Letter to the Editor

Liver transplantation for cholangiocarcinoma: exploring a new land

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Liver transplantation (LTx) for cholangiocarcinoma (CCA): exploring a new land

CCA is a rare malignancy arisen from biliary system, whose incidence is increasing in these years. According to the tumor anatomical location with the second-order bile ducts, CCA is classified as intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA). Surgical resection is a preferred management of cholangiocarcinoma, when radiofrequency ablation, transarterial chemoembolisation, and radiotherapy are optional treatments for those unresectable tumors (1). LTx is a considerable treatment with some liver diseases, especially early-stage hepatocellular carcinoma and is widely performed over the world, providing better prognosis. However, CCA is considered as contraindication of LTx for a long time until some studies reveal the potential management in selected patients.

Recently, Laughlin *et al.* published a retrospective single-center study in the *Journal of Gastrointestinal Oncology* and reported the different outcomes for patients with eCCA undergoing three different regimens: neoadjuvant chemoradiotherapy (nCRT) and orthotopic LTx, surgical resection and adjuvant chemoradiotherapy (aCRT), and definitive chemoradiotherapy (dCRT) (2). In their study, 20 out of 65 patients underwent orthotopic LTx after nCRT, 16 patients were treated with surgical resection and aCRT, and the rest 29 patients received dCRT only. The overall survival (OS) of patients at 3 and 5 years in nCRT group (78% and 59%) and aCRT group (49% and 38%) was significantly improved than that in dCRT group (16% and 0%), resulting from treatment strategy only in multivariate analysis. Also, the local progression-free survival and disease-free survival were higher in nCRT group (50% and 61%) and aCRT group (30% and 30%) than these in dCRT group (0% and 0%). Unlike poor outcomes reported in LTx treatment alone, undergoing nCRT before LTx improved the prognosis. In the era of neoadjuvant treatment for CCA combining LTx with chemoradiotherapy, this research provides a new potential approach to manage some featured patients with eCCA.

For CCA, the treatments are limited, especially for unresectable tumors, and risk of recurrence is high (3,4). So, good survivals of LTx treatment are encouraging. LTx for eCCA, especially perihilar CCA (pCCA), began long times ago but the outcomes were not so satisfactory until

Table 1 Recruiting prospective clinical trials of liver transplantation for cholangiocarcinoma

Type	Estimated participants	Stage	Combined therapy	Institution/country	Study start date	Estimated study completion date	Phase	ClinicalTrials.gov ID
iCCA	30	Very early	NA	University Health Network, Canada	April 2018	January 2029	Phase II	NCT02878473
iCCA	15	Unresectable	nCRT	Oslo University Hospital, Norway	June 2020	May 2035	NA	NCT04556214
pCCA	15	Unresectable	nCRT	Oslo University Hospital, Norway	September 2021	May 2045	NA	NCT04993131
pCCA	34	Unresectable	nCRT	Hospital Vall d'Hebron, Spain	April 2020	June 2025	NA	NCT04378023
CCA	100	Unresectable	nCRT	Washington University School of Medicine, USA	August 2005	December 2022	NA	NCT00301379

iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; NA, not applicable; nCRT, neoadjuvant chemoradiotherapy.

the use of neoadjuvant chemoradiotherapy before LTx in Mayo protocol (5). In the protocol, patients should be with pathologically confirmed pCCA or evaluated carbohydrate antigen 19-9 (>100 ng/mL) with radiologically malignant stricture. Besides, the size of tumor should be under 3 cm without distant metastases and lymph node metastases. Appropriate patients will receive a consecutive therapy of external-beam irradiation with intravenous 5-fluorouracil (5-FU), brachytherapy and oral maintenance capecitabine when they are waiting for LTx. The 5-year OS of patient was up to 82%. A more recent multi-center retrospective research also reported similar result in strict selected patients with pCCA undergoing neoadjuvant regime of Mayo protocol (6). Patients undergoing LTx had better OS (3-year: 72%; 5-year: 54%) than that of resection (3-year: 44%; 5-year: 19%). Similarly, a meta-analysis involving 428 patients shows improved 5-year OS rates and less recurrence in neoadjuvant chemoradiation group (65.1%; 24.1%) compared to the LTx only (31.6%; 51.7%) (7).

Regime of neoadjuvant chemoradiation before LTx is also suitable for iCCA. Sapisochin *et al.* perform a retrospective multicenter study on neoadjuvant chemoradiation before LTx in very early iCCA, defined as single tumors ≤2 cm. The 5-year OS is better in very early iCCA group (65%) than that in advanced iCCA group (45%). Meanwhile, the 5-year cumulative risk of recurrence in very early iCCA group (18%) is lower than that in advanced iCCA group (61%). Interestingly, McMillan *et al.* provided good outcomes for patients with locally-advanced, unresectable iCCA receiving LTx after neoadjuvant therapy (8). The locally-advanced, unresectable iCCA is defined as a single tumor ≥2 cm or multiple tumors without distant metastases, lymph node metastases and encasement or involvement of major vascular structures. Patients received neoadjuvant therapy for 6 months and disease should be stable without extrahepatic disease before LTx was performed. The OS at 1-, 3-, and 5-year is 100%, 71%, and 57%, which supported LTx with neoadjuvant therapy as an effective regime for locally-advanced, unresectable iCCA.

In summary, some highly-selected patients with CCA may be the potential candidate for LTx along with neoadjuvant chemoradiation. Remarkably, the roles of LTx as a reasonable therapeutic strategy for CCA is being extensively studied (*Table 1*) and we await the outcomes of large-scale randomized prospective studies. Additionally, targeted therapy and immunotherapy are widely applied to the treatment of cholangiocarcinoma as more and more molecular therapeutic targets of are revealed (9,10). Combining targeted therapy and immunotherapy with neoadjuvant therapy before LTx may lead to a more satisfying prognosis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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