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

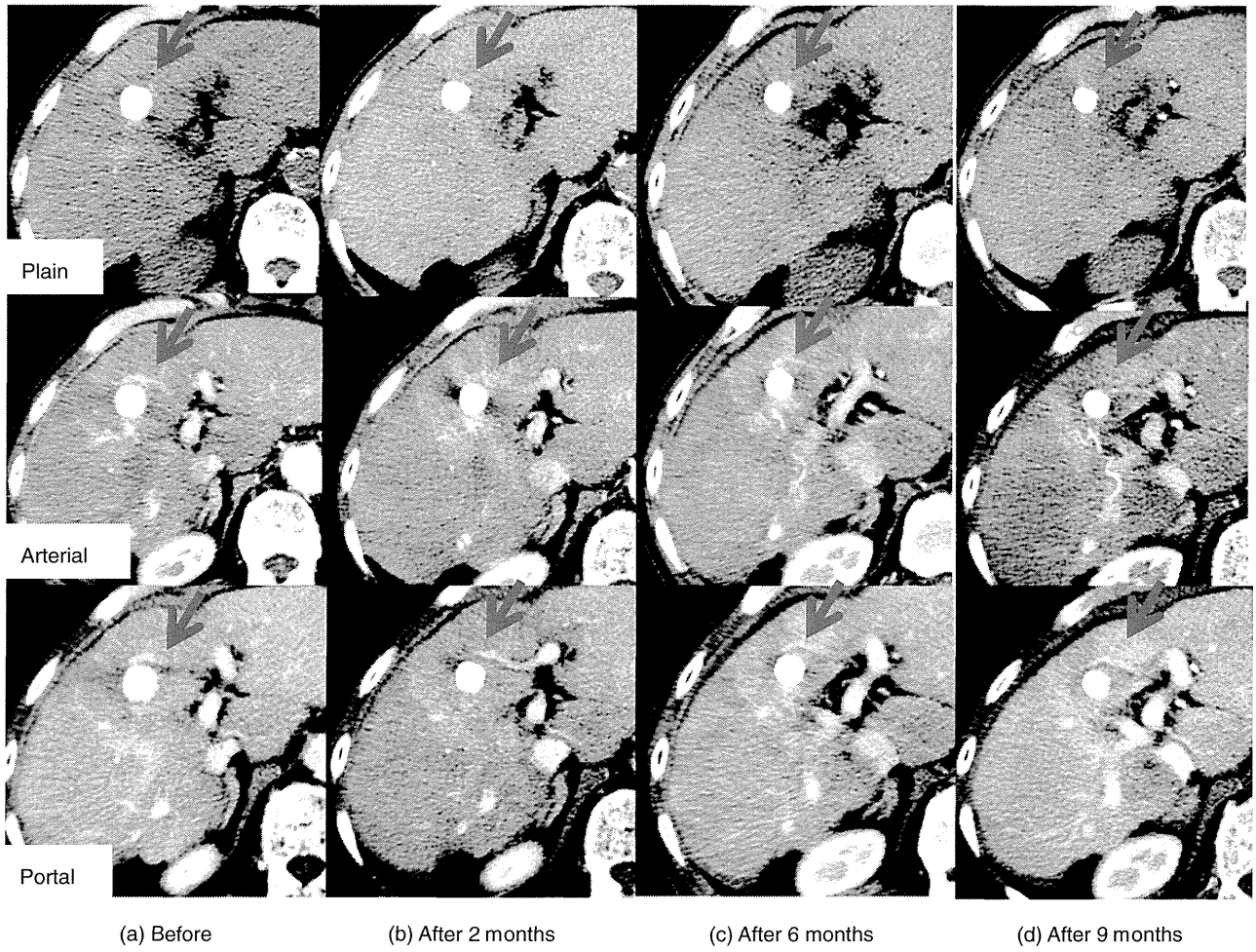

Figure 1 Dynamic computed tomography appearance of tumor response type 1 (plain, arterial and portal phase in case 37). (a) Before stereotactic body radiation therapy; (b) 2 months after; (c) 6 months after, and (d) 9 months after. Note the continuous presence of dense lipiodol accumulation without early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

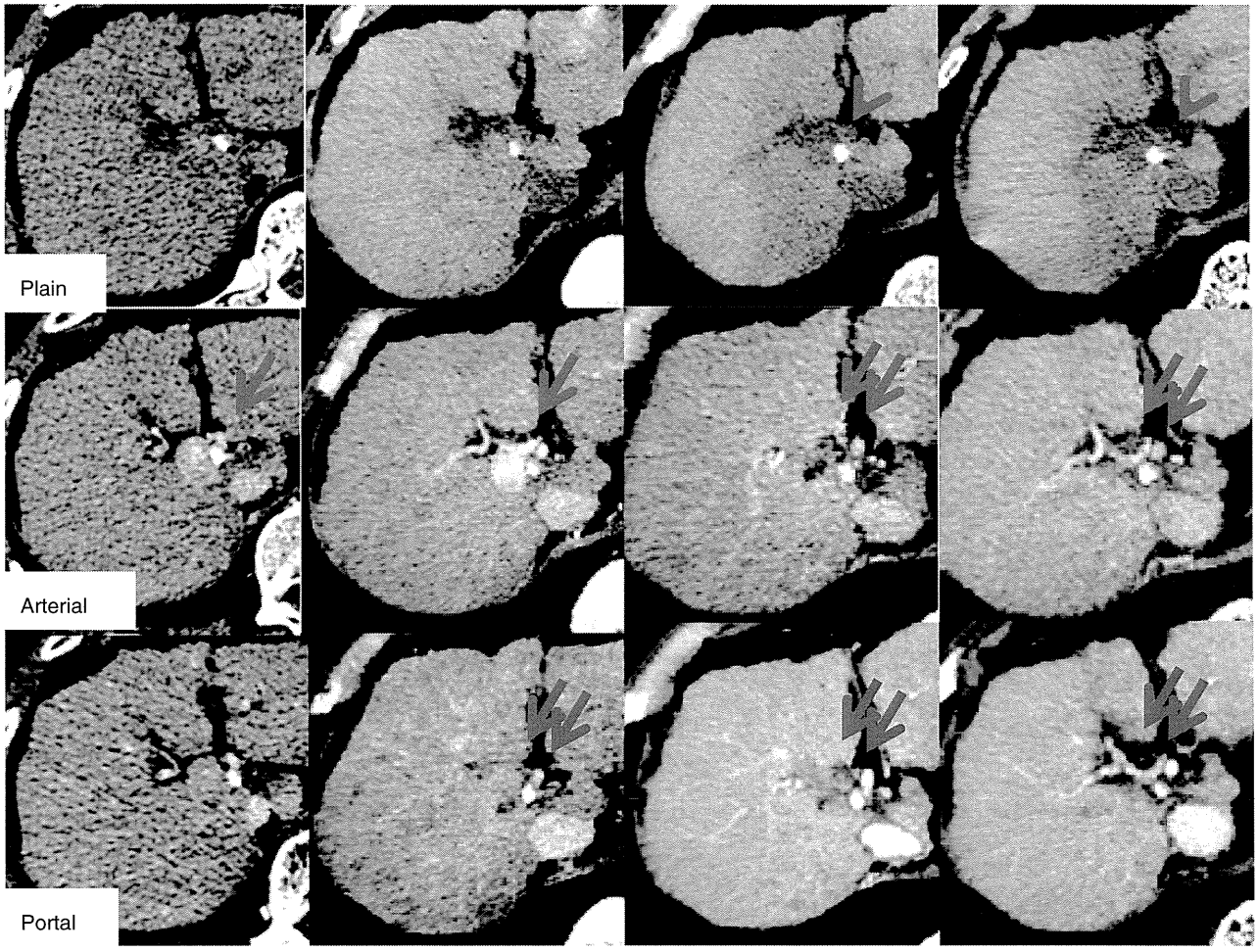

Figure 2 Dynamic computed tomography appearance of tumor response type 2 (plain, arterial and portal phase in case 9). (a) Before stereotactic body radiation therapy (SBRT); early arterial enhancement and partial residual lipiodol were observed (red arrow). (b) One month after SBRT, early arterial enhancement 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

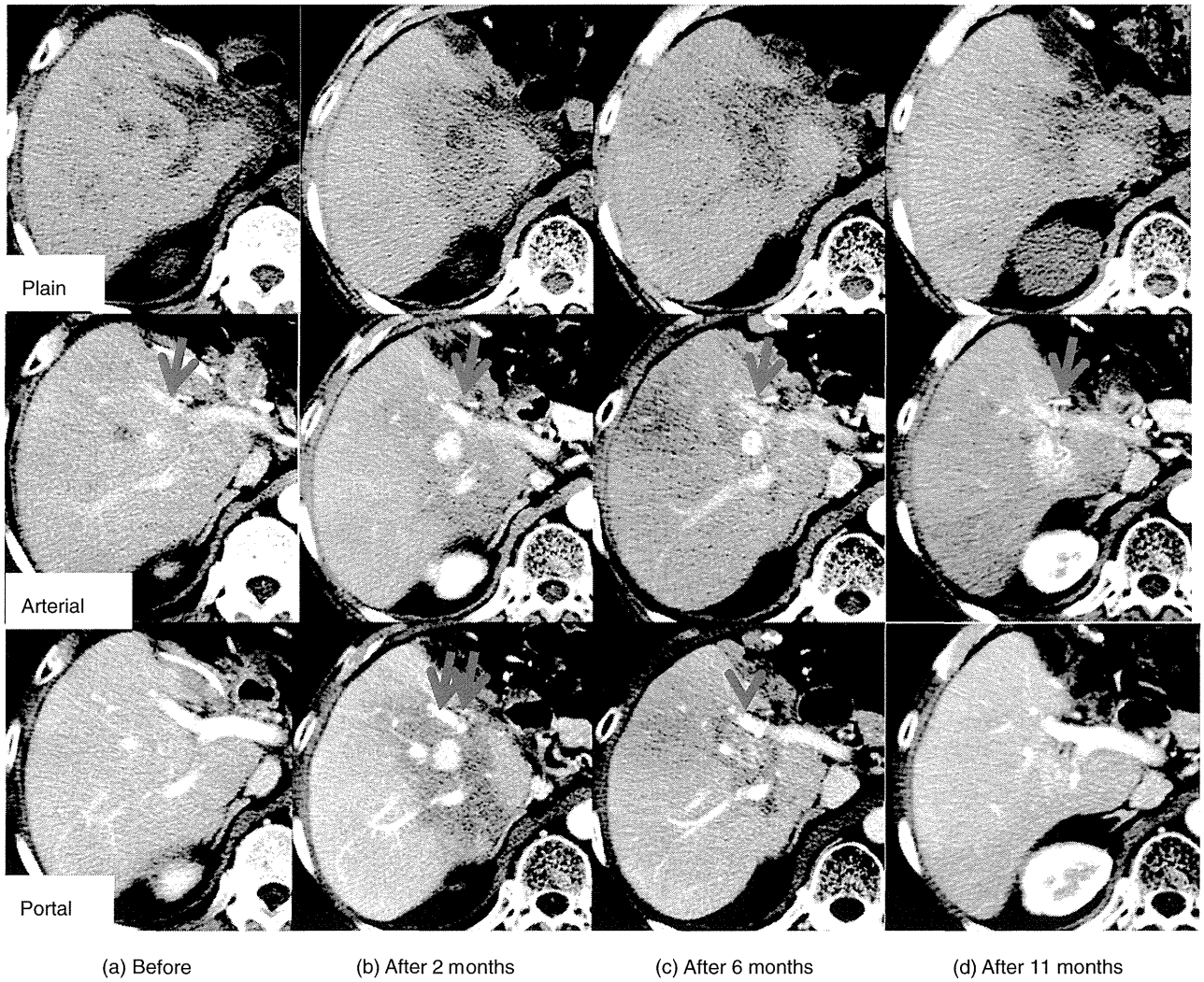

Figure 3 Dynamic computed tomography appearance of tumor response type 3 (plain, arterial and portal phase in case 39). (a) Before stereotactic body radiation therapy (SBRT), early arterial enhancement is visible (red arrow). (b) Two and (c) 6 months after SBRT, early arterial enhancement is more evident 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

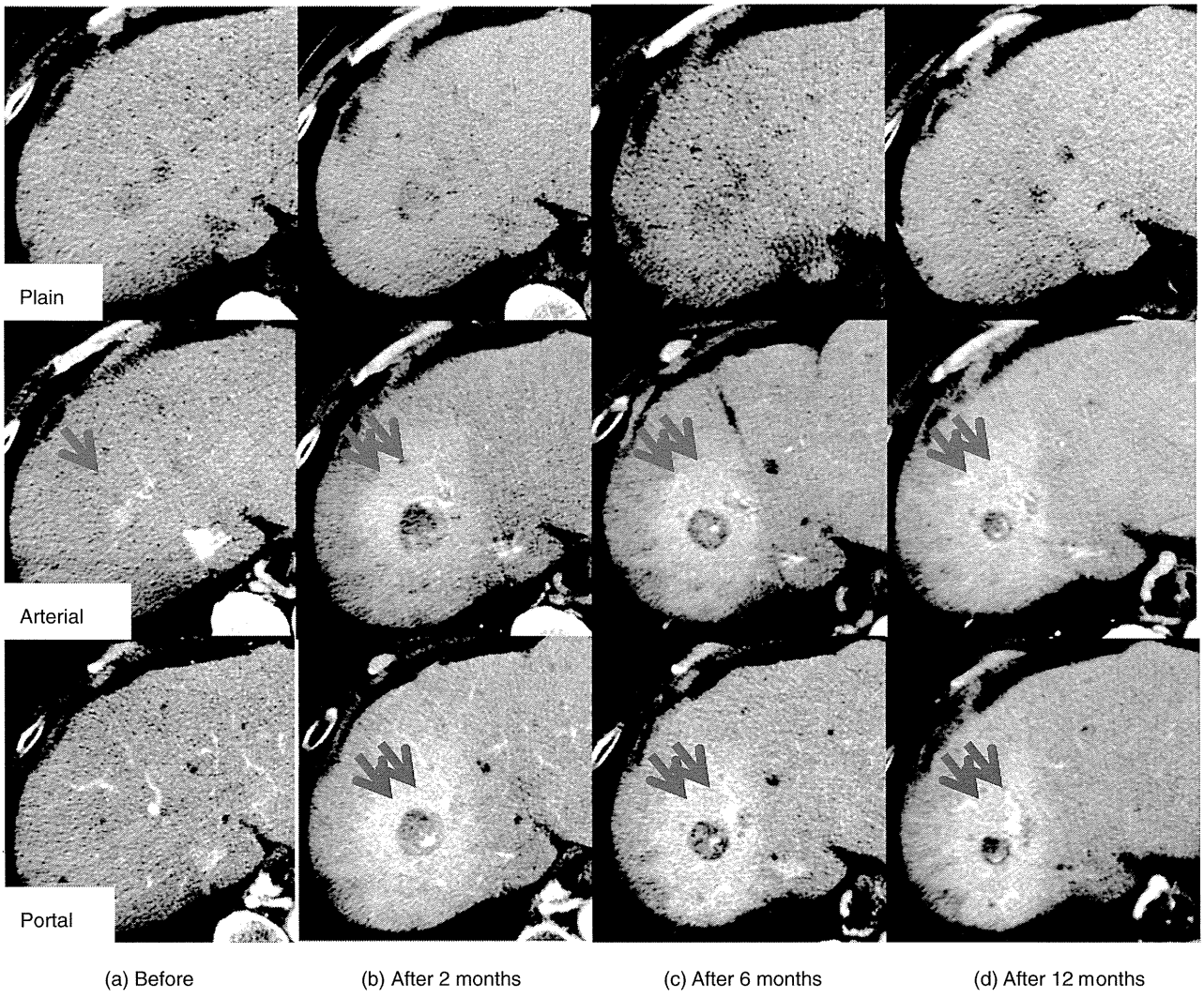

Figure 4 Dynamic computed tomography appearance of tumor response type 4 (plain, arterial and portal phase in case 11). (a) Before stereotactic body radiation therapy (SBRT), early arterial enhancement is visible (red arrow). (b) Two, (c) 6 and (d) 12 months after SBRT, hypodensity of the tumor changed 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.

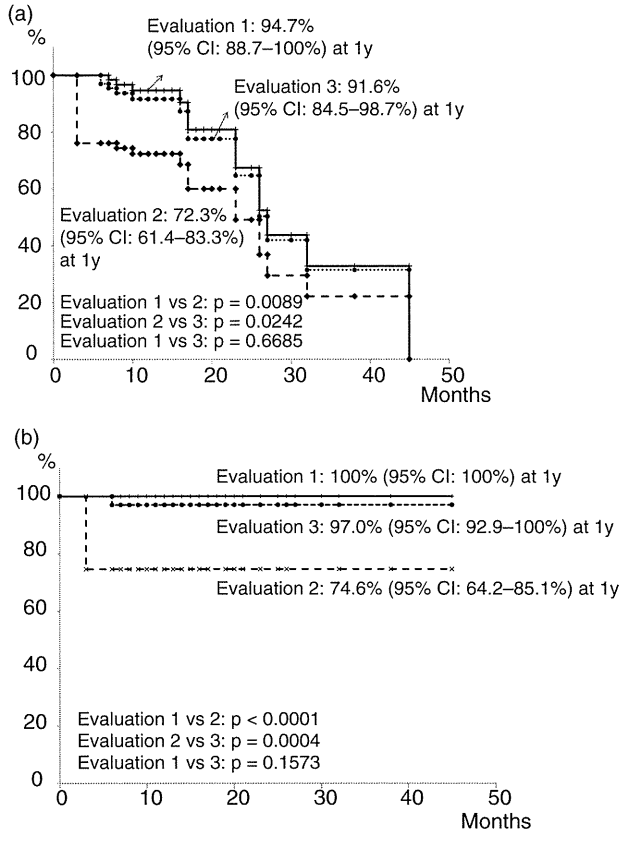

Figure 5 Treatment results of stereotactic body radiation therapy (SBRT) based on the different evaluation criteria. (a) Local progression-free survival rate (LPFS) according to evaluations 1–3. LPFS according to evaluation 2 was significantly lower than that according evaluations 1 and 3. (b) Local 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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食道癌

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■ はじめに

食道は頸部から腹部までの広範囲にわたる長大な管腔臓器である。食道癌の原発巣は長軸方向に広く進展し，しばしば食道内の複数箇所に病巣が認められる。浸潤の程度すなわち深達度はT病期に反映されており治療方針と予後に関わる重要な因子である。さらに原発巣の深達度に加えてリンパ節転移の部位と個数も予後因子となる。原発巣が存在する食道の部位に応じて転移が生じるリンパ節の場所とリスクは大きく異なるが，放射線治療が必要な食道癌と診断された時点でリンパ節転移を生じるリスクは決して小さくはないことがわかっている[1]。可視的なリンパ節を認めない場合でも食道癌の手術に際しては原発巣を含む食道の切除に加えて2群や3群までのリンパ節領域まで郭清する術式が標準であり，食道抜去のみの手術は根治性が低いとされている[2]。一方で放射線治療の場合にはどのリンパ節領域まで標的体積に含めるかすなわち放射線治療の対象とするかについての十分なコンセンサスがない。過去の臨床試験をみてもリンパ節領域に対する標的体積の設定は様々である。臨床現場では症例ごとにコンツーリングを行う範囲を決めることとなるが，あらかじめ各医療機関においてコンセンサスを設けておくことが望ましい。

本稿では食道癌の治療計画について，総論として準備について記した後で，標的体積の設定を原発巣，転移リンパ節，潜在的リンパ節領域にわけて解説する。コンセンサスがない事項については考え方を記すこととする。さらに計画表的体積の設定と治療に際して配慮を要するリスク臓器とその線量制約についても触れるが，病変に対する線量処方については述べないこととする。本稿で用いる標的体積の定義を表1と図1に記す。

表1　標的体積の定義

略号	定義
GTVprimary	原発巣（同じレベルの食道を含む）
GTVnode	転移陽性としたリンパ節
CTVprimary	GTVpに対応するCTV
CTVnode	GTVnに対応するCTV
CTVsubclinical	潜在的（予防的）リンパ節領域
CTV	CTVp，CTVn，CTVsをまとめたもの

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〔索引用語：食道癌，放射線治療，標的体積〕

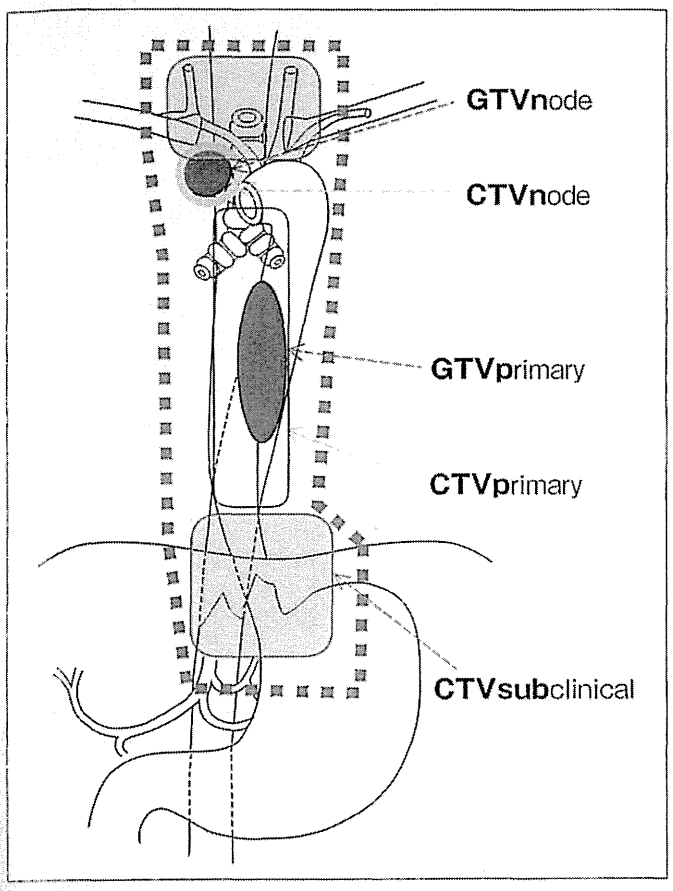

図1　標的体積定義の概略

① 治療計画準備

CT画像では食道癌の原発巣の部位と進展範囲の把握は困難なことがしばしばある。特に治療計画に用いられる水平断で腫瘍の上下端を正確に同定することは難しい。またリンパ節を転移陽性とするか否かも判断が難しい。放射線治療の計画に際しては実際にコンツーリングに用いるCT画像のみではなく，内視鏡，食道造影，FDG-PET等から得られた情報を総合して取り組むことが求められる。

食道癌の評価において内視鏡は必須の検査である。原発巣が壁内にとどまりCT画像では存在部位が同定できない表在癌(T1aおよびT1b)と一部のT2の症例では治療計画に先立って内視鏡検査を行って病巣の辺縁部にマーキング（クリッピング）を行っておく必要がある。クリップは時間がたつと脱落する可能性があるため放射線治療の計画の直前に内視鏡検査を行うようにする。内視鏡で確認できる病巣部の上下端に止血クリップなどX線吸収のある素材でできたマーカーを脱落しないように留置する。噴門部や頸部食道など両端へのマーカー留置が困難な場合には上端もしくは下端の一方に留置し，そこからの腫瘍の長径を記録して参照する。食道癌はしばしば同時多発するため，主病巣の他にも表在性の病巣がないか内視鏡で慎重に確認する。

リンパ節転移の評価に際してはFDG-PETの併用が有用である。PET検査結果には偽陽性，偽陰性があることを踏まえた上で個々のリンパ節を転移陽性とするか否かを慎重に判断しながら治療計画を行う。根治を目的として放射線治療を行う際は病期診断の際に転移ありと判断したリンパ節は標的体積に含めることが基本である。またPET画像は進行例で原発巣の浸潤範囲を同定する際にも役に立つ。

瘻孔形成が疑われる深い潰瘍を伴う病巣や内視鏡が通過しない程に狭窄を来した病巣の評価には食道造影が有用である。食道透視によって潰瘍の深さを知ることは穿孔のリスク評価にも役に立つ。食道造影に用いる硫酸バリウムはCTではアーチファクトが生じるため，治療計画の妨げとならないように食道造影の実施時期を調整する。治療計画用CTの撮像に続いて食道造影を同日に行っておくのも一案である。

照射範囲に含まれる正常臓器，特に肺と心臓の体積を減らすためにはCTVからPTVを作成する時のマージンを小さくすることが重要である。頸部食道の病変の場合には下咽頭癌など頭頸部癌と同様にシェルによる固定が役に立つ。肩まで覆うシェルを用いるか肩下げでの上肢固定が望ましい。胸部下部から腹部にかけての病巣では呼吸に伴う移動が無視できない。放射線治療の準備の際にその移動量を評価して1cmを大きく超える場合にはそれを減じるための対策を検討した方がよい。呼吸移動対策を行ってinternal marginを減らすと心臓の照射体積を小さくすることができ，晩期の有害事象の低減につながる可能性がある。なお，食道癌の放射線治療では一定の条件を満たして息止めや呼吸同期など呼吸移動への対策を施した場合，診療報酬上で加算の算定が可能である。

原発巣が噴門部に及ぶ場合や胃周囲のリンパ節まで転移を認める場合など上腹部が標的に含まれる場合には放射線治療に際して食事の影響が避けられない。照射体積を小さくするために胃病変の治療に準じて治療前の飲食制限を行うことが望ましい。

表2　GTVp：原発巣のGTV　横断面方向

T stage	GTVp
T1a, T1b	病巣部を食道外壁まで 全周性に囲む （厳密にはGTV+CTVの一部）
T2	
T3	食道周囲への可視的進展領域を含む CT：軟部組織濃度上昇域 FDG-PET：SUV高値域
T4	

表3　CTVp：原発巣のCTV　横断面方向

T stage	CTVp
T1a, T1b	食道外壁まで（GTVpと同じ）
T2	食道周囲への進展可能領域を含む GTVpから0.5～1cm程の範囲 解剖学的障壁を考慮 （骨・血管・肺は浸潤がなければ除く）
T3	
T4	

❷ 肉眼的腫瘍体積（GTV）および臨床標的体積（CTV）

1）原発巣

原発巣のコンツーリングでは，各水平断面で腫瘍を含む食道外壁を全周に囲んでGTVp（原発巣に対するGTV）とする。主病巣の深達度が筋層までにとどまるT2以下の場合は食道壁の外縁までをGTVpとする（病変が全周性でない場合，厳密にはここで示すGTVpはCTVpの一部を含んだものとなる）。T3-T4病変ではCTおよびPET/CTなどを参照して食道壁外への進展を含めてGTVpの輪郭を書く。表2にGTVpの設定の要点を記す。

GTVpの食道長軸方向のコンツーリング，すなわち何枚のスライスに渡ってGTVpを設定するかは食道癌の治療計画で最も大切な点である。内視鏡で腫瘍の全域が観察できた場合にはGTVpの長軸サイズは報告書に記されている腫瘍長径サイズに一致する。表在癌などCTでの病変の同定が難しい病巣は内視鏡で留置したマーカーを参照してGTVpを設定する。複数の病巣が存在する場合，内視鏡レポートでは主病巣以外については簡単な記載で済まされていることもあるので注意しておく。

内視鏡や食道造影，CTなど様々な画像診断のレポートに記載されている原発巣のサイズと設定したGTVpのサイズに乖離がないかをコンツーリング後に確認しておくことは重要である。例えば内視鏡レポートで「門歯から28cmから34cmに渡って……」と記載される病変の場合にはGTVpの長径は少なくとも6cmになるはずである。水平断画像を用いてGTVpのコンツーリングを行った後にその範囲が妥当かを矢状断と冠状断画像で見直し，食道造影やPET画像と対比させて確認することも大切である。

次いで原発巣から周囲への微視的な進展を考慮してCTVpを設定する（表3）。粘膜下層までにとどまる表在癌（T1b以下）ではそれぞれの水平断面でのGTVpとCTVpは同一としてよい。一方，筋層以深に浸潤する病巣（T2以上）ではGTVp周囲の軟部組織に1cm程度のマージンを設定してCTVpのコンツーリングを行う。この時，GTVpに自動的に一律のマージンを加えてCTVpとするのではなく，解剖学的な障壁を考慮して病変が進展しうる方向に対して加筆と修正を行う。通常は椎体の骨梁部分や心臓と大血管の内部，気管，気管支内部の空気はCTVpに含めない。一方で，大動脈や気管支の壁に沿って回り込むように腫瘍が進展しうることを念頭に置いておく。図2に水平断方向のコンツーリングの例を示す。

食道癌は粘膜面，粘膜下を食道の長軸方向に広く進展することが知られている。手術例の病理標本を検討した報告で原発巣の壁内での微視的進展は多くは可視的な辺縁から3cmまでの範囲と記されている[3]。これに従ってGTVpに対して食道長軸方向に2～4cm程度のマージンを加えてCTVpとすることが一般的である。この時もGTVpとして設定した範囲を自動的に頭尾側方向に2cm拡張するのではなく，解剖学的に妥当と考えられる方向に向けて拡大してCTVpを設定する必要がある。表在癌の場合は食道外壁のコンツーリングを行うスライスを2～4cm分増やすようにする。

原発巣が離れて複数カ所に認められる場合，いわゆるスキップ病変がある場合にはその間の部分の食道をすべて含めて連続した一つのCTVpとすることも考慮する。内視鏡で認めるルゴール不染領域や狭

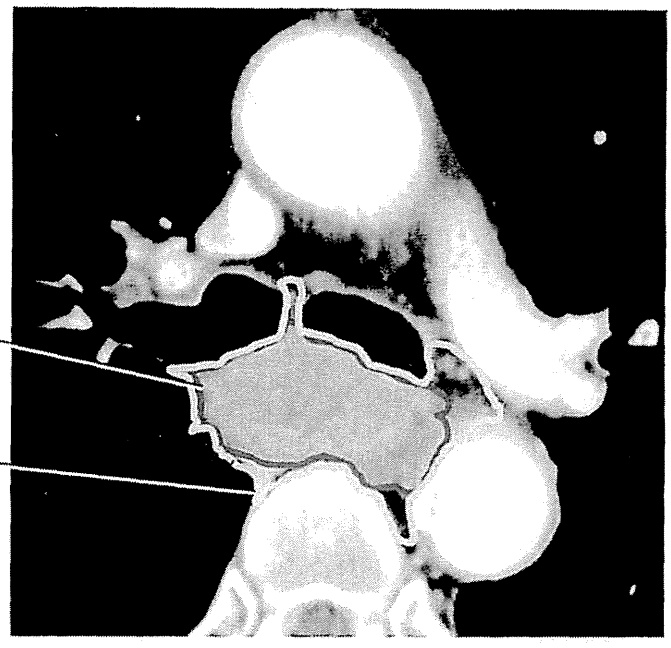

図2　T3病変に対する解剖学的障壁を考慮した臨床的標的体積の設定（CTVp）

帯域光観察（Narrow Band Imaging）での形態変化領域などのいわゆる前がん病変をCTVpとするか否かについてはコンセンサスがない。表在性病変の存在が疑わしい部位のすべてを生検して確認することも実際には困難である。これから行う放射線治療によって原発巣が制御できる可能性が高いことが予想され，広いCTVpを設定した際の照射体積の増加が容認できる程度にとどまるのであれば，これらの領域もCTVpに加えておき，主病巣と同時に治療を行うことは妥当と思われる。近接する部位に新たな病巣が出現した場合に追加で放射線治療を行うことが難しい場合もあるためである。一方でこれらの領域をCTVpに含めないでおく場合には治療後に密な経過観察を行い，もし新たな病巣が出現した場合には時期を逸することなく，内視鏡的切除などが行えるように備えておく。

2）転移リンパ節

画像診断で転移陽性と判断したリンパ節の輪郭をとってGTVn（リンパ節に対するGTV）とする。CT診断ではリンパ節のサイズをもとに短径が1cmもしくは5mmを超える場合に陽性とされることが多い。しかし，これよりもサイズが小さくともFDG-PETで強い集積を認めるリンパ節や球形で辺縁が良く造影され内部は低吸収域となるリンパ節は転移があるものとみなしておくことが妥当である。

リンパ節への転移は通常は被膜内にとどまっているものとしてCTVマージンを設定せずに，GTVn＝CTVnとする。しかし，食道癌ではしばしば腫大したリンパ節が被膜外に進展し，その周囲への浸潤が臨床的に問題となる。腫大したリンパ節の変形が強い場合や辺縁が不整の場合には節外への浸潤があるものと考えて対応することが妥当である。嗄声がある症例で反回神経リンパ節の腫大を伴う場合には，リンパ節による神経の圧迫と浸潤も疑う。嚥下困難が原発巣ではなく腫大したリンパ節によって生じていることもある。このようにリンパ節転移病巣が周囲に進展している可能性がある場合は，原発巣に対するCTVpの設定に準じてGTVnの周囲に1cm程度のマージンを設定してCTVnを定義する。

3）潜在的リンパ節領域

画像診断で転移はないとするが臨床的にはリンパ節転移のリスクがある領域，すなわち微視的（micro）なリンパ節転移が生じうる領域を潜在的リンパ節領域とし，本稿ではCTVsと定義する。これらは予防領域ともいわれ，手術の際には食道切除とあわせてこの領域のリンパ節郭清が行われる。食道癌はセンチネル理論が確立されていない分野であり，最初に転移が生じるリンパ節が原発巣の近傍に位置しているとは

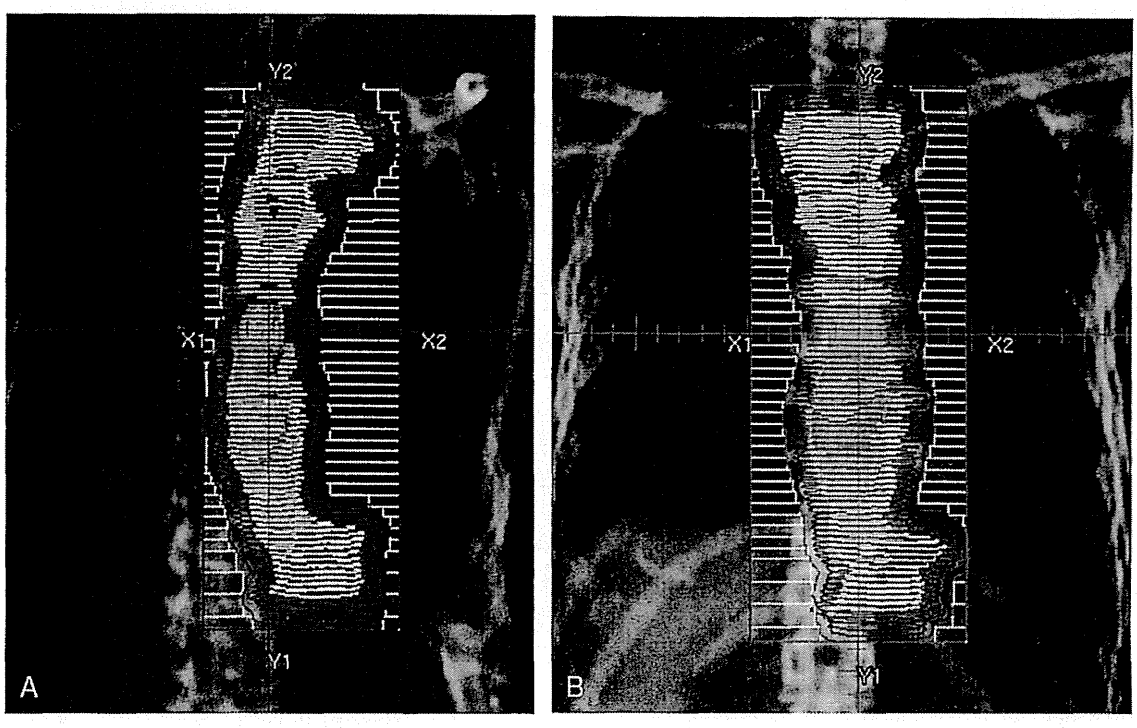

図3　CTVsを含んだ標的体積設定
A　ガントリ角度　320°の照射野　B　ガントリ角度　0°の照射野　原発巣Mt-Lt：CTVsに#101, #106rec, #1, #2を含む場合のPTV。

限らない。胸部中部食道癌のリンパ節転移は下頸部から上腹部までの広範囲に生じうる。食道癌取扱い規約では転移が生じるリスクを反映させてリンパ節の群分類が行われている。

手術例では3群もしくは2群の領域の予防郭清を行うことが予後を改善にすると本邦から報告されている[1]。食道癌取扱い規約には原発巣の部位ごとに郭清の対象となるリンパ節群が提示され，病期にも反映されている[4]。一方，放射線治療においては計画時にどのようにCTVsを設定して，治療の対象とするかに関しての十分なエビデンスとコンセンサスがない。国内外で過去に行われた臨床試験でもCTVsを設定するものとしないもの，設定する場合のその範囲に関しては様々である。

CTVsの設定に際しては食道癌取扱い規約第10版に示される図を参照し，食道原発巣の部位に対応するリンパ節領域をコンツーリングする。ガイドラインにはCTVsとする際にN1およびN2に対応する領域（いわゆる2群）までを含めることが示されている[5]。ただし取扱い規約に記載されるリンパ節領域は，「この領域にリンパ節が存在した場合XX番とする」というように画像や肉眼で同定できるリンパ節に番号を付して病期を決定するためのものであり，図で面塗りされる領域全体が一様に潜在的な転移リスクを有しているのではないことに留意する。実際に2群とされる領域の全体を一律にCTVsとして治療計画を進めると照射体積が大きくなりすぎることがあるので注意する。図3にCTVsを含んだ標的体積設定の1例を示す。

反回神経リンパ節（#106recRおよびL）は食道癌が転移を来すリスクが高いリンパ節であり，手術例では郭清が不十分な際にはしばしば再発する部位として知られている。放射線治療の際には，原発巣が頸部～胸部中部に存在するとき，少しの工夫で反回神経リンパ節の領域を照射体積に十分含めることができるため，この領域をCTVsに設定して治療の対象としておくことが妥当である。上縦隔から再発した病巣は救済手術が難しく，照射体積の辺縁部に生じると再度放射線治療を行うとしても十分な線量投与が困難となり，これが予後にも関わりうるためである。私見だが頸部気管傍リンパ節（#101）は反回神経リンパ節等の上部縦隔のリンパ節を転移陽性とする場合には含めたほうがよい。この領域をCTVsに含めることによる有害事象リスクの増加は大きくはない。転移陽性のリンパ節があってGTVnを設定した場合に，

その近傍で転移のリスクが高いことが判明している領域をCTVsとして含んでおくという考え方は理にかなっている。

一方，原発巣が胸部上部や頸部にあってGTVnとして設定するリンパ節がない場合すなわち臨床的にN0の場合には噴門部リンパ節（#1，#2）をCTVsに含めないでよいと思われる。もし噴門部リンパ節に対して予防的な放射線治療を行うとしても，心臓の有害事象発生のリスクを減じるために原発巣周囲とは切り離してこの領域に別個に照射体積を設定する方法もある。原発巣のサイズが大きく，放射線治療を行っても制御できる可能性が決して高くないと予想される場合には，そこから離れた潜在的なリンパ節領域までCTVsとしないでよいだろう。もし放射線治療後に原発巣が制御できているようであれば，後発病変についても生じた際に追加の放射線治療によって制御できる可能性がある。

食道癌のリンパ節転移は病態が多様なため臨床試験で結論を出すことが難しい分野である。時には照射体積の辺縁部にリンパ節再発を認めて痛い思いをすることがある。最終的に潜在的な領域をどこまでCTVpとして設定して放射線治療の対象とするかは担当する医師の判断に委ねられる。予防照射を行った領域ではリンパ節に再発する率は低下すると予想されるが，それが生存率の改善にどの程度貢献するかは定かではない。離れた領域に転移が出る患者は遠隔転移を生じるリスクも高く，領域のみを制御するのでは不十分という考え方もある。再発率の低下が生存に結びつく可能性と照射体積が拡大することによって新たな有害事象が発生する可能性を勘案してCTVsの設定を判断することとなる。いずれにしても医療機関での基本となる考え方を持っておき，基準を設けておくことが望ましい。

③ 内的標的体積（ITV）および計画標的体積（PTV）

上記の過程で設定したCTV（CTVp，CTVn，CTVsを総合したもの）に対してどの位のマージンを加えて内的標的体積（ITV）を設定し，最終的に計画標的体積（PTV）を作成するかは治療現場の状況によって異なる。教科書にはCTVに対するPTVマージン（Internal margin：IMとSet-up margin：SMを併せたもの）は左右と背腹方向は1cm程度，頭尾側方向は1～2cmと記されていることが多い。しかし，頸部食道と腹部食道では1回の治療時間中の動き，特に呼吸に伴うって生じる移動量は随分と異なる。GTVが大きい場合や予防領域（CTVs）を設定してCTVが大きくなった場合には，このPTVマージンの取り方によって正常臓器，特に心臓と肺の照射体積が大きく違ってくる。PTVマージンを大きく設定したために脊髄の線量制約に触れてしまい，やむを得ずPTVを一部切り込んだ照射門を設定しなければいけないこともある。治療計画の準備段階からPTVマージンを減じるための様々な工夫を行い，安全で確実な治療を目指すことが大切である。なお食道癌の治療においては中部から下部縦隔で左右方向の照射野サイズは8cmを超えないようにすることが推奨されている。

④ リスク臓器

食道はその周囲を心臓，大血管，肺など生命機能を維持するために重要な臓器によって取り囲まれている。食道癌の治療後にもこれらの臓器の機能が維持されている必要があることから，治療計画の段階でリスク臓器のコンツーリングを行い，設定した線量制約を満たすようにしておくことは重要である。

症例ごとに照射体積が異なり，関わる臓器と有害事象が発生するリスクも異なることが食道癌放射線治療の特徴である。リスク臓器として設定する臓器（OAR：Organ at Risk）としては，心臓，肺，脊髄が重要である。その他に甲状腺，腕神経叢，大動脈や鎖骨下動脈などの大血管もあげられる。腹部のリンパ節では肝臓や腎臓などが照射体積に含まれることがある。CTVpの外部となる食道と胃もリスク臓器と考えてよい。治療計画に際して各リスク臓器に対してセットアップや動きを考慮したマージンを加えてPRV（Planning Risk organ Volume）を設定し，このPRVに対して線量制約を設ける。その案を表4に示す。ただしOARからPRVをどのように設定するかすなわちOARに対するマージン設定についてはまだ十分なコンセンサスがない。マージンを設定せずにそのままOAR＝PRVとして取り扱うことがある一方

表4　食道癌の治療計画におけるリスク臓器設定と線量制約の例

臓器	PRV（Planning Organ at Risk Volume）	線量制約
心臓 (SERIAL)	心臓全体（OAR → PRV 未確定）	照射体積を最小に $D_{mean} < 50$ Gy
肺 (PARALLEL)	肺全体	V20 Gy < 30% V10 Gy < 45%
脊髄 (SERIAL)	脊柱管＋2～5mm	$D_{max} < 50$ Gy $D_{1cc} < 45$ Gy
甲状腺 (PARALLEL)	甲状腺全体	食道癌治療では 設定しない

で，周囲 5mm とすることもある。脊髄については脊柱管もしくは脊柱管+数 mm とすることがある。

肺では肺癌治療に準じて V20 Gy（全肺のうち 20 Gy が照射される体積の割合）が線量制約の基準となる。近年は V10 Gy や V5 Gy などのより小線量が照射される体積の重要性を指摘する報告もある。喘息など慢性呼吸器疾患を持つ症例ではより厳しい線量制約を適用することが望ましい。心臓については照射体積と線量の両方が有害事象発生に関与することが示されている。心筋梗塞や難治性の心嚢水貯留を避けるためには可能な限り線量と体積を低減する。甲状腺や CTVp の外となる食道には一般に線量制約を設定しない。しかし甲状腺に高線量が照射された場合には甲状腺機能低下症を生じるリスクがある。腹部食道から胃に対しては難治性潰瘍のリスクを考慮して最大線量を 50 Gy から 56 Gy 程度までとしている施設もある。振り返って有害事象の評価を行うことを念頭においてリスク臓器のコンツーリングを行い，線量体積ヒストグラム（DVH）を作成しておくことが求められる。

■ ま と め

食道癌の治療計画では病変の存在，進展部位に応じて症例ごとに特化した照射体積の設定が必要であり，あらかじめ十分な情報を入手しておくことが求められる。放射線治療計画に際しては病期診断を踏まえつつ，浸潤と転移の可能性を臨床的に妥当か否かの立場から再検討して標的体積を設定することが求められる。丁寧なコンツーリングに基づく適切な照射方法の設定が治癒率の改善と有害事象の低減に役立ちうることを心において治療計画に取り組んでいただければ幸いである。

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Summary

Target contouring for esophageal cancer

Tailor maid setting of target volume according to the tumor location and invasion is essential for radiotherapy planning of esophageal cancer. When contouring the gross tumor volume and clinical target volume, estimation of microscopic invasion and subclinical lymph nodes metastases and evaluation of clinical validity is needed.

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Long-term results of concurrent chemoradiotherapy using cisplatin and vinorelbine for stage III non-small-cell lung cancer

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Concurrent chemoradiotherapy is the standard treatment for unresectable stage III non-small cell lung cancer (NSCLC). The long-term feasibility and efficacy of vinorelbine and cisplatin with concurrent thoracic radiotherapy were investigated. Eighteen patients received cisplatin (80 mg/m^2) on day 1 and vinorelbine (20 mg/m^2 in level 1, and 25 mg/m^2 in level 2) on days 1 and 8 every 4 weeks for four cycles in a phase I trial. Ninety-three patients received the same chemotherapy regimen except for the fixed vinorelbine (20 mg/m^2) dosage and consolidation therapy with docetaxel (60 mg/m^2, every 3 weeks). The thoracic radiotherapy consisted of a single dose of 2 Gy once daily to a total dose of 60 Gy. A total of 111 patients were analyzed in the present study: male/female, 91/20; median age, 60 years; stage IIIA/IIIB, 50/61; and squamous/non-squamous histology, 26/85. The 3-, 5-, and 7-year overall survival rates (95% CI) were 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.2% (15.8–31.4), respectively. The median progression-free survival and median survival time (95% CI) were 13.5 (10.1–16.7) months and 30.0 (24.3–38.8) months, respectively. Four patients (4%) experienced Grade 5 pulmonary toxicities from 4.4 to 9.4 months after the start of treatment. In conclusion, approximately 15% of patients with unresectable stage III NSCLC could be cured with chemoradiotherapy without severe late toxicities after 10 months of follow-up. Although based on the data from highly selected population participated in phase I and phase II trial, this analysis would strengthen and confirm the previous reports concerning concurrent chemoradiotherapy with third generation cytotoxic agents. (*Cancer Sci* 2013; 104: 93–97)

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for 25–30% of all lung cancer cases.[1,2] Because of the equal frequency of local and distant recurrences, the combination of systemic chemotherapy and thoracic radiotherapy has been established as a standard of care for patients with stage III NSCLC.[3] Concurrent chemoradiotherapy is superior to a sequential approach, as shown by phase III trials in stage III NSCLC.[4,5]

Ohe *et al.*[6] reported the long-term follow-up analysis of concurrent chemoradiotherapy with former generation chemotherapy agents (median survival time 16.1 months, and 7-year overall survival rate 12.0%). Few researchers, however, have reported follow-up data of longer than 5 years after concurrent chemoradiotherapy with third-generation chemotherapy. The long-term safety and efficacy of vinorelbine and cisplatin with concurrent thoracic radiotherapy were investigated.

Materials and Methods

Study selection. Two previous studies were included in this analysis. One was a phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine, and the other evaluated docetaxel consolidation therapy following concurrent chemoradiotherapy.[7,8] These studies were approved by the institutional review board at each institution. Written, informed consent was obtained from all participating patients.

Patient selection. The two studies had similar eligibility criteria. They were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and adequate organ function, including bone marrow, liver, kidney, and lung. Patients were diagnosed to have unresectable disease based on a consensus of thoracic oncologists including surgeons in each institution. The exclusion criteria were reported in previous papers.[7,8]

Treatment schedule. In the phase I study, treatment consisted of chemotherapy with four cycles of cisplatin and vinorelbine (20 mg/m^2 in level 1, and 25 mg/m^2 in level 2) and concurrent thoracic radiotherapy (see below). In the other study, treatment consisted of a chemoradiotherapy portion with three cycles of cisplatin and vinorelbine followed by a consolidation portion with three cycles of docetaxel. Cisplatin (80 mg/m^2) was administered every 4 weeks by intravenous infusion for 60 min with 2500–3000 mL of fluid for hydration. Vinorelbine 20 mg/m^2 diluted in 50 mL of normal saline was administered intravenously on days 1 and 8 every 4 weeks. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid. In the docetaxel (60 mg/m^2, every 3 weeks) consolidation trial, consolidation therapy was started sequentially in patients whose general condition was acceptable. Follow-up computed tomographies after chemoradiotherapy were scheduled as follows; every 2–4 months during the 1 year, every 6 months in the 2 and 3 years, and every 1 year thereafter.

Thoracic radiotherapy was delivered with megavoltage equipment ($\geq$6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions, including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor

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and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. Computed tomography (CT) scan-based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking into account subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in the shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5–1.0-cm margins laterally and 1.0–2.0-cm margins craniocaudally, taking into account setup variations and internal organ motion. Lung heterogeneity corrections were not used.

Toxicity assessment. Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria version 2.0 issued in 1998, and late toxicities associated with thoracic radiotherapy were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.[9] Late toxicities were defined as those that occurred or persisted 90 days after completion of radiotherapy. The detailed methods of treatment modification due to toxicity were reported in previous papers.[7,8]

Response evaluation. In the phase I trial, the objective tumor response was evaluated according to the World Health Organization (WHO) criteria issued in 1979.[10] The Response Evaluation Criteria in Solid Tumors were used to evaluate objective tumor response in the docetaxel consolidation trial.[11] Local recurrences were defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence was defined as the development of malignant pleural and pericardial effusions; and distant recurrence was defined as the appearance of distant metastases.

Statistical analyses. Progression-free and overall survival times were estimated by the Kaplan–Meier method, and confidence intervals (CIs) were based on Greenwood's formula.[12] Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Patients who were lost to follow-up without an event were censored at the date of their last known follow-up. A CI for response rate (RR) was calculated using methods for exact binomial CIs. To investigate the association between survival and factors related to patient characteristics, the Cox regression model was used. Potential factors investigated were as follows: age (in 10-year increments), sex, body weight loss ($\leq 5.0\%$ *vs* $\geq 5.1\%$), histology (squamous cell carcinoma versus non-squamous cell carcinoma), T factor (T1/2 *vs* T3/4), N factor (N0-2 *vs* N 3), and stage (IIIA *vs* IIIB). The STATA 10 for Windows software package (StataCorp LP, College Station, TX, USA) was used for statistical analyses.

Results

Characteristics of the patients. From October 1999 to June 2003, 13 patients were registered at dose level 1 and five at dose level 2 of the phase I study, and 93 patients were enrolled in the docetaxel consolidation trial. Thus, a total of 111 patients were analyzed in the present study. The participants' characteristics were as follows (Table 1): male/female 91/20; median age (range) 60 (31–74) years; body weight loss $\leq 5.0\%/\geq 5.1\%$ 96/14; stage IIIA/IIIB 50/61; and squamous/non-squamous histology 26/85.

Table 1. Patients' characteristics

	Clinical trial		
	Phase I trial†	DTX consolidation‡	Total
Number of patients	18	93	111
Age (years)			
Median	58.5	60	60
Range	48–69	31–74	31–74
Sex			
Male	15	76	91
Female	3	17	20
Performance status			
0	4	32	36
1	14	51	65
Unknown	0	10	10
Body weight loss (minus, %)			
0	11	72	83
0.1-5.0	4	9	13
5.1–	3	11	14
Unknown	0	1	1
Clinical stage			
IIIA	9	41	50
IIIB	9	52	61
N factor			
N0	0	6	6
N1	0	3	3
N2	11	58	69
N3	7	26	33
T factor			
T1	1	18	19
T2	6	31	37
T3	7	13	20
T4	4	30	34
Unknown	0	1	1
Histology			
Adenocarcinoma	14	57	71
Squamous cell carcinoma	3	23	26
Adenosquamous	1	0	1
Large cell carcinoma	0	6	6
NOS§	0	6	6
Others	0	1	1

†The phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine. ‡The docetaxel consolidation therapy following concurrent chemoradiotherapy study. §Non-small cell lung cancer not otherwise specified.

Treatment delivery. Full cycles (four in the phase I trial, three in the docetaxel consolidation trial) of cisplatin and vinorelbine and the full dose (60 Gy) of thoracic radiotherapy were administered in 94 (85%) and 102 (92%) patients, respectively. The delay in radiotherapy was less than 5 days in 74 (67%) patients. In the docetaxel consolidation trial, 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy, mainly because of toxicities. Of 91 patients with relapses, 27 (30%) received gefitinib as salvage treatments.

Objective tumor response and survival. The objective response rate was 82.0% (95% CI, 74.5–89.1). The 3-, 5-, and 7-year progression-free and overall survival rates (95% CI) were 21.0% (13.9–29.1), 15.7% (9.5–23.4), 14.4% (8.4–22.0), and 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.1% (15.7–31.4), respectively (Fig. 1). The median progression-free survival and median survival time (95% CI) were 13.4 (9.8–16.4)

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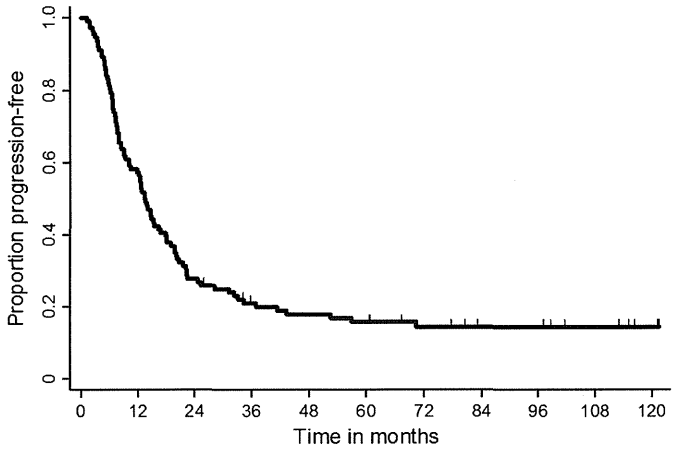

Fig. 1. Progression-free survival (n = 111). The median progression-free survival is 13.5 months (95% confidence interval [CI] 10.1–16.7).

months and 30.0 (24.5–38.8) months, respectively (Fig. 2). There was no significant difference in survival results between subgroups; patients with or without docetaxel consolidation and patients with or without gefitinib.

Pattern of relapse. Relapses were noted in 91 (82%) of 111 patients. Initial relapse sites were local alone in 39 (42%) patients, regional alone in 5 (5%), and distant alone in 38 (41%), including 17 (18%) patients with brain metastases as a sole recurrence site. Brain metastases were detected in 19 (21%) patients and were the most frequent sites of distant metastases. Brain metastases were detected within 3 years of initial treatment, and the last brain relapse was observed after 33 months of follow-up (Table 2). Three (3%) patients experienced adrenal metastases as a first relapse site.

Late toxicities. Grade 1, 2, 3, and 5 late pulmonary toxicities were observed in 18 (16%), 15 (13%), 3 (3%), and 4 (4%) patients, respectively. Seventy-two (64%) patients did not experience late pulmonary toxicities (Table 3). Four cases of grade 5 pulmonary toxicity developed at 4.4, 5.9, 9.4, and 9.6 months, respectively, after the treatment started. Late esophageal toxicities were observed in three patients (one grade 1 and two grade 3).

Causes of death in long-term survivors. There were 67 (60%) patients that survived 24 months or more from the initial treatment. Among them, five patients died because of reasons other than lung cancer. One patient was diagnosed as having pharyngeal cancer at the point of 35 months and died 4 months later. Other than malignancies, community-acquired pneumonia (one patient at 43 months), sudden death due to unknown etiology (two patients at 41 and 42 months) and suicide (one patient at 29 months) were reported, respectively.

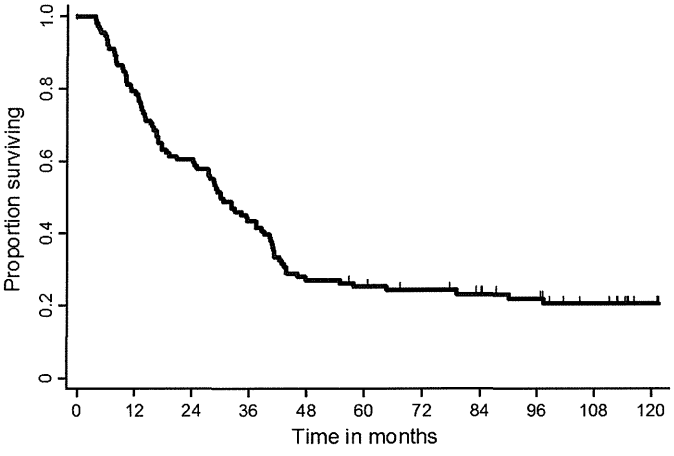

Fig. 2. Overall survival (n = 111). The median overall survival is 30.0 months (95% confidence interval [CI] 24.3–38.6).

Table 2. Sites of initial relapse

Site of recurrences	Number of relapses			
	<1 year	1–3 years	>3 years	Total (%)
Local	16	21	2	39 (42)
Distant	23	12	3	38 (41)
Distant without brain	12	4	3	19 (21)
Distant including brain	1	1	0	2 (2)
Brain only	10	7	0	17 (18)
Regional	3	2	0	5 (5)
Others (L/D/R)†	3	5	1	9 (10)
Unknown	–	–	–	2 (2)

†Others includes 2 Local+Regional relapses, 6 Local+Distant relapses, and 1 Local+Regional+Distant relapse.

Table 3. Late pulmonary toxicities§

Toxicity grades	Clinical trial		Total (%)
	Phase I trial†	DTX consolidation‡	
Without late toxicity	10	62	72 (64)
Grade 1	4	14	18 (16)
Grade 2	3	12	15 (13)
Grade 3	1	2	3 (3)
Grade 4	0	0	0
Grade 5¶	0	4	4 (4)

†The phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine. ‡The docetaxel consolidation therapy following concurrent chemoradiotherapy study. §Late toxicities were defined as those that occurred or persisted 90 days after completion of radiotherapy. ¶The Grade 5 pulmonary toxicities developed at 4.4, 5.9, 9.4, and 9.6 months after the treatment started.

Predictive factors for survival. The associations between overall survival and patients' characteristics (age [in 10-year increments], sex, body weight loss [$\leq 5.0\%$ *vs* $\geq 5.1\%$], histology [squamous cell carcinoma versus non-squamous cell carcinoma], T factor [T1/2 *vs* T3/4], N factor [N0-2 *vs* N 3], and stage [IIIA *vs* IIIB]) were also examined using Cox regression analysis. Age was significantly associated with survival (hazard ratio [HR] 1.34, 95% CI 1.02–1.75, Table 4).

Discussion

Concurrent chemoradiotherapy has been established as a standard treatment for patients with unresectable locally advanced NSCLC. The long-term feasibility and efficacy of vinorelbine and cisplatin chemotherapy with concurrent thoracic radiotherapy were investigated. The 3-, 5-, and 7-year overall survival rates (95% CI) were 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.1% (15.7–31.4), respectively. Older age was associated with poor survival on multivariate analysis (HR 1.34, 95% CI 1.02–1.75).

Two phase III trial examined the efficacy and safety of newer generation cytotoxic agents in concurrent chemoradiotherapy for patients with locally advanced NSCLC.[13,14] The 5-year survival rates (around 20%) were comparable to cur-