8. New, Effective Treatment Using Proton Irradiation for Unresectable Hepatocellular Carcinoma

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Key words: proton irradiation, hepatocellular carcinoma, Bragg peak

In 34 hepatocellular carcinoma patients (44 lesions), proton irradiation was performed and assessed. Proton irradiation was effective for the nodular HCC in terms of tumor size reduction and histology and almost 100% local tumor control was obtained during the observation period of at least 2 years, which is still undergoing up to 4 years. This therapy is safe and has the merit of excellent QOL during the treatment without any complaints. Further, this method is feasible for patients of deep-seated tumors, and for those with serious complications. Due to the excellent local tumor control, the determining factor for the survival is not affected by the proton irradiation but by the associated complications such as liver cirrhosis.

Background

Conventional external radiotherapy has limited success in hepatocellular carcinoma (HCC), and is not always a recommendable approach among the treatment options. The reason is the severe adverse effects, such as hepatic failure, caused by irradiation accompanying cirrhotic liver. Thus, doses large enough to achieve anticancer effects cannot be accomplished. The proton beam has a Bragg peak that can limit distribution of the beam, which reduces radiation to the non-targeted area while increasing that hitting the target. Recently, we preliminary reported that a large quantity of protons can be safely...
administered to HCC patients with pre-existing cirrhosis (1).

In the present study, we demonstrate the details of the first trial of proton irradiation for hepatocellular carcinoma.

**Patients and Methods**

**Patients**

Our study was approved by the Ethical Committee for Proton Radiotherapy at Tsukuba University Hospital. Thirty-four patients with HCC gave their informed consent and received proton beam radiotherapy at the Proton Medical Research Center (PMRC), University of Tsukuba, in collaboration with the National Laboratory for High Energy Physics (KEK) between January 1988 and October 1992. Table 1 lists the characteristics of these 34 patients and their 44 tumors.

**Proton irradiation procedures**

The protons were provided by a booster synchrotron of KEK and their energy was reduced from 500 to 250 MeV before use. The quantity of radiation was 3-4 Gy per treatment and the duration of therapy was 17 to 69 days. The total amount of radiation ranged from 50 to 87 Gy (76.5±9.5, mean±SD).

Twenty-six lesions were treated with proton monotherapy (Mono) targeted at the tumor because Lipiodol®-targeted chemotherapy was not available. The other 18 lesions were treated with radiation as an additional therapy (Combi) due to an insufficient accumulation of Lipiodol®.

**Treatment evaluation**

The efficacy of proton therapy for HCC was assessed as local tumor control one year after radiation when no sign was observed on CT or ultrasound examination that suggested the growth of the irradiated carcinoma or the development of a new lesion at the irradiated site.

**Results**

**Reduction of tumor size and local tumor control**

The number of tumors which reduced in size 3 weeks after irradiation was 26 out of 26 lesions (100%) receiving monotherapy and 18 out of 18 lesions (100%) in the additional-therapy group; after 1 year, 24 out of 25 lesions (96%) in Mono, and 13 out of 13 (100%) in Combi; after 2 years, 7 out of 8 (88%) in Mono, 5 out of 5 lesions (100%) in Combi; 3 years after, 5 out of 5 lesions (100%) in Combi; after 4 years, 4 out of 4 lesions (100%) in Combi (Fig. 1).

Thus, almost all lesions were reduced in size and approximately 100% of local tumor control was accomplished in both groups throughout the 2-years periods. In addition, 19 lesions under observation all have good local control of tumor up to 4 years.

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**Table 1. Characteristics of Proton Irradiated Lesions**

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>No. of Tumors</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>right lobe</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>left lobe</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>3.6±2.2</td>
<td>4.6±2.1</td>
</tr>
<tr>
<td>Range of size (cm)</td>
<td>1-12</td>
<td>1.5-9.2</td>
</tr>
</tbody>
</table>

(Mean±SD)

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**Fig. 1. Tumor size reduction.**
Previous reports on conventional radiation therapy for HCC reserved hepatic function. Curative in limited patients with a single nodular tumor or major treatment options for HCC available today are surgical and percutaneous ethanol injection therapy (PEIT). Surgical resection may be curative in limited patients with a single nodular tumor or limited area of HCC. However, approximately as many as 85% of the cases with HCC are complicated with liver cirrhosis (2) and there are many unresectable cases because of reduced reserved hepatic function.

Previous reports on conventional radiation therapy for HCC have shown disappointing results (3–6). It has been assumed that more than 50 Gy should be targeted for killing HCC cells (7). But the conventional approaches in which the whole liver is irradiated have caused radiation hepatitis and eventual hepatic failure, especially in patients complicated with cirrhosis. Therefore, sufficient irradiation of a large quantity and long duration to obtain effective antineoplastic effects for most cases of HCC has not been possible (6–7).

Unlike the conventional radiation beam, the proton beam has a unique beam distribution: the beam distribution rate is less in deeper sites than in thinner, superficial sites and there is a peak area (Bragg peak) which rapidly stands around the end of the range at a specific depth-responding energy. The technique has an advantage in that a large amount of radiation can be focused only on the lesion and the exposure of surrounding nontumor tissue can be limited to as little as possible. In fact, with this proton beam it is possible to safely deliver a large quantity of radiation (an amount as large as 3 to 4 Gy per treatment for a total of 76.5 Gy [mean]).

In the present study, we selected the patients with HCC who could not be treated by other conventional methods because of unresectable tumor, serious complications or the patient’s refusal. Despite these handicap conditions proton therapy was effective enough to reduce the tumor size and to make viable cancer cells disappear.

It is noteworthy that the incidence of side effects of proton therapy were very low, and none of the patients have experienced any serious adverse effects necessitating discontinuation of the irradiation protocol. All of the patients maintained typical usual life style during proton therapy. Therefore, satisfactory QOL was insured.

According to an international survey, approximately 10,000 patients were been treated with proton beams between 1954 and June 1991 at 11 facilities in 5 countries (8). Worldwide experience with proton radiotherapy have indicated substantial clinical advantages in relatively superficial and slowly growing tumors (9, 10), but not in deep-seated tumors. However, the present results have demonstrated that the proton beam was effective even for tumors which are deep seated.

In conclusion, proton irradiation therapy is safe and has the special merit of excellent QOL during the treatment without any complaints. This method is advantageous because it is applicable for deep-seated tumors and for patients with serious complications.

Table 2. Side Effects in Proton Radiotherapy

<table>
<thead>
<tr>
<th>Side effects</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever up (&gt;38°C)</td>
<td>0/34 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0/34 (0)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0/34 (0)</td>
</tr>
<tr>
<td>Elevation of transaminase (twice more than baseline level)</td>
<td>9/34 (26)</td>
</tr>
<tr>
<td>Elevation of bilirubin (&gt;3.0mg/dl)</td>
<td>0/24 (0)</td>
</tr>
<tr>
<td>Anemia (Hb &gt;2g/dl more than baseline level)</td>
<td>1/34 (3)</td>
</tr>
<tr>
<td>Leucocytopenia (&lt;3,000/mm³)</td>
<td>7/34 (21)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;50,000/mm³)</td>
<td>5/34 (15)</td>
</tr>
</tbody>
</table>

**Tumor marker**

The measurable serum AFP levels each time were significantly reduced after proton therapy from 571.0±1266.6 (mean±SD) to 145.4±346.3 ng/ml (p<0.005) during a 3-month period.

**Side effects**

None of these patients have experienced any other serious adverse effects necessitating discontinuation of the irradiation protocol (Table 2). During the treatment and followup period, satisfactory quality of life (QOL) maintained.

**Discussion**

Major treatment options for HCC available today are surgical resection, Lipiodol®-targeted chemotherapy or percutaneous ethanol injection therapy (PEIT). Surgical resection may be curative in limited patients with a single nodular tumor or limited area of HCC. However, approximately as many as 85% of the cases with HCC are complicated with liver cirrhosis (2) and there are many unresectable cases because of reduced reserved hepatic function.

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