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Original article

Optimal follow-up duration for evaluating objective response to radiotherapy in patients with hepatocellular carcinoma: a retrospective study

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Abstract

The time to complete or partial (objective) response to radiotherapy in patients with hepatocellular carcinoma (HCC) is variable; thus, the reported frequency of these responses depends on the length of follow-up. However, the optimum follow-up duration is unknown. We sought to determine the optimal follow-up duration by analyzing the medical records of 25 patients with 39 HCC lesions who received definitive helical tomotherapy at a daily dose of 2 to 4 Gy at 5 fractions per week, for a total dose of 40 to 60 Gy, between January 2008 and January 2013. We determined the time to objective treatment response and local recurrence after radiotherapy and assessed several predictors of delayed treatment response. The median follow-up duration was 15.2 months (range, 7.8 to 52.1 months). Among all 39 lesions, objective responses were observed for 36 (92.3%). The median time to objective response was 3.9 months (range, 1.5 to 9.8 months). The objective response rates increased over time from 15.4% at 3 months to 71.8% at 6 months and 87.2% at 9 months. Age 60 years old or older and post-radiotherapy α-fetoprotein concentrations higher than pre-radiotherapy concentrations predicted delayed treatment response. The objective response rate continued to increase over 9 months. Therefore, to fully evaluate the treatment response of HCC, we recommend continuous observation for at least 9 months after radiotherapy.

Key words Hepatocellular carcinoma, radiotherapy, objective response pattern, follow-up duration, local recurrence

Recent advances in radiotherapy, such as intensity-modulated radiotherapy and stereotactic ablative radiotherapy, have provided more definitive therapy to more patients with unresectable hepatocellular carcinoma (HCC)[1,2]. In addition, many researchers have reported treatment outcomes of radiotherapy in patients with unresectable HCC[3-8]. However, the evaluation time for treatment response following radiotherapy varied significantly in these studies. In our previous study, we evaluated treatment response at 1 to 2 months after radiotherapy[7]; Park *et al*.[6] also reported treatment response rates at 1 to 2 months after radiotherapy. However, Katz *et al*.[9] and Facciuto *et al*.[10] evaluated treatment response at 3 months after radiotherapy. In other studies, treatment response was evaluated at 6 months[11] and at 6 to 12 months after radiotherapy[12]. Currently, there is no consensus on the optimal period over which treatment response should be assessed after radiotherapy in patients with HCC.

We determined the pattern of treatment response according to the duration of follow-up after radiotherapy in patients with HCC in an effort to define the optimal evaluation period.

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Materials and Methods

Patient selection

We retrospectively reviewed the hospital records, laboratory results, and imaging studies for patients with HCC who received radiotherapy at our institution between January 2008 and January 2013. Patient eligibility criteria included HCC confirmed by clinical or histological examination, inoperability due to underlying disease or technical unresectability, unfeasible percutaneous radiofrequency ablation, receipt of definitive radiotherapy, good general condition with Eastern Cooperative Oncology Group (ECOG) performance status

of 2 or less, a Child-Pugh classification of A or B, no extrahepatic metastases, and a follow-up duration of at least 12 months.

Clinical evaluation

Each patient underwent basic laboratory studies and liver function tests including α-fetoprotein (AFP) concentration detection, abdominal ultrasonography, and computed tomography (CT). Most patients also underwent liver magnetic resonance imaging (MRI). A diagnosis of HCC was based on the practice guidelines of the Korean Liver Cancer Study Group[13]. The cancer stage of each patient was assigned based on the American Joint Committee on Cancer staging system (7th edition).

The institutional review board of our institution approved this study, and the research was carried out in compliance with the Helsinki Declaration.

Radiotherapy

For CT simulation, patients were immobilized supinely with their arms above their heads using posterior vacuum bags and anterior vacuum-sealed cover sheets (BodyFix, Medical Intelligence Medizintechnik GmBH, Schwabmünchen, Germany). To reduce the movement of the liver during respiration, patients were instructed to take shallow breaths. All patients received intravenous contrast agents, and axial CT images were acquired with a 3-mm slice thickness.

The simulation CT data were transferred to the Hi•Art Planning Station (TomoTherapy Inc., Madison, WI, USA) for inverse planning. The gross tumor volume (GTV) was delineated according to all tumors identified on the abdominal CT and MRI scans. Subsequently, a 5-mm margin was added to create the clinical target volume (CTV), and the planning target volume (PTV) was created by adding an additional 10- to 15-mm margin to the CTV, taking into account target movement during respiration.

The prescription dose was determined by the physician according to the patient's general condition, PTV, and the radiation dose to normal liver. A daily dose of 2 to 4 Gy was delivered at 5 fractions per week, resulting in a total dose of 40 to 60 Gy. The biologically equivalent dose was calculated using a linear quadratic model with respect to acute tumor effects as an α/β ratio of 10[14].

We evaluated each treatment plan using a dose-volume histogram and visually inspecting isodose curves. In general, we considered plans acceptable if the PTV was covered by 95% isodose curves, inhomogeneity of the PTV ranged from 95% to 107%, and doses to normal structures were limited in their tolerances. The dose constraints for normal liver were as follows: no more than 30% of a normal liver should have received more than 27 Gy, and no more than 50% of a normal liver should have received more than 24 Gy. Additionally, the mean normal liver dose should have been less than 28 Gy. For the spinal cord, the maximum dose constraint was to be less than 45 Gy. The dose constraints for the stomach and small intestine were as follows: no more than 10% of each normal organ should have received more than 50 Gy, and no more than 15% of each normal organ should have received more than 45 Gy. All radiation doses are biologically corrected doses. The biologically equivalent dose was calculated as an α/β ratio of 3.

Radiotherapy was administered using a tomotherapy system (TomoTherapy Inc., Madison, WI, USA). Triangulation marks were used to verify that the patient did not roll and to quickly position the patient correctly. Before each treatment, a 3.5-MV fan beam CT image was acquired using a CT detector mounted on a ring gantry and matched to the planning CT image for comparison. Then, if necessary, the patient's position was corrected.

Outcome evaluation and statistical analyses

After treatment, the patients were examined monthly. Liver function, blood cell counts, and AFP concentrations were measured with standard laboratory tests. Treatment responses and tumor recurrence were determined by using CT or MRI every 1 to 2 months.

Treatment response was defined according to the Modified Response Evaluation Criteria in Solid Tumors[15]. An objective response was defined as complete response (CR) or partial response (PR). Local recurrence was defined as the appearance of a new enhanced tumor within the PTV after an objective response, and intrahepatic recurrence was defined as the appearance of a new tumor outside the PTV. Tumors indicating progressive disease (PD) or local recurrence received further treatment, such as trans-arterial chemoembolization (TACE) or surgical resection. Tumors with an objective response without local recurrence or stable disease (SD) received no further treatment. Patients with intrahepatic recurrence were treated for the recurrence.

Radiation-induced general and gastrointestinal toxicities were assessed using the Common Terminology Criteria for Adverse Events, version 4.0. Radiation-induced liver disease and hepatitis B virus reactivation were also evaluated; detailed definitions are given elsewhere[7]. Treatment response time was calculated from the date of radiotherapy completion to the date of the imaging study on which a treatment response was determined. In cases of PR, treatment response time was calculated to the date at which the enhanced tumor stopped becoming smaller. The times to local and intrahepatic recurrences were also calculated from the date of radiotherapy completion.

We also sought to identify factors potentially influencing treatment response time: age, sex, ECOG performance status, tumor size, GTV, pre-radiotherapy AFP concentrations, change in AFP concentration after radiotherapy (calculated as post-radiotherapy concentration/pre-radiotherapy concentration), total radiotherapy dose, daily radiotherapy dose, and pre-radiotherapy TACE.

Actuarial rates were estimated using the Kaplan-Meier method, and groups were compared with log-rank tests for univariate analysis. The Cox proportional regression hazard model was used for multivariate analysis. For all analyses, alpha was set at 0.05. All analyses were performed using SPSS version 18.0 (SPCC Inc., Chicago, IL, USA).

Results

Patient characteristics

Between January 2008 and January 2013, 50 patients with HCC received radiotherapy at our institution. Of these patients, 25 (39 tumors) were included in the study (**Table 1**). Of the 25 patients, 15 had 1 tumor, 7 had 2, 2 had 3, and 1 had 4. Underlying liver cirrhosis

Table 1. Characteristics of 25 patients (39 tumors) treated for hepatocellular carcinoma with radiotherapy

Characteristic	Value
Age (years)[a]	60.7 (40.7 to 76.2)
Gender [cases (%)]	
Men	18 (72)
Women	7 (28)
ECOG performance status [cases (%)]	
0	10 (40)
1	11 (44)
2	4 (16)
Underlying hepatitis [cases (%)]	
B	20 (80)
C	2 (8)
Alcoholic	1 (4)
No hepatitis	2 (8)
Child-Pugh classification [cases (%)]	
A	19 (76)
B	6 (24)
Tumor size (cm) [a]	1.7 (0.7 to 16.3)
GTV (cm^3) [a]	6.84 (0.72 to 114.7)
T category [cases (%)]	
1	1 (4)
2	12 (48)
3	12 (48)
Pre-radiotherapy AFP concentration (IU/mL) [a]	25.94 (1.42 to 34,132)
AFP concentration change [a]	0.9 (0.01 to 1,132.5)
Total radiotherapy dose (Gy) [a]	55.0 (40.0 to 60.0)
Daily radiotherapy dose (Gy) [a]	2.5 (2 to 4)
Biologically equivalent dose (Gy_{10}) [a]	67.1 (56.0 to 78.0)
Previous TACE [number of tumors (%)]	
Yes	23 (58.9)
No	16 (41.1)
Interval between radiotherapy and TACE (months) [a]	3.2 (0.5 to 13.0)

ECOG, Eastern Cooperative Oncology Group; GTV, gross tumor volume; AFP, α-fetoprotein; TACE, trans-arterial chemoembolization. [a]These data are presented as median values with ranges in parentheses.

was found in 24 patients. The median follow-up duration was 15.2 months (range, 7.8 to 52.1 months) for all 25 patients and 17.2 months (range, 12 to 52.1 months) for the surviving patients.

Seventeen patients had received other treatments before radiotherapy. Fifteen patients were treated with TACE, and 2 were treated with TACE and surgical resection. The most commonly prescribed dose fractionation schedule was a total dose of 50 Gy with a daily dose of 2.5 Gy. Among the 39 tumors, this dose fractionation schedule was applied to 13 tumors. All patients received the complete course of scheduled radiotherapy without treatment interruption. Radiation-induced toxicities were not severe. No patient experienced grade 2 or severer general toxicity, and 3 experienced grade 2 gastrointestinal toxicities (duodenal ulcer in 1 patient and nausea in 2 patients). No patient experienced radiation-induced liver disease, and 3 experienced radiation-induced hepatitis B virus reactivation.

Four patients died during the follow-up period. Three died at 7.8, 9.2, and 10.0 months from intrahepatic recurrence. The fourth, a 53-year-old woman with underlying liver cirrhosis (Child-Pugh classification B) and a 6.1-cm tumor in the right hepatic lobe, received a total dose of 60 Gy with a daily dose of 2.5 Gy. She experienced a radiation-induced hepatitis B virus reactivation 2 months after radiotherapy and died of liver failure and hepatic decompensation 3.3 months after radiotherapy.

Treatment outcomes

Among the 39 tumors, 24 had CR, 12 had PR, 1 was stable, and 2 had progressed. Thus, objective responses (CR or PR) occurred in

36 tumors (92.3%). The median time to an objective response was 3.9 months (range, 1.5 to 9.8 months). The objective response rates increased over time from 15.4% at 3 months to 71.8% at 6 months and 87.2% at 9 months. The latest objective response occurred at 9.8 months (**Figure 1A**).

Among the 36 tumors with objective responses, local recurrence developed in 6 at a median of 9.3 months (range, 4.5 to 22 months) after radiotherapy. The local recurrence rates increased over time from 0% at 3 months to 2.9% at 6 months, 8.7% at 9 months, and 11.7% at 12 months (**Figure 1B**). The intervals between objective response and local recurrence were less than 12 months in 5 patients (range, 2.6 to 9.7 months). However, 1 patient experienced local recurrence at 20.5 months after objective response.

Among all 25 patients, intrahepatic recurrences occurred in 15 at a median of 7.5 months (range, 4.1 to 48.1 months). Intrahepatic recurrences developed after CR in 7 patients, after PR in 5 patients, and after SD in 1 patient. Two patients experienced intrahepatic recurrence and PD at the same time. Therefore, treatment for intrahepatic recurrence did not influence the assessment of treatment response.

Predictive factors

We analyzed factors that may influence treatment response time. In univariate analysis, age and AFP concentration change were significantly associated with treatment response time (**Table 2**). Patients of 60 years old or older and patients with an AFP concentration change ⩾1 had delayed objective responses. In

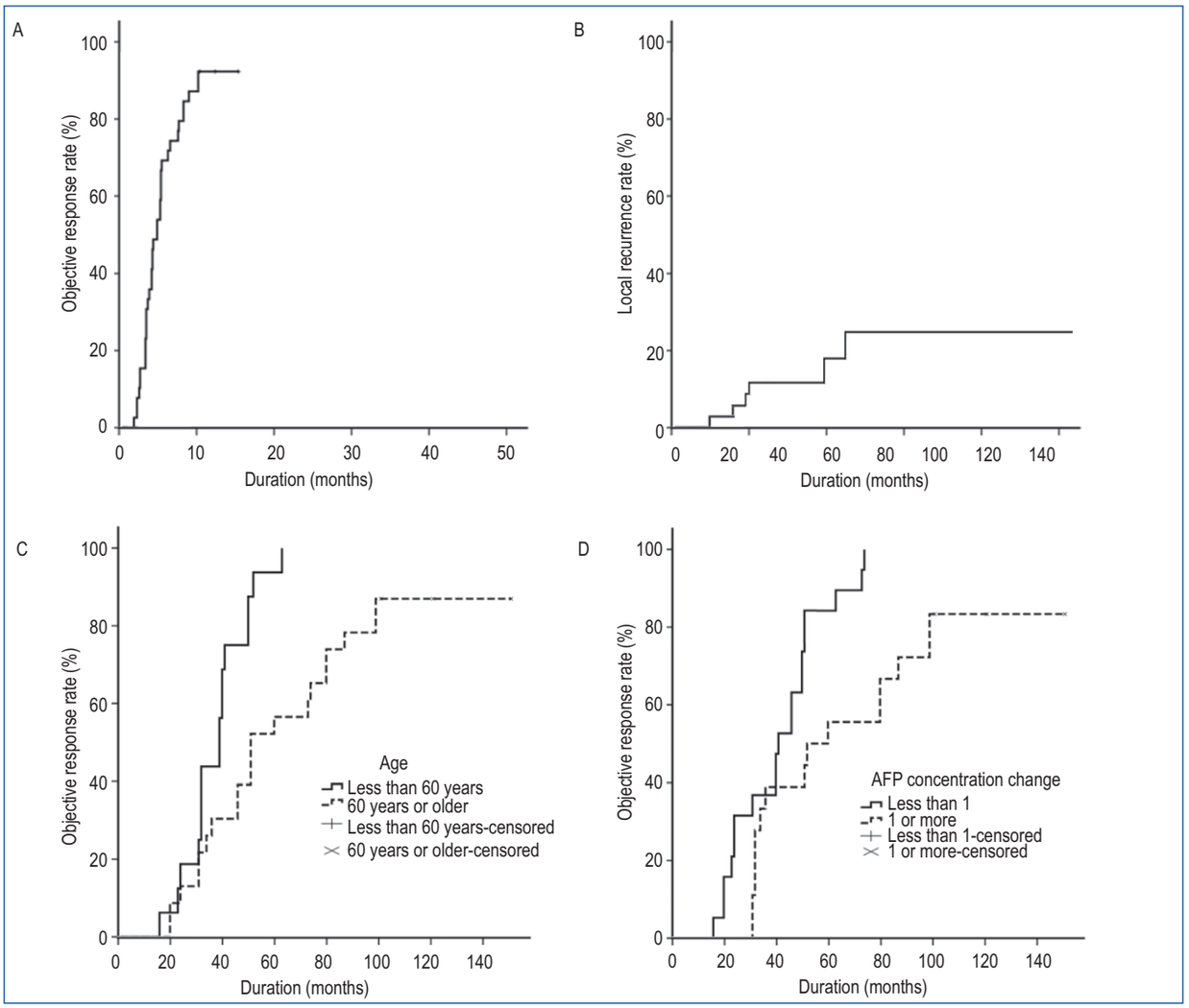

Figure 1. **Development patterns of objective response and local recurrence according to the follow-up duration in hepatocellular carcinoma (HCC) patients treated with radiotherapy.** A, the objective response rate increased over time during follow-up. B, the local recurrence rate increased over time during follow-up. C, development pattern of objective response according to age. Older patients showed delayed objective responses. D, development pattern of objective response according to α-fetoprotein (AFP) concentration change. The patients whose post-treatment AFP concentrations were higher than their pre-treatment AFP concentrations (AFP concentration change ⩾1) showed delayed objective responses.

Table 2. Analysis of potential predictors of time to treatment response among 25 patients (39 tumors) with hepatocellular carcinoma treated with radiotherapy

Variable	Cases	Median time to objective response (months)	*P* value	
			Univariate	Multivariate
Age (years)			0.001	0.005
< 60	16	3.8		
⩾ 60	23	5.0		
Sex			0.081	0.342
Men	27	4.0		
Women	12	5.0		
ECOG performance status			0.391	0.785
0	18	3.8		
1–2	21	5.0		
Tumor size (cm)			0.489	0.380
< 1.7	18	4.5		
⩾ 1.7	21	3.9		
GTV (cm^3)			0.195	0.847
< 7	20	4.9		
⩾ 7	19	3.8		
Pre-radiotherapy AFP concentration (IU/mL)			0.270	0.625
< 25	20	4.0		
⩾ 25	19	4.5		
AFP concentration change			0.003	0.047
< 1	19	4.0		
⩾ 1	20	6.1		
Total radiotherapy dose (Gy_{10})			0.586	0.666
< 67	18	4.5		
⩾ 67	21	3.9		
Daily radiotherapy dose (Gy)			0.672	0.928
< 2.5	13	3.0		
⩾ 2.5	26	4.9		
Pre-radiotherapy TACE			0.178	0.650
Yes	23	3.8		
No	16	4.9		

Abbreviations as in Table 1.

multivariate analysis, age [hazard ratio (HR), 0.32; 95% confidence interval (CI), 0.12 to 2.52; χ^2 = 7.872; *P* = 0.005] and AFP concentration change (HR, 0.43; 95% CI, 0.06 to 0.69; χ^2 = 4.100; *P* = 0.047) remained significant predictors of treatment response time (**Table 2**, **Figure 1C** and **1D**).

Discussion

Some researchers have reported patterns of treatment response according to the duration after radiotherapy in patients with HCC. Sanuki *et al*.[16] treated 42 HCC tumors in 38 patients with stereotactic ablative body radiotherapy and reported that CR rates increased over time from 24% at 3 months to 67% at 6 months and 71% at 12 months. Price *et al*.[17] treated 29 HCC tumors in 26 patients with stereotactic ablative body radiotherapy and reported that the percentage of tumor dimension decrease was increased by 35%, 37%, 48%, and 55%, and the frequency of tumor necrosis was increased by 59%, 69%, 81%, and 92% at 3, 6, 9, and 12 months, respectively. These two studies found that treatment response varied by time after radiotherapy and was improved with longer follow-up. We also found that response rates increased over time after radiotherapy. The objective response rates were 15.4% at 3 months, 71.8% at 6 months, and 87.2% at 9 months. The latest objective response occurred at 9.8 months. Therefore, to fully evaluate the

true response of HCC after radiotherapy, continuous observation is needed for at least 9 months after treatment.

Normal liver tissue surrounding a tumor after radiotherapy has a unique appearance on imaging, with sharply demarcated regions around a high-radiation dose area and presented as enhanced tumors that are not washed out in the portal venous phase[18,19]. Therefore, normal tissue can be misinterpreted as local recurrence and makes measuring the exact size of the tumor difficult. These radiation-induced focal liver reactions have been reported to begin at a median of 3 months, peak at 6 months, and disappear 9 months after radiotherapy[18]. In our study, local recurrence first appeared at 4.5 months after treatment and at a median of 9.3 months. In addition, tumor response started to develop at 1.5 months, and the latest tumor response occurred 9.8 months after radiotherapy. Because radiation-induced focal liver reactions, local recurrences, treatment responses could occur during the same period after treatment, careful observation is crucial in the first 9 months after radiotherapy for HCC.

According to our results, patients of 60 years old or older and patients with an AFP concentration change $\geqslant 1$ showed delayed objective responses after treatment. Therefore, to fully assess the treatment response after radiotherapy in those patients, a longer follow-up duration is required. The reasons that those patients showed delayed treatment responses after radiotherapy have not been investigated. To confirm our results, further studies on identifying the optimal time for evaluating treatment response after radiotherapy in patient with HCC are warranted.

There were some limitations in this study. First, our study was retrospective and may have inherent biases. For example, treatment response was evaluated at the physician's discretion rather than by an established protocol, so the imaging modality (CT vs. MRI) and the time of acquisition of imaging studies varied among the enrolled patients. However, all tumors were easily visible on both CT and MRI, and the choice of imaging modality did not affect the evaluation of treatment response. Second, the sample size was also small. Finally, patients and tumor characteristics were heterogeneous. These limitations may make it difficult to interpret the results of this study. However, we believe our results resolve some of the inconclusive issues on radiotherapy for HCC. We hope this study will be followed by a prospective trial with a larger and more homogeneous patient group.

In conclusion, we found that the objective response rates after radiotherapy in patients with HCC gradually increased over 9 months and believe that our data support a recommendation for cautiously and continuously observing patients with HCC for at least 9 months after radiotherapy.

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References

[1] Krishnan S, Dawson LA, Seong J, et al. Radiotherapy for hepatocellular carcinoma: an overview. Ann Surg Oncol, 2008,15:1015–1024.

[2] Chen WQ, Zheng RS, Zhang SW. Liver cancer incidence and mortality in China, 2009. Chin J Cancer, 2013,32:162–169.

[3] Huang WY, Jen YM, Lee MS, et al. Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. Int J Radiat Oncol Biol Phys, 2012,84:355–361.

[4] Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys, 2011,81:e447–e453.

[5] Dewas S, Bibault JE, Mirabel X, et al. Prognostic factors affecting local control of hepatic tumors treated by stereotactic body radiation therapy. Radiat Oncol, 2012,7:166.

[6] Park W, Lim DH, Paik SW, et al. Local radiotherapy for patients with unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol Phys, 2005,61:1143–1150.

[7] Kong M, Hong SE, Choi WS, et al. Treatment outcomes of helical intensity–modulated radiotherapy for unresectable hepatocellular carcinoma. Gut Liver, 2013,7:343–351.

[8] Kim YI, Park HC, Lim do H, et al. Changes of the liver volume and the Child-Pugh score after high dose hypofractionated radiotherapy in patients with small hepatocellular carcinoma. Radiat Oncol J, 2012,30:189–196.

[9] Katz AW, Chawla S, Qu Z, et al. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. Int J Radiat Oncol Biol Phys, 2012,83:895–900.

[10] Facciuto ME, Singh MK, Rochon C, et al. Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: evaluation of radiological and pathological response. J Surg Oncol, 2012,105:692–698.

[11] Kang JK, Kim MS, Cho CK, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. Cancer, 2012,118:5424–5431.

[12] Kim EY, Choi D, Lim do H, et al. Change in contrast enhancement of HCC on 1-month follow-up CT after local radiotherapy: an early predictor of final treatment response. Eur J Radiol, 2009,72:440–446.

[13] Korean Liver Cancer Study Group and National Cancer Center, Korea. Practice guidelines for management of hepatocellular carcinoma 2009. Korean J Hepatol, 2009,15:391–423. [in Korean]

[14] Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol, 1989,62:679–694.

[15] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for

hepatocellular carcinoma. Semin Liver Dis, 2010,30:52–60.

[16] Sanuki N, Takeda A, Mizuno T, et al. Tumor response on CT following hypofractionated stereotactic ablative body radiotherapy for small hypervascular hepatocellular carcinoma with cirrhosis. AJR Am J Roentgenol, 2013,201:W812–W820.

[17] Price TR, Perkins SM, Sandrasegaran K, et al. Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. Cancer, 2012,118:3191–3198.

[18] Sanuki-Fujimoto N, Takeda A, Ohashi T, et al. CT evaluations of focal liver reactions following stereotactic body radiotherapy for small hepatocellular carcinoma with cirrhosis: relationship between imaging appearance and baseline liver function. Br J Radiol, 2010,83:1063–1071.

[19] Herfarth KK, Hof H, Bahner ML, et al. Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumors. Int J Radiat Oncol Biol Phys, 2003, 57:444–451.