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CLINICAL INVESTIGATION **Liver**

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY–BASED THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN TUMOR THROMBUS

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Purpose: To evaluate the safety and efficacy of three-dimensional conformal radiotherapy (3D-CRT) using single photon emission computed tomography (SPECT) in unresectable hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT).

Methods and Materials: Patients with HCC with PVTT in the first branch and/or main trunk were selected for this study. The optimal beam directions for 3D-CRT were explored using a Tc-99m-galactosyl human serum albumin SPECT image for guidance. The SPECT image was classified as either wedge type or localized type. The clinical target volume to a total dose of 45 or 50 Gy per 18–20 fractions included the main tumor and PVTT in the wedge type and PVTT alone in the localized type.

Results: Twenty-six patients were enrolled: 18 with wedge type and 8 with localized type. Mean tumor size was 7.1 cm (range, 4.4–12.3 cm). Clinical target volumes of wedge type vs. localized type were 111.2 cm^3 vs. 48.4 cm^3 ($p = 0.010$), respectively. Mean dose to normal liver and mean dose to functional liver were 1185 cGy and 988 cGy ($p = 0.001$) in wedge type and 1046 cGy and 1043 cGy ($p = 0.658$) in localized type, respectively. Despite an incidence of Child–Pugh B and C of 57.7%, no patients experienced radiation-induced liver disease. The progression of PVTT was inhibited, with an incidence of 92.2%; survival rates at 1 and 2 years were 44% and 30%, respectively.

Conclusion: Single photon emission computed tomography–based 3D-CRT enables irradiation of both the main tumor and PVTT with low toxicity and promising survival.

Functional image-guided radiotherapy, Three-dimensional conformal radiotherapy, Hepatocellular carcinoma, Portal vein tumor thrombus, Tc-99m-galactosyl human serum albumin.

INTRODUCTION

Portal vein tumor thrombus (PVTT) in the first branch and/or main trunk is one of the most progressive forms in the clinical course of hepatocellular carcinoma (HCC). The prognosis of HCC patients with PVTT remains poor. When radiotherapy (RT) is attempted to improve the prognosis of such patients, we face the problem of how to design a RT plan that ensures patient safety without leading to the complication of radiation-induced liver disease (RILD) (1). Hepatocellular carcinoma is usually associated with liver cirrhosis, and cirrhotic liver is more sensitive to radiation than normal liver. Several studies (2–4) performed three-dimensional conformal radiotherapy (3D-CRT) with a focus on PVTT alone and using a limited radiation field. The adverse effects in these studies did not lead to RILD; however, the median survival was 5.3–10.0 months.

In Japan, surgical treatment has been attempted for Stage IV HCC in a number of institutes (5, 6). Ikai *et al*. (6) reported a median survival of 13.6 months after surgical intervention for HCC patients with PVTT. These survivals cannot be directly compared because of varied tumor distribution and varying degrees of liver cirrhosis. It is important to determine whether RT can cover both the main tumor and PVTT when RT provides a promising response for HCC.

As the clinical target volume (CTV) expands, the irradiated dose to the surrounding cirrhotic liver increases, thereby leading to increased risk of RILD. Xu *et al*. (7) reported that of 109 patients with a mean hepatic CTV of 479.5 cm^3 who underwent 3D-CRT for HCC, 17 (15.6%) experienced RILD, including 13 (11.93%) who died of liver failure. Similarly, Cheng *et al*. (8) reported that of 68 patients with a mean hepatic CTV of 737–780 cm^3 and who underwent 3D-CRT,

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12 (17.65%) experienced RILD, including 6 (8.82%) who died of liver failure. The majority of these patients were classified as Child–Pugh A, whereas more than half of the HCC patients with PVTT in the first branch and/or main trunk included in this series were classified as Child–Pugh B and C. Radiotherapy in HCC patients with Child–Pugh B and C might be attributable as a contraindication because it is anticipated to lead to a higher incidence of RILD.

Previous reports in the field of radiation oncology have provided no solution to this difficult problem, but studies in the field of surgery provide some clues. In the case of obstruction of portal vein flow of the right first branch due to PVTT, surgeons undertake hepatic right lobectomy, viewing the right lobe with impaired portal vein flow as dysfunctional liver. Radiotherapy could not be used in this case because the majority of the patients with unresectable HCC are classified as having Child–Pugh B or C cirrhosis; however, it is possible to determine whether the right lobe is dysfunctional.

We attempted to evaluate liver function using images obtained with single photon emission computed tomography (SPECT) using Tc-99m-galactosyl human serum albumin (Tc-99m-GSA) (9–11). In HCC with PVTT, SPECT delineates cirrhotic liver as areas of hyper-, hypo-, or non-accumulation and delineates HCC as areas of either hypo- or non-accumulation. For cirrhotic liver, we defined areas of the same hypo- or non-accumulation as HCC as dysfunctional liver, and areas of hyper-accumulation as functional liver. When 3D-CRT is designed to irradiate the CTV and irradiate the hyper-radioisotope accumulation area as little as possible, using the SPECT image for guidance, we considered that RT might enable us to minimize any deterioration in liver function. We therefore undertook a prospective study of SPECT-based 3D-CRT (SPECT-3D-CRT) in HCC patients with PVTT in the first branch and/or main trunk.

METHODS AND MATERIALS

Patient and tumor characteristics

This clinical investigation was approved by the ethics committee of our institute, and informed consent was obtained from all patients. The study procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000. The eligibility criteria comprised the following: (*1*) unresectable HCC with PVTT in the first branch and/or the main trunk, (*2*) the absence of extrahepatic metastasis, (*3*) no ascites or under medical control of ascites, (*4*) 5–10 points on the Child–Pugh score, and (*5*) performance status of between 0 and 2 on the Eastern Cooperative Oncology Group scale. Hepatocellular carcinoma with PVTT was initially diagnosed on dynamic helical computed tomography (CT) using contrast medium or on magnetic resonance imaging (MRI) and then reconfirmed on CT during hepatic arteriography and CT during arterial portography in each case.

Transcatheter arterial chemoembolization (TACE) using 3–10 mL lipiodol (Guerbet, Charles de Gaulle, France) with or without gelatin sponge particles (Spongel; Yamanouchi, Tokyo, Japan) was performed in each patient during almost the same term as radiation treatment and at follow-up when intrahepatic metastases recurred. As anticancer agents, 40–60 mg of epirubicin hydrochloride (Kyowa Hakko, Tokyo, Japan) and 10 mg of mitomycin (Kyowa Hakko) were mixed with lipiodol. Transcatheter arterial chemoembolization using lipiodol was attempted for the whole tumor, and TACE using lipiodol and gelatin sponge particles was performed superselectively for tumor located outside the irradiated volume, to preserve liver function.

Radiotherapy

All patients underwent 3D-CRT in the supine position with both arms raised above the head. We used no special apparatus for respiratory immobilization. To minimize the effects of respiration, the subjects practiced breath-holding for 10–15 s at the time of end-expiration until the position could be maintained within 5 mm under X-ray fluoroscopic monitoring. Both simulation and treatment-planning CT were performed during breath-holding. Radiotherapy using a 10-MV linear accelerator was repeatedly delivered during breath-holding at end-expiration for 10–15 s at a time.

Simulation CT data were transferred to a 3D RT planning system (Pinnacle; ADAC Labs, Milpitas, CA). Using these data, we contoured the whole liver, main tumor, PVTT, and other hepatic tumors for each patient with reference to the MRI or diagnostic enhanced CT images taken within 1 week before treatment planning (Fig. 1). We defined normal liver as the area that remained after subtracting hepatic tumor from the whole liver. The kidneys, spinal cord, and gastroduodenum and intestine of each patient were contoured and reconstructed to form a 3D representation.

We then used the SPECT image acquired using Tc-99m-GSA (Nihon Medi-Physics, Tokyo, Japan) for functional hepatic imaging. The SPECT image was acquired before radiation planning. The degree of SPECT-delineated areas of non- or hypo-accumulation differed in each patient because they covered either a hepatic lobe, hepatic segment, or localized region; however, the boundary between hypo- or non- and hyper-accumulation areas was relatively clearly defined in the majority of cases. We classified wedge-shaped SPECT-delineated areas of non- and hypo-accumulation mainly corresponding to the main tumor, PVTT, and dysfunctional liver as wedge type (Fig. 1), and classified localized SPECT-delineated areas of non- or hypo-accumulation that mainly correspond to PVTT alone surrounded by functional liver as localized type (Fig. 2). In the localized type the main tumor was barely visualized on MRI or contrast-enhanced CT.

The subsequent CT treatment planning is illustrated in Figs. 1 and 2. Clinical target volume was outlined on the CT simulator with reference to CT images or MRI. Planning target volume (PTV) included CTV with a 10-mm margin, accounting for respiratory-induced motion, semi-shadow covering, and variations in daily setup. Computed tomographic images or MRI before 3D-CRT were used compared with SPECT images. Under the guidance of the SPECT image (Figs. 1c and 2c), the optimal beam directions for 3D-CRT were explored. The directions of two high-dose beams were first designed to cover the main tumor and PVTT and to irradiate functional liver as little as possible. The doses of the high-dose beams were limited to 38.25 Gy/18 fractions/4 weeks or 40 Gy/20 fractions/4 weeks to prevent adverse effects to the duodenum, spinal cord, and kidneys (12, 13). In terms of the kidneys, the volume irradiated at 20 Gy or more was planned to not exceed 30% of the total volume. Three additional low-dose beams of 6.75 Gy/18 fractions/4 weeks or 10 Gy/20 fractions/4 weeks were required to elevate the dose to the CTV, resulting in a total dose of 45–50 Gy (14). These low-dose beams were designed to avoid irradiating risk organs such as the stomach, duodenum, and spinal cord. The doses of 6.75/3 to 10/3 Gy in each beam