Ann Surg Oncol (2026) 33:561–567
https://doi.org/10.1245/s10434-025-18437-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

REVIEW ARTICLE – HEPATOBILIARY TUMORS

Transplant Oncology—A New Frontier in Liver Cancer Care

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ABSTRACT This report examines the emerging field of transplant oncology, with a focus on liver transplantation for intrahepatic cholangiocarcinoma and colorectal liver metastases, highlighting recent clinical developments, policy implications, and future directions.

TRANSPLANT ONCOLOGY—A NEW FRONTIER IN LIVER CANCER CARE

Transplant oncology is an innovative and rapidly evolving discipline that unites oncologic principles, transplantation science, immunology, and surgery to achieve optimal outcomes for patients with liver malignancies. Through multidisciplinary collaboration among hepatologists, surgeons, and oncologists, the field is transforming how we approach otherwise fatal liver cancers—offering liver transplantation (LT) as a curative or life-extending strategy for highly selected patients.

Although LT for hepatocellular carcinoma (HCC) has been performed for decades—most notably shaped by the establishment of the Milan Criteria in the 1990s—recent advancements have propelled transplant oncology into a new era. Now, integrating molecular profiling, next-generation sequencing, and neoadjuvant therapies allows for precise patient selection based on tumor biology and response, not just tumor size or number.

Breakthroughs in donor pool expansion, perioperative management, and personalized immunosuppression have further improved access and outcomes. The adoption of formal guidelines by the International Liver Transplantation Society and the rise of specialized, nationally coordinated tumor boards reflect the move toward standardized, equitable, and evidence-based care across centers.[1–4]

In today's value-driven, multidisciplinary landscape, transplant oncology re-imagines what is possible for patients with liver cancer, expanding the definition of "cure" and delivering new hope through science, technology, and collaboration.

LIVER TRANSPLANTATION (LT) FOR INTRAHEPATIC CHOLANGIOCARCINOMA (ICCA)

Intrahepatic cholangiocarcinoma (iCCA) is a rare malignancy associated with a poor prognosis. Surgical resection with negative margins remains the only curative-intent treatment for this diagnosis.[5,6] However, most patients are not candidates for resection at the time of presentation because of the typically advanced, locally invasive, or metastatic nature of the disease, often attributed to its asymptomatic progression in early stages.[5,6]

A major challenge in managing iCCA is its clinical and radiographic resemblance to HCC. Accurate staging and diagnosis are critical and can be supported by magnetic resonance imaging for tumor characterization, computed tomography imaging for vascular assessment, and positron emission tomography scanning to detect nodal involvement and extrahepatic disease. In cases with suspicious imaging features, a pretransplant biopsy is recommended to establish a definitive diagnosis, to potentially identify targetable mutations through genetic screening platforms, and to guide appropriate management.

Historical Perspective

Historically, LT for iCCA was often performed under the mistaken preoperative diagnosis of HCC, with final

First Received: 27 May 2025
Accepted: 15 September 2025
Published online: 24 October 2025

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explant pathology revealing either iCCA or mixed hepatocellular cholangiocarcinoma (referred to as cholangiocellular carcinoma).[7-10] Early reports demonstrated poor outcomes, leading to LT being considered a contraindication for iCCA. Recurrence rates were high, with 2-year recurrence-free survival (RFS) of 35% and median time to recurrence of approximately 11 months reported in one series, and 1-year RFS of 52% with all recurrences occurring within 10 months post-transplantation.[7-10] Overall survival (OS) rates were similarly poor, with one study reporting a 21% survival rate.[7-10]

However, these discouraging early results were largely influenced by the lack of standardized selection criteria, small patient cohorts, inconsistent application of adjuvant therapies, and limited understanding of tumor biology. Together, these highlight the need for a more refined and systematic approach to patient selection.

Underlying Biological Heterogeneity of iCCA

Tumor biology is a key factor in determining response to therapy. Retrospective series have shown that differentiation of tumor and vascular invasion are associated with recurrence in iCCA, with moderately and poorly differentiated tumors having earlier recurrence (28.6% in well-differentiated tumors, 39.1% in moderately differentiated tumors, 83.3% in poorly differentiated tumors) and decreased RFS (13 months with 1- and 3-year RFS of 56% and 22%) compared with well-differentiated tumors.[11] In addition, the presence of vascular invasion can also lead to early recurrence.[12,13]

Recent studies have highlighted that tumor biology rather than absolute tumor burden (tumor size and number) is likely more highly associated with outcomes in patients undergoing surgery for iCCA.[14]

Evolution of Transplant Strategy

Given the complex nature of this disease, the often locally advanced state at presentation, and an understanding of the need to define the nature of the biology of the particular tumor, there has been an emphasis in locoregional downstaging modalities to improve long-term outcomes. Orthotopic liver transplantation (OLT) for iCCA in patients with primary sclerosing cholangitis with or without cirrhosis offers the advantage of achieving oncologically maximal negative margins with complete replacement of the diseased liver, addressing not only the tumor and potential intrahepatic micro metastases and but also the underlying field defect in the diseased liver.

Hong et al.[15] looked at 37 patients with iCCA, of which 35/37 (95%) had locally advanced disease. Adjunctive therapy was used in 35 patients (61%). Of note, the authors looked at both resection and LT. The 5-year tumor RFS was higher in the LT group than in the resection group (33% vs 0%; $p=0.05$). In the LT group, neoadjuvant and adjuvant therapies resulted in better patient survival than no therapy or adjuvant therapy (47% vs 20% vs 33%, respectively; $p=0.03$).

Sapisochin et al.[11] published on the role of LT in the treatment of very early iCCA. This study was a multi-institutional retrospective study looking at patients who were transplanted for what was thought to be HCC in the setting of decompensated cirrhosis and were incidentally found to have iCCA on final explant (81 patients). Of these 81 patients, 33 had separate nodules of mixed iCCA and HCC, and 48 had only iCCA—this served as the study group. Within the study group, 15 (31%) patients were further classified as having "very early" (single tumor ≤ 2 cm) iCCA, and 33 (69%) were classified as having advanced iCCA (single tumor >2 cm or multifocal disease). At a median follow-up of 35 months, the 1-, 3-, and 5-year cumulative risk of recurrence was 7%, ??%, and 18% in the very early group versus 30%, 47%, and 61% in the advanced iCCA group ($p=001$). The 1-, 3-, and 5-year actuarial survival rates were 93%, 84%, and 65% in the very early group versus 79%, 50%, and 45% in the advanced group ($p=0.02$). Given these findings, the authors concluded that patients with cirrhosis and very early iCCA may experience survival benefit from LT. Further, as the recurrences in this group were largely extrahepatic, the authors concluded that there may be a role for neoadjuvant therapy to reduce rates of systemic recurrence in patients who would qualify for LT. Therefore, there has been growing interest in neoadjuvant and adjuvant therapies in the care paradigms of patients with iCCA as a bridge to LT.

Lunsford et al.[16] looked at 21 patients with locally advanced, unresectable iCCA without extrahepatic disease or vascular involvement who were treated with neoadjuvant chemotherapy followed by LT. Of the 21 patients referred for evaluation, 12 were accepted and six underwent LT for iCCA. The median duration from diagnosis to transplantation was 26 months, with a median follow-up from LT of 36 months. All patients received neoadjuvant chemotherapy while awaiting LT. OS at 1, 3, and 5 years was 100%, 83.3%, and 83.3%, with 50% RFS at 1, 3, and 5 years.

McMillan et al.[14] published the largest experience of a prospective protocol for patients with locally advanced, unresectable iCCA who were treated with neoadjuvant systemic chemotherapy for at least 6 months with proven disease stability followed by staging and LT. A total of 37 patients were listed for LT, of whom five underwent resection based on their response to neoadjuvant chemotherapy. Of the 32 patients listed, 18 underwent LT. A total of 14 patients did not undergo LT; three because they developed extrahepatic disease, two were reported as death related to disease, two patients had

transplants that were aborted, and—at the time of analysis—seven patients remained on the transplant list. The most commonly utilized chemotherapy regimen was gemcitabine and cisplatin based on the results from the ABC II trial. Most patients did not have a high Model for End-Stage Liver Disease (MELD) score; the median MELD was around 8. Most patients underwent deceased donor transplants (14 of which were brain-dead donors, one was a donor after circulatory death), and three were split livers. OS from time of transplant listing was calculated for all 32 patients as an intention-to-treat analysis. The 1-, 3-, and 5-year survival for patients on the protocol were 90%, 61%, and 49%, respectively. Further analysis was completed on patients who were listed and transplanted versus those who were listed but not transplanted. The median follow-up time was 26 months. The 1-, 3-, and 5-year survival from the time of listing for patients who were transplanted was 100%, 71%, and 57%, respectively. The 1-year survival from time of listing for patients who did not receive a liver transplant was 71%, with a decline after 1 year. In total, 38.9% (7/18) of patients had an RFS at 1 and 3 years of 70% and 52%, with a median time to recurrence of 11 months. Patterns of recurrence included extrahepatic (lung, bone), peritoneal, and portal recurrences.

Based on these historical evolving experiences, the transplant community now recognizes OLT for iCCA as a relevant option in two distinct clinical scenarios. First, OLT is considered appropriate for patients with very early-stage disease (single tumor ≤ 2 cm) who have underlying cirrhosis and are not candidates for surgical resection. Second, OLT is an emerging consideration for patients with locally advanced tumors where liver resection is not technically feasible because of vascular involvement, complex anatomy, or an insufficient future liver remnant.

Three prospective trials are under way to further clarify the role of LT in the management of iCCA. The results of these studies are expected to support the development of standardized selection criteria and to define the utility and sequence of neoadjuvant downstaging strategies, including transarterial chemoembolization, radioembolization, and systemic chemotherapy and immunotherapy, to better define tumor biology and identify patients most likely to benefit from transplantation.

Policy Update: MELD Exception and the Role of the National Transplant Oncology Review Board (NTORB)

Rationale and Development of the NTORB

There is growing recognition at the regulatory level of the need to standardize transplant evaluation for liver cancers historically considered relative contraindications. Significant variability in MELD exception use across United Network for Organ Sharing (UNOS) regions has highlighted inconsistent access, and traditional liver disease metrics fail to capture oncologic urgency and potential benefit. In response, in 2024, the Adult National Hepatocellular Review Board was renamed the Adult National Transplant Oncology Review Board (NTORB).[17] This was established to create a unified framework for case review and exception allocation for potential oncological indications for transplant. These efforts aim to redefine LT as a curative option for select malignancies, emphasizing standardized criteria, equitable access, and alignment with evolving oncologic outcomes.

MELD Exception Pathways for iCCA

Broadly, MELD exception points allow for patients without decompensated cirrhosis, and specifically patients with either benign diagnoses or oncologic diagnoses, an opportunity to be allocated elevated MELD points to obtain a score that would allow them access to organs, which would enable timely transplantation.

Several diagnoses qualify for MELD exception points based on specific UNOS-determined criteria. As of spring 2025, the NTORB will provide MELD exception points (median MELD at transplant: 3) for patients who have biopsy-proven unresectable solitary iCCA or mixed HCC–iCCA ≤ 3 cm with 6 months of tumor stability after locoregional or systemic therapy. Transplant programs applying for MELD exception points should provide the following documentation for consideration: biopsy-proven iCCA or mixed HCC–iCCA, presence of cirrhosis, unresectable disease, treatment with locoregional or systemic therapy, 6 months from time of diagnosis or last treatment of tumor stability (tumor < 3 cm, no new lesions or development of extrahepatic disease).[18]

LT FOR COLORECTAL LIVER METASTASES (CRLM)

Rationale for LT in CRLM

Colorectal liver metastases (CRLM) remain the main cause of mortality in patients with colon cancer. Therefore, the development of CRLM has a strong impact on OS, with a median 5-year OS of $< 14\%$ with palliative-intent systemic chemotherapy.[19-21] Mortality is driven by liver disease. For patients with liver-limited metastatic disease, surgical resection was historically the only curative-intent modality for treatment, with 5- and 10-year survival rates of 42% and 25%, respectively.[20,21] Over the last few decades, improvements in systemic chemotherapy and locoregional treatment options has meant that increasing numbers of patients have been converted from unresectable to resectable liver disease. Further, the use of hepatic arterial infusion pumps and radiofrequency ablation[22-24] have offered results that

may justify consideration of these as destination therapy in selected cases.

Since 2013, few studies have shown the benefit of LT in selected patients with unresectable CRLM.[25,26] Several landmark trials with an emphasis on evolving selection criteria have helped pave the way for optimal patient selection with rigorous criteria to define tumor biological response to treatment, allowing for favorable outcomes.

Landmark Trials and Evolving Selection Criteria

The first trial to look at OLT in patients with metastatic colorectal cancer (mCRC) was the Norwegian SECA-I trial.[27] This was the first prospective pilot study to assess the safety and effectiveness of LT for mCRC. Of the 25 patients listed, 21 underwent LT (84%). After a median follow-up of 27 months, 1-year and 5-year OS was 95% and 60%, respectively, and the disease-free survival rate at 1 year was 35%. The SECA-I trial helped identify prognostic factors associated with CRLM that were associated with survival. These included lesion diameter, time interval from primary tumor resection < 2 years, elevated carcinoembryonic antigen levels (>80 ng/mL), and progression of disease at the time of LT. Based on these factors, patients were given a score known as the Oslo prognostic score (Table 1). This study also highlighted that patients who had high positron emission tomography–computed tomography avidity in liver metastases proximal to LT had worse OS. Median time to recurrence was 8 months. The most frequent pattern of recurrence was in the lung (80%), followed by the transplanted liver (33%).

The SECA-II trial[28] applied more stringent selection criteria and included 15 patents with mCRC with unresectable liver only metastases. Unlike SECA-I, inclusion criteria included patients who received first-line treatment with a 10% response measured with Response Evaluation Criteria in Solid Tumors after chemotherapy. After a median follow-up of 36 months, OS rates at 1, 3, and 5 years was 100%, 83%, and 83%, respectively. Disease-free survival (DFS) rates at 1, 3, and 5 years were 53%, 44%, and 35%, respectively, with a median follow-up of 13.7 months. Compared with patients in SECA-I, those in SECA-II did not have evidence of disease progression on chemotherapy or carcinoembryonic antigen levels >80 ng/L at the time of LT.

The TRANSMET trial[29] was published in 2024 and was the first multicenter, open-label, prospective, randomized controlled trial involving 20 tertiary centers in Europe. Inclusion criteria included Eastern Cooperative Oncology Group performance score of 0–1, up-front unresectable CRLM from *BRAF* non-mutated colorectal cancer with primary removed, responsive to systemic chemotherapy (defined as stable or partial response on last chemotherapy protocol [based on RECIST criteria] lasting ≥ 3 months while on ≤ 3 lines of chemotherapy) with no evidence of extrahepatic disease. Patients were randomized in a 1:1 fashion to LT and chemotherapy or chemotherapy alone. Time from randomization to LT in that group was ≤ 2 months after the last chemotherapy cycle. In total, 94 patients were accrued over a 5-year period, and ultimately 36 and 38 patients were assigned to the LT and chemotherapy group and chemotherapy-only group, respectively. Median follow-up was 59.3 months (interquartile range 42.4−60.2). The 5-year OS rate was 57% with chemotherapy + LT and 13% with chemotherapy alone in the intention-to-treat analysis, 73% with chemotherapy + LT versus 9% with chemotherapy alone (in the per protocol analysis) with median PFS of 174 months with chemotherapy + LT and 6.4 months with chemotherapy alone. Of note, 74% of transplanted patients developed recurrence, with almost half of them being amenable to surgery or ablation.

TABLE 1 Oslo criteria

Parameter	Criteria
Histology	Moderate or well-differentiated
Stable extrahepatic disease	No evidence of progression
CEA level	≤ 100 μg/L
Number of liver lesions	≤ 6
Response to chemotherapy	At least stable disease

CEA carcinoembryonic antigen

National Policy Perspective

MELD Exceptions for CRLM Under NTORB

With the initiation of the Transplant Oncology Task Force for liver malignancies—including iCCA and mCRC—the primary goal is to advocate for MELD exception points that ensure equitable and timely access to LT for eligible patients. However, achieving this requires a robust, multidisciplinary validation process and consensus across transplant centers to minimize institutional bias in patient selection. For instance, in the TRANSMET trial, 40% of patients deemed eligible by specialized centers were ultimately rejected by the central committee, 32% because of tumor progression and 8% based on potential resectability, a criterion that remains subjective and variable across institutions. This underscores the urgent need to establish standardized, consensus-driven selection criteria to promote fairness and consistency in transplant eligibility.

Gaps in Evidence and Ongoing Needs

In mCRC, it is increasingly evident that a deep understanding of tumor biology—and the identification of reliable biomarkers that reflect it—is critical to improving outcomes. The evolution of clinical trials supporting LT as a viable option for patients with initially unresectable, liver-only metastases has reinforced the importance of tumor biology and recurrence risk in guiding patient selection, optimizing organ allocation, and shaping best practices in clinical care.

Emerging data support the use of liquid biopsy to detect circulating tumor DNA (ctDNA) as a strong prognostic marker for RFS in liver-only mCRC. Multiple trials have demonstrated that patients with positive post-surgical ctDNA are at significantly higher risk of recurrence than those with negative results.[30-33]

In addition to the work with ctDNA, advances in artificial intelligence, radiomics, genomics, and molecular profiling are playing an increasingly vital role in risk stratification and personalized treatment planning.[4,34]

These findings also underscore the reality that recurrence remains a significant challenge. As such, they highlight the need to tailor post-transplant surveillance strategies, explore immunosuppression modulation, and proactively consider the use of adjuvant systemic or locoregional therapies.

THE FUTURE OF TRANSPLANT ONCOLOGY: SYSTEMS, ETHICS, AND OUTCOME REDEFINITION KEY POINTS

The Multidisciplinary Model

Integrated collaboration among hepatology, medical oncology, transplant surgery, radiology, pathology, and interventional radiology forms the foundation of transplant oncology. This multidisciplinary approach enables a comprehensive strategy that effectively merges cancer care with transplant expertise, ensuring optimal patient selection, treatment planning, and long-term outcomes.

Evolution of the NTORB

Historically, there has been significant variability in the use of MELD exception points across UNOS regions. Overall, patients granted MELD exceptions have been nearly twice as likely to undergo LT (70.8% vs 39.1%) and are half as likely to be removed from the waitlist because of death or clinical deterioration (9.2% vs 18.2%).[35] Importantly, the use of MELD exception points in conditions such as HCC and perihilar cholangiocarcinoma has demonstrated favorable outcomes for patients awaiting LT.

This precedent underscores the transformative potential of expanding MELD exceptions to include select non-traditional indications, such as liver-limited mCRC and iCCA, offering hope and a meaningful chance at improved survival and quality of life. Embracing such a model exemplifies a forward-thinking, patient-centered approach to transplant oncology.

Role of Prospective Registries and Real-World Evidence

The development of prospective, granular, and transparent registries is essential in this emerging and largely undefined field. The American Registry for Transplant Oncology, sponsored by the ASTS and located at University of Rochester under the direction of Dr Hernandez Alejandro, serves as an excellent foundational model. Designed to collect outcomes data specifically for LT in patients with unresectable CRLM, the American Registry for Transplant Oncology will gather multi-institutional data from centers across the USA and Canada. The registry plans to report on perioperative outcomes, followed by 2-, 3-, and 5-year survival and recurrence outcomes.[36–38]

To truly advance the field, this registry model must be expanded and enhanced—ideally through the integration of real-world data and artificial intelligence tools—to support continuous learning and improved clinical decision-making.

Ethical and Equity Considerations

Ethical concerns and equitable access remain central issues in the allocation of organs, particularly in light of the ongoing shortage of suitable donor organs. However, advancements in technology—such as machine perfusion systems and normothermic regional perfusion—are helping expand the donor pool by enabling the use of organs that were previously considered marginal or unsuitable.[39–41]

In addition, emerging data support the feasibility of living donor LT for select patients with advanced malignancies, offering a potential pathway to transplant for those who might otherwise be excluded because of organ scarcity.

To uphold principles of equity and responsible innovation, it is essential to continue expanding and standardizing access to these technologies and approaches. Doing so will ensure that expanded indications for LT are pursued in a way that is both ethically sound and clinically effective, balancing innovation with fairness, especially when considering the risks and implications of living donation.

Expanding the Metrics of Success

Traditional metrics such as 1-year patient and graft survival are insufficient to fully capture the complexity of success in transplant oncology. This is particularly evident in indications such as CRLM, where there is often a marked discrepancy between DFS and OS, highlighting

the limitations of conventional endpoints. A more comprehensive assessment of outcomes is therefore needed. Incorporating DFS, OS, and quality-of-life metrics allows for a nuanced understanding of patient trajectories, especially in recognizing the impact of secondary treatments following recurrence. For instance, in the SECA-I study, approximately 33% of patients experienced lung-only recurrences, many of which were amenable to curative-intent interventions such as ablation or resection. These findings underscore the importance of tracking recurrence patterns and the feasibility of subsequent therapies. In parallel, patient-reported outcomes and survivorship models are increasingly recognized as essential components of success. The integration of quality-of-life measures and the development of dedicated survivorship programs tailored to the unique needs of transplant oncology patients will be critical in shaping the next generation of outcome standards in this evolving field.

CONCLUSION

Transplant oncology stands at the cutting edge of curative cancer care, offering new hope for patients with select malignancies once deemed untreatable by surgical means. Yet, the true promise of this field can only be realized through a more deliberate, evidence-informed, and ethically guided evolution.

As our collective experience grows, drawing on retrospective data, prospective studies, and emerging clinical trials, it is essential that the field embraces dynamic protocols that are continuously updated based on real-world outcomes and robust evidence. Future progress hinges on the creation and refinement of multidisciplinary validation committees, ensuring transparent, equitable, and contextually sensitive decision-making for every candidate.

We must couple innovation with a deep sense of responsibility. This includes a rigorous commitment to the just allocation of the limited donor organs, stewardship guided by ongoing outcome data, and ongoing dialogue on the ethical implications of novel indications. Institutional protocols must be living documents: regularly reviewed, rapidly adaptable, and rooted in shared learning, supported by national and international registries as well as collaborative research networks.

Above all, equity must be a central pillar. As we push the boundaries of what transplant oncology can achieve, we must actively identify and address disparities in access to evaluation and care, guaranteeing that advances benefit all populations, regardless of geography, background, or circumstance.

We issue a call to action for the transplant oncology community: Advance innovation with prudence, foster broad-based collaboration, implement robust and equitable practices, and place patient-centric, multidisciplinary excellence at the heart of every decision. Only then can transplant oncology fulfill its potential as a model of precision, compassion, and global leadership in cancer care.

DISCLOSURE The authors declare no conflicts of interest.

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