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Original Research

Hepatectomy after down-staging of hepatocellular carcinoma with portal vein tumor thrombus using chemoradiotherapy: A retrospective cohort study

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HIGHLIGHTS

- Hepatectomy is not recommended in patients with portal vein tumor thrombus.
- Chemoradiotherapy can downstage tumors effectively, leading to curative resection.
- Conversion resection was an independent prognostic factor of overall survival.

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ABSTRACT

Background: This study evaluates the survival benefit and safety of hepatectomy after down-staging by 3-dimensional conformal radiation therapy (3D-CRT) for major portal vein tumor thrombus (PVTT) combined with hepatic arterial infusion chemotherapy (HAIC) for advanced hepatocellular carcinoma (HCC).

Methods: Fifty-two patients with unresectable advanced HCC treated with HAIC combined with 3D-CRT for PVTT, from January 2002 to March 2015, were analyzed in this retrospective study. Hepatectomy was offered to patients if, based on radiologic findings, all gross lesions were considered resectable. The safety of hepatectomy was investigated and overall survival (OS) was compared between the resection group ($n = 7$) and non-resection group ($n = 43$).

Results: OS was significantly higher in the resection group than in the non-resection group. Results of multivariate analysis identified conversion to surgery (hazard ratio, 0.35; 95% confidence interval, 0.10 −0.99; $P = 0.048$) as an independent factor influencing OS. There were no serious postoperative complications and no case of mortality in patients who underwent hepatectomy.

Conclusions: Our findings suggest that hepatectomy after down-staging by 3D-CRT for PVTT combined with HAIC for advanced HCC is safe and results in good long term outcome.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer and the third highest cause of cancer-related mortality worldwide [1]. It has a tendency to invade the portal venous system, resulting in portal vein tumor thrombus (PVTT). PVTT is reportedly identified in 10–40% of patients with HCC at the time of initial diagnosis [2,3]. The prognosis of patients with PVTT is generally poor. Previous studies reported a median survival time

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(MST) of 2–4 months if left untreated [2–4].

According to the Barcelona Clinic Liver Cancer (BCLC) Staging System, systemic therapy using sorafenib is considered the standard of care for patients with HCC with PVTT [5]. However, the reported MST of patients with advanced HCC treated with sorafenib is as short as 10.7 months; this underscores the need for better treatment strategies [6]. In recent years, there have been attempts to develop alternative treatments, including transarterial chemoembolization (TACE) [7,8], hepatic arterial infusion chemotherapy (HAIC) [9–11], external beam radiation therapy (RT) [12,13], transarterial radioembolization (TARE) [14–17], and various combination strategies [18–20]. Although hepatectomy is not recommended, it is the only therapy offering a chance for long-term survival in these patients [21,22]. However, hepatectomy for HCC with PVTT is technically demanding and extensive resection is often required. Therefore, the surgical indications for HCC with PVTT differ widely among institutions.

Our therapeutic strategy for unresectable HCC patients with PVTT is to combine HAIC with three-dimensional conformal radiation therapy (3D-CRT) for PVTT. It was diagnosed as unresectable when removal of all detected tumors was impossible with sufficient hepatic functional reserve. Fujino H. et al. [23] previously reported the efficacy of this treatment. This combination therapy may result in unresectable HCC becoming eligible for surgical resection in some patients. However, the survival benefit and safety of hepatectomy after this therapy remains uncertain. In this retrospective cohort study, we investigated the survival benefit and safety of this treatment strategy.

2. Methods

This retrospective study enrolled patients with unresectable advanced HCC treated with HAIC combined with 3D-CRT for PVTT from January 2002 to March 2015 atour institute. Inclusion criteria were: (i) HCC with PVTT in the first portal branch (Vp3) or in the main portal trunk or contralateral portal branch (Vp4); (ii) removal of all detected tumors is impossible with sufficient hepatic functional reserve even if thrombectomy using peel-off technique is considered [24]; (iii) absence of extrahepatic metastasis; (iv) Child-Pugh score of 5–7; (v) performance status of 0 or 1; (vi) no history of sorafenib treatment; and (vii) at least a 4-week rest period of no treatment since any previous therapy for HCC. The therapeutic protocol for combination therapy was the same as those described previously [23]. Briefly, patients underwent arterial infusions of anticancer agents via the injection port. Two drug regimens were used for HAIC: intra-arterial low dose cisplatin (CDDP; Nihonkayaku, Tokyo, Japan) combined with 5-fluorouracil (5-FU; Kyowa Hakko, Tokyo) or intra-arterial 5-FU with subcutaneous interferon (IFN) combination therapy (5-FU/IFN). Patients received 3D-CRT that was started with the first cycle of HAIC. Gross tumor volume was defined as only the PVTT. The prescribed doses and fractionations were 30–45 Gy in 10–15 fractions.

We followed up all patients who survived after discharge by performing clinical physical examinations and blood chemistry tests, and measuring the serum levels of tumor markers monthly. The treatment response was estimated by contrast-enhanced computed tomography at 4 weeks after completion of treatment, and then every 2–3 months. Local tumor response of the main tumor and PVTT was categorized into four grades (treatment effect (TE) 1–4) based on the Response Evaluation Criteria in Cancer of the Liver (RECICL) by the Liver Cancer Study Group of Japan [25]. For instance, TE3 means the tumor-necrotizing effect or tumor size reduction rate is between 50% and <100%. After estimating the treatment response, hepatectomy was offered to patients when it was determined that curative resection, i.e. all tumors including the PVTT, were resectable with sufficient hepatic functional reserve. We provided various additional therapies such as radiofrequency ablation (RFA), TACE, or HAIC repeatedly for patients who were not able to undergo hepatectomy.

Hepatectomy was performed through an upper midline incision with or without transverse extension. During surgery, we carefully searched the abdominal cavity for lesions such as extrahepatic metastasis and peritoneal dissemination. After mobilization of the liver, we performed intraoperative ultrasound and hepatectomy using the Cavitron Ultrasonic Surgical Aspirator (CUSA). Thrombectomy was performed according to the location and extent of PVTT. For patients with PVTT located within the resected area, the PVTT was resected en bloc with the tumor. For patients with PVTT protruded beyond the resection line, the PVTT was extracted out from the opened stump of the portal vein. Intraoperative frozen section diagnosis of the stump of the portal vein was performed. The severity of postoperative complications was classified using the Clavien-Dindo classification [26]. Operative mortality was defined as death within 30 days postoperative.

This study was conducted in accordance with the 1975 Declaration of Helsinki after receiving approval from the institutional review board of Hiroshima University, Hiroshima, Japan (approval number E–387). Written informed consent was obtained from each patient after detailed explanation about the therapy.

All statistical analyses were performed using JMP® 11 software (SAS Institute Inc., Cary, NC, USA). The Wilcoxon rank-sum test was used to compare continuous variables, and the chi-square test or Fisher exact probability test was used to compare categorical variables. The overall survival (OS) rates were calculated using the Kaplan-Meier method, and compared using the log-rank test. Only variables that were statistically significant in univariate analysis were included in the multivariate analysis, which was performed using a Cox proportional hazard model to identify independent prognostic factors of OS. Two-tailed values of $P < 0.05$ were considered significant.

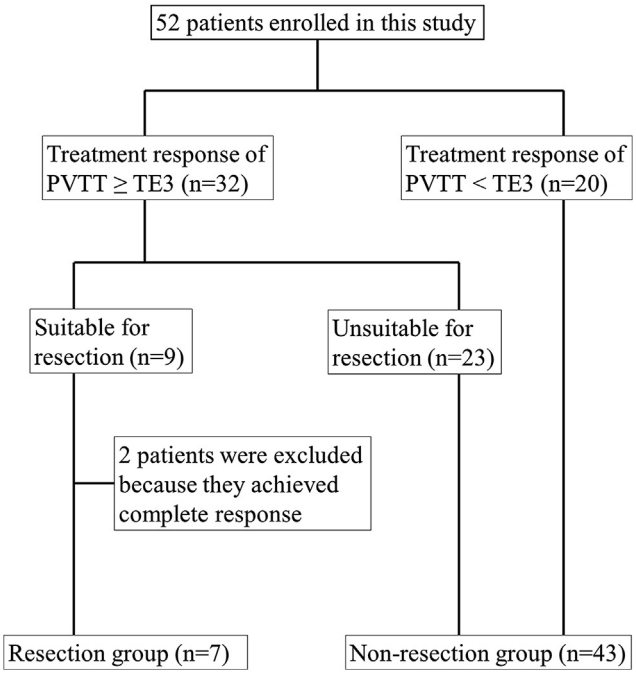

Fig. 1. Patients' flow chart.
PVTT, portal vein tumor thrombosis; TE3 the tumor-necrotizing effect or tumor size reduction rate is between 50% and <100%.