Proton Beam Therapy for Hepatocellular Carcinoma with Inferior Vena Cava Tumor Thrombus: Report of Three Cases

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Three patients with hepatocellular carcinoma (HCC) and inferior vena cava tumor thrombus (IVCTT) were treated using proton beam therapy at the University of Tsukuba, Japan. A total dose of 50–70 Gy in 10–35 fractions was given to the primary tumor and IVCTT. All the patients survived for more than 1 year from the beginning of proton beam therapy (13–55 months) and no treatment-related toxicity of grade 3 or higher was observed. These cases suggest that proton beam therapy is safe and effective for patients with HCC associated with IVCTT.

Key words: hepatocellular carcinoma — inferior vena cava tumor thrombus — proton beam therapy — radiation — hepatoma

INTRODUCTION

There are a variety of treatment modalities for advanced hepatocellular carcinoma (HCC) associated with inferior vena cava tumor thrombus (IVCTT), including surgery, transarterial embolization (TAE) and ablation therapies, but no method has yet been proven effective for this condition (1–4). We initiated the use of proton beam therapy for HCC at the University of Tsukuba in 1983 and by the end of March 2005 we had treated a total of 427 patients at the present and previous facilities. Of these patients, three had HCC associated with IVCTT. Here, we describe these three cases and discuss the role of proton beam therapy in the management of this disease.

CASE 1

This case was previously reported as a typical case of HCC (5), but here we have included a review of the data from a different perspective. A 57-year-old man with hepatitis C viral infection was diagnosed by dynamic computed tomography (CT) with HCC of a maximum diameter of 8 cm in S6, with an IVCTT and an elevated alpha-feto protein (AFP) level (690 ng/ml); this diagnosis was not confirmed pathologically. The clinical target volume (CTV), which encompassed the primary tumor and IVCTT with a margin of 0.5–1 cm, was delineated on serial CT images during planning of treatment. Proton beams were administered to the CTV through the posterior port with a margin of 0.5–1 cm in all dimensions, with a further adequate margin added for respiratory movement. The patient underwent proton beam therapy of 50 Gy in 13 fractions over 19 days (15 Gy in three fractions and 35 Gy in 10 fractions) 3 months after TAE. One month after proton beam therapy, the primary tumor had shrunk markedly and the inferior vena cava (IVC) had reopened with disappearance of the IVCTT (Fig. 1a–c). Five months after proton beam therapy, a tumor that was enhanced with contrast agent in the early phase was observed in the follow-up CT at the boundary of the irradiated and non-irradiated volumes and another tumor was found in the IVC. The patient was diagnosed with marginal recurrence and underwent a second course of proton beam therapy of 70 Gy in 20 fractions over 49 days for the recurring tumor and the IVCTT, after which the tumor shrunk.
markedly. The IVC reopened with disappearance of the IVCTT one month after the second course of proton beam therapy (Fig. 1d–f). No acute or late treatment-related toxicities of grade 2 or more were observed. Newly developed tumors in the liver and multiple bone metastases were found at 1 and 7 months after the second course of proton beam therapy, respectively, and the patient died due to disseminated tumors 26 months after the first course of proton beam therapy.

CASE 2

A 64-year-old man with hepatitis C viral infection was diagnosed by dynamic CT with HCC of 4-cm maximum diameter in S4, with a portal vein tumor thrombus (PVTT) in the right main branch of the portal vein. A second HCC of 3-cm maximum diameter in S8 was also present, with an IVCTT and an elevated AFP level (2200 ng/ml) (Fig. 2a,b). Neither of the lesions was confirmed pathologically. Proton beams were administered to the CTV through the right lateral anterior port with a margin of 0.5–1 cm in all dimensions and an additional 0.5-cm margin in the caudal direction to account for uncertainty in positioning due to breathing under the respiratory gating system (Fig. 2c). The patient underwent proton beam therapy of 50 Gy in 10 fractions over 18 days for both the primary and intravascular...
tumors (Fig. 2c), after which all tumors were well controlled (Fig. 2d,e). Multiple new tumors developed in the liver 26 months after irradiation and were successfully treated by TAE, but multiple bone metastases occurred and the patient died as a result of the disseminated tumors 55 months after the first irradiation. No acute or late treatment-related toxicities of grade 2 or more were observed. Autopsy revealed that there were no tumors at the sites of the primary tumors, PVTT and IVCTT, or in the lung.

CASE 3

A 57-year-old woman with hepatitis C viral infection was diagnosed by dynamic CT with HCC in S4/8 and an elevated AFP level (14 000 ng/ml), without pathological confirmation. Despite treatment by transcatheter chemoembolization and percutaneous ethanol injection, the tumor had invaded the IVC and extended to the inlet of the right atrium at the time the patient first visited our hospital. Proton beams were administered to the CTV through the anterior and right anterior oblique ports with a margin of 0.5–1 cm in all dimensions; using a similar procedure to that described for case 2 under the respiratory gating system (Fig. 3a,b). The patient received 70 Gy in 35 fractions over 54 days. CT taken one month after the end of treatment revealed a marked decrease in tumor size (Fig. 3c). However, multiple lung metastases were found, one of which was associated with hemorrhage and a second course of proton beam therapy of 54 Gy in 18 fractions over 29 days was applied to the lung tumor. This therapy was effective in controlling the hemorrhage, but nine months after the first course of proton beam therapy local recurrence was found in the IVC. One month later the tumor was shown to have re-grown in the IVC (Fig. 3d), with direct extension to and occupation of the entire right atrium, causing mitral valve insufficiency. The patient underwent a third course of proton beam therapy to palliate the disease in the hope of improving cardiac function by reducing the volume of the intravascular tumor. However, the treatment course was discontinued after completion of a dose of 16 Gy in eight fractions over 10 days owing to development of disseminated intravascular coagulation. Liver function remained at Child–Pugh class A until the beginning of the third course of proton beam therapy and no other acute or late treatment-related toxicity of grade 2 or more was observed. The patient eventually died of cardiac failure due to the intravascular tumor 13 months after the first course of proton beam therapy.

DISCUSSION

The prognosis of patients with HCC accompanied by IVCTT is extremely poor, with untreated survival reported to be approximately 3 months from diagnosis (6). Intravenous chemotherapy and transcatheter chemoembolization have yielded only limited improvements in survival (2), and ablation therapies such as percutaneous ethanol injection and radiofrequency ablation appear unsuitable for treatment of IVCTT, because insertion of the needle may carry a risk of embolization (3,4). Surgery is an effective treatment for HCC patients with IVCTT, but has only a limited benefit in improving survival to 7 or 8 months (7).

Radiotherapy is advantageous for treatment of IVCTT because it delivers the same radiation dose to the IVCTT as to the primary tumor. Zeng et al. treated 33 patients with HCC and IVCTT using X-rays and 14 of these patients also received radiotherapy (8). Nine of the 14 patients treated with radiotherapy had a complete response and two showed a partial response; moreover, median survival was 22 months, compared with 4 months for the 19 patients who did not receive radiotherapy (8). These results indicate the efficacy of radiotherapy in combination with X-rays for patients with HCC and IVCTT. Efficacy is limited, however, because the tolerance of the whole liver to irradiation is too low to allow delivery of a curative dose to the tumor (9).

In contrast to radiotherapy, the excellent dose-localization capability of proton beam therapy allows administration of a tumoricidal dose to the target (10). We have shown that proton beam therapy is safe and effective for patients with HCC, irrespective of tumor size and location (11), and also for those with portal vein tumor thrombus (5,11,12). Among 50 HCC patients with a solitary HCC and liver function of Child–Pugh class A, the local control rate and survival rate...
after 5 years was 86.9 and 53.5%, respectively (11). These data are comparable with those in the most successful surgical series and the results suggest that improvement of local control enhances survival rate. In the present series, all IVCTTs were well controlled and the three patients survived for 55, 26 and 13 months after the first course of proton beam therapy, respectively; similarly, these data suggest that local control of an IVCTT contributes to a longer survival period. It is of note that all patients survived for more than 1 year, which is longer than other survival periods reported to date for similar patients (8).

In our early use of proton beam therapy, we were unwilling to treat a patient with IVCTT using this method, because the condition was considered to be incurable. In addition, many HCC patients with IVCTT (excluding the three reported here) have extrahepatic metastases, which we judged made them ineligible for entry into a clinical study of proton beam therapy. Therefore, we have treated only three patients with HCC associated with IVCTT using proton beam therapy. We also note that these three patients were treated for a long period by different physicians. Prior to the opening of our hospital-based facility, machine time was limited and this required use of various dose/fractionation regimens. Under our current, more optimal conditions, we have treated only three patients with HCC associated with IVCTT using proton beam therapy. Therefore, the three cases reported here suggest that proton beam therapy, may increase this risk.

In the present series, all four tumors in three patients responded well to proton irradiation and all IVCs reopened, although in one patient the tumor in the IVC recurred 10 months after the first course of proton beam therapy. Therefore, the three cases reported here suggest that proton beam therapy is safe and effective for patients with HCC associated with IVCTT. However, because all three patients eventually died of progressive HCC, additional modalities are required to improve survival further.

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**Conflict of interest statement**

None declared.

**References**