

Review

# Updates and Expert Opinion in Liver Transplantation for Gastrointestinal Malignancies

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**Abstract:** Transplant oncology is a relatively new field in which transplantation is used to treat patients who would otherwise be unresectable. New anticancer treatment paradigms using tumor and transplant immunology and cancer immunogenomics are emerging. In turn, liver transplantation (LT) has become a potential therapy for certain patients with colorectal cancer (CRC) with liver metastasis, hepatocellular (HCC), cholangiocarcinoma (CCA), and metastatic neuroendocrine tumor (NET) to the liver. Although there are established criteria for LT in HCC, the evidence regarding LT as a treatment modality for certain gastrointestinal malignancies is still debated. The aim of this review is to highlight updates in the role of LT for certain malignancies, including HCC, metastatic CRC, hilar CCA, and neuroendocrine tumor (NET), as well as contextualize LT use and discuss controversies in transplant oncology.

**Keywords:** Transplant Oncology; Liver Transplant; Gastrointestinal Malignancies

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## 1. Introduction

Surgical resection or transplantation are the only potentially curative treatment options or primary liver cancers such as hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), as well as metastatic disease including colorectal cancer (mCRC) and gastroenteropancreatic neuroendocrine tumors to the liver. These cancers are aggressive and many patients present with advanced disease.[1-4] Consequently, a small proportion of patients may be eligible for resection at time of diagnosis.[5]

Liver transplantation (LT) has gained increased acceptance as a potential therapy for well-selected patients with HCC, hilar or intrahepatic CCA, as well as mCRC and neuroendocrine metastasis.[6,7] Transplant oncology is a relatively new field that may benefit patients with unresectable disease and allow for the study of new anticancer treatment paradigms focused on tumor and transplant immunology and cancer immunogenomics.[8] The four pillars of transplant oncology include: evolution of multidisciplinary cancer care by integrating LT, elucidating self and non-self recognition by linking tumor and transplant immunology, the exploration of biomechanisms of disease through genomic studies, and extending the limits of safe surgical resection by applying transplant surgical techniques.[9]

LT has been proposed as a mechanism to treat hepatobiliary cancers as far back as the 1970s.[10-13] Excising the entire liver en-bloc serves two purposes: it removes the primary cancer and removes the pro-carcinogenic environment from which the tumor arises.[14,15] Initial clinical series were underwhelming and outcomes generally poor until the Milan Criteria were established for LT in

HCC.[16] Since then, criteria for transplantation in the setting of malignancy have been expanded with an increasing body of evidence suggesting efficacy in select patients. We herein highlight the role of LT for HCC, hilar CCA, mCRC, and neuroendocrine tumor (NET), as well as discuss several controversies in the field of transplant oncology.

## 2. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer related death worldwide.[1-3] Prognosis can be poor given that patients often present with advanced stage in the setting of chronic liver dysfunction or cirrhosis, precluding surgical resection.[17] Unfortunately, even among patients who undergo curative intent resection, the incidence of recurrence can be high.[18] Multi-disciplinary treatment with surgical, medical, and radiation oncology is crucial. The Barcelona Clinic Liver Cancer (BCLC) guidelines provide staging criteria, prognostic information, and treatment recommendations based on tumor burden, liver function, and performance status.[19]

### 2.1. Liver Transplant Criteria in HCC

LT offers the best chance for optimal long-term outcomes with 5-year post LT survival of approximately 65-80% and lifetime recurrence risk of 8-15%.[20] LT is limited by the scarcity of organs making patient selection crucial. The Milan Criteria was published in 1996 and laid the foundation for HCC LT patient selection. Patients with HCC and either a solitary lesion  $\leq 5$  cm or up to three lesions each  $\leq 3$  cm without vascular invasion or extra-hepatic involvement are candidates for LT.[16] Due to the success of LT among patients with HCC who met Milan criteria, transplant surgeons and oncologists have worked to expand eligibility criteria. The University of California San Francisco (UCSF) criteria recommends LT for patients with a single tumor  $\leq 6.5$  cm, three tumors each  $\leq 4.5$  cm with total tumor diameter  $\leq 8$  cm, or the “up to 7 criteria” where the sum of the maximum tumor diameter and number of tumors must be  $\leq 7$  cm. Similar to the Milan criteria, exclusion criteria for the UCSF criteria include the presence of major vascular invasion or extra-hepatic disease.[21,22] Post-transplant survival at 5 years was 80.9% and 71.2% for the UCSF and “up-to-7 criteria,” respectively.

Additional studies have continued to expand LT criteria of eligible patients. Toso et al. applied total tumor volume (TTV)  $<115$  cm<sup>3</sup> and alpha-fetoprotein (AFP) levels  $<400$  ng/mL as criteria for LT among patients with HCC. The authors demonstrated a recurrence-free survival and post-transplant survival at 4 years of 68% and 74.6%, respectively.[23] The Kyoto criteria incorporated the HCC tumor marker des- $\gamma$ -carboxy prothrombin (DCP)  $<400$  AU/mL, an abnormal variant of prothrombin, and  $\leq 10$  tumors each  $<5$  cm as criteria for LT. The authors reported 5-year overall survival (OS) of 82% and a recurrence incidence of 7%.[24] Shimamura et al. proposed the “5-5-500” criteria based on a retrospective review of 965 living donor liver transplantations (LDLT) among patients with  $<5$  lesions each  $<5$  cm and an AFP  $<500$  ng/mL of which 301 (31%) were beyond Milan Criteria; the 5-year recurrence rate was 7.3%.[25] The transplant group from Toronto proposed even broader criteria in which patients with any number or size of tumors were potentially eligible for LT as long as there was no vascular invasion, extrahepatic disease, or poorly tumor differentiation. In this study that included 210 patients who underwent transplantation for HCC from 2008-2012, 105 (50%) were beyond Milan Criteria. The authors reported a 5-year survival comparable to patients treated within the Milan criteria (69% for beyond Milan criteria and 78% for those within Milan criteria).[26] Table 1 summarizes selection criteria for LT for HCC.

**Table 1.** Criteria for Liver Transplant in patients with Hepatocellular Carcinoma.

Criteria	Year Published	Definition
Milan Criteria	1996	Single tumor <5 or 3 tumors <3 cm
University of California at San Francisco Criteria	2001	Single tumor <6.5 cm or 3 tumors <4.5 cm with total diameter of tumors <8 cm Total tumor volume <115 cm <sup>3</sup> and serum AFP < 400 ng/ml
Total Tumor Volume Criteria	2008	
Up to 7 Criteria	2009	Total diameter of all tumors <7 cm and number of tumors <7
Kyoto Criteria	2013	Number of tumors <10, largest tumor <5 cm, and DCP < 400 mAU/ml
Toronto Criteria	2016	No size or number of tumor cut off. Must not have vascular invasion, extrahepatic disease or poor differentiation
5-5-500 Rule	2019	Size of tumor <5 cm, number of tumors <5 and AFP < 500 ng/ml

Abbreviations: AFP (alpha-fetoprotein), DCP (des-gamma-carboxyprothrombin).

## 2.2. Downstaging HCC for LT

Locoregional therapies such as ablation, transarterial chemoembolization (TACE), and stereotactic body radiation therapy (SBRT) are employed to downstage patients in an attempt to make patients candidates for definitive surgical therapy (resection or transplant). In a phase IIb/III trial, 45 patients were downstaged within the Milan criteria using locoregional or systemic therapy.[27] Patients who underwent LT (n=23) had a 5-year OS of 77.5% versus 31.2% among patients who did not undergo LT. Locoregional therapies resulted in a complete pathologic response in the explanted liver in 23% of patients, which was associated with improved OS and disease free survival (DFS).[28] Conversely, patients with a poor response to locoregional therapies on final pathology were at high risk of post-transplant recurrence.[29] Response to treatment can be evaluated through imaging and tumor markers (e.g. AFP or gamma glutamyl transpeptidase).[30] Other studies have also demonstrated that a reduction of AFP to <500 ng/mL was associated with decreased risk of HCC recurrence and improved post-transplant mortality.[31]

## 2.3. Organ Availability

The finite donor pool is a rate-limiting step in transplant oncology. While the data are controversial, one way to expand the donor pool is through LDLT. Initial studies raised concerns for an increased risk of recurrence of HCC after LDLT, however more recent studies have demonstrated improved 5 year OS in LDLT versus individuals who had a deceased donor.[32-34] The reason for this may be because patients spend less time on the wait list and are less decompensated prior to transplantation. However, LDLT should be limited to high volume centers to minimize the risk to the donor.[35] Other options to expand the donor pool include use of “marginal grafts” from older donors, donors after cardiac death (DCD), split livers and hepatitis C infected grafts.[36-39]

#### 2.4. Future Directions for LT in HCC

Preventing HCC recurrence in the setting of chronic immunosuppression will be crucial to maximize the longevity of transplanted livers. Certain immunosuppression medications, such as calcineurin inhibitors, have been associated with increased risk of HCC recurrence.[40] [41] The SiLVER trial (NCT00355862) assessed the effect of sirolimus, a mammalian target of rapamycin (mTOR) inhibitory, on HCC recurrence after LT. Sirolimus use for >3 months was independently associated with reduced mortality, and demonstrated a benefit in OS, DFS, and decreased recurrence among patients with elevated AFP (>10 ng/mL).[42]

Equally important in the future of LT for HCC is identification of predictors of recurrence. Established pathologic characteristics such as T-stage, histologic grade, as well as microvascular invasion and tumor markers such as AFP have been associated with risk of recurrence; there is also a growing body of literature regarding use of fluorodeoxyglucose (FDG) PET/CT to predict recurrence of HCC after LT.[43-49] In turn, the use of FDG PET/CT may play a role in future for patient selection for LT.

### 3. Cholangiocarcinoma

Cholangiocarcinoma (CCA) is categorized into anatomical subtypes: intrahepatic and extrahepatic (hilar and distal common bile duct) each with distinct biology and behavior.[50] While surgical resection is a potential treatment option for CCA, many patients present with locally advanced CCA and are not candidates for surgery. As such, LT has been proposed as a potential curative-intent option for patients with hilar or intrahepatic CCA. Similar to other malignancies, initial outcomes associated with LT for CCA were underwhelming, with a 5-year OS ranging from 0-18%.[51,52] Subsequent studies demonstrated a 3- and 5-year OS of 40% and 30%, respectively, yet the incidence of recurrence was high.[53,54] Hong et al. retrospectively compared LT versus resection among patients with locally advanced hilar or intrahepatic CCA. LT was associated with an improved 5-year RFS versus resection (33% Resection vs 0% LT).[55] These studies were limited, however, as the cohort included both hilar and intrahepatic CCA, which have distinct underlying biological natural histories.

#### 3.1. Liver Transplantation for Hilar CCA

The Mayo protocol includes the administration of neoadjuvant chemoradiation to patients with hilar CCA prior to LT. Patients with nodal disease, metastases, or tumors >3 cm are excluded from LT consideration. Using the Mayo protocol, LT was associated with an improved DFS and OS versus standard chemotherapy.[56] Gores et al. reported a 5-year OS of 65-70% after neoadjuvant external beam radiation, brachytherapy, and capecitabine followed by LT.<sup>87</sup> In a separate study by the European Liver and Intestine Transplant Association, a 5-year OS was 59% among patients with hilar CCA who underwent LT following the Mayo protocol..[57,58] A large multicenter trial evaluating 287 patients with hilar CCA who underwent LT similarly demonstrated a 5-year DFS of 65%.[59]

Different neoadjuvant therapeutic regimens have been studied prior to LT including gemcitabine and capecitabine with radiation.[60] There are a few retrospective analyses comparing LT to resection for hilar CCA. Ethun et al. assessed OS among patients who underwent LT versus resection for hilar CCA and noted a higher 5-year OS among patients who underwent transplant (LT 64% vs resection 18%).[61] Hoogwater et al. reported that, while neoadjuvant chemotherapy and LT had lower risk of tumor recurrence, there was a higher rate of post-operative vascular complications.[62] In a recent meta-analysis, neoadjuvant therapy followed by LT provided a benefit in terms of OS and tumor recurrence compared with upfront transplant.[63] Similar findings have been reported in other retrospective studies, however, there is a relative dearth of prospective study on the topic.[63-66] There is an ongoing randomized controlled trial (TRANSPHILL, NCT02232932) that compares resection versus neoadjuvant therapy followed by LT with results expected in the coming years.

3.2. Liver Transplantation for Intrahepatic CCA

Intrahepatic CCA has been associated with generally poor results following LT. Initial data was based on patients who underwent LT for a different indication and were incidentally noted to a small intrahepatic CCA in the explanted liver. Patients with early or intermediate stage intrahepatic CCA had higher median OS versus individuals with advanced disease.[67] A small cohort of 29 patients who underwent LT for early stage intrahepatic CCA had lower rates of recurrence and improved OS at 5-years versus patients with more advanced tumors.[68] A recent study from France demonstrated that there was a survival benefit with LT versus liver resection among cirrhotic patients with early stage intrahepatic CCA.[69] As with HCC, LT removes the underlying field defect of chronic liver disease that can contribute to the development and progression of CCA and improves patient overall health by restoring liver function. Several studies have demonstrated that neoadjuvant therapy followed by LT may confer a survival benefit compared with resection.[55,70,71] Additionally, several large retrospective analyses have confirmed the survival benefit of LT for early intrahepatic CCA.[72,73] Lee et al. noted, however, that LT for intrahepatic CCA was associated with a worse OS and higher risk of recurrence than patients undergoing LT for HCC.[74] There is a paucity of high quality prospective data to provide evidence that LT should be adopted as a routine treatment approach to patients with intrahepatic CCA. An ongoing phase II clinical trial investigating LT in cirrhotic patients with early stage intrahepatic CCA (NCT02878473) should help define the role of LT. Table 3 demonstrates ongoing clinical trials related to LT for CCA.

Future studies should focus on selection criteria for LT for patients with CCA and identify which patients with intermediate or advanced disease are optimal candidates for LT. Genetic profiling may identify patients at higher risk for recurrence, such as individuals with mutations in *KRAS*, *BAP1*, or *CDKN2A* in intrahepatic CCA or mutations in *P53*, *BRCA1-2*, and *PIK3CA* in hilar CCA.[75-77] The role these mutations play in the selection of patients for LT requires further investigation.

**Table 3.** Ongoing clinical trials evaluating Liver Transplant in the Treatment of Cholangiocarcinoma.

Trial Name	Start Date	End Date	Enrollment	Treatment	Patient Population	Primary End Point
NCT04378023	2020	2025	34	Neoadjuvant chemo-radiation + LT	Unresectable Hilar CCA	1, 3, 5 year OS
NCT02878473	2018	2029	30	LT	Early Intrahepatic CCA	5 year patient survival
NCT04556214 (TESLA)	2020	2035	15	LT	Unresectable intrahepatic CCA	3 year OS
NCT04993131 (TESLA II)	2021	2035	15	LT	Unresectable Perihilar CCA	3 year OS

Abbreviations: LT (Liver Transplant), CCA (Cholangiocarcinoma), OS (Overall Survival).

4. Metastatic Colorectal Cancer to the Liver

Over the past few decades, survival among patients with CRC has improved due to improved screening modalities, aggressive surgical resection, and advancements in chemotherapy and targeted therapy.[78] However, for unclear reasons, the incidence of CRC has increased in younger populations.[79,80] Additionally, because the screening guidelines are age-dependent, CRC in the younger population is often diagnosed at a more advanced stage. Approximately 50-60% of patients with CRC will develop metastases with the liver being the most common site.[81,82] Unfortunately, 80-90% of patients will have unresectable disease, commonly due to an insufficient liver remnant.[83,84] In



these patients with isolated liver metastases, LT has been proposed as a potential curative-intent option.

#### 4.1. Liver Transplantation Criteria for CRC Liver Metastases

Initial data on LT for CRC liver metastases were published in the early 1990s; long-term outcomes were poor with low 5-year OS and a high incidence of recurrence.[12,85] Given the poor outcomes and the scarcity of grafts, LT was largely abandoned as a treatment option for metastatic CRC. Over the last decade, a Scandinavian consortium reinvigorated interest in LT for CRC liver metastases.[86,87] In a landmark study from Hagness et al., the 5-year survival following LT of 21 patients with liver only CRC metastases who had a resected primary tumor and at least 6 weeks of chemotherapy (SECA-I study) was evaluated. The authors reported an OS of 95%, 68%, and 60% at 1-, 3-, and 5-years, respectively. Liver tumor burden >5.5 cm, CEA >80 micrograms/L, and disease progression on chemotherapy were strong prognostic indicators of poor outcomes.[88] Of note, 19 of the 21 patients had tumor recurrence, but primarily as pulmonary metastases (n=17).[89] A smaller study from Toso et al. evaluated 12 patients with CRC liver metastasis who underwent LT and demonstrated a DFS of 56%, 38%, and 38% at 1-, 3-, and 5-years, respectively.[90]

Currently, LT for metastatic CRC remains somewhat controversial. Dueland et al. compared DFS, PFS, and OS among patients in the SECA-I cohort who underwent LT versus patients who received palliative chemotherapy (NORDIC VII study, n=47). Although there was no difference in DFS and PFS, there was a marked difference in 5-year OS (LT cohort: 56% versus palliative chemotherapy: 9%).[91] It should be noted, however, that the palliative chemotherapy cohort only received first-line treatment. A follow-up study assessed OS among patients with liver only CRC metastases who had progressed on various standard lines of chemotherapy at the time of LT. Of note, 5-year OS was 44% in this cohort, which was better than any other treatment option reported in the literature.[92]

Using the momentum from these studies, the SECA-II study prospectively assessed patients with liver-only metastatic CRC who underwent LT. More selective criteria were employed including time from diagnosis to transplant <1 year and at least a 10% response to chemotherapy. Using these criteria, OS was 100%, 83%, and 83% at 1-, 3-, and 5-years, respectively.[93] One arm of the SECA-II study examined expanded criteria for both donors and patients by including patients with resectable pulmonary metastases. Ten patients were included in the analysis with a DFS and OS of 4 and 10 months, respectively.[94] Additionally, compared with patients who had HCC within the Milan criteria, individuals with low risk CRC liver metastases (low CEA, good response to neoadjuvant therapy, low tumor burden, and short interval from primary surgery to transplant) had a similar 5-year OS. [95]

Tumor burden in the liver also demonstrated an impact on outcomes. Dueland et al. compared OS among patients who underwent LT versus individuals who had portal vein embolization (PVE) and extended liver resection for high burden liver metastasis. Patients in the LT cohort had improved 5-year OS versus the PVE/resection cohort (45.3% vs 12.5%, respectively).[96] Similarly, in a separate study, LT was associated with an improved survival compared with liver resection among patients with high tumor burden.[97] Additionally, Giannis et al. reported a survival benefit of LT in a recent systematic review.[98] A recent meta-analysis from Varley et al. also concluded that there was a survival benefit for LT in setting of non-resectable CRC metastases; however, the authors cautioned that further study was needed.[99]

#### 4.2. Adjuvant Chemotherapy after LT in Metastatic CRC

Adjuvant chemotherapy in the setting of tumor recurrence after LT is not well studied. The Oslo group attempted to define the role of adjuvant therapy after LT for recurrent CRC metastases. These investigators noted that adjuvant therapy was safe and did not increase the risk of graft rejection. However, over 80% of patients reported grade 3-4 toxicity events including pancytopenia, diarrhea, and mucositis. The authors concluded that adjuvant therapy may increase long term survival and should be considered in the post-LT setting.[100] The role of adjuvant chemotherapy post-transplant still requires further evaluation, however.

#### 4.3. Future Directions for LT for CRC Liver Metastases

Future directions of LT for CRC metastases should investigate staged procedures, also known as the RAPID procedure (Resection and Partial Liver Segment 2/3 Transplantation with Delayed Total Hepatectomy). [101,102] The aim of this two-stage procedure is to perform a left lateral hepatectomy with implant of a left lateral segment graft. The completion hepatectomy is delayed thereby allowing growth of the graft. This approach may allow for transplantation of smaller, partial grafts and increase the availability of organs. At this time, this technique has only been reported in case series.[103] An ongoing clinical trial is currently evaluating the two-stage approach (NCT03488953).[104]

The utilization of LDLT is also growing for CRC metastases. A recent study from Hernandez-Alejandro et al. demonstrated a RFS and OS at 1.5 years after LDLT for CRC metastases of 62% and 100%, respectively. A low incidence of perioperative morbidity was observed for both recipients and donors.[105] A recent paper from Endo et al. noted promising results for LDLT versus deceased donor LT.[106] In this study, the authors reported an improved 3-year OS for LDLT versus deceased donors (66.7% vs 45.1%, respectively) with a relatively flat hazard curve of death among patients with LDLT.[106] Jackson et al. reported a survival benefit associated with LDLT for patients with Model for End-stage Liver Disease with sodium (MELD-Na) as low as 11 and suggested that the years of life gained were comparable or greater than with deceased donor transplantation.[107] Table 2 demonstrates currently ongoing clinical trials evaluating LT for CRC liver metastases.

**Table 2.** Ongoing clinical trials evaluating Liver Transplant in the Treatment of Colorectal Cancer Liver Metastases.

Trial Name	Start Date	End Date	Enrollment	Treatment	Patient Population	Primary End Point
NCT04161092 (SOULMATE)	2020	2029	45	LT vs best alternative care	Nonresectable CRC Liver metastases	5 year OS
NCT02597348 (TRASMET)	2016	2026	94	LT + chemotherapy vs chemotherapy alone	Nonresectable CRC Liver metastases	5 year OS
NCT02864485	2016	2025	20	LDLT	Nonresectable CRC Liver metastases	5 year patient survival and DFS
NCT05248581	2019	2027	25	LT or LDLT	Nonresectable CRC Liver metastases	5 year RFS and OS
NCT05175092	2023	2030	50	NT + LDLT	Nonresectable CRC Liver metastases	5 year OS
NCT038003436	2019	2024	22	LT vs Chemotherapy	CRC Liver metastases	5 year OS
NCT03494946 (SECAIII)	2016	2027	30	LT vs Chemotherapy, TACE, or SIRT	Nonresectable CRC Liver metastases	2 year OS
NCT04874259	2022	2026	20	LDLT	CRC Liver metastases without prior treatment	1 year patient survival

NCT03488953 (Liver Two Heal)	2018	2023	40	LDLT with two staged hepatec- tomy	Nonresectable CRC Liver me- tastases, stable disease or re- gression after NT	3 year OS
NCT05186116 (LIVERMORE)	2022	2027	25	LDLT	Nonresectable CRC Liver me- tastases	5 year OS and DFS
NCT02215889	2014	2028	20	Partial Liver segment 2/3 transplantation	Nonresectable CRC Liver me- tastases	% of patients receiving 2 <sup>nd</sup> stage hepatec- tomy

Abbreviations: LT (Liver Transplant), CRC (Colorectal Cancer), OS (Overall Survival), LDLT (Living Donor Liver Transplant), DFS (Disease Free Survival), RFS (Recurrence Free Survival), NT (Neoadjuvant Therapy), TACE (Transarterial Chemoembolization), SIRT (Selective Internal Radiation Therapy).

5. Neuroendocrine Tumor

LT for neuroendocrine tumor (NET) is rare and represents only 0.3% of all LT.[108] Most NET liver metastases arise from primary small bowel and pancreatic NET. [109] Given the lack of high-quality long-term data and rarity of the procedure, there is no consensus on LT eligibility criteria for this patient population. [110] Mazzaferro et al. published a set of criteria that recommended patients <60 years old with low grade tumors, resection of their primary tumor, metastatic disease in <50% of their liver volume, and no progression of disease on systemic therapy as eligibility criteria for LT.[111,112]

Although data are limited, a few studies have evaluated LT in the setting of unresectable metastatic liver NET. One study assessed 213 patients who underwent LT for metastatic NET and noted a 5-year OS of 73%.[113] Pancreatic primary tumors, poor tumor differentiation, and metastatic lymph nodes were associated with poor outcomes.[113] In a separate study, Vilsteren et al. reported that primary pancreatic NET was predictive of poor outcomes after LT for metastatic NET.[114] In a separate study that compared LT versus supportive care for metastatic NET among patients who had disease over 122 months, there was an improvement in 5- and 10-year OS in the LT group (97.2 % LT vs 88.8% no transplant and 50.9% LT and 22.4% no transplant, respectively).[115] Given that NET are generally indolent and slow growing, some investigators have proposed time for progression as a criterion for patient selection for transplant.[116] Despite these studies, the long term benefits of LT for metastatic unresectable NET remains unclear, and further prospective study is required.

6. Expert Opinion

Transplant oncology is a quickly evolving field. While LT has been well established for HCC, controversy remains relative to the use of LT for other malignancies. Data have suggested that in appropriately selected patients, LT can prolong OS and potentially be curative. Better patient selection criteria, as well as identification of more accurate prognostic factors that will predict recurrence, as well as ongoing discernment about the ethical considerations are needed.

An area of ongoing research is investigation into prognostic factors to predict which patients may benefit and have the best outcomes from LT especially for CRC liver metastases. The SECA-I study demonstrated that tumor diameter>5.5 cm, CEA level > 80, time from resection of primary to LT <2 years, and progression of systemic therapy were predictors of poor prognosis. The Fong score has been a long-used validated measure to predict recurrence of CRC liver metastases after resection and may be useful in determining which patients have tumors that are high risk for recurrence and thereby may not be good transplant candidates. [117] [118] There are also some data that suggest low metabolic tumor volume (MTV <70 cm<sup>3</sup>) on FDG-PET scan is associated with better patient outcomes.[119] Other proposed prognostic factors include performance status, lymph node metastases,



response to chemotherapy, and biomarkers such as ctDNA.[120-125] However, the evidence for these as true predictors of outcome is limited to retrospective studies and will need to be better elucidated with prospective data.

Additionally, a direct comparison of liver sparing resection versus LT has not been performed. R0 resection is the gold standard curative-intent treatment of patients with liver metastases or primary liver cancers.[126,127] However, among patients with CRC liver metastases with extensive disease defined as >3 metastases 5-year OS can be <40%.[126,127] The SECA-I study demonstrated a much better 5-year OS, however these patients were highly selected so direct comparisons are not feasible[128] There is also some debate about the role of LT in patients with borderline resectable disease, as this would increase the number of patients on the wait list for grafts.[129] Additionally, there are no high quality data directly comparing locoregional therapies such as hepatic artery infusion pumps, Y90, transarterial chemoembolization (among others) to LT relative to oncologic outcomes.

The role of immunosuppression in post-transplant is also another understudied area that requires further study as LT becomes increasingly adopted to treat malignancies. Much of the existing data surround use of mTOR inhibitors, but the role of other more common immunosuppressive regimens such as calcineurin inhibitors has not been extensively studied in terms of graft survival and long-term outcomes. Future studies will need to focus on how immunosuppression impacts tumor recurrence given the role the immune microenvironment plays in tumor development and progression in the liver.[15]

In addition, there are ethical considerations related to transplanting organs for malignancy. The wait list for organs is already long and adding cancer patients as candidates will only increase the wait time for patients with non-oncologic indications. It is imperative that outcomes for transplant oncology recipients be comparable to that of non-oncologic patients. If oncology patients are added to the wait list, how will they be prioritized on the wait list? HCC and hilar CCA patients receive MELD exception points to increase their priority on the wait list.[130-133] However, no such exception points are currently made available for other types of malignancies. As the data continues to grow in support of LT for oncologic indications, the need to prioritize these patients versus other patients on the list will need to be discussed to prevent increased mortality on the wait list. Methods to increase the donor pool become crucial such as LDLT, RAPID procedure, and use of marginal deceased donor grafts. The SOULMATE trial (NCT04161092) is a randomized study assessing LT with higher risk allografts in nonresectable CRC liver metastases that aims to decrease the risk of long wait times for patients on the wait list.[134]

## 7. Conclusion

The field of transplant oncology has increased rapidly over the last few decades in terms of LT for primary and secondary liver cancer. LT for oncologic indications has quickly become an increasingly viable option to treat patients and has been associated with favorable long-term outcomes. Expanding LT to patients with malignant indications may strain organ allocation, and the donor pool will need to be increased through RAPID procedure and LDLT. Pending the results of upcoming clinical trials, LT for oncologic indications will likely become more common in the future.

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