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# Liver Transplantation for Cholangiocarcinoma and Mixed Hepatocellular-cholangiocarcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference.

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**Abstract**

Liver transplantation for cholangiocarcinoma has been an absolute contraindication worldwide due to poor results. However, in recent years and thanks to improvements of patient management and treatments of this cancer, this indication has been revisited. This consensus paper, approved by the International Liver Transplant Society (ILTS), aims to provide a collection of expert opinions, consensus and best practices surrounding liver transplantation for cholangiocarcinoma.

## INTRODUCTION

Cholangiocarcinoma (CCC) is a tumor of the bile duct epithelium with poor prognosis. CCC is classified according to location, with ~5-10% of lesions being intrahepatic (iCCA). The remaining 90% are extrahepatic, with the majority being perihilar (pCCA).[1] The incidence in the US is 1.2 in 100 000, while it is significantly higher in Eastern Europe and Asia and appears at least for iCCA to be increasing worldwide probably explained by better identification and classification.[2,3] Standard treatment for CCC is resection; advances in operative techniques, such as the use of vascular reconstruction and preoperative biliary drainage have led to improved outcomes.[4-8] pCCA-patients who are eligible for resection can reach 5-year overall survival (OS) rates of 25 to 40%. Unfortunately many patients present with unresectable disease.[4-9] For iCCA, the survival depends on the extent of disease at presentation. Those with metastatic disease do not benefit from resection, while those with single tumors that can be completely resected may have excellent long-term outcomes. In cases were the tumor is unresectable but confined to the liver, liver transplantation (LT) may be an option. This work is the result of an expert Consensus Conference in Transplant Oncology. The proposed recommendations are based on the GRADE system.

### Liver Transplantation for Perihilar Cholangiocarcinoma (pCCA)

Due to high recurrence and unacceptably low survival, LT was initially contra-indicated in patients with pCCA.[10-12] However, a protocol combining neoadjuvant radiotherapy followed by LT in patients with early-stage disease was developed. After several promising single-center reports, a large multicenter retrospective study of 216 patients with early stage, unresectable pCCA treated with neoadjuvant chemo-radiotherapy followed by LT from 12 US centers demonstrated 5-year disease-free survival (DFS) rates of 65%.[13-15] Subsequent reports have identified risk factors for

waitlist drop-out and disease recurrence, which has not only validated the current selection criteria but also identified those who could be selected for investigation of future potential therapies.[16-19] In order to qualify for MELD exceptions in the current US allocation system, a patient must have unresectable disease (either due to locally advanced tumor with extensive vascular and/or biliary invasion precluding complete resection or because of poor hepatic functional reserve due to underlying liver disease predisposing the patient to posthepatectomy liver failure) which is originating above the cystic duct and is <3 cm in radial diameter, with no evidence of intrahepatic or extrahepatic metastases, and must be treated with neoadjuvant therapy at a center with an approved protocol. Even with a MELD score exception, given the critical organ shortage, the waiting time is still very long. Living donor liver transplantation (LDLT) provides the opportunity for more timely access to transplantation thus reducing waitlist morbidity and mortality.

Technical modifications for deceased donor LT include replacing the native hepatic artery with an arterial conduit from the aorta using decease donor iliac artery interposition graft as injury from radiation is progressive and thus, the artery is more damaged over time. In LDLT, avoidance of hilar dissection ~~and so of~~to prevent tumor spilling usually results in a short recipient portal vein requiring a vein graft to restore allograft venous inflow, though typically the native artery is still suitable for use given the reduced interval from neoadjuvant therapy and transplant. However, the team should also be prepared for an arterial jump-graft from the abdominal aorta to the hepatic artery of the graft liver (autologous venous conduit either from the great saphenous vein or superficial femoral vein is a potential graft) in this setting, which is the standard technique for arterial reconstruction established by Mayo Clinic to overcome delayed radiation injury in the native hepatic artery in deceased donor LT cases (because of the waiting time on the list).

The majority of the published experience has been using a protocol of external beam radiotherapy plus brachytherapy with a continuous infusion of 5-~~FU~~fluorouracil as a radiosensitizing agent, followed by oral capecitabine until transplant. There are reports using stereotactic beam radiotherapy, and gemcitabine plus cisplatin,[20] and there are no comparative studies between the different regimens.

Diagnosis of pCCA is challenging due to the location and desmoplastic nature of the tumor. Current diagnostic criteria include a dominant stricture and 1 or more of the following: positive cytology by endoscopic brushing or biopsy demonstrating pCCA, ~~FISH~~ fluorescence in situ hybridization polysomy or elevated ~~CA~~carbohydrate antigen 19-9 > 100 U/mL in the absence of cholangitis.[1,2]

Controversies have centered on the challenge of establishing the diagnosis, whether the neo-adjuvant therapy is actually needed, and most recently whether combined neo-adjuvant chemoradiotherapy should also be offered to patients with resectable disease. Concern regarding establishing the diagnosis was addressed by a study from Mayo Clinic which examined those with and without a tissue diagnosis prior to initiation of neoadjuvant therapy and found no difference in the rates of residual malignancy in the explanted liver, and no difference in the risk of recurrence disease following transplantation.[21] The question of whether the therapy is actually needed has been raised by a study of 249 patients in the European Liver Transplant Registry transplanted during 1990-2010. They selected 28 patients who met the selection criteria currently used by UNOS except they did not receive neoadjuvant therapy.[22] This group had a 5-year OS of 59% and thus the authors argue that selection alone is the essential component. However, concerns about the impact of selection bias have limited the interpretation of these findings, and there are multiple other reports which note high recurrence rates and poor survival in patients transplanted with

incidental, early pCCA. A recent multicenter retrospective study found patients with unresectable pCCA undergoing combined neoadjuvant therapy and LT had superior 5-year OS (64% vs 18%; P < 0.001), versus those undergoing resection who otherwise met LT criteria. Results remained significant in an intention-to-treat analysis, even after accounting for tumor size, nodal status, and PSC (P=0.049).[23] The critical shortage of available liver allografts plus the need for life-long immunosuppression are important considerations that must also be considered, and there is an ongoing prospective randomized trial in France (NCT02232932), which has the potential to answer this question. This is a multicenter study comparing an interventional group with LT preceded by neoadjuvant chemoradiation therapy and a control group undergoing liver and extrahepatic bile duct resection for "resectable" pCCA, with overall survival at 5 years being the primary endpoint.

**Recommendations:**

1. **LT for pCCA can be considered in patients with unresectable disease after neoadjuvant chemo-radiation in centers with a specific protocol (Moderate level of evidence, conditional recommendation).**
2. **Transplant teams should prepare for arterial and venous jump grafts in the setting of LT for pCCA (Moderate level of evidence, strong recommendation).**
3. **Diagnostic criteria for pCCA in the setting of LT include a dominant stricture of the perihilar bile duct and 1 or more of the following: positive cytology by endoscopic brushing or biopsy demonstrating pCCA, FISH polysomy or elevated CA 19-9 > 100 in the absence of cholangitis (Moderate level of evidence, conditional recommendation).**

**Liver Transplantation for Intrahepatic Cholangiocarcinoma (iCCA)**

iCCA can arise both in cirrhotic and noncirrhotic patients. Typically, Typically, iCCA in cirrhotic patients are found through surveillance ultrasounds. When the detected nodule does not demonstrate typical features of hepatocellular carcinoma (arterial enhancement with washout during the portal phase on dynamic imaging) a biopsy is performed and the diagnosis of iCCA is obtained. Meanwhile, iCCA in noncirrhotic livers with large (≥5–7 cm), mass-forming tumors or multicentric tumors are associated with decreased prognoses.[24]

Diagnosis of iCCA should be confirmed with a tumor biopsy after cross-sectional imaging has been performed. Given the new discoveries in molecular pathways (see molecular profiling section) it is suggested to perform genomic profiling through whole genome sequencing.

The treatment of choice of iCCA is liver resection (LR). Unfortunately, a majority of patients are unresectable at the time of diagnosis. For some of these patients, LT may be an option when the tumor is confined to the liver.

*LT for iCCA in cirrhotics*

Since the early 2000's, several publications have shown that LT might be an option for patients with unresectable iCCA. Sapisochin et al. assessed a cohort of 29 patients who underwent LT for HCC and found to have iCCA in the explant.[25] Their 5-year OS was 45%.[25] Patients with very-early iCCA (defined as single tumor ≤2 cm) had lower 5-year risk of recurrence (18% vs 65%,p=0.01) and greater 5-year OS (65% vs 45%,p=0.02) than those with multifocal and larger tumors. This observed benefit of LT for patients with early stages of iCCA was confirmed in an international collaborative study containing 48 patients. Their 5-year cumulative risk of recurrence was 18% (very-early iCCA) and 61% (more advanced disease)(p=0.01); the 5-year OS were 65% and 45%, respectively(p=0.02).[26] The application of LT for cirrhotic patients with unresectable

(due to impaired liver function) very-early iCCA still requires validation by a prospective study. This study is currently accruing (NCT02878473) and results are expected within 5 years.[27] Until further investigation, iCCA should remain a contraindication for LT out of clinical trials.

*LT for iCCA in noncirrhotics*

In the noncirrhotic population, situations where iCCA are deemed unresectable and LT is considered include: local enhancement of the vital vessels (hepatic artery, portal vein, and hepatic vein) and/or extensive bilateral infiltration of the bile duct, and multifocal, bilobar disease in which curative resection cannot be achieved even by aggressive approaches, such as combined vascular resection and extended hepatectomy, provided that there is no lymph node involvement and extrahepatic disease. Lunsford et al. have published a prospective case-series of 21 patients with unresectable iCCA who were assessed for LT.[28] This series had a well-defined neoadjuvant protocol. Inclusion criteria were solitary tumor >2 cm or multifocal disease confined to the liver without evidence of macrovascular or lymph node involvement and sustained response to neoadjuvant systemic chemotherapy. Among the initial 21 patients, 12 were listed and 6 underwent LT. After a median follow-up of 36 months, 3 patients recurred. However, patient survival was 80% at 3 years.[28] This approach of neoadjuvant chemotherapy with or without radiotherapy could be useful as downstaging therapy in patients with unresectable iCCA or as a selection criteria for LT.[17,28-30] In a study from Rayar et al. patients with unresectable iCCA were treated with Y90 combined with systemic chemotherapy. In this study, 8/45 (18%) patients were successfully converted to resection.[31] The use of neoadjuvant therapies aiming to convert unresectable patients might be preferable to LT under the light of organ scarcity. However, even though some patients could be successfully downstaged to resection, it would be fair to offer LT for patients who

remained unresectable in the absence of disease progression during the neoadjuvant treatment. LT for iCCA should only be offered under clinical trials at this stage.

**Recommendations:**

1. **Patients with very-early iCCA (single tumor ≤ 2cm) in a cirrhotic liver may benefit from upfront LT, whereas those with advanced iCCA deemed unresectable in a noncirrhotic liver may become LT candidates if the disease remains stable after neoadjuvant therapy. (Moderate level of evidence, conditional recommendation).**
2. **When LT is planned for a cirrhotic patient with a nodule demonstrating atypical radiological features of HCC on cross-sectional imaging and iCCA is suspected, the diagnosis can be confirmed with a tumor biopsy (Moderate level of evidence, strong recommendation). Given the new discoveries in molecular pathways (see molecular profiling section) it is suggested to perform genomic profiling through whole genome sequencing for future basic and translational studies (Low level of evidence, conditional recommendation).**
3. **The treatment of choice of iCCA is liver resection (LR) (High level of evidence, strong recommendation) and LT is reserved for unresectable cases and should only be performed under strict clinical protocols or trials (Moderate level of evidence, strong recommendation)**

**Molecular Profiling of Cholangiocarcinoma**

Until recently, there have been very few clinical advances in the systemic management of patients with CCA and gemcitabine-based chemotherapy remains the standard of care for advanced disease over the past decade.[32] This paradigm is expected to change in the near future with the advent of molecular profiling. Molecular profiling for somatic mutations is now the standard of care for hematologic malignancies and increasingly being utilized for the management of solid tumors, like nonsmall cell lung cancer, melanoma and breast cancer. The goal of molecular profiling is to identify novel biomarkers and targets, which can be explored for their therapeutic value using novel inhibitors. Furthermore, molecular profiling also facilitates disease stratification into subgroups with prognostic implications. Whole-exome sequencing studies have vastly improved our understanding of biliary cancers and their molecular heterogeneity.[33-35] Next-generation sequencing (NGS) technologies, which can sequence a panel of 'actionable' mutations rapidly at a reasonable cost have revolutionized the field and can potentially change the treatment paradigm of several cancers including CCA.[36] Unfortunately, NGS is feasible in only a minority of patients (particularly iCCA) who undergo needle biopsies or surgical resection.[37] Liquid biopsies for circulating tumor DNA (ctDNA) and on-treatment biopsies to assess dynamic alterations in somatic mutations are also likely to be transformative in this field. Mutation profiling has highlighted the genomic differences between intrahepatic, extrahepatic CCA and gallbladder cancer.[36,38] Intrahepatic CCA has a relatively large number of actionable mutations, perhaps more so than any other gastrointestinal cancer.[39,40] The mutational spectrum of iCCA also differs according to geographic location and ethnicity. There is a higher incidence of chromatin modulating gene mutations in Western patients as compared with Asian patients with liver-fluke associated cholangiocarcinoma.[34,35] *KRAS* and *p53* mutations may be associated with an

aggressive disease prognosis while *FGFR* mutations may signify a relatively indolent disease course of iCCA.[40,41] *FGFR, IDH* and *BRAF* mutations have promising agents in clinical trials at this time.[42-44] An estimated 10-15% of CCA have DNA repair mutations and 1% have microsatellite instability (MSI).[45,46] These patients are potential candidates for clinical trials with immune therapies with checkpoint inhibitors. The incorporation of targeted therapy and NGS in the liver transplant setting is at its infancy at this time. However, the promise of targeted therapies in this setting can be fulfilled with well-designed, prospective, multicenter clinical trials. Recommendation is made to perform tumor biopsy for CCA sequencing in cases of LT for CCA.

**Liver Transplantation for Mixed Hepato-Cholangiocellular Cancer**

Hepatic progenitor cells (HPC) can give rise to both hepatocytes and cholangiocytes, so it is not surprising that biphenotypic cancers may develop. Several types of mixed tumors have been described, the most frequent being the mixed hepatocellular cholangiocarcinoma (HCC-CC).[47,48] Allen identified in 1949 three types of mixed tumors: separate HCC and iCCA within the liver (type A); adjacent, but intermingled, tumors (type B) and finally tumors harboring both tumor types (type C). Goodman later on simplified this classification in 1985 by grouping the 2 first types. The 'real' HCC-CC type represents about two-thirds of all mixed tumors.[49,50] The reported incidence (0.6 to 14 % depending on the methodology used) is an underestimation as correct tumor type identification can indeed only be made on liver specimen.[51] Better knowledge of hepatic oncogenesis, imaging pathology (including advanced immunohistochemistry staining), molecular and genetic screening all led to a more frequent diagnosis of HCC-CC.[52,53] These tumors carry a poor prognosis, especially in case of a dominant CCC component.[54,55] Due to their low prevalence, solid data about their natural evolution, diagnostic and prognostic criteria, clinicopathologic presentation, imaging features and outcome are still lacking.

Diagnosis of HCC-CC tumors can be very difficult. Imaging of HCC-CC is challenging as no pathognomonic patterns have yet been described. The 'typical' dynamic contrast-enhanced CT imaging reveals an early peripheral or diffuse progressive enhancement throughout the arterial and portal venous phases, followed in the portal and venous phases by a *peripheral* wash out and central enhancement.[47,56] Magnetic resonance imaging shows during the delayed phase the absence of contrast wash out after a progressive arterial uptake. In half of such patients, these findings are in agreement with the pathologic diagnosis of HCC-CC.[47,56-58] In case of atypical 'HCC-imaging' a biopsy is warranted in order to refine the diagnosis. Unfortunately, biopsy not only lacks sensitivity but can even be misleading due to the presence of the different cellular components. Moreover in the rare occasion of diagnostic confirmation, pathology does not allow reliable grading.[59,60] Recent molecular analysis demonstrated that stem-cell type tumors within mixed HCC-CC characterized by spalt-like transcription factor 4 positivity, progenitor-like signatures, etc. were associated with poor outcomes and the investigators proposed redefinition of the current pathological classification.[61]

Tumor markers also lack specificity in HCC-CC. Elevation of AFP and CA 19-9 may reflect the proportion of the 2 components of the mixed tumor.[60] If the HCC component dominates, AFP level is higher; if the CCC component dominates CA19.9 level is higher. CA19.9 is elevated in a fair proportion of the mixed tumor patients.[58-60,62]

The analysis of the recent literature does not allow to make firm conclusions about the best therapeutic approach. The reports which contain small numbers of patients, are heterogeneous and retrospective and frequently relate to different types of mixed tumors. Despite these shortcomings, all series confirm that outcomes of LR and LT for mixed tumors are worse than those obtained for HCC and CCC.[56,57,58-60,63-67,68-70] The survival benefit of LT for HCC-CC has yet to be

defined.[59,66,69] Grossly, 3-years OS after partial LR reaches 10 to 40% and DFS 10 to 25%; OS and DFS rates after LT range widely from 16 to 66 % and 33 to 93% respectively.

The reported HCC-CC LT experience concerns only around 200 recipients; the largest series containing 25 and the largest registry series 220 patients.[63,66] Based on these limited experiences some prognostic factors could be identified : tumor diameter >2 cm, lymph node invasion (present in 10 to 20% of patients), Milan-Out criteria, poor differentiation, multinodularity, presence of microvascular invasion, Goodman II type and high(er) level of CA19.9 (>37mg/ml) . All reports confirm that mixed tumors have a more aggressive behavior than HCC as reflected by a less favorable outcome and a higher, and also more rapid, recurrence rate.[59,66] The clinical behavior seems to be linked to the dominant ~~tumor~~CC component.[71] The reported results clearly indicate that multimodal treatment combining radical surgery and neo- as well as adjuvant therapies will be needed ~~to progress~~to further improve outcomes.[72-74]

In conclusion it can be said that there is still no consensus about the actual role of LT in the therapeutic algorithm of HCC-CC tumors. Improved selection criteria and multimodal treatment will be key factors to progress in this new field of transplant oncology, the application of transplantation medicine and surgical oncology to the treatment of cancer patients. Prognostic factors need to be identified in order to allow a better patient selection and therefore a better outcome after LT.

**Recommendations:**

1. **In case of atypical 'HCC-imaging' a biopsy is warranted in order to refine the diagnosis (and rule out pure HCC) and discuss indication for LT (Moderate evidence, strong recommendation).**

2. **HCC-CC is currently not an established indication for LT (Low evidence, conditional recommendation).**

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