative tumor diameter > 5 cm	*N*	Median follow-up (years)	Overall survival (OS)			Recurrence-free survival (RFS)			Overall recurrence (%)
				1 year (%)	3 years (%)	5 years (%)	1 year (%)	3 years (%)	5 years (%)	
Sapisochin et al.,2014 [49]	No	27	5	78	66	51	–	–	–	36
Sapisochin et al., 2016 [50•]	≤ 2 cm	15	4.8	93	84	65	–	–	–	18
	> 2 cm	33	2	79	59	45	–	–	–	61
Lunsford et al., 2018 [53••]	Yes	6	3	100	83.3	83.3	50	50	50	50
De Martin et al., 2019 *In Press* [51•]	No (all patients)	24	3.2	90	76	67	87	79	75	18
	2–5 cm	14		88	65	65	81	74	74	21
Lunsford et al., 2019 *Abstract* [54]	Yes	9	3	100	83	83	83	50	50	33

preexisting advanced fibrosis and cirrhosis [59, 60]. Similar to iCCA, HCC/CCA is currently considered a contraindication to liver transplant due to high recurrence rates and poor OS [61, 62]. Unfortunately, diagnosis of these tumors prior to liver transplantation is difficult due to poorly defined radiographic diagnostic criteria and difficulty with accurate pathologic diagnosis in small biopsy samples [63]. As a result, 0.7–3.3% of tumors initially diagnosed as HCC are later identified as HCC/CCA on explant pathologic evaluation [64–66]. Given that the aggressive tumor biology bears resemblance to iCCA and the rare nature of the tumor, the two entities are often combined for evaluation and analysis, making analysis of the role of liver transplant for this subset of patients unclear.

Several retrospective studies have evaluated outcomes for HCC/CCA following liver transplant for patients incidentally identified with the disease on explant. The international retrospective series by Sapisochin et al. identified 15 patients with HCC/CCA on explant pathology. Recurrence occurred in 7% of transplanted patients compared with 4% in control HCC patients matched based on tumor pathology, number, and size [49]. While these outcomes exceeded those previously reported, results may have been skewed due to a limit on tumor size in the analysis as well as inclusion of few poorly differentiated tumors. In contrast, 9 patients with HCC/CCA reported by the Cleveland Clinic exhibited a 33% (3/9) incidence of recurrence following transplant [67], and 27 patients with HCC/CCA reported by the Mayo Clinic Jacksonville exhibited recurrence in 40.7% of patients [46]. Due to the small number of patients within each series, as well as their inclusion of iCCA patients, definitive determination of the recurrence risk status post-transplant for patients with HCC/CCA is difficult to assess.

One retrospective analysis of patients undergoing transplant at the University of California, Los Angeles (UCLA), did analyze HCC/CCA liver transplant recipients in isolation. This study evaluated outcomes of 12 patients with HCC/CCA in comparison with outcomes of patients transplanted with HCC, matched by either radiographic criteria or explant pathology. Overall, patients with HCC/CCA trended toward higher recurrence rates and lower disease-free survival compared with HCC; however, patients with HCC/CCA more commonly exhibited a higher pathologic grade and more poorly differentiated tumors. When compared with outcomes for patients with HCC matched based on pathologic grade and tumor size, there was no significant difference between HCC and HCC/CCA in terms of OS or RFS. Furthermore, all recurrences occurred in patients with poorly differentiated tumors, with no recurrences in patients with well or moderately differentiated tumor pathology [63]. These data suggest that patients with well- or moderately differentiated HCC/CCA might be candidates for liver transplantation. However, given the difficulty with determining this diagnosis prior to transplant, additional technology is necessary to delineate biology of these rare tumors prior to transplant. Furthermore, the value of pre-transplant systemic and liver-directed therapy to optimize outcomes for this subgroup needs to be included in future analyses.

Targeted Therapy, Future Directions

Cholangiocarcinoma is a complex entity with aggressive tumor behavior and poor OS. Studies of perihilar and intrahepatic cholangiocarcinoma, including hepatocholangiocarcinoma, clearly show that tumor biology is key to tumor behavior. As genetic profiling and

actionable tumor mutations become better understood, novel targeted therapies promise to improve patient outcomes, as well as identify and potentially stratify patients by aggressive versus indolent tumor behavior. Targeted therapies for intrahepatic cholangiocarcinoma have been under particularly rigorous study, and data shows that close to 40% of patients with iCCA have actionable mutations, most commonly FGFR fusion, IDH, BRAF, and EGFR mutations. Immune therapy with checkpoint inhibitors, such as against PDL1, is also under review [42, 53••, 68, 69]. Tumor surveillance will also be an important component of future therapy for cholangiocarcinoma. In particular, circulating tumor cells may allow early detection, and be predictive of tumor behavior and patient survival [70]. As these therapies/diagnostics become better understood, and more commercially available, they will pave the way for tailored therapy, improved tumor control, higher chance of successful resection or transplantation, improved disease-free survival in the adjuvant setting, and better allocation of treatment resources.

Conclusion

Although rare, cholangiocarcinoma represents an increasingly important primary liver malignancy. While an established therapy for perihilar cholangiocarcinoma under strict patient selection and treatment protocol criteria, the role of liver transplant for intrahepatic and mixed cholangiocarcinoma tumors remains to be elucidated through ongoing clinical trials. To date, the culmination of published clinical data suggests that at least some patients with iCCA and HCC/CCA may be candidates for liver transplantation, a therapy with the potential to greatly prolong overall survival and even cure patients with this aggressive disease. Disease biology, as well as tumor characteristics such as size and differentiation, is likely central to recurrence risk following transplantation, and outcomes may need to be reexamined as additional therapies are added to our armamentarium for the treatment of this disease.

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Compliance with Ethical Standards

Conflict of Interest Guergana G. Panayotova, Flavio Paterno, James V. Guarrera, and Keri E. Lunsford declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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