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ORIGINAL ARTICLE

Imaging characteristics of local recurrences after stereotactic body radiation therapy for stage I non-small cell lung cancer: Evaluation of mass-like fibrosis

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Keywords
Local neoplasm recurrence; lung cancer; positron-emission tomography; radiation fibrosis; stereotactic body radiotherapy.

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Abstract

Background: This study aimed to evaluate stereotactic body radiation therapy (SBRT) in patients with stage I non-small cell lung cancer (NSCLC) in terms of radiation-induced changes and computed tomography (CT) features of local recurrence by 18F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET).

Methods: From January 2006 to December 2012, 81 patients with NSCLC received SBRT. Follow-up consisted of non-contrast enhanced CT scans performed before and every four months after SBRT. In addition, 18F-FDG-PET/CT was conducted before SBRT for each patient, and one year later for each case suspected of recurrence. The CT findings were classified into two categories: mass-like fibrosis and others. The mass-like fibrosis category was subdivided into two patterns: mass-like consolidation (with air bronchogram) and mass-like opacity.

Results: Six patients had histologically confirmed local recurrence, including 83% (5/6) with mass-like opacity pattern and one case of modified conventional pattern ($P = 0.02$). In contrast, the non-recurrent group exhibited only 7% (5/75) with mass-like opacity and 13% (10/75) with mass-like consolidation pattern. Five patients with local recurrence presented with the mass-like opacity pattern, compared with 33% of patients (5/15) from the non-recurrent group ($P = 0.01$) and showed an increase in maximum diameter at ≥12 months after SBRT. The recurrent group also had a significantly higher standardized uptake value (SUVmax) than the non-recurrent group ($P < 0.001$), with all values >5 (range: 5.7–25.4).

Conclusion: The following characteristics of mass-like fibrosis should be considered indicators of local recurrence after SBRT: opacity pattern, increasing maximum diameter, and SUVmax > 5.

Introduction

Stereotactic body radiotherapy (SBRT) is a promising treatment for patients with stage I non-small cell lung cancer (NSCLC) who are medically inoperable or refuse surgery.[1,2] The outcomes of SBRT have been reported to be similar to surgical outcomes, and the rates of local control for stage I NSCLC with SBRT are approximately 90%.[1–4]

Computed tomography (CT) is an important imaging modality for the evaluation of tumor response and detection of local recurrence after SBRT. However, it is difficult to distinguish radiation-induced pulmonary changes and local recurrence because late radiation fibrotic changes can be dynamic and continue for many years, and there are no typical CT findings for local recurrence. Dahele *et al*. showed that mild-moderate radiological changes are common after lung SBRT, and clinicians should be aware of these radiological changes, which must be distinguished from local failure.[5] After 7–68% of SBRT treatments,[4–8] radiation-induced fibrosis appears as mass-like consolidation on CT, and can be difficult to distinguish from local recurrence.[9] Takeda *et al*. compared the evaluation of local recurrence by ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) and CT. They reported that CT has a more limited ability to detect local recurrences than ^{18}F-FDG-PET.[10] Nonetheless, CT remains the first-line modality for the detection of local recurrence, whereas ^{18}F-FDG-PET is only performed when recurrence is suspected. Accordingly, it is important to learn how to analyze CT findings to identify local recurrences and to avoid misuse of ^{18}F-FDG-PET.

Herein, we retrospectively analyzed CT findings of radiation-induced changes and local recurrence in patients with stage I NSCLC >6 months after SBRT. Mass-like fibrosis was evaluated by ^{18}F-FDG-PET in terms of pattern, diameter growth rate, and maximum standardized uptake value (SUVmax).

Methods

Patients

From January 2006 to December 2012, 81 patients with NSCLC received SBRT. Inclusion criteria in this study were as follows: (i) identification of T1N0M0 or T2aN0M0 (stage I) primary lung cancer, according to the Union for International Cancer Control in the 7th lung cancer tumor node metastasis (TNM) classification; (ii) pathologically or cytologically confirmed NSCLC, when a diagnosis of NSCLC could not be confirmed histologically or clinically by our multidisciplinary tumor board using clinical information (i.e. SUVmax on ^{18}F-FDG-PET, tumor enlargement on CT images, or elevated tumor marker levels during the observation period); (iii) peripheral location of the tumor; and (iv) regular radiological follow-ups for at least one year. Our institutional Medical Ethics Committee approved the treatment protocol, and all patients submitted written informed consent before participation in this study.

Radiotherapy

SBRT was performed using 6-MV X-rays from a linear accelerator (CLINAC C21EX, Varian Medical Systems, Palo Alto, CA, USA [from 2006 to 2009] or Novalis Tx, BrainLAB, AG, Germany [from 2010 to 2012]). A CT simulator and a 3D radiotherapy planning system (ECLIPSE, Version 6.5, 7.5; Varian Medical Systems) were used to perform treatment planning for all patients. To stabilize tumor position during irradiation, patients were instructed to use a self-controlled breath-hold technique using a respiratory monitoring system (Abches, APEX Medical, Tokyo, Japan), as previously described.[11] This system has been used during CT scanning, treatment planning, and irradiation, while holding the breath at inspiration or expiration. The clinical target volume (CTV) was equal to the gross tumor volume (GTV). The planning target volume (PTV) was determined as CTV plus the maximum difference in tumor position on three successive CT scans performed during self-breath-holding. The leaf margin was 5 mm. In most cases, a prescription dose of 48 Gy was delivered in four fractions at the isocenter using eight to 11 conformal static ports. The patients received this treatment biweekly. For tumors adjacent to a central lesion, or critical organs with large CTVs, the prescribed dose was 60 Gy in 10 fractions given over three weeks. The dose calculation algorithm was performed using the convolution method, and the Batho Power Law method was used to correct for tissue inhomogeneities. The dose constraints for the organs at risk were based on protocol criteria recommended by the Japan Clinical Oncology Group 0403.[12,13]

Follow-up evaluation

After SBRT, the patients were monitored by non-contrast enhanced CT scans performed after one month, and then at three-month intervals during the first two years. Thereafter, follow-up CT scans were conducted every four months. Local recurrence was diagnosed by pathological confirmation. All CT scans were performed with a LightSpeed 16-detector row helical scanner (GE Healthcare, Tokyo, Japan). Multi-slice helical chest CT scans were conducted without contrast material using the following imaging parameters: slice thickness 5 mm; collimator 1.25 mm; electric current 100–400 mA; electric voltage 120 kVp; and pitch, 0.938:1.

Each patient underwent ^{18}F-FDG-PET/CT before SBRT, and one year afterward when recurrence was suspected. Prior to ^{18}F-FDG-PET/CT, all patients underwent five hours of fasting to ensure that their blood sugar levels were <200 mg/dL. Sixty minutes before imaging, all patients received 200–250 megabecquerel (MBq) FDG. PET/CT was performed using a Biograph 16 scanner (Siemens Medical Systems, Munich, Germany), with low-dose unenhanced CT for attenuation correction and anatomic localization. Image emission data were acquired from the parietal region to the mid-thigh area over a period of 20 minutes. The images were reconstructed into axial, sagittal, and coronal views using an ordered subset expectation maximization algorithm. SUVmax, a decay-corrected dimensionless parameter, was calculated as follows: ([maximum activity in VOI]/[VOI])/([injected FDG dose]/[patient weight]), whereby VOI is the volume of the interest around the lesion.

A diagnostic radiologist and radiation oncologists reviewed all CT images and SUVmax on ^{18}F-FDG-PET. Late CT findings were evaluated >6 months after SBRT, and classified according Dahele *et al*.[5] and Trovo *et al*.'s[8] classifications, with some modifications. The image findings were classified into two categories: mass-like fibrosis and others. Furthermore, mass-like fibrosis was subdivided into two patterns: mass-like consolidation (well-confined focal consolidation limited to the tumor region with air bronchogram, but larger than the original tumor) and mass-like opacity (mass-like consolidation without air bronchogram). Accordingly, five patterns were identified based on these characteristics: modified conventional pattern (consolidation, volume loss, and bronchiectasis); mass-like consolidation (with air bronchogram); mass-like opacity (without air bronchogram); scar-like fibrosis (linear opacity in the tumor with associated volume loss); or no evidence of increased density (regressing

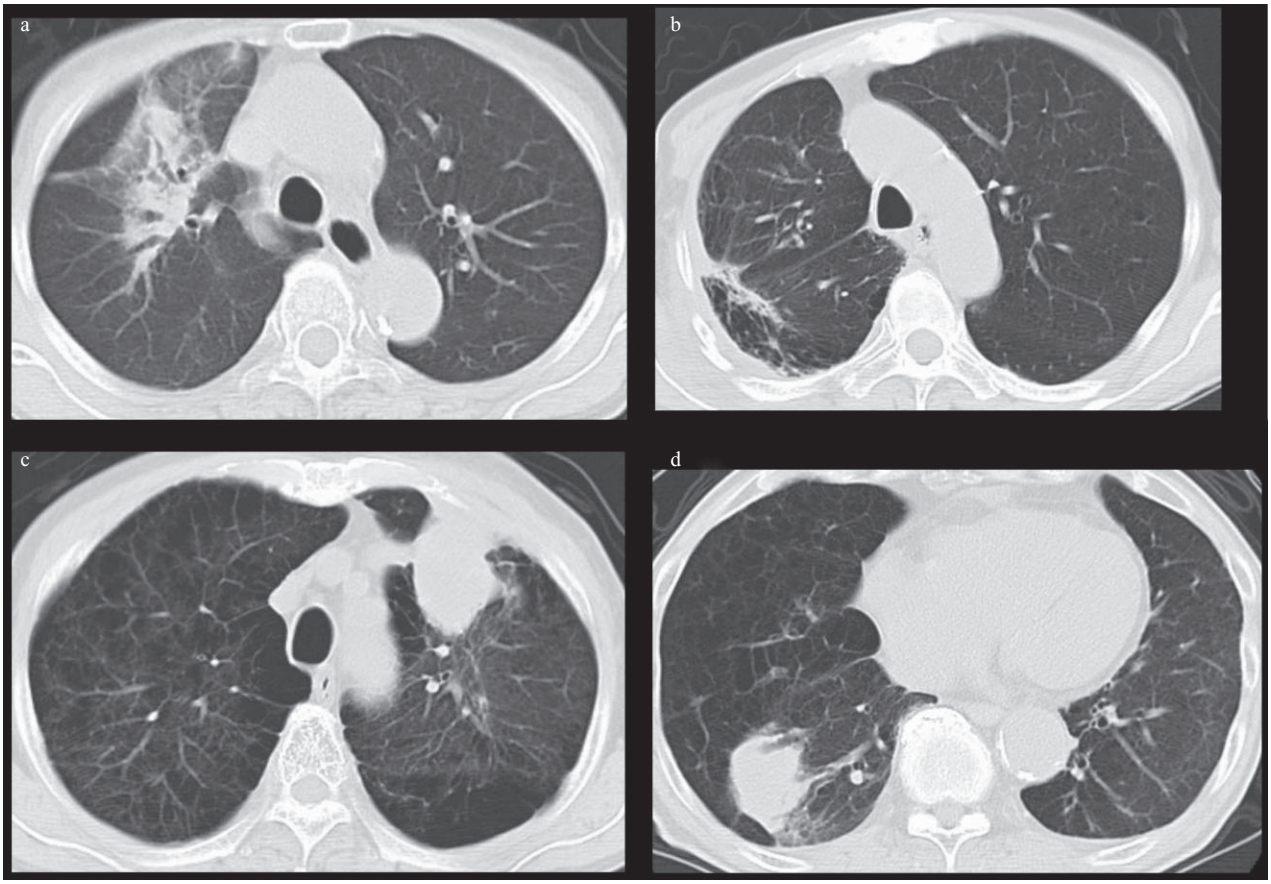

Figure 1 Typical computed tomography (CT) findings of late radiological fibrosis. (**a**) Modified conventional pattern, (**b**) scar-like fibrosis pattern, (**c**) mass-like opacity (mass-like fibrosis without air bronchogram), and (**d**) mass-like consolidation (mass-like fibrosis with air bronchogram).

mass at the location of the treated tumor or only normal lung) (Fig 1).

The CT changes were evaluated after the final diagnosis, according to these categories. Furthermore, we measured the maximum diameter of the discrete opacity or consolidation at points where we could clearly measure on the same slice level of the follow-up CT and evaluated the diameter growth rate. The following equation was used to calculate the diameter growth rate: diameter growth rate = (maximum diameter at final diagnosis − maximum diameter 12 months after SBRT)/number of months between each measurement.

Statistical analysis

The following statistical tests were used: student's t-test to compare continuous quantitative variables, Mann–Whitney *U*-test to compare ordinal quantitative variables, and chi-square test with Fisher's exact test to compare qualitative variables. The Kaplan–Meier method was used to calculate survival and response duration, and the log-rank test was used for group comparisons. A *P*-value of <0.05 was considered significant. StatView software version 5.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Patient characteristics

The median follow-up duration for all patients was 29.0 months (range: 8.0–84.0 months), and the median follow-up for cases with mass-like fibrosis was 32.5 months (range: 13.5–66.0 months). Six patients had histologically confirmed local recurrence, with a median time lapse of 22 (8–48) months after SBRT. Five cases of local recurrence were detected >13.5 months after SBRT; one case was detected after only eight months. Table 1 shows the comparable baseline characteristics for the patients without or with local recurrence.

Radiological changes

Table 2 compares the post-procedure CT findings identified in the recurrent and non-recurrent groups. In all patients, the

Table 1 Patient characteristics

	All ($n = 81$)	No recurrence ($n = 75$)	Recurrence ($n = 6$)	*P*-value
Age (years)				
Median (range)	80 (64–93)	80 (64–93)	79 (69–86)	0.99
Gender				0.78
Female	17	16	1	
Male	64	59	5	
Performance (ECOG)				0.69
0/1/2/3/4	55/24/2/0/0	55/18/2/0/0	0/6/0/0/0	
T stage				0.74
T1a/T1b/T2a	42/21/18	38/20/17	4/1/1	
Histology				0.34
Adenocarcinoma	35	32	3	
Squamous cell carcinoma	27	25	2	
Unclassified NSCLC	2	2	0	
Unproven	17	16	1	
Tumor location				0.37
Central/Peripheral	6/75	5/70	1/5	
Total dose				
48 Gy/60 Gy	60/21	55/20	5/1	0.59
PTV (cc)				
Mean ± SD (range)	69.1 ± 49.7	67.4 ± 48.0	90.3 ± 70.0	0.27

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell cancer; PTV, planning target volume; SD, standard deviation.

modified conventional pattern was the most common finding (48.1%), followed by scar-like, mass-like consolidation (12.3%), mass-like opacity (12.3%), and no evidence of increased density (8.6%). In the six patients with recurrence, five patients (83%) had mass-like opacity patterns. The only patient with recurrence who exhibited the modified conventional pattern had early failure at eight months after SBRT. Compared with the other patterns, the recurrent group had significantly more instances of the mass-like fibrosis pattern ($P = 0.02$).

Table 3 shows the CT findings of 20 patients with mass-like fibrosis at final diagnosis according to time. All cases of no evidence of increased density patterns at 12 months or after more than 12 months were types of regressing masses at the

Table 2 Impact of local recurrence on CT findings after stereotactic body radiotherapy

CT findings	All ($n = 81$)	No recurrence ($n = 75$)	Recurrence ($n = 6$)	*P*-value
				0.02
Mass-like fibrosis	20 (24.7%)			
Mass-like consolidation	10 (12.3%)	10 (13.3%)	0	
Mass-like opacity	10 (12.3%)	5 (6.7%)	5 (83%)	
Others	61 (75.3%)			
Modified conventional	39 (48.1%)	38 (50.7%)	1 (17%)	
Scar-like fibrosis	15 (18.5%)	15 (20.0%)	0	
No evidence of increased density	7 (8.6%)	7 (9.3%)	0	

CT, computed tomography.

Table 3 CT findings of 20 patients with mass-like fibrosis at final diagnosis according to time

CT findings	6 months ($n = 20$)	12 months ($n = 20$)	18 months ($n = 19$)	24 months ($n = 17$)	36 months ($n = 11$)
Final diagnosis					
Mass-like consolidation ($n = 10$)	6	11	9	9	5
Mass-like opacity ($n = 10$)	3	5	7	7	6
Modified conventional	5	0	0	0	0
Scar-like fibrosis	0	0	0	0	0
No evidence of increased density	6	4	3	1	0

CT, computed tomography.

Table 4 Impact of recurrence on CT findings, fibrosis growth rate, and SUVmax after stereotactic body radiotherapy

	All ($n = 20$)	No recurrence ($n = 15$)	Recurrence ($n = 5$)	*P*-value
CT findings				0.01
Mass-like consolidation	10 (50%)	10 (66.7%)	0	
Mass-like opacity	10 (50%)	5 (33.3%)	5 (100%)	
Diameter growth rate				0.04
Mean ± SD (mm) (range)	0.37 ± 0.97 (–1.1–3.25)	0.33 ± 0.67 (–1.1–1.6)	1.37 ± 1.12 (0.33–3.25)	
SUVmax				<0.001
Mean ± SD (range)	5.98 ± 6.4 (1.85–25.4)	2.95 ± 0.81 (1.85–4.5)	15.1 ± 7.43 (5.7–25.4)	

CT, computed tomography; SD, standard deviation; SUVmax, maximum standardized uptake value.

Table 5 Impact of the mass-like fibrosis pattern on diameter growth rate and SUVmax after stereotactic body radiotherapy

	Mass-like consolidation ($n = 10$)	Mass-like opacity ($n = 10$)	*P*-value
Diameter growth rate			0.13
Mean ± SD (mm) (range)	0.38 ± 0.69 (–0.84–1.6)	0.48 ± 1.04 (–1.1–3.25)	
SUVmax			
Mean ± SD (range)	3.13 ± 0.78 (2.2–4.5)	8.84 ± 7.40 (1.85–25.4)	0.43

SD, standard deviation; SUVmax, maximum standardized uptake value.

location of the treated tumor, which had discrete consolidation or opacity. All cases with modified conventional patterns at six months changed into mass-like fibrosis patterns at 12 months. All cases changed into mass-like fibrosis patterns after 36 months.

The impact of local recurrence on the CT findings of mass-like fibrosis was evaluated in terms of pattern, diameter growth rate, and SUVmax (Table 4). All five patients with local recurrence presented with the mass-like opacity pattern, compared with 33% of patients (5/15) from the non-recurrent group ($P = 0.01$). Diameter growth rates were significantly higher for the recurrent group than for the non-recurrent group ($P = 0.04$). The mean diameter growth rate of the recurrent mass-like fibrosis was 1.37 mm, and all cases of local recurrence showed an increase in diameter over time. The recurrent group had a significantly higher SUVmax than the non-recurrent group ($P < 0.001$). All patients with a recurrence that had a mass-like opacity pattern had a SUVmax >5. In the non-recurrent group, the type of fibrotic pattern did not influence the diameter growth rate and SUVmax (Table 5).

Local control and survival

Kaplan–Meier curves were constructed to determine survival and response duration to SBRT (Fig 2). The two and three-year rates of local control (LC) were 95.9% and 91.8%, respectively. The two and three-year overall survival (OS) rates were 82.9% and 69.4%, respectively.

Discussion

Surgery is currently the standard treatment for stage I NSCLC. However, SBRT is commonly considered the primary treatment option for patients with stage I NSCLC who are medically inoperable or refuse surgery because of similar outcomes that have been reported for SBRT.[1,2] The three-year LC rates for inoperable patients receiving SBRT at stage I NSCLC have been between 92.0% and 97.6%.[1,2] Similarly, we reported two and three-year LC rates of 95.9% and 91.8%. Whereas these LC rates are excellent, and local recurrence is uncommon, it is important to detect local recurrence as soon as possible for salvage therapy because these patients are less likely to receive invasive treatments.

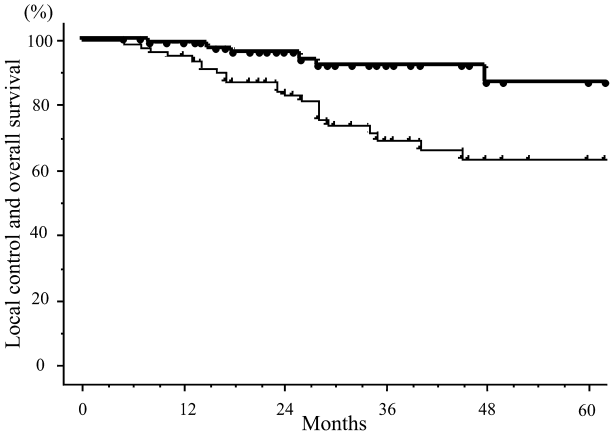

Figure 2 Local control (bold line) and overall survival (thin line) curve of 81 patients after stereotactic body radiotherapy (SBRT). The three-year local control and overall survival rates were 91.8% and 69.4%, respectively. ━, Local control; ──, Overall survival.

CT constitutes the first-line imaging modality for the follow-up of cancer patients to detect local recurrence and distant metastases. Dynamic changes in CT findings are reported during the first year after SBRT in terms of pattern and location.[14] Radiological changes are generally categorized as acute (within the first 6 months) or late (after 6 months).[5] In this study, we evaluated late radiological changes because most local recurrences occur >6 months after SBRT, and the reported median time to local recurrence is 14.9 months.[15] Late changes after SBRT are categorized into five patterns: modified conventional; mass-like opacity; mass-like consolidation; scar-like fibrosis; and no change.[5,8] A modified conventional pattern was reported as the predominant CT density pattern (46–62%).[5,6,8] In contrast, mass-like fibrosis (opacity or consolidation) was reported in 7–20% and scar-like fibrosis in 11–22% of the late period CT scans.[5,6,8] In this study, modified conventional, mass-like fibrosis, and scar-like patterns were observed in 48.1%, 24.7%, and 18.5% of all cases, respectively, in agreement with these studies.

CT changes are often dynamic and continual evolution in morphology is observed.[5] We evaluated the time course for the CT findings of mass-like fibrosis at final diagnosis. Dahele *et al*. mentioned that a modified conventional pattern after one year evolved thereafter into scar or mass-like patterns and the proportion of mass-like changes seemed to increase in those patients with more than two years of imaging follow-up.[5] In our study, all cases (5 cases) with modified conventional patterns at six months changed into mass-like fibrosis patterns at 12 months. Compared with the results by Dahele *et al*., the modified conventional pattern changed into the mass-like pattern earlier in our study.[5] We think this discrepancy comes from differences in the definition in the patterns of the CT findings; some cases with mass-like consolidation that we defined in this study as well-confined focal consolidation limited to the tumor region with air bronchogram may have been included in the modified conventional patterns using the definition by Dahele *et al*.[5]

In lung cancer, local recurrence often exhibits a mass-like fibrosis pattern, either as consolidations (with air bronchogram) or opacities (without air bronchogram). Matsuo *et al*.[7] reported that 68% (27/40) of lung cancer patients developed mass-like consolidations five months after SBRT, including 24 cases of radiation-induced injury and three cases of local recurrence. In contrast, the present study identified mass-like fibrosis in five of the six cases of local recurrence 12 months after SBRT. Similarly, Takeda *et al*. reported on 21 (9.8%) cases of local recurrence after SBRT for NSCLC, which had predominantly (81%) adopted a nodule pattern (radiation-induced lung opacities) similar to mass-like fibrosis in late images.[10] Interestingly, Kato *et al*. detected air bronchograms in three of the five cases of local recurrence, which subsequently disappeared in all three cases 13 months after SBRT.[16] In our study, five cases with recurrences with mass-like opacity had recurrences after 13 months, and all CT follow-ups of mass-like fibrosis were performed after 13.5 months. These studies suggested that air bronchograms developed early after SBRT, and gradually disappeared during the conversion of a mass-like consolidation into a mass-like opacity pattern. In our five local recurrence cases with mass-like fibrosis patterns, two cases that showed mass-like consolidation patterns at 12 months evolved into mass-like opacity patterns at the final diagnosis and locally failed at 26 and 28 months.

Kato *et al* reported that growing abnormal opacities after 12 months were the most reliable indicator of local recurrence.[16] The present study compared the diameter growth rates of the mass-like fibrosis patterns of the non-recurrent and recurrent groups. We used the maximum diameter at 12 months as a comparator for the size difference, because the first CT changes became apparent more than 12 months after SBRT;[5] all of our modified conventional patterns at six months changed into mass-like fibrosis patterns at 12 months, so that diameters of both mass-like fibrosis and no evidence of increased density patterns (a type of regressing mass at the location of the treated tumor) at 12 months, which had morphological discrete opacities or consolidations, could be measured. In addition, some previous studies compared the size of the CT findings at 12 months.[7,16] The growth rates were four-fold higher in the recurrent group than in the non-recurrent group. Matsuo *et al*.[7] reported that the size of the mass-like consolidations increased in all of their cases with recurrence after 12 months, as in the present study. Collectively, these data suggested that the mass-like opacity pattern and increasing maximum diameter of the mass-like fibrosis were reliable markers of local recurrence in late (≥12 months) follow-up CT images for patients with NSCLC after SBRT.

Nonetheless, it is important to remember that CT has a limited ability to detect local recurrence. In our study, five (50%) cases of mass-like opacity were assigned to the non-recurrent group, and there was no significant difference in the diameter growth rate between the mass-like opacity and mass-like consolidation patterns. Takeda *et al*. reported that radiation-induced fibrosis was difficult to distinguish from tumor recurrence on follow-up CT scans, even in the presence of growing opacities.[17] Therefore, local recurrence cannot be diagnosed conclusively based on CT findings. Conversely, ^{18}F-FDG-PET is an effective whole-body imaging technique that can detect metabolic changes preceding structural findings.[18] Takeda *et al*. showed that ^{18}F-FDG-PET was a more sensitive tool to detect local recurrence.[10] Therefore, we performed ^{18}F-FDG-PET on all patients with NSCLC presenting with mass-like fibrosis based on CT examination. Although similar SUVmax for the two mass-like fibrosis patterns were obtained, the SUVmax was significantly higher for the recurrent cases than for the non-recurrent cases. All

patients with recurrence with a mass-like opacity pattern had SUVmax > 5. A systematic review revealed that recurrence should be suspected if high-risk CT changes were detected with SUVmax ≥5 on ^{18}F-FDG-PET.[19] Nakajima *et al*. reported that among the ^{18}F-FDG-PET/CT findings of recurrent tumors, a mass-like shape was the most common (21/23; 91%), and all cases of tumor recurrence had a SUVmax >4.5 at the diagnosis of local failure.[20] Their results were similar to ours, although their 59 patients included 12 cases of metastatic lung cancer, and pathological confirmation of tumor recurrence was obtained in only a few cases. The small number of patients with recurrence limited our study; however, pathological confirmation was obtained at radiological diagnosis, and the CT findings of 81 patients treated with SBRT were evaluated.

Conclusion

The present study suggested that a mass-like opacity pattern, an increasing maximum diameter ≥12 months after SBRT, and SUVmax > 5 of the mass-like fibrosis on ^{18}F-FDG-PET should be considered indicators of local recurrence in patients with NSCLC.

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Disclosure

No authors report any conflict of interest.

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