Pilot Study of Local Radiotherapy for Portal Vein Tumor Thrombus in Patients with Unresectable Hepatocellular Carcinoma

Kazunari Yamada, Toshinori Soejima, Koji Sugimoto, Hiroshi Mayahara, Kenta Izaki, Ryohei Sasaki, Tsutomu Maruta, Shinichi Matsumoto, Shozo Hirota and Kazuro Sugimura

Department of Radiology, Kobe University School of Medicine, Kobe, Japan

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Background: Patients suffering from hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) generally have a poor prognosis. We therefore conducted a prospective pilot trial of combined transcatheter arterial chemoembolization (TACE) and local radiotherapy (RT) for PVTT in unresectable HCC. The aim of the study was to investigate the efficacy and toxicity of this preliminary trial regime and to explore RT guidelines for cirrhosis.

Methods: Eight patients with unresectable HCC accompanied by first branch PVTT were entered into the study from February 1998 to December 1999. TACE was performed using Lipiodol, epirubicin hydrochloride and mytomycin followed by gelatin sponge cubes. RT was started 10–14 days following TACE. A total delivered dose of 60 Gy was given as daily 2 Gy fractions, with the clinical target volume defined as PVTT only. We observed a relationship between deterioration of liver function and the percent volume of the total liver receiving a dose exceeding 30 Gy ($V_{30}$).

Results: An objective response was observed in three of the eight patients. However, on follow-up angiograms the protrusion of PVTT into the main portal trunk was decreased in all cases. Deterioration of liver function was observed in all patients with $V_{30} > 40\%$.

Conclusion: It is possible that this combined therapy prevents PVTT from spreading to the main trunk and that indicates a further benefit of TACE. Our results indicate that $V_{30}$ constitutes a predictive test for the development of liver failure. More detailed evaluations of liver function and determination of the safe irradiation volume are necessary.

Key words: hepatocellular carcinoma – radiotherapy – transcatheter arterial chemoembolization – portal thrombus

INTRODUCTION

Transcatheter arterial chemoembolization (TACE), using iodized poppy oil, Lipiodol and anticancer drugs, has been actively performed for the treatment of unresectable hepatocellular carcinoma (HCC), particularly in Asia (1). In our institute, TACE with Lipiodol, epirubicin hydrochloride (Farmorubicin) and mytomycin (Mytomycin C) has been the most popular treatment for patients with unresectable HCC. Improved survival rates of HCC treated with TACE have been reported, particularly for capsulated expanding type HCC (1).

HCC carries a high risk of invasion of the portal vein. Portal vein tumor thrombus (PVTT) is an important prognostic factor as it can lead not only to the wide dissemination of tumor throughout the liver but also marked deterioration of hepatic function. Multivariate analysis has shown that PVTT is the clinicopathological variable that most influences survival (2,3). TACE provides effective palliation in cases of HCC, although pre-existing tumor thrombosis of the main trunk of the portal vein has been considered a contraindication for such treatment owing to the risk of necrosis of the non-cancerous portion of the liver and deterioration of hepatic function (4). Most histological examinations performed after hepatectomy indicated that TACE had a poor anticancer effect on PVTT. Ryu et al. (5) observed no histological evidence of necrosis of PVTT in seven out of eight patients who underwent hepatectomy after TACE. Thus, as systemic chemotherapy for HCC...
Radiotherapy for portal tumor thrombus reportedly yields unsatisfactory results, there is a strong need to remedy the weaknesses of TACE.

Radiation therapy (RT) alone has been of only limited benefit in the treatment of HCC owing to the low tolerance of the whole liver to RT (6). However, in several reports of studies examining the effect of combined radiation and chemotherapy treatment on HCC, beneficial interactions between RT and chemotherapy have been suggested (7). Recently, local, rather than whole-liver, RT has been attempted by several investigators and the results suggested that high doses of radiation could be safely delivered to a portion of the liver (8,9), indicating that local RT might be an effective component in a treatment regimen for HCC. Therefore, we conducted a prospective pilot trial of combined TACE and additional local RT for PVTT in unresectable HCC. The aim of the present study was to investigate the efficacy and toxicity of this preliminary trial and explore RT guidelines for liver cirrhosis.

MATERIALS AND METHODS

ELIGIBILITY CRITERIA

Patients with unresectable HCC accompanied by tumor thrombus in the first branch of the portal vein and liver cirrhosis were eligible for study. Exclusion criteria included (i) the presence of extrahepatic metastasis; (ii) complete obstruction of the main portal trunk; (iii) tumors occupying more than two-thirds of the whole liver; (iv) the presence of uncontrollable ascites; and (v) performance status >3 on the ECOG scale. The presence of PVTT was confirmed in all cases using the following criteria: (1) a low attenuation intraluminal mass that expanded the portal vein on enhanced CT or US; (2) portal vein filling defects by indirect portgrams obtained from the venous-phase angiogram of the superior mesenteric artery; or (3) ‘thread and streaks’ signs, which reflect intraportal tumor growth and observation of arterioportal shunting on hepatic angiograms.

Informed consent was obtained from all patients in accordance with the procedures of the Institutional Review Board of Kobe University School of Medicine.

PATIENTS AND TUMOR CHARACTERISTICS

From February 1998 to December 1999, eight patients (five men and three women) were entered into the study. Patients’ characteristics are shown in Table 1. The median age was 65 years (range 63–79 years) and the performance status according to the ECOG scale was 1 in four cases and 2 in four cases. The mean tumor size was 7.1 cm (range 4–13 cm). In five patients, there was opacification of the first branches of the left portal vein and in three patients the first branches of the right. HCC were grossly classified as nodular, massive and diffuse, according to criteria of the Liver Cancer Study Group of Japan. According to UICC staging, all patients were IVA (all with T4N0M0).

TACE PROCEDURES

TACE was performed using an infusion of a mixture of iodized oil contrast medium (Lipiodol 1–3 ml), epirubicin hydrochloride (Farmitubulin 40 mg) and mytomycin (Mytomycin C 10 mg), followed by gelatin sponge cubes (Gelfoam) embolization.

RADIATION THERAPY

RT was started 10–14 days following TACE using a 10 MV linear accelerator. A daily dose of 2 Gy was used, five fractions per week, to a total delivered dose of 60 Gy. The RT regime was designed with the purpose of preserving liver function and protecting uninvolved liver. For each patient, CT planning was utilized to determine radiation fields, with the clinical target volume (CTV) defined as only the portal tumor thrombus. Hepatic tumor was included only if the tumor was directly involved with the portal vein. Intrahepatic metastatic nodules were not included in the CTV. The planning target volume

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>Tumor characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case No.</td>
<td>Age (years)/gender</td>
</tr>
<tr>
<td>1</td>
<td>64/F</td>
</tr>
<tr>
<td>2</td>
<td>64/M</td>
</tr>
<tr>
<td>3</td>
<td>64/F</td>
</tr>
<tr>
<td>4</td>
<td>75/F</td>
</tr>
<tr>
<td>5</td>
<td>63/M</td>
</tr>
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<td>6</td>
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<tr>
<td>7</td>
<td>75/M</td>
</tr>
<tr>
<td>8</td>
<td>66/M</td>
</tr>
</tbody>
</table>

*Gross features defined according to the criteria of the Liver Cancer Study Group of Japan. †Portal vein tumor thrombus.
(PTV) included the CTV plus a 1–2 cm margin for daily set-up variation in the cranial–caudal dimension to account for the ventilatory motion of the liver.

**Follow-up Evaluation**

During treatment, patients were monitored weekly with complete blood counts and liver function tests. Deterioration of liver function was defined as lowering of the Child–Pugh score (10,11). The scoring was performed 2 weeks after RT because of follow-up angiogram and second TACE was performed for 2 weeks after RT. We observed a relationship between deterioration of liver function and the percent volume of the total liver exceeding a dose of 30 Gy ($V_{30}$) due to doses in the 30 Gy range being considered the limit of ‘whole-liver tolerance’ (12). Tumor thrombus response was based on serial CT scans 4–6 weeks following completion of the treatment and then at 1–3 month intervals. Complete disappearance of the portal tumor thrombus was defined as a complete response (CR), >50% decrease of thrombus size as a partial response (PR), <50% decrease of thrombus size or no change defined as stable disease (SD) and tumor growth as progressive disease (PD). Response rates were calculated for CR or PR, while SD or PD was considered no response. Hematological and gastrointestinal side effects were documented by use of the RTOG score.

**Statistical Methods**

Overall survival was calculated from the day of commencement of TACE until the day of death. The probability of survival was calculated according to the methods of Kaplan and Meier.

**Results**

**Treatment**

The full RT dose was delivered to six (75%) patients (Table 2). RT was terminated in one patient for extrahepatic metastasis (No. 2) and in one patient for choledocholithiasis (No. 3). The mean tumor dose was 57 Gy (range 46–60 Gy) in daily 2 Gy fractions. Anterior–posterior parallel opposing portals were mostly used, with multiport combinations of three ports or more applied depending on tumor location. Total liver volumes ranged from 1032 to 2108 cm$^3$ (mean ± SD, 1460 ± 369 cm$^3$). Clinical target volumes ranged from 19 to 162 cm$^3$ (59 ± 43 cm$^3$), while planning target volumes ranged from 168 to 963 cm$^3$ (463 ± 265cm$^3$). There was little correlation between the CTV and $V_{30}$. Patients who used the multiport or two orthogonal combinations had larger $V_{30}$ than the patients who used the two parallel-opposed photon beam arrangements.

**Response**

Objective responses in the CT study were observed in three of the eight patients, giving a response rate of 37.5% (Table 2). None of our patients showed CR or PD at the time of response evaluation. On follow-up angiograms of five patients performed from 2 weeks to 3 months following RT, recanalization of the first portal branches was not observed. However, the protrusion of PVTT into the main portal trunk was decreased and TACE was performed again in all five cases (Fig. 1).

Median survival after TACE was 5.7 months. Three patients died from progressive disease, which was evident from 4 to 19 months. Two patients died from liver failure and extra-field tumor progression, which were evident 3 and 4 months after treatment, respectively.

**Tolerance and Side Effects**

The results of the assessment of toxicity are summarized in Table 3. While no patient showed radiation pneumonitis, every patient had transient elevation of liver function tests, particularly in aspartate aminotransferase and alanine aminotransferase, and three patients developed ascites. Deterioration of liver function was not encountered until 40% $V_{30}$ with deterioration observed in all patients with $V_{30} >40%$.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>RT dose (Gy)</th>
<th>Type of photon beam arrangement</th>
<th>CTV* (cm$^3$)</th>
<th>$V_{30}$ (%)</th>
<th>Tumor response</th>
<th>Survival period (months)</th>
<th>Patient outcome</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>50</td>
<td>Two orthogonal</td>
<td>27</td>
<td>51</td>
<td>NC</td>
<td>2.9</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>Three equally</td>
<td>48</td>
<td>50</td>
<td>NC</td>
<td>3.9</td>
<td>Dead</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>Two orthogonal</td>
<td>162</td>
<td>50</td>
<td>PR</td>
<td>5.7</td>
<td>Dead</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Two opposed</td>
<td>21</td>
<td>47</td>
<td>NC</td>
<td>3.8</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>Two opposed</td>
<td>68</td>
<td>36</td>
<td>NC</td>
<td>5.2</td>
<td>Dead</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>Two opposed</td>
<td>19</td>
<td>36</td>
<td>PR</td>
<td>3.8</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>Two opposed</td>
<td>72</td>
<td>35</td>
<td>PR</td>
<td>10.4</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>Two opposed</td>
<td>55</td>
<td>20</td>
<td>NC</td>
<td>19.3</td>
<td>Dead</td>
</tr>
</tbody>
</table>

*Clinical target volume. †The percent volume of the total liver exceeding 30 Gy.
For gastrointestinal complications, one patient was scored as RTOG grade 1 and two patients were scored as grade 2 due to gastric ulcers inside the radiation field. Two patients showed a grade 3 leucopenia (white blood cells <2000/mm³) and three patients showed grade 3 thrombocytopenia (platelets <50 000/mm³).

**DISCUSSION**

Patients suffering from HCC with PVTT generally have a poor prognosis, as tumor proliferation is often extreme and accompanied by intrahepatic metastases, liver dysfunction, portal hypertension and esophageal varices. Fujii et al. (3) reported that 1- and 2-year survival rates in patients with tumor thrombus in the portal vein trunk, in the right, left or both portal veins, were 20.9 and 6.2%, respectively. Nishimura et al. (13) reported that the 1- and 2-year survival rates of similar patient groups treated with conventional TACE were 20.0 and 5.5%, respectively, for PVTT in the first branch.

The variation in the reported treatment results makes it difficult to compare our data and it is not clear whether our treatment regimen is a superior modality to TACE alone in unresectable HCC with PVTT, so that further study is required to compare the therapeutic efficacy of this regimen. However, on follow-up angiograms, the protrusion of PVTT into the main portal trunk was decreased in all cases. TACE was clinically considered a contraindication in patients with main portal trunk obstruction as it could theoretically result in hepatic decompensation due to hepatic ischemia (4). For this reason, our results indicate that combined therapy may prevent PVTT from spreading to main trunks, therefore suggesting further benefits of TACE.

Recently, the use of 3D conformal RT (3D CRT) has been introduced for the treatment of intrahepatic malignancies (8,14). These studies suggest that the radiation dose level with respect to the volume of normal liver to be radiated depends on the percentage of normal liver receiving >50% of the prescribed isocenter doses: 66 Gy whole-liver dose for <33% of the total liver volume, 48 Gy for 33–66% and 24 Gy for >66%, in 1.5 Gy twice-daily fractions with concurrent bromodeoxyuridine (8).

On the other hand, there is a paucity of literature outlining clear treatment guidelines for clinical decision-making for liver cirrhosis. Because cirrhosis is frequently associated with HCC, any regional therapy should be aimed at preserving non-tumor liver function as much as possible. Hence it is important to integrate an assessment of liver function into the radiation treatment-planning process to allow the treatment of patients with cirrhosis.

The liver is often considered a ‘parallel’ structure. For parallel tissues, fewer treatment ports are better because giving higher doses to fractions of the volume containing less than the critical reserve of the organ will tend not to result in complications, while giving a high dose to the entire organ may cause enough damage to produce toxicity (15).
The dose–volume histogram (DVH) has been widely accepted as a useful means of displaying such complex information in an understandable format. Marks et al. (16) reviewed the results for 100 patients after 3D CRT for the development of pneumonitis, pulmonary fibrosis and/or pulmonary symptoms. The best predictors of ‘pulmonary symptoms’ after RT were the percent of the total lung volume receiving more than 30 Gy ($V_{30}$) and the normal tissue complication probability (NTCP; Lyman model). Graham et al. (17) reported that $V_{30}$ was statistically significant to the development of grade 2 pneumonitis in 99 patients with non-small cell lung cancer.

We evaluated $V_{30}$ as a predictor of liver damage in RT in this study because doses in the range of 30 Gy are often considered the limit of ‘whole-liver tolerance’ (12). Absence of prior knowledge of the relationship between $V_{30}$ and liver function deterioration or other parameters with which to assess risk of deterioration of liver function and the use of unique beam arrangements unfortunately led to the development of liver failure in some patients. Our results indicate that the volume of the liver receiving a dose in excess of 30 Gy could be used as a predictive test for the development of liver failure.

In predicting the possible deterioration of liver function with irradiation, the degree of impairment of liver function of the patient is as important as the volume of the liver to be irradiated. According to local high doses radiation therapy using a proton beam for HCC, the initial Child–Pugh score was irrelevant to liver function damage and the transient increase of transaminase was well correlated with the NTCP (18). More detailed evaluation of liver function and determination of the safe irradiation volume are therefore necessary before performing radiotherapy, in order to prevent hepatic failure resulting from the loss of irradiated non-cancerous liver parenchyma. This may be possible using 3D CRT, which we are currently investigating.

### References


