Neoadjuvant Locoregional Therapy and Recurrent Hepatocellular Carcinoma after Liver Transplantation

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BACKGROUND: Neoadjuvant locoregional therapies (LRTs) have been widely used to reduce tumor burden or to downstage hepatocellular carcinoma (HCC) before orthotopic liver transplantation (OLT). We examined the impact of LRT response on HCC recurrence after OLT.

STUDY DESIGN: We performed a retrospective study of 384 patients with HCC treated by OLT. Tumor necrosis was determined by pathologic evaluation. The vascular and lymphatic vessels were localized by immunofluorescence staining in formalin-fixed, paraffin-embedded tissue; expressions of vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3 were analyzed by Western blot. Plasma vascular endothelial growth factor (VEGF)-A and VEGF-C levels of a consecutive cohort of 171 HCC patients were detected by ELISA.

RESULTS: Of the 384 patients with HCC, 268 had undergone pretransplantation neoadjuvant LRTs. Patients with no tumor necrosis ($n = 58$; 5.2% recurrence) or complete tumor necrosis ($n = 70$; 6.1% recurrence) had significantly lower 5-year recurrence rates than those with partial tumor necrosis ($n = 140$; 22.6% recurrence; $p < 0.001$). Lymphatic metastases were significantly more numerous in patients with partial tumor necrosis than in those without tumor necrosis after OLT ($p < 0.001$). With immunofluorescence staining of peritumor zone, lymphatics were visualized around partially necrotic tumors, but not around tumors without necrosis. Plasma levels of VEGF-A and VEGF-C were elevated significantly in patients with evidence of tumor necrosis ($n = 102$) compared with those without necrosis ($n = 69$; $p < 0.001$). By Western blot, VEGFR-2 and VEGFR-3 expression in the peritumoral tissue associated with partially necrotic tumors was significantly higher than in peritumoral tissue of non-necrosis tumors ($n = 3$/group, $p < 0.020$ and $p < 0.006$, respectively).

CONCLUSIONS: Locoregional therapy-induced or spontaneous partially necrotic HCC was associated with increased risk of lymphatic metastases compared with tumors with no or complete tumor necrosis. Anti-lymphangiogenic agents with neoadjuvant LRTs can decrease the pattern of lymphatic metastasis after OLT. (J Am Coll Surg 2017;225:28–40. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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The incidence of hepatocellular carcinoma (HCC) in the US is increasing rapidly, from approximately 10,000 cases per year in the 1980s to a projected incidence of 34,000 cases per year by 2019.[1] Orthotopic liver transplantation (OLT) is the optimal treatment option for HCC in cirrhosis because of the removal of the "field defect" of the cirrhotic liver, and establishment of normal hepatic synthetic function.[2] However, only patients presenting with early-stage HCC and cirrhosis are currently recognized as appropriate candidates for OLT.[2] Organ allocation by the United Network for Organ Sharing for HCC is based on the Milan criteria under the Model

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Abbreviations and Acronyms

CN = complete necrosis
FFPE = formalin-fixed, paraffin-embedded
HCC = hepatocellular carcinoma
HR = hazard ratio
LRT = locoregional therapy
MELD = Model for End-Stage Liver Disease
NN = non-necrosis
OLT = orthotopic liver transplantation
PN = partial necrosis
RFA = radiofrequency ablation
TACE = transarterial chemoembolization
VEGF = vascular endothelial growth factor
VEGFR = vascular endothelial growth factor receptor

for End-Stage Liver Disease (MELD); since 2002, only patients with stage II tumors receive automatic exception points. Selected by these criteria, liver transplantation results for HCC are similar to those for chronic liver disease without malignancy. Prolonged waiting times due to the shortage of donor organs can increase the risk for disease progression.[3] Neoadjuvant locoregional therapies (LRTs), such as transarterial chemoembolization (TACE), transarterial radioembolization, and radiofrequency ablation (RFA), have been used to prevent tumor progression for early-stage patients or to downstage potential candidates.[3,4]

The effect of LRT on the outcomes of transplantation for HCC has been an area of active investigation. The use of preoperative LRT using TACE, transarterial radioembolization, RFA, or some combination, has been variable among transplantation centers. Several studies have reported remarkable anti-tumor activity with TACE, but no long-term oncologic benefits were observed.[2,5,6] Therefore in principle, it was recognized that downstaging could have served as an additional selection tool for tumors with more favorable biology and better prognosis, which can be assessed by response to LRT.[7,8] It was also demonstrated that continued use of TACE while on the wait list for OLT should be considered, as long as the patient and the lesions were suitable for re-treatment; the wait time before OLT appeared to be related to survival and recurrence after OLT, which could reflect the presence of more-aggressive tumor biology in patients prematurely undergoing transplantation.[9] However, some randomized controlled trials demonstrated that a small portion of selected patients benefited from TACE.[10,11] Transarterial chemoembolization has been reported to be more effective in terms of histologic tumor necrosis when performed for tumors between 3 and 5 cm in diameter[12]; both single vs multiple tumor nodules and tumor nodules >3 cm vs smaller ones were more likely to show complete or partial necrosis vs non-necrosis.[9] Theoretically, the necrosis and blood flow reduction resulting from LRT could limit the dissemination of tumor cells. Therefore, LRT might provide a beneficial effect beyond prevention of tumor progression.

Some have suggested that there are upper limits in tumor size and number beyond which downstaging was not likely to be successful and the outcomes might be significantly worse as well.[13] Our previous study and reports from other groups have shown that long-term outcomes of OLT in patients downstaged to meet Milan criteria for the purpose of transplantation were similar to those of stage II recipients.[3] Intention-to-treat analysis demonstrated that excellent long-term prognosis after successful downstaging of HCC to within T2 criteria was associated with a low risk of HCC recurrence and excellent post-transplantation survival, comparable with those meeting T2 criteria without downstaging. However, the dropout rate for downstaging was significantly higher than that of the T2 group.[13]

To examine the impact of neoadjuvant LRT on HCC recurrence after liver transplantation at our institution, we performed a retrospective study on patients who underwent liver transplantation for HCC.

METHODS

Study conduct

The research protocol was approved by the IRB of Washington University School of Medicine, St Louis, and used a prospectively maintained clinical database of patients after liver transplantation. Data consisting of demographics, clinical characteristics, LRT before liver transplantation, pathology findings, tumor status, tumor recurrence, and outcomes were obtained for all recipients of liver transplants for HCC from January 1, 1989 to December 31, 2014.

Locoregional therapies

Locoregional therapy was not routinely performed at our institution before 1998. Since then, LRT, predominately TACE, has been used in patients with stage II HCC as diagnosed on cross-sectional imaging. Locoregional therapies were performed by experienced interventional radiologists in a standardized fashion using either a femoral or brachial approach. Patients with substantial hepatic dysfunction were not considered appropriate candidates for TACE. Superior mesenteric angiography was performed to evaluate portal vein status and evaluate for the presence of anatomic variation. Celiac angiography was performed with a selection of the tumor-bearing