Chapter 15
Liver Transplantation for Cholangiocarcinoma

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Abbreviations

CCA   Cholangiocarcinoma
ERCP   Endoscopic retrograde cholangiopancreatography
hCCA   Hilar cholangiocarcinoma
iCCA   Intrahepatic cholangiocarcinoma
LT   Liver transplantation
MELD   Model for end-stage liver disease
PSC   Primary sclerosing cholangitis

Introduction

Biliary tract cancers arise from the biliary epithelium and include cholangiocarcinoma (CCA) and gallbladder carcinoma. The incidence in most developed countries is low, with approximately 9000 new cases in the United States each year. Of all biliary tract cancers, CCA is the most common, with approximately 5000 new cases diagnosed in the United States annually [1]. Although primary sclerosing cholangitis

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(PSC), biliary ductal cysts, parasitic infections, and hepatolithiasis are established risk factors, most patients present without an identifiable underlying cause, thereby obscuring any chance of systematically anticipating this disease. Subsequently, the majority of patients present with unresectable, advanced-stage tumor burden.

CCAs are classified as distal (dCCA), hilar or perihilar (hCCA, i.e., Klatskin's tumor), or intrahepatic (iCCA), depending on their anatomical location – with surgical extirpation being the only curative-intent treatment. However, for the 60–70% of all CCAs which present within 2 cm of the proximal biliary bifurcation (i.e., hCCA), complete margin-negative resection is achieved in only 30–80% of cases following surgical resection [2, 3]. In addition, iCCAs can be large and multifocal and often occur in patients with advanced underlying liver disease and cirrhosis, all of which may limit the ability to perform curative-intent major hepatic resections [4].

Despite recent modest improvements in survival with the use of systemic chemotherapy, immunotherapy, and targeted palliative chemotherapeutic approaches [5–9], median survival without surgery remains a dismal 6–12 months [10, 11]. Even for patients who undergo curative-intent surgical resection, the 5-year survival approaches only 40%, mainly due to negligible 5-year survival rates for the significant proportion of patients in whom a margin-negative resection is not obtained (i.e., R1 resections) [3]. Because achieving negative margins is paramount, liver transplantation (LT) for hCCA and iCCA has emerged as a logical strategy. LT affords complete resection with negative margins even in patients who have locally unresectable disease or insufficient hepatic reserve to support resection.

LT for CCA was first introduced in the 1990s, with underwhelming success. Thomas Starzl's group reported a 5-year survival of 25% in a cohort of 38 patients [12], while Jonas et al. reported the German experience to have a 4-year survival of only 30% and unacceptable morbidity [13] (Table 15.1). However, in these early experiences, there were no stringent patient selection protocols, and utilization of neoadjuvant or adjuvant systemic therapies was highly variable. In fact, the majority of these patients were found to have advanced stage disease, including identification of involved regional lymph nodes and even distant abdominal metastases recognized after total hepatectomy. Not surprisingly, disease-free survival was thus short.

In this chapter, we will review recent data on outcomes of LT for both hCCA and iCCA given the considerable improvements in protocol-driven patient selection and utilization of neoadjuvant and adjuvant therapy.
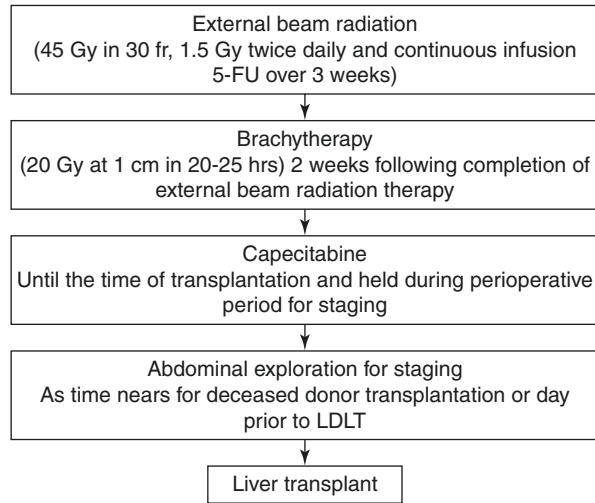
Hilar Cholangiocarcinoma (hCCA)

Neoadjuvant Therapy

Despite the overall poor results reported in these early studies of LT for hCCA, it was recognized that all 5-year survivors were node-negative at the time of LT. This realization, coupled with the known aggressive natural history of the disease, leads

Table 15.1 Selected series of liver transplantation for hilar cholangiocarcinoma

Author, year	Center	N	Patient selection	Neoadjuvant chemoradiotherapy %	1-year survival %	5-year survival %	R0%	5-year disease recurrence %
Iwatuski et al., 1998 [12]	Pittsburg, single center	38	None	61%	60	25	81	–
Jonas et al., 1998 [13]	Germany, single center	14	None	0%	56	30 at 3 years	92	57
Sudan et al., 2002 [14]	Nebraska, single center	11	None	100%		33	100	55
Heimbach et al., 2004 [15]	Mayo, single center	28	Mayo	100% Mayo	88	82	–	14
Rea et al., 2005 [24]	Mayo, single center	38	Mayo	100% Mayo	92	82	97	13
Kaiser et al., 2008 [46]	Germany, multi-center	47		0%	61	22	–	–
Rosen et al., 2008 [47]	Mayo, single center	90	Mayo	100% Mayo	90	71	–	–
Darwish et al., 2012 [17]	United States, national	216	Variable	100%	–	53	–	20
Schule et al., 2013 [21]	Germany, single center	16	+LN −LN	0% 0%	–	50 0	100 100	50
Weling et al., 2014 [48]	Michigan, single center	6	Mayo	100%	83	–	100	–
Mantel et al., 2016 [20]	Europe, multinational	105	Mayo (28) Beyond (77)	0% 0%	–	59 21	93 89	46 79
Ethun et al., 2018 [23]	United States, multi center	41	Varied	95%	93	64	90	24
Zabarowski et al., 2020 [49]	Ireland, single center	26	Mayo	100% Mayo	81	55	96	48

Fig. 15.1 Mayo Clinic
neoadjuvant therapy and
liver transplantation
protocol

| External beam radiation |
| (45 Gy in 30 fr, 1.5 Gy twice daily and continuous infusion 5-FU over 3 weeks) |

↓

| Brachytherapy |
| (20 Gy at 1 cm in 20-25 hrs) 2 weeks following completion of external beam radiation therapy |

↓

| Capecitabine |
| Until the time of transplantation and held during perioperative period for staging |

↓

| Abdominal exploration for staging |
| As time nears for deceased donor transplantation or day prior to LDLT |

↓

| Liver transplant |

physicians at the University of Nebraska to develop the first neoadjuvant chemoradiotherapy protocol to aid in temporizing locally advanced hCCA as bridge to LT [14]. This protocol concept was soon thereafter applied at Mayo Clinic to carefully selected early-stage, unresectable hCCA, yielding unprecedented survival outcomes [15]. In their approach, neoadjuvant external beam radiation was combined with intravenous fluorouracil (5-fluorouracil) sensitization, followed by intraluminal brachytherapy and oral capecitabine while awaiting LT (Fig. 15.1). Their initial results, published in 2000 [16], were updated in 2004 to report an 82% 5-year survival [15]. While there was some criticism regarding the fact that 7/28 (25%) patients had no residual tumor identified in the explant pathology, raising the question of whether these patients truly had hCCA (as opposed to more indolent or precancerous conditions, e.g., PSC), these nonetheless excellent results revived interest in LT for CCA that had been largely abandoned. In fact, numerous contemporary series have reported 5-year survival rates following LT for hCCA that are equivalent to other non-cancer indications for LT utilizing similar neoadjuvant protocols and strict selection criteria (Table 15.1). These uniformly acceptable results have formed the basis for the granting of MELD exception points to prioritize unresectable hCCA patients who meet strict criteria [17].

Patient Selection

Table 15.2 summarizes the inclusion and exclusion criteria as outlined in the initial Mayo Clinic experience. Saliently, this process selects patients with early-stage hCCA which is deemed unresectable or arises within the setting of PSC. Although vascular encasement of hilar vessels is not a contraindication, tumors >3 cm and gallbladder involvement represent contraindications to LT. Prior to LT all patients

Table 15.2 Inclusion and exclusion criteria for Mayo protocol

Inclusion criteria	Exclusion criteria

Diagnosis:
    Pathologically confirmed hilar cholangiocarcinoma
        or
    Malignant appearing stricture + one of the following:
        Mass at the site of stricture on imaging
        Serum CA 19-9 > 100
        Polysomy on fluorescent in situ hybridization
	Intrahepatic cholangiocarcinoma

Radial tumor diameter <3 cm	Prior resection or attempted resection
Absence of intrahepatic or extrahepatic metastases on imaging by cross-sectional imaging and Negative nodal involvement on staging laparotomy	Presence of intrahepatic or extrahepatic metastases
Candidate for LT	History of malignancy within 5 years
Unresectable cancer above the cystic duct	Prior radiation or chemotherapy
Resectable cancer in setting of PSC	Transperitoneal biopsy

undergo a staging abdominal exploration to evaluate for regional lymph node involvement, locally extensive disease, or peritoneal metastases which preclude LT. Although the success of the Mayo Clinic protocol is impressive, it is difficult to assess the relative contribution of neoadjuvant chemoradiotherapy and more rigorous selection practices on the improved outcomes given that they were instituted concurrently. Furthermore, many series utilizing the Mayo Clinic protocol for patient selection report only the post-LT (i.e., per protocol) outcomes and not intent-to-treat analyses, thus limiting the ability to incorporate dynamic changes on the waitlist such as progression versus response to neoadjuvant therapy as potentially useful markers to aid patient selection.

At the tissue level, diagnosis of hCCA can be challenging because intraductal brushing or biopsy is often inconclusive [18]. To address this challenge, the combination of a malignant-appearing stricture on percutaneous transhepatic or endoscopic retrograde cholangiography (ERCP) and *one* of the following additional findings has been deemed sufficient for diagnosis: (1) a mass at the site of stricture by cross-sectional imaging, (2) serum CA 19-9 > 100 U/mL, or (3) polysomy on fluorescent in situ hybridization. Considering this latitude for establishing a diagnosis of hCCA, many patients enter treatment protocols without pretreatment pathologic confirmation of malignancy. However, when studied in multivariate analysis, the absence of pretreatment tissue diagnosis does not inflate 5-year survival except in patients with underlying PSC, where the incidence of benign strictures is much higher [17, 19].

Underscoring the importance of proper patient selection, a recent retrospective analysis of the European Liver Transplant Registry data reported a 5-year overall survival rate of 59% *without* the use of neoadjuvant therapy [20]. In this experience, the authors identified 28 patients of 147 who had undergone LT for hCCA who met strict Mayo Clinic criteria (Table 15.2) but had *not* received neoadjuvant

chemoradiotherapy. Given that the results in this small subset of patients were comparable to patients with a pretreatment diagnosis of hCCA who underwent neoadjuvant therapy and subsequent LT, the authors cautiously concluded that patient selection alone may generate improved outcomes following LT for hCCA. Unfortunately, due to a lack of uniformity of neoadjuvant practices in the remaining hCCA patients undergoing LT within this dataset, a comparative analysis to evaluate for a possible benefit of neoadjuvant treatment in addition to strict patient selection could not be performed. Similarly, Schule et al. retrospectively assessed prognostic factors associated with survival in the absence of neoadjuvant therapy. By controlling only for negative lymph node status, they reported an acceptable 5-year survival of 50% *without* multimodal therapy [21]. Considering the 5-year survival in this study was 0% for patients with node-positive disease, this once again raises the question of whether the successful outcomes of the Mayo Clinic protocol are primarily due to its rigorous assessment of nodal involvement as opposed to a benefit of neoadjuvant chemoradiotherapy. As depicted in Table 15.1, patient selection practices and neoadjuvant approaches have varied considerably across studies. Current recommendations to address early hCCA include combination neoadjuvant chemoradiotherapy prior to LT.

Comparing Transplantation with Resection

The rationale of LT in the treatment of unresectable hCCA is intuitive; in fact, outcomes of unresectable patients treated within the Mayo Clinic protocol demonstrate superior 5-year survival to patients undergoing curative-intent resection [22–24]. Foremost, LT offers superior rates of R0 resection despite addressing surgically "unresectable" cohorts (Table 15.1). Even in the most experienced centers, R0 final margin status rates approach only 70% for resection compared to a 90% R0 rate with LT. In addition to superior rates of margin-negative resection following total hepatectomy, LT also appears to confer a lower 90-day mortality than partial hepatectomy for CCA [23, 25]. This fact is likely owed to the complexity of resection required, which often combines extended hepatectomy with bilioenteric anastomosis and vascular reconstruction.

Several nonsurgical factors also affect the disparate outcomes that are reported when comparing surgical resection and LT. A key factor is the variation observed in the proportion of patients that actually make it to surgical resection versus LT. Progression of disease while undergoing neoadjuvant therapy and subsequent "waitlist dropout" while awaiting allograft availability are real issues and may confer a significant positive bias when reporting outcomes in only the patients who make it to LT. Moreover, as wait times for allografts are variable by region and country, waitlist dropout may be variable by geography. Although the practice of granting MELD exception points for this disease, coupled with neoadjuvant therapy, has decreased dropout rates, a significant number of listed hCCA patients still

ultimately do not make it to LT, with waitlist dropout reported as high as 23.9% at 12 months [26]. Conversely, resection for hCCA often requires only preoperative biliary drainage, with or without portal vein embolization to support extended hepatectomy. This abbreviated preoperative phase yields less time for aggressive biology to declare itself; subsequently, reported dropout rates for patients undergoing preoperative preparation for non-transplant surgical resection of hCCA are comparably low (less than 20%) [27]. Furthermore, there are no upfront restrictions on making sure lymph node-positive patients do not undergo surgical resection. As such, it is important to appraise any comparison between resection and LT within the context of intent-to-treat analyses.

Interpreting reported differences in outcomes between surgical resection and LT is also challenged by significant cohort heterogeneity between resection and LT patients. To date, this challenge has perhaps been most completely addressed by Ethun et al. describing a retrospective review of LT versus resection in 304 patients from a US multicenter cohort [23], where they report a 5-year overall survival strongly favoring LT over resection for pathologically confirmed hCCA (64% vs 18%, $p = 0.001$). Even after excluding resection cases for patients with variables known to negatively impact survival (e.g., tumors >3 cm and lymph node positivity), the LT group still demonstrated superior 5-year survival compared to surgical resection (54% vs 29% $p = 0.001$). These compelling results have raised the question of whether LT should be considered as preferred therapy even in patients with *resectable* hCCA. This very question is currently under investigation with the European TRANSPHIL study (NCT02232932), an open-label, randomized multicenter trial comparing outcomes for resectable hCCA in patients undergoing either surgical resection or neoadjuvant chemoradiation followed by LT utilizing the Mayo Clinic protocol. The community awaits the results of this study with great anticipation, as they are certain to inform the best curative-intent treatment strategy for patients with this difficult malignancy.

Intrahepatic Cholangiocarcinoma (iCCA)

Intrahepatic cholangiocarcinoma (iCCA) is much less common than hCCA, accounting for under 10% of new cases each year. Similar to HCC, iCCA is strongly associated with underlying cirrhosis and chronic viral hepatitis, and its incidence has been increasing significantly over the past decade [28], which is in part due to the increasing incidence of obesity and the metabolic syndrome [29]. Although iCCA has traditionally been considered a contraindication to LT (Table 15.3), this tenet has recently been challenged due to numerous single-center and retrospective multicenter studies demonstrating acceptable outcomes in well-selected recipients [30]. Similar to hCCA, appropriate patient selection, coupled with neoadjuvant and/or adjuvant protocols, appears to offer an avenue toward favorable post-LT outcomes in this traditionally excluded group of patients.

Table 15.3 Selected series and outcomes of liver transplantation for intrahepatic cholangiocarcinoma

Author, year	Center	N	1-year survival %	5-year survival %	Neoadjuvant treatment	5-year disease-free survival %
Shimoda et al., 2001 [50]	Los Angeles, single center	16	62	39 at 3 years	None	35
Robles et al., 2004 [33]	Spain, single center	23	77	42	None	35 at 2 years
Sotiropolus et al., 2008 [51]	Germany, single center	10	70	33	None	–
Vallin et al., 2013 [52]	France, multicenter	10	80	24	None	–
Sapisochin et al., 2014 [53]	Spain, multicenter	27	71	57	None	36
Facciuto et al., 2015 [54]	New York, single center	7	71	57	None	44
Vilchez et al., 2016 [55]	UNOS, national	440	79	47	None	–
Sapisochin et al., 2016 [34]	International, multicenter	15 early[a] 33 advanced[b]	93[a] 79[b]	65[a] 45[b]	None	18[a] 61[b]
Lunsford et al., 2017 [37]	Huston, single center[c]	12	100	83	6-month chemotherapy	50
De Martin et al., 2020 [36]	France, multicenter	49	92	69	Variable	–

[a]Sapisochin et al. found that patients with a single iCCA <2 cm (considered very-early iCCA) had a 5-year survival of 65% after LT and disease recurrence of only 18%. In contrast, patients with advanced disease
[b]Reported a 5-year survival and recurrence rate of 45% and 65%, respectively
[c]Only prospective study on this topic

Initial experiences with LT for iCCA reported very poor survival, mostly attributable to large tumor burden at the time of LT [31, 32]. Subsequently, nearly all published data regarding LT for iCCA is retrospective in nature, with CCA diagnosis identified *after* LT explant tissue analysis. In 2004, Robles et al. retrospectively analyzed a multicenter cohort of 23 patients with iCCA who underwent LT; 5-year survival was 42% [33]. As outlined in Table 15.3, multiple retrospective analyses beginning in 2014 have presented acceptable results for LT in iCCA. The first study to overtly champion the importance of a patient selection strategy to facilitate LT for iCCA was reported by Sapisochin et al. in 2016 [34].

In this multicenter retrospective study, the authors found that patients with a single iCCA <2 cm (considered very-early iCCA) had a 5-year survival of 65% after LT and disease recurrence of only 18%. In contrast, patients with tumors >2 cm reported a 5-year survival and recurrence rate of 45% and 61%, respectively. However, in this subset, it was notable that patients with a known (i.e., non-incidental) iCCA prior to LT had lower tumor recurrence rates and superior actuarial 1-, 3-, and 5-year survival compared to incidentally diagnosed iCCA >2 cm, likely attributable to the fact that 69% of patients with a pre-LT diagnosis received neoadjuvant therapy. Supporting this contention, a UCLA study by Hong et al. of 37 iCCA cases demonstrated that the addition of neoadjuvant and adjuvant therapy with LT significantly reduced recurrence rates for iCCA after LT, with LT recipients receiving both having a 28% recurrence rate compared to 40% for those receiving adjuvant therapy alone and 50% for those receiving neither neoadjuvant nor adjuvant therapy [35]. A multicenter prospective clinical trial is currently underway to validate these retrospective findings, with results expected in 2026 (NCT02878473).

Despite the promise of these selection practices, detection of very-early, <2 cm iCCA in unresectable cirrhotic patients is a challenge. More recently, several groups have also reported their experience with LT with tumors larger than 2 cm with acceptable results. De Martin et al. studied outcomes of 24 patients with iCCA >2 cm and ≤5 cm who underwent LT and reported an overall recurrence rate of 21% and overall survival of 65% at 5 years [36], which represent superior results compared to the multicenter study reported by Sapisochin et al. [34]. A recent prospective study from Lunsford et al. employed LT in patients with *locally advanced* unresectable iCCA, pushing the traditionally acceptable limits by inclusion of iCCA patients with multifocal and large lesions which would be considered beyond the Milan Criteria for HCC [37]. This study enrolled patients with either large (iCCA >5 cm) or multifocal disease (median pre-LT number of four lesions) without vascular invasion, extrahepatic disease, or lymph node involvement. By allowing only iCCA patients demonstrating a sustained response to gemcitabine and cisplatin for a minimum 6 months to receive LT, they were able to achieve 5-year survival of 83% after LT despite large tumor burden identified at explant (median number of seven lesions with median cumulative tumor diameter of 14.2 cm). While the number of patients undergoing LT was quite small ($n = 6$) in this initial report, it provided a strong framework to allow for life-saving LT in highly selected patients with unresectable but not extrahepatic disease.

In summary, LT for iCCA remains controversial, and extrapolating results from retrospective data is challenged by heterogeneity among treatment protocols and small sample sizes. To solidify the practice of LT for iCCA or make an argument for MELD exception, further prospective data will be necessary. Currently available data support consideration of LT either for (1) very-early stage (<2 cm) and intermediate stage (2–5 cm) iCCA diagnosed within the context of chronic liver failure or (2) locally advanced disease in highly selected patients who have demonstrated a sustained tumor response to neoadjuvant treatment.

Perioperative and Technical Considerations

Preoperative Preparation

With the current landscape necessitating neoadjuvant chemoradiotherapy for the majority of patients undergoing LT for CCA, several common sequelae should be anticipated. Radiation therapy confers patients a relatively high rate of duodenal ulceration [38]. As such, it is recommended to employ proton pump inhibitors in these patients during therapy and for a minimum of 1 month afterward. In addition to challenges with tumor cachexia, patients undergoing neoadjuvant chemoradiotherapy are uniquely nutritionally challenged, as radiation therapy often begets gastropathy, gastritis, and gastric dysmotility. The severity of these symptoms may be exacerbated by perioperative narcotics at time of LT. Subsequently, close monitoring for these symptoms preoperatively is important, and surgeons should have a low threshold to employ jejunal feeding access for this at-risk population. Preoperative nutritional optimization has been associated with improved survival in patients undergoing resection for CCA [39]. Although not specifically studied in the context of malignancy, many studies support the benefit of preoperative nutritional optimization to support LT survival as well [40].

Due to the nature of CCA, biliary obstruction and cholangitis are frequent problems encountered in the preoperative course. Despite initial controversy, the use of covered self-expanding metal stents to alleviate these problems does not preclude effective radiotherapy. Such stents are proven to prevent tumor ingrowth but carry a higher rate of migration and cholecystitis [41, 42]. Perhaps most importantly, providers should have low threshold to initiate empiric antibacterial coverage in any patient with suspected acute cholangitis. Prophylactic antibiotics should be considered peri-ERCP and post-procedure according to practice guidelines [43]. As time to repeat ERCP and stent occlusion can be variable, some centers also provide patients with indwelling biliary stents a prescription for antibiotics and instructions to empirically begin treatment at the onset of symptoms indicating worsening biliary obstruction or infection.

Similar to biliary obstruction, cholecystitis often develops in patients awaiting LT for CCA. Its frequent incidence is derivative to tumor obstruction of the cystic duct or complications of biliary stenting. Diagnosis is reliable by ultrasound, as in conventional cases; however, treatment should avoid cholecystectomy as there is a high risk of tumor dissemination [44]. Treatment includes prompt initiation of antibiotics and decompression, with both ERCP and percutaneous stenting as acceptable options.

Operative Considerations

Both deceased donor and living donor LT have been successfully employed to treat CCA. When described, surgical technique for LT follows institutional protocol but favors a bicaval approach when there is caudate involvement. Staging laparotomy described in the Mayo Clinic protocol is performed through a right or bilateral

subcostal incision and includes a thorough abdominal exploration, including manual palpation of the hilum. Routine biopsies of nodes overlying the common bile duct as well as the distal hepatic artery at the level of the gastroduodenal artery are performed at this time. Extrahepatic disease or lymph node metastases preclude LT. While this staging laparotomy has initially been described as being performed prior to LT, many centers have now incorporated this staging to be done at the time of an organ offer.

LT performed for hCCA should include very low dissection of the portal structures and routine frozen section of the distal bile duct margin. A positive distal bile duct margin needs to prompt consideration of a pancreaticoduodenectomy to achieve a margin-negative curative intent operation. If a pancreaticoduodenectomy is required, proton pump therapy is recommended for life [45]. Finally, recipients undergoing neoadjuvant intraluminal brachytherapy have been noted to have a higher incidence of vascular complications, particularly hepatic artery thrombosis. Subsequently, routine employment of an infrarenal aortic conduit using donor iliac vessels to supply the donor artery has been described and should be considered.

Conclusion

While LT has been the gold standard treatment for patients with unresectable hepatocellular carcinoma for nearly three decades, a new era of "transplant oncology" has been ushered in with the recognition that LT is also a viable curative therapy for patients with CCA. Given the relative scarcity of available donor liver allografts, rigorous patient selection must be applied to mitigate oncologic risk and ensure meaningful organ utilization (Table 15.4). Although questions exist regarding the

Table 15.4 Data-supported recommendations for LT in hilar vs intrahepatic cholangiocarcinoma

	hCCA	iCCA
Age	<68, absence of comorbidities precluding LT	<65, absence of comorbidities precluding LT
Histologic confirmation	Optional, excluding transperitoneal	Mandatory, often transperitoneal
Size staging	<3 cm	Unresectable <2 cm in setting of chronic liver failure *or* Unresectable >2 cm with sustained response to chemotherapy ± RT
CA 19-9	No upper limit reported	>100 relative contraindication
Multifocality	Contraindication	To be defined
Preoperative lymph node assessment	Mandatory – rule out nodal disease	Mandatory – rule out nodal disease
Neoadjuvant treatment	Chemoradiotherapy	Very early disease – to be defined Advanced disease – recommended as selection tool
Eligibility for MELD exception	Yes	Not currently

application of LT for resectable hCCA and iCCA, diligent patient selection and multimodal neoadjuvant and adjuvant therapy seem to be of paramount importance. With increasing rates of living donor LT, extended criteria organ utilization, and the advances seen within the field of xenotransplantation, the promise of a supply-side fix to organ shortages may further expand opportunities to offer LT as a treatment for CCA.

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