Review

Expanding Indications in Transplant Oncology

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Expanding Indications in Transplant Oncology

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Abstract: Liver transplantation is well described as the only curative treatment for cirrhosis and cirrhosis with co-morbid hepatocellular carcinoma (HCC). However, it's utility in the management of various other primary and secondary liver cancers is gaining traction rapidly, with more thorough and broader populations continuing to qualify. This includes most prominently colorectal cancer liver metastasis (CRLM), as well as cholangiocarcinoma (CCA), neuroendocrine tumors (NET) and more. Furthermore, despite being a well-described treatment for HCC for many years, growing evidence supports a change in oncologic strategy for HCC, with broadened selection criteria and more advanced systemic and loco-regional therapies. Our review aims to describe the evidence supporting expanding indications and selection criteria for liver transplantation for various oncologic indications of primary and secondary liver tumors.

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1. Introduction

Liver transplantation (LT) has become increasingly accepted as a curative-intent treatment option in the setting of unresectable hepatic malignancies. As recently as 2021, hepatocellular carcinoma (HCC) and perihilar cholangiocarcinoma (pCCA) were the only hepatic malignancies widely accepted for treatment with liver transplantation.[1] A comprehensive review of the literature in 2023 revealed increased utility of liver transplantation with curative intent for colorectal cancer liver metastasis (CRLM), primarily in patients with low Oslo and Fong Clinical Risk Score (FCRS).[2] Further, interest has increased on treatment of intrahepatic cholangiocarcinoma (iCCA) with LT due to the overall poor prognosis of this disease. Recent publications point to the importance of tumor biology, response to therapy, and long-term disease stability in cases with favorable outcomes[61]. With the wider application of locoregional therapies (LRT) and downstaging treatments, as well as the increasing percentage of patients with unresectable hepatic malignancies, discussion of expanding liver transplant oncology indications is pertinent. This article aims to provide a review of currently accepted indications for liver transplant, as well as a summary of recent publications on expanded indications with positive outcomes. Our hope is to foster discussion on new oncological treatment protocols that may increase transplant access with potentially curative intent.

2. Hepatocellular Carcinoma

Liver transplant has shown to be the best treatment option for early-stage hepatocellular carcinoma (HCC). In 2018, HCC was the primary diagnosis for 10.5% of liver transplant waitlist candidates, and 20.5% of transplanted recipients in the U.S. alone.[4] Liver transplant in the setting of HCC has been historically guided by the Milan Criteria.[23] However, later publications have pointed to the potential limitations of these criteria due to tumor size restrictions. Data from UCSF showed 1- and 5-year survival of 90% and 75.2%, respectively, in a cohort of 70 patients who received transplant with lesions beyond the Milan criteria (tumors ≤6.5 cm or ≤3 nodules with the largest lesion ≤4.5 cm and total tumor diameter ≤8cm). Additionally, Kyoto criteria incorporated tumor markers for patients with up to 10 tumors at the time of transplant, with 5-year OS of 88% in patients within

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Kyoto but outside of Milan criteria. Most significantly, HCC recurrence did not differ significantly between the two groups. Furthermore, poor tumor differentiation and microvascular invasion have been emphasized by both the Kyoto and Milan groups as contraindications for transplant due to high risk of recurrence. The application of LRT protocols prior to LT led to the expanded downstaging USCF criteria, in addition to the Milan criteria. Locoregional therapy has been shown to improve outcomes in HCC patients within Milan and UCSF criteria when tumors demonstrated a complete pathologic response (cPR) pre-transplant (cite UCLA study).

In 2018, the Milan group introduced the Metroticket 2.0 Model, which emphasized the predictive significance of tumor size, tumor number, and AFP levels towards survival and recurrence risk in HCC patients.[22] Further validation reported 3- and 5-year OS of 88.6% and 79.1%, respectively. Of note, HCC recurrence increased in patients with higher AFP values, as well as those patients outside Milan criteria who underwent chemoembolization.[31,32,65]

In 2024, a comprehensive analysis comparing multiple selection criteria for LT for HCC was performed (SRTR national database n=26,409; Milan & UCSF n=547).[31] Transplant candidacy and outcomes (3-year OS) were compared among Milan, UCSF, 5-5-500, U7, Metroticket 2.0 and HALT-HCC. Results showed that Metroticket 2.0, UCSF, and U7 criteria could increase transplant utilization for patients with HCC while maintaining positive outcomes. It was also noted in this analysis that HALT-HCC and Metroticket 2.0 were the best criteria to predict recurrence. For this reason, expansion of criteria beyond Milan is gaining traction, with Metroticket 2.0 shown in this study to be both the most discriminative and least restrictive criteria yet described that is able to maintain post-LT outcomes.[31]

Downstaging has led to comparable survival for patients within and outside of Milan and UCSF criteria in HCC. Washington University and Houston Methodist Cancer Center based patient eligibility on disease stability over 6-9 months, as well as response to LRT. Washington University reported successful downstaging for 63/210 patients with HCC who made it to transplant.[3] RFS for down-staged patients was shown to be similar to those within Milan and UCSF criteria. HCC recurrence was also reported to be similar between groups, with 8.9% for down-staged, 5.6% for UCSF, and 9.2% initially within Milan. Expanded indications may support patients with favorable tumor biology, disease stability over time, and complete pathologic response (cPR) to LRT pre-transplant. Despite concerns of risk of recurrence, aggressive post-transplant LRT and surgical treatments appear to provide some benefit to long-term survival.

Combination treatments with LRT and immunotherapy have shown promising outcomes. Ablation techniques such as radiofrequency ablation (RFA) and microwave ablation (MWA) have shown comparable outcomes to resection for well-defined and low-grade HCC tumors, though both present some limitations.[33] Histotripsy, a non-invasive, non-thermal, and non-ionizing ablation technique has recently emerged as a potential downstaging treatment. Though data is limited, early-stage reports show promising abscopal effect using this technique.[44] With regard to combination treatments, the review by Kumar et al. found that the combination of LRT with sorafenib, atezolizumab-bevacizumab, or Lenvatinib has shown potential OS benefits, but these techniques require further refinement due to frequent adverse events.[33] Yttrium-90 (Y-90) radioembolization.

In summary, management of HCC remains difficult due to nonresponse to cytotoxic chemotherapy, resistance to systemic immunotherapy, as well as variability of disease burden among patients. Milan selection criteria have historically proven successful in terms of outcomes for LT for HCC. However, new transplant selection criteria for this cohort are emerging that could increase access without compromising outcomes. It is of utmost importance that these criteria are validated to increase access to a lifesaving treatment. Emerging data on new LRT modalities such as histotripsy and combination treatments with LRT and immunotherapies have shown survival benefits, showing promise for downstaging HCC patients within acceptable selection criteria. In light of these recent developments, new guidelines ought to be soon established to apply pre-transplant LRT or combination therapies, as well as to expand selection criteria beyond the currently used and outdated Milan criteria.

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3. Colorectal Liver Metastasis

Liver metastasis manifests in at least 25% of patients with metastatic colorectal cancer during the course of their illness.[16] Currently, liver resection remains the golden standard for resectable CRLM, with 5- and 10-year OS of 44-50% and 24-33%, respectively.[17] The introduction of hepatic artery infusion pump (HAIP) after liver resection (LR) has also improved the 10-year OS rate to 38%.[17,19] However, 40-50% of CRLM cases are unresectable upon diagnosis, and management with chemotherapy has led to poor outcomes (5-year OS < 10%).[18]

Liver transplantation for unresectable CRLM was most notably supported by the SECA I trial out of Oslo University, which reported 1- and 5-year OS of 95% and 60%, respectively.[26] These findings were validated by multiple centers showing OS between 89-100% 1-year post-LT, though RFS was highly variable across each center (25-60%)[9]. This pilot study led to the development of the Oslo score, which is now a commonly used predictor of recurrence (Table 1).[2] The Oslo score is based upon four criteria, with the manifestation of each criteria posing increased risk of recurrence for patients with CRLM. The SECA I trial reported significantly improved OS in patients with Oslo ≤1 (10-year OS 88.9%, median OS 92.0 months), compared to patients with Oslo ≥3 (10-year OS 0%, median OS=24.8 months) in the setting of unresectable CRLM. Overall survival (OS) in the setting of unresectable CRLM significantly improved with liver transplantation as opposed to resection for patients with Oslo score ≤ 2, both in short-term and long-term follow-up (69.1% vs 14.6%, respectively).[2] This finding is well-complemented by data from Dueland et al., who reported poor long-term outcomes in patients with Oslo scores 3-4.[9,26] However, the SECA-I trial had limitations, most notably the lack of a control group. Even with the more stringent selection criteria of the SECA-II trial showing improved OS in 1, 3, and 5-year follow-up (100%, 83%, 83%, respectively), this limitation remained.[25]

Table 1. Oslo Score Criteria[2].

Oslo Score
Largest Tumor Size > 5.5 cm
Progressive Disease at Time of LT
Pre-operative CEA > 80ug/L
Less than 2 years from primary tumor resection and liver transplant

In 2024, Adam et al. published results of TRANSMET, a multicenter, prospective randomized trial comparing outcomes of patients with unresectable CRLM undergoing chemotherapy (Group C) versus chemotherapy plus LT (Group LT+C) (n=94, 1:1 randomization). In intent-to-treat analysis, 5-year OS for patients undergoing chemotherapy plus LT was 57%, compared to 13% in the chemotherapy-alone group.[24] In per-protocol analysis, the 5-year OS was 73% versus 9%, respectively. This trial also showed an improved PFS in patients receiving chemotherapy plus LT versus chemotherapy alone (17.4 months vs. 6.4 months). The selection criteria for this trial are listed in Table 2 (CT.gov NCT 02597348). These results reflect once again the strong potential of LT in treating unresectable CRLM, however further trials are warranted to determine the proper pre- and post-transplant therapies to improve poor DFS post-transplant.[26]

Table 2. TRANSMET Selection Criteria.

Inclusion Criteria	Exclusion Criteria
• ≥ 18 and ≤ 65 years	• Participation refusal
• Good performance status, ECOG 0 or 1 (39).	• No health insurance facilities

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• Histologically proved adenocarcinoma in colon or rectum	• General contraindication to LT (Severe cardiopulmonary disease or other life-limiting coexisting medical conditions, extrahepatic malignancy, active alcohol or substance abuse, active infection or uncontrolled sepsis, lack of psychosocial support or inability to comply with medical treatment)
• BRAF wild-type CRC on primary tumor or liver metastases	• Other malignancies either concomitant or within 5 years before liver transplantation
• High standard oncological surgical resection of the primary defined by : ○ Safe margin of resection ○ Curative resection of primary tumor according to oncological principles ○ TNM adequate staging	• Patients not having received standard treatment for the primary CRC according to recommended guidelines
• Absence of local recurrence on colonoscopy performed in the 12 months prior to inclusion (except in case of primary tumor resection < 12 months)	• Prior extra hepatic metastatic disease or local relapse
• Confirmed non resectable colorectal liver metastases by the validation committee	• Pregnancy at the time of inclusion
• ≥ 3 months of tumor control during the last chemotherapy line: Stable or Partial Response on RECIST criteria (40)	
• ≤ 3 lines of chemotherapy for metastatic disease	
• CEA < 80 microg/L or a decrease ≥ 50% of the highest serum CEA levels observed during the disease	
• Absence of extrahepatic tumor localisation according to CT scan and PET-CT	
• Renal function should be within the normal limits	
• No need for extra-renal purification procedure, hemodialysis or kidney transplantation associated (nephrologist assessment)	
• A platelet count> 80,000 / mm3	
• White blood cell count> 2500 / mm3	
• Eligible for both treatments groups	
• Signed informed consent and expected cooperation of the patient for the treatment and follow up	

https://www.clinicaltrials.gov/study/NCT02597348

Another critical discussion is the management and selection of potential LT candidates. In addition to the Oslo score validation, Dueland et al. also demonstrated improved OS in patients with pre-transplant PET-MTV <70cm[3].[20] The combined groups from Cleveland and University of Rochester recently validated MTV as a selection criteria, critically finding further that lower MTV values can maximize outcomes.[21,65] Most notably, 1- and 2- year OS were 100% and 85%, respectively in the PET-MTV low groups.[21]

The Cleveland Protocol of 2024 found that pre-liver transplant (pre-LT) detectable disease serves as a predictor of recurrence in patients with CRLM.[27] The protocol described a novel pre-liver transplant plan of care focused on locoregional therapy and systemic chemotherapy to reduce disease burden prior to transplantation. Locoregional therapy included Y90, ablation, resection, and HAIP,

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while systemic therapy included chemotherapy +/- bevacizumab and/or anti-EGFR. Data on eligible candidates (n=16) showed that long-term systemic therapy (minimum 6 months) and locoregional therapy with repeat evaluation every 3-6 months led to improved survival when compared to patients who were not candidates (n=11).

Finally, selection criteria may continue to expand incorporating personalized medicine approaches, such as tissue-based or circulating tumor DNA (ctDNA) .[28]-[31] These approaches are new but demonstrate potential in both the surveillance and selection setting.

4. Cholangiocarcinoma

Cholangiocarcinoma (CCA) originates from cholangiocytes of the bile duct and carries a high risk of recurrence. It is the second leading cause of primary liver malignancy, and a common cause of death in patients with primary sclerosing cholangitis.[11] CCA currently manifests as intrahepatic, hilar, and distal. Unresectable perihilar CCA (pCCA) has become an accepted indication for liver transplant.[1,11]. Data shows OS of 68% and 53%, and RFS 78% and 65% at 2- and 5-year marks, respectively (International LT Society Guidelines, 2016)[61,62].

The treatment of intrahepatic CCA (iCCA) remains controversial with regard to liver transplant. iCCA represents 10-20% of all CCA tumors, with poor OS survival of 10-40%. Small-size tumors, well-differentiated tumors and tumors without lympho-vascular invasion are shown to have best outcomes for this cohort of patients[61]. Treatment of iCCA with LT showed poor survival (20-30%) and high recurrence rates >50% during initial studies. While surgical options are limited due to the aggressive nature of the disease, medical therapy and LRT have shown benefit in RFS. Nonetheless, OS remains poor. A retrospective analysis from Sapisochin et al. indicated that patients with solitary nodules ≤2cm in diameter have comparable 5-year OS to HCC patients after transplant (62% vs 80%, respectively) (Sapisochin et al)[63]. These results were validated by the Mayo Clinic, specifically for early stage iCCA without vascular invasion, with reported 5-year OS of 63.6% compared to 70.3% for patients with HCC within Milan criteria. A French study compared iCCA cases treated with resection vs. transplant and reported that iCCA lesions between 2 and 5 cm showed a 5-year RFS of 74% for patients receiving pre-transplant LRT, which indicates that the 2cm diameter cut-off may be too conservative. The aforementioned studies did not explore the effects of adjuvant and neoadjuvant therapies pre-transplant, but UCLA data have shown improved survival with neoadjuvant therapy pre-transplant for patients with CCA. Houston Methodist and MD Anderson published data on a small cohort of 6 patients who received >6 months of neoadjuvant chemotherapy, showing 5-year OS of 83.3% and RFS of 50% for iCCA patients with sustained tumor stability, median cumulative tumor diameter of 14.2 cm and no lesions < 5cm. This study therefore emphasized that tumor response to pre-transplant treatment may be more important criterion for survival than tumor size in the case of iCCA. Protocols continue to evolve as more promise is shown with the implementation of treatment modalities prior to liver transplantation.

5. Neuroendocrine tumors

Neuroendocrine tumors (NET) are rare, dormant neoplasms that metastasize to the liver primarily through the portal venous system. NET liver metastasis occurs at a rate of 40-93%, with lower frequency in bone and lungs.[34,35] OS at 5 years for metastatic liver NET is 20-40%. Given the variability in presentation and symptoms, patients can often be unaware of the presence of NET until metastatic disease reaches advanced stages. Metastatic liver NET can be treated with a combination of RFA, TACE, chemotherapy or resection.

However, for unresectable metastatic liver NET, orthotopic liver transplant remains the best plan of treatment. 5-year OS and DFS after LT have been shown to be 52% and 30%, respectively, for well-differentiated metastatic liver NET (histologic grade 1-2), compared to 27% for poorly differentiated tumors (histologic grade 3) (ELTR, n-213).[37] The European study also identified common predictors of poor outcome to be hepatomegaly, age ≥ 45 years, and any amount of resection

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concurrent with LT.[37] Other criteria have also been shown to affect the prognostic outcome of OLT with regard to NET, including rate of tumor invasion, Ki-67 index ≥ 5%, number of tumors, and presence of portal venous drainage.[34,38] The Milan-NET criteria has demonstrated significant outcomes when used to determine LT recipients in this cohort. Mazzaferro et al. reported in 2016 that metastatic liver NET patients within Milan-NET criteria who were transplanted (n=42) had 5- and 10-year survival of 97.2% and 88.8%, respectively, compared to 50.9 and 22.4% in non-transplanted patients (n=46).[36] The Milan-NET criteria also showed strong advantages with regard to time-to-progression, at 13.1% vs 83.5% in 5-year follow-up and 13.1% vs. 89% at 10-year follow-up.[36] A summary of Milan-NET criteria is included in Table 3.

Table 3. Milan-NET Inclusion Criteria.

Confirmed histology of low-grade (G1/G2 grading according to the World Health Organization classification)
neuroendocrine tumor
primary tumor removed with curative resection
metastatic diffusion to liver parenchyma ≤50%
stable disease for at least 6 months before liver transplant
age ≤55 years.

Multiple studies have observed that LT can be also beneficial for patients with metastatic liver NET when selection criteria are not highly restrictive.[37,38] A retrospective review by Thao et al. noted that since the introduction of the MELD score, OS for metastatic liver NET patients improved significantly in the 1, 3 and 5-year follow-up compared to the pre-MELD era.[39] As previously noted, exception-MELD criteria play a significant role in higher access to patients where LT could improve OS and RFS. Another potential predictor of survival is wait time prior to transplant. Gedaly et al. reported improved patient survival when allowing for disease stability prior to LT longer than 2 months.[40] A systematic review of the literature has also supported the survival benefits of LT in patients with metastatic liver NET, advocating for stricter selection criteria.[41]

Further investigations are needed to support this treatment option, with better-refined selection criteria, such as downstaging and implementation of a pretransplant monitoring period.

6. ,Other Malignancies

The role of liver transplantation has also been explored in rare tumors of the liver, including hepatic epithelioid hemangioendothelioma (HEHE), hepatoid adenocarcinoma (HAC), and fibrolamellar carcinoma (FLC). HEHE affects approximately one in one million people worldwide.[42] Tumor involvement is present in the liver in 30% of cases. Other sites of infiltration include the lungs, peritoneum, abdominal lymph nodes, bone, and spleen, albeit at a lower rate.[42]·[43] Liver resection has led to the best outcomes for resectable HEHE cases, specifically 100% 1-year survival and 75% 5-year survival.[42] However, over 80% of patients present with bilobar involvement, excluding surgical resection as a treatment option.[49] Liver transplantation has had best outcomes and is the supported treatment modality for unresectable HEHE patients, while data remains scarce on the effectiveness of other therapies. One review of 434 primary HEHE cases reported that 44.8% of patients were treated with transplantation, with 1- and 5-year survival rates 96% and 55.4%, respectively.[42] The same study reported 1- and 5-year survival of 73.3% and 30%, respectively, after treatment with chemotherapy or radiotherapy. UNOS data from 2002 to 2018

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identified 131 adults listed for LT with an indication of HEHE.[43] Eighty-eight of 131 patients were transplanted, with 1-, 3-, and 5-year OS reported as 88.6%, 78.9%, and 77.2%, respectively. Though we recognize the rarity of HEHE and subsequently the scarcity of the data available, current reports point to transplantation as an effective treatment plan.[42,50,51] Further studies are required to determine the effectiveness of other therapies and best oncological treatment plans.

Fibrolamellar carcinoma (FLC) is another rare primary liver cancer that predominantly affects adolescents and young adults without underlying liver conditions.[45,46] The disease was thought to be a sub-type of HCC, accounting for roughly 1% of all cases.[46] Yet recent studies point to clear distinctions between FLC and HCC tumors, suggesting that it should be treated as a separate entity.[47] Such distinctions, including genomic and histologic alterations of FLC tumors, raise questions regarding the valid number of historic FLC cases and, subsequently, whether the proper prioritization and treatment plans are being implemented. Currently, surgical resection is the primary treatment modality for resectable FLC (5-year OS 76%), while outcomes of unresectable FLC cases remain poor (5-year OS 10-20%).[48] The predominant surgical resection treatment is major hepatectomy (70% of cases), with data pointing to significantly improved outcomes when complete resection (R0) is performed.[52] However, disease recurrence remains high following resection, with one study reporting recurrence rate as high as 86%.[53] Some studies have reported improved OS when resection is followed by chemotherapy (median OS 23.1 months), however data remains limited on the best systemic treatment modality.[57] Liver transplantation has shown to be a viable treatment option for unresectable FLC. Multiple large-scale retrospective studies have reported 5-year OS 48-55%, with mean OS 47.5 months.[54]-[56] However, OS is dependent on multiple factors such as tumor size, number, lymph node involvement, vascular invasion and utilization of systemic therapy, with one study reporting OS to range between 34 and 120 months.[57] It is important to further explore liver transplantation for unresectable FLC in the prospective setting to establish best treatment practices.

Hepatoid adenocarcinoma (HAC) is another rare type of cancer which closely resembles HCC, with an incidence rate of 0.014 per 100,000 people. It most commonly occurs in elderly patients over 60 years old (66.1% of cases).[58,59] This disease predominantly presents in the lungs and stomach, with fewer cases presenting in other digestive organs (i.e. Pancreas, gallbladder, bile duct). Data on HAC is very limited, with most information coming from case reports. One study compiling 258 patients with HAC reported 1-year survival of 35%, with 3- and 5-year survival only 16.9% (mean survival 5 months).[58] The most common treatment regimens are radiotherapy and/or chemotherapy for metastatic disease or lymph node involvement cases (71.9%), and surgery for local tumor cases (28.1%). It is worth noting that studies have found improved disease-free survival in patients undergoing neoadjuvant therapy when compared to patients who received post-operative therapy alone, especially in patients with metastatic disease.[60] Liver transplantation is grossly unexplored in the literature. One study reviewing 112 historical cases found that 1-, 3- and 5-year OS following LT was 78%, 63% and 57%, respectively. The 5-year survival rate for hepatitis B (HBV) patients undergoing LT with antiviral therapy was comparable to non-HBV patients (77%).[61] This study reported vascular invasion significantly decreased 5-year survival (33%) and increased chances of tumor recurrence (65% of patients at 5 years). Given the highly challenging diagnosis and differentiation of HAC, more studies have to be conducted to better differentiate this malignancy from HCC, and subsequently determine whether liver transplantation improves outcomes.

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7. Conclusions

Hepatocellular carcinoma and hilar cholangiocarcinoma have become accepted indications for liver transplantation with curative intent[1]. As more studies are emerging on expansion of oncologic indications for liver transplantation, it is becoming increasingly clear that tumor biology and response to pre-transplant therapy are key factors for optimal oncologic outcomes. In addition, disease stability over time portends better outcomes post-operatively. More studies continue to support downstaging via locoregional therapy to bring patients within acceptable criteria for hepatic malignancies. Novel LRT treatments such as histotripsy are emerging, however data remains limited on these approaches. It is worth exploring the importance of adjuvant and neoadjuvant therapies during pre-transplant treatment, especially in cases of iCCA and HCC-CCA, as data are limited on overall survival when these therapies are applied in combination with liver transplant.

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