

ORIGINAL ARTICLE

Hepatocellular carcinoma with main portal vein tumor thrombus: a comparative study comparing hepatectomy with or without neoadjuvant radiotherapy

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Abstract

Background: Hepatocellular carcinoma (HCC) with main portal vein tumor thrombus (mPVTT) has a poor prognosis even after surgical resection. Whether neoadjuvant radiotherapy improves surgical outcomes is currently unknown. The aim of this study was to compare the survival of patients with resectable HCC and mPVTT who underwent neoadjuvant therapy to those who underwent surgery alone.

Methods: A non-randomized comparative study was performed. For patients in the neoadjuvant radiotherapy group, three-dimensional conformal radiotherapy was administered with a daily fraction of 300 cGy in 6 consecutive days. Hepatectomy was carried out 4 weeks after completion of irradiation.

Results: 95 patients were enrolled into this study. In the neoadjuvant radiotherapy group (n = 45), 12 patients showed gross radiological reduction in extent of PVTT. In 6 patients, the extent of PVTT was reduced to be within the ipsilateral side of the portal vein. When compared with patients who underwent surgery alone (n = 50), neoadjuvant radiotherapy significantly decreased the rates of HCC recurrence and HCC-related death, with hazard ratios of 0.36 (95% CI, 0.19–0.70) and 0.32 (95% CI, 0.18–0.57), respectively.

Conclusion: For patients with HCC with mPVTT, neoadjuvant radiotherapy before partial hepatectomy provided better postoperative survival outcomes than partial hepatectomy alone.

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Nan Li, Shuang Feng, Jie Xue and Xue-biao Wei contributed equally to this work.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death in the world.¹ It has a great propensity to invade the portal venous system, resulting in portal vein tumor thrombus (PVTT), which is a significant poor prognostic factor.^{2,3} Surgical treatment may offer a chance of cure, but the extent and location of PVTT influence post-operative long-term survival outcomes. For patients with HCC and PVTT in segmental, sectoral, and right or left portal veins, post-operative 5-year overall survival (OS) have been reported to range from 10% to 59%.^{4–6} Once PVTT invades the main portal vein (mPVTT), post-operative outcomes become poor, with a peri-operative mortality of 0–28%, and a 5-year OS of 0–26.4%.^{7–9}

Radiotherapy has been reported to “downstage” HCC, making unresectable HCC eligible for surgical resection and unresectable HCC transplantable.^{10,11} However, whether neoadjuvant radiotherapy improves post-operative survival outcomes of patients with HCC with mPVTT is unknown. The aim of this study was to compare the survival outcomes of neoadjuvant radiotherapy before partial hepatectomy with partial hepatectomy alone in a non-randomized study on patients with resectable HCC with mPVTT.

Methods

Study design

The study protocol which conformed to the 1975 Declaration of Helsinki was approved by the Ethics Committee of the Eastern Hepatobiliary Surgery Hospital (Shanghai, China). All participants provided written consent for their data to be used for research. No patients who were enrolled in this study were included in any previous studies or clinical trials.

The study was carried out at the Department of Hepatic Surgery VI, the Eastern Hepatobiliary Surgery Hospital (EHBH). After hospital admission, the patients underwent a routine three-phase dynamic CT examination. A diagnosis of PVTT was made when there was presence of low-attenuation intraluminal masses that expanded the portal vein, or when there were filling defects in the portal venous system on CT images. The extent of PVTT was classified using the Cheng's classification^{12,13}: type I, tumor thrombus involving segmental or sectoral branches of the portal vein, or more proximal; type II, involvement of the right or left portal vein; type III, invasion of the main trunk of portal vein (mPVTT); and type IV, involvement of the superior mesenteric vein.

If there were multiple and disseminated intrahepatic nodules (>3) on imagings, patients were not considered for surgical treatment. The liver functional reserve was assessed by the Child-Pugh grading. Liver functional reserves of Child-Pugh class C were considered as a contraindication for surgical treatment. Major hepatectomy, which was defined as resection of 3 or more Couinaud's liver segments, was only carried out on patients with

Child-Pugh class A liver function. Selected patients with Child-Pugh class B liver function underwent hepatectomy if the tumor could be removed by minor hepatectomy, which was defined as resection of 2 or fewer Couinaud's liver segments.

The inclusion criteria for this study were: (i) patients aged between 20 and 70 years; (ii) HCC with PVTT as shown on preoperative imagings; (iii) the PVTT had invaded the main portal vein (mPVTT, Cheng's type III); (iv) resectable lesion(s) in the liver with adequate hepatic functional reserve. The exclusion criteria were: (i) patients with a previous history of other cancer; (ii) severe co-existing systemic disease; (iii) Child-Pugh class C liver function; (iv) previous radiotherapy, chemotherapy or other invasive treatments for cancer.

Patients who met the inclusion criteria were interviewed by a multidisciplinary team of clinicians. The pros and cons of the two treatment plans were explained to the patients in detail. If the patients refused surgical treatment, they were excluded from further analysis. The remaining patients were then asked to select to enter either into the neoadjuvant radiotherapy group or the surgery only group. The sole difference between the two groups was determined by the patient's willingness to undergo neoadjuvant radiotherapy. The rest of the treatment was the same for the two groups throughout the study period.

Neoadjuvant radiotherapy

Preoperative radiotherapy was given within 3 days after completion of all preoperative investigations. Three-dimensional conformal radiotherapy was carried out using a 10-mV linear accelerator (Aowo International Technology Development, Shenzhen, China). The irradiation regimen was based on authors' previous unpublished data (in submission). Furthermore, the authors have previously identified (unpublished data) the optimal interval between partial hepatectomy and irradiation to be 4 weeks in order to minimize liver injury, intraoperative blood loss and postoperative liver failure. As a consequence, a daily fraction of 300 cGy was administered in 6 consecutive days for patients in the neoadjuvant radiotherapy group, to deliver a total irradiation dose of 1800 cGy. The dose was prescribed to the 50–80% isodose distribution areas. 3D view techniques were used to minimize the irradiation dose delivered to organs other than the tumor and the PVTT by designing the irradiated volumes and angles. Four weeks after completion of irradiation, the liver function and CT imagings were carried out before surgery. The revised response evaluation criteria in solid tumors (mRECIST) guideline¹⁴ was used to evaluate the therapeutic effects of radiotherapy on PVTT and tumor. At least a 30% decrease in the sum of diameters (partial response, PR) was considered as an effective reduction of the extent of PVTT. The PVTT type was also re-evaluated according to the Cheng's classification. If patients developed any contraindications to surgery as described previously, they were treated with transcatheter arterial chemoembolization (TACE), Sorafenib or supportive care.

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