Objective: The purpose of our study was to evaluate the feasibility and treatment outcomes of fractionated stereotactic radiotherapy (SRT) for primary hepatocellular carcinoma (HCC).

Methods: We enrolled 20 patients who had been histologically diagnosed as HCC patients and treated by fractionated SRT. Tumor size was 2–6.5 cm (average: 3.8 cm). We prescribed 50 Gy in 5 or 10 fractions at the 85–90% isodose line of the planning target volume for 2 weeks. The follow-up period was 3–55 months (median: 23 months).

Results: The overall response rate was 80%, with 4 patients showing complete response (20%), 14 patients showing partial response (60%) and 4 patients showing stable disease (20%). The 1-year and 2-year survival rates were 70.0 and 43.1%, respectively (median: 20 months). The 1-year and 2-year disease-free survival rates were 65.0 and 32.5%, respectively (median: 19 months). The fractionated SRT was well tolerated, because grade 3 or grade 4 toxicity was not observed.

Conclusion: These results suggest that fractionated SRT is a relatively safe and effective method for treating small primary HCC. Thus, fractionated SRT may be suggested as a local treatment of choice for small HCC when the patients are inoperable or when the patients refuse operation.

Key words: fractionation – hepatocellular carcinoma – stereotactic radiotherapy

INTRODUCTION

Primary hepatocellular carcinoma (HCC), which comprises 90% of all malignant tumors developed in the liver, is a fatal disease that causes death within a few months unless treated properly (1). Nevertheless, if it is diagnosed at the early stage and treated by surgical resection, one can expect a high survival rate (2). For most patients, however, primary HCC is often accompanied by chronic viral hepatitis or liver cirrhosis, and curative surgery may not be indicated in such circumstances (3,4). Treatment methods other than surgical resection include liver transplantation (5), transarterial chemoembolization (6), percutaneous ethanol injection (7), radiofrequency ablation (8) and radiation therapy (RT) (9); any of these can be administered alone or in combination. Although there are many treatment options, the standard treatment modality for primary HCC is not yet established, and RT is used primarily for palliative purposes. Recently, however, with developments in RT techniques, the focus of the treatment has been shifting from palliative purposes to cure-oriented therapies, including three-dimensional conformal RT (10–12), stereotactic radiotherapy (SRT) (13–15), proton therapy (16) and cyberknife (17).

Leksell (18) introduced SRT as a treatment technique for arteriovenous malformation in 1951, and subsequently Lax et al. (19) initiated the application of SRT to extracranial tumors in 1990. SRT has been used primarily for treatment of intracranial diseases. However, recently the range of its uses has been expanded to the treatment of various cancers, such as those of the head and neck, the lung, the liver and the pancreas (13–15,20,21). Therefore, we evaluated the treatment outcome using fractionated SRT for small primary HCC.

PATIENTS AND METHODS

ELIGIBILITY

The study was retrospectively and consecutively analyzed on 20 patients who had been histologically diagnosed as primary HCC patients and treated by fractionated SRT from July 1999
to June 2002 at the Department of Radiation Oncology, Saint Mary’s Hospital, the Catholic University, Seoul, Korea. The criteria for patients to be included in the study were as follows: (1) not showing extrahepatic metastasis, (2) belonging to a group lower than B on Child’s classification, (3) ECOG score $<2$, (4) no previous experience of radiation treatment and (5) having a single lesion. Among the total of 20 patients, 16 had been treated previously by transarterial chemoembolization alone (12), percutaneous ethanol injection alone (3) and radiofrequency ablation in combination (1). The characteristics of patients are shown in Table 1. The median age was 59 years (range: 43–76 years), and males were predominant, with 16 male patients. The general condition of most patients was good, with 18 cases having ECOG scores of 0–1. Using the orthogonal diameter estimated by computed tomography (CT), the maximum tumor size was measured, which ranged from 2 to 6.5 cm (mean: 3.8 cm.).

**Table 1. Patient characteristics ($n = 20$)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>43–76</td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>18 (90)</td>
</tr>
<tr>
<td>2</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (80)</td>
</tr>
<tr>
<td>No</td>
<td>4 (20)</td>
</tr>
<tr>
<td>PVT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (20)</td>
</tr>
<tr>
<td>No</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Child class</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>15 (75)</td>
</tr>
<tr>
<td>B</td>
<td>5 (25)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; PVT, portal vein thrombosis.

FRACTIONATED SRT PROCEDURE AND SRT

We used the Point Reference System (Northwest Medical Physics Center, Seattle, WA, USA), where a stereotactic three-dimensional coordinate was used to maximize the precision of the treatment target and also to minimize the injury of normal tissues in the vicinity (15,22).

In brief, the procedures of the treatment were as follows. First, as a preparatory step for SRT, the lesion site and adjacent structures were assessed by abdominal ultrasound imaging, and subsequently three gold markers (1 × 3 mm) were inserted by a specialist from the Department of Diagnostic Radiology. Each patient was immobilized in the supine position with shallow respiration using a vacuum cushion during all procedures of the treatment planning and SRT. A simulation of SRT was performed during inhalation while the patient was practicing respiration. The abdominal CT and SRT were also performed under conditions identical to those for SRT. The abdominal CT was performed at 5 mm intervals. At that time, a virtual three-dimensional coordinate was determined using the three gold markers; based on this coordinate, the target localization of the tumor was found and the center of target was determined (Fig. 1). The CT images were transferred to the three-dimensional treatment planning system (NMPE 3D RTP, Seattle, WA, USA). The transferred CT images were reconstructed as a three-dimensional image and used for dose planning. For fractionated SRT, irradiation of 5 or 10 Gy was used per dose and each dose was prescribed based on the planning target volume (PTV). Dose prescription was done normalized at 85–90% isodose line. To assess the accuracy of patient position and target volume localization, orthogonal verification films were taken before SRT. At that time, the three gold markers were identified. These images were entered into the isocenter localization program (ISOLOC, NMPE, Seattle, WA, USA) and compared with the isocenter using the isocenter localization software. If there were discrepancies between the CT images and the verification film with respect to isocenter localization, the actual marker location was identified using a micropositioner (TORSO system, NMPE, Seattle, WA, USA), and then orthogonal verification films were taken again. SRT was performed after the error range was brought down to $<5$ mm by repeating these localization and verification procedures. The breath-holding technique was employed during irradiation. Respiratory motion of the tumor was halted by holding the breath at maximum expiration. The breath-holding process and estimated time were as follows: the time from ‘breath-holding exhalation’ to ‘image acquisition for

![Figure 1. Coordinates of Point Reference System of patients receiving fractionated stereotactic radiotherapy.](image)
target localization’ was 15 s. If the target was localized within the acceptable range, a skin marker was drawn and matched with a point generated by a movable laser device attached on a ceiling. The patient was irradiated for 15 s for the treatment while maintaining expiration after the agreement between the skin marker and the laser point had been confirmed, and then the irradiation was stopped for 15–20 s. Owing to the lengthy sequence of breath holding and rest periods for the patient, the duration of each single fraction treatment ranged from 60 to 90 min.

We used 6–7 non-coplanar static beams generated by a 6 MV linear accelerator and used custom-made lead blocks to fit the target shape. At the time of treatment planning, the dose volume histogram of target volume and the adjacent organs, including remaining normal liver, was confirmed to minimize the side effects. Using a 6 MV linear accelerator and radiation dose of 5 or 10 Gy per fraction, fractionated SRT was performed 3 or 5 times per week for 2 weeks, with the total irradiation dose of 50 Gy (median dose: 50 Gy).

**RESPONSE AND TOXICITY EVALUATION**

All patients were evaluated for response and toxicity. Treatment responses were determined by measuring the largest size on the abdominal CT scans checked at 1 month after completion of SRT and subsequently at 2–3 months intervals. A complete response (CR) was defined as complete disappearance of the lesion, a partial response (PR) was defined as a decrease in the tumor size or necrosis by >50% of the initial lesion size, a stable disease (SD) was defined as a decrease in the tumor size or necrosis by <50% of the initial lesion size, and a progressive disease (PD) was defined as a progression of the initial lesion. Toxicity was evaluated according to the NCI common toxicity criteria (CTC, 2.0 version) (23).

**STATISTICAL ANALYSIS**

Analysis was performed after 20 patients had been enrolled. In this study, the survival time was measured as the period from the date of first SRT to the date of death or the last follow-up, and disease-free survival time as the period from the date of first SRT to the date of disease progression or death. The survival rate and disease-free survival rate were determined using the Kaplan-Meier method (24) using SAS for Windows 8e.

**RESULTS**

**TREATMENT OUTCOMES**

All patients were followed up, with a median follow-up period of 23 months (range: 3–55 months). The summary of fractionated SRT of patients is shown in Table 2. Among the total of 20 patients, 16 were classified as showing higher than PR, with the total response rate being 80% (Table 3). Of the 16 patients, 4 patients indicated CR (20%) and 12 indicated PR (60%). The remaining 4 patients were classified as NR, and PD was not detected. Figure 2 shows the result for a patient who was classified as CR. The patient was first classified as PR at 1 month after fractionated SRT, but as the lesion was not clinically detectable at 3 months after the treatment he was confirmed as CR. During the 34 months of follow-up after the treatment, there was no evidence of recurrence in this patient. Currently, 4 of 20 patients are alive. The median survival time was 22 months, and the 1-year and 2-year survival rates were 70.0% and 43.1%, respectively. The median disease-free survival time was 19 months, and 1-year and 2-year disease-free survival rates were 65.0% and 32.5%, respectively (Fig. 3).

**TOXICITY**

All patients tolerated the fractionated SRT. Toxicities associated with the treatment are shown in Table 4. Treatment-
related toxicities were negligible in all patients. None of the patients was observed to have more than grade-3 toxicity. Gastrointestinal toxicity was observed in 12 patients (60%). Six patients (30%) showed abnormal liver functions without evidence of tumor progression. Abnormal liver functions developed 2–4 weeks after the completion of fractionated SRT, but the liver functions were recovered or stabilized into at least the upper limit of normal function or of the pretreatment level within 3–6 months. In additional, hematological toxicity was thrombocytopenia in 3 patients (15%) and leukopenia in 2 patients (10%). Nevertheless, all patients recovered following supportive therapy and there were no fatal toxicities.

DISCUSSION

This study was performed on patients with a comparatively small tumor containing a single lesion. Of the 20 patients who were studied, 16 had previous experiences of transarterial chemoembolization alone (12 patients), percutaneous ethanol injection alone (3 patients) and radiofrequency ablation in combination (1 patient). We focused on these 16 patients in whom local treatments had failed to control the tumor. Each of these local treatments has advantages as well as disadvantages. For example, transarterial chemoembolization is ineffective if the tumor has a collateral blood supply. It is not easy to apply ethanol evenly to the entire tumor when performing percutaneous ethanol injection, and the use of radiofrequency ablation is limited to tumors that are not near the blood vessels or the surface of the liver. Moreover, such invasive techniques carry considerable morbidity such as bleeding, infection and pain. On the other hand, some of these problems are easily avoidable using SRT. In fact, patients do not have to bear the risks of hemorrhage, infection or anesthesia when using SRT. On all these considerations, it is a relatively comfortable and safe treatment method, except for the fact that it is not possible to predict the response of the tumor to RT prior to treatment. Nevertheless, according to our data, a high local elimination rate may be anticipated if a high single fractionation dose, such as 5 or 10 Gy, is used for the treatment.

In contrast to the treatment of intracranial tumors, it is not easy to target an extracranial tumor accurately. However, recent advances in the techniques of immobilization, verification and respiration control for extracranial tumors have resulted in safer and more effective methods of three-dimensional RT, SRT, proton therapy and cyberknife for the treatment of tumors of the lung, liver and pancreas (15,16,20–23,25–27). SRT has produced good results in treating various cancers that had low responsiveness to conventional RT (28,29). Recently, the application of SRT has expanded to cancers including lung, liver and pancreas, and results of the clinical use of fractionated SRT for lung cancer have been frequently reported (20,21).
In clinical practice, Lax et al. first reported the successful application of SRT to abdominal cancer (19,30). Blomgren et al. (31), who applied SRT to HCC, proposed that it was more effective when tumors were smaller and thus suggested the possibility of using SRT for treating HCC. Sato et al. (13) and Herfarth et al. (14) reported that the application of a single or fractionated SRT to primary or metastatic HCC improved the local control. The present study was performed based on these results. In our study, the local control rate was 80%, and since most of the tumors showing response were <3 cm in diameter, we postulate that the smaller the tumor size, the more effective SRT becomes. At the same time, since fractionated SRT uses a large amount of radiation per fractionation, methods of minimizing the movement of the liver must be devised to safely use SRT in treating primary HCC. In the treatment of HCC by SRT, there is also a need to establish a thorough treatment plan that includes objective criteria such as dose per irradiation, number of fractionations and total radiation dose.

In conclusion, it is confirmed that fractionated SRT is a relatively safe and effective local treatment for small primary HCC and is also useful for patients who are medically inoperable or who refuse surgery. We therefore believe that fractionated SRT is a challenging treatment modality of choice for patients with small HCC. Further studies are necessary to evaluate fractionated SRT as method of a local treatment for small primary HCC. Studies should also be carried out to compare the results for local control rate and survival rate with those for other conventional treatments.

References