# Particle radiotherapy, a novel external radiation therapy, versus liver resection for hepatocellular carcinoma accompanied with inferior vena cava tumor thrombus: A matched-pair analysis

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***Background.*** *Hepatocellular carcinoma accompanied with inferior vena cava tumor thrombus carries a dismal prognosis, and the feasibility of local treatment has remained controversial. The present study aimed to compare the outcomes of particle radiotherapy and liver resection in patients with hepatocellular carcinoma with inferior vena cava tumor thrombus.*

***Methods.*** *Thirty-one and 19 patients, respectively, underwent particle radiotherapy and liver resection for hepatocellular carcinoma with inferior vena cava tumor thrombus. A matched-pair analysis was undertaken to compare the short- and long-term outcomes according to tumor stage determined using the tumor-node-metastasis classification.*

***Results.*** *Both stages IIIB and IV (IVA and IVB) patients were well-matched for 12 factors, including treatment policy and patient and tumor characteristics. The median survival time of matched patients with stage IIIB tumors in the particle radiotherapy group was greater than that in the liver resection group (748 vs 272 days,* P = *.029), whereas no significant difference was observed in the median survival times of patients with stage IV tumors (239 vs 311 days, respectively). There were significantly fewer treatment-related complications of grade 3 or greater in the particle radiotherapy group (0%) than in the liver resection group (26%).*

***Conclusion.*** *Particle radiotherapy is potentially preferable in hepatocellular carcinoma patients with stage IIIB inferior vena cava tumor thrombus and at least equal in efficiency to liver resection in those with stage IV disease, while causing significantly fewer complications. Considering the relatively high survival and low invasiveness of particle radiotherapy when compared to liver resection, this approach may represent a novel treatment modality for hepatocellular carcinoma with inferior vena cava tumor thrombus. (Surgery 2017;■:■-■.)*

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Hepatocellular carcinoma (HCC) tends to involve vascular structures in the liver, such as portal and hepatic veins. In the presence of inferior vena cava tumor thrombus (IVCTT), patients with HCC have an extremely poor prognosis with survival in the absence of treatment reported to be ≈ 3 months.[1-3] These patients are classified as having advanced-stage HCC in the staging system of the American Association for the Study of the

Liver Diseases/Barcelona Clinic for Liver cancer,[4] and sorafenib is recommended as a first-line treatment based on the recent randomized control trial comparing it with placebo,[5,6] but the reported survival benefit of sorafenib for HCC patients with vascular invasion including IVCTT is quite limited.[7]

In Eastern countries, most centers do not adhere to the guidelines of the European Association for the Study of the Liver[8] and American Association for the Study of the Liver Diseases,[9] and certain HCC patients with IVCTT are thought to possibly benefit from other available treatment modalities rather than sorafenib monotherapy. These other treatment approaches include liver resection, transarterial chemoembolization, hepatic arterial infusion chemotherapy, intensity-modulated radiotherapy, and particle radiotherapy. Of these, liver resection, one of the few curative treatments, theoretically has advantages, because IVCTT can be removed mechanically and the risk of pulmonary infarction due to the embolized tumor thrombus may be decreased. The median survival time of patients with HCC and IVCTT after liver resection is reported to be 9–16 months.[10-12]

Particle radiotherapy is considered another curative treatment for HCC patients with IVCTT. It is a newer type of external radiation therapy characterized by an inverted depth-dose curve, thus leading to low dose radiation within the entry channel and a well-defined, high local dose delivery in the Bragg peak region.[13-15] Particle radiotherapy consists of proton and carbon ion radiotherapy, and both proton and carbon beams are equally effective in treating HCC.[16-19] Moreover, we demonstrated previously excellent clinical outcomes of particle radiotherapy for HCC with IVCTT in a single-arm study with a median survival time of 24.2 months.[20] Particle radiotherapy, therefore, holds great potential to be an alternative first-line treatment for this type of HCC. Thus, there is an urgent need for a comparative study of particle radiotherapy and liver resection. This study aimed to determine the most suitable treatment option for HCC with IVCTT through a concurrent, case-matched comparison of particle radiotherapy and liver resection.

## PATIENTS AND METHODS

**Study population.** All consecutive patients who underwent liver resections for HCC with IVCTT from June 2001 to June 2016 at Kobe University Hospital and all consecutive patients with HCC with IVCTT treated with particle radiotherapy at Hyogo Ion Beam Medical Center during the same period were included in the present study. The demographic, clinical, and pathologic data were recorded prospectively and analyzed retrospectively. IVCTT was diagnosed based on identification of an intraluminal filling defect in the inferior vena cava by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Several imaging modalities were used to assess the status of disease progression and determine indications for treatment. Impairment of liver function associated with underlying liver disease was assessed by biochemical tests, the Child-Pugh classification, and indocyanine green retention rate at 15 minutes (ICGR15). The present study was conducted in accordance with the ethical standards set forth by the Declaration of Helsinki, and all patients provided written informed consent.

**Indications for particle radiotherapy and treatment details.** Detailed descriptions of the selection criteria, protocol, and treatment planning for particle radiotherapy for HCC with IVCTT have been provided in our previous reports.[20-22] In summary, the following conditions were considered as absolute contraindications for particle radiotherapy: (1) uncontrolled ascites, (2) tumors >15 cm (the upper limit of the irradiation field), and (3) extensive tumors broadly adjacent to the gastrointestinal tract.

A CT-based, 3-dimensional treatment planning system (FOCUS-M, CMS Japan, Tokyo and Mitsubishi Electric, Kobe, Japan) was used to design the radiation treatments. Briefly, each patient was immobilized with a custom-made, thermoplastic immobilization cast in the supine or prone position depending on the tumor location. The CT slice thickness was 2 mm, and the MRI slice thickness was 5 mm. CT images were obtained at expiration using a respiratory gating system. Target volumes and organs at risk of irradiation, such as the liver and gastrointestinal tract, were delineated on CT-MRI fusion images. Dose-volume histograms were made for all patients to evaluate the risk of radiation-induced complications. All treatment plans were executed according to the Quantitative Analysis of Normal Tissue Effects in the Clinic guidelines for the lungs[23] and heart.[24] Seven protocols for proton radiotherapy, including 56 Gray equivalents (GyE) in 8 fractions; 60 GyE in 10 fractions; 66 GyE in 10, 15, and 20 fractions; 76 GyE in 20 fractions; and 76 GyE in 38 fractions were used for treatment, as were 4 protocols for carbon ion