Liver Transplantation for Cholangiocarcinoma

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Abstract

Cholangiocarcinomas (CCAs) are highly aggressive, primary liver cancers with rising incidence and mortality rates. The current 5-year overall survival is less than 20%. There are no standardized screening protocols, and current diagnostic methods include serum biomarkers and imaging techniques with suboptimal sensitivities and specificities. The most commonly used treatment options, including combination systemic therapies, locoregional therapies, and surgical resection, offer improving but nonetheless limited progression-free and overall survival. Liver transplantation has shown promising results as a potentially curative treatment for two types of CCA, namely, perihilar and intrahepatic. However, the evidence is largely from retrospective series of small to moderate sample sizes. There is a need to define optimal types and sequencing of neoadjuvant and adjuvant peritransplant therapies, as well as criteria for CCA patient transplant eligibility. Here, we conduct a granular review of the evidence available on every step of the transplant care pathway for perihilar and intrahepatic CCA patients. We aim to inform best practices to inform future avenues of research and maximize the number of patients eligible for this potentially life-prolonging therapy.

Keywords
- perihilar cholangiocarcinoma
- intrahepatic cholangiocarcinoma
- liver transplantation

Cholangiocarcinoma (CCA) is an adenocarcinoma of the biliary system. There are three recognized subtypes: perihilar (pCCA, 50–60% of cases), intrahepatic (iCCA, 10–20%), and distal (dCCA, 20–30%).[1–3] Common risk factors include smoking, chronic inflammation from gallstones, infections (flukes, viral hepatitis), autoimmune conditions, and congenital abnormalities (e.g., choledochal cysts).[4–6] As these tumors are relatively uncommon and lack effective biomarkers, there is no evidence-based approach to screening. Different management approaches, including surgical, locoregional, and systemic, are used for each subtype with little evidence to inform their most appropriate sequence, resulting in variations in overall survival (OS) and recurrence-free survival (RFS) reported in the literature. Due to the aggressive natural history of CCA, around 65% of patients present at advanced stages or with severe liver dysfunction due to underlying cirrhosis and are therefore ineligible for local therapy options such as percutaneous and endoscopic ablation, local tumor resection (by wedge, minor or major hepatectomy), or radiotherapy.[7–18] Mortality rates are

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alarmingly high with reported 5-year OS of less than 20% without intervention.[2,8,19–22] Guidelines recommend margin-negative (R0) liver resection (LR) as the only potentially curative treatment option for iCCA and pCCA with reported OS of 45% and 20 to 40%, respectively. However, in 50 to 70% of iCCA patients, tumor recurrence is seen at a median time of 26 months post-LR.[23] This has led hepatobiliary and transplant specialties to explore other treatment modalities, specifically liver transplantation (LT), with more recent studies showing promising results. Historically, LT for CCA had poor RFS and OS, with early studies reporting a 5-year OS of only 20% in iCCA patients.[2,8,24–29] Yet, recent evidence has shown improved outcomes in those with small, early-stage tumors.[30,31] When combined with neoadjuvant chemotherapy, post-LT 5-year OS for patients with iCCA improved up to 78%, and 5-year RFS up to 65% in pCCA patients treated with neoadjuvant chemoradiotherapy.[14,32–35] This suggests that careful selection and stratification of CCA patients based on prognostic clinicopathological factors such as tumor size, burden, multifocality, response to neoadjuvant therapy, and lymphovascular invasion would increase the number of iCCA and pCCA patients eligible for LT as a potentially curative therapy and will be the focus of this review.[3,31,36–39] This is also summarized in ►**Fig. 1**.

Diagnosis, Referral, and Evaluation

The pretransplant evaluation process for patients with CCA is variable, beginning with a referral to a transplant center often due to underlying primary sclerosing cholangitis (PSC) or liver dysfunction (cirrhosis), and sometimes prior to a confirmed diagnosis of malignancy. This is in part as patients with CCA are typically asymptomatic until advanced stages. After referral to a transplant center, patients are evaluated by a tumor board composed of a multidisciplinary team (including hepatology, medical oncology, surgery, and radiation oncology among others), where recommendations given by cardiopulmonary specialists and psychosocial assessments are combined with a thorough review of imaging studies to assess patient eligibility for transplant and to recommend personalized neoadjuvant regimens. Not all transplant centers have developed this integrated, subspecialized care, and a possible volume–outcome relationship has been suggested in the literature.[40] There are no standardized screening protocols for CCA due to possible need for invasive procedures and a lack of promising evidence found in prospective series.[41] Diagnosis of CCA using noninvasive methods is challenging owing to difficulties accurately distinguishing CCA from other primary liver cancers. Currently, the only accepted serum biomarker for diagnosis and screening is CA19–9, with known sensitivity and specificity of 60 to 93% and 78 to 98%, respectively, in patients with underlying PSC and around 75 and 80%, respectively, in the absence of PSC.[42–51] However, studies have previously reported sensitivities as low as 33% in patients with resectable CCA, suggesting limited value to the use of serum CA 19–9 levels in identifying patients with early stage, surgically resectable disease.[50] Imaging with modalities such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) with or without contrast have also been suggested as tools in the screening and diagnosis of CCA.

In patients with underlying cirrhosis undergoing screening for HCC, iCCA may be detected incidentally at early stages. One large retrospective study identified incidental iCCA in 1% of explants from LT patients suspected of having HCC (23 out of 2,301),[52] though the exact rate of incidental iCCA found on liver explant remains unclear. There are difficulties in radiologically distinguishing between the two primary malignancies, leading to cases of confirmed diagnosis only after LR and/or transplantation on final explant pathology, a concerning occurrence due to rising promising evidence in favor of neoadjuvant systemic therapy for iCCA.[3,53–55] In around 30 to 42% of cases, PSC-associated CCA was reported to be found incidentally on autopsy or on liver explants post-

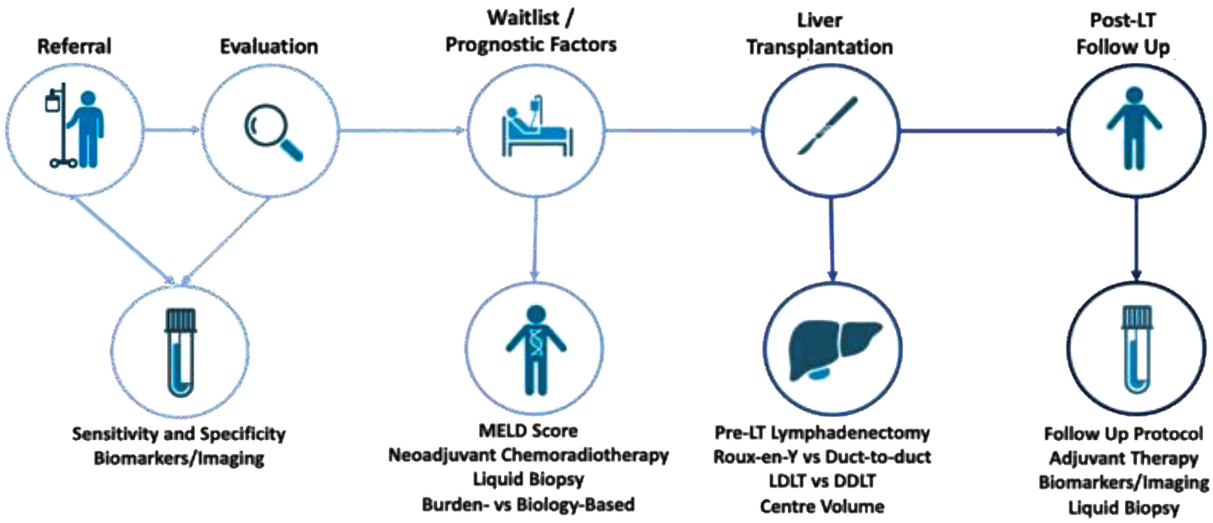

Fig. 1 Integration of standard liver transplant care (top row) with cholangiocarcinoma-specific medical approaches (bottom row) to optimize liver transplantation process.

OLT.[56–58] While MRI can provide a more comprehensive assessment of the primary mass, CT is more suited for the detection of hepatic vasculature and is therefore critical in determining resectability.[59] 18F-fluorodeoxyglucose (18F-FDG) PET imaging has shown poor performance in the detection of primary tumors but surprisingly high sensitivity and specificity for the detection of lymph node and distant metastasis and, therefore, is important in the staging of all CCA subtypes.[60,61]

In patients with pCCA and dCCA, initial CT features may warrant additional imaging with magnetic resonance cholangiopancreatography (MRCP), which has a sensitivity and specificity of 87 and 85%, respectively, in differentiating between benign and malignant causes of hilar obstruction.[62,63] MRCP also has an additional benefit of being able to map a patient's biliary anatomy prior to endoscopic intervention with ERCP. ERCP is employed as a diagnostic and therapeutic tool as it enables the detection of malignant strictures and acquisition of biliary brushings for cytology and confirmation of the underlying tumor biology.[19] However, one meta-analysis examining the use of biliary brushings for pCCA detection found a low sensitivity of only 43%.[64] Endoscopic ultrasonography (EUS) has been previously recommended in the diagnosis and staging of pCCA owing to its ability to provide a detailed assessment of the extrahepatic bile duct and concurrent tissue acquisition via fine-needle aspiration (FNA).[19] However, EUS-FNA has demonstrated a higher sensitivity for dCCA than for pCCA (81 vs. 59%), with controversies arising concerning the potential risk of tumor dissemination associated with EUS-guided tissue biopsy of pCCA.[19,65,66]

While there are many tools available for the diagnosis and staging of CCA (►**Fig. 1**), overall, these have shown subpar sensitivity and specificity, suggesting the need for further investigations aimed at finding standardized, effective methods involving a combination of these protocols, primarily aimed at confirming CCA diagnosis pretransplant to best guide neoadjuvant therapy.

Prognostic Factors and Waitlist Selection

Although LT is becoming one of the most promising treatments for CCA, concerns regarding national organ shortages combined with early studies demonstrating poor prognosis for iCCA patients' post-LT has led to hesitancy in incorporating these cancers as formal indications in the United Network for Organ Sharing (UNOS) standards. While this was previously true for all CCA subtypes, a study conducted by the Mayo Clinic showed favorable results in patients with pCCA comparable to benign indications for LT. UNOS subsequently granted an exception to the Model for End Stage Liver Disease (MELD), allowing patients who had suitable tumor size and met other diagnostic criteria to be added to the waiting list for LT with MELD scores equivalent to those of a patient with stage 1 HCC (an existing indication for LT). This resulted in a greater number of patients having access to LT.[67,68] The standard MELD exception point for pCCA is set at Median MELD at transplant (MMAT) −3 points.[69] A patient must have unresectable disease either due to locally advanced tumor with vascular and/or biliary invasion preventing R0 resection, or poor functional reserve due to underlying liver disease to qualify for MELD exception points.[69,70] There must also be only a single tumor <3 cm in diameter with no intra- or extrahepatic metastasis seen, and patients must be treated with neoadjuvant therapy at centers with approved protocols.[70] Currently, there are no formal UNOS indications for LT for curative intent in patients with iCCA, and hence no established, standardized inclusion criteria. A recent propensity score–matched National Cancer Database (NCDB) study has shown that neoadjuvant chemotherapy was associated with longer OS in select patients with CCA compared with those directly undergoing surgical resection with subsequent adjuvant chemotherapy[71] confirming results seen in studies of CCA patients pretransplant,[72–74] and suggesting the need for further studies looking at tailored neoadjuvant therapy to improve the tumor response rate and increase the number of patients eligible for LT.

Historically, for patients with pCCA, registry-based LT outcomes were poor,[26] even for small tumors identified incidentally on explant.[75] Improved outcomes of 5-year RFS of 65% were seen with the introduction of neoadjuvant chemo-radiotherapy for systemic control prior to LT.[32–35] This suggested that the use of biology-based selection criteria for LT may result in more favorable outcomes than those seen with the use of size or burden-based criteria alone.[3] Many transplant centers within the United States, and internationally, now use the Mayo Clinic protocol of chemo-radiation prior to LT for the treatment of unresectable pCCA with few deviations.[76] This protocol involves pretreatment with radiation and 5FU followed by brachytherapy with iridium and concomitant 5FU followed by maintenance single-agent chemotherapy until LT. A recent meta-analysis of retrospective series of LT for pCCA reported improved 5-year OS of 51.7% and 3-year RFS of 51.7% in those given neoadjuvant therapy compared with those without (5-year OS: 31.6%, 3-year RFS: 24.1%), confirming the importance of neoadjuvant therapy in the pre-LT period. However, patient dropout rate during neoadjuvant therapy cited in the literature ranges from 10 to 66.7%, with common causes including disease progression (41%) and death prior to transplantation (10.7%).[76,77] Following advances in systemic therapy for other cancers, including pancreatic and rectal, the continued role of radiotherapy in those neoadjuvant settings prior to surgery has been called into question, and may require further investigation to determine true benefit.[78,79]

Historically, for patients with iCCA, LT without adjunctive treatment has dismal outcomes, with early studies showing 1- and 3-year OS of only 19.4 to 38% and 4.9 to 10%, respectively. This resulted in iCCA becoming a relative contraindication for LT.[80,81] More recent studies have challenged this, showing improved outcomes (1- and 3-year OS rates of 83.3–100% and 47.91–83.3%, respectively) with improved patient selection and standardized use of neoadjuvant therapy (►**Table 1**).[22,31,36–39,82–88] In a study conducted by Hong et al, 38 CCA cases (iCCA and pCCA) received LT with significant differences seen in 5-year OS (47, 33, and 20%, $p = 0.03$)

Table 1 OS and RFS rates for CCA subtypes with and without LT

CCA subtype	OS		RFS	
	Without LT	With LT	Without LT	With LT
pCCA	20–40%[172]	82.8%[76]	50–70%[12,173,174]	75.9%[76]
iCCA	45%	75%[109]	30–50%[23]	70%[109]
dCCA	48–52%[175,176]	NA	~48%[175,176]	NA

Abbreviations: dCCA, distal cholangiocarcinoma; CCA, cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; LT, liver transplantation; OS, overall survival; pCCA, perihilar cholangiocarcinoma; RFS, recurrence-free survival.

in patients who received neoadjuvant and adjuvant, adjuvant therapy only, or no therapy, respectively.[82] The neoadjuvant protocol consisted of transarterial chemoembolization or radiotherapy combined with chemotherapy. In 2014, a multicenter retrospective cohort reported 1-, 3-, and 5-year OS rates of 93, 83, and 65%, respectively, and low recurrence rates for 48 LT patients with existing cirrhosis and small (<2 cm) incidental iCCA.[31] These outcomes are similar to those achieved in patients transplanted for well-selected hepatocellular carcinoma and are superior to those seen with local resection (LR). In 2022, University of California, Los Angeles (UCLA) reported 1-, 3-, and 5-year OS rates of 80, 63, and 49%, respectively, for CCA patients undergoing LT.[39,89] Studies have reported strong associations between poor tumor differentiation, microvascular invasion, and worse post-LT outcomes.[90–92] Researchers at UCLA established a prognostic scoring system that has been shown to correlate with LT outcomes in iCCA patients.[36,84] Predictive risk factors included lack of neoadjuvant or adjuvant therapy, multifocality, infiltrative growth, history of PSC, and perineural and lymphovascular invasion.[36] Considering these factors, the team at Houston Methodist reported prospective case series of patients with unresectable iCCA treated with LT and neoadjuvant chemotherapy with promising results of 1-, 3-, and 5-year OS rates of 100, 83, and 83%, respectively, in the first study[37] and 100, 71, and 57%, respectively, in the second study.[38] Patients in these studies who were listed but not transplanted had a decline in survival after 1 year, with no patients alive within 2 years, outcomes consistent with those seen in previous iCCA patients treated with only systemic therapy.[93] The relative scarcity of iCCA LT series that employ neoadjuvant therapy impedes development of standardized treatment algorithms. Recent series from Houston Methodist has shown excellent LT outcomes in iCCA patients treated with neoadjuvant gemcitabine and cisplatin without radiation with 1-year OS of 100% and 5-year OS of 75%.[94] These results correspond to those at UCLA[39] and demonstrate that LT is a potentially curative treatment option in well-selected iCCA patients.

The utilization of other neoadjuvant therapies such as stereotactic body radiation therapy (SBRT) has shown promise in preventing disease progression with lower toxicity than traditional radiotherapy.[95,96] Recent studies have found that neoadjuvant selective internal radiotherapy with Y90 either alone or combined with systemic chemotherapy can be used to bridge or downstage patients with unresectable iCCA tumors to resection with good survival outcomes, disease control, and an acceptable safety profile, although not specifically in the transplant setting.[97–103] Advances in oncological therapy have led to improved management of CCA with greater survival seen with the combination of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) as a second-line chemotherapy agent for use as either neoadjuvant or adjuvant therapy in CCA patients considered for LT.[95,104] Promising results have also been seen in trials testing immunotherapy for CCA; however, more research is needed before these treatments can be routinely recommended in the peritransplant setting.[95,105]

Two possible approaches to patient selection currently used include burden-based and biology-based. Initial studies advocated for selection based on iCCA size and number,[31] and later studies demonstrated promising outcomes in patients selected based on response to neoadjuvant therapy, independent of tumor size.[37–39,87] Following the success of patient selection based on tumor burden for HCC and pCCA, most centers perform LT only for patients with small iCCA tumor burden, supported by reports from Mount Sinai Medical Center and Sun Yat-sen University.[106–108] A recent meta-analysis found similar results and agree that smaller tumor size is associated with improved OS.[106,109] However, using size-based criteria limits LT to a small percentage of iCCA patients with very small tumors, with most patients being ineligible to receive potentially lifesaving treatment. An international retrospective study showed that tumor size did not independently predict tumor recurrence.[31] Later studies supported these results and showed that tumor burden is not an accurate predictor of patient outcomes after LT.[39,110] Shifting toward biology-based selection criteria has shown promise. With reports from Houston Methodist Hospital showing that tumor response to neoadjuvant therapy is a better predictor of OS than tumor size.[37,38,106] Additionally, recent advances in next-generation sequencing (NGS) of solid tumor biopsies and liquid biopsy of cell-free DNA, RNA, and/or protein expression is promising in the pre-LT identification of tumor genetic mutations responsive to neoadjuvant therapies and capable of predicting patient prognosis to optimize selection of patients amenable to LT. Identification of these mutations could also assist in personalizing therapies, surveillance, and to predict and treat recurrence.[3,7,111] Studies of patients receiving LT for iCCA have identified mutations in genes such as *FGFR2* and *IDH1* which have approved targeted therapies.[38,112] Worse overall prognosis in iCCA patients has been observed with intratumoral heterogeneity; however, more research is needed to

ascertain its significance in predicting post-LT outcomes.[113–116] An important factor to consider when determining selection criteria is that excessive expansion of inclusion criteria will likely result in a significant increase in organ demand, at the time of organ shortages, with potential decreases in OS due to increased waiting times among all patients on the waitlist irrespective of underlying hepatic malignancy.[117]

Liver Transplantation

With a current shortage in organs, optimization of the LT procedure for CCA remains of the utmost importance to minimize risk of rejection, graft failure, or tumor recurrence.

A recent meta-analysis of patients with iCCA found pooled 1-, 3-, and 5-year OS rates of 75, 56, and 42%, respectively.[109] The pooled 1-, 3-, and 5-year RFS rates were 70, 49, and 38%, respectively, with patients with underlying cirrhosis showing higher RFS rates.[109] Superior 5-year RFS rates were seen in patients with very early (single $\leq$2 cm) iCCA (67%) compared with patients with advanced iCCA (34%).[109] Another meta-analysis comprising 20 studies and 428 patients looked at pooled OS and RFS rates following LT for pCCA patients.[76] They found 1-, 3-, and 5-year OS in LT patients without neoadjuvant therapy to be 71.2, 48.0, and 31.6%, respectively. These improved to 82.8, 65.5, and 65.1% in patients with completed neoadjuvant chemoradiotherapy regimens.[76] Three-year recurrence rates were reported to be 24.1% in patients given neoadjuvant chemoradiotherapy, and 51.7% in those without. Interestingly, patients with PSC seemed to have the most favorable outcomes.[76]

Currently, there remains a poor accuracy of preoperative imaging assessment and models to identify patients at high risk of nodal disease. In patients with small iCCA, nodal status was found to be the main determinant of prognosis with 5-year OS reported to be 0 to 20% in N1 patients compared with 35 to 50% in N0 patients.[118–121] Predicting LN size by CT or MRI has shown poor PPV of only 2.8 to 48%, possibly due to nodal enlargement secondary to reactive hyperplasia.[120] This led to a focus on ^{18}FDG-PET for nodal staging which showed an accuracy of 81% for size $>$1 cm LNs, and a sensitivity and specificity of 69.1 and 88.4%, respectively, making it highly predictive for nodal involvement.[61,120,122] EUS with fine needle aspiration (FNA) is increasingly being used in clinical practice preoperatively to assess the presence of nodal disease; however, few studies are available in the literature to recommend routine use.[120]

Some studies have recently investigated the effect of pretransplant lymphadenectomy on OS rates in iCCA patients. Yet, it remains a topic of ongoing debate. The 8th edition of the TNM staging system proposed by the AJCC highlighted that hepatic pedicle lymphadenectomy according to tumor location is recommended to ensure precise staging.[123] Regional LNs associated with iCCA are defined as inferior phrenic, hilar, and gastrohepatic LNs for left liver iCCAs (draining stations 12 to 8, and 7, 1, 3) and hilar, periduodenal, and peripancreatic LNs for right liver iCCAs (draining stations 12 to 8, and 13). Spread of the tumor to the celiac, periaortic, and/or pericaval LNs is considered M1 disease irrespective of primary location.[22,120,123] Despite the AJCC's recommendation of a minimum of six harvested lymph nodes (HLNs) for adequate nodal staging, routine lymphadenectomy with histologic examination is poorly practiced.[124–126] A study by Bagante et al found that 5-year OS in N0 patients improved with an increased number of HLNs, 54.9% in patients with six or more HLNs versus 39.4% in patients with less than six HLNs. Of note, patients with less than six nodes harvested also tended to have an increased risk of death compared with those with six or more HLNs (hazard ratio: 1.39).[126] No significant change was observed in patients with N1 disease, irrespective of number of lymph nodes harvested ($p = 0.71$); however, only 25% of patients in the study had adequate nodal staging performed.[126] The 5-year OS of patients with negative lymph nodes (NLNs) was 44.4 versus 15.2% for patients with metastatic lymph nodes (MLNs) ($p < 0.001$), illustrating the importance of adequate nodal staging in predicting patient prognosis and optimizing pretransplant patient risk factors. In patients with positive N1 iCCA, Kim et al found that expanding dissection to station nos. 12 and 8 covered 82.0% ($n = 50$) of metastatic cases.[127] In patients with cN0 disease, a study by Sposito et al found that adequate lymphadenectomy provided better survival outcomes for patients with cN0 disease found to be N positive on pathology with longer OS (28 vs. 23 months) and DFS (13 vs. 9 months).[128] This supports the push for more surgeons to use adequate lymphadenectomy as routine practice even in patients with cN0 iCCA.

In pCCA patients, lymph node metastasis is common, seen in 31 to 58% of patients, likely due to a thin bile duct wall and remains one of the most important prognostic factors.[129–131] The most common sites of metastasis are around the bile duct (27.1–42.7%), portal vein (30.9–35.7%), common hepatic artery (27.3–31.3%), para-aorta (17.3%), posterior pancreatic head (14.5–50%), and celiac trunk (6.4–14.3%).[132,133] Mantel et al reported that in N0 patients, the 5-year OS of patients with MLNs was significantly lower than those without (27 vs. 54%, $p = 0.01$), and not significantly different from N1 patients (27 vs. 15%, $p = 0.54$).[129,134] As a result, the Japan Society of Hepatobiliary and Pancreatic Surgery recommends dissection of the first and second stations (stations 8, 12, and 13) for pCCA differing from the National Comprehensive Cancer Network (NCCN) guidelines that suggest standard lymph node dissection of stations 12 and 13 with any further metastasis considered a contraindication to radical surgery.[135,136] A study by Kitagawa et al found that 3- and 5-year OS rates were 31.8 and 14.6% for patients without lymph node metastasis, 31.8 and 14.7% for patients with regional lymph node metastases, and 12.3 and 12.3% for patients with para-aortic lymph nodes metastases.[132] Of the patients with para-aortic lymph node metastases, seven patients had no obvious signs of lymph node involvement during surgery and was confirmed by postoperative pathology examination. The outcomes of these patients were significantly better than those with lymph node metastases confirmed intraoperatively and were equal to that of patients with regional lymph node metastases.[129,132] This suggests

that even in patients with para-aortic MLNs, extended lymphadenectomy can provide better outcomes with no increased risk of procedural complications.[13,132,137,138] The 5-year OS rates of pCCA with regional lymphadenectomy were 7 to 20% versus 26 to 46% in pCCA patients with extended lymphadenectomy, supporting the value of extended lymphadenectomy in resectable pCCA.[139–145] Ma et al found that extended lymphadenectomy significantly increases lymph node retrieval, reducing risk of understaging, improving prognosis predictions, and OS in patients with M0 diseases with R0 resection.[146] However, no OS benefit was found in patients with M1 disease, concluding that extended lymphadenectomy should not be performed in pCCA patients with intraoperatively confirmed distant MLNs.[129] Some studies found no significant difference in OS between patients with N1 and N2 MLNs, challenging the accuracy of the AJCC staging system which relies on site of lymph node metastasis.[131,139,147]

Intraoperatively, there remains some debate regarding whether Roux-en-Y choledochojejunostomy or duct-to-duct choledochocholedochostomy for biliary reconstruction provided better outcomes. No studies were done directly comparing these methods in the context of LT for CCA. One meta-analysis looking at LT in PSC patients found no significant differences in anastomotic bile leak rates, graft survival, PSC recurrence, and incidence of de novo CCA following transplantation.[148] Another study comparing both methods in all patients receiving right lobe living donor LT (LDLT) irrespective of indication found an increased incidence of stricture but a significantly lower incidence of leakage with duct-to-duct choledochocholedochostomy, with 74.5% of the strictures later managed with endoscopic treatment.[149] Overall consensus recommends duct-to-duct choledochocholedochostomy when feasible.

There is also debate on the use of LDLT versus deceased donor liver transplant (DDLT) on patient outcomes. Studies have shown that longer time elapsed between neoadjuvant therapy and LT leads to decreased incidence of recurrence. However, patients with prolonged intervals may develop radiation-induced fibrosis which could complicate the staging and operative process.[73] This may be in part solved with LDLT by removing waitlist for a deceased donor and aiding physicians in optimizing operative timings. Series have shown no significant differences in outcomes post-LT for PSC-associated pCCA in patients receiving LDLT versus DDLT.[150] LDLT for de novo pCCA showed trends toward increased recurrence and worse OS when compared with DDLT, though the differences were not statistically significant. Researchers are more focused toward understanding the underlying mechanism of disease progression after neoadjuvant treatment to better select patients and prevent posttransplant recurrences.[151] Another study confirmed these findings by suggesting that while LDLT may offer shorter waiting times, it is associated with higher risks of biliary complications compared with DDLT (34 vs. 17%, $p < 0.001$).[152] Using extended criteria donors of advanced age, steatosis or circulatory death may increase the number of organs available but is associated with higher 3-year graft failure rates of 27.3% for DCD livers versus 18.2% for donation after brainstem death.[95,153] A possible solution involves the use of normothermic machine perfusion to evaluate graft function preoperatively and help select grafts with optimal function thereby increasing the donor pool and improving patient outcomes.[154]

These considerations have led to consensus criteria for exception points for LT in the United States for pCCA. Transplant centers should have an approved written protocol outlining selection criteria, neoadjuvant therapy, and operative staging protocols. Patients should be deemed unresectable at multidisciplinary cancer conference, have cross-sectional imaging demonstrating a single lesion less than 3 cm in maximum size without extrahepatic spread, and have no lymph node or peritoneal involvement on operative staging after completion of neoadjuvant therapy.[155] There are no adopted LT consensus criteria for iCCA, but American Association for the Study of Liver Disease (AASLD) guidelines suggest that unresectable solitary tumors up to 5 cm with stability or response to neoadjuvant therapy can be considered for LT under institutional research protocols.[156]

Post-LT outcomes may also vary with transplant center expertise. A database study of all LT patients with CCA in the United States found low center volume to be associated with worse post-LT OS and graft survival, while a multicenter study of LT for pCCA found equivalent outcomes irrespective of center volume.[3,35,40,109]

Post-LT Follow-up

Currently, there are no standardized approaches to follow-up protocols for patients with CCA post-LT. The length of follow-up, need for scans, blood tests, or adjuvant chemotherapy is center specific with no clear evidence or high-quality studies performed. The recent BILCAP study provided the best evidence for the use of adjuvant capecitabine post-LR with median OS reported as 53 months in the capecitabine group versus 36 months in the observation group, and median RFS was 25.9 months in the capecitabine group and 17.4 months in the observation group with prespecified per-protocol analysis.[157] However, no evidence was provided for patients >70 years of age, and the trial was not able to meet its primary endpoint of improved OS in the intention-to-treat population. A follow-up publication of the same trial focusing on intention-to-treat analysis found median OS of 49.6 months in the capecitabine group compared with 36.1 months in the observation group, further supporting the previous study and suggesting that capecitabine can be used as adjuvant chemotherapy after surgery to improve OS in patients with resected CCA and should be considered the standard of care.[158] One meta-analysis showed statistically significant improvements in OS in patients receiving chemotherapy or chemoradiotherapy compared with those receiving radiotherapy alone (OR: 0.39, 0.61, and 0.98, respectively; $p = 0.02$), with the greatest benefit seen in patients with LN+ and R1 disease.[159] THE SWOG S0809 study found that chemotherapy and radiotherapy post-LR may increase OS and decrease rates of local recurrence citing a 2-year OS of

65%.[160] Jeong et al conducted a randomized controlled study comparing outcomes in patients with pCCA or dCCA divided into two groups, one receiving adjuvant gemcitabine and cisplatin (GemCis) and the other receiving adjuvant capecitabine, with no statistically significant differences in OS and DFS reported.[161] No studies were conducted looking at the effect of adjuvant capecitabine after LT. Therefore, more research is required to ascertain whether improved survival would be found in patients undergoing LT for CCA.

There is a shortage of studies in the literature focusing on optimal length of follow-up for patients with CCA. Some authors have based their clinical decisions on presenting symptoms, physical examinations, serum CEA and CA19–9, and CT scan results.[162–164] Rizzo et al published a 20-year retrospective study focused on this topic where biliary tract cancers (BTC) patients were followed up every 3 months during the first 2 years post-LR and every 6 months from the third to the fifth postoperative year. At each follow-up visit, the patients were examined, blood work was obtained (CEA and CA 19–9), and an abdominal/chest CT scan with IV contrast was performed.[164] Results suggest that intensive follow-up after surgical resection should be implemented to help identify disease relapse and allow for early treatment and prolonged survival in such cases.[164]

Few studies have been conducted investigating the use of NGS, molecular profiling, and minimal residual disease (MRD) on cancer surveillance and recurrence in CCA patients. A study by Lamarca et al showed a trend toward increased risk of recurrence in patients with pancreatic and biliary tract malignancies when circulating tumor DNA (ctDNA) was present after LR; however, the results were not statistically significant.[165] Another study attempted to stratify iCCA patients post-LR for risk of recurrence and OS using clinical variables and tumor sequencing.[166] Patients were stratified into low-risk (solitary nodules, LN−) and high-risk (multifocal and/or LN+) categories and further divided by the presence or absence of mutations in TP53, KRAS, and/or CDKN2A.[166] The presence of these mutations was independently associated with worse patient prognosis. More research is needed to determine the clinical utility of NGS and ctDNA analysis in the post-LT follow-up period to assess risk of recurrence and the presence of MRD.

Future Directions

Advances made in the past few years have improved patient outcomes after LT for CCA. Additional studies are needed to validate these findings and aid in the development of standardized protocols. Biomarkers have shown promise in potentially prognosticating patient survival post-LT and predicting response to neoadjuvant therapy, leading to better outcomes overall. Additional research into these biomarkers would allow for noninvasive prediction of post-LT outcomes, identification of aggressive tumor subtypes, and prioritization of LT in patients with a low risk of recurrence.[106] Additionally, these biomarkers could be used in the peri-LT period to tailor neoadjuvant and adjuvant targeted therapies to the individual patients' tumor genetic profile, further optimizing patient posttransplant survival and improving LT candidate selection criteria by increasing response to neoadjuvant therapy. Further basic and translational research in drug development is needed to create novel treatments for CCA tumors that are not responsive to current therapies.[106,167]

At present, LT in CCA literature consists mainly of retrospective case series, with heterogeneous patient populations with respect to disease stage, neoadjuvant therapies, LT donor type, and postoperative management. Ideally, more prospective multicenter observational studies or randomized controlled trials are needed for evaluation of the effectiveness of the currently employed protocols and whether any modifications could be favorable. However, establishing these trials remains challenging owing to the rarity of CCA, aggressiveness of the tumor subtypes, and difficulties in accurately diagnosing and screening patients, among other confounding factors that act as obstacles in the recruitment of suitable patients using standardized inclusion criteria to achieve a homogenous patient population. This could be aided, in part, through the development of international registries to increase the number of cases and providing a platform for the systematic collection of relevant variables. An ongoing trial since 2014, TRANSPHILL in France, aimed to recruit 54 patients with pCCA for randomization to either curative resection or LT, with primary outcomes of 3-year RFS and 5-year OS. Results are still pending and could represent a shift toward increased use of LT for curative intent in patients with pCCA.[95,168]

Advancements in neoadjuvant therapies such as SBRT and newer chemotherapy agents have shown promising results in reducing disease progression. SBRT has been shown to have lower toxicity than traditional external beam radiotherapy and therefore may become the preferable treatment pre-LT.[96] A recently reported combination of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) has shown improvement in survival when used as a second-line chemotherapy agent, with recent studies also advocating for the benefits of immunotherapy in CCA.[104,105] The BILCAP trial suggested capecitabine as an effective adjuvant therapy post-LR for CCA, citing improved patient OS rates; however, studies are needed in the transplant setting to see if similar results are found.[157,158]

The use of immunosuppression, however, is known to increase the risk of recurrence and development of malignancy. Therefore, there needs to be an optimized regimen established and a balance found between the risk of graft rejection and tumor recurrence after LT for CCA. A recent study conducted on iCCA and pCCA patients undergoing LT found that a reduced dose of immunosuppressives was associated with a significantly increased odds ratio of survival after recurrence (4.2, $p = 0.02$).[169]

Future research into novel biological agents and chemotherapy regimens will result in better selection of patients for LT, better personalization of neoadjuvant and adjuvant therapies, and improved patient outcomes.[170]

For the standardized establishment of LT as an effective curative treatment option for CCA, iCCA needs an established

indication for MELD exception, and both iCCA and pCCA literature require consistent reports of more than 50% 5-year survival rates for patients selected using inclusion criteria consistent with existing established LT indications. There will also be a need for increased supply of donor livers to match the increased demand that may, in part, be solved through improvements in technologies such as normothermic machine perfusion and changes to policies such as shifts toward opt-out organ donation.[69,106,171]

Conclusion

In conclusion, LT is a promising curative treatment for pCCA and iCCA, showing improved OS in most patients. However, more research is needed to establish standardized selection criteria to ensure fair access of a greater number of patients to LT. Much of the evidence on peri-LT care is borrowed from LR, locoregional, and systemic therapy literature. Additionally, the field is currently lacking consensus on post-LT follow-up protocols, specifically the length of follow-up time, type of imaging or blood tests used, and use of adjuvant therapy, an important step in the optimization of patient treatment. While neoadjuvant chemoradiotherapy has been associated with improved outcomes, more studies should be conducted looking at tailoring these treatments, perhaps with the use of NGS and molecular profiling, to each patient's tumor subtype. Overall, there is a lack of high-quality studies present in the literature most likely due to a heterogeneous patient population and a lack of consistency in variables collected that may in part be solved with the establishment of national and international databases aimed at reducing confounding factors and center bias. Owing to the current organ shortage, strict indications and contraindications to LT are necessary alongside existing efforts to improve the national organ supply.

Conflict of Interest
None declared.

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