Proposal of selection criteria for operative resection of hepatocellular carcinoma with inferior vena cava tumor thrombus incorporating hepatic arterial infusion chemotherapy

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Background. *Because operative resection of hepatocellular carcinoma with inferior vena cava tumor thrombus has been associated with a substantial risk of recurrence and postoperative morbidity, adequate patient selection for resection is necessary. Our aim was to propose selection criteria for resection of hepatocellular carcinoma with inferior vena cava tumor thrombus.*

Methods. *Long-term outcomes were analyzed retrospectively in 39 operative cases of hepatocellular carcinoma with inferior vena cava tumor thrombus (1996–2015). Since 2003, preoperative hepatic arterial infusion chemotherapy instead of immediate resection has been performed in patients with advanced inferior vena cava tumor thrombus, defined as those patients with suspected extrahepatic metastasis, who will need extracorporeal circulation, or who have marginal liver function and/or multiple bilobar tumors. Indication for resection has been based on the tumor response to hepatic arterial infusion chemotherapy thereafter.*

Results. *The median survival time for all patients was 15.2 months. Multivariate analysis revealed that preoperative hepatic arterial infusion chemotherapy (hazard ratio: 0.30), use of extracorporeal circulation (3.12), and extrahepatic metastasis (2.67) were independent prognostic factors for overall survival. Among patients with initially advanced inferior vena cava tumor thrombus, preoperative hepatic arterial infusion chemotherapy was associated with a much more favorable prognosis compared with no hepatic arterial infusion chemotherapy (median survival time: unreached vs 8.3 months,* P = *.007). Overall survival was significantly worse in patients with uncontrolled, advanced inferior vena cava tumor thrombus than in those without advanced inferior vena cava tumor thrombus or with advanced inferior vena cava tumor thrombus controlled by preoperative hepatic arterial infusion chemotherapy (median survival time: 10.4 vs 26.1 months,* P = *.039).*

Conclusion. *An effective response to hepatic arterial infusion chemotherapy and subsequent operative resection salvaged patients with initially advanced inferior vena cava tumor thrombus. Our results suggest that operative resection should be indicated only in patients without advanced inferior vena cava tumor thrombus or with advanced inferior vena cava tumor thrombus controlled by preoperative hepatic arterial infusion chemotherapy. (Surgery 2017;■:■-■.)*

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Accepted for publication May 10, 2017.

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0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2017.05.011

Hepatocellular carcinoma (HCC) is one of the most common cancers and the third-leading cause of cancer-related death worldwide.[1] The presence of extrahepatic metastasis or major vascular invasion is considered to be advanced HCC, and only sorafenib has been recommended as a treatment option for advanced HCC in Western guidelines.[2-4] Inferior vena cava tumor thrombus (IVCTT) is a

manifestation of advanced hepatic vein invasion with a reported frequency of 1.4%.[5] IVCTT is associated frequently with synchronous and metachronous extrahepatic metastasis, including metastases to the lung,[6-10] due to direct cancer cell dissemination into the systemic circulation,[8,11] and the prognosis is extremely poor. Therefore, operative resection of HCC with IVCTT may be beyond the standard treatment. A few, high-volume institutions have reported outcomes after resection of a limited number of cases, but the outcomes have been unsatisfactory primarily because of the extremely high incidence of systemic recurrence.[8-10,12,13] Given the inordinate risk of recurrence as well as postoperative morbidity due to the complexity of the operation, resection should be performed only for selected patients who can benefit sufficiently from the invasive procedure.

Since 2003, we have attempted to treat patients with advanced IVCTT, including IVCTT with extrahepatic metastasis, preoperatively with hepatic arterial infusion chemotherapy (HAIC), a treatment that had been reported to show substantial efficacy for portal vein tumor thrombus.[14,15] The purpose of this study was to propose optimized selection criteria for resection of HCC with IVCTT incorporating preoperative HAIC based on our outcomes.

MATERIALS AND METHODS

Patients. Between 1996 and 2015, 1,200 patients with HCC underwent hepatectomy at the Department of Surgery, Kyoto University Hospital. Of these, 39 patients (3.3%) with IVCTT or direct invasion of the IVC, as confirmed by operative findings and pathologic examination, were reviewed retrospectively. Written informed consent was obtained from all patients. This study was performed in accordance with the Japanese ethics guidelines for epidemiologic research and was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval code: R0498).

Operative procedures. In principle, hemihepatectomy or a more extended hepatectomy was performed to resect the involved main hepatic vein. Transection of the Glissonean pedicle and hepatic parenchyma preceded removal of the IVCTT. Under complete occlusion of the hepatic vascular inflow, the IVC was clamped infrahepatically and suprahepatically (total hepatic vascular exclusion [THVE]), unless the tumor thrombus expanded into the right atrium. THVE usually was required for only about 20 minutes. The anterior wall of the IVC was incised along the IVCTT. The IVC was resected partially if direct invasion was suspected and reconstructed if severe stenosis was anticipated when closed primarily. The following 3 types of extracorporeal circulation were used: veno-venous bypass with a centrifugal pump for hemodynamic instability caused by massive bleeding or THVE[16]; cardiopulmonary bypass for IVCTT expanding into the right atrium; and the ante-situm procedure for large tumors involving the confluence of the main hepatic veins to precisely ensure appropriate operative margins and preserve the contralateral hepatic vein.[17-19]

Operative indications and preoperative treatment. Because of the potential risk of acute death from liver failure due to obstruction of hepatic outflow or to a fatal pulmonary embolism,[20] patients with IVCTT in our early experience were considered for resection if there was adequate liver function even if curative resection could not be expected. Since 2003, however, we altered our indication for resection of HCC with IVCTT, and those patients with advanced IVCTT have not been offered immediate resection, but rather have received HAIC and only then considered for resection. Advanced IVCTT was defined as the following: 1) suspected extrahepatic metastasis; 2) the expected need for extracorporeal circulation, especially those with right atrial tumor thrombus; 3) marginal liver function; and/or 4) multiple bilobar tumors. Adequate liver function was determined comprehensively based on the finding of a future liver remnant × indocyanine green plasma clearance rate of ≥0.03 combined with other parameters, including the Child-Pugh classification, platelet counts, and the results of asialo-scintigraphy as described previously.[21,22] The protocol for HAIC consisted of administering cisplatin (10 mg) and 5-fluorouracil (250 mg) on days 1 to 5 for 3 consecutive weeks via a subcutaneously implanted injection port, followed by a 1-week rest.[23] Sorafenib, radiation therapy (RT), and transcatheter arterial chemoembolization (TACE) were added as supportive treatments for HAIC; sorafenib generally was used to control extrahepatic metastasis, RT was used to control the IVCTT that was refractory to HAIC, and TACE was used to control contralateral intrahepatic metastasis or to occlude any feeding arteries other than the access vessel used for the HAIC.[6,7,24,25] Tumor responses were evaluated monthly by computed tomography or magnetic resonance imaging to reevaluate the potential indication for resection. After 1 to 4 (median 2) courses of HAIC, patients were determined to be candidates for resection if their tumors were