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ABOUT COVER

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Expanding indications for liver transplantation in the era of liver transplant oncology

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Abstract

Despite numerous advances and emerging data, liver transplantation in the setting of gastrointestinal malignancies remains controversial outside of certain accepted indications. In an era of persistent organ shortage and increasing organ demand, allocation of liver grafts must be considered carefully. While hepatocellular carcinoma and hilar cholangiocarcinoma have become accepted indications for transplantation, tumor size and standardized multi-disciplinary treatment protocols are necessary to ensure optimal patient outcomes. As more studies seeking to expand the oncologic indications for liver transplantation are emerging, it is becoming increasingly clear that tumor biology and response to therapy are key factors for optimal oncologic outcomes. In addition, time from diagnosis to transplantation appears to correlate with survival, as stable disease over time portends better outcomes post-operatively. Identifying aggressive disease pre-transplant remains difficult with current imaging and tissue sampling techniques. While tumor size and stage are important prognostic predictors for most malignancies, patient and tumor selection protocols are necessary. As the fields of medical and surgical oncology continue to evolve, it is clear that a protocolized interdisciplinary treatment approach is necessary for combatting any cancer effectively. Disease stability over time and response to neoadjuvant therapy may be the best predictors for successful patient outcomes and can be easily incorporated in our treatment paradigms. Current data evaluating liver transplantation for expanded oncologic indications such as: expanded criteria hepatocellular carcinoma, intrahepatic cholangiocarcinoma, mixed tumors, and

liver limited metastatic colorectal carcinomas, incorporate multi-modal therapies and evaluation of tumor treatment response. While further investigation is necessary, initial results suggest there is an expanded role for transplant surgery in malignancy in a new era of liver transplant oncology.

Key Words: Liver transplantation; Transplant oncology; Intrahepatic cholangiocarcinoma; Hepatocellular carcinoma; Colorectal metastases; Mixed hepatocholangiocarcinoma

Core Tip: Liver transplantation in the setting of malignancy is currently limited to patients with hepatocellular carcinoma and hilar cholangiocarcinoma who meet specific criteria. While more expanded indications remain controversial, data that a wider spectrum of gastrointestinal malignancies may be amenable to liver transplant is emerging. Pre-transplant tumor characteristics and peri-transplant multi-modal treatment protocols can be combined to successfully refine patient selection and dramatically improve patient outcomes. Here we review the current literature for liver transplantation in the setting of select hepatic and nonhepatocellular liver-limited gastrointestinal malignancies.

INTRODUCTION

With the success of liver transplant as a cure for end-stage-liver disease, demand continues to exceed the supply of available donor organs. While cancer is considered a contraindication to transplant for most organs, liver transplant as a curative strategy in the setting of malignancy is evolving. Hepatocellular carcinoma (HCC) has become a leading indications for liver transplant, representing the primary diagnosis for 10.5% of waitlisted candidates and 20.5% for transplanted recipients in 2018 in the United States alone[1]. Adoption of liver transplantation for additional oncologic indications has been slow due to poor early outcomes. The initial series evaluating liver transplant in the setting of biliary tract malignancies, as well as liver-limited metastatic disease, showed poor survival (20%-30% at five years) and high recurrence rates (greater than 50% with most occurring within two years of transplant)[2-6]. In 2002, the success of liver transplant for early-stage hilar cholangiocarcinoma (hCCA) at the Mayo clinic[7] was, perhaps, the first step in the reevaluation of liver transplant as an indication for other types of primary hepatobiliary cancers. Subsequently, refinement in patient and tumor selection criteria has demonstrated potential efficacy for certain liver-limited metastatic disease in which the primary tumor has been resected. The United Network of Organ Sharing (UNOS) and Organ Procurement and Transplantation Network currently grant Model for End-Stage Liver Disease (MELD) exception points to adult patients with HCC and hCCA who meet specific size criteria in the absence of metastatic disease. In addition, MELD exception is considered by the National Liver Review Board for unresectable liver-limited neuroendocrine tumors of gastro-entero-pancreatic origin and hepatic epithelioid hemangioendotheliomas[8,9].

Expanding indications for liver transplant for gastrointestinal malignancies, however, still remains controversial. In light of donor organ shortage relative to demand, critics raise concerns regarding resource allocation in the setting of possible cancer recurrence and related death[10]. The requirement for immunosuppression in the post-transplant period may result in decreased immunologic tumor surveillance compounding the risk for cancer recurrence in comparison to liver resection[11]. In addition, cancer is likely a systemic rather than a local disease, and current diagnostic tests lack sensitivity to detect microscopic seeding that may later form metastases. Finally, determination of aggressive tumor behavior based on biopsies is often

inaccurate due to sampling error limiting pre-transplant risk stratification. Despite these criticisms, emerging published data support the concept that a wider spectrum of malignant disease may be amenable to liver transplant. As experience with HCC and hCCA has demonstrated, pre-transplant tumor characteristics and multi-modal treatment protocols can be combined to successfully refine patient selection and dramatically improve patient outcomes. Since early experience with transplant for non-HCC liver cancers was often non-discriminatory in its selection criteria, reevaluation of expanded oncologic indications for liver transplantation is actively being debated, ushering forth a new era of liver transplant oncology[12,13]. While surgical resection remains the gold standard therapy, emerging data suggest that there may be a role for liver transplant in select patients with unresectable, liver-limited malignancy other than HCC. Here we review the current literature for liver transplantation in the setting of select hepatic and nonhepatocellular liver-limited malignancies.

HCC: BEYOND UNIVERSITY OF CALIFORNIA SAN FRANCISCO CRITERIA

HCC is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide[14,15]. Hepatic resection is the preferred treatment modality for patients with small (≤ 5 cm), focal tumors without background cirrhosis or in the setting of Child-Pugh Class A chronic liver disease without clinically significant portal hypertension[16]. While survival outcomes with resection for these lesions are acceptable, risk of recurrence in the remnant liver remains high, with some reporting recurrence rates as high as 50%-70%, despite strict patient selection[17,18]. Median survival for those with unresectable disease managed with supportive therapy is 6.8 mo, with 1-year survival of 32%[19]. Liver transplantation offers the possibility of curative resection with improved recurrence-free survival (RFS)[20], and has the added benefit of treating underlying liver disease, thereby decreasing the risk of development of sequential de novo tumors. Early data evaluating liver transplant for HCC reported low survival and high recurrence due to unstructured patient and tumor selection[21]. The initial report for successful liver transplantation in patients with small, unresectable HCCs in the setting of cirrhosis was published in 1996, introducing the now widely-accepted Milan criteria (Milan criteria, Table 1)[22]. Mazzaferro *et al*[22] reported four-year post-transplant actuarial survival of 75% and RFS of 83%. In addition, survival and recurrence were similar between those who received pre-transplant locoregional therapy (LRT) and those who did not, suggesting patient selection by tumor size and tumor number criteria was a critical factor affecting survival after transplantation[22].

Since then, HCC within Milan criteria has become a standard indication for liver transplant, and accounts for approximately 20%-40% of all liver transplants performed worldwide[23]. Patients within Milan criteria who undergo transplantation have an overall quoted 4-year RFS of 92% and a 4-year overall survival (OS) of 85%[22]. Despite this success, the Milan criteria are often criticized due to stringent tumor size restrictions. Subsequent data from the University of California, San Francisco (USCF), evaluating 70 patients with HCC and cirrhosis undergoing liver transplant over 12 years, reported 1- and 5-year survival of 90% and 75.2%, respectively, for patients with larger lesions beyond Milan: Solitary tumors ≤ 6.5 cm, or ≤ 3 nodules with the largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm (UCSF criteria, Table 1). These results were nearly equivalent to previously reported outcomes for tumors within Milan criteria[24]. A more recent analysis of the UNOS database of 1972 liver transplants performed in the United States, of which 59 were outside of Milan but within UCSF criteria, similarly reported comparable 4-year OS of 51% *vs* 72% for patients within UCSF *vs* Milan criteria. On multivariate analysis, neither criteria offered a comparative survival benefit. HCC downstaging *via* LRT prior to LT was more common for those within UCSF criteria (61% *vs* 35%)[25]. These and follow-up data established the expanded downstaging UCSF criteria for liver transplant for the management of HCC, in addition to the Milan criteria, with both achieving post-transplant OS similar to those for non-malignant indications.

As we gain more longitudinal experience with patients undergoing liver transplant for HCC, more data are emerging showing promising results for patients with multiple and larger tumors[26], prompting further debate over optimized patient selection criteria. Data from Japan have described expanded criteria incorporating tumor markers for patients with up to 10 tumors at the time of transplant (Kyoto criteria, Table 1)[27]. In a validation study of 198 patients, 118 within Milan, 80 within

Table 1 Liver transplant selection criteria for hepatocellular carcinoma

Reference	Criteria	Definition	OS	Recurrence
Mazzaferro *et al* [22]	Milan criteria	Solitary tumor ≤ 5 cm or total ≤ 3 tumors and each tumor ≤ 3 cm	4-yr 75%	4-yr RFS 83%
Yao *et al*[24]	UCSF criteria	Solitary tumor ≤ 6.5 cm or total ≤ 3 nodules with the largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm	5-yr 75.2%	5-yr RR: 17%
Takada *et al*[27]	Kyoto criteria	Tumor number ≤ 10 and maximal diameter of each tumor ≤ 5 cm and serum des-gamma-carboxy prothrombin levels ≤ 400 mAU/mL	5-yr 87%	5-yr RR: 5%
Mazzaferro *et al* [26]	Up-to-Seven criteria	Sum of number of tumors ≤ 7 and maximal size of the largest tumor ≤ 7cm	5-yr 71.2%	5-yr RR: 9.1%

OS: Overall survival; RFS: Recurrence free survival; NR: Not reported; RR: Risk ratio.

UCSF, and 147 within Kyoto criteria, Kaido *et al*[28] reported 5-year OS of 82% within Kyoto criteria compared to 65% for those within Milan and USCF criteria. In subgroup analysis for those who exceeded Milan, but met Kyoto criteria, 5-year OS was 88%, and was similar to those who were within both Milan and Kyoto criteria. Furthermore, HCC recurrence did not differ significantly between these two groups[28]. These data highlight expanded indications for larger tumors are possible, without compromising outcome and cancer recurrence. Interestingly, 73% of patients in the Kyoto study received locoregional therapies with curative intent pre-transplant, but OS and RFS did not differ with pre-treatment. However, when evaluating tumor-specific factors, it was noted that microvascular invasion and poorly-differentiated disease (*i.e.* more aggressive tumors) were more common for patients outside of Kyoto criteria, likely contributing to the survival/recurrence risks reported[28]. It is important to note that while these data support expanded indications for patient selection for transplantation in the setting of HCC, the results from the Kyoto experience pertain to living donor transplantation, *vs* the more common deceased donor liver transplantation in western countries. Therefore, global application may be limited.

The Up-to-Seven criteria, first described by the same group who established the Milan criteria, allow for sum of tumor size (in cm) and tumor number of up to seven and have been studied in both cadaveric and living donor liver transplantation for HCC (Up-to-Seven criteria, Table 1)[26,29]. In the initial multi-center international series, evaluating 1556 patients, Mazzaferro *et al*[22] evaluated patients within (*n* = 444) and outside of Milan criteria (*n* = 1112). RFS and OS at five and 10-years was significantly better within Milan criteria to those beyond Milan (5-year: 94.5% *vs* 64.1% RFS, 73.3% *vs* 53.6% OS; 10-year: 94.5% *vs* 58.1% RFS, 69.6% *vs* 38.7% OS, respectively). Via subgroup analysis, utilizing a cut-off 5-year survival of 70% in combination with absence of microvascular invasion, the authors identified 283 patients who fell within the now final Up-to-Seven criteria. Five-year OS in this group was 71.2%, which was similar to Milan criteria. Of note, tumors outside of Milan criteria were more likely to display aggressive tumor characteristics, such as poor differentiation and vascular invasion. On analysis, the presence of microvascular invasion doubled the hazard of death and was the strongest covariate predictor of patient survival[26]. In a subsequent attempt to better characterize predictors of HCC-specific survival post-liver transplantation, the group from Milan developed the Metroticket Model, a mathematical predictive model incorporating tumor characteristics, treatments, and response to treatments pre-operatively, in addition to explant pathology and clinical outcomes post-operatively[30]. Neoadjuvant treatment response correlated significantly with tumor biologic characteristics, supporting current patient selection criteria. The c-statistic for predicting cumulative incidence of HCC-related death of the model is 0.7, underscoring that tumor biology significantly affects survival and recurrence risk[30]. As a result of this work[26,30], a web-based medical calculator (the Metroticket Project) is available to calculate 5-year predicted HCC-specific survival after liver transplantation. The tool incorporates pre-operative tumor characteristics (size of largest vital tumor and number of vital nodules) and alpha-fetoprotein levels, as well as post-operative pathology, to generate survival outcomes[31].

In addition to identifying and selecting for tumor biology, a declining trend in HCC recurrence and patient survival with liver transplantation may be attributed to more aggressive use of LRT. Data has emerged demonstrating the benefit of these treatments as pre-transplant and bridging therapies[32,33]. However, data on LRT effect on post-transplant HCC recurrence and patient survival is limited. Over 50% of

patients in the initial studies establishing the Milan, UCSF, Up-to-Seven, and Kyoto criteria received LRT pre-transplant, but effects on survival and HCC recurrence were ambiguous[22,24,26,28]. More recently, the benefit of aggressive LRT has been demonstrated in a large retrospective review of patients undergoing transplant for HCC from the University of California, Los Angeles (UCLA)[34]. Of the 501 patients evaluated, 80% were within Milan criteria, 13% within UCSF, and 7% beyond. Over 50% of patients underwent at least one pre-transplant session of LRT. Those demonstrating a complete pathologic response (cPR) to pre-transplant therapy were more likely to fall within Milan and UCSF criteria. Overall, disease-specific survival and RFS was significantly higher with cPR[34].

Finally, both Washington University in St. Louis and Houston Methodist Hospital (HMH) have demonstrated equivalent survival for patients with HCC beyond Milan and UCSF criteria compared to patients within Milan, by incorporating aggressive LRT and tumor downstaging protocols[35-37]. Rather than size or tumor number, these centers base patient eligibility for transplant on tumor response to LRT (as evidenced by residual tumor burden or progressive disease on imaging)[37] or tumor stability for at least 6-9 mo prior to transplant[35]. Evaluating 210 HCC patients beyond Milan criteria over a period of 12 years, the group from Washington University reported successful down-staging in 63 patients (30%) who proceeded to transplant. Overall, disease-specific and RFS for down-staged recipients was similar to those meeting Milan and UCSF criteria; HCC recurrence was also similar between groups (8.9% in down-staged *vs* 5.6% initially within UCSF and 9.2% initially within Milan). Of note, longer interval between last LRT and transplantation (> three months) was independently associated with improved RFS, indicating that a stable treatment response over time is a key predictor of disease control[37]. In the HMH single center experience, Victor *et al*[35] reported transplant outcomes for 220 patients, 59 of which were beyond both Milan and UCSF criteria. Patient survival and RFS at 1-, 3-, and 5-years was similar between groups. When assessed by explant pathology, tumors outside of UCSF criteria were more likely to exhibit poor differentiation and microvascular invasion, both of which were associated with increased risk of recurrence. Disease stability while on the wait list, especially for patients waiting longer than nine months, appeared to equalize recurrence risk[35].

Expanded indications for liver transplantation for HCC appear possible for a select group of patients with favorable tumor biology, disease stability over time, and complete response to pre-transplant therapy. In the current era of advanced genomics and sequencing, it is becoming increasingly clear that tumor biology is key in determining aggressive malignant behavior and recurrence risk[38]. Despite the aforementioned refined selection criteria, risk of recurrence for HCC after liver transplant remains a concern. To mitigate this, the group from UCLA has developed a nomogram which includes factors most significantly associated with HCC recurrence risk: tumor biology (such as grade and differentiation), tumor size, tumor marker levels, and neutrophil-to-lymphocyte ratio. Taking these parameters into account may help predict post-operative recurrence risk and further improve patient selection[39]. For those patients that do recur, aggressive post-transplant surgical and LRT treatments appear to provide additional long-term survival benefit[40]. In addition, incorporating aggressive LRT pre-transplant for down-staging is an effective technique, as evidenced by the recent multi-center validation of the UCLA study, which achieves equalization of OS and RFS for successfully down-staged HCC patients undergoing transplant[36]. These outcomes justify continued evaluation of expansion of liver transplant criteria for select patients with HCC.

LIVER TRANSPLANTATION FOR INTRAHEPATIC CHOLANGIOCARCINOMA

Intrahepatic cholangiocarcinoma (iCCA) originates from the intrahepatic biliary epithelium and represents 10%-20% of all CCA tumors[41]. While incidence of iCCA has increased over the last decade[42], long-term survival remains poor at 10%-40% among patients undergoing any therapy. Small or solitary nodules, well-differentiated tumors, and tumors without lympho-vascular invasion portend the best out-comes [41-43]. Although hCCA has become an accepted indication for liver transplan-tation over the last decade, iCCA remains a contraindication due to previously reported poor survival (20%-30%)[44] and high recurrence rates (> 50%)[45], resulting in transplant outcomes well below those published for standard indications[46]. Initial studies evaluating liver transplant in iCCA demonstrated 5-year OS and RFS of 18%-25%

[2,3,47], leaving surgical resection as the mainstay of treatment. However, given the aggressive and invasive nature of the disease, surgical options are often limited by tumor location, size, multifocality, or extension outside of the liver. For unresectable intrahepatic tumors, medical therapy offers the next best option for disease control. Current gold standard treatment with gemcitabine and cisplatin results in an OS of 18.9 mo and progression-free survival (PFS) of 11.1 mo[48]. LRT is also utilized as definitive or adjunctive therapy and has shown benefit in controlling disease recurrence[42,49]. Despite these advances, OS remains poor. Since liver transplantation can offer an R0 oncologic resection with the widest possible margins, neoadjuvant/adjuvant therapies are undergoing renewed investigation as combination or down-staging treatments in order to optimize patient selection[50].

As iCCA is not an accepted indication for transplant, the majority of outcomes data has come from retrospective analyses of incidentally discovered tumors on explants. In 2014 Sapisochin *et al*[51] published one of the first large, multi-center retrospective analyses comparing outcomes for liver transplant in patients with iCCA (*n* = 27) or hepatocholangiocarcinoma (HCC-CCA) (*n* = 15), which were incidentally discovered or misdiagnosed as HCC, compared to matched patients with HCC (*n* = 84). Notably, unlike prior studies, outcomes were assessed based on tumor type, allowing direct comparison between patients with iCCA to those with HCC. Patients receiving pre-transplant chemotherapy were excluded, but the study included patients receiving LRT. Despite a high risk of recurrence and mortality for large, multinodular iCCAs compared to HCC controls, patients with solitary nodules ≤ 2 cm in diameter demonstrated a 5-year OS of 62% *vs* 80% for matched HCC controls. No significant difference was observed for tumor recurrence[51]. A larger multinational cohort similarly demonstrated statistically significant improvements in tumor recurrence, cumulative recurrence risks, and 5-year OS of 65% for "very early" iCCA (single lesions ≤ 2 cm)[52]. More recently, a retrospective analysis from the Mayo Clinic, Jacksonville, compared 44 patients with explant diagnosis of iCCA or HCC-CCA, to 574 patients with HCC within Milan criteria. Overall iCCA recurrence and survival rates were inferior compared to HCC; however, when stratified by pathologic category, those with early iCCA or HCC-CCA (lesions ≤ 2 cm without vascular invasion) demonstrated 1- and 5-year survival of 63.6% and 63.6% *vs* 90% and 70.3% for those with HCC within Milan criteria. While there was a trend for lower OS, results did not reach significance. Disease recurrence rates remained significantly higher for cholangiocarcinoma. Vascular invasion and incomplete response to pre-transplant LRT were independently associated with recurrence risk[53]. These data have led many to question whether liver transplantation is appropriate to consider for cirrhotic patients with very early (≤ 2 cm) iCCA.

While "very early" iCCA may have improved outcomes, one concern is that identification of such small lesions pre-transplant is difficult. In an attempt to evaluate this cut-off further, three French hepatobiliary centers retrospectively compared liver resection *vs* transplant for larger incidental or initially misdiagnosed iCCA or HCC-CCA. The authors ultimately compared 49 patients who underwent transplant to 29 patients treated with resection for disease control. Incidental iCCA or HCC-CCA between 2 and 5 cm in diameter demonstrated a RFS of 74% at 5-years, similar to patients with iCCA ≤ 2 cm, suggesting that a 2 cm threshold may be too conservative as a patient selection criterion for iCCA treated with LRT alone prior to transplant[54]. None of these studies, however, evaluated effects of neoadjuvant chemotherapy on patient outcomes, which may potentially impact survival and recurrence for larger tumors.

UCLA was, perhaps, the first to demonstrate the benefits of neoadjuvant chemotherapy when combined with transplant in the management of iCCA, but results are difficult to interpret as iCCA and hCCA are considered in combination. Nevertheless, patients undergoing liver transplant with adjuvant or neoadjuvant therapy have improved survival compared with patients receiving no treatment or receiving post-transplant adjuvant therapy alone[55], indicating a pre-transplant multimodal approach is best. Most recently, the group from Houston Methodist and MD Anderson Cancer Center published the first single center case series of protocolized neoadjuvant chemotherapy followed by liver transplant for iCCA[56]. Consideration for transplant was based on sustained tumor radiographic stability in response to > 6 mo of neoadjuvant chemotherapy. Outcomes for the first six patients showed 5-year OS of 83.3% and RFS of 50%[56]. An update by the group in 2019 reported outcomes for three additional patients with persistence of the previous survival outcomes[57]. Patients were not excluded based on tumor size, with median cumulative tumor diameter of 14.2 cm on explant pathology and no lesions < 5 cm [56,57]. Therefore, tumor response to therapy, a potential surrogate for tumor biology,

rather than lesion size may be the more important predictor of recurrence and survival. Patients who show pathologic response or stability with pre-transplant treatment may be eligible candidates for this life-saving therapy. Incidence and liver transplant outcomes for patients with iCCA are summarized in Figure 1.

LIVER TRANSPLANTATION FOR HCC-CCA

Mixed HCC-CCA is a combination of pure HCC and iCCA from a tumor biology standpoint. Thought to arise from hepatic progenitor cells, these tumors often occur in the presence of pre-existing, advanced liver disease, making tumor resection difficult [58-60]. Similar to iCCA, HCC-CCA is currently considered a contraindication to liver transplant due to historically high recurrence rates and poor OS[61]. Diagnosis prior to liver transplantation is difficult due to poorly defined radiographic criteria. Furthermore, due to small sample size and sampling error associated with percutaneous biopsy, accurate tissue diagnosis pre-transplant is often not possible[60]. As a result, in different series for patients undergoing liver transplantation, up to 3% of tumors initially diagnosed as HCC are later identified as HCC-CCA on explant[62,63]. Given the difficult diagnosis of HCC-CCA and iCCA, as well as the overall rarity of these tumors, most studies report combined results, making interpretation of individual outcomes difficult.

Several retrospective analyses have evaluated outcomes for HCC-CCA following liver transplant for patients with incidentally identified disease. Incidence of recurrence after transplant is reported as high as 40% by some authors[51,64,65]. Due to the small number of patients within each series and the combined outcomes for tumor types, recurrence risk status-post transplant for patients with these mixed tumors is difficult to assess. In their multicenter matched cohort analysis, Sapisochin *et al*[51] identified 42 patients with cholangiocarcinoma over a 10-year period, 15 of whom were diagnosed with HCC-CCA on final explant pathology. Comparing these patients to within-Milan criteria HCC-matched controls (matched by tumor size and nodule number), the authors noted similar 5-year OS (78% *vs* 86%) and recurrence risk (7% *vs* 4%), irrespective of lesion size[51]. While the OS for this matched cohort is intriguing, it must be interpreted with caution. The sample size is small, and the patients showed less advanced disease on explant pathology than what had previously been published by other groups who reported worse outcomes. In addition, wait list time for this cohort was short, therefore disease stability over time cannot be assessed to stratify patient risks. Nevertheless, the data are intriguing and suggest further study may yet show a select group of patients with HCC-CCA for whom the benefits of liver transplantation would outweigh the risks in this era of persistent organ shortage.

In a more recent propensity matched analysis from UCLA, liver transplant recipients diagnosed with HCC-CCA at explant (*n* = 12) were matched by pre- and post-transplant tumor characteristics 1:3 to patients with HCC (*n* = 36). Median tumor diameter was approximately 4cm for both groups. HCC-CCA tumors were more likely to be poorly differentiated and of higher grade. When matched by pre-transplant characteristics, OS and RFS were inferior for HCC-CCA, but the results were not statistically significant. When patients were compared by explant pathologic criteria (diameter, differentiation, grade, vascular invasion), recurrence rates remained minimally elevated for HCC-CCA, but OS and RFS equalized (42% *vs* 48% and 42% *vs* 44%, at five years, respectively)[60]. All recurrences occurred in patients with poorly differentiated tumors, and no recurrences were noted with well or moderately differentiated pathology[60]. These data suggest that patients with well- or moderately-differentiated HCC-CCA might be candidates for liver transplantation. However, improvements in diagnostic criteria are necessary to delineate biology of these rare tumors for accurate diagnosis and patient stratification pre-transplant. Furthermore, the benefit of pre-transplant systemic and liver directed therapies as adjuncts in the setting of liver transplantation to improve outcomes bears further assessment. Incidence and liver transplant outcomes for patients with mixed HCC-CCA are summarized in Figure 1.
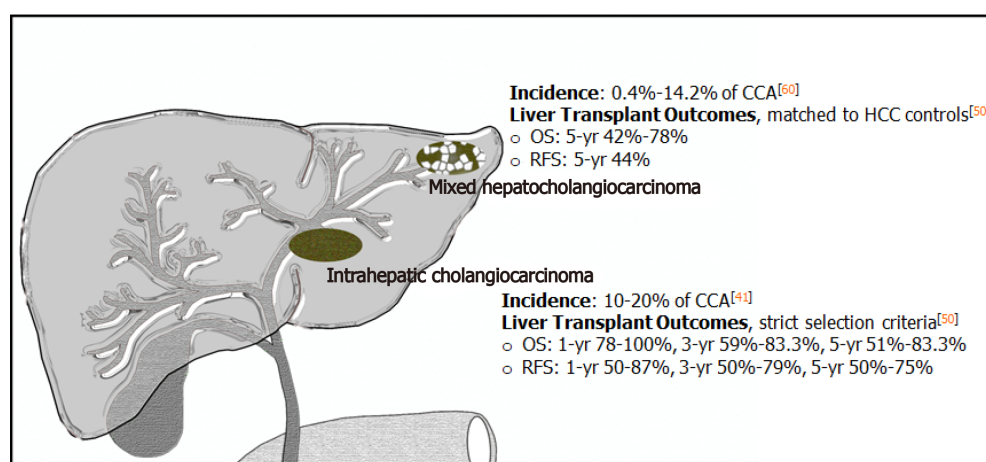
Figure 1 Incidence and liver transplant outcomes, intrahepatic and mixed cholangiocarcinoma. CCA: Cholangiocarcinoma; OS: Overall survival; RFS: Recurrence Free Survival.

LIVER TRANSPLANTATION FOR METASTATIC DISEASE: COLORECTAL CARCINOMA

Colorectal carcinoma (CRC) is the third leading cause of cancer-related death in men and women in the United States, and the third most common malignancy world-wide [66]. At the time of CRC diagnosis, only 20% of patients are resectable; patients with widespread systemic disease are otherwise limited in terms of curative op-tions[67]. Those with unresectable disease most commonly receive palliative medical therapy, with median OS of approximately 2-years and 5-year OS of 10%[68,69]. Even with resection, survival remains poor, with high disease recurrence rates and 5-year OS of only 30%-40%[70]. The liver is the most frequent site of metastatic CRC, and while extrahepatic spread is common, patients who present with liver-limited disease are suitable for surgical treatment. Surgical resection of colorectal liver metastases (CLM) with curative intent, in combination with locoregional and/or systemic therapies, achieves improved long-term results[71], but risk for recurrence after resection is 60%-70% within three years[67]. For patients not amenable to resection, liver transplantation may offer a possible cure.

The first aggregate outcomes of liver transplantation for the treatment of CLM were reported from the European Liver Transplant Registry. Based on 55 cases performed before 1995, the results were disappointing, with 1- and 5-year OS of 62% and 18%, respectively[4,5]. While approximately one third of deaths occurred due to surgical or peri-operative complications rather than disease-recurrence/progression[72,73], based on these initial data, CLM were considered to be a contraindication to liver trans-plantation. More recently, in an effort to evaluate outcomes for select patients with CLM, Dueland *et al*[74] from Oslo University re-examined liver transplantation for nonresectable CLM, causing a resurgence in interest in liver transplantation for this indication[74]. In the SECA-I trial (NCT00294827), which began enrollment in 2006, they evaluated outcomes for 21 patients transplanted with CLM. Included recipients were required to have liver-limited disease with complete oncologic resection of their primary tumor. In addition, all patients received at least six weeks of pre-transplant chemotherapy. In this initial series, 1-, 2-, and 5-year OS was 95%, 68%, and 60%, respectively; however, metastatic recurrence, mainly in the lungs, occurred in 90% of patients. Of these recurrences, the majority were treatable with either LRT or resection, resulting in an ultimate RFS of 33%. Factors associated with poor prognosis were hepatic tumor load, time to liver transplant from primary tumor resection, and disease progression while on chemotherapy[75].

In light of improved outcomes for unresectable CLM status post-transplant, with 5-year survival of 60% *vs* the previously reported 18%, the same group sought to compare survival following transplant *vs* standard of care medical therapy. Patients from the SECA-I trial were matched to those enrolled in the NORDIC VII trial (NCT00145314, FLOX in combination with cetuximab trial, *n* = 47)[74,76]. The PFS was similar between groups. Among those who recurred in SECA-I, 53% were alive at 5 years *vs* 6% for those who recurred with medical therapy. In addition, while all patients in NORDIC VII were initiated with first-line medical therapy, 57% of patients in SECA-I received second- and third-line regimens, with approximately 30% showing

Ref.	Study	n	Characteristics	Intervention	Overall survival	Progression free survival
Table 2 Clinical trials in transplantation *vs* best medical therapy for liver-limited colorectal metastases						
Hagness *et al*[75]	SECA-I	21	Unresectable; > 6 mo of neoadjuvant therapy	Liver transplant	5-yr OS: 60%	5-yr RFS: 33%
Dueland *et al*[68]	SECA-II	15	Unresectable; at least a 10% response to systemic therapy; disease stability 12 mo	Liver transplant	5-yr OS: 83%	3-yr RFS: 35%
Tveit *et al* [76]	NORDIC VII	566	Metastatic CRC; treatment-naïve; no resection with curative intent	A: FLOX alone; B: FLOX + Cetuximab; C: Cetuximab + Intermittent FLOX	3-yr OS: 6-8%	1-yr PFS: 20-32%

OS: Overall survival; PFS: Progression free survival; RFS: Recurrence free survival; CRC: Colorectal cancer.

progressive disease on third-line therapies. Despite this, 5-year OS was 56% for those who underwent liver transplant compared with 9% for medical therapy. Factors associated with worse outcomes included largest metastases > 5.5 cm, elevated tumor markers, lack of response to chemotherapy, and shorter time elapsed between resection of primary tumor to the time of transplantation[74,77]. The authors attribute some of the discrepancy in outcomes to the recurrence patterns among groups, with liver transplant recipients more often developing lung-limited metastases *vs* progression of liver metastatic disease in patients receiving medical therapy alone. Nevertheless, liver transplantation offers a clear survival advantage for select patients with liver limited CRC, especially in the setting of multimodal therapy with appropriate disease response.

Based on these data, a more selective inclusion protocol was developed by the group in Oslo in an attempt to refine survival benefit for transplantation in the setting of CLM, opening enrollment for the SECA-II trial (NCT01479608). Patients with at least 10% response to chemotherapy and at least one year of disease stability were enrolled. Ultimately, 15 patients underwent transplant. One-, three- and five-year OS was 100%, 83%, and 83%. A longer pre-transplant period of disease stability improved median RFS to 13.7 mo, with 1-, 2-, and 3-year RFS of 53%, 44%, and 35%, respectively. Similar to SECA-I, recurrences were mainly pulmonary and were often amenable to resection or LRT. While these results are certainly impressive, it is important to note that refinement of prognostic factors, such as response to chemotherapy, limited tumor size and number, and low CEA tumor marker, significantly impacted cancer recurren-ce [68]. However, with a 3-year RFS of less than 50%, which many consider the minimal acceptable threshold for a transplant indication, additional fine-tuning is necessarily for this indication to be widely accepted by the liver transplant com-munity. These results do, however, show vastly favorable outcomes compared with traditional medical therapy, raising the question of whether disease control rather than cure is an appropriate metric by which to measure success of transplantation. In select cases of CLM, liver transplantation appears to be a viable option and confers the greatest survival benefit; therefore, expanded indications warrant further debate. Clinical trials evaluating liver transplant *vs* medical therapy for treatment of liver-limited CRC metastases are summarized in Table 2.

CONCLUSION

Liver transplantation in the setting of gastrointestinal malignancy has an accepted role in the modern treatment paradigm for patients with certain liver-limited primary or metastatic malignancies. Emerging data favor expanding the current criteria and types of tumors that may be considered for transplantation. These expanded indications favor a multimodal approach, combining aggressive pre-transplant therapy with longitudinal evaluation of response to medical treatment. Post-transplant cancer recurrence remains a concern; however, liver transplantation in combination with LRT and systemic treatments warrants consideration in select patients with larger HCCs or liver-limited non-HCC malignancies. Choosing patients with the most biologically responsive tumors may allow for selection of candidates with the greatest likelihood of cure with transplantation, especially in the setting of underlying liver disease. Preliminary studies across tumor types consistently demonstrate that tumor biologic characteristics, response to pre-transplant therapy, and disease stability over time provide the best risk stratification for transplantation. As our data and experience

increase, tumor genetics may provide further evidence for optimized patient risk stratification. Regardless of tumor-type, a strictly protocolized approach at a multidisciplinary specialized digestive diseases center, with early surgical referral, are critical for identification of candidates that might benefit from liver transplant.

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