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

Lin-Feng He¹,²,³, Tao Lv¹,², Yong-Fa Huang⁴,⁵, Yao Xiao⁶, Gang Xu¹,², Jia-Yin Yang¹,²

¹Liver Transplant Center, Organ Transplant Center, West China Hospital of Sichuan University, Chengdu, China; ²Laboratory of Liver Transplantation, Frontiers Science Center for Disease-Related Molecular Network, West China Hospital of Sichuan University, Chengdu, China; ³West China School of Medicine, Sichuan University, Chengdu, China; ⁴Liver Transplantation Center, National Clinical Research Center for Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, Beijing, China; ⁵Clinical Center for Pediatric Liver Transplantation, Capital Medical University, Beijing, China; ⁶Division of Transplant Surgery, Department of Surgery and Transplant Surgery Research Laboratory, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

Correspondence to: Dr. Gang Xu, MD. Liver Transplant Center, Organ Transplant Center, Laboratory of Liver Transplantation, Frontiers Science Center for Disease-related Molecular Network, West China Hospital of Sichuan University, 37 Guoxue Lane, Wuhou District, Chengdu 610041, China. Email: gangxu@wchscu.cn; Prof. Jia-Yin Yang, MD, PhD. Liver Transplant Center, Organ Transplant Center, Laboratory of Liver Transplantation, Frontiers Science Center for Disease-Related Molecular Network, West China Hospital of Sichuan University, 37 Guoxue Lane, Wuhou District, Chengdu 610041, China. Email: doctoryjy@scu.edu.cn.

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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
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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