Table 2 Hematologic and hepatic toxicity according to CTCAE ver.4

	SBRT group ($n = 30$)				TACE group ($n = 38$)			
	Post-SBRT grade				Post-TACE grade			
	1	2	3	4	1	2	3	4
Leukocytopenia	20	8	2	0	30	8	0	0
Thrombocytopenia	21	8	1	0	27	8	3	0
Low hemoglobin	27	3	0	0	36	2	0	0
Hyperbilirubinemia	27	3	0	0	34	2	2	0
High serum transaminases	30	0	0	0	33	5	0	0
High serum alkaline phosphatase	30	0	0	0	34	4	0	0

CTCAE, Common Terminology Criteria for Adverse Events; SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

Complications. All patients of these groups completed the prescribed course of treatment. Evaluation of the results of blood tests in either group newly showed no cases of acute hematologic toxicity of more than Grade 3 (Table 2). Figure 5 shows the lack of significant changes in liver function in SBRT group. Furthermore, none of the patients experienced RILD. Within 6 months of the initiation of treatment, one patient of the SBRT group experienced an increase in CTP class, followed by progression in score from 6 to 8. However, there was no relationship between hepatotoxicity and the dose delivered to the normal liver.

Discussion

Following the Clinical Practice Guideline for Hepatocellular Carcinoma,[22] there are some potentially curative options for primary HCC, but they have some limitations.

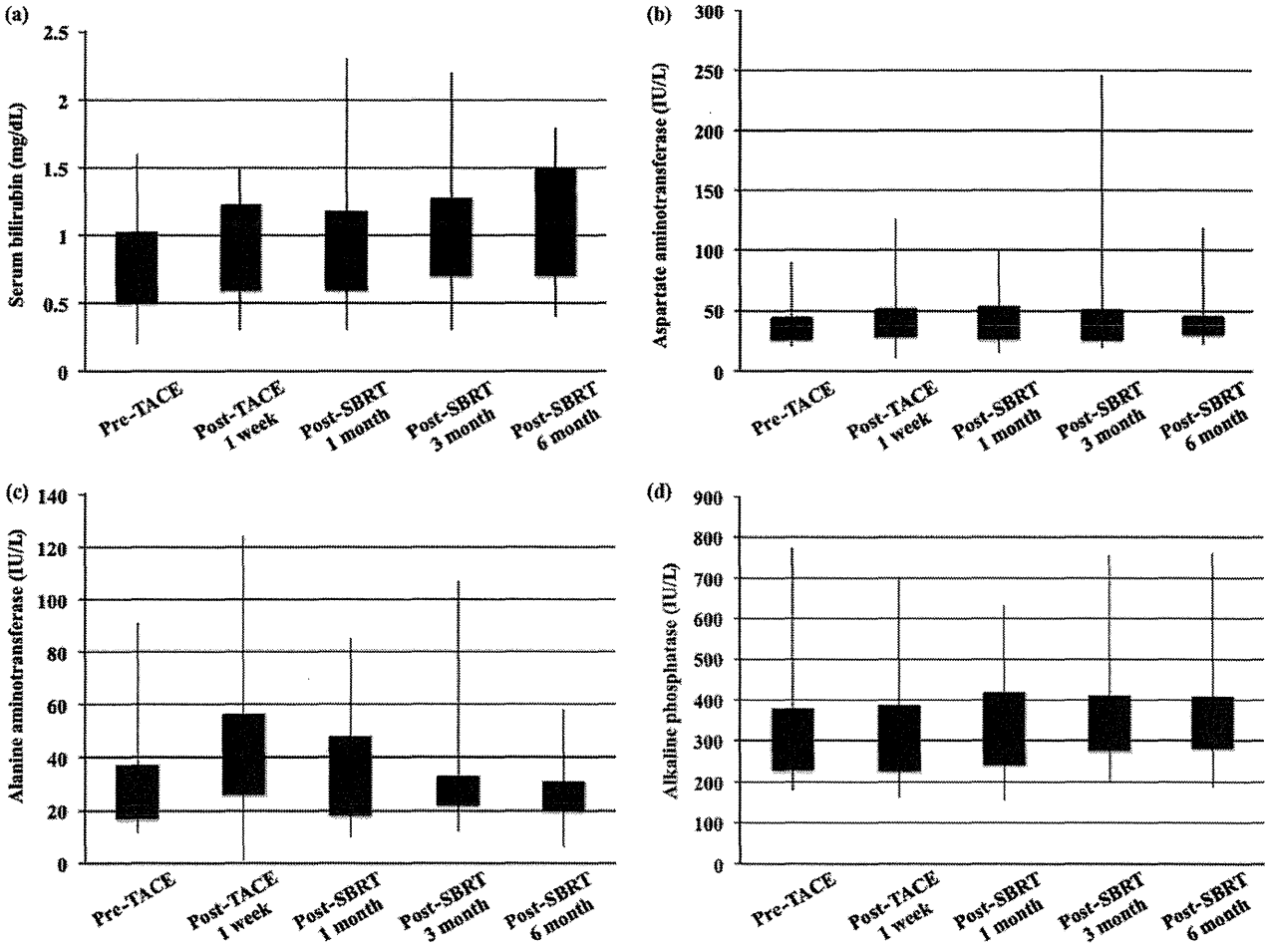

Figure 5 Serial changes in the levels of (a) total bilirubin, (b) aspartate aminotransferase, (c) alanine aminotransferase, and (d) alkaline phosphatase, from pre-TACE to 6 months after SBRT in SBRT group. Data are mean ± SD. SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization.

The use of radiotherapy for HCC remains limited because of risk of RILD and the availability of more efficient or less time-consuming treatment options. However, recently, technological advances in radiation planning, breathing motion reduction strategies, and image guidance have enhanced the feasibility of radiotherapy for HCC, with low risk of toxicity. SBRT delivers a high dose of radiation to HCC within a short period of time and is an effective and less invasive for the delivery of high radiation doses to the tumor with hypofractionation. The role of radiotherapy in the treatment of small HCC has recently been emphasized in the context of the development of SBRT. Andolino *et al.*[23] examined patients with HCC and reported 2-year local tumor control and overall survival rates of 90% and 67%, respectively. Choi *et al.*[24] also reported that the 1- and 2-year survival rates after SBRT for primary HCC were 70.0% and 43.1%, respectively. The difference between these groups was the size of the HCC tumor. Similar results were reported by Sato *et al.*[25] and Herfarth *et al.*[26] But our result is better than theirs. We expect a better outcome free of adverse effects for TACE with SBRT based on the present results. Further large-scale clinical trials are required to confirm this hypothesis.

TACE and SBRT have limitations when used alone. TACE has the problem of incomplete necrosis due to dual blood supply around the HCC capsule or multiple collateral feeding circulation, and this seems to be one of the reasons for the incomplete response. Actually, in our study, the lipiodol accumulation rate in HCC has become decreased in about half of the cases 3 months later. On the other hand, SBRT can be problematic in relation to the irradiation dose and RILD. Several studies[27–29] demonstrated that the response of HCC to SBRT increased with increasing radiation dose, however, others showed that the use of lower dose (e.g. 24–48 Gy[30] or 44 Gy[23]) provided equal local tumor control. Andolino *et al.*[23] also suggested that SBRT might not be safe for patients with Child–Pugh score of ≥ 8. The exact mechanism of RILD remains elusive, but severe congestion of the sinusoids in the central portion of the lobules, reduced flow towards the portal areas, and death of large number of hepatocytes have been suggested.[31] Tumor recurrence and overlap of the surrounding area with the previously irradiation area should raise concern of impending heavier liver damage. Accordingly, we argue that a repeat SBRT to the neighboring recurrence is off-label. In addition, interstitial pneumonia and other pulmonary disorders are known radiation-induced complications.[32] So we particularly hesitate to irradiate in these cases. Further, if patients could not stop breathing because of cognitive function and so on, it is impossible to deliver the appropriate irradiation dose to the targeted region accurately.

SBRT combined with TACE may provide additional benefits. It is possible that radiation could interact with the chemotherapeutic agent while the drug remains in the tumors.[33] Rotman *et al.*[34] also reported that cis-diamminedichloroplatinum hindered the repair of DNA-chain damage and enhanced the sensitivity of tumor cells to irradiation.

In conclusion, our study demonstrated that SBRT combined with TACE is a safe and effective modality for locoregional treatment of small solitary primary HCC, even in patients with contraindication for hepatic resection and ablative therapy. Further large-scale studies are needed to assess the benefit of the combination therapy.

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Hepatology Research

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Original Article

Dynamic computed tomography appearance of tumor response after stereotactic body radiation therapy for hepatocellular carcinoma: How should we evaluate treatment effects?

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Aim: To evaluate the dynamic computed tomography (CT) appearance of tumor response after stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC) and reconsider response evaluation criteria for SBRT that determine treatment outcomes.

Methods: Fifty-nine patients with 67 tumors were included in the study. Of these, 56 patients with 63 tumors underwent transarterial chemoembolization using lipiodol prior to SBRT that was performed using a 3-D conformal method (median, 48 Gy/four fractions). Dynamic CT scans were performed in four phases, and tumor response was evaluated by comparing tumor appearance on CT prior SBRT and at least 6 months after SBRT. The median follow-up time was 12 months.

Results: The dynamic CT appearance of tumor response was classified into the following: type 1, continuous lipiodol accumulation without early arterial enhancement (26 lesions, 38.8%); type 2, residual early arterial enhancement within 3 months after SBRT (17 lesions, 25.3%); type 3, residual early arterial enhancement more than 3 months after SBRT (19 lesions, 28.4%); and type 4, shrinking low-density area without early arterial enhancement (five lesions, 7.5%). Only two tumors with residual early arterial enhancement did not demonstrate remission more than 6 months after SBRT.

Conclusion: The dynamic CT appearance after SBRT for HCC was classified into four types. Residual early arterial enhancement disappeared within 6 months in most type 3 cases; therefore, early assessment within 3 months may result in a misleading response evaluation.

Key words: dynamic computed tomography appearance, hepatocellular carcinoma, stereotactic body radiation therapy

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is closely associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections and the increasing prevalence of viral infections has led to an increased incidence of HCC. The curative therapy for HCC involves surgery including resection or transplantation.[1,2] However, only 10–30% patients initially presenting with HCC would be eligible for surgery either due to liver dysfunction, underlying cirrhosis or presence of multifocal tumors arising from viral infection.[3] For such patients, locoregional therapies such as ablative therapies or transarterial chemoembolization (TACE) are recommended.[1,2] Radiation therapy is a locoregional therapy that can be considered as an alternative to ablation/TACE or when these therapies have failed.[1] Recently, advances in imaging and radiation techniques that deliver high doses of radiation to focal HCC have helped to avoid

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radiation-induced liver damage (RILD). Several studies have reported good treatment outcomes with either stereotactic body radiation therapy (SBRT) or particle therapy with or without TACE for HCC,[4–7] and experience with radiation therapy for HCC has increased rapidly during the past decade.[8] These reports used various methods, such as the Response Evaluation Criteria in Solid Tumors (RECIST),[9] the World Health Organization (WHO) response evaluation criteria,[10] and dynamic CT with or without tumor enhancement[5] to evaluate tumor response. However, no significant progress has been made in establishing a consensus from the various studies that have evaluated the response of HCC to SBRT or particle therapy. Furthermore, no detailed studies have reported the use of CT to monitor tumor response after SBRT or particle therapy. It is extremely important to record the CT appearance at regular intervals to accurately evaluate tumor response because HCC demonstrates changes with time after SBRT.

The purpose of our study was to evaluate the dynamic CT appearance of tumor response after SBRT in conjunction with TACE for HCC and to reconsider response evaluation criteria for SBRT to determine treatment outcomes.

METHODS

Patient background

FROM MARCH 2002 to December 2011, 73 patients with 88 tumors underwent SBRT at our institution. Our study included 59 patients with 67 tumors who were analyzed using dynamic CT for more than 6 months after SBRT. There were 37 men and 22 women with a median age of 71 years (range, 49–90), including five patients with chronic hepatitis B and 47 patients with chronic hepatitis C. Six patients simultaneously underwent SBRT for two tumors each and two patients each with a solitary tumor were treated at different times. The inclusion criteria for curative SBRT were as follows: (i) patients over 20 years of age; (ii) an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2; (iii) Child–Pugh score A or B; (iv) less than three HCC nodules, each up to 50 mm in diameter, without portal venous thrombosis or extrahepatic metastases; (v) inoperable patients because of their poor general condition or refusal of surgery; and (vi) patients unsuitable for radiofrequency ablation (RFA) because of tumor location (e.g. on the liver surface and near the porta hepatis), invisibility of tumor on ultrasonography or bleeding tendency. The exclusion criterion was presence of uncontrolled ascites. The majority of patients had previously undergone surgery or ablation therapies, and SBRT was recommended when these options were limited by technical difficulties or if the patient was inoperable or refused surgery. The clinical characteristics of the patients including age, sex, type of viral infection, Child–Pugh score, primary tumor location and size, ECOG PS and previous treatments are summarized in Table 1.

Hepatocellular carcinoma was diagnosed by its characteristic appearance of early enhancement in the arterial phase and hypodensity in the portal venous phase, which was revealed in most of the patients using either dynamic CT or angiography combined with CT. However, for five patients in whom these CT appearance were not observed, HCC was diagnosed histologically.

Treatment procedure

Before SBRT, 56 patients with 63 HCC underwent TACE using iodized lipiodol (lipiodol). Anticancer chemotherapies, such as epirubicin, cisplatin combined with lipiodol (7–70 mg/body at a concentration of 10 mg/mL lipiodol) or miriplatin mixed with lipiodol (20–80 mg/body at a concentration of 20 mg/mL lipiodol), administrated by injecting the drug into the hepatic artery feeding a segment or subsegments of the target tumor. The selected dose was based on tumor size and liver function. A small amount of gelatin sponge particles was used to induce embolization until the flow through the feeding artery was markedly decreased. The median time interval between TACE and SBRT was 1 month (range, 1–7). The interval was 1–2 months in most of the patients, but was 6–7 months in four patients. They were treated only with TACE because two patients were elderly and had some complications, and the other two patients wanted to be treated only with TACE at first.

Stereotactic body radiation therapy was performed using a 3-D conformal method in which a single high dose is delivered to the tumor. A vacuum cushion (Vac-Lok; CIVCO, Kalona, IA, USA) was used to immobilize the patient. Respiratory motion was evaluated using an X-ray simulator. If respiratory motion was greater than 5 mm, it was coordinated by either voluntary breath-holding using a spirometer or Abches (APEX Medical, Tokyo, Japan), which is a device that allows the patient to control the respiratory motion of their chest and abdomen. Patients held their breath in the end-expiratory phase because the interbreath-hold reproducibility of organ position in end-expiratory phase was better than that in the end-inspiratory phase.[11] This

Table 1 Patients background

Age	49–90 (median, 71)	Tumor size	3–54 mm (median, 19 mm)
Sex		Tumor location	
Male	37 patients	S1	1 lesion
Female	22 patients	S2	1 lesion
ECOG PS		S3	4 lesions
0	55 patients	S4	12 lesions
1	3 patients	S5	8 lesions
2	1 patient	S6	6 lesions
Type of viral infection		S7	15 lesions
HBV	5 patients	S8	20 lesions
HCV	47 patients	Previous treatment	
NBNC	7 patients	Surgery	21 patients
Child–Pugh class		RFA	17 patients
A	46 patients	PEI	9 patients
B	13 patients	TACE	56 patients
Child–Pugh score			
5	33 patients		
6	13 patients		
7	8 patients		
8≧	5 patients		

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-hepatitis B non-hepatitis C; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

method was employed in 55 patients with 62 tumors. The free-breathing method was used in two patients with three tumors, and respiratory-gating using the Real-time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA) was used in two patients with two tumors. For simulation, dynamic CT scans (Lightspeed QX/I; GE Medical Systems, Waukesha, WI, USA), including non-enhanced and contrast-enhanced scans, were performed in four phases, before contrast enhancement, and arterial, portal and venous phases. CT was performed using bolus injection of non-ionic iodinated contrast material (100 mL at a rate of 3 mL/s). CT volume data in the arterial phase were transferred to a 3-D treatment planning system (Pinnacle^3 ver. 9.0; Phillips Medical Systems, Fitchburg, WI, USA). Gross tumor volume (GTV) was defined as the volume of tumor containing the remains of lipiodol used with TACE and from early enhancement in the arterial phase of dynamic CT. A clinical target volume (CTV) margin of 3 mm was usually added to GTV for subclinical invasion. A planning target volume (PTV) margin of 5–8 mm, which included the reproducibility of respiratory motion and setup error to CTV, was usually added. Eight non-coplanar ports were selected in all patients, including four or five coplanar beams and three or four non-coplanar beams in a direction that avoided the stomach, intestine, gall bladder and spine, if possible. The prescribed dose and fractionations were 60 Gy/eight fractions in 10 tumors, 50 Gy/five fractions in five tumors, 40 Gy/four fractions in one tumor and 48 Gy/four fractions in 51 tumors. Beams were delivered using 6–10-MV photons of linear accelerator (CLINAC 2300 C/D or iX; Varian Medical Systems, Palo Alto, CA, USA) that delivered 600 monitor units/min so that the duration of breath-holding could be 15 s or less for each treatment field.

Evaluation

Follow-up dynamic CT was performed every 1–3 months after SBRT. Serum HCC-specific tumor markers including α-fetoprotein were also investigated every 1–2 months. If the level of the tumor markers were increased significantly, additional dynamic CT was performed. Dynamic CT of the entire liver was performed using multidetector row helical CT (16 channels, Light Speed Ultra 16 or 64 channels, Light Speed VCT; GE, Milwaukee, WI, USA) with a 5-mm reconstructed slice width and a 5-mm slice interval. The scanning parameters were 120 kV, Auto mA (noise index, 10), 5-mm section thickness, 1.375 beam pitch, and a 0.7 or 0.4 rotation speed.

Images were obtained in four phases, which included before-contrast enhancement, early arterial, late arterial and portal venous phase after injection of 100 mL of non-ionic iodinated contrast material at a rate of 4 mL/s using an automatic injector. Hepatic arterial, portal venous and equilibrium phase scans were performed for 15–17 s, 45–47 s and 145–147 s, respectively, after triggering using an automatic bolus-tracking program. The dynamic CT appearance was evaluated using a soft-tissue window (level, 40 HU; width, 200 HU), and was confirmed following a consensus between one of the authors (T. K.) and two radiologists for each of the 67 tumors.

The dynamic CT appearance of tumor response and the relationship between tumor appearance and clinical features were evaluated from these results. In addition, local treatment results, such as the local progression-free survival rate (LPFS) and local control rate (LCR), were compared based on several evaluation methods. Treatment-related toxicities were evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4. 0.

Median follow up at the time of evaluation was 12 months (range, 6 –45).

Statistical methods

Univariate analysis using the Mantel–Haenszel χ^2-test or Student's *t*-test and multivariate analyses using the logistic regression test for comparison of statistical significance were used. The LPFS and LCR were calculated using the Kaplan–Meier method. All statistical analyses were performed using StatMate for Windows (StatMate ver. 4.01; ATMS, Tokyo, Japan). Statistical significance was defined as $P < 0.05$.

RESULTS

Dosimetric factors

THE MEDIAN GTV and PTV were 2.9 cc (range, 0.2–38.8) and 27.5 cc (range, 5.5–132.6), respectively. The median dose of PTV was 47.6 Gy (range, 39.4–60.0) and the median percentage of PTV dose relative to the isocenter dose was 98.5% (range, 95.6–102.7%) which is considered to be good dose coverage to PTV.

Dynamic CT appearance of tumor response

The dynamic CT appearance of tumor response was classified into the following four types: type 1, continuous lipiodol accumulation without early arterial enhancement (26 tumors, 38.8%) (Fig. 1); type 2, residual early arterial enhancement within 3 months after SBRT (17 tumors, 25.3%) (Fig. 2); type 3, residual early arterial enhancement more than 3 months after SBRT (19 tumors, 28.4%) (Fig. 3); and type 4, shrinking low-density area without early arterial enhancement after SBRT (five tumors, 7.5%) (Fig. 4). None of the tumors increased in size during the follow-up period. Two tumors (3.0%) demonstrated residual early arterial enhancement for more than 6 months after SBRT; however, most of these features disappeared within 6 months.

Relationship between the dynamic CT appearance of tumor response and clinical features

Table 2 presents the results of univariate analysis between the dynamic CT appearance of tumor response and clinical features, such as Child–Pugh class, sex, age, total dose, PTV, tumor location, history of resection and duration of initial treatment. *P*-value was defined as the clinical factors in each type of dynamic CT appearance as compared to those in the other types. The clinical features of patients with each of the four types of dynamic CT appearance were compared. Significant differences were observed in Child–Pugh class for type 4, sex for type 3, total dose and PTV for types 1 and 4, history of resection for type 4, and duration of initial treatment for type 2.

Table 3 presents the results of multivariate analysis between the dynamic CT appearance of tumor response and clinical features that showed significant differences in univariate analysis. History of resection in type 1 was the only significant factor in multivariate analysis.

Local treatment results

Figure 5(a,b) shows LPFS and LCR, respectively, based on the evaluation criteria 1–3 (shown below). An event was defined as local tumor progression and death in LPFS and local tumor progression in LCR; death without local tumor progression was censored. Evaluation criteria were: (1) local tumor progression defined as growth of an irradiated tumor and presence of a hypervascular nodule adjacent to the treated area; (2) local tumor progression defined as growth of an irradiated tumor, residual early arterial enhancement for more than 3 months and presence of a hypervascular nodule adjacent to the treated area; and (3) local tumor progression defined as growth of an irradiated tumor, residual early

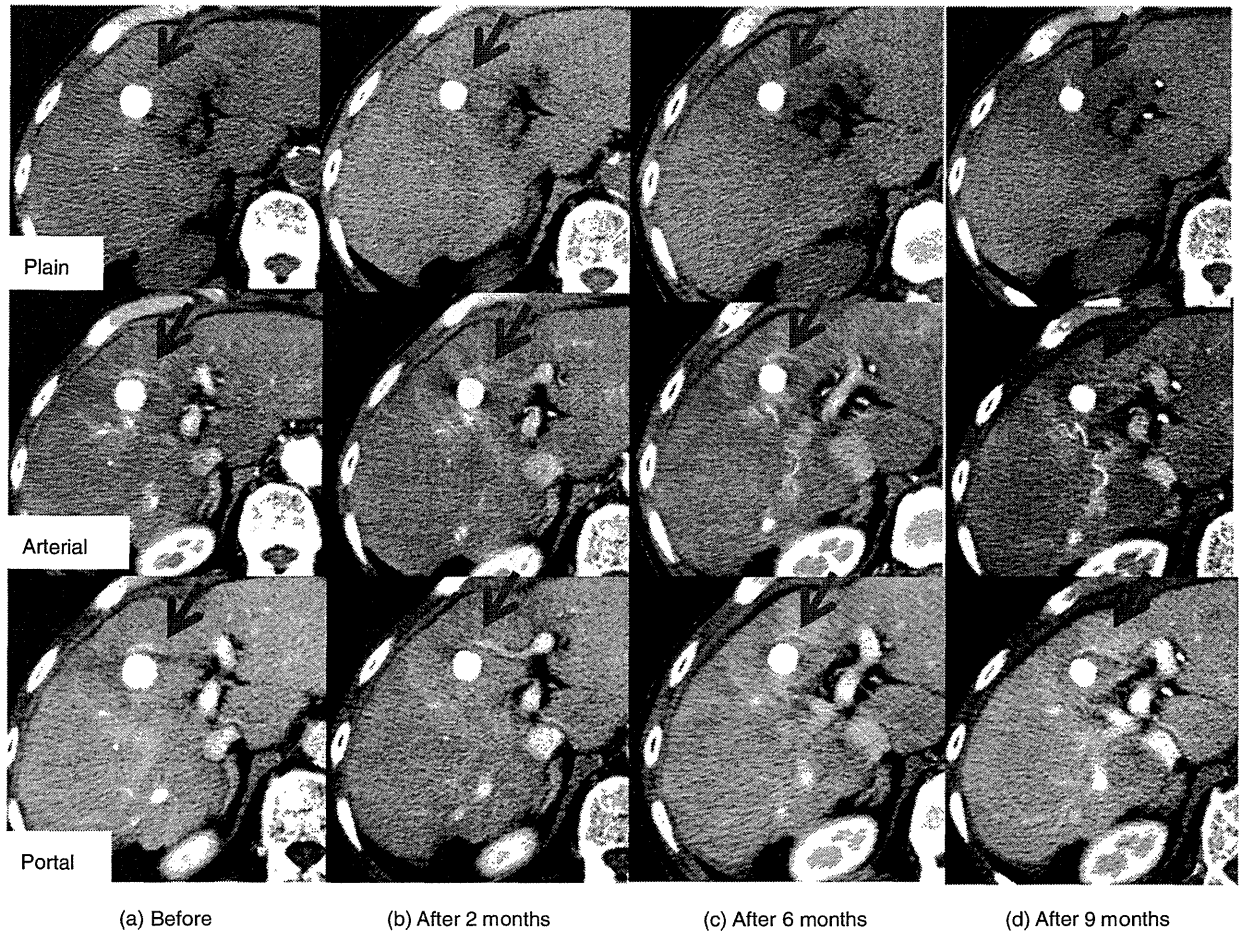

Figure 1 Dynamic computed tomography appearance of tumor response type 1 (plain, arterial and portal phase in case 37). (a) Before stereotactic body radiation therapy; (b) 2 months after; (c) 6 months after, and (d) 9 months after. Note the continuous presence of dense lipiodol accumulation without early arterial enhancement in all phases (red arrow).

arterial enhancement for more than 6 months and presence of a hypervascular nodule adjacent to the treated area.

Significant differences in LPFS were observed between evaluations 1 and 2 and between evaluations 2 and 3 ($P = 0.0089$ and 0.0242, respectively). Significant differences in LCR were observed between evaluations 1 and 2 and between evaluations 2 and 3 ($P < 0.0001$ and 0.0004, respectively).

We also evaluated the tumor response according to the Response Evaluation Criteria in Cancer of the Liver (RECICL).[12] Type 1 and 2 were equivalent to complete response (CR). Most type 3 tumors were also equivalent to CR because residual early arterial enhancement disappeared within 6 months. Two type 3 tumors demonstrated residual early arterial enhancement for more than 6 months after SBRT, however, the reduction rate of these two tumors was more than 50%, equivalent to partial response (PR). All five type 4 tumors were also equivalent to PR because of its reduction rate of more than 50%. From these results, response rate (CR + PR) was 100% and CR rate was 89.6% (60/67 tumors) according to RECICL in this study.

Treatment-related toxicities

None of the patients experienced new acute hematological or physical toxicities of more than grade 3 after TACE. However, seven patients (11.9%) developed grade 3 toxicities, such as bilirubin and ascites eleva-

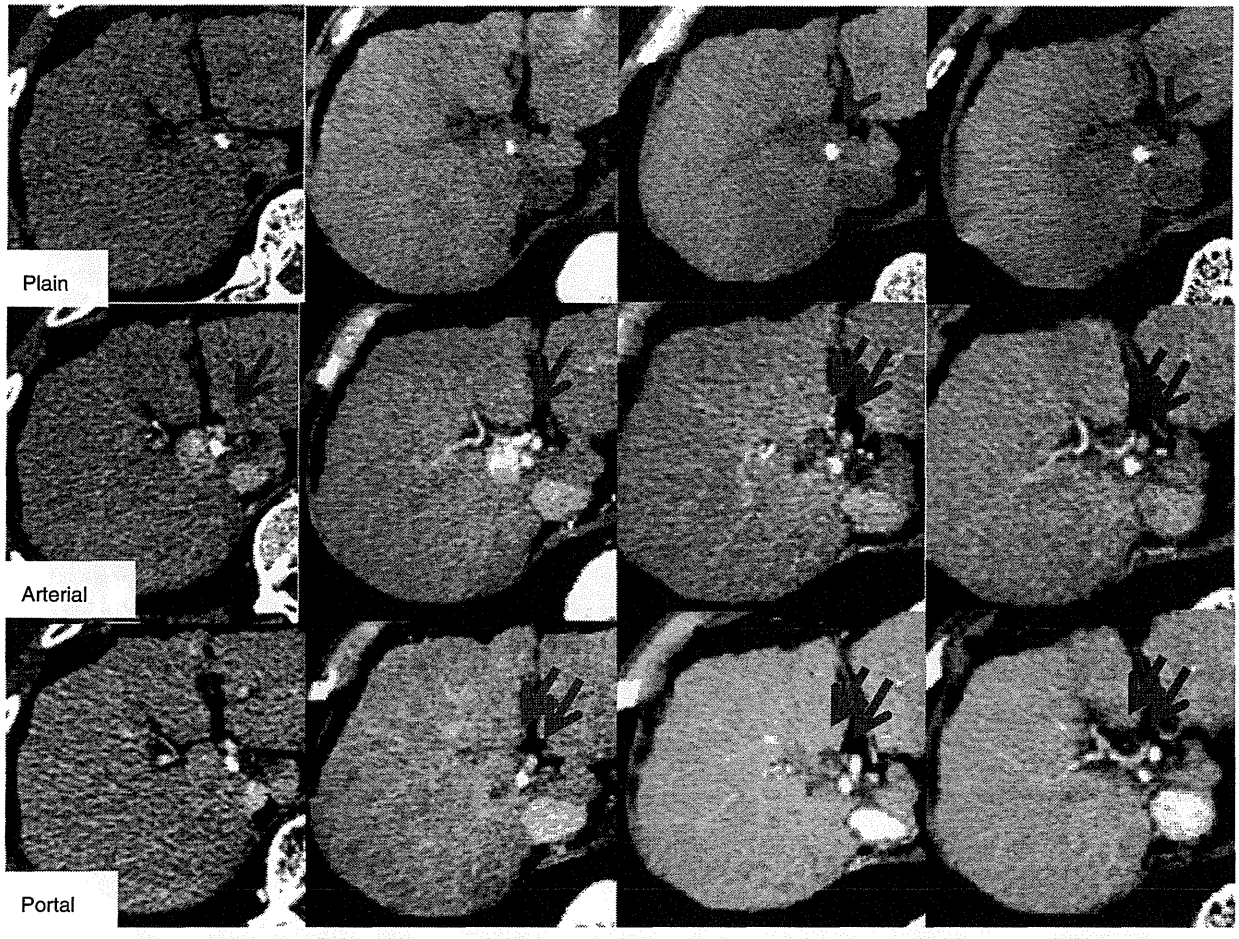

Figure 2 Dynamic computed tomography appearance of tumor response type 2 (plain, arterial and portal phase in case 9). (a) Before stereotactic body radiation therapy (SBRT); early arterial enhancement and partial residual lipiodol were observed (red arrow). (b) One month after SBRT, early arterial enhancement was still present (red arrow). Hypodensity of this tumor changed in the portal venous phase (two red arrows). (c) Three and (d) 5 months after SBRT, early arterial enhancement was no longer evident and hypodensity changed (two red arrows). Residual lipiodol accumulation is still noted (red arrow head).

tions, and one and six patients were in Child–Pugh classes A and B, respectively. None of the patients experienced RILD.

DISCUSSION

SEVERAL AUTHORS HAVE reported the typical CT appearance of RILD after SBRT; typical areas of high-dose radiation reaction appear hypodense in most non-enhanced scans and hyperdense in contrast-enhanced delayed scans.[13,14] These findings could be based on the histopathological features of veno-occlusive disease (VOD), which was recognized as radiation injury to the liver.[15,16] Olsen *et al.* described VOD with marked sinusoidal congestion and venous damage in two patients who underwent exploratory surgery following SBRT.[15] Willemart *et al.* reported that the appearance of hypodensity in the portal venous phase that becomes hyperdense in the delayed phase could be explained by decreased vascular perfusion and reduced hepatic venous drainage with subsequent stasis of the contrast medium.[16] However, the appearance of a tumor response in CT is different from that of RILD, and a tumor response after SBRT has not been reported in

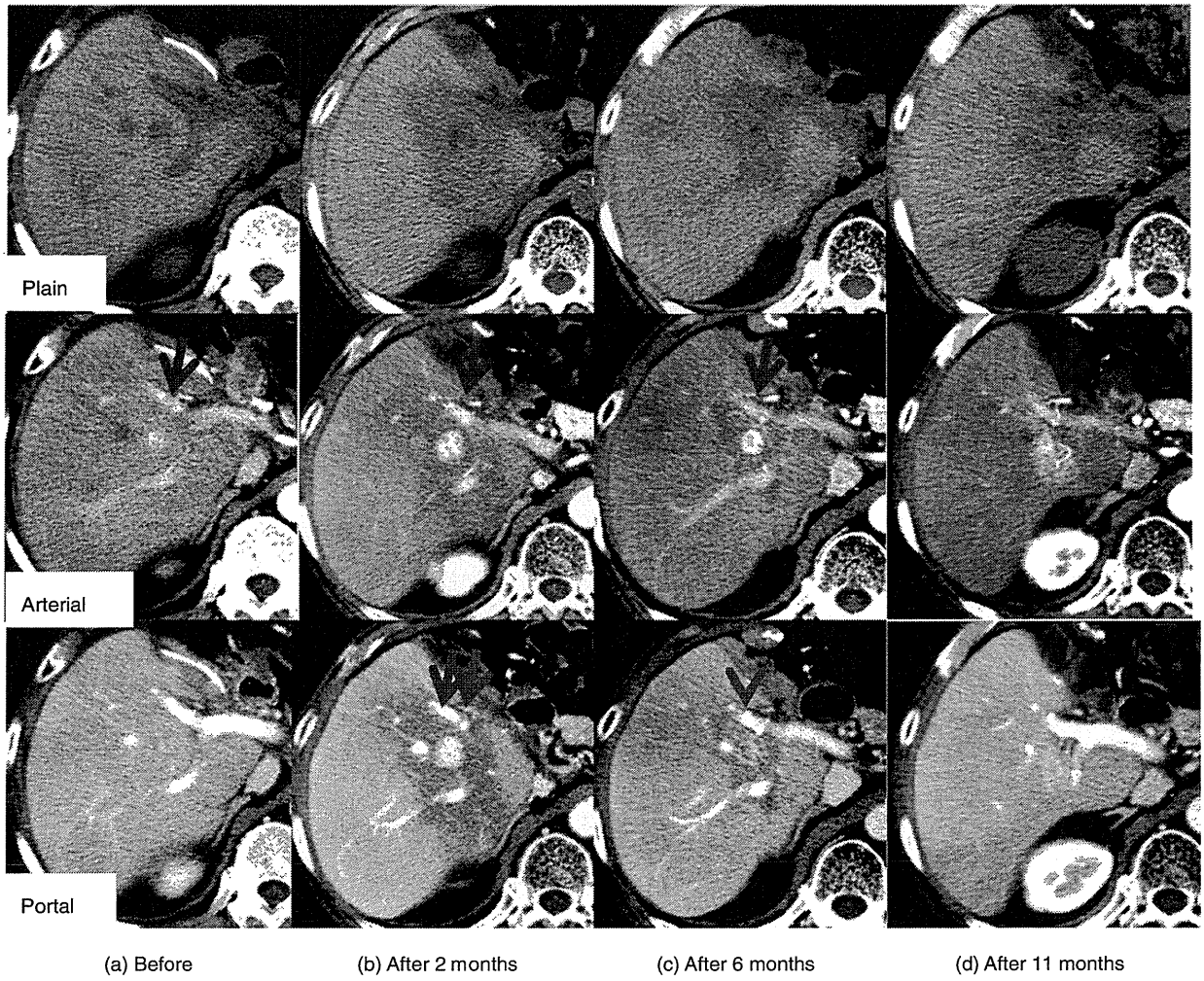

Figure 3 Dynamic computed tomography appearance of tumor response type 3 (plain, arterial and portal phase in case 39). (a) Before stereotactic body radiation therapy (SBRT), early arterial enhancement is visible (red arrow). (b) Two and (c) 6 months after SBRT, early arterial enhancement is more evident than that before SBRT in arterial (red arrow) and portal phase (two red arrows). (d) Eleven months after SBRT, although shrinking, it remains (red arrow).

detail. In this study, we classified the dynamic CT appearance of tumor response into four types. Most patients underwent TACE using lipiodol before SBRT and demonstrated a combination of residual early arterial enhancement with or without residual lipiodol. Therefore, early arterial enhancement was a characteristic dynamic CT finding for viable HCC, and the existence of residual early arterial enhancement after SBRT may indicate residual or recurrent HCC histologically.

Evaluation of the relationship between the dynamic CT appearance of tumor response and clinical features showed that history of resection in type 1 was the only significant factor in multivariate analyses. Sanuki-Fujimoto *et al.* described the CT appearance of RILD after SBRT and demonstrated that liver tissue with preserved function was more likely to be well enhanced in the delayed phase of dynamic CT.[14] However, our analysis of tumor response did not demonstrate a significant relationship between Child–Pugh class and residual early arterial enhancement observed in types 2 and 3.

Although RECIST and WHO criteria are widely used to evaluate solid tumor responses to chemotherapy or radiation therapy,[9,10] they may be inappropriate for evaluating tumor response to locoregional therapies

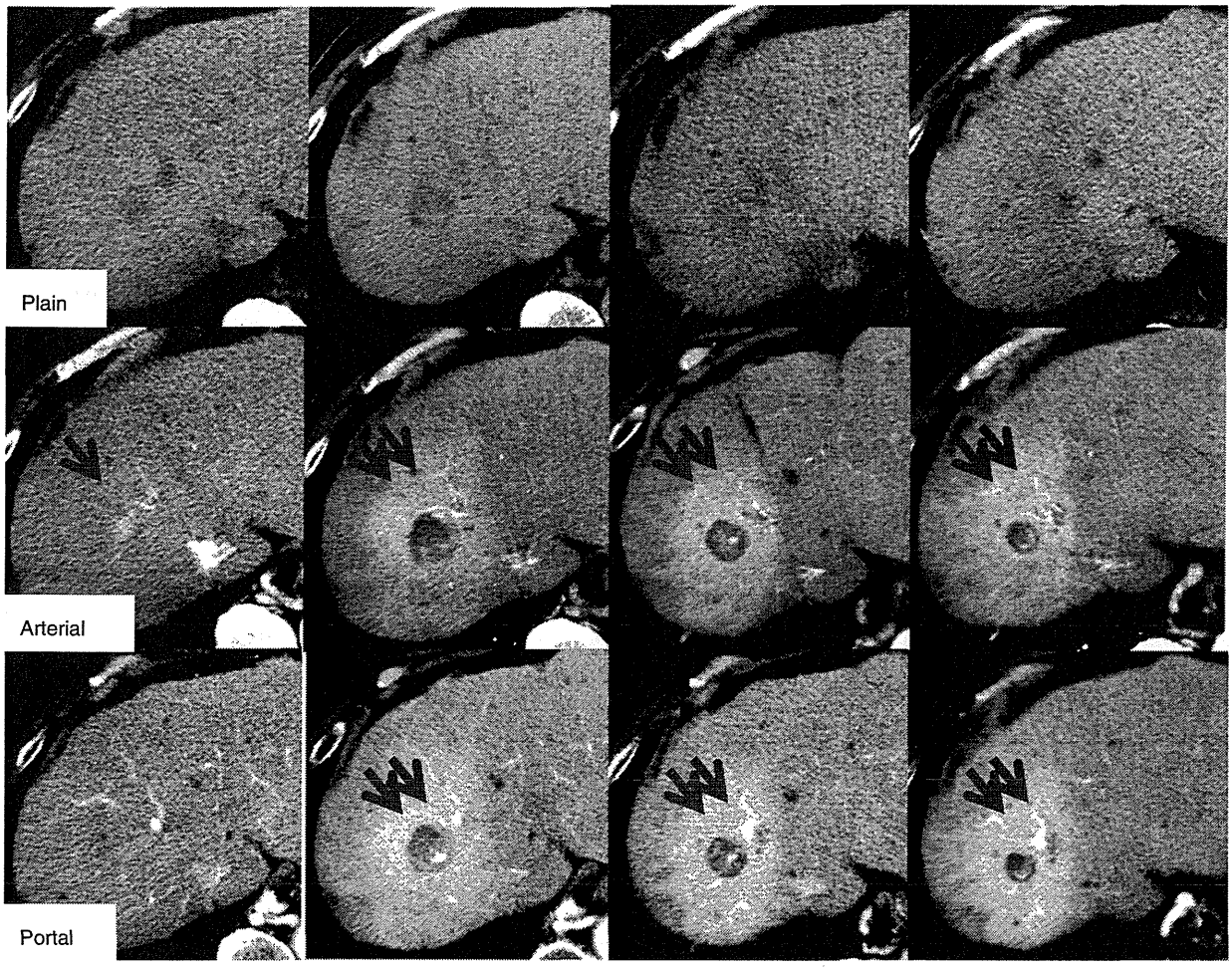

Figure 4 Dynamic computed tomography appearance of tumor response type 4 (plain, arterial and portal phase in case 11). (a) Before stereotactic body radiation therapy (SBRT), early arterial enhancement is visible (red arrow). (b) Two, (c) 6 and (d) 12 months after SBRT, hypodensity of the tumor changed and the tumor shrank without early arterial enhancement in arterial and portal phase (two red arrows). Radiation-induced liver damage is visible around the tumor.

such as ablation therapies and TACE in most patients with HCC because they only rely on tumor size reduction as a measure of effect and do not consider any necrotizing effects or tumor blood flow. RECICL were proposed by the Liver Cancer Study Group of Japan.[12] This study group addressed these concerns by including criteria that consider the biological characteristics of HCC. Tumor necrosis is regarded as a direct effect of treating a target tumor, and the dense accumulation of lipiodol is regarded as necrosis. In addition, although RECIST and WHO criteria do not specify the timing when overall treatment outcomes should be assessed, RECICL suggests that the maximum response within 3 months for TACE or local ablative therapies and 6 months for radiotherapy should be regarded as the overall treatment effects. Although the above criteria should be kept in mind for ablative therapies, which typically result in necrosis, most CT appearances after SBRT in our study did not show obvious tumor necrosis. In addition, RECICL may be inappropriate for the evaluation of tumor response by SBRT because the healing stage of ablative therapies and SBRT are different. The

Table 2 Univariate analysis between the dynamic CT appearance of tumor response and clinical features

		Type 1	*P* Uni†	Type 2	*P* Uni	Type 3	*P* Uni	Type 4	*P* Uni
Child–Pugh class	A	21	0.622	15	0.278	14	0.628	2	0.036
	B	5		2		5		3	
Sex	Male	19	0.112	11	0.731	8	0.044	3	0.955
	Female	7		6		11		2	
Age	>75 years	10	0.877	5	0.436	9	0.284	1	0.405
	≤75 years	16		12		10		4	
Total dose	>48 Gy	4	<0.001	6	0.14	3	0.415	2	0.033
	≤48 Gy	22		11		16		3	
Planning target volume	>40 cc	3	0.024	4	0.719	6	5842	5	0.0001
	≤40 cc	23		13		13		0	
Tumor location	Peripheral	24	0.082	12	0.152	15	0.729	4	0.899
	Central	2		5		4		1	
History of resection	+	10	0.877	6	0.842	5	0.242	4	0.04
	–	16		11		14		1	
Duration from first treatment	>12 months	13	0.134	14	0.038	10	0.366	4	0.37
	≤12 months	13		3		9		1	

**P*-value was defined as the clinical factors in each type of dynamic computed tomography (CT) appearance as compared to those in the other types.
†Uni: univariate analysis by the Mantel–Haenzel χ^2-test or Student's *t*-tests.

treatment results in our study were also different according to the evaluation methods, such as RECICL and our criteria including residual early arterial enhancement.

Several authors have reported treatment results of SBRT or particle therapy for HCC and their evaluation methods.[4–7] Andolino *et al.* used RECIST to evaluate tumor response after SBRT on the basis of tumor size.[4] Takeda *et al.* reported that when no tumor enhancement was detected within PTV on enhanced dynamic CT 6 months or more after SBRT, patients were considered to have no relapse.[5] With regard to particle therapies, Fukumitsu *et al.* defined local progression as growth of the irradiated tumor or the appearance of new tumors within the treatment volume after proton therapy.[6] In

Table 3 Multivariate analysis between the dynamic CT appearance of tumor response and clinical features

		Type 1	*P* Multi†	Type 2	*P* Multi	Type 3	*P* Multi	Type 4	*P* Multi
Child–Pugh class	A	21	0.999	15	0.999	14	0.999	2	0.226
	B	5		2		5		3	
Sex	Male	19	0.845	11	0.331	8	0.587	3	0.997
	Female	7		6		11		2	
Total dose	>48 Gy	4	0.505	6	0.5	3	0.999	2	0.307
	≤48 Gy	22		11		16		3	
Planning target volume	>40 cc	3	0.333	4	0.981	6	0.869	5	0.996
	≤40 cc	23		13		13		0	
History of resection	+	10	0.028	6	0.056	5	0.712	4	0.996
	–	16		11		14		1	
Duration from first treatment	>12 months	13	0.104	14	0.056	10	0.773	4	0.998
	≤12 months	13		3		9		1	

**P*-value was defined as the clinical factors in each type of dynamic computed tomography (CT) appearance as compared to those in the other types.
†Multi: multivariate logistic regression analysis.

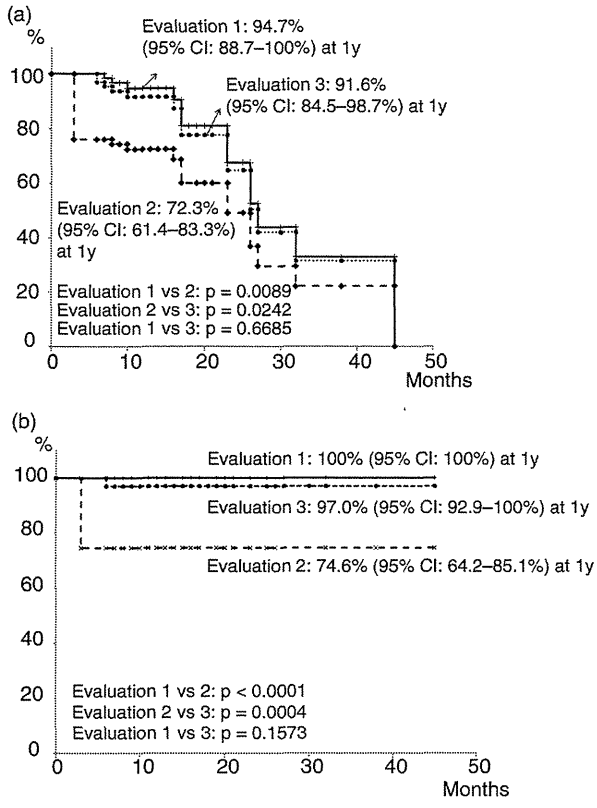

Figure 5 Treatment results of stereotactic body radiation therapy (SBRT) based on the different evaluation criteria. (a) Local progression-free survival rate (LPFS) according to evaluations 1–3. LPFS according to evaluation 2 was significantly lower than that according evaluations 1 and 3. (b) Local control rate (LCR) according to evaluations 1–3. LCR according to evaluation 2 was also significantly lower than that according to evaluation 1 and 3. CI, confidence interval; y, years.

this study, no tumors showed enlargement during the follow-up period, which should be included as a good tumor response among the other criteria described above. Takayasu *et al.* correlated histological and radiological data and indicated that accumulation of lipiodol within the tumor occurred primarily in areas of tumor necrosis.[17] They concluded that dense accumulation of lipiodol was a reliable indicator of necrosis. Based on our results, continuous dense accumulation of lipiodol without early arterial enhancement after SBRT (dynamic CT appearance, type 1) may also be included as a criterion of tumor response. However, the optimal method for evaluating early arterial enhancement after SBRT has not been confirmed. In this study, residual early arterial enhancement for more than 3 or 6 months after SBRT was observed in 19 (28.4%) and two lesions (3.0%), respectively. According to our evaluation methods (described above), residual early arterial enhancement was regarded as local progression. However, most of these findings that were noted for more than 3 months after SBRT disappeared within 6 months. We also observed shrinkage or disappearance of residual early arterial enhancement for more than 6 months after SBRT in two patients at 10 and 11 months. Our results indicate that when residual early arterial enhancement for more than 3 or 6 months was regarded as local progression, the treatment results differed significantly, especially when the treatment outcomes were assessed as early as 3 months after SBRT, which may be too early. Therefore, patient evaluation should be carefully performed. If the treated tumors are not enlarged, tumor markers are within the normal range, and residual early arterial enhancement for more than 6 months is noted, we recommend that an additional follow up should be performed, at least 12 months after SBRT. Other modalities should also be considered, such as gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-MRI; GE Healthcare, Chalfont St. Giles, UK) or enhanced (Sonazoid; Daiichi Pharmaceutical, Tokyo, Japan) ultrasound (US) in these cases. However, in dynamic studies of Gd-EOB-MRI or Sonazoid US, appearances were similar to CT; therefore, there were few hepatocytes or Kupffer cells in the irradiated normal liver tissues, including those of HCC. Thus, it may be difficult to distinguish between tumor response and irradiated liver damage.

We recommend the following criteria for the evaluation of tumor response after SBRT with TACE based on dynamic CT appearance: (i) no tumor enlargement; (ii) continuous dense lipiodol accumulation; and (iii) disappearance of early arterial enhancement for a minimum of 6 months. However, tumors showing continuous residual early arterial enhancement should be followed up and reassessed at 12 months if no tumor enlargement is noted.

The dynamic CT scans used to study the effects of SBRT with TACE for HCC tumors had 4 patterns of response. Residual early arterial enhancement of a tumor observed 3 months after SBRT should not be considered a sign of tumor recurrence unless it persists until 6 months. Early assessment within 3 months may result in a misleading response evaluation.

Because of its retrospective nature, we are aware that this study has certain limitations, such as the low number of patients, extremely short follow-up periods,

no pathological findings for the described types of CT appearances and the effects of previous treatment. SBRT can still be considered an alternative to surgery, ablation and TACE when these therapies fail, and most of our patients had undergone those therapies previously, which possibly influenced the CT appearance of tumor responses after SBRT. We are currently planning a prospective study to address the points mentioned above.

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Original article

Monotherapeutic high-dose-rate brachytherapy for prostate cancer: A dose reduction trial

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ABSTRACT

Purpose: To report preliminary results of our second regimen with 45.5 Gy/7 fractions aiming to reduce toxicity, compared with our first regimen with 54 Gy/9 fractions, using high-dose-rate (HDR) brachytherapy as monotherapy for prostate cancer.

Materials and methods: From 2005 through 2010, 63 patients with localized prostate cancer were treated with HDR brachytherapy alone in 45.5 Gy/7 fractions for 4 days. Thirty-four patients were considered as intermediate-risk and 29 as high-risk. Thirty-seven patients also received neoadjuvant and/or adjuvant hormonal therapy. Biologically effective dose assuming $\alpha/\beta = 1.5$ Gy ($BED_{1.5}$) was reduced from 270 Gy to 243 Gy, and $BED_{3.0}$ from 162 Gy to 144 Gy, compared to previous 54 Gy/9 fractions for 5 days.

Results: Median follow-up time was 42 months (range 13–72). Grade 2 acute toxicities occurred in six (9.5%), late toxicities in five (7.9%) patients, and Grade 3 or higher in none. Grade 2 late gastrointestinal toxicity rate was 1.6%, compared with 7.1% for the 54 Gy regimen. Three-year PSA failure-free rates for intermediate- and high-risk patients were 96% and 90%, which were comparable to 93% and 85% for the 54 Gy regimen.

Conclusions: Compared to the 54 Gy/9 fractions regimen, dose-reduced regimen of 45.5 Gy/7 fractions using HDR brachytherapy as monotherapy preliminarily showed an equivalent or lower incidence rate for acute and late toxicities without compromising the excellent PSA failure-free rate. Further studies with more patients and longer follow-up are warranted.

There are multiple treatment options for clinically localized prostate cancer, including radical prostatectomy, external beam radiotherapy (EBRT) [1,2], low-dose-rate (LDR) brachytherapy as monotherapy [3,4], and a combination of EBRT plus LDR brachytherapy [5,6] or high-dose-rate (HDR) brachytherapy [7,8]. Brachytherapy as LDR permanent seed implant or HDR afterloading can deliver a high localized radiation dose to the tumor. LDR brachytherapy has been examined and evaluated the most and become a standard treatment option; while recently HDR brachytherapy is gaining momentum as an alternative to LDR. Several features of HDR brachytherapy, including uniformly accurate, precise, and reproducible dosimetry resulting from optimization capabilities, radiobiologic and radioprotection advantages and reduced costs, make HDR appealing for the treatment of prostate cancer. These merits eliminate the dosimetric uncertainties of LDR related to postimplant volume changes due to needle trauma and subsequent edema during the several months of overall treatment time. HDR significantly improves the radiation dose distribution because it can modulate and accurately control both the spatial source position and dwell time during treatment.

Researchers first used HDR brachytherapy for boosting EBRT in the 1980s. However, to maximize the above-mentioned physical and biological advantages of HDR, HDR monotherapy seems to be the most efficacious with the shortest treatment period. Having used regimens of 48 Gy/8 fractions or 54 Gy/9 fractions since 1995, we were the first to report on the use of HDR brachytherapy without EBRT [9]. We subsequently reported promising preliminary and interim outcomes [10–12]. In 2005, however, we terminated those regimens after using them for 10 years and moved onto a new regimen of 45.5 Gy/7 fractions in order to reduce the radiation dose. We made a hypothesis that we could reduce toxicity by a moderate dose de-escalation, while keeping the excellent outcomes. The aim of the current study is to report the preliminary results of trial with this de-escalated dose regimen, discuss its rationale in terms of biologically effective dose (BED), as well as review the literature on HDR brachytherapy as monotherapy.

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Patients and methods

Patient selection and characteristics

Between 2005 and 2010, a total of 63 consecutive patients were treated with HDR brachytherapy as monotherapy for clinically localized prostate cancer in the scheme of prospective trial. The eligibility criteria were (1) clinical TNM Stage T1c–T3b, or T4 with only bladder neck invasion and without nodal or other distant metastases as established by clinical, biochemical, and imaging studies, including magnetic resonance imaging, computed tomography (CT), and bone scans; (2) candidacy for epidural anesthesia; (3) data on pretreatment transrectal ultrasound (TRUS) and serum prostate-specific antigen (PSA) levels accessible; and (4) informed consent. Patients were eligible for treatment independent of gland size provided a sufficiently broad pelvic inlet and freedom from lower urinary tract symptoms. Patients were considered ineligible when they had previous pelvic radiotherapy for another malignancy, previous surgery or transurethral resection of the prostate, or prostate cancer recurrence. This study was approved ethically by the institutional review board.

The median age at diagnosis was 69 years (range, 50–82). All patients had biopsy-proven adenocarcinoma of the prostate. According to the 2002 International Union Against Cancer TNM staging system, 15 patients had T1, 32 had T2, 14 had T3 and two had Stage T4. Pretreatment PSA level was 3.9–378.5 ng/ml (median 11.5), including 26 patients with a PSA level <10.0 ng/ml, 22 with 10.0–19.9 ng/ml, and 15 with a PSA level ⩾20.0 ng/ml. Eleven patients had a Gleason score of ⩽6, 34 a score of 7, and 18 a score of 8 or 9. We defined low-risk patients as those with a pretreatment PSA level of <10.0 ng/ml, Gleason score of ⩽6, and Stage T1c–T2a; intermediate-risk patients as those with PSA ⩾10 but <20 ng/ml, Gleason score 7, or Stage T2b–T2c; and high-risk patients as those with PSA ⩾20.0 ng/ml, Gleason score ⩾8, or Stage T3–T4. Thirty-four patients were classified as intermediate risk, and the other 29 as high risk.

In our protocol, patients with only one intermediate-risk feature were not given hormone therapy. The other intermediate-risk and all high-risk patients received 6–12 months of neoadjuvant hormone therapy but no adjuvant. However, if the patients refused hormone therapy, it was skipped. If high-risk patients preferred long-term hormone therapy after being informed of survival benefit of it in case of EBRT, adjuvant hormone therapy was allowed up to 3 years as a total duration. A total of 37 patients (59%) received hormone therapy, consisting of androgen deprivation. Hormone therapy was administered neoadjuvantly to these patients and continued adjuvantly for 14 (38%). The median duration of neoadjuvant and adjuvant hormone therapy was 7 and 18 months. Hormone therapy was administered more frequently to high-risk patients (25 of 29 patients, 86%) than to intermediate-risk patients (12 of 34 patients, 35%). Patient and tumor characteristics are shown in Table 1.

Monotherapeutic HDR brachytherapy technique

The implant technique has been previously described in detail by us [9]. In brief, it involved continuous epidural anesthesia, real-time TRUS guidance, the use of metallic applicators and applicator stoppers (Trocar Point Needles and Needle Stoppers; Nucletron, Veenendaal, The Netherlands), and an original template and its cover plate (Taisei Medical, Osaka, Japan).

The clinical target volume (CTV) included the whole prostate gland with a 5 mm margin except for the posterior (rectal) margin, which varied from 2 to 5 mm depending on the distance to the rectal wall. If extracapsular and/or seminal vesicle invasion was observed or strongly suspected, that area was included in the CTV and applicators were placed there. The planning target volume (PTV) was equal to the CTV, except for in the cranial direction, where it was 1 cm larger and included the bladder base. The top 2 cm of the applicators were placed within the bladder pouch, such that the PTV included a 1-cm margin in the cranial direction from the CTV. This margin was established, not only to avoid the cold area at the base of the prostate, but also to compensate for possible needle displacement in the caudal direction.

CT-based treatment planning was performed with the aid of PLATO (Nucletron) using geometric optimization (volume method) and manual modification. The prescription dose point was positioned 5 mm distant from one source in the central plane. The following dose constraints were applied: the dose to the whole urethra should be 100–150% of the prescription dose, preferably <125%, and the dose to the whole rectal mucosa should be <100% of the prescription dose, preferably <80%. The PTV coverage requirements were D90 >100%, D95 >100% and V100 >97%. The dose-volume constraint for the rectum was D5 cc <55%, which was drawn from our previous analysis, where D5 cc <27 Gy was a significant cut-off value for late rectal toxicity [13]. The BED of 27 Gy in 9 fractions corresponded to 55% of the prescription dose in this study.

The epidurally anesthetized patients remained in bed for 4 days from Monday to Thursday and underwent irradiation twice daily with an interval of ⩾6 h. The treatment consisted of 7 fractions of 6.5 Gy each (total 45.5 Gy). Its BED and biologically equivalent dose in 2-Gy fractions (EQD_{2Gy}) are discussed in detail in the Discussion section together with our rationale. Prophylactic antibiotics were administered twice daily from the day of implant to Day 5. Air-pumping devices were attached to the patients' lower legs to prevent deep vein thrombosis from the day of implant to Day 4. One hour before administration of each irradiation fraction, a urinary balloon catheter was clipped in place to keep the urine within the bladder pouch so that the opposite side of the bladder wall and the bowels were kept away from the irradiation field. To ensure the correct needle position, radiation oncologists confirmed that no

Table 1
Patient characteristics.

Characteristic	Value
Number of patients	63
Age	
Median	69
Range	50–82
T classification	
T1	15 (24%)
T2	32 (51%)
T3	14 (22%)
T4	2 (3%)
Gleason score	
6	11 (17%)
7	34 (54%)
8/9	18 (29%)
Pretreatment PSA (ng/ml)	
<10.0	26 (41%)
10.0–19.9	22 (35%)
⩾20.0	15 (24%)
Median	11.5
Range	3.9–378.5
Risk group	
Intermediate	34 (54%)
High	29 (46%)
Hormone therapy	
Yes	37 (59%)
No	26 (41%)
Follow-up (mo)	
Median	42
Range	13–72

PSA = prostate-specific antigen.

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abnormal space was present between the perineum and template, no unexpected edema was present in the perineum, and none of the needle ends protruded unexpectedly compared with the others before each irradiation fraction. However, routine repositioning of the inserted needles before each session (for example, radiography before each session) was not performed. Instead, as mentioned above, we used a 1-cm PTV margin in the cranial direction so that it covered the CTV adequately even when the needles had moved ≤1 cm in the caudal direction. We had collected data on needle displacement in the very early period of our previous study [12] and had found that unexpected changes in needle position were distributed between 0 and 1 cm in the caudal direction in most sessions for most patients. However, the data were not meant for publication. We are now testing a new method to adjust the source dwell positions to an original position by moving them to the tip-side space in the displaced needles, referring to the gravity of implanted metal markers for an indicator, using CT before each irradiation fraction; but we had not yet done so in the current study.

Follow-up and toxicity assessment

A radiation oncologist and urologist conducted the follow-up evaluations at least every 3 months, including PSA determinations and queries about urinary and bowel symptoms. PSA failure was defined as the nadir plus 2 ng/ml in accordance with the Radiation Therapy Oncology Group/American Society for Therapeutic Radiology and Oncology Phoenix Consensus Conference recommendations. Acute and late toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 3.0. Acute toxicity was defined as symptoms observed during or after treatment that had completely resolved by 6 months after treatment. Treatment-related toxicity that persisted >6 months after treatment completion was considered late toxicity. Primary endpoints of this study were acute and late toxicities of Grade 2 or more. Secondary endpoint was PSA failure-free rate. The expected outcomes were as follows; Grade 3 toxicity being minimized to be near zero, and Grade 2 toxicity reduced, while PSA failure-free rate maintained, in comparison to our previous report [12]. Erectile function was not evaluated in this study due to the hormone therapy in the majority of patients. The median follow-up time was 42 months (range 13–72).

Statistical analysis

Fisher's exact test was used to compare percentages for the two groups, while the unpaired t test was used to compare the average values. PSA failure-free rates were calculated with the Kaplan and Meier method. Values of $p < 0.05$ were considered significant. Statistical analysis was performed with IBM SPSS Statistics 20 software (IBM, Armonk, NY, USA).

Results

Clinical outcome

No patients were lost to follow-up. Of the 63 patients, five developed PSA failure, three without clinical events and two showing evidence of bone metastases. The three-year actuarial overall survival and metastasis-free survival rates were 100% and 98%. The three-year actuarial PSA failure-free rates for intermediate-risk and high-risk patients were 96% and 90% (Figs. 1 and 2). Hormone therapy had no impact on PSA failure-free rate ($p = 0.985$).

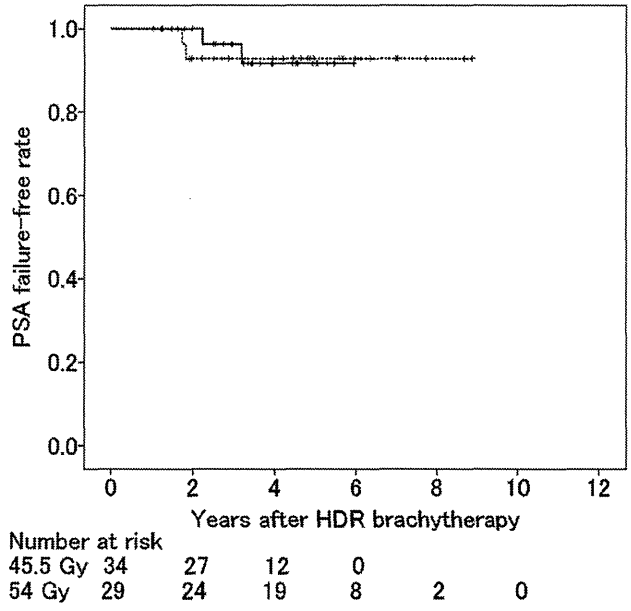

Fig. 1. PSA failure-free rates for intermediate-risk patients (solid line = 45.5 Gy/7 fractions; dashed line = 54 Gy/9 fractions).

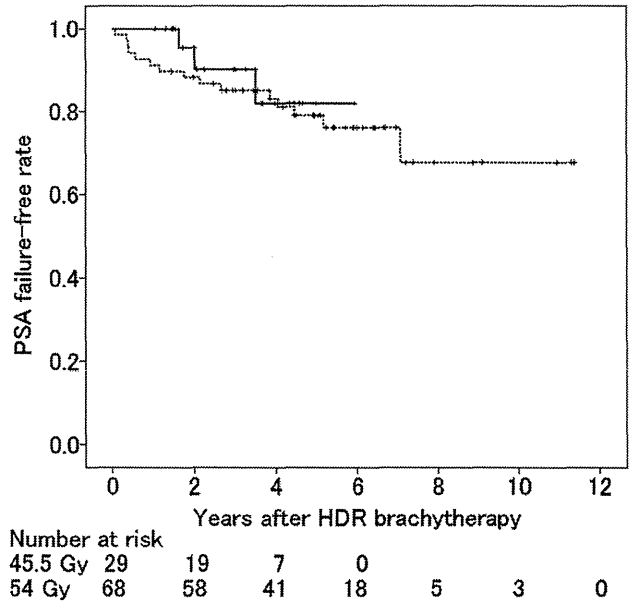

Fig. 2. PSA failure-free rates for high-risk patients (solid line = 45.5 Gy/7 fractions; dashed line = 54 Gy/9 fractions).

Acute toxicity

While no Grade 3 or higher acute toxicity was detected, 6 patients (10%) experienced Grade 2 acute toxicity (all with urinary frequency/urgency). For comparison, Table 2 shows details of acute toxicity for both this study (45.5 Gy/7 fractions group) and our previous study (54 Gy/9 fractions group) [12]. The average of D10 of the urethra was significantly higher in the patients with Grade 2 acute toxicity (70.6 ± 8.7 Gy, average ± standard deviation) than in the other patients with Grade 0/1 (62.5 ± 4.7 Gy) ($p = 0.009$). The other dosimetric parameters (D_{max}, D5, D30, D90, V100, V110, V120, V130, V140, V150 of the urethra, or D1 cc, D2 cc,

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Table 2
Acute and late toxicity of grade 2 or more in two groups of 45.5 Gy/7 fractions and 54 Gy/9 fractions.

Toxicity	45.5 Gy/7 fractions				54 Gy/9 fractions			
	Total	Toxicity grade			Total	Toxicity grade		
		2	3	4		2	3	4
Acute toxicity								
Genitourinary toxicity								
Hematuria	63	0	0	0	112	3 (3%)	1 (1%)	0
Urethral pain	63	0	0	0	112	0	1 (1%)	0
Urinary frequency/urgency	63	6 (10%)	0	0	112	13 (12%)	3 (3%)	0
Urinary retention	63	0	0	0	112	3 (3%)	1 (1%)	0
Gastrointestinal toxicity								
Anal pain	63	0	0	0	112	1 (1%)	0	0
Constipation	63	0	0	0	112	1 (1%)	0	0
Late toxicity								
Genitourinary toxicity								
Hematuria	63	1 (2%)	0	0	112	1 (1%)	0	0
Urethral stricture/stenosis	63	0	0	0	112	1 (1%)	1 (1%)	0
Urinary frequency/urgency	63	2 (3%)	0	0	112	2 (2%)	0	0
Urinary pain	63	1 (2%)	0	0	112	2 (2%)	0	0
Urinary retention	63	0	0	0	112	1 (1%)	0	0
Gastrointestinal toxicity								
Rectal bleeding	63	1 (2%)	0	0	112	6 (5%)	0	0
Rectourethral fistula	63	0	0	0	112	0	1 (1%)	0
Sigmoid colon perforation	63	0	0	0	112	0	1 (1%)	0

Grade: the Common Terminology Criteria for Adverse Events, version 3.0.

D5 cc, D10 cc of the bladder) did not correlate significantly to Grade 2 acute toxicity.

Late toxicity

No Grade 3 or higher late toxicity was detected, but four patients (6%) experienced Grade 2 late genitourinary toxicity (two with urinary frequency/urgency, and one each with hematuria and urinary pain), and one patient (2%) suffered Grade 2 late rectal bleeding. For comparison, Table 2 shows details of late toxicity for both this study (45.5 Gy/7 fractions group) and our previous study (54 Gy/9 fractions group) [12]. The above-mentioned dosimetric parameters of the urethra or the bladder in the patients with Grade 2 late genitourinary toxicity were not significantly different from the other patients with Grade 0/1. The only patient with Grade 2 late rectal bleeding did not have any peculiar value in terms of D1 cc, D2 cc, D5 cc, or D10 cc of the rectum.

Discussion

Historically, HDR brachytherapy was introduced to boost EBRT [7,8]. However, this combination typically adds 4–5 weeks to the time needed for completion of EBRT in addition to hospitalization for HDR brachytherapy. In contrast, if a satisfactory dose distribution could be achieved with HDR brachytherapy alone without EBRT, it would definitely be the most efficient method to achieve a high degree of conformity and dose escalation. For this purpose, we initiated HDR brachytherapy without EBRT, which is, to the best of our knowledge, the first such treatment reported in published studies [9]. In 1995, we launched HDR monotherapy with 48 Gy/8 fractions/5 days, and escalated the dose to 54 Gy/9 fractions/5 days the next year and continued it until 2005 eventually treating a total of 119 patients [10–12]. The method we used to determine our dose-fractionation schedule has been previously reported [11].

With a median follow-up of 5.4 years, we achieved a satisfactory biochemical control rate of around 90% for low- and intermediate-risk, and of around 80% for high-risk patients, which may be associated with high BED. On the other hand, the toxicity rate, while acceptable, was not very satisfactory, because some patients experienced Grade 3 and 2 toxicity in spite of an excellent dose distribution of HDR brachytherapy. Specifically, 5% acute and 3% late Grade 3 toxicity occurred in this study cohort, as well as 7.1% each for late Grade 2 gastrointestinal and genitourinary toxicity for the 54 Gy regimen [12]. This first prompted us to reduce the dose of our regimen. In addition, Brenner and Hall in 1999 [14], as well as others later on [15–18], reported a very low α/β ratio for prostate cancer mostly in the range of 1.2–3.1 Gy. Although the real α/β value is still under debate, we assumed 1.5 Gy as the most representative one in this study. Because such α/β values of around 1.5 Gy were significantly lower than estimated in 1995 or 1996 when we had determined the 54 Gy/9 fractions regimen, we began to consider the BED of the 54 Gy regimen as perhaps higher than necessary. The third reason for dose reduction was that our regimen, in comparison to other dose-fractionation regimens reported in the literature (Appendix 1), had a rather high BED of 270 Gy (EQD_{2Gy} = 116 Gy, assuming α/β = 1.5 Gy). The list in Appendix 1 shows that the median BED was 256 Gy (range: 208–299) and the median EQD_{2Gy} = 110 Gy (range: 89–128). We therefore terminated the 54 Gy regimen in 2005 and proceeded to using 45.5 Gy/7 fractions while aiming for a BED of 243 Gy and EQD_{2Gy} of 104 Gy. The fourth and final reason for wanting to make our treatment period shorter was that patients felt the length of the 5-day regimen was inconvenient and made them feel uncomfortable, while it also increased the risk of deep vein thrombosis and infection. We therefore decided to reduce the regimen from 5 days to 4 days.

Thus far, the preliminary results have been favorable and met our expectations. Three-year biochemical control rates for intermediate- and high-risk patients were 96% and 90%, respectively, compared with 93% and 85% for the 54 Gy regimen [12]. No toxicity of Grade 3 or higher was observed with the 45.5 Gy regimen, whereas 5% acute and 3% late Grade 3 toxicity was associated with the 54 Gy regimen. The incidence rate of Grade 2 or higher acute toxicity was significantly lower for the 45.5 Gy than for the 54 Gy (p = 0.026). The Grade 2 late gastrointestinal toxicity rate was 1.6%, which was lower than the 7.1% for the 54 Gy regimen. The Grade 2 late genitourinary toxicity rate was 6.3%, which was comparable to 7.1% for the 54 Gy regimen. Overall, our initial impression is that the dose-reduced regimen of 45.5 Gy/7 fractions

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resulted in toxicity equivalent to or less than that for the 54 Gy/9 fraction regimen without compromising the biochemical control rate.

However, the present study had several limitations. First, the number of patients was as small as 63, and the median follow-up time was only 42 months (range 13–72). These indicate that the presented data are only preliminary, so that longer further follow-up and more patients are needed before any general conclusions can be drawn. Secondly, there should be a selection bias. Because this study was not a randomized controlled trial, a possibility remained that patients with better prognosis tended to be enrolled. In fact, we selected at least a candidate for epidural anesthesia and a patient who agreed to 4-day bed rest. Thirdly, more than half of the patients (59%) received hormone therapy, which might affect favorably on PSA failure-free rate, although the rate of use of hormone therapy was lower in this study than in our previous one (84%) [12]. Lastly, effect of "learning curve" should be considered. When the present study started, we had already treated more than 100 patients in our previous study; therefore, the reduced rate of toxicity seen in this study might be attributable partly to our technical improvement, not only to the de-escalation of BED.

Appendix 1 lists as many data on dose fractionations and their clinical results as we could collect from the literature on HDR brachytherapy used as monotherapy for prostate cancer. We discovered that very few institutions were using HDR monotherapy in the 1990s, so that the publications by these institutions in the 2000s were also very few. In the 2000s, however, the number of institutions that started to use HDR monotherapy increased, and the resultant publications have also been increasing in the 2010s. In these findings we could find some interesting trends. The first is toward a smaller number of fractions and shorter treatment duration. In the 1990s and early 2000s, many institutions started using 4-fraction regimens, for example, 38 Gy/4 fractions [19–22]. However, 3-, 2-, or even 1-fraction regimens are being adopted recently. Zamboglou et al. [23], Hoskin et al. [24], and Barkati et al. [25] used 30–34.5 Gy/3 fractions (10–11.5 Gy per fraction), and Hoskin et al. [24] and Ghilezan et al. [26] 26–27 Gy/2 fractions (13–13.5 Gy per fraction). Prada et al. [27] reported their findings for a 19 Gy/1 fraction regimen. On the basis of the linear-quadratic model and the assumption that the α/β value of prostate cancer was lower than the surrounding normal tissue [14–18,28], it appears that a one-fraction regimen would maximize the therapeutic ratio and at the same time resolve the disadvantages of HDR brachytherapy, that is, hospitalization and needle displacement during the treatment period. However, a one-fraction regimen might, by its very nature, undermine the advantages of fractionation, that is, reoxygenation and redistribution (reassortment). Careful watching should thus be essential for such an exciting new regimen.

The second trend appeared to be that the indication for monotherapeutic HDR brachytherapy is being extended from only low-risk or low- to intermediate-risk to intermediate- and high-risk prostate cancer. While we were the first to describe the indication for low- to high-risk groups, subsequent reports limited their indications to only low- or low- to intermediate-risk patients [19,20,22,29,30]. In this context, some authors insisted that HDR monotherapy was suitable only for low- or low- to intermediate-risk, while a combination of EBRT and HDR brachytherapy was suitable for intermediate- to high-risk patients, thus emulating the scheme for permanent LDR seed implant brachytherapy. However, we insisted that there should be no reason for the addition of EBRT, even for the high-risk group, because HDR brachytherapy could adequately irradiate even extracapsular lesions. The most recent publications include more and more reports on intermediate- to high-risk patients treated with HDR monotherapy. Zamboglou et al. [23], who belong to the same institution as Martin et al. [20] who had included only low- to intermediate-risk prostate cancer, recently reported their findings for HDR monotherapy for a large cohort of 718 patients ranging from low- to high-risk. Hoskin's group [24] is carrying out HDR monotherapy for low- to high-risk patients based on a concept similar to ours, while Rogers et al. [31] did so only for an intermediate-risk group of 284 patients. All these recent studies seem to indicate that there is no reason to limit indication for HDR monotherapy to low-risk patients, while the second trend suggests that such indication is being extended to high-risk patients.

As in our case, many institutions implemented dose escalation for HDR monotherapy. As a result, the biochemical control rates thus obtained were generally satisfactory at approximately 90% (Appendix 1). On the other hand, some Grade 2 or even Grade 3 toxicities were seen. The incidence rate for late Grade 2 genitourinary toxicity reportedly ranged from 0.0% to 59.0%, and that for gastrointestinal toxicity from 0.0% to 13.0%. Some authors reported Grade 3 late toxicities, which are undesirable by any standard. On the assumption of $\alpha/\beta = 3.0$ Gy, BED for normal tissue ranged from 120 to 167 Gy (median 144 Gy), and EQD_{2Gy} from 72 to 100 Gy (median 86 Gy). The above-mentioned toxicity rates may well be associated with such high doses. We anticipate that the next trend, i.e., the third, should be dose reduction with the aim of reducing the toxicity rate without compromising the high biochemical control rate achieved thus far. In other words, we should try to determine the optimal BED and, if possible, the true α/β value for prostate cancer by examining results from various dose-fractionation regimens.

In conclusion, after 10 years' experience with the 54 Gy/9 fractions regimen of HDR brachytherapy as monotherapy, we embarked on a dose-reduction trial with a regimen of 45.5 Gy/7 fractions. In comparison to the 54 Gy/9 fractions regimen, our preliminary results showed an equivalent or lower incidence rate for acute and late toxicities, without compromising the excellent biochemical control rate, so that further studies with more patients and longer follow-up are clearly warranted.

Conflict of interest statement

All authors have indicated that they do not have any conflicts of interest in relation to this work.

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Appendix 1. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.10.015.

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