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ORIGINAL ARTICLE

Computed tomography appearances of local recurrence after stereotactic body radiation therapy for stage I non-small-cell lung carcinoma

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Abstract
Purpose. The aim of this study was to characterize computed tomography (CT) manifestations of local recurrence after stereotactic body radiation therapy (SBRT) for stage I non-small-cell lung cancer (NSCLC).
Materials and methods. A total of 27 stage I NSCLC patients who were treated with SBRT, including 5 patients with local recurrence, were retrospectively analyzed for serial CT examinations.
Results. A bulging margin appeared in 4 of the 5 cases (80%) with local recurrence and 1 of 22 cases (5%) without local recurrence. Air bronchograms were seen in 3 of 5 cases with local recurrence and 21 of 22 cases without local recurrence, but they subsequently disappeared in all 3 cases (100%) with local recurrence and in 4 of the 21 cases (19%) without local recurrence. Ipsilateral pleural effusion was observed in all 5 cases (100%) with local recurrence and in 5 of 22 cases (22%) without local recurrence. The opacity increased in size even after 12 months from the completion of SBRT in cases with local recurrence, whereas it decreased or did not change in size in cases without recurrence.
Conclusion. Local recurrence should be suspected on CT when there was (1) a bulging margin, (2) disappearance of air bronchograms, (3) appearance of pleural effusion, or (4) increase in the abnormal opacity after 12 months.

Key words Stereotactic body radiation therapy · Non-small-lung carcinoma · Local recurrence · Radiation pneumonitis

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Introduction

Stereotactic body radiation therapy (SBRT) for lung cancer is a novel treatment technique that allows us to deliver a higher dose to the tumor while decreasing irradiation of the surrounding normal tissue. Early reports documented that SBRT provided a good survival rate comparable to that of surgery without significant radiation-induced complications. SBRT holds promise to become the standard treatment for stage I lung cancer in place of surgery.[1-4]

On follow-up computed tomography (CT) examinations after SBRT, it is most important to detect a locoregional recurrence or distant metastasis for a second salvage treatment. However, it is often indeterminate if local recurrence is present on CT as radiation-induced lung parenchymal change is always present.[5-8] Detecting local recurrence is difficult with SBRT because radiation pneumonitis after SBRT does not have typical manifestations, such as a straight border conforming to the radiation portal, as seen with conventional radiotherapy; and its appearances on CT are still not well understood. Although positron emission tomography (PET) is emerging as a modality of choice for evaluating the treatment effect, it is known that there are a significant number of false-positive findings after radiotherapy.[9] In addition, PET is not an easily available modality.

We think that CT is still the mainstay for evaluating recurrence in patients with lung cancer after radiotherapy. Although there have been a few reports describing CT findings of radiation injury after SBRT, no report has focused on CT findings of local recurrence after SBRT. In this study, we tried to determine the CT features of local recurrence after SBRT by comparing the CT scans of patients with local recurrence with those of patients without evidence of recurrence.

Materials and methods

Patients

Our institutional review board does not require its approval or patients' informed consent for a retrospective study using obtained routine clinical data.

Treating lung cancer with SBRT was started during April 2001 in our institution. SBRT was selected as treatment for stage I non-small-cell lung carcinoma (NSCLC) when the lesions were inoperable or the patient refused surgery. From then to June 2003, a total of 54 patients with NSCLC underwent SBRT in our institution. Of them, 27 patients who were followed up by periodic CT examinations for more than 18 months were enrolled in this study. The remaining 27 patients were lost to follow-up or their follow-up lasted less than 18 months. In all, 5 patients had histologically confirmed local recurrence by CT-guided biopsy, and the remaining 22 patients were free from recurrence by our routine workup, including physical examination or tumor marker examination. T staging and pathological subtypes of the patients are summarized in Table 1.

Radiotherapy techniques

Treatments were delivered using a newly developed unit comprising a linear accelerator (linac) (EXL-15DP; Mitsubishi Electric, Tokyo, Japan) coupled to a CT scanner (Hi-Speed DX/I; GE Yokogawa Medical Systems, Tokyo, Japan) sharing a common couch.

The planning target volume (PTV) was determined as the clinical tumor volume (CTV) plus the maximum difference of the tumor position measured on the three repeated CT scans performed during self breath-holding with an additional margin of 5 mm.[2,4,10] Elective nodal irradiation to the hilar or mediastinal regions was not delivered.

Ten non-coplanar dynamic arcs (couch angles between –20° and +25°) were used for irradiation. The isocenter was single for all arcs. The radiation port was made with dynamic, sliding, 5-mm thick multileaves at the isocenter, adjusted at the border of the PTV. Each radiotherapy fraction had one arc. A total dose of 60 Gy in 10 fractions (two fractions daily for 5–8 days) at the minimum dose point in the PTV was delivered using a 6-MV X-ray. According to the linear-quadratic model,[11] the biologically effective dose (BED) at the isocenter was approximately 120 Gy.

CT examination

The CT was carried out with an Aquilion (Toshiba Medical Systems, Tokyo, Japan) 16 detector rows helical scanner in all cases. The whole chest and liver were scanned in one breath-hold before and after administration of contrast material. Contrast material was generally used unless the patient had a contraindication to its usage, such as refusal by the patient, poor renal function, bronchial asthma, or a history of an allergic reaction to the material. A total of 100 ml of contrast medium (iohexol, Omnipaque; Daiichi, Tokyo, Japan) was administered intravenously with an injection rate of 2 ml/s. Saline flush was not done. Enhanced CT scanning was started 60 s after the initiation of contrast material injection. The imaging parameters of CT scans were as follows: 1 mm collimation, electric current 200–300 mA, electric voltage 120–140 kvP, and pitch 15. Three types of thin-section CT targeting to the irradiated site as well as 5-mm slice thickness CT of the whole chest and liver were reconstructed from the raw data: precontrast and postcontrast standard algorithm images for observing the contrast enhancement of the opacity and precontrast or postcontrast bone algorithm images for viewing the lung. CT examination was performed about every 3 months. The follow-up period after completion of SBRT ranged from 18 to 39 months (median 24 months).

Table 1. T staging and pathological subtypes of the patients

	T staging		Pathological subtype		
Recurrence status	T1	T2	Adenocarcinoma	Squamous cell carcinoma	Indeterminate pathology[a]
Local recurrence ($n = 5$)	1	4	4	1	—
Without local recurrence ($n = 22$)	17	5	14	4	4

[a] Indeterminate pathology indicates that the tumor is absolutely a non-small-cell lung carcinoma, but its subtype is indeterminate

Evaluation of CT findings

All CT scans of the 27 patients were retrospectively reviewed independently by two chest radiologists who were unaware of the presence or absence of a local recurrence. The scans were assessed for any of the following abnormalities: bulging margin, linear or concaved margin, air bronchogram, pleural effusion of the ipsilateral side, enlarged hilar or mediastinal lymph node. As abnormal opacities often had multiple components of the margin, bulging and linear or concaved margins could coexist. A lymph node was considered enlarged when its short-axis diameter exceeded 10 mm. In addition, in 18 patients (3 with local recurrence, 15 without local recurrence) who underwent contrast CT examination, the presence of the angiogram sign and inhomogeneity of contrast enhancement of the abnormal opacity were evaluated as well with precontrast and postcontrast thin-section CT using a standard algorithm. The angiogram sign was defined as well-enhanced branching structures in the abnormal opacity conforming to the vasculature of the segment, occasionally next to an air bronchogram. The maximum diameter of the abnormal opacity, including the inherent irradiated tumor, was also measured.

The final decision regarding the presence of these findings was made by consensus between the two radiologists. Kappa values between two readers were calculated for each evaluated finding. As each patient had undergone serial CT examinations, we were interested in the interval changes of these findings: appearance or disappearance, or interval change in the size of the opacity. Statistical analysis was not performed between the readers, except for kappa values, because of the small sample size.

Results

The kappa values between the two readers for each finding ranged from 0.469 to 0.727, indicating moderate or good inter-reader agreement.

A bulging margin appeared in 4 of the 5 cases (80%) with local recurrence and 1 of the 22 cases (5%) without local recurrence during the follow-up period (Tables 2, 3; Figs. 1–3). Air bronchograms were seen in 3 of 5 cases

Table 2. Periods of the presence of each CT finding in the five cases with recurrence

Cases with local recurrence	CT finding				
	Bulging margin	Linear margin	Air bronchogram	Pleural effusion	Lymph node enlargement
Case 1	~2, 20~	2~16	~13	8~	22~
Case 2	17~	1~17	—	9~	29~
Case 3	All period	—	—	21~	—
Case 4	~3, 15~	6~12	~12	6~	17~
Case 5	8~	5~8	~8	5~	—

The numbers show the months after completion of SRT. All period means that the bulging margin was shown during the entire observation period
CT, computed tomography; SRT, stereotactic radiation therapy

Table 3. CT findings of cases with and without local recurrence after stereotactic body radiation therapy

CT findings	Local recurrence ($n = 5$) (contrast-enhanced cases, $n = 3$)	Without local recurrence ($n = 22$) (contrast-enhanced cases, $n = 15$)
Bulging margin during follow-up period		
Appearance	4/5 (80%)*	1/22 (5%)
Persistence	1/5 (20%)	5/22 (23%)
Linear margin during the follow-up period		
Appearance	4/5 (80%)	22/22 (100%)
Disappearance	4/4 (100%)	2/22 (9%)
Air bronchogram during follow-up period		
Observed at least once	3/5 (60%)	21/22 (95%)
Disappearance	3/3 (100%)	4/21 (19%)
Appearance of pleural effusion during follow-up period	5/5 (100%)	5/22 (23%)
Appearance of lymph node enlargement during follow-up period	3/5 (60%)	4/22 (18%)
Angiogram sign during follow-up period		
Observed at least once	3/3 (100%)	12/15 (80%)
Disappearance	0/3	0/12
Inhomogeneity of contrast enhancement observed at least once	3/3 (100%)	10/15 (67%)

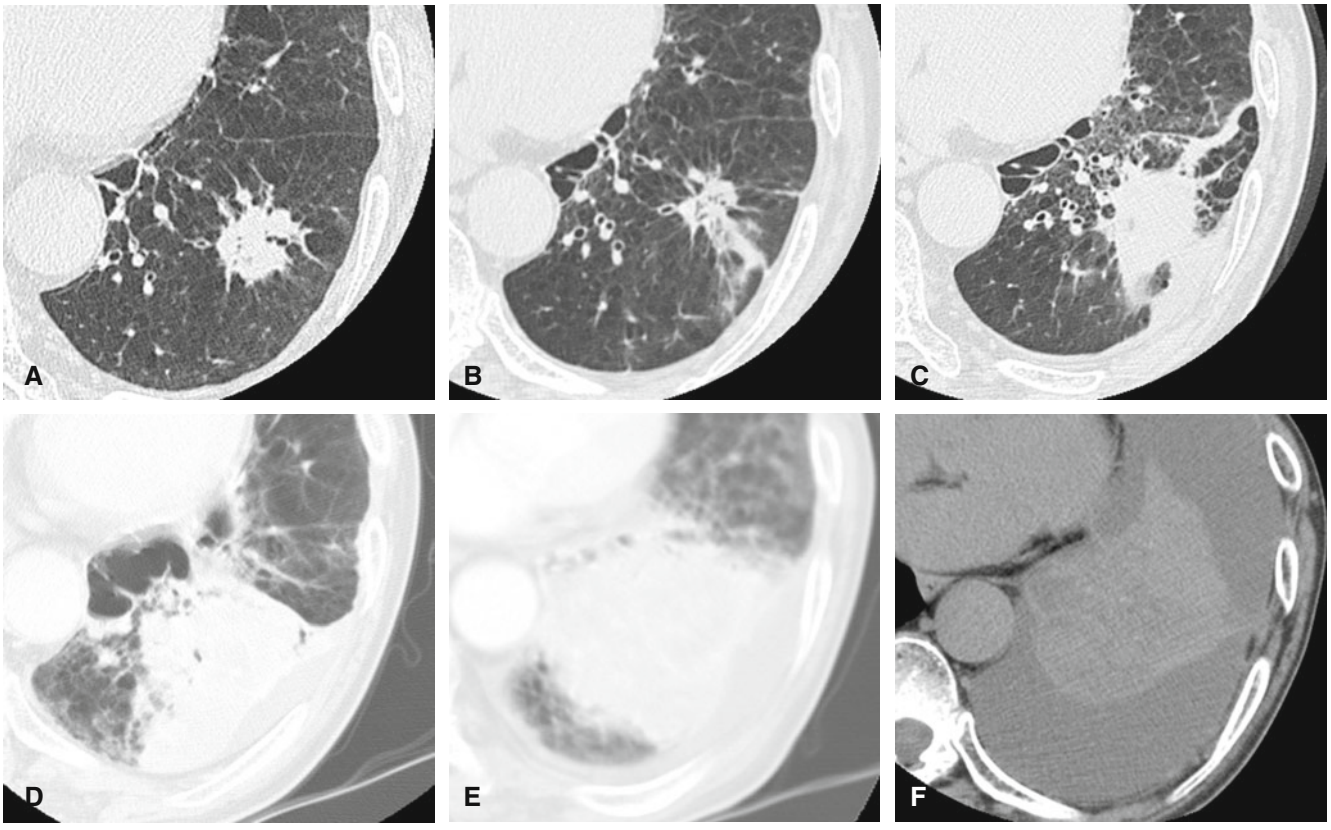

Fig. 1. A 77-year-old man with lung adenocarcinoma had a local recurrence. **A** Axial computed tomography (CT) scan before stereotactic body radiation therapy (SBRT) shows a lung carcinoma in the left lower lobe. **B** CT scan 3 months after SBRT shows a decrease in the size of the tumor. A band-like opacity is noted posterior to the tumor, presumably representing radiation-induced change. **C** CT scan 6 months after SBRT shows an increase in the size of the consolidation. A linear margin and air bronchogram are observed. **D** CT scan 12 months after SBRT shows further increase in the size of the consolidation. Note that pleural effusion has appeared. **E** CT scan 15 months after SBRT shows appearance of a bulging margin. Air bronchogram has disappeared. **F** CT scan 17 months after SBRT shows an increase in the amount of pleural effusion. Local recurrence was confirmed by needle biopsy

with local recurrence and 21 of 22 cases without local recurrence. However, the air bronchograms subsequently disappeared in all 3 cases (100%) with local recurrence and 4 of the 21 cases (19%) without local recurrence. In the three local recurrence cases, the air bronchograms subsequently disappeared by 13 months. Ipsilateral pleural effusion was observed in all 5 cases (100%) with local recurrence and in 5 of 22 cases (23%) without local recurrence. Lymph node enlargement was identified in 3 cases (60%) with local recurrence and in 4 cases (18%) without local recurrence. The angiogram sign was seen in all 3 cases (100%) with local recurrence and in 12 of 15 cases (80%) without local recurrence. Disappearance of the angiogram sign during the follow-up period was observed in none of these cases.

Inhomogeneity of contrast enhancement of the opacity was seen in 3 of 3 cases (100%) with local recurrence and in 10 of 15 cases (67%) without local recurrence. Pleural effusion appeared within 12 months after completion of SBRT in four of five cases with local recurrence. Air bronchograms disappeared within 12 months after completion of SBRT in two of the three cases with local recurrence.

Changes in the maximum diameters of the opacities with time are shown in Figs. 4 and 5. The size of the opacity increased in cases with local recurrence and remained so even 12 months or more from the completion of SBRT; in contrast, it decreased or did not change in size in cases without local recurrence after 12 months.

Discussion

During CT follow-up of SBRT for lung cancer, differentiation between local recurrence and radiation pneumonitis is difficult because radiation pneumonitis after SBRT does not have a simple, straight border conforming to the portal seen in usual radiation pneumonitis; in fact, it may appear as a mass-like opacity due to the complex multicoplanar irradiation technique.[12,13]

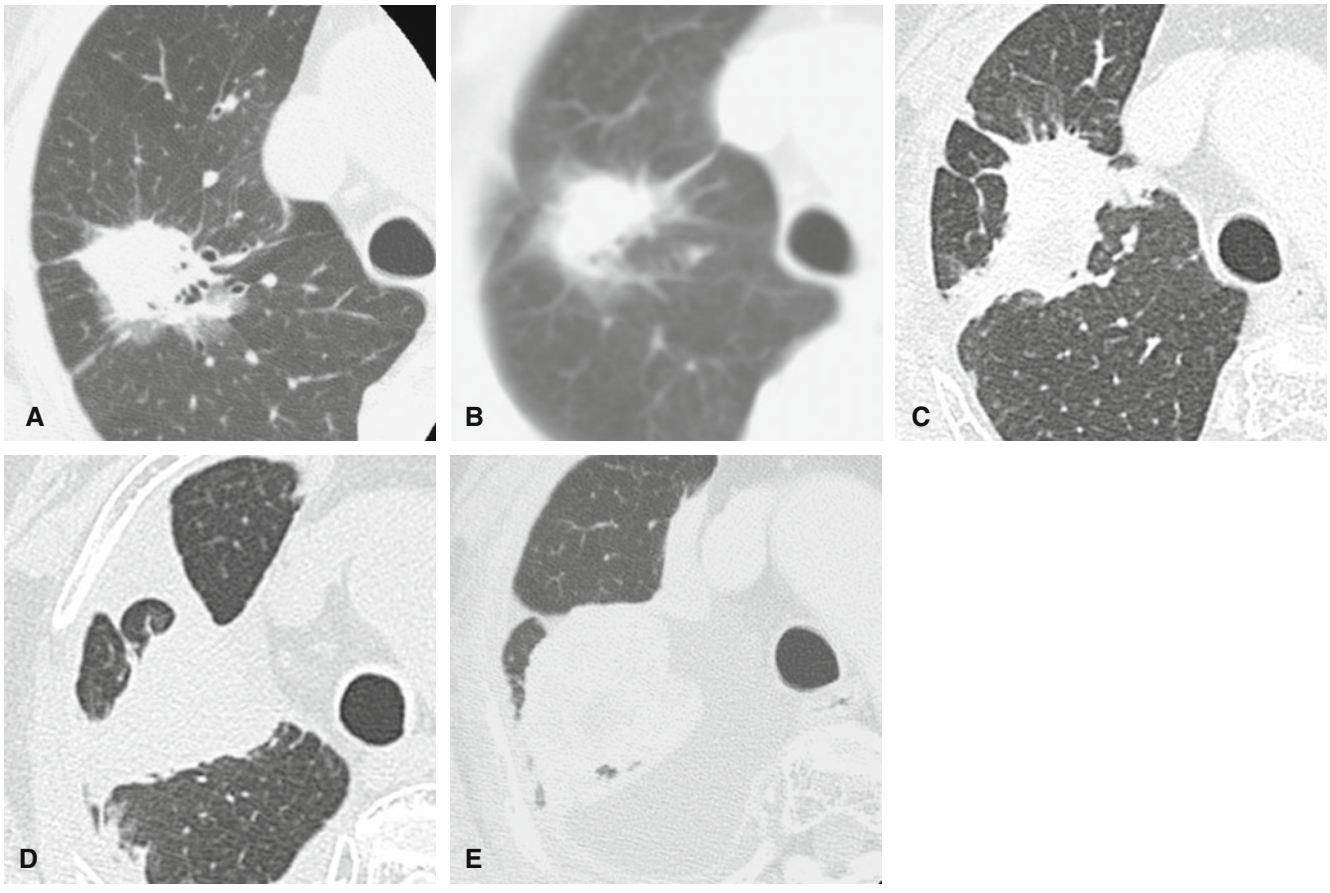

Fig. 2. An 82-year-old woman had lung adenocarcinoma with local recurrence. **A** Axial CT scan before SBRT shows a lung carcinoma with air bronchogram in the right upper lobe. **B** CT scan 2 months after SBRT shows a decrease in the size of the tumor. **C** CT scan 8 months after SBRT shows an increase in size of the consolidation. The linear margin is still preserved. **D** CT scan 16 months after SBRT shows appearance of pleural effusion and a bulging margin. **E** CT scan 22 months after SBRT shows further increases in the size of the consolidation. A bulging margin is noted

In this study, we found four clues for detecting local recurrence on CT. First, a bulging margin generally appears on the follow-up CT scan of a patient with a local recurrence in contrast to those without local recurrence, in whom margins are usually linear or concave although conformity to the portal is not identified. We think that an expanding nature of the recurrent tumor is reflected in the CT appearance. In this study, nonrecurrence opacities, including radiation pneumonitis, tend to show linear or concave margins regardless of using a complex multicoplanar irradiation technique. We think that inflammatory changes of radiation pneumonitis spread along existing interlobular septa.

The second clue is the disappearance of air bronchograms during the follow-up CT in patients with tumor recurrence. Bourgouin et al. reported that air bronchograms were frequently seen with radiation fibrosis.[6] In our study as well, air bronchograms were common findings on follow-up CT examinations even in patients with local recurrence. However, in those with local recurrence, air bronchograms subsequently disappeared on serial CT examinations.

Third, all patients with local recurrence had pleural effusion, which usually increasing with time, whereas pleural effusion was seen in only 23% of the patients without local recurrence. Koenig et al. reported CT findings of radiation injury of the lung after three-dimensional conformal radiation therapy and documented that no patient had pleural effusion after radiotherapy.[13] We think that the presence of pleural effusion is not specific for local recurrence as it can also appear as a result of radiation-induced pleuritis. However, pleural effusion might be a sensitive finding for local recurrence. In one of the five patients with local recurrence, the effusion was confirmed to be malignant. However, we still cannot conclude that the pleural effusion always indicates pleural carcinomatosis.

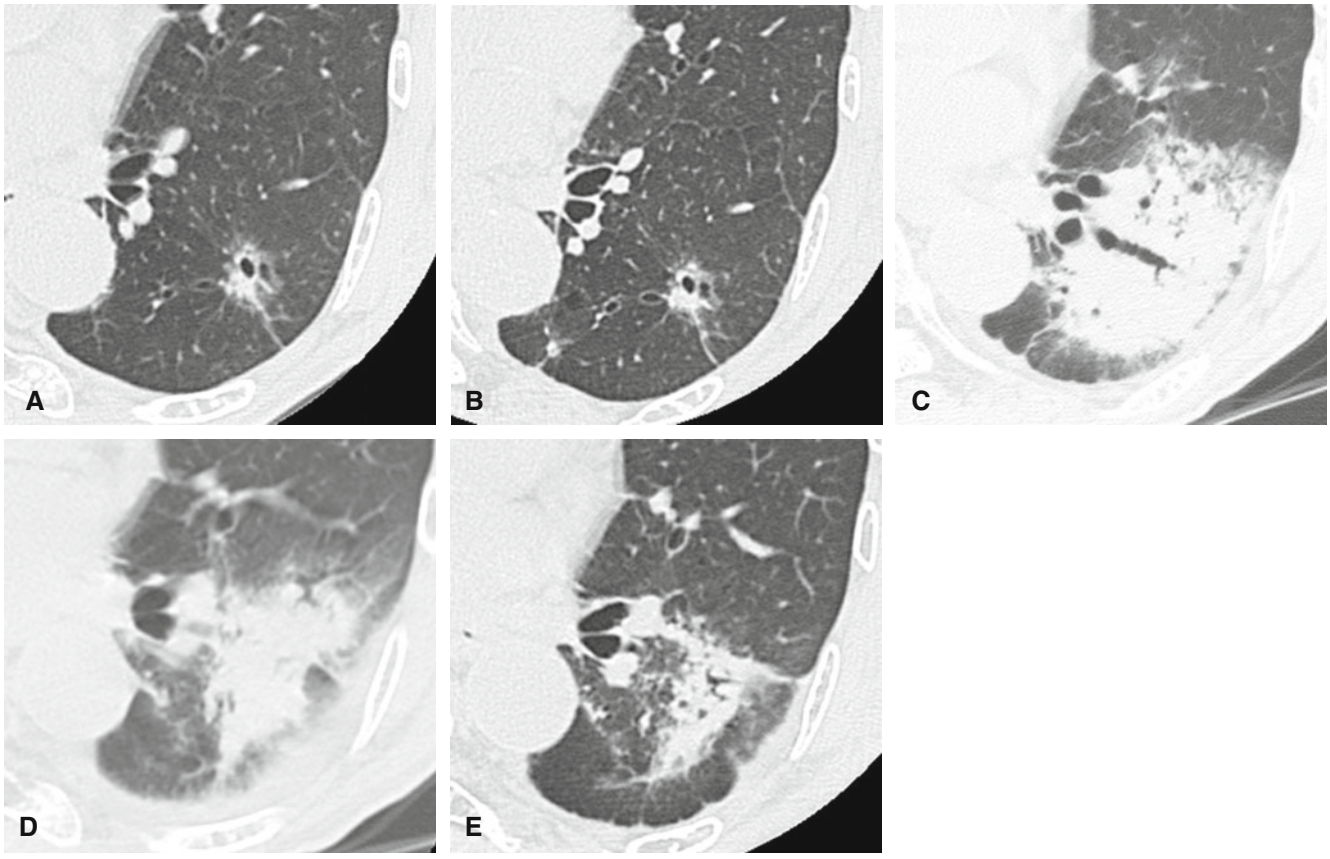

Fig. 3. A 75-year-old man had lung adenocarcinoma without local recurrence. **A** Axial CT scan before SBRT shows a lung carcinoma in the left lower lobe. **B** CT scan 1 month after SBRT shows no marked change. **C** CT scan 5 months after SBRT shows a rapid increase in the size of the consolidation, in which air bronchograms are observed. **D** CT scan 9 months after SBRT shows preservation of the linear margin. **E** CT scan 13 months after SBRT shows a decrease in the size of the consolidation

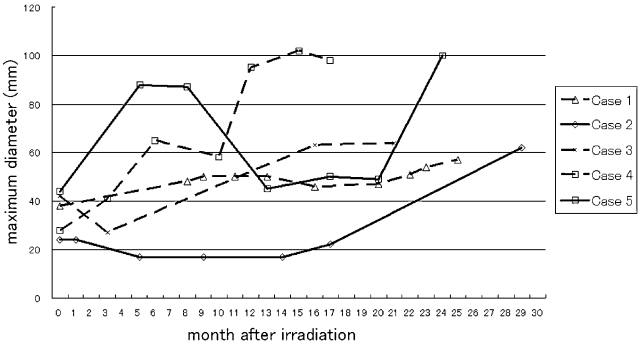

Fig. 4. Changes in the maximum diameters of the opacities during the follow-up period in patients with local recurrence

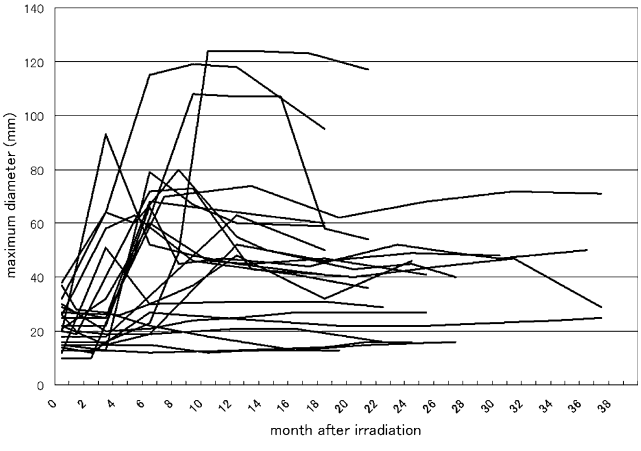

Fig. 5. Changes in the maximum diameters of the opacities during the follow-up period in patients without local recurrence

Fourth, the size of the radiation-induced pulmonary parenchymal change did not increase after 12 months from the completion of SBRT, whereas recurrent tumors continued to grow even after 12 months. The size of the abnormal opacity did not increase in all cases without local recurrence in our study. Takeda et al. also documented that the abnormal opacity after SBRT was stable after 12 months in patients without recurrence.[12] We think that the increased size of the opacity after 12 months is the most reliable indicator of local recurrence.

Recurrent tumors generally had these four features. Only one patient lacked the appearance of a bulging margin. We think that recurrent tumors after SBRT have similar appearances, as shown in our study. In addition, the disappearance of air bronchograms and emergence of pleural effusion tended to appear early during the follow-up period, usually within 12 months after SBRT. Therefore, these finding might be valuable for early detection of local recurrence.

We also found that the presence of the angiogram sign, or inhomogeneity of contrast enhancement, was of no help in distinguishing between local recurrence and radiation-induced changes. We do not understand why the angiogram sign, a hallmark of the preservation of underlying pulmonary architecture, can persist even in locally recurrent tumors. It is possible that a hard, fibrous framework produced by radiotherapy prevents the destructive growth of the recurrent tumors. Another possible explanation is that recurrent tumors might have lepidic growth as seen with bronchioloalveolar cell carcinoma. This hypothesis is supported by the fact that well-differentiated tumors are generally resistant to radiotherapy. Based on these results, we could say that contrast enhancement may be omitted in the evaluation of local recurrence, although it still seems to be useful in the assessment of mediastinal or hilar lymph node recurrence or liver metastasis.

Our study had limitations. First, the follow-up period was too short to judge definitively that there was no local recurrence. Therefore, the cases we regarded as free from local recurrence may have potential local recurrence, which may affect the CT appearance. These finding were not clarified from our results. Second, as the number of the cases with local recurrence was small, we did not employ statistical analysis. Therefore, our results are not supported by statistical evidence. Further study is needed with a larger number of patients and longer follow-up period to overcome these limitations. Nevertheless, the relatively uniform CT appearances of local recurrence after SBRT for NSCLC seen from our data can be useful for suggesting the possibility of local recurrence.

Conclusion

During follow-up CT examinations after SBRT for stage I lung cancer we found four clues that suggest the possibility of local recurrence: (1) appearance of a bulging margin; (2) disappearance of air bronchograms; (3) appearance of pleural effusion; and (4) an increase in the size of the abnormal opacity after 12 months. The presence of these findings warrants needle biopsy or thoracocentesis.

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