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Transplant oncology in locally advanced intrahepatic cholangiocarcinoma: One more step on a long road

Tommy Ivanics
Henry Ford Health, tivanic1@hfhs.org

Christian Toso

Sumera I. Ilyas

Gonzalo Sapisochin

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EDITORIAL

Transplant oncology in locally advanced intrahepatic cholangiocarcinoma: One more step on a long road

In the current issue of *American Journal of Transplantation*, McMillan et al. analyze the survival after liver transplantation (LT) for patients with locally advanced, unresectable, intrahepatic cholangiocarcinoma (iCCA), building upon their earlier experience.[1,2] iCCA has long represented a contraindication for LT due to historically poor results, largely driven by an absence of strict selection criteria and limited understanding of tumor biology. The re-appraisal of LT as a curative-treatment modality for iCCA has been catalyzed by favorable oncologic results in patients with iCCA discovered after LT in several single- and multi-institutional studies.[3] Many iCCA patients present with locally advanced disease that precludes resection, resulting in dismal outcomes. Available treatment options for these patients include systemic and locoregional therapy—none of which have curative potential.

In contrast to previous studies in the field, all patients in the study by Mcmillan et al. had an iCCA diagnosis before listing. Their iCCA LT protocol is based on receipt of neoadjuvant therapy (with first-line being gemcitabine-cisplatin[4]) and demonstration of disease stability for at least six months (based on radiographic assessment).[2] To be included, patients could have any tumors confined to the liver in the absence of vascular or lymph node involvement. Over eleven years, 65 patients were referred, of which 28 were denied transplant listing. Five patients listed became eligible for resection due to disease regression with neoadjuvant therapy and were excluded. Of the thirty-two patients included, eighteen underwent LT, and fourteen did not. Seven patients dropped out due to disease progression. The intention-to-treat 1-, 3-, and 5-year survival was 90%, 61%, and 49%. However, the exclusion of the five listed patients who underwent resection may have led to an underestimation of the survival in the non-LT group. Patients able to undergo LT had better survival than patients who did not (1-, 3-, and 5-year LT: 100%, 71%, 57% vs. 1-year non-LT 71%;$p = 0.004$), though this comparison is susceptible to selection bias. Notably, the recurrence-free survival at 3-years was 52%, with seven of the eighteen patients transplanted developing recurrence (four of which recurred within the first year).

The authors should be commended for pushing the envelope in transplant oncology and helping move the needle in this realm. This progress has been afforded by way of a well-developed protocol and a highly experienced multi-disciplinary team effort. As in any study, some limitations should be acknowledged, as building upon these will support future efforts in understanding the role of LT for iCCA. Patients included in the study represented a highly selected group. As acknowledged by the authors, one reflection of this is the lack of racial and ethnic diversity. Another is the potential for systematic bias regarding socioeconomic status and access to health care. Consequently, these points call into question the generalizability of the findings, along with the potential for unmeasured and residual confounding. Moreover, the patient population and pre-LT treatment strategies were heterogeneous (including various types of locoregional therapies, liver resection, and targeted therapies including IDH-1-, FGFR-, and PARP-inhibition). Though there were no statistically significant differences between the groups in the distribution of such treatments, possibly due to a small sample size, there may be residual confounding with regards to the nuances in these therapies. In addition, the range of time between diagnosis and listing was wide (74–1054 days), suggesting variability in the ability to assess tumor biology clinically. The pre-LT treatment heterogeneity is understandable given the rarity of these tumors and is also reflective of "real-life" individualized treatment strategies. However, it somewhat opacifies our understanding for which patients LT may come to represent a realistic option. Next-generation sequencing was performed for almost all patients, but the patterns of genetic alterations did not differ between groups. Nevertheless, prior studies would suggest that patients with more favorable alternations will be better candidates for LT.[5] The small study size limits the potential of performing a risk-factor analysis to identify factors associated with better or worse outcomes, including early recurrence. Therefore, it is imperative that future studies, ideally using multicenter designs, aim to amass a sufficient number of patients to yield adequate statistical power to detect inter-group differences. Such differences can help refine prognostication and improve treatment selection strategies. External validation of these results with well-defined neoadjuvant protocols will be essential in the effort to standardize this as a treatment option for a subset of iCCA patients. Several potential strategies can be considered for refining future iCCA liver transplant protocols (Table 1). Finally, we must be mindful of which patients should represent the comparison group for iCCA patients considered/listed for LT as the other treatment options are non-curative. Despite several challenges to performing randomized controlled trials in transplant oncology, there should be a global effort in that direction.[6] The authors should be congratulated on their efforts in the transplant oncology domain. Their study shows that, while LT is not the panacea for all iCCA patients, it can represent the much-needed beacon of hope for some.

TABLE 1 Potential strategies for refining future iCCA liver transplant protocols

Strategy	Example
Identification of genetic determinants that portend a better or worse prognosis	- A recent bi-institutional study of unresectable iCCA patients identified specific genetic determinants, such as TP53, KRAS, and cyclin-dependent kinase inhibitor 2a (CDKN2A), to portend a worse prognosis.[6]
Clarifying the static and dynamic role of biomarkers such as CA 19-9	- Elevated CA19-9 is a risk factor for mortality in iCCA similar in impact to nodal metastases and positive resection margins.[7]
The use of new innovative technologies	- Radiomics, a field of imaging-based research that can extract data from imaging and be used as an imaging-based biomarker, can also possibly improve the characterization of more indolent disease. - Machine learning technology can be leveraged to identify favorable and unfavorable disease phenotypes based on all available clinical, genetic, and radiographic information.
Novel therapies	- Targeted therapies, such as FGFR-inhbition for iCCA with FGFR2 fusion.[8] - The addition of immune checkpoint inhibition to chemotherapy has shown early promise and potential benefit compared to standard-of-care chemotherapy (gemcitabine-cisplatin) and may help more patients reach the point of being considered for LT in the setting of ongoing and future trials.[9]

KEYWORDS

cancer/malignancy/neoplasia, clinical research/practice, liver disease: malignant, liver transplantation/hepatology,

DISCLOSURES

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Tommy Ivanics[1,2,3]
Christian Toso[4]
Sumera I. Ilyas[5]
Gonzalo Sapisochin[1,6]

[1]*Multi-Organ Transplant Program, University Health Network, Toronto, Ontario, Canada*
[2]*Department of Surgery, Henry Ford Hospital, Detroit, Michigan*
[3]*Department of Surgical Sciences, Akademiska Sjukhuset, Uppsala University, Uppsala, Sweden*
[4]*Division of Abdominal Surgery, Geneva University Hospitals, University of Geneva, Geneva, Switzerland*
[5]*Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota*
[6]*Division of General Surgery, University Health Network, Toronto, Ontario, Canada*

Correspondence
Gonzalo Sapisochin, Division of General Surgery, University Health Network, 585 University Avenue, 11PMB184, Toronto, M5G 2N2 ON, Canada.
Email: Gonzalo.sapisochin@uhn.ca

ORCID

Tommy Ivanics https://orcid.org/0000-0002-1312-4470
Christian Toso https://orcid.org/0000-0003-1652-4522
Sumera I. Ilyas https://orcid.org/0000-0002-2709-3003
Gonzalo Sapisochin https://orcid.org/0000-0001-9527-8723

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