Jpn J Clin Oncol 2004;34(9)532–539
doi:10.1093/jjco/hyh089

Three-dimensional Conformal Radiation Therapy for Unresectable Hepatocellular Carcinoma Patients who had Failed with or were Unsuited for Transcatheter Arterial Chemoembolization

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Received March 18, 2004; accepted June 3, 2004

Background: The purpose of our study was to evaluate the outcome of unresectable hepatocellular carcinoma (HCC) patients, who had either failed with or were unsuited for transcatheter arterial chemoembolization (TACE), treated with three-dimensional conformal radiation therapy (3DCRT) and to determine the prognostic outcome factors.
Methods: From September 1999 to March 2003, 44 patients with unresectable HCC underwent 3DCRT. Thirty-seven patients were male and seven female. Mean age was 62 years, ranging from 34 to 88. Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 10 patients, 1 in 19 patients, and 2 in 15 patients. According to Child–Pugh classification for cirrhosis of the liver, 32 patients were in class A and 12 patients in class B. There were 14 patients with main portal vein thrombosis. Twenty patients had alpha-fetoprotein (AFP) level >400 ng/ml. Tumor size was <5 cm in 16 patients, 5–10 cm in 16 patients, and >10 cm in 12 patients. Thirty-two patients had tumors of confluent type, the remaining patients presented a single hepatic tumor. Serum hepatitis antigen markers were positive for type B in 35 patients and type C in nine patients. Twenty-one patients had Okuda Stage I, 22 patients Stage II, and one patient Stage III. According to the AJCC staging system (5th edition), eight patients were in Stage II (T2N0M0), 19 in Stage IIIA (T3N0M0) and 17 in Stage IVA (T4N0M0).
Results: An objective response was observed in 27 of 44 patients, giving a response rate of 61.4%.The survival rates at 1, 2 and 3 years were 60.5%, 40.3% and 32.0%, respectively. In the analysis of prognostic factors, Okuda stage, AJCC stage, portal vein thrombosis, pretreatment AFP level, and total dose of radiotherapy all had significant impact on survival.
Conclusions: 3DCRT induced a substantial tumor response rate of 61.4% with survival rates at 1, 2 and 3 years of 60.5%, 40.3% and 32.0%, respectively, and a median survival time of 15.2 months in patients with unresectable HCC who had either failed with or were unsuited for TACE. The complications are acceptable and can be managed with conservative treatment. Although we do not know whether there is a survival benefit through the use of this treatment, 3DCRT seems to be a practical method of salvage for this subset of patients. Further study is warranted to evaluate the survival of such patients with and without this treatment.

Key words: conformal radiation therapy – hepatocellular carcinoma – transcatheter arterial chemoembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, especially in Asian contries (1). Surgical resection has been considered the treatment of choice for long-term control of the disease. However, <20% of patients are surgical candidates at diagnosis (2–4). For the

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treatment of unresectable HCC, transcatheter arterial chemoembolization (TACE) has been actively performed, particularly in Asia (5–9). The efficacy of TACE in HCC has been reported from many institutions (5–9); however, the inadequacy of single TACE in inducing complete tumor necrosis has also been well documented (10,11). Therefore, TACE is usually repeated at regular intervals. Nevertheless, repeated TACE frequently becomes ineffective due to tumor progression. Furthermore, TACE is not suitable for patients with main portal vein thrombosis or inferior vena cava invasion. Several institutions have reported promising responses in patients with unresectable HCC treated with radiotherapy to a portion of the liver (12–14). With the advances in three-dimensional conformal radiation technique (3DCRT), local radiation to the liver has become safer (15,16). The purpose of this study was to evaluate the outcome of unresectable HCC patients, who had either failed with or were unsuited for TACE, treated with 3DCRT and to determine the prognostic outcome factors.

SUBJECTS AND METHODS

From September 1999 to March 2003, 53 patients with unresectable HCC were referred to the Department of Radiation Oncology, Chang-Hua Christian Hospital, for 3DCRT. There were 39 patients who had failed with TACE and 14 patients with main portal vein thrombosis who were unsuited for TACE. No patient had received prior radiotherapy to the liver. Nine patients were excluded owing to Child–Pugh class C or Eastern Cooperative Oncology Group (ECOG) performance status >3.

The diagnosis of HCC was based on histological confirmation or on radiographic findings (liver tumor in CT scan as well as hypervascular mass in hepatic angiography) and a serum alpha-fetoprotein (AFP) value exceeding 400 ng/ml. Those patients with AFP values <400 ng/ml underwent liver biopsy for diagnosis. The judgment of TACE failure was based on tumor progression demonstrated on CT scan after several sessions of TACE. The frequency of TACE was 2–9 sessions (median 3) and time interval between the last TACE and the start of 3DCRT was 4–8 weeks.

Patient characteristics are shown in Table 1. Thirty-seven patients were male and seven female. Mean age was 62 years, ranging from 34 to 88. ECOG performance status was 0 in 10 patients, 1 in 19 patients and 2 in 15 patients. According to Child–Pugh classification for cirrhosis of the liver, 32 patients were in class A and 12 in class B. There were 14 patients with main portal vein thrombosis, which was present on CT scan. Twenty patients had AFP level >400 ng/ml. Tumor size was defined as the mean of three diameters on CT scan. Size was <5 cm in 16 patients, 5–10 cm in 16 patients and >10 cm in 12 patients. Thirty-two patients had tumors of massive type, the remaining patients presented with single hepatic tumors. The rate of positivity of HCV/HBV of the patients was 20.5% and 79.5%, respectively. Twenty-one patients had Okuda Stage I, 22 patients Stage II, and one patient Stage III. According to AJCC staging system (5th edition) eight patients were in Stage II (T2N0M0), 19 in Stage IIIA (T3N0M0) and 17 in Stage IVA (T4N0M0).

Table 1. Patient characteristics (n = 44)

Characteristic	No. patients
Age (mean)	
34–88 years (62)	
Sex	
Male/Female	37/7
Performance status (ECOG)	
0	10
1	19
2	15
Viral antigen	
HBV	35
HCV	9
Tumor size	
<5 cm	16
5–10 cm	16
>10 cm	12
Tumor type	
Single	12
Massive	32
Portal vein thrombosis	
Yes	14
No	30
Alpha-fetoprotein (ng/ml)	
>400	20
≤400	24
Liver cirrhosis	
Child–Pugh A	32
Child–Pugh B	12
AJCC stage	
II	8
III	19
IV	17
Okuda stage	
I	21
II	22
III	1

ECOG, Eastern Cooperative Oncology Group.

Radiation Treatment Planning

Patients were placed in a supine position with both arms raised above the head and with the head in a natural position. In order to suppress the movement of respiration, patients were immobilized using a low-density body cradle and the breathing of the

patient was repressed by applying thermoplastic material on the abdomen. A treatment-planning CT scan was performed that included a portion of the inferior chest and the entire abdomen to allow for planning of non-axial fields. The gross tumor volume (GTV) was defined as high CT value area in early phase contrast-enhanced CT images. The clinical target volume (CTV) was defined as the GTV plus 1 cm. The planning target volume (PTV) was defined as the CTV plus 0.5 cm for daily patient setup variation, and 0.5–2.5 cm (usually 1–1.5 cm) in the cranial–caudal dimension to account for the ventilatory motion of the liver. This addition was determined individually using fluoroscopy. Treatment plans were designed for each patient in whom the high-dose region encompassed the PTV and maximally spared normal liver outside of the PTV (12). Each treatment plan was evaluated with a cumulative dose–volume histogram (DVH). Ultimately, radiotherapy volume involved a portion of the liver and whole liver radiation was always avoided. Figure 1 shows the dose distribution of the 3DCRT of a typical case including DVH of tumor and the surrounding organ/tissues. Seven portals were used. The beam arrangement was anterior, posterior, right lateral, left lateral, right anterior oblique, left anterior oblique and left posterior oblique portal, respectively.

All treatment was delivered by a linear accelerator with 6 or 15 MV photons. Radiation therapy was given 5 days a week at 1.8 Gy per day. The total dose of radiation ranged from 39.60 to 60 Gy. Median tumor dose was 50.40 Gy. During the treatment, the patients were monitored weekly with physical examination and blood chemistry evaluation.

Evaluation of tumor response was based on serial CT scans. All patients had CT scans before initiation of radiation therapy and 4–6 weeks after completion of radiation therapy and then at 1–3-month intervals. Complete disappearance of hepatic tumor or main portal vein tumor thrombus was considered as complete response (CR), decrease of >50% of the tumor size or portal vein tumor thrombus as partial response (PR), decrease of <50% of the tumor size (or portal vein tumor thrombus) or no change as stable disease (SD), and progression as progressive disease (PD). Acute toxicity was evaluated weekly during the treatment and 1 month following the treatment using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG–EORTC) scale (17). Subacute or chronic toxicity was defined as occurring after 1 month. Survival was estimated from the date of diagnosis according to the Kaplan–Meier method. Log rank test was used in the analysis of prognostic factors.

RESULTS

All patients underwent evaluation of tumor response based on CT scan. Among 30 patients with unresectable hepatic tumors, four patients achieved CR and 17 patients achieved PR.

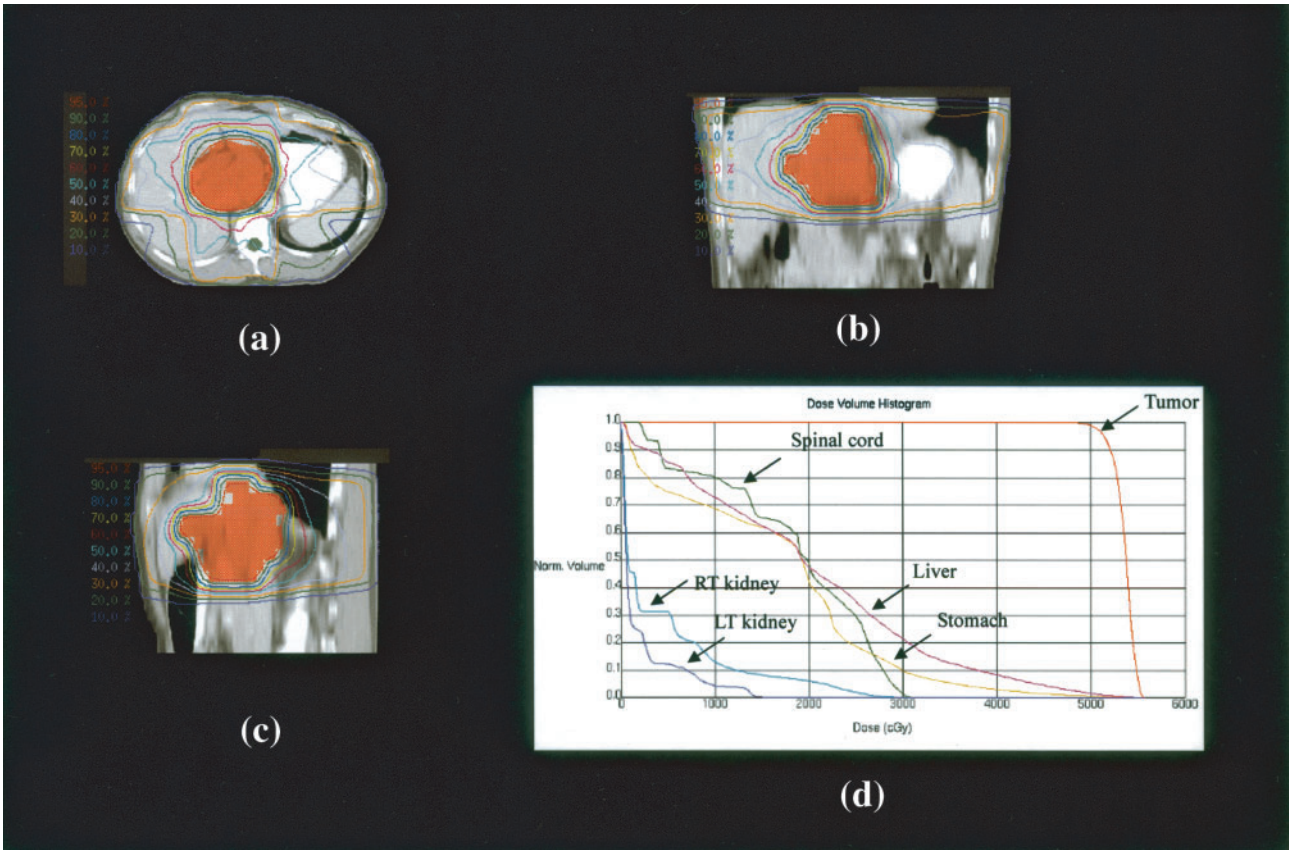

Figure 1. Isodose curves of a three-dimensional radiotherapy using seven coplanar gantry angles delivered for a patient with unresectable hepatocellular carcinoma displayed on the axial (a), coronal (b) and sagittal (c) planes and the dose–volume histogram (DVH) for the relevant structures (d).

Among 14 patients with main portal vein tumor thrombosis, two patients achieved CR and four patients achieved PR. In total, an objective response was observed in 27 of 44 patients, including six patients with CR and 21 patients with PR, giving a response rate of 61.4% (Table 2). After a median follow-up of 8.3 months, 11 patients remained alive and 33 were dead. Nineteen patients (43.2%) developed intrahepatic metastasis outside the radiation field. Distant metastasis developed in six patients (13.6%), including two in lung and four in bone. Time to distant metastasis ranged from 4 to 18 months.

Survival rates were evaluated in all patients from the time of diagnosis. The survival rates at 1, 2 and 3 years were 60.5%, 40.3% and 32.0%, respectively, with a median survival time of 15.2 months.

Toxicity of 3DCRT is summarized in Table 3. Elevation of transaminase (either aspartate aminotransferase or alanine aminotransferase) was seen in five patients (two patients of grade 1 and three of grade 2), bilirubin in three patients (one of grade 1 and two of grade 2), albumin in five patients (two of grade 1 and three of grade 2) and alkaline phosphatase in four patients (two of grade 1 and two of grade 2). Hematologic toxicity included thrombocytopenia in six patients (three of grade 1 and three of grade 2), anemia in eight patients (five of grade 1 and three of grade 2) and leucocytopenia in three patients (two of grade 1 and one of grade 2). No patient had radiation-related gastrointestinal bleeding. There were no treatment-related deaths.

In the analysis of prognostic factors (Table 4), Okuda stage had significant impact on survival. The 2-year survival rates were 59.9% for Stage I and 18.3% for Stage II+III patients ($P = 0.003$; Fig. 2). AJCC stage had significant impact on survival. The 2-year survival rates were 54.2% for Stage

Table 2. Response of unresectable hepatic tumor and PVT to 3DCRT

Response	Hepatic tumor No. patients	PVT No. patients	No. patients (%) Sum
Complete response	4	2	6 (13.6)
Partial response	17	4	21 (47.8)
Stable disease	5	6	11 (25.0)
Progressive disease	4	2	6 (13.6)

PVT, portal vein thrombosis; 3DCRT, three-dimensional conformal radiation therapy.

Table 3. Acute toxicity of 3DCRT ($n = 44$)

	Toxicity grade			
	1	2	3	4
Hepatic				
Transaminase*	2	3	–	–
Bilirubin	1	2	–	–
Albumin	2	3	–	–
Alkaline phosphatase	2	2	–	–
Hematologic				
Anemia	5	3	–	–
Leucopenia	2	1	–	–
Thrombocytopenia	3	3	–	–

*Aspartate aminotransferase and alanine aminotranferase. 3DCRT, three-dimensional conformal radiation therapy.

Table 4. Prognostic factors potentially affecting overall survival

Factor	Patients (%)	Survival rate (%)			*P*
		1-year	2-year	3-year	
Age (years)					
<50	7 (16.9)	57.1	57.1	57.1	0.402
⩾50	37 (83.1)	57.4	34.0	27.8	
Gender					
Male	37 (83.1)	60.5	45.9	39.4	0.092
Female	7 (16.9)	57.1	14.3	14.3	
ECOG performance status					
0–1	29 (65.9)	53.9	32.3	28.9	0.238
2	15 (34.1)	57.1	40.0	40.0	
Liver cirrhosis					
Child–Pugh Class A	30 (68.2)	64.5	38.5	30.0	0.478
Child–Pugh Class B	14 (31.8)	38.5	30.7	30.7	
Tumor size (cm)					
<5	16 (36.4)	68.8	50.0	43.8	0.718
5–10	16 (36.4)	65.3	34.8	26.1	
>10	12 (27.2)	33.3	25.0	25.0	
Tumor type					
Single	12 (27.2)	50.0	50.0	40.0	0.278
Massive	32 (72.8)	57.0	32.9	29.3	
AJCC stage					
II+III	27 (61.4)	65.8	54.2	45.9	0.037
IV	17 (38.6)	43.9	18.8	9.4	
Okuda stage					
I	21 (47.7)	75.4	59.9	59.9	0.003
II+III	23 (52.3)	41.2	18.3	9.2	
Alpha-fetoprotein (ng/ml)					
≤400	24 (54.5)	69.6	47.4	47.4	0.007
>400	20 (45.5)	42.7	25.6	12.8	
Portal vein thrombosis					
Yes	14 (31.8)	30.1	7.7	7.7	0.006
No	30 (68.2)	69.3	55.3	43.4	
Total dose of radiotherapy					
<50.40 Gy	29 (65.9)	71.6	53.7	42.2	0.013
≥50.40 Gy	15 (34.1)	28.7	14.3	14.3	

ECOG, Eastern Cooperative Oncology Group.

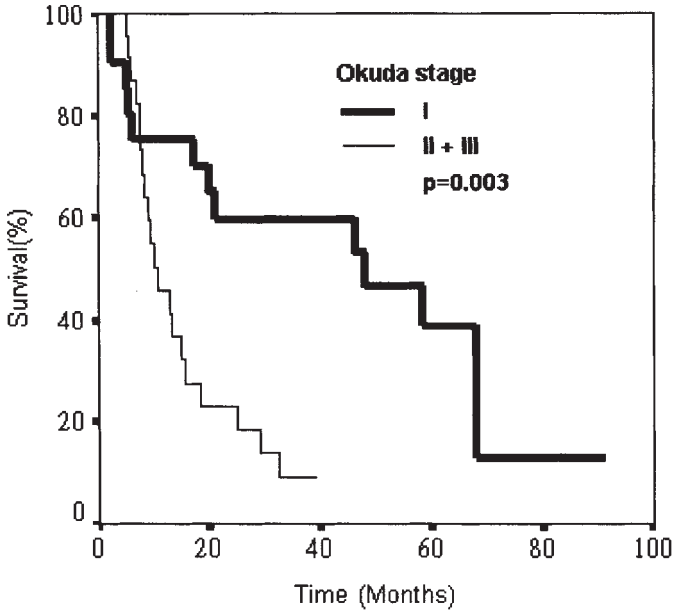

Figure 2. Overall survival of patients treated with local radiotherapy based on Okuda stage.

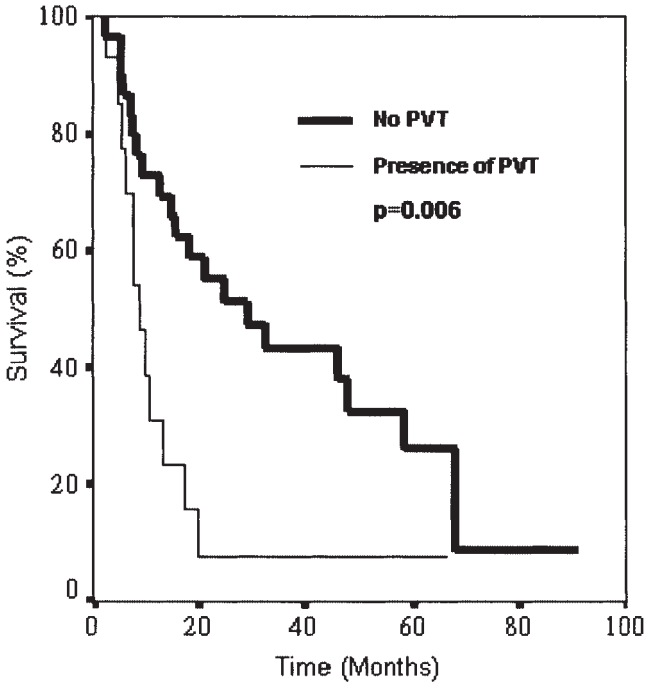

Figure 4. Overall survival of patients treated with local radiotherapy based on presence of portal vein thrombosis.

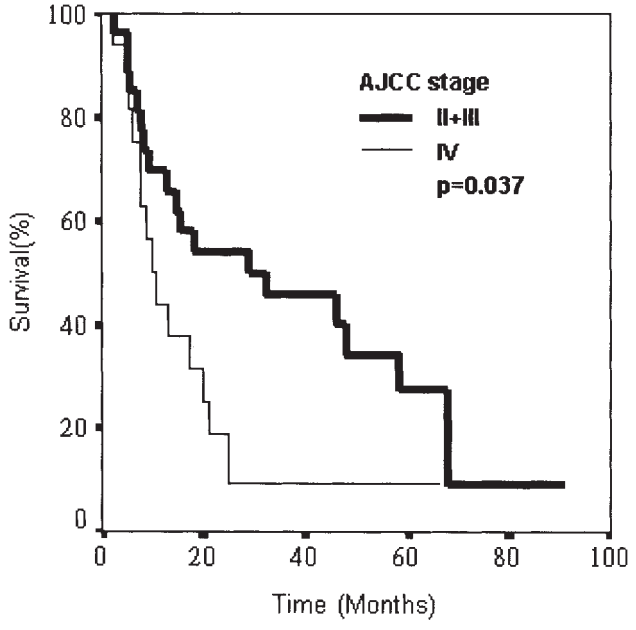

Figure 3. Overall survival of patients treated with local radiotherapy based on AJCC stage.

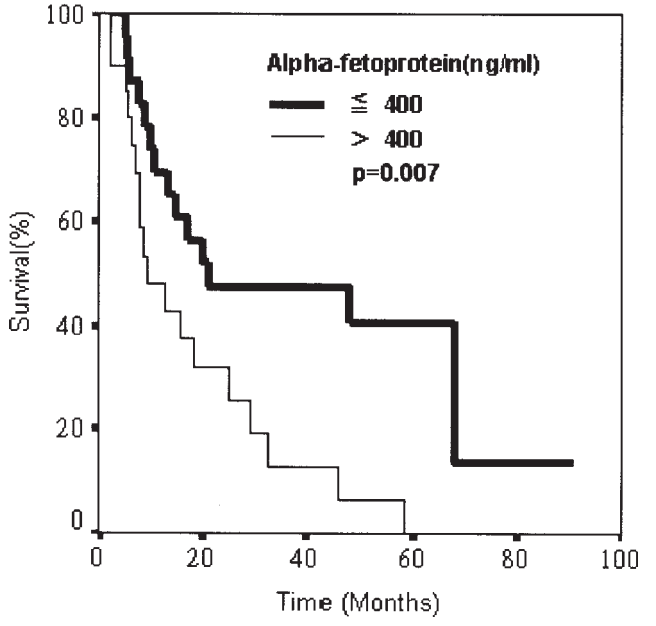

Figure 5. Overall survival of patients treated with local radiotherapy based on alpha-fetoprotein.

II+III and 18.8% for Stage IV patients (P = 0.037; Fig. 3). Portal vein thrombosis had significant impact on survival. The 2-year survival rates were 7.7% and 55.3% for patients with and without portal vein thrombosis (P = 0.006; Fig. 4). Pre-treatment AFP levels of >400 ng/ml had a similar impact on survival. The 2-year survival rates were 47.4% and 25.6% for patients with AFP less than and more than 400 ng/ml, respectively (P = 0.007; Fig. 5). Total dose of radiotherapy >50.40 Gy also had a significant impact on survival (Fig. 6). Age, gender, performance status, Child–Pugh class, tumor size and number of tumors did not influence survival significantly.

DISCUSSION

Radiotherapy for the treatment of HCC has been attempted for decades. Early trials applied whole liver irradiation but used an

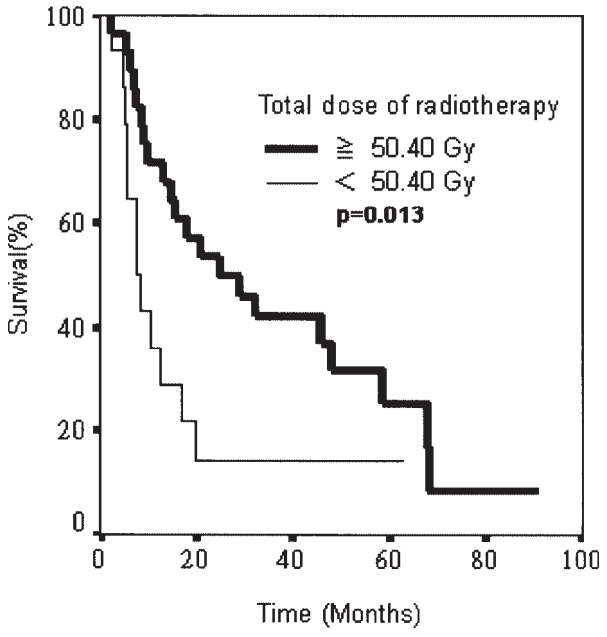

Figure 6. Overall survival of patients treated with local radiotherapy based on radiation dose.

inadequate radiation dose (18–20). Because of hepatic toxicity and ineffectiveness of such low-dose whole-liver irradiation, radiotherapy has not been considered for the treatment of HCC for some time. However, recently, partial hepatic irradiation has been performed by several investigators, who have shown that high doses of radiation can be safely delivered to a portion of the liver (13,14,21–24). Although the low whole-organ tolerance of the liver had previously limited radiation to a palliative role, 3DCRT treatment planning allows significant portions of normal liver to be excluded from the treatment volume when hepatic involvement is not diffuse (25). Because normal liver is spared, a potentially tumoricidal dose of radiation (much higher than whole-liver tolerance) can be administered with acceptable complications (15,25–28). Tanaka et al. (29) reported that a novel, powerful radiotherapy with proton beams had been successfully introduced in the treatment of HCC. Proton irradiation is a safe and effective therapeutic option for treatment of nodular HCC in terms of tumor size reduction, and excellent local tumor control was obtained during the observation period (29–31). The proton beam has a unique dose distribution. There is a peak area (Bragg peak) in which rapidly increasing doses are deposited at the end of the beam range defined by the particular beam energy. The technique has the advantage that a large dose of radiation can be focused on the target, with very limited irradiation of surrounding non-tumorous tissues (29–31). 3DCRT and proton irradiation are effective therapeutic options for treatment of unresectable HCC.

Seong et al. (14) reported that local radiotherapy (44.0 ± 9.3 Gy) in combination with TACE resulted in a tumor response rate of 63.3% in unresectable HCC. In a study of local radiotherapy for unresectable HCC patients who had failed with TACE, Seong et al. (23) reported a response rate of 66.7%, comparable to the result of the previous study. The response rate was 61.4% in our study, which is comparable to the results in both previous studies.

Survival rates of TACE for unresectable HCC have been reported by several investigators. Lin et al. (6) reported a survival rate of 42.2% at 21 months. Venook et al. (32) reported a median survival of 7 months. Choe et al. (33) reported the survival rates of repeated TACE for unresectable HCC to be 42.0%, 16.5% and 16.5% at 1, 2 and 3 years, respectively, with a median survival of 13 months. Pelletier et al. (34) and Groupe d'etude et de traitment du carcinome hepatocellulaire (35) reported 1-year survival rates of 24% and 62%, respectively, in two randomized studies. Matsuura et al. (13) reported a 2-year survival rate of 36.4% for 22 patients with HCC treated with radiotherapy alone or with TACE and PEIT (percutaneous ethanol injection therapy). Cheng et al. (36) reported the 2-year survival rate of 41% and median survival duration of 19 months for 25 patients with unresectable HCC following radiotherapy treatment with or without TACE. Seong et al. (14) reported a 2-year survival rate of 33.3% and a median survival of 17 months for 30 patients with unresectable HCC treated with combined TACE and local radiotherapy. Robertson et al. (12) reported long-term results with a 4-year survival rate of 20% and a median survival of 16 months for patients with primary hepatobiliary cancers treated with hepatic artery fluorodeoxyuridine infusion and conformal radiation therapy.

The prognostic factors of HCC reported in the literature include tumor size, tumor type, tumor stage, portal vein thrombosis, serum AFP status, and several serum parameters related to hepatic function (36–39). Some authors have also advocated that a combination of several factors can define prognostic groups (38,39). In our study, Okuda stage, AJCC stage, AFP level, presence of portal vein thrombosis and radiation dose had significant impact on survival. Other known factors were not significant.

The significance of the radiation dose has been suggested in terms of induction of tumor regression as well as in overall survival. Robertson et al. (15) reported a higher response rate and prolonged hepatic control in their high-dose conformal radiation group. In the report of Order et al. (37), a high-dose group also showed better results. Seong et al. (38) showed the presence of a dose–response relationship in radiotherapy for HCC. Dawson et al. (24) reported that tumor control and survival could be improved with an increased radiation dose to unresectable intrahepatic malignancies. These reports strongly support the importance of dose escalation in inducing tumor regression and ultimate success in terms of increased survival (40). In our study, the total dose of radiotherapy had significant impact on survival. The 2-year survival rates were 53.7% and 14.3% for patients with total dose more than and less than 50.40 Gy, respectively ($P = 0.013$).

However, it should be mentioned that the function of the non-tumorous part of the liver might be compromised during radiotherapy owing to preexisting parenchymal disease,

especially cirrhosis of the liver. Most HCC patients referred for radiation therapy present with advanced unresectable disease, usually associated with cirrhosis of the liver. In the report of Cheng et al. (36), six patients developed radiation-induced liver disease (RILD). Four of them died of hepatic failure. The authors suggested that hepatic irradiation might render patients presenting with subclinical, ongoing, or preexisting cirrhosis of the liver, more susceptible to hepatic failure. In the early experience of Seong et al. (40), even low-dose radiation disrupted patients' narrowly maintained liver function and eventually caused fatal hepatic failure in those with poor liver function. In our study, we excluded patients with Child–Pugh class C and ECOG performance status >3. A certain number of patients were eligible to receive sufficient radiation dose at levels that do not induce severe hepatic toxicity. In our series, there was no treatment-related fatal hepatic toxicity. With regard to subacute or chronic toxicity, gastroduodenal complications often occurred in patients with tumors in the left lobe of the liver, especially when the radiation field included stomach and/or duodenum. Seong et al. (23) reported that five patients developed gastroduodenal complication, including three patients with gastroduodenal ulcer and two patients with duodenitis. Cheng et al. (36) reported that four patients developed radiation-related gastrointestinal bleeding, one of whom died of this complication. Using 3DCRT in our study, treatment plans were designed for each patient, in which the high-dose region encompassed the planning target volume and spared normal tissues, including the stomach and duodenum. No patient developed gastrointestinal complications, including gastroduodenal ulcer and bleeding, in the present study. Our study had no treatment-related deaths.

In conclusion, 3DCRT induced a substantial tumor response rate of 61.4% with survival rates at 1, 2 and 3 years of 60.5%, 40.3% and 32.0%, respectively, and a median survival time of 15.2 months in patients with unresectable HCC who had either failed with or were unsuited for TACE. Patients with Okuda Stage II/III, AJCC Stage IV, portal vein thrombosis, pretreatment AFP level of >400 ng/ml and total dose of radiotherapy <50.40 Gy had significantly shorter survival. With the advance of this radiation technique, local radiation applied to the liver has become safer. The complications are acceptable and can be managed with conservative treatment. Although we do not know whether there is a survival benefit through the use of this treatment, 3DCRT seems to be a practical method of salvage for this subset of patients. Further study is warranted to evaluate the survival of such patients with and without this treatment.

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