TABLE 4. Reports of Stereotactic Radiotherapy for Stage I Non-small Cell Lung Cancer

Author (ref.)	No. of Patients	Total Dose* (Gy)	Single Dose* (Gy)	BED† (Gy)	Median Follow-up (mo)	Local Progression, %	3-yr Overall Survival, %
Uematsu et al.[3]	50	72	7.2	124	60	6	66
Nagata et al.[4]	42	48	12	106	52	3	82
Fukumoto et al.[5]	17	48–60	6–7.5	99–137	24	6	NA
Onishi et al.[6]	28	72	7.2	124	24	8	75
Hof et al.[19]	10	19–26	19–26	55–94	15	20	NA
McGarry et al.[20]	47	75	25	263	15	13	NA
Wulf et al.[21]	12	26–57	19–26	94–165	11	5%	NA

BED, biologically effective dose; NA, not assessed.
*Stereotactic radiotherapy dose is calculated at the isocenter.
†BED (α/β = 10) recalculated at the isocenter.

results of ongoing phase II studies on SRT for stage I NSCLC conducted in Japan (12 Gy × 4 = 48 Gy prescribed to the isocenter) and the United States (20 Gy × 3 = 60 Gy prescribed to cover 95% of the PTV).

The 5-year overall survival rate for medically operable patients with HypoFXSRT is encouraging (Table 6). Representative 5-year overall survival rates for clinical stage IA and IB with surgery range from 61% to 72% and 40% to 50%, respectively.[23–25] According to our data, the survival rate for SRT was not worse than that for large surgical series. Furthermore, concerning toxicity, approximately 3% of patients died as a result of surgery, and chronic morbidity occurs in 10% to 15% of patients after surgery.[26] HypoFXSRT is much less invasive than surgery, and it is postulated that SRT will become a major treatment choice for stage I NSCLC, at least for medically inoperable patients.

TABLE 5. Comparison of the Results between the Multi-institutional Study and the Uematsu et al. Study

	Uematsu et al. [3]	Multi-institutional
Total no. of cases	50	215
T1N0M0	24	141
T2N0M0	26	75
Follow-up duration, mo (median)	22–66 (36)	2–128 (38)
Local control, %	94	90
Regional lymph nodes metastases, %	4	7
Distant metastases, %	14	19
Grade ≥3 toxicity, %	0	3
3-yr overall survival rate, %	66	64
3-yr cause-specific survival rate, %	88	83
5-yr overall survival rate, %	55	55
5-yr cause-specific survival rate, %	81	77
3-yr overall survival rate in operable patients, %	86	82
5-yr overall survival rate in operable patients, %	77	72

TABLE 6. Comparison of 5-Year Overall Survival Rate between Stereotactic Radiotherapy and Surgery

Stage	Author			
	Mountain[23]*	Naruke et al.[24]*	Shirakusa and Koybayashi[25]*	Onishi†
IA	61%	71%	72%	72%
IB	40%	44%	50%	66%

*Surgery.
†HypoFXSRT presented here.

Multi-institutional phase II studies of SRT for stage I NSCLC have been started in Japan (JCOG0403)[27] and the United States (RTOG0236).[28] However, it will take several years to obtain conclusive results, and an inevitable selection bias exists in comparing SRT with surgical series for patients in retrospective or phase II studies.

Although the differences in techniques and schedules of the institutions enrolled in this study may be large, it is meaningful that a safe, effective BED was suggested because the optimal dose-fraction schedule of SRT for stage I NSCLC is not known. Furthermore, this is the only report that gives the results of SRT for a large number of medically operable stage I NSCLC patients. Based on our excellent SRT results, it is arguable that a phase III study comparing surgery and SRT for medically operable patients is warranted. However, it is very difficult to perform a phase III study because most patients will opt for less invasive therapy such as SRT. We need much more experience and must study more patients with a longer follow-up duration to establish a safe, effective irradiation method that will instill both medical and social confidence in SRT for treatment of stage I NSCLC.

When we compare the results of conventional RT and surgery with those of HypoFXSRT, we conclude that HypoFXSRT has the following benefits for stage I NSCLC. First, HypoFXSRT is a safe and promising treatment modality. Second, the local control and survival rates are superior to those of conventional RT. Third, HypoFXSRT should be a standard of care for medically inoperable patients. Fourth, HypoFXSRT should be randomly compared with surgery for medically operable patients. Finally, we need additional experience with a longer follow-up duration to conclusively validate these points.

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Lung cancer SBRT

Differences in the definition of internal target volumes using slow CT alone or in combination with thin-slice CT under breath-holding conditions during the planning of stereotactic radiotherapy for lung cancer

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Abstract

Purpose: To investigate how the delineations of the internal target volume (ITV) made from 'slow' CT alter with reference to 'thin-slice' CT.

Materials and methods: Thin-slice CT images taken under breath-holding conditions and slow CT images taken under shallow-breathing conditions (8 s/image) of 11 lung cancers were used for this study. Five radiation oncologists delineated ITV of the 11 lesions using slow CT images (ITV1), and then redefined them with reference to thin-slice CT images (ITV2). SD-images (standard deviation image) were created for all patients from ITV images in order to visualize the regional variation of the ITVs.

Results: The mean value of ITV2 was smaller than that initially defined by ITV1. There was no significant change in ITV1 and ITV2 between operators with regard to standard deviation in volume. There was a significant difference in the distribution of the ratio of ITV1 to ITV2 obtained on thin-slice CTs between cases with and without ground glass opacity. In cases without ground glass opacity there was a tendency for ITV2 to have a smaller volume than ITV1.

Conclusions: Combined use of slow CT and thin-slice CT in delineation of ITV contours appeared to be useful in making adjustments for obscured tumor images caused by respiratory movement.
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Keywords: Stereotactic radiotherapy; Lung cancer; Target volume delineation; Slow CT

Stereotactic irradiation can deliver high radiation doses to localized lesions with great accuracy, allowing a strong anti-tumoral effect while lessening radiation injury to normal tissues. Although historically it has been applied to the treatment of small intracranial tumors with excellent results [1], its indications have been widened recently to include the treatment of lesions of the trunk [2–6]. Defining the extent of the area to be targeted is crucial for this treatment. Inadequate target volumes alter the dose distribution to the lesion, as well as to the surrounding normal tissues, and may therefore lead to inadequate therapeutic outcomes. For tumors of the trunk, such as lung cancer, target tumors move with the respiration-induced motion of the thorax or diaphragm [7].

If a large internal margin (IM) is defined, excessive doses of irradiation may be delivered to normal tissues. Conversely, if small internal target volume (ITV) is defined, potentially insufficient irradiation doses are delivered to the tumors, as tumor mobility may extend beyond the previously defined target region [8–10].

Although CT data acquired under breath-holding conditions can be used to visualize tumor shape, it cannot be used directly to determine the planning target volume, due to movement during the respiratory cycle or for other reasons. Even with CT images acquired under free breathing, limited tumor trajectory volumes can be detected if conventional short scanning times are used [11].

Four-dimensional CT (4D CT) has been used to investigate the motion of the anatomical structure and the tumor [12–16]. This technique is superior for detecting respiration-induced, three-dimensional motion of the tumor and will become the dominant technique in the near future [12–16]. However, it requires multi-detector low CT (MD-CT) as well as a device that can detect respiratory motion [17].

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The visualization of respiration-induced tumor mobility has been attempted using CT scans taken with very long scan times per slice (slow CT) [18–20]. However, this technique can fail to visualize fine structures surrounding solid parts of the tumor [21]. There is a possibility that more precise definitions of target volumes could be achieved by combining thin-slice CT obtained under breath-holding conditions that are capable of visualizing fine tumor shape, and slow CT capable of visualizing the entire volume of the tumor trajectory. The purpose of our study was to investigate how the delineations of ITV made from slow CT alter with reference to thin-slice CT.

Materials and methods

Five experienced radiation oncologists were selected as operators for CT images from 11 patients with T1 to T3 lung cancer (mean tumor diameter = 2.8 ± 1.0 cm) who were scheduled to undergo hypofractionated stereotactic radiotherapy. The locations of the lesions are shown in Fig. 1. Thin-slice helical CT under conventional breath-holding conditions and slow CT under steady respiration were performed using a CT scanner (X-Vigour, Toshiba, Tokyo, Japan) on all 11 patients. Thin-slice CT scanning was conducted with a slice thickness of 2 mm (pitch 1:1, 120 kVp, and 200 mA) at 1 s per image under breath-holding conditions. Thin-slice CT series were taken for the target lesion and the adjacent range during a single breath-hold, with the inspiration levels being approximately the mid point of shallow inspiration and shallow expiration following training of shallow and regular respiration of the patients.

For slow CT scanning, patients were instructed to breathe shallowly. If fluoroscopic observation revealed that tumor mobility exceeded 1 cm in the cranio-caudal direction, a corset was used to inhibit movement of the abdominal wall and diaphragm. Slow CT scans were performed between 20 mm from the cranial and 20 mm from the caudal tumor edge, with a slice thickness of 2 mm, at 120 kVp and 400 mA. Scan time per image was 8 s, which was longer than the duration of one respiratory cycle.

Definition of target delineation

Each operator independently defined the target delineation from the CT images using the radiation therapy planning system (RTPS; XiO, CMS, St. Louis, Missouri). To avoid discrepancies in the appearance of ITV depending on different window levels, targets were delineated under the lung window setting with a window width of 2000 HU and window level of −700 HU for all experiments.

Delineation of ITV with slow CT alone (ITV1)

As the first step, the ITV outline image was delineated using slow CT (ITV1). No particular common guideline criteria were laid down at this point regarding the degree to which speculation, atelectasis and so on were to be included, with judgment instead being left to the discretion of each individual operator.

Second delineation of ITV with slow CT, while referring to thin-slice CT (ITV2)

Following the delineation of ITV1 as described above, ITV outline was delineated by using slow CT images once again. While simultaneously referring to thin-slice CT images taken under breath-holding conditions, the previously created ITV was modified with the aid of RTPS (ITV2).

The thin-slice CT images taken under breath-hold conditions were displayed on a computer display adjacent to the display of RTPS. During the delineation of ITV2, the operators were allowed to scroll both the displays when required.

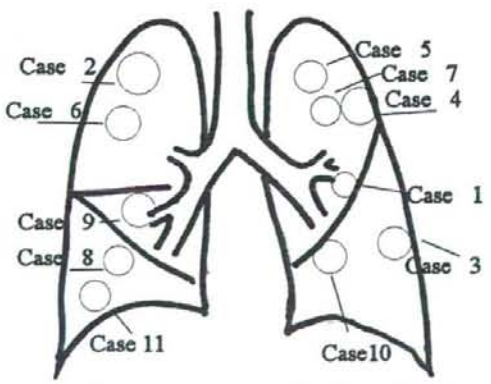

Fig. 1. Calculation of delineated target area and volume. Localizations of lung tumors in cases 1–11 are shown in the figure. The numbers of the circles indicate the case numbers. The position and size of each tumor are as follows. Case 1: lingula of left lung, T1 Φ2 cm, case 2: upper lobe of right lung, T3 Φ4 cm, case 3: lower lobe of left lung, T1 Φ2 cm, case 4: upper lobe of left lung, T2 Φ4 cm, case 5: upper lobe of left lung, T2 Φ3 cm, case 6: upper lobe of right lung, T2 Φ3 cm, case 7: upper lobe of left lung, T1 Φ2 cm, case 8: lower lobe of right lung, T2 Φ3 cm, case 9: middle lobe of right lung, T3 Φ3 cm, case 10: lower lobe of left lung, T2 Φ3 cm, case 11: lower lobe of right lung, T1 Φ2 cm.

The slice positions of both the breath-holding CT and slow CT may not correspond with each other, as the inspiration level of the former CT series was not necessarily totally reproducible or stable. Therefore, adjustments of the two CT series were made according to the view of the operators, based on careful observation of the detailed morphological characteristics of the lesion and other structures such as vessels or bronchi.

The number of pixels included inside the ITV1 delineations was counted to obtain the tumor area for each slice. The ITV1 was then calculated from the sum of the areas multiplied by the slice thickness. ITV2 was calculated in the same way.

Statistical images

To visualize the differences in individual target definitions between operators, the extent of target delineation was statistically analyzed pixel by pixel. Prior to statistical analysis, contour shapes were converted to binary images by replacing each pixel inside and outside the delineated area with pixel values 1 and 0, respectively.

The standard deviation (SD) of each pixel was then calculated using the formula shown below. Statistical images for ITV1 and ITV2 were generated from the binary images of all patients using the programming language Matlab (Ver. 2006a, The MathWorks, Inc., Natick, MA, USA).

SD-image (standard deviation image):

$$\text{Pixel value: } \sigma = \frac{1}{N}\sum_{i=1}^{N}(Z_i - \mu)$$

N: number of operators;
i: operator;
Z_i: pixel value of operator i for the corresponding pixel;
μ: mean of pixel values obtained by all operators.

Results

Comparison of ITV

The mean and standard deviation of ITVs amongst all operators for each case are shown in Table 1. The ratio of ITV2 to ITV1 was used in order to examine the changes between ITV1 defined with slow CT alone, and ITV2, which is a modification of ITV1 with reference to thin-slice CT.

Table 1
Mean volume

	ITV1	ITV2	ITV2/ITV1	GGO
Case 1	2.9 ± 1.4	3.0 ± 2.0	1.03 ± 0.20	(+)
Case 2	46.2 ± 7.5	35.6 ± 4.3	0.77 ± 0.09	(−)
Case 3	3.9 ± 0.4	4.2 ± 1.2	1.06 ± 0.24	(+)
Case 4	48.2 ± 6.0	47.1 ± 4.9	0.98 ± 0.02	(+)
Case 5	11.3 ± 2.5	11.5 ± 4.6	1.02 ± 0.27	(+)
Case 6	17.2 ± 1.5	15.4 ± 1.5	0.90 ± 0.04	(−)
Case 7	8.0 ± 2.9	6.0 ± 1.6	0.74 ± 0.19	(−)
Case 8	16.4 ± 4.4	12.7 ± 3.6	0.78 ± 0.27	(−)
Case 9	21.1 ± 5.4	17.0 ± 3.5	0.80 ± 0.24	(+)
Case 10	11.2 ± 3.2	8.6 ± 3.2	0.77 ± 0.12	(−)
Case 11	25.4 ± 8.9	18.7 ± 9.4	0.73 ± 0.28	(−)

ITV, internal target volume; GGO, ground glass opacity; ITV1, ITV delineated using slow CT only; ITV2, ITV delineated using slow CT images, referring to breath-holding thin-slice CT.

The ITVs were compared by two-way analysis of variance (ANOVA) to estimate the effect of the ITV delineation among operators and cases. While there was no significant difference between the five operators for the size of ITV delineations, there was a significant difference between ITV1 and ITV2 volumes ($p < 0.01$). The ITV2 volumes were on average 18% smaller than the ITV1 volumes (Table 1).

A radiologist (S.S.) independently evaluated each case and categorized them into those with ground glass opacity in the surrounding area of the tumor and those without ground glass opacity (Fig. 2). The definitions of ground glass opacity were made using thin-slice breath-hold CT. There was a significant difference in the ratio of ITV2 to ITV1 between the cases with and without ground glass opacity (Fig. 3). That is, there were no evident decreases in target

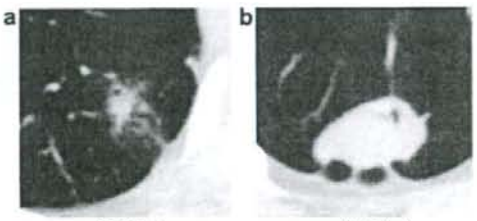

Fig. 2. Example of a case with ground glass opacity (a), and a case without ground glass opacity (b).

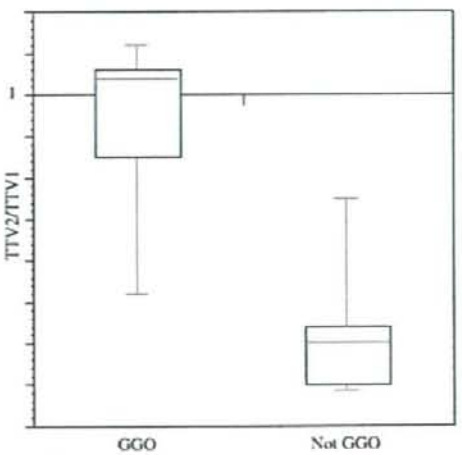

Fig. 3. The distribution of the ratio of ITV2 to ITV1 between the cases with and without ground glass opacity. There was a clear tendency for smaller ratio of ITV2 to ITV1 in cases without ground glass opacity than in cases with ground glass opacity.

volume when the operators refer to thin-slice CT in cases with ground glass opacity.

We performed more detailed analyses of target delineations by means of SD-images (Figs. 4 and 5). Although there were differences in the area of tumor delineation between ITV2 and ITV1 in many cases, relatively small changes in the distribution pattern of SD values were observed. The analyses indicated that there were some cases in which the reference to thin-slice CT images had influenced the target outline recognition (Fig. 5). In this case (case 10), the structure seen as a spiculation on the left lower site of the tumor shown on the slow CT image corresponded to the region with high SD values for ITV1. A higher value meant there was a greater degree of inconsistency between the decisions of the operators as to whether or not the area should have been included in the ITV. The regions with high SD values for ITV1 were excluded from the target delineations by the operators in ITV2 (in which thin-slice CT of the same position was considered). The thin-slice CT apparently revealed this region to be a part of the bronchi. Table 2 shows the

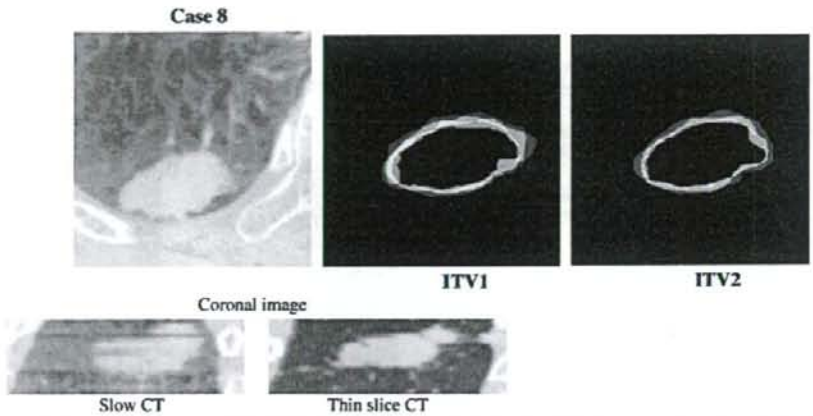

Fig. 4. SD-image (ITV1, ITV2) for case 8. Highest pixel SD values are shown in yellow, followed by green, and blue in descending order. The central part of the target (shown as black) means that all operators recognized it as the target volume. The outer part of the target (also shown as black) means that no operators recognized it as the target volume.

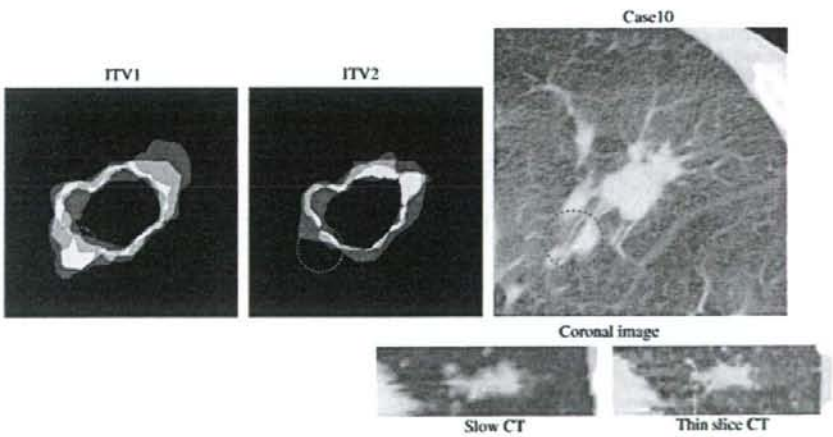

Fig. 5. SD-image (ITV1, ITV2) for case 11. The regions with high SD values for ITV1 were excluded from the target delineations by the operators in ITV2. The thin-slice CT apparently revealed this region to be a part of the bronchi.

Table 2
Volumes that all operators recognized as the internal target volume

	ITVc1	ITVc2	ITVc1/ITV1	ITVc2/ITV2
Case 1	1.3	1.1	0.47	0.38
Case 2	28.7	23.6	0.62	0.66
Case 3	2.9	2.4	0.73	0.57
Case 4	37.2	34.7	0.77	0.74
Case 5	6.9	6.2	0.61	0.54
Case 6	12.1	11.0	0.71	0.72
Case 7	4.4	3.7	0.55	0.63
Case 8	8.7	8.4	0.53	0.66
Case 9	11.7	11.1	0.55	0.65
Case 10	5.3	5.1	0.48	0.60
Case 11	12.1	7.0	0.48	0.38

ITVc, the volume that all operators recognized as the internal target volume; ITVc1, ITVc delineated using slow CT only; ITVc2, ITVc delineated using slow CT images, referring to breath-holding thin-slice CT.

volumes that all the operators judged as the target volume, ITVc1 or ITVc2 (i.e., the union of all target volumes determined by operators) in each case.

Discussion

To minimize the effect of respiratory motion, stereotactic radiotherapy for lesions of the trunk has been conducted using various techniques, including breath-holding [22,23], respiratory-gated tracking [24,25] and real-time tumor tracking [26,27]. The ICRU (International Commission on Radiation Units and measurements) report 62 [28] proposed a definition for four tumor volumes, gross tumor volume (GTV), clinical target volume (CTV), internal target volume (ITV), and planning target volume (PTV). The term ITV was adopted into the ICRU-62 report and was taken to represent the CTV plus the Internal Margin (IM), and was intended to compensate for movement and variation in site, size, and shape of organs and tissues contained within or adjacent to the CTV. In a review article in 2004, Purdy discussed some of the limitations and potential pitfalls of the recommendations contained in the current ICRU Reports 50 and 62, particularly in regard to issues of organ motion [29].

Free breathing irradiation

Although the planning target volumes tend to be larger, irradiation under free breathing is a simple and reliable method, which can be performed without the need for special equipment to detect respiratory motion, providing that appropriate internal margins are used. However, the question of how to determine these internal margins remains a difficult problem [29,30]. If large margins are used, then the irradiation volume increases, resulting in excessive radiation exposure to normal tissues. However, if small margins are used, then it becomes unlikely that the periphery of the target will receive a sufficient radiation dose. More sophisticated margin recipes to create the PTV have been proposed by several investigators [31,32].

While fluoroscopy-based observation of the tumor trajectory is another possible approach to define the margin, margins based on fluoroscopically two-dimensional tumor trajectories may not adequately cover substantial tumor mobility, as tumor motion associated with respiration occurs not only in the cranio-caudal direction but also in the antero-posterior direction.

4D CT

4D CT (acquisition of a sequence of CT image sets over consecutive segments of a breathing cycle) [12] is able to demonstrate both respiratory and cardiac motion and has been applied to the treatment planning of radiotherapy. 4D CT can provide three-dimensional data on tumor position at several points during the breathing cycle, with a somewhat reduced temporal resolution compared to conventional CT, thus providing a compromise between the high-quality time resolution of a fluoroscopic study and the detailed 3D information of a CT scan. Although it requires dedicated devices with which conventional radiotherapy departments are not commonly equipped, this technique has a fundamental advantage in terms of detecting tumor motion [33].

Slow CT

Lagerwaard et al. used a slow CT technique with a scanning time of 4 s per slice, in addition to conventional CT for radiotherapy planning, in an attempt to generate more accurate target volumes during shallow respiration. Based on the images obtained, they reported being able to define target volumes with high reproducibility and reliability without the need for specialized equipment [34,35]. De Koste et al. analyzed seven lung tumors located in the lower lobes, which is the most mobile location [35]. They showed that slow CT scans generated larger and more reproducible target volumes than rapid planning scans. They proposed PTVs derived from a single slow CT scan plus a 5-mm margin to represent the "optimal" PTV, and concluded that a full rapid scan of the entire thorax and a limited slow scan were necessary for treatment planning in patients with peripheral lung cancers. Wurstbauer et al. reported that the use of slow CT enabled the drawing of tighter margins in the planning of external beam treatment for lung cancer [36].

Takeda et al. also performed slow CT at a rate of 8 s per slice in order to define an optimal ITV that included the entire tumor trajectory volume [21]. However, these scanning strategies were devised to visualize the average density of the anatomical structures in the tumor trajectory, and therefore that movement during a long scanning time can lead to obscure images of the tumor and adjacent anatomical structures such as bronchi or vessels. Thus, slow CT is generally thought to be unable to visualize complicated tumors or areas of fine spiculation, consolidation, or emphysematous changes with any degree of accuracy, which suggests that optimal ITV definition may not always be possible with the use of slow CT alone.

Based on target tumor delineation, differences between the spatial distribution of ITV1 and ITV2 were assessed to investigate the impact on ITV delineation of referring to thin-slice CT under breath-holding conditions.

A comparison of the volumes of ITV delineated with slow CT alone, and ITV determined using thin-slice CT showed that the latter was smaller with regard to target volume overall. It is thought that this is related to blurring of the image, which occurs with slow CT under free breathing conditions, due to the respiration-induced motion effect of the tumor, thorax, bronchus and blood vessels. The outline of the tumor periphery cannot be visualized clearly with slow CT. Differentiation of normal structures (i.e., blood vessels, etc.) from tumors was often impossible. It is assumed that wider target delineations were preferred by the operators during the ITV1 definitions, in order to avoid a situation in which the tumor was no longer included in the target volume.

By referring to breath-holding CT images, the detailed structure of the tumor periphery can be visualized with increased clarity. It is thought that operators were able to recognize structures, within the region indistinct with slow CT, that do not need to be included as part of the target volume.

On the other hand, there were also cases in which ITV2 became larger than ITV1, such as in cases 1, 3 and 5. By examining the characteristics of the images in cases such as these, we were able to conclude that when a large amount of ground glass opacity was included within the tumor there was a tendency for ITV2 to be larger than ITV1, or for it not to get smaller.

It would be fair to say that by referring to thin-slice CT, there is a possibility that ITV may be delineated as smaller than necessary. However, creating a standard that would serve as the "correct way" to carry out ITV delineation is an extremely difficult and almost unsolvable problem. For this reason, this study did not fully examine the question as to whether or not the change corresponded to the "real" lesion confirmed by pathological findings. However, this study indicated there was a tendency for ITV2 to have a smaller volume than ITV1, especially in cases without ground glass opacity.

Breath-hold CT is considered to be a standard for target delineation for small lung tumors because of its ability to show detailed structures if internal margins and reproducibility of the target position are not taken into account. On the other hand, slow CT has superior reproducibility for target positioning and detecting the range of interfractional motion.

Using thin-slice breath-hold CT as a planning CT may cause systemic errors in target positioning, as the inspiration level at breath-hold is not always reproducible [32]. However, our proposed technique uses thin-slice breath-hold CT as a reference for observing the detailed structure of the tumor peripheral and does not use it as a reference for the "position" of the tumor. For these reasons, we consider it reasonable to use breath-hold CT with slow CT for treatment planning of small lung lesions.

Regarding the standard deviation (SD) of target volume of all the operators, there was no tendency towards a clear increase or decrease between the SDs for ITV1 and ITV2. In other words, referring thin slice, high-resolution CT did not improve the variation in target volume recognition between the operators.

The regional analyses with SD-images indicated that there were some cases in which the reference to thin-slice CT images influenced target outline recognition (Fig. 5). Trying to determine the proportion of actual tumor from the opacity visualized in the original CT image is fraught with great difficulty, and it is not possible to prepare a standard outline delineation. It is thought that the variation observed among operators is due to uncertainty regarding outline delineation. Although it is necessary to make comparisons with more detailed pathological findings in order to eliminate variation among operators, such comparisons fall outside the scope of this study.

While there is no fixed standard for GTV delineation among radiation oncologists, reference to thin-slice CT images may be a useful strategy to correct information in images that are unclear due to respiratory movement, thereby improving the accuracy of ITV description.

Positron emission tomography (PET) or single photon emission tomography (SPECT) is usually performed with longer data acquisition time than CT. Therefore, these techniques may provide a more accurate representation of the GTV encompassing motion of such tumors and therefore have the potential to provide patient-specific motion volumes for an individualized ITV [29]. However, to date the resolution of PET and SPECT may be insufficient for delineating small lung lesions without using CT. Future development of these modalities may widen their application for delineating small lung lesions.

Conclusion

We compared target delineation for lung tumors with slow CT alone, and then with slow CT and high-resolution thin-slice CT. Standard deviation images were created from the delineations of each operator in order to analyze the inter-operator differences for individual structures. The use of slow CT images together with thin-slice CT would be a useful technique for achieving more elaborate treatment plans concerning fine structures in the tumor peripheral area. With slow CT alone, there is a possibility that tiny lesions in the tumor area or ground glass opacities may be delineated inaccurately. Furthermore, there is a tendency to erroneously incorporate surrounding structures such as blood vessels in the target volume.

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CLINICAL INVESTIGATION **Lung**

HISTOPATHOLOGIC CONSIDERATION OF FIDUCIAL GOLD MARKERS INSERTED FOR REAL-TIME TUMOR-TRACKING RADIOTHERAPY AGAINST LUNG CANCER

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Purpose: Internal fiducial gold markers, safely inserted with bronchoscopy, have been used in real-time tumor-tracking radiotherapy for lung cancer. We investigated the histopathologic findings at several points after the insertion of the gold markers.
Methods and Materials: Sixteen gold markers were inserted for preoperative marking in 7 patients who subsequently underwent partial resection of tumors by video-assisted thoracoscopic surgery within 7 days.
Results: Fibrotic changes and hyperplasia of type 2 pneumocytes around the markers were seen 5 or 7 days after insertion, and fibrin exudation without fibrosis was detected 1 or 2 days after insertion.
Conclusions: Because fibroblastic changes start approximately 5 days after gold marker insertion, real-time tumor-tracking radiotherapy should be started >5 days after gold marker insertion. © **2008 Elsevier Inc.**

Real-time tumor-tracking radiotherapy, RTRT, Four-dimensional radiotherapy, Fiducial gold marker, Preoperative marking, Video-assisted thoracoscopic surgery.

INTRODUCTION

For radiotherapy (RT) of mobile lesions, such as lung tumors, it has been necessary to develop four-dimensional planning systems and improve irradiation synchrony with target motion (1, 2). We have previously shown differences in tumor location caused by respiratory conditions or unexpected changes in baseline values (3, 4) and reported on the utility of fiducial gold markers near lung tumors for real-time tumor-tracking RT (RTRT) (5). At our institution, we have used 1.5-mm-diameter fiducial gold markers, inserted by bronchoscopy (6, 7). We previously analyzed the reliability of the fiducial markers by measuring the distance between the internal markers and the chest wall using computed tomography and reported on the relationship between the interval after insertion and the risk of dislocation of the fiducial marker from its initial position (8). We found that the rate of the marker moving from its inserted position decreased with time after insertion and suggested that a biologic reaction might be the reason for this phenomenon. We have also suggested that long-term changes in the distance between the marker and the chest wall on transaxial computed tomography would result from a decrease in tumor size or pulmonary fibrosis after RT (8). These speculations, however, were not determined from the results of histopathologic examinations. To find answers to these questions, we investigated the histopathologic findings at several points after the insertion of gold markers.

METHODS AND MATERIALS

Patients

Between January 2005 and December 2005, 16 gold markers were inserted into 7 patients (4 women and 3 men; average age, 59.4 years; standard deviation, 12.8; range, 37–78 years), who subsequently underwent partial tumor resection using video-assisted thoracoscopic surgery. The interval between marker insertion and surgery was 1–7 days. The institutional ethics committee of Hokkaido University School of Medicine approved this study. All subjects were provided with a detailed description of the study, and all patients provided written informed consent.

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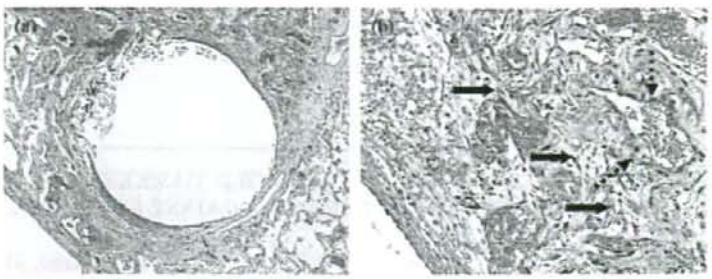

Fig. 1. Microscopic findings in tissue section received 5 days after gold marker insertion. Original location of gold marker detected as round cavity. Blue indicates dye used to mark location of marker. Hematoxylin-eosin stain, original magnification (a) ×4 and (b) ×20. Round cavity in which gold marker had been placed was accompanied by thin layer of fibrosis with active fibroblastic proliferation (black arrows) and hyperplasia of type 2 pneumocytes (black dotted arrows). Tissue section of patient whose gold marker was inserted 7 days before surgery had similar features.

Insertion of gold marker

Details on the technique for inserting the 1.5-mm-diameter gold markers into the lung have been previously reported (6). In brief, special equipment that was developed for the insertion of gold markers using bronchoscopy was used to insert the markers into small bronchi with a diameter of ≤1.5 mm (Olympus, Tokyo, Japan).

Histopathologic analysis

The resected specimens were fixed in formalin for 4–6 days. The 4-μm-thick sections were stained with hematoxylin-eosin and Elastica-Masson.

RESULTS

Of the 7 patients with preoperative markings, gold marker insertion was performed 1 day before surgery in 4 patients, 2 days before in 1 patient, and 5 or 7 days before surgery in 2 patients. The histologic analysis revealed slight hemorrhaging in the terminal bronchi and alveolar spaces and mild fibrin exudation around the markers in the 5 patients who underwent surgery 1 or 2 days after marker insertion. Of the 2 patients who underwent partial resection 5 or 7 days after markers insertion, the round cavity in which the marker had existed was accompanied by slight fibrotic changes and hyperplasia of type 2 pneumocytes (Fig. 1). In contrast, the tissue sections from the 5 patients with a 1- or 2-day interval showed no such findings around the cavities where the markers were originally located.

DISCUSSION

This is the first report of the histopathologic findings in pulmonary parenchyma after marker insertion. Although we previously reported that fiducial gold markers were useful and clinically safe in RTRT for three-dimensional calculations, the fiducial gold markers had a tendency to move within the first week of insertion compared with their location in the second week after insertion and thereafter (8). In the present study, 5 or 7 days after insertion, a slight fibrosis and hyperplasia type 2 pneumocytes had occurred. If these changes occurred in a peripheral bronchus into which a marker had been inserted, the bronchial lumen could be narrowed, preventing the marker from dropping. Although it is not known whether it is a direct effect of the marker itself or a secondary reaction to its insertion, such as hemorrhage or parenchymal destruction, fibroblastic changes could be an important step in limiting the motion of inserted markers. These results suggest that we should choose an appropriate point for starting RTRT (*i.e.*, >5 days after the insertion of gold markers).

To investigate the histopathologic findings of long-term follow-up after insertion of gold markers is another important issue. In our small series of long-term follow-up cases, the marker material seems to be harmless to humans, but additional studies are required to evaluate whether gold markers are really harmless to lung parenchyma after long-term retention.

CONCLUSIONS

Because the fibroblastic changes start approximately 5 days after gold marker insertion, RTRT should be started >5 days after gold marker insertion so that gold marker fixation in the pulmonary parenchyma is complete.

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CLINICAL INVESTIGATION **Lung**

STEEP DOSE–RESPONSE RELATIONSHIP FOR STAGE I NON–SMALL-CELL LUNG CANCER USING HYPOFRACTIONATED HIGH-DOSE IRRADIATION BY REAL-TIME TUMOR-TRACKING RADIOTHERAPY

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Purpose: To investigate the clinical outcomes of patients with pathologically proven, peripherally located, Stage I non–small-cell lung cancer who had undergone stereotactic body radiotherapy using real-time tumor tracking radiotherapy during the developmental period.

Methods and Materials: A total of 41 patients (25 with Stage T1 and 16 with Stage T2) were admitted to the study between February 2000 and June 2005. A 5-mm planning target volume margin was added to the clinical target volume determined with computed tomography at the end of the expiratory phase. The gating window ranged from ±2 to 3 mm. The dose fractionation schedule was 40 or 48 Gy in four fractions within 1 week. The dose was prescribed at the center of the planning target volume, giving more than an 80% dose at the planning target volume periphery.

Results: For 28 patients treated with 48 Gy in four fractions, the overall actuarial survival rate at 3 years was 82% for those with Stage IA and 32% for those with Stage IB. For patients treated with 40 Gy in four fractions within 1 week, the overall actuarial survival rate at 3 years was 50% for those with Stage IA and 0% for those with Stage IB. A significant difference was found in local control between those with Stage IB who received 40 Gy vs. 48 Gy ($p = 0.0015$) but not in those with Stage IA ($p = 0.5811$). No serious radiation morbidity was observed with either dose schedule.

Conclusion: The results of our study have shown that 48 Gy in four fractions within 1 week is a safe and effective treatment for peripherally located, Stage IA non–small-cell lung cancer. A steep dose–response curve between 40 and 48 Gy using a daily dose of 12 Gy delivered within 1 week was identified for Stage IB non–small-cell lung cancer in stereotactic body radiotherapy using real-time tumor tracking radiotherapy.

Real-time tumor-tracking radiotherapy, Stereotactic radiotherapy, Lung cancer.

INTRODUCTION

External beam radiotherapy (RT) using rather a conventional fractionation and total dose has been the standard treatment for Stage I non–small cell lung cancer (NSCLC) in patients who are medically inoperable (1–4). Sibley (5) reviewed clinical data and found that the overall survival rates at 3 years ranged from 17% to 55% using a conventional radical dose and treatment time in conventional RT.

Recently, stereotactic body RT (SBRT) using a high focal dose within a short period for peripheral lung tumors has been reported to produce high local control rates. This treatment has been indicated for Stage I NSCLC and has resulted in survival rates at least as great as those after conventional RT. Hof *et al.* (6) reported a 64% 2-year overall survival rate with a single dose of SBRT. Uematsu *et al.* (7) reported a 66% 3-year overall survival rate. Nagata *et al.* (8) reported an 83% and 72% 3-year overall survival rate for patients with Stage IA and Stage IB, respectively. Onishi *et al.* (9) summarized the results of a Japanese series retrospectively and reported a 47% 5-year overall survival rate. A study from Sweden also showed a 55% 3-year overall survival rate with a high local control rate of 80% (10).

These observations have strongly suggested a steep dose–response curve for the control of NSCLC and resultant survival (11, 12). However, no sufficient dose-response data at the dose level beyond the conventional radiation dose have been available. We have seen high local control rates in retrospective surveys of SBRT for Stage I NSCLC in Japanese

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institutions, but the retrospective nature of the analyses, wide range of dose fractionation, and use of different techniques have prevented us from drawing a dose–response relationship with confidence (9).

We have developed a real-time tumor-tracking RT (RTRT) system and have reported on its reliability and possible uncertainty between 1999 and 2005 (13–17). The appropriate clinical target volume (CTV) margin to cover the gross tumor volume (GTV) and the planning target volume (PTV) margin for the CTV were both critical subjects related to technical developments. During this development stage, we performed a simultaneous dose-finding phase I-II study of high-dose focal irradiation for patients with peripheral NSCLC (18). These confounding variables made it difficult to perform a simple dose-escalation study for the same category of patients. The clinical protocols have had to be revised several times because of the technical and conceptual developments of SBRT during this period.

In this study, we analyzed the clinical outcomes of patients with Stage I NSCLC who underwent SBRT through the RTRT system during this developmental period to shed a light on the dose–response curve of Stage I NSCLC.

METHODS AND MATERIALS

Patients

Between February 2000 and June 2005, 41 patients were diagnosed with pathologically proven Stage I NSCLC and underwent SBRT using the RTRT system at Hokkaido University Hospital. Patients with peripheral tumors, which were located in the lung peripheral to the secondary bronchus, were included. The patient characteristics are given in Table 1. Three patients had a Karnofsky performance status of ≤70. The clinical stage according to the TNM classification of Malignant Tumors, version 6 (19), is given in Table 1. Of the 41 patients, 25 had Stage T1N0M0 and 16 had T2N0M0. The number of medically inoperable patients was 35. The reasons for inoperability were poor lung function in 11 patients, a history of cardiac disease in 9, a history of other cancer in 7, poor renal function in 2, poorly controlled schizophrenia in 1, and old age in 11. No patients received chemotherapy before confirmation of recurrence or metastasis. Follow-up examinations were performed every 3 months in the first year, every 4 months in the second year, and every 6 months thereafter. Patients were examined in the outpatient clinic at the Department of Radiation Oncology and Department of Respiratory Internal Medicine at Hokkaido University Hospital. Acute and late radiation reactions were assessed using the Common Terminology Criteria Adverse Effects, version 3.0. The median follow-up period for patients who were still alive at the last follow-up was 27 months (range, 9–62 months).

Table 1. Patient characteristics

Characteristic	Value
Age (y)	
Median	76
Range	52–85
Gender (*n*)	
Male	28
Female	13
KPS	
Median	90
Range	50–90
T stage (*n*)	
T1	25
T2	16
Pathologic finding	
Adenocarcinoma	30
SCC	10
Large	1
Tumor size (cm)	
Median	2.7
Range	1.0–7.0
Dose (Gy)	
40	13
48	28
Margin	
Wide	31
Narrow	10
Calculation algorithm	
Clarkson	31
Superposition	10

Abbreviations: KPS = Karnofsky performance status; SCC = squamous cell carcinoma.

Radiotherapy

Treatment plans were made using Focus (CMS, St Louis, MO) or XiO (CMS). The RT planning system was changed in April 2004 from Focus to XiO in our institute. The beam energy was 6 MV for 25 patients who were treated after June 2003 when the new RTRT system was installed. Before that, 10- and 4-MV X-rays were available and used for 12 and 4 patients, respectively, with the prototype RTRT system. The 4-MV X-rays were used for small tumors in that period. The dose was prescribed at the center of the PTV. Four to six non–coplanar ports were used. All ports were treated in the same day. The dose fractionation schedule was four fractions within 1 week for all patients.

After insertion of gold markers by bronchoscopy near the tumor (18), a planning computed tomography (CT) scan was taken with the patients in the supine position. Patients were asked to hold their breath at the end of expiration, the point at which a previous study had showed the variation in tumor position was minimal (16). The slice thickness of the planning CT scan was 2 mm near the tumor. The GTV was measured as the portion of the tumor that was visible on CT and whose display conditions were a window width of −700 Hounsfield units and a window level of −1,000 to 1,500. The CTV was equal to the GTV for narrow margin or a 6–8-mm margin to the GTV for a wide margin, after Giraud *et al.* (20) reported the necessity of adding these margins to cover 95% of the tumor. We added a 6-mm CTV margin for squamous cell carcinoma and 8 mm for adenocarcinoma and large cell carcinoma when we used the wide margin in this study. Elective nodal irradiation was not performed.

Usually, the PTV margin is larger in the craniocaudal direction for SBRT, considering that the tumor motion is greater in the craniocaudal direction than in the lateral and anteroposterior directions (8, 21, 22). However, no increase in the PTV margin for the craniocaudal direction was used in this study because the RTRT can reduce the size of the margin for respiratory movement. The PTV was set as the CTV plus a 5-mm margin three-dimensionally throughout the study period. Thus, in patients treated with the narrow margin, the GTV-PTV margin was 5 mm and in patients treated with the wide margin, the GTV-PTV margin was 11 mm for squamous cell carcinoma and 13 mm for adenocarcinoma. The leaf margin to the PTV was 2–5 mm for inclusion of the PTV in an 80% isodose line in dose

distribution. Inhomogeneity was corrected by the Clarkson method in the initial half and by the superposition method in the latter half of the study period. The gating window ranged from ±2 to 3 mm for the lateral, craniocaudal, and anteroposterior directions isotropically.

In our working hypothesis, the appropriate total dose would be 40–48 Gy in four fractions within 1 week. Assuming an α/β ratio of 10 for tumor, 40 Gy in four fractions within 1 week would be equivalent to a conventional radiation dose of 67 Gy using 2-Gy daily fractions. The regimen of 48 Gy in four fractions within 1 week represented a tumor dose equivalent to the standard dose used in non-gated SBRT in Japan (8). The biologically effective dose assuming α/β ratios of 10 Gy (BED_{10}) of 40 Gy in four fractions within 1 week and 48 Gy in four fractions within 1 week was 80 Gy and 105.6 Gy, respectively.

We adapted the continual reassessment approach rather than the serial escalation approach to investigate the appropriate dose and GTV-PTV margin. Because apparently many confronting biases existed owing to the technical and conceptual developments during this period, a strict Bayesian approach was abandoned, and a simple principle was used to determine the levels of dose and margin. First, we started at 40 Gy with a narrow margin. Second, when a local relapse was detected without serious adverse effects, we increased the dose to 48 Gy with a wide margin. Third, the dose was then decreased to 40 Gy, keeping the wide margin when a Grade 3 adverse effect without tumor relapse was detected. Finally, the dose was again increased to 48 Gy with a narrow margin when a local relapse was detected in the third group of patients. Before the relapses or radiation pneumonitis were detected, the same dose and margin had been used for patients sequentially entered into the study.

Using this strategy, between February 2000 and October 2001, 40 Gy with a narrow margin was used for 8 patients. Between November 2001 and May 2004, 48 Gy with a wide margin was used for 26 patients. Between June 2004 and November 2004, 40 Gy with a wide margin was used for 5 patients, and between December 2004 and June 2005, 48 Gy with a narrow margin was used for 2 patients.

As a whole, of 25 patients with Stage T1 tumors, 7 received 40 Gy, 5 with a narrow margin and 2 with wide margin; 18 received 48 Gy, 2 with a narrow margin and 16 with a wide margin. Of 16 patients with Stage T2 tumors, 6 received 40 Gy, 3 with a narrow margin and 3 with a wide margin, and 10 patients received 48 Gy, none with a narrow margin and 10 with a wide margin.

Statistical analysis

The overall actuarial survival (OAS) and cause-specific survival (CSS) rates were calculated from the first day of treatment using the Kaplan-Meier method. Deaths from causes other than lung cancer were counted as censored cases to calculate the CSS. The local control rate was also calculated from the first treatment day. If a tumor was not larger than that on the pretreatment CT scan, it was judged to be controlled. Deaths were counted as censored to calculate the local control rate.

The log–rank test was used to calculate the statistically significant differences in OAS, CSS, and local control rates between T stage (T1 vs. T2), dose (40 vs. 48 Gy), and margin status (narrow vs. wide margin). Stepwise Cox regression multivariate analyses of these covariates were also performed to determine whether the covariates were prognostic for OAS and local control.

The difference of monitor unit (MU) calculated by Clarkson and superposition was re-examined in 19 patients whose plans were available for recalculation. The mean ± standard deviation of MUs calculated by Clarkson and superposition was $(14.5 \pm 1.1) \times 10^2$ MU and $(15.0 \pm 1.1) \times 10^2$ MU, respectively, to give the same dose to the center of the PTV. The difference was statistically significant using a paired t test ($p < 0.001$).

The Statistical Package for Social Sciences, version 11.0 (SPSS, Chicago, IL), was used for statistical analysis.

RESULTS

The OAS rate for all patients at 2 and 3 years was 64% and 47%, respectively. The OAS rate at 3 years for 48 Gy in four fractions within 1 week and 40 Gy in four fractions within 1 week was 53% and 27%, respectively. The CSS rate for all patients at 2 and 3 years was 73% and 53%, respectively. The CSS rates at 3 years for 48 Gy in four fractions within 1 week and 40 Gy in four fractions within 1 week was 77% and 27%, respectively. The local control rate for all patients at 2 and 3 years was 73% and 57%, respectively.

In patients treated with 48 Gy in four fractions within 1 week, the OAS and CSS rate at 3 years was 82% and 88% for those with Stage IA and 32% and 50% for those with Stage IB, respectively (Fig. 1). In patients treated with 40 Gy in four fractions within 1 week, the OAS and CSS rate at 3 years was 50% and 68% for those with Stage IA and 0% and 0% for those with Stage IB, respectively (Fig. 1).

A significant ($p = 0.0011$) difference was found in the OAS between those with Stage T1 ($n = 25$) and Stage T2 ($n = 16$; Fig. 2a). No significant difference was found in OAS between those receiving 40 Gy ($n = 13$) and 48 Gy ($n = 28$), those with a narrow margin ($n = 10$) and a wide margin ($n = 31$), or the Clarkson algorithm ($n = 31$) and superposition algorithm ($n = 10$).

Significant differences were found in CSS between those with Stage T1 and T2 ($p = 0.0059$) and between those receiving 40 Gy and 48 Gy ($p = 0.0327$; Fig. 2c,d). The margin and calculation algorithms did not influence CSS.

A significant difference was seen in local control between those with Stage T1 and T2 ($p = 0.0373$) and between those receiving 40 and 48 Gy ($p = 0.0042$; Fig. 3a,b). Subset analysis showed a significant difference in local control between 40 and 48 Gy in those with Stage IB ($p = 0.0015$) but not those with Stage IA ($p = 0.5811$; Fig. 3c,d). The margin and calculation algorithms did not influence local control.

In 28 patients treated with 48 Gy, the OAS was better for those with Stage IA ($p = 0.0366$) but not CSS ($p = 0.1994$) or local control ($p = 0.9494$) compared with those with Stage IB.

Cox regression analysis examined whether the covariates were associated with OAS and local control. T stage (T1 vs. T2), dose (40 vs. 48 Gy), margin status (narrow vs. wide), and calculation algorithm (Clarkson vs. superposition) were the initial covariates. Of these, T stage was significant for OAS and T stage and dose were significant for local control (Table 2).

No serious radiation morbidity was observed using either dose schedule. Regarding acute radiation morbidity, 2 patients had radiation pneumonitis requiring steroid therapy without continuous oxygenation within 90 days from the last day of RTRT. Their symptoms were relieved by the

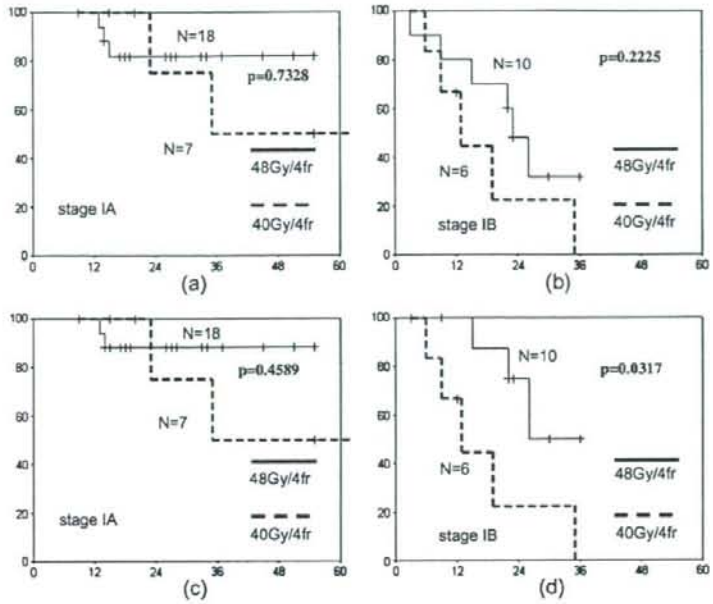

Fig. 1. (a) Overall actuarial survival (OAS) of Stage IA non–small-cell lung cancer (NSCLC) treated with 40 Gy and 48 Gy in four fractions. (b) OAS of Stage IB NSCLC treated with 40 Gy and 48 Gy in four fractions. (c) Cause-specific survival (CSS) of Stage IA NSCLC treated with 40 Gy and 48 Gy in four fractions. (d) CSS of stage IB NSCLC treated with 40 Gy and 48 Gy in 4 fractions.

steroids. Nine patients had late radiation morbidities. Radiation pneumonitis occurred in 4 patients. Of these 4 patients, 1 had received 40 Gy and 3 had received 48 Gy. All 4 had been treated with a wide margin. One patient who had received 48 Gy with a wide margin and one who had received 40 Gy with a wide margin needed house oxygenation therapy, corresponding to Grade 3 morbidity in Common Terminology Criteria Adverse Effects, version 3.0. Both patients had had poor lung function before RT, and one had had pleural effusion after local recurrence as the cause of the oxygen insufficiency. Four patients experienced chest wall pain from radiation pleuritis. Their symptoms were controlled by nonsteroidal anti-inflammatory drugs. Pleural effusion not related to tumor recurrence developed in 3 patients and was well managed conservatively. No significant relationship was observed between the adverse effects and radiation morbidity.

DISCUSSION

To reduce the adverse effects of hypofractionated RT, it is essential to avoid serial-structure organs (*i.e.*, spinal cord, esophagus, main bronchus, and large vessels at the pulmonary hilum and mediastinum) and to reduce the treated volume of parallel-structure organs (23). These goals can be achieved using the concept of SBRT to improve the setup accuracy and X-ray beams focused on tumors. Several image-guided radiotherapy techniques, such as diagnostic CT in the treatment room or megavoltage cone-beam CT, could be useful to reduce interfractional setup errors and to avoid serial-structure organs. The present study showed that SBRT using the RTRT system was equally effective as, but not more effective than, treatment of Stage I NSCLC as SBRT without RTRT using the same prescribed dose, 48 Gy in four fractions for either Stage T1 or T2. The possible benefit of the RTRT system for improving the tumor control rate might appear in situations in which the intrafractional internal organ motion is so large that, when RTRT is used, the actual absorbed dose is greater in the tumor and lower in the normal tissue (24).

Because most Stage I NSCLC disease requires a small PTV, irrespective of the treatment method, no difference was apparent in the adverse effects between our series and other SBRT series. Hof *et al.* (6) reported that no major clinical symptom associated with radiation morbidities was seen with single-dose stereotactic RT of 19–26 Gy. Nagata *et al.* (8) reported that no morbidities of Grade 3 or greater developed after treatment with 48 Gy in four fractions. Our results of 2 patients requiring continuous oxygenation intake was compatible with other investigators' reports on SBRT. Although we should be cautious about these results because of the small number of patents in this series, there seems to be no apparent difference in the occurrence of morbidity compared with other nongated SBRT studies (8, 25).

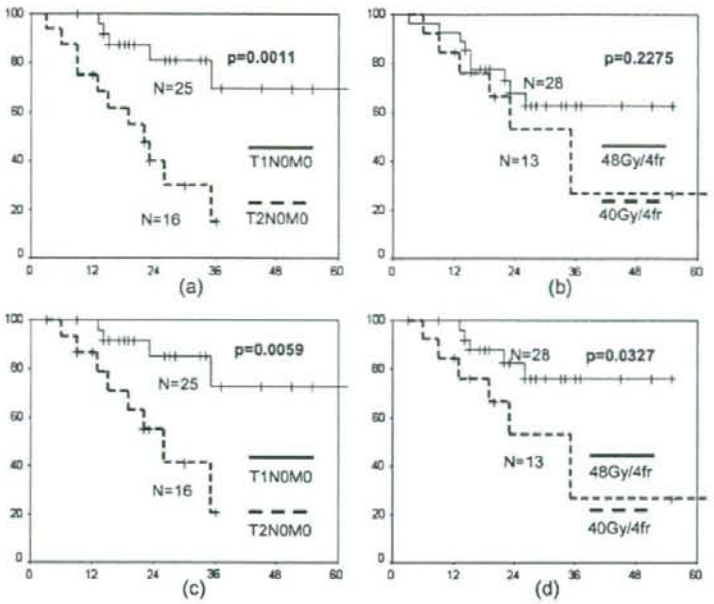

Fig. 2. (a) Overall actuarial survival (OAS) of Stage IA (T1N0M0) and IB (T2N0M0) non–small-cell lung cancer (NSCLC), with significant difference between Stage T1 and T2 ($p = 0.0011$). (b) OAS of patients treated with 40 Gy and 48 Gy in four fractions. (c) Cause-specific survival (CSS) of those with Stage IA (T1N0M0) and IB (T2N0M0) NSCLC, with significant difference between Stage T1 and T2 ($p = 0.0059$). (d) CSS of patients treated with 40 Gy and 48 Gy in four fractions, with significant difference between 40 and 48 Gy ($p = 0.0059$).

Much greater doses would be tolerable for peripheral lung tumors. McGarry *et al.* (25) reported the 72 Gy in three fractions is the maximal tolerance dose for tumors >5 cm. The biologically effective dose assuming α/β ratios of 2 Gy (BED_2) of 72 Gy in three fractions is 936 Gy, much greater than that of 48 Gy in four fractions (336 Gy). However, Fowler *et al.* (26) have shown that we must be careful when increasing the dose and volume in terms of late morbidity with hypofractionated RT. We are planning to start a dose-escalation study for Stage IB NSCLC using a strict stratification for PTV according to the precise prediction of radiation pneumonitis. The possible benefit of using the RTRT system to reduce adverse effects might be seen in a dose-escalation study of tumors with large respiratory motion, such as those in the lower lung field or tumors with large diameters (27).

In this study we were unable to find differences in clinical outcome between a narrow CTV margin and a wide CTV margin. This was possibly because the many confounding prognostic parameters, such as T stage and prescribed dose, masked the difference between the narrow and wide margins. This matter could be answered by a study in which the margin is decreased intentionally using the same CT scanner, dose, and calculation algorithm. However, the rapid improvement in advanced imaging modalities prevented us ethically from use of the same CT scanner. Once we applied the newer and better imaging quality available with CT scanning, the significance of the GTV and CTV margins changed considerably. The uncertainty in the delineation of the GTV in SBRT for NSCLC should be investigated more carefully in accordance with the advances in imaging modalities. We are still not certain that a narrow margin is as good as a wide margin because of the heterogeneity of the patients in this study. We are now using the wide margin and 48 Gy because of the low incidence of adverse effects with the wide margin in the present study.

The superposition algorithm resulted in greater MU for the same prescription dose than with the Clarkson algorithm, but no difference in clinical outcomes was apparent in our series for either tumor control or adverse effects. Because the superposition algorithm is known to have a smaller discrepancy from the measurement in lung tissue, we are now using it in the clinic. However, because of the small number of patients in this study, a careful dose-finding study of the superposition algorithm is still warranted.

In this study, we found a steep dose–response relationship in local control rates between 40 and 48 Gy for Stage I NSCLC. As stated, the BED_{10} of 40 Gy in four fractions within 1 week and 48 Gy in four fractions within 1 week was 80 Gy and 105.6 Gy, respectively. Our results agreed with those of the dose-escalation study at the University of Wisconsin that a total BED_{10} of 90–100 Gy is necessary for

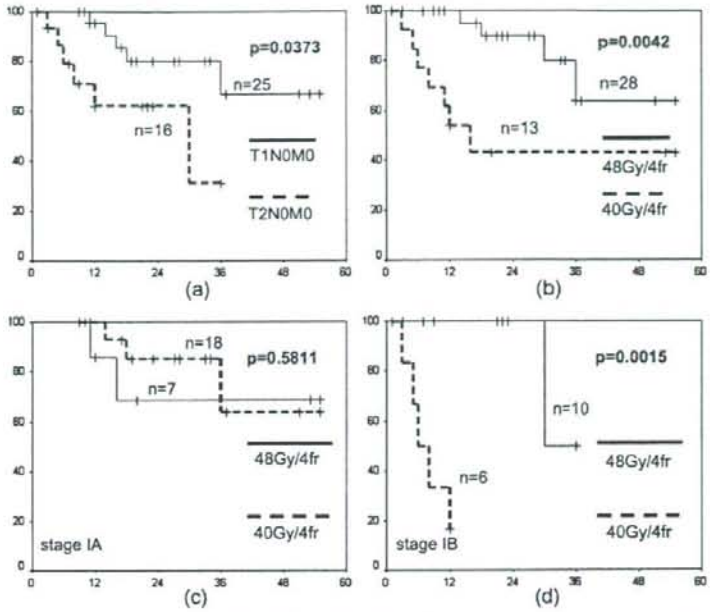

Fig. 3. (a) Local control rate of Stage IA (T1N0M0) and IB (T2N0M0) non-small-cell lung cancer (NSCLC), with significant difference between T1 and T2 ($p = 0.0373$). (b) Local control rate of patients treated with 40 Gy and 48 Gy in four fractions, with significant difference between 40 and 48 Gy ($p = 0.0042$). (c,d) Local control subset analysis. Subset analysis showed significant difference in local control between (d) those receiving 40 and 48 Gy with Stage IB ($p = 0.0015$) but (c) not those with Stage IA ($p = 0.5811$).

Stage I NSCLC control (12). A Japanese multi-institutional retrospective survey has also shown that a BED >100 Gy results in significantly better survival and local control than a BED of <100 Gy for Stage I NSCLC control using SBRT (9). In particular, a large difference was found in local control between 40 and 48 Gy for Stage T2 tumors. A dose of 40 Gy in four fractions within 1 week was strongly suggested to be insufficient for the treatment of Stage IB NSCLC. The number of patients was too small to conclude that 48 Gy in four fractions within 1 week was sufficient for Stage T2 tumors. The small number of patients also prevented finding the difference in the local control rate between those receiving 40 Gy in four fractions within 1 week and 48 Gy in four fractions within 1 week for Stage IA patients.

The 3-year overall survival rate was 55% in the series of Nyman *et al.* (10), 56% in a Japanese experience from 13 institutions (8, 9), and 66% in the series of Uematsu *et al.* (7). The survival rate for those with Stage I NSCLS in our series at 3 years, 47%, was somewhat lower than that in these previous series. One probable reason was that our study was a phase I-II study and included patients treated with the 40 Gy in four fractions within 1 week, for which the BED_{10} was equivalent to conventional RT, 67 Gy in 2-Gy fractions. Sibley *et al.* (5) found that the OAS rates at 3 years ranged from 17% to 55% using conventional RT (median dose, 60–66 Gy) for inoperable Stage I NSCLC. The OAS rate for those receiving 40 Gy in four fractions within 1 week in our study was 27%, within the range of conventional RT. The OAS rate for those receiving 48 Gy in four fractions within 1 week in our study was 53%, consistent with previous studies of SBRT.

Table 2. Cox proportional hazard model

Covariate	B	Standard error	Wald	df	*p*	Exp(B)
T stage	−1.653	0.700	5.582	1	0.018	0.210
Dose	2.003	0.705	8.074	1	0.004	7.409

Nagata *et al.* (8) reported a 3-year OAS and CSS rate of 72% and 83% for 32 patients with Stage IA, and 71% and 72% for 13 patients with Stage IB, respectively, using 48 Gy in four fractions within 2 weeks in their nongated SBRT study. In our series for Stage IA patients treated with 48 Gy, the OAS and CSS rate at 3 years was 82% and 88%, respectively, both greater than the rate reported by Nagata *et al.* (8). However, for those with Stage IB, the OAS and CSS rate at 3 years was 32% and 50%, respectively, both lower than in their series. The apparent difference between the series of Nagata *et al.* (8) and our series of patients with Stage IB was that they included only patients with tumors <4 cm in diameter and we included those with larger

tumors ≤7.0 cm. The small number of patients prevented a meaningful comparison for tumors <4 cm in diameter in Stage IB in our series. The low local control rate for those with Stage IB receiving 48 Gy in four fractions within 1 week in our series can be explained by the diameter of the tumor, although the number of patients was also too small to draw conclusions.

We used the BED based on the linear-quadratic model to define the dose fractionation schedule (9). It might be inappropriate to use the linear-quadratic model to compare the biologic effects of such a large dose per fraction with a 2-Gy daily dose, although Fowler *et al.* (26) reported that the linear-quadratic model fitted the radiation response of epithelial tissues ≤23 Gy/fraction. Tumor proliferation was neglected in our study, and more work is required to answer the question about the linearity between the biologic response and the BED.

A tumor size of >3 cm, or Stage IB, was shown to be a poor prognostic factor for peripheral Stage I NSCLC. This is consistent with the findings of previous studies of surgery (28, 29), conventional RT (30), and SBRT (31). In conventional RT, contradictory results have been reported by Firat *et al.* (32) and Ball *et al.* (33). The T stage did not have a statistically significant effect on the OAS of patients treated with a median dose of 61.2 Gy in the study by Firat *et al.* (32), and Ball *et al.* (33) reported that T stage was not a prognostic factor in patients treated with 60 Gy in 30 fractions within 3 or 6 weeks. The dose used in conventional RT might be insufficient to control even T1 tumors. Thus, there might have been no difference between T stages in prognosis in their series. The small number of patients in our study made it difficult to compare the OAS rate and local control rate between Stage IA and IB patients who received the same dose and margin with the same technological background.

Because we have used gated RT with the RTRT system, the dose distribution in the lung might have been different from that of nongated RT in which organ motion could blur the absorbed dose. If RT with the RTRT system can be performed perfectly, as planned, the dose distribution in the lung should be very close to the static irradiation (13). In nongated RT, the dose at the periphery of the PTV would be sufficient to eradicate microscopic tumor cells located around the GTV but lower than the dose producing radiation pneumonitis. In contrast, the dose at the periphery of the PTV might be too low to eradicate the microscopic tumor cells but great enough to produce radiation pneumonitis in nongated RT. These various possible situations would blur the dose–response curve of tumor control and adverse effects of nongated RT for tumors in motion. In other words, gating is a confounding factor when the clinical outcomes of RTRT are compared with other SBRT methods.

CONCLUSION

A steep dose–response curve between 40 and 48 Gy using a daily dose of 12 Gy delivered within 1 week was identified for local control of Stage I NSCLC, especially for Stage IB NSCLC, using SBRT with the RTRT system. We found that 48 Gy in four fractions within 1 week is a safe and effective treatment for Stage IA NSCLC, achieving an 81.9% and 88.2% OAS and CSS rate, respectively, at 3 years after treatment. Because we have used gated RT with the RTRT system, the dose distribution in the lung could be different from that with nongated RT, for which organ motion could blur the absorbed dose. Our study has confirmed that hypofractionated high-dose RT using a dose beyond that of conventional RT is a logical step forward to treat NSCLC, as long as the adverse effects are tolerable.

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