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PHYSICS CONTRIBUTION

REPRODUCIBILITY OF ORGAN POSITION USING VOLUNTARY BREATH-HOLD METHOD WITH SPIROMETER FOR EXTRACRANIAL STEREOTACTIC RADIOTHERAPY

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Purpose: To evaluate in healthy volunteers the reproducibility of organ position using a voluntary breath-hold method with a spirometer and the feasibility of this method for extracranial stereotactic radiotherapy in a clinical setting.

Methods and Materials: For this study, 5 healthy volunteers were enrolled. After training sessions, they held their breath at the end-inspiration and the end-expiration phase under spirometer-based monitoring. Computed tomography (CT) scans were performed twice at each respiratory phase, with a 10-min interval, on 2 separate days. The total number of CT scans was four at each respiratory phase. After CT volume data were transferred to a three-dimensional treatment-planning system, digitally reconstructed radiographs (DRRs) were calculated for anterior–posterior and left–right beams. Verification was performed with DRRs relative to the diaphragm position, bony landmarks, and the isocenter in each healthy volunteer at each respiratory phase. To evaluate intrafraction reproducibility, we measured the distance between diaphragm position and bony landmarks. To evaluate interfraction reproducibility, we measured the distance between diaphragm position and the isocenter. Reproducibility and setup error were defined as the average value of the differences between each DRR with regard to the first DRR.

Results: Intrafraction reproducibility of the caudal–cranial direction was 4.0 ± 3.5 mm at the end-inspiration phase and 2.2 ± 2.0 mm at the end-expiration phase. Interfraction reproducibility of the caudal–cranial direction was 5.1 ± 4.8 mm at the end-inspiration phase and 2.1 ± 1.8 mm at the end-expiration phase. The end-expiration phase was more stable than the end-inspiration phase.

Conclusions: The voluntary breath-hold method with a spirometer is feasible, with relatively good reproducibility. We are encouraged about the use of this technique clinically for extracranial stereotactic radiotherapy.
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Spirometer, Breath-hold, Reproducibility, End-inspiration, End-expiration.

INTRODUCTION

Extracranial stereotactic radiotherapy (ESRT) for lung or liver tumors has been widely performed and has been shown to be a highly effective treatment (1–3). With delivery of a single high dose in ESRT, large irradiated volumes of lung or liver due to large internal margins under free breathing might result in fetal pneumonitis or liver dysfunction. It is important to compensate for breathing motion to reduce pulmonary or liver complications by some method. There are several methods for coordinating respiratory motion, including, for example, active breathing control or coordination (ABC) (4), real-time tumor-tracking systems (5), respiratory gating systems (6–8), abdominal pressure (9), and the voluntary deep inspiration breath-hold (DIBH) technique (10, 11).

Breath-hold methods, such as ABC and DIBH, might be especially demanding, and therefore less feasible, in elderly patients or those with pulmonary dysfunction. To improve feasibility, we developed a voluntary breath-hold method using spirometer-based monitoring to reduce respiratory motion, whereby patients can hold their breath within their comfortable respiratory phase. We consider this method to have higher feasibility for elderly patients or patients with pulmonary dysfunction.

For clinical application, we performed a study to confirm

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the feasibility and reproducibility of this method, using healthy volunteers. The purpose of this study was to evaluate the intrafraction and interfraction reproducibility of organ position with a spirometer and the feasibility of this method for ESRT in a clinical setting.

METHODS AND MATERIALS

Spirometer-based monitoring

For respiratory phase and breath-hold monitoring, healthy volunteers breathed through a mouthpiece connected to a gas-monitoring sensor (sensor-D-light, Datex-Ohmeda, Helsinki, Finland). The other end of the gas-monitoring sensor was attached to a three-way connector, and 5 L/min of oxygen was inhaled through one tube of the three-way connector to assist the breath hold. A nose clip was used to prevent nasal breathing and to ensure that volunteers breathed through the mouthpiece (Fig. 1). We used a commercially available spirometer (Ultima, Datex-Ohmeda), which is usually used in anesthesia management. This spirometer displays a flow–time curve, which shows the state of inspiration, expiration, and breath-hold (Fig. 2).

Training

For this study, 5 healthy volunteers were enrolled. To inform them of the procedure, we gave them training sessions before the CT scans. They held their breath at the end-inspiration and the end-expiration phase, which they felt to be comfortable, under spirometer-based monitoring, and we instructed them to keep a stable tidal volume at each respiratory phase. The reproducibility of the maneuver as determined by the spirometry level was carefully monitored, and the volunteers repeated this maneuver three to four times until they became familiarized.

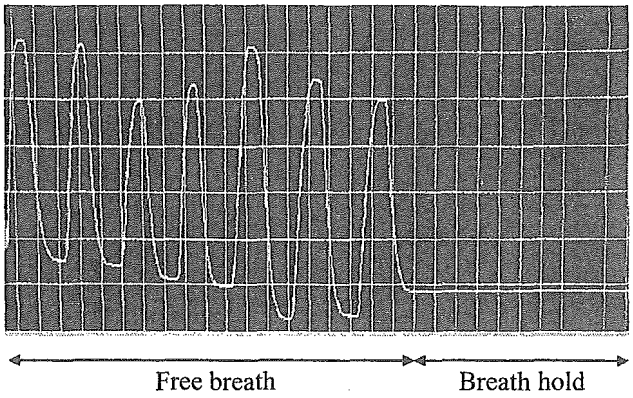

Fig. 2. Representation of spirometry tracings. It is possible for this spirometer to display only a flow–time curve, which can show the state of inspiration, expiration, and breath-hold.

Simulation

For the simulation, each volunteer was placed in the supine position on the X-ray simulator (Ximatron; Varian, Palo Alto, CA). To set up the volunteers in the same position, the isocenter was set on the lower end of the ensiform process at the center of body thickness. First, to measure the diaphragmatic motion from the end-inspiration phase to the end-expiration phase in the cranial–caudal (CC) direction, the volunteers breathed freely under X-ray fluoroscopy (Fig 3). Second, the volunteers held the mouthpiece and held their breath as in the training sessions under

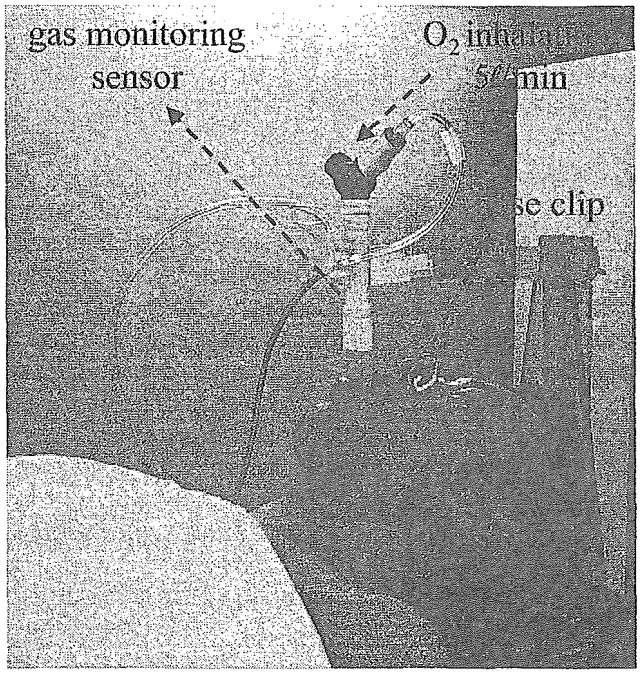

Fig. 1. A healthy volunteer breathes through a mouthpiece connected to a gas-monitoring sensor. A nose clip is used to prevent nasal breathing and ensure that the volunteer breathes through the mouthpiece.

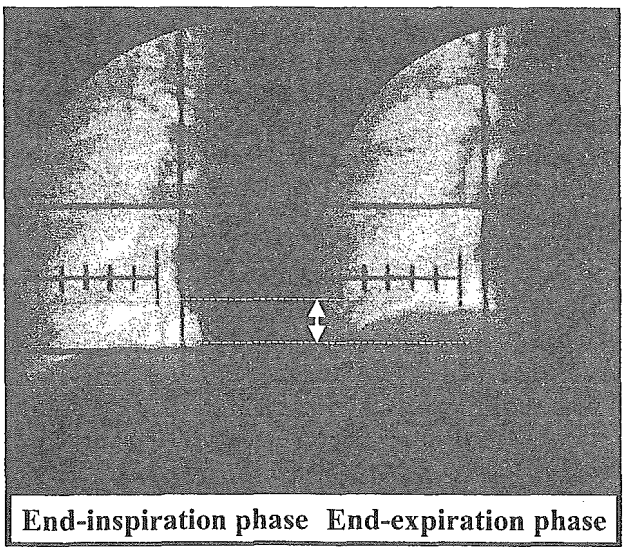

Fig. 3. Diaphragm motion distance under free breathing. To measure the diaphragmatic motion from the end-inspiration phase to the end-expiration phase in the CC direction, the volunteers breathed freely under X-ray fluoroscopy.

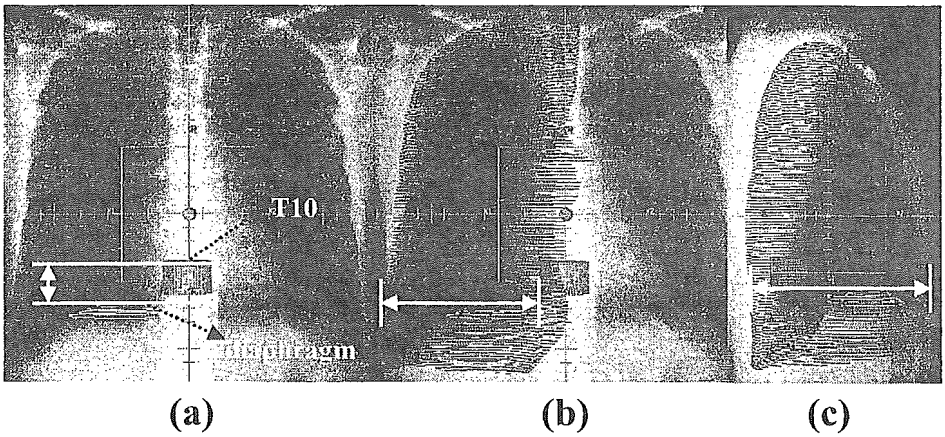

Fig. 4. Evaluation method for intrafraction reproducibility. (a) Cranial-caudal (CC) distance. (b) Left-right (LR) distance. (c) Anterior-posterior (AP) distance. We measured CC distance between T10 and the diaphragm, LR distance between T10 and the thoracic wall at the diaphragmatic level, and AP distance of the right lung at the diaphragmatic level.

X-ray fluoroscopy. We verified the reproducibility of the diaphragm level in the CC direction obtained at each respiratory phase.

CT scan procedure

Participants enrolled in this study were all healthy volunteers. Informed consent, outlining the risk of low-dose radiation exposure, was gained from all. To avoid unnecessary radiation exposure, CT scans were performed with low voltage and current. Each volunteer was set up on the CT scanner (Lightspeed QX/I; GE Yokogawa Medical System, Tokyo, Japan) at the isocenter. Computed tomography scans were performed four times at each respiratory phase. Slice thickness and interval were each 2.5 mm. Scans were performed twice at each respiratory phase with a 10-min interval on 2 separate days. We ran through the setup process every time before each CT scan was performed. Computed tomography volume data were transferred to a three-dimensional (3D) treatment-planning system (Pinnacle^3 version 6.0; ADAC, Milipitas, CA), and digitally reconstructed radiographs (DRRs) were calculated for anterior–posterior (AP) and left–right (LR) beams.

Verification and data analysis

Verification was performed with DRRs relative to bony landmarks, the diaphragm, and the isocenter. The reasons for using DRRs for verification were as follows: (*1*) because we also use DRRs and lineacgraphys (LG) for verification clinically, (*2*) to evaluate systematic error of CT and the 3D treatment-planning system, and (*3*) because bony landmarks are often unclear on radiographic simulations, especially on the lateral view; thus DRRs, which reflect marked bony landmarks on CT, would be more correct. To evaluate intrafraction reproducibility, we measured lung volume, CC distance between T10 and the diaphragm, LR distance between T10 and the thoracic wall at the diaphragmatic level, and AP distance of the right lung at the diaphragmatic level (Fig. 4). Lung volume was calculated automatically by the 3D treatment-planning system (the threshold of CT value was between 700 Hounsfield units [HU] and 4096 HU).

To evaluate interfraction reproducibility, we measured CC distance between the isocenter and the diaphragm, LR distance between the isocenter and the thoracic wall, and AP distance of the right lung at the isocenter level (Fig. 5). To evaluate setup error, we measured CC, LR, and AP distances between the isocenter and T10 (Fig. 6). Reproducibility and setup error were defined as the average value of the differences between each DRR with regard to the first DRR.

From these data, geometric uncertainties were determined. Geometric uncertainties in radiotherapy consist of internal organ movement and external setup deviations. Both deviations consist of a systematic component (i.e., the same for each fraction of the treatment) and a random component (i.e., varying from day to day) (12, 13). The overall deviations of internal organ motion and setup were calculated by standard deviations (SDs) of the mean differences between first scan DRR and each subsequent DRR, averaged over all the volunteers. The systematic deviations were calculated by determining the spread (1 SD) in the individual means of the differences between the first DRR and each subsequent DRR. The random deviations were calculated by the spread (1 SD) of these differences around the corresponding mean in each volunteer and subsequent calculation of the average of these SDs for the whole group (14).

Statistical significance in the differences was determined with the Student t test. Statistical significance was established at the level of $p < 0.05$.

RESULTS

Diaphragm motion under free breathing

The diaphragm motion distance in the CC direction from end-inspiration to end-expiration ranged from 10 mm to 22.6 mm, with an average of 15.8 ± 5.6 mm (mean and overall SD).

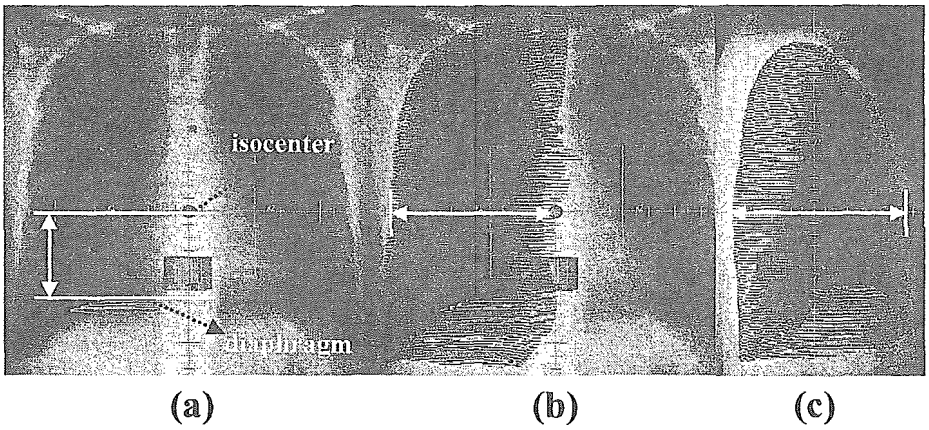

Fig. 5. Evaluation method for interfraction reproducibility. (a) Cranial-caudal (CC) distance. (b) Left-right (LR) distance. (c) Anterior-posterior (AP) distance. We measured CC distance between the isocenter and the diaphragm, LR distance between the isocenter and the thoracic wall, and AP distance of the right lung at the isocenter level.

Intrafraction reproducibility

Intrafraction reproducibility of the lung volume was 6.4% ± 4.3% at the end-inspiration phase and 3.6% ± 2.5% at the end-expiration phase. Between each breath-holding phase, there was no significant difference (p = 0.342).

Intrafraction reproducibility of the CC, LR, and AP directions was 4.0 ± 3.5 mm, 2.3 ± 2.2 mm, and 2.3 ± 2.1 mm at the end-inspiration phase and 2.2 ± 2.0 mm, 1.4 ± 1.3 mm, and 2.0 ± 1.1 mm at the end-expiration phase, respectively. Between each breath-holding phase, there was no significant difference in all directions (p = 0.297, 0.227, and 0.686 in CC, LR, and AP directions, respectively).

Interfraction reproducibility

Interfraction reproducibility of the CC, LR, and AP directions was 5.1 ± 4.8 mm, 2.9 ± 2.2 mm, and 3.0 ± 3.2 mm at the end-inspiration phase and 2.1 ± 1.8 mm, 1.1 ± 0.8 mm, and 1.9 ± 1.6 mm at the end-expiration phase, respectively. Between each breath-holding phase, interfraction reproducibility at the end-expiration phase was better than that at the end-inspiration phase. There was no significant difference in the CC and AP directions (p = 0.181 and 0.423, respectively) but a significant difference in the LR direction (p = 0.046).

Setup error

Setup error of the CC, LR, and AP directions was 2.8 ± 2.3 mm, 2.9 ± 2.2 mm, and 2.9 ± 2.9 mm at the end-inspiration phase and 2.2 ± 1.7 mm, 1.4 ± 1.1 mm, and 1.4 ± 0.9 mm at the end-expiration phase, respectively. Between each breath-holding phase, there was no significant difference (p = 0.352, 0.382, and 0.109 in the CC, LR, and AP directions, respectively).

Table 1 shows a summary of the results. In all directions, especially in the CC direction, the reproducibility and setup were relatively better at the end-expiration phase than at the end-inspiration phase. Between the breath-holding phase and free breathing, there was a significant reduction of diaphragm motion in the CC direction (p = 0.0015) (Fig. 7).

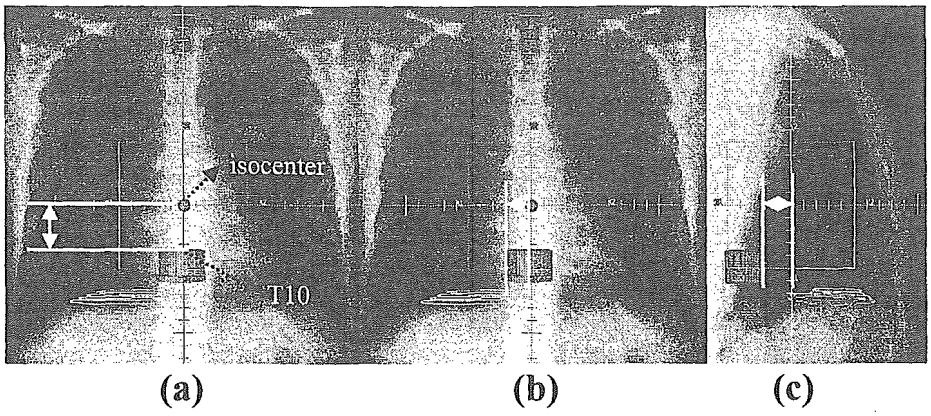

Fig. 6. Evaluation method for setup error. (a) Cranial-caudal (CC) distance. (b) Left-right (LR) distance. (c) Anterior-posterior (AP) distance. We measured CC, LR, and AP distance between the isocenter and T10.

Table 1. Summary of results

		Inspiration	Expiration	*p* value
Intrafraction (mm)	CC	4.0 ± 3.5	2.2 ± 2.0	0.3
	LR	2.3 ± 2.2	1.4 ± 1.3	0.23
	AP	2.3 ± 2.1	2.0 ± 1.1	0.69
Interfraction (mm)	CC	5.1 ± 4.8	2.1 ± 1.8	0.18
	LR	2.9 ± 2.2	1.1 ± 0.8	0.046
	AP	3.0 ± 3.2	1.9 ± 1.6	0.42
Setup (mm)	CC	2.8 ± 2.3	2.2 ± 1.7	0.35
	LR	2.9 ± 2.2	1.4 ± 1.1	0.38
	AP	2.9 ± 2.9	1.4 ± 0.9	0.11

Abbreviations: CC = cranial–caudal; LR = left–right; AP = anterior–posterior.

Geometric uncertainties

Table 2 shows the results of geometric uncertainties. Systematic deviations of intrafraction in the CC, LR, and AP directions were 3.3 mm, 1.4 mm, and 1.6 mm at the end-inspiration phase and 1.4 mm, 0.8 mm, and 0.7 mm at the end-expiration phase, respectively. Systematic deviations of setup in the CC, LR, and AP directions were 1.5 mm, 2.1 mm, and 1.7 mm at the end-inspiration phase and 0.6 mm, 0.7 mm, and 0.8 mm at the end-expiration phase, respectively. Random deviations of intrafraction in the CC, LR, and AP directions were 1.9 mm, 1.6 mm, and 1.5 mm at the end-inspiration phase and 1.6 mm, 1.2 mm, and 1.1 mm at the end-expiration phase, respectively. Random deviations of setup in the CC, LR, and AP directions were 2.0 mm, 1.2 mm, and 2.2 mm at the end-inspiration phase and 1.8 mm, 1.0 mm, and 0.5 mm at the end-expiration phase, respectively. Between each breath-holding phase, there was significant difference in systematic deviations of setup (p = 0.0045).

DISCUSSION

The breath-hold method is one of the methods used to coordinate respiratory motion. Several approaches have been used in the breath-hold method. One is the ABC method, which temporarily immobilizes the patient's breathing. Wong *et al.* (4) reported on an ABC apparatus

Table 2. Geometric uncertainties

		Inspiration		Expiration	
		Σ	σ	Σ	σ
Intrafraction (mm)	CC	3.3	1.9	1.4	1.6
	LR	1.4	1.6	0.8	1.2
	AP	1.6	1.5	0.7	1.1
Setup (mm)	CC	1.5	2	0.6	1.8
	LR	2.1	1.2	0.7	1
	AP	1.7	2.2	0.8	0.5

Abbreviations: Σ = systematic deviations; σ = random deviations. Other abbreviations as in Table 1.

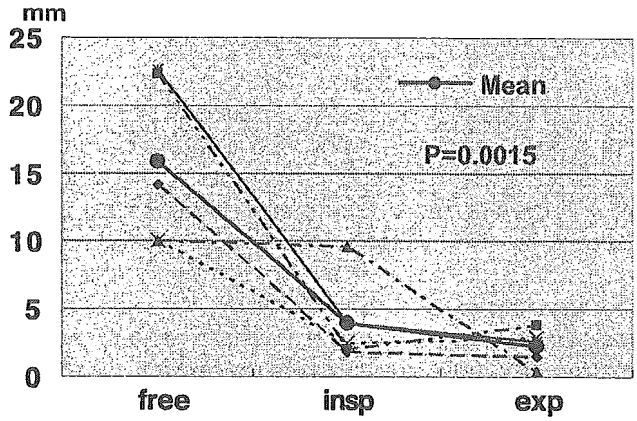

Fig. 7. Reduction of diaphragm movement with the breath-hold method using a spirometer. Between the breath-holding phase and free breathing, there was significant reduction of the diaphragm motion in the cranial-caudal direction (p = 0.0015). Insp = inspiration; Exp = expiration.

constructed of two pairs of flow-monitoring and scissor valves, one each to control the inspiration and expiration paths to the patients; the operator closes both valves to immobilize breathing motion. From the analyses of positioning radiographs, the average intrafraction and interfraction CC reproducibility of the diaphragm relative to the bony landmarks with ABC was 2.5 mm and 4.4 mm, respectively (15). The reproducibility of ABC is good, but the apparatus is relatively expensive and rather demanding of patients. The second breath-hold method is the DIBH technique with a commercially available spirometer. The DIBH technique is able to displace normal lung or heart out of the high-dose treatment field. Rosenzweig *et al.* (10) showed that calculated normal tissue complication probability (NTCP) of the lung for 7 lung cancer patients decreased with the DIBH technique as compared with free breathing at their prescribed dose. Sixel *et al.* (16) showed that the DIBH technique during tangential breast irradiation has the potential to significantly decrease irradiated cardiac volume for suitably selected patients. Another benefit is relatively good reproducibility: Hanley *et al.* (17) analyzed data from 5 lung cancer patients with the DIBH technique and found that intrafraction and interfraction reproducibility was 1.0 ± 0.9 mm and 2.5 ± 1.6 mm, respectively, as determined from the diaphragm position. However, Mah *et al.* (18) reported that a disadvantage of the DIBH technique is patient compliance, because only approximately half of the lung cancer patients they evaluated could perform this method. The third method is the self-breath-hold method without respiratory monitoring devices. Onishi *et al.* (11) demonstrated that the reproducibility of tumor position during 20 lung cancer patients' self-estimated breath-holding at the inspiration phase was 2.2 mm in the CC direction, 1.4 mm in the AP direction, and 1.3 mm in the LR direction. They concluded that they were able to obtain good reproducibility with this technique in combination with a linear accelerator

and without respiratory monitoring devices. However, in some institutions, including ours, where clinicians depend on conventional LG without the fusion of CT and a Linac (FOCAL) unit (1) or an electronic portal imaging device (EPID) for verification, it could not be verified whether patients held their breath during treatment appropriately. We therefore think it would be better to monitor respiratory motion with some kind of method in these institutions.

In our study, we developed a voluntary breath-hold method using a commercially available spirometer. We think the advantage of this method will be feasibility to many patients and adaptability to many institutions. This study was preclinical and used healthy volunteers; however, they could hold their breath comfortably at the end-inspiration or the end-inspiration phase under inhalation of oxygen. Considering that most lung cancer patients are elderly and have respiratory dysfunctions, this method, which allows for holding the breath at the comfortable respiratory phase, would be more feasible than other breath-hold methods, in which breath-holding is mandatory, such as ABC or DIBH. Additionally, verification is performed by conventional LG and DRR in this method, therefore this method would be adaptable to institutions without an apparatus, such as a FOCAL unit or EPID, to monitor respiratory motion during treatment, with relatively lower cost.

Our study demonstrated the feasibility of this method, with relatively good reproducibility of the diaphragm position, which was better at the end-expiration phase than at the end-inspiration phase. Between the end-expiration phase and free breathing, diaphragm movement was significantly reduced to a range of 7.1–19 mm (mean, 13.4 mm) in the CC direction. There is discussion as to whether patients should hold their breath at the inspiration or the expiration phase, because an advantage and a disadvantage exist in each phase. The advantage of breath-holding at the inspiration phase, as with the DIBH technique, is described above. On the other hand, at the expiration phase, Balter *et al.* (19) reported that the reproducibility of the diaphragm position was better than that at the inspiration phase. They analyzed the ventilatory time courses of diaphragm movement for 15 patients, and the average patient's diaphragm remained within 25% of the range of ventilatory excursion from the average expiration position for 42% of the typical breathing cycle and within 25% of the range from the average inspiration position for 15% of the cycle. Reproducibility of the expiration position over multiple cycles was 0.9 mm, as opposed to 2.6 mm for inspiration. Planning target volume (PTV) in ESRT is smaller than that in conventional radiotherapy, thus there was no large difference of NTCP in ESRT. Considering the feasibility of this method, patients can select a more comfortable respiratory phase, the end-inspiration phase or the end-expiration phase. However, to secure the accuracy of reproducibility for ESRT, we considered it better to hold the breath at the end-expiration phase, if possible, for more sufficient reproducibility.

Although we did not use immobilization devices such as a stereotactic body frame in this study, mean setup error was also within 3 mm in all directions. It was also slightly better at the end-expiration phase than at the end-inspiration phase, because the motion of the thoracic walls, which are attached to the skin mark, was greater on inspiration than on expiration at setup. Regarding setup error, our results also demonstrated that the end-expiration phase was better.

We calculated geometric uncertainties from our results. Systematic deviations included setup error and organ motion on the CT scanner, delineation errors, and equipment calibration errors. Random deviations included target movement and day-to-day variation in the patient setup or equipment. Systematic deviations that occur during treatment execution are called preparation errors because these types of errors are caused by the preparation of the equipment (20). Stroom *et al.* (13) evaluated the effect of systematic and random deviations on target dose and demonstrated a clinical target volume (CTV)-to-PTV margin size that ensures at least a 95% dose to (on average) 99% of CTV, which seems to be equal to approximately $2\Sigma + 0.7\sigma$, where Σ and σ are combined systematic and random deviations for a prostate, cervix, lung cancer case. Herk *et al.* (20) also demonstrated that a CTV-to-PTV margin size must be approximately $2.5\Sigma + 0.7\sigma - 3$ mm to give 90% of patients at least 98% equivalent uniform dose. They concluded that systematic deviations have a much larger impact on target dose, thus it is most efficient to address systematic deviations first when working to improve the quality of radiotherapy. In our results, between the end-inspiration and the expiration phase, random deviations of intrafraction and setup did not have large difference in all directions, but systematic deviations of intrafraction and setup at the end-inspiration phase tended to be worse than those at the end-expiration phase in all directions. Systematic deviations of setup especially had significant difference between these phases ($p = 0.045$). Large CTV-to-PTV margin size is therefore necessary at the end-inspiration phase. We also recommend holding the breath at the end-expiration phase in radiotherapies in which the accuracy of reproducibility from the analysis of geometric uncertainties is needed, like ESRT.

Because we used healthy volunteers in this study, we evaluated the reproducibility of the diaphragm position as a landmark. However, the correlation between the diaphragm and lung or liver tumor position is still unclear. Regarding liver tumors, Balter *et al.* (21) demonstrated that the range of ventilatory movement of different locations of coils within the liver is predicted by diaphragm position and suggested that the diaphragm is an acceptable anatomic landmark for radiographic estimation of liver movement in AP projections for most patients. Regarding lung tumors, Seppenwoolde *et al.* (22) demonstrated that the trajectory of the tumor during inhalation is different from the trajectory during exhalation (i.e., hysteresis) by analyzing 3D motion of lung tumors during radiotherapy, using the real-time tumor tracking system. They also suggested that when hysteresis in tumor motion is caused by the dynamic properties of lung tissue, breath-hold scans will not give a representative position of the tumor. According to the complexity of tumor motion from this analysis, we should take into consideration that diaphragm position does not necessarily re-

flect lung tumor position directly, especially tumors in the lower lobe, and from now on evaluate not only the reproducibility of the diaphragm or other organ position but also that of tumor position in a clinical setting.

CONCLUSIONS

The voluntary breath-hold method using spirometer-based monitoring is feasible, with relatively good intrafraction and interfraction reproducibility, especially at the end-expiration phase in healthy volunteers. However, we need to improve interfraction reproducibility for more accurate organ positioning; therefore, daily film verification and repositioning will play a more important role in a clinical setting. We encourage the use of this technique clinically for ESRT and plan to demonstrate not only the reproducibility of organ position but also that of target immobilization in lung and liver tumor patients.

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Clinical outcomes of stereotactic radiotherapy for stage I non-small cell lung cancer using a novel irradiation technique: patient self-controlled breath-hold and beam switching using a combination of linear accelerator and CT scanner☆

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Stage I;
Breath-hold;
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Summary We have developed a novel irradiation technique for lung cancer that combines a linear accelerator and CT scanner with patient-controlled breath-hold and radiation beam switching. We applied this technique to stereotactic three-dimensional (3D) conformal radiotherapy for stage I non-small cell lung cancer (NSCLC) and evaluated the primary therapeutic outcomes. A total of 35 patients with stage I (15 IA, 20 IB) primary NSCLC (20 adeno, 13 squamous cell, and 2 others) were treated with this technique. Patients ranged from 65 to 92 years old (median, 78 years). Twenty-three (66%) patients were medically inoperable due to mainly chronic pulmonary disease or high age. Three-dimensional treatment plans were made using 10 different non-coplanar dynamic arcs. The total dose of 60 Gy was delivered in 10 fractions (over 5–8 days) at the minimum dose point in the planning target volume (PTV) using a 6 MV X-ray. After adjusting the isocenter of the PTV to the planned position by a unit comprising CT and linear accelerator, irradiation was performed under patient-controlled breath-hold and radiation beam switching. All patients completed the treatment course without complaint. Complete response (CR) and partial response (PR) rates were 8/35

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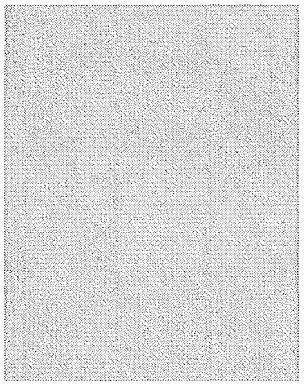

(23%) and 25/35 (71%), respectively. Pulmonary complications of National Cancer Institute-Common Toxicity Criteria grade >2 were noted in three (9%) patients. During follow-up (range, 6–30 months; median, 13 months), two (6%) patients developed local progression and five (14%) developed distant or regional lymph node metastases. Two-year overall survival rates for total patients and medically operable patients were 58 and 83%, respectively. In conclusion, this new irradiation technique, utilizing patient-controlled radiation beam switching under self-breath-hold after precise alignment of the isocenter, allows safe high-dose stereotactic radiotherapy with sufficient margins around the CTV and reduced treatment times. Based on the initial results, excellent local control with minimal complications is expected for stage I NSCLC.
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1. Introduction

Lung cancer is the leading cause of mortality among males in Japan. Despite continued research into novel therapeutic strategies, 5-year survival rates for lung cancer remain at approximately 15% [1]. One of the main reasons for this disappointing survival rate is the relatively late diagnosis of lung cancer. However, lung cancers are increasingly being detected in the earlier stages, thanks to the routine use of computed tomography (CT). For early stage lung cancers, the cure rate is 29–72% if surgical resection of the tumor can be achieved [2]. Surgical resection may not be an option for lung cancer patients with tobacco-related illnesses, severe cardiovascular disease, or other medical conditions. Other patients refuse surgery for personal reasons. Historical 5-year survival rates for early stage lung cancer patients treated using conventional radiotherapy are 0–42% [3]. Recently, fractionated high-dose stereotactic radiotherapy (SRT) has been actively performed for early stage lung cancer [4–6]. In a landmark study by Uematsu, SRT was performed using a novel combination of CT scanner and linear accelerator (linac) [4,7]. This combined unit allowed visualization of the tumor at the time of radiotherapy, directing multiple non-coplanar beams of radiation to converge on the tumor with great accuracy. Such real-time CT-guided treatment provides precise targeting of the tumor and maximal sparing of normal lung tissues.

SRT has focused attention on the need to control tumor motion due to respiration using methods that prevent enlargement of the irradiated lung volume, such as respiratory gating, active breath control, or breath-holding. We developed a new irradiation technique comprising breath-hold and patient-controlled radiation beam switching with a moving CT scanner and linac unit (linac-CT) [8]. The current study aimed to apply this technique to SRT for stage I non-small cell lung cancer (NSCLC) and to evaluate the resultant primary clinical outcomes.

2. Material and methods

2.1. Eligibility criteria

All patients enrolled in this study satisfied the following eligibility criteria: (1) identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdomen CT, bronchoscopy, bone scintigram, and brain magnetic resonance imaging; (2) histologically confirmed NSCLC; (3) tumor diameter <60 mm; (4) performance status according to World Health Organization guidelines ≤2; (5) demonstrated ability to maintain breath-hold for more than 10 s; (6) demonstrated ability to understand and perform self-breath-hold and radiation beam control. Patients were informed as to the concept, methodology, and rationale of this treatment. Written informed consent was obtained from all patients. This study was approved by the ethics committee of our institution.

2.2. Patient characteristics

Between July 2000 and October 2002, a total of 38 patients were identified as candidates for the irradiation procedure. However, three patients (8%) were excluded, as they could not suitably perform self-breath-holding and beam switching techniques. A summary of patient characteristics is provided in Table 1. A total of 35 patients were treated using this irradiation procedure. Fourteen patients displayed pulmonary emphysema or fibrosis before treatment. Twelve patients were considered medically operable, but had refused surgery or were advised to select SRT by medical oncologists. The remaining 23 patients were judged medically inoperable due to poor respiratory function, advanced age, or other chronic illness.

2.3. Treatment methods

Treatments were delivered using our newly developed unit, comprising a linear accelerator (linac)

Table 1 Patient characteristics

Total number of cases	35
Age (years)	
Median	78.0
Range	65–92
Gender	
Male	27
Female	8
Histology	
Adenocarcinoma	20
Squamous cell carcinoma	13
Unclassified non-small cell lung cancer	2
Stage	
IA (T1N0)	15
IB (T2N0)	20
Tumor diameter (mm)	
Median	33
Range	10–48
Performance status	
WHO-0	15
WHO-1	17
WHO-2	3
Reason for non-surgical treatment	
Poor respiratory function	12
Other disease	5
Old age	6
Patient refusal	4
Physician recommendation	8

(EXL-15DP, Mitsubishi Electric, Tokyo, Japan) coupled to a CT scanner (Hi-Speed DX/I, GE Yokogawa Medical Systems, Tokyo, Japan) and sharing a common couch (Fig. 1A). The center of the CT image was aligned with the isocenter of the linac accelerator when the couch was rotated 180°. During scanning, the CT-gantry moved along rails on the floor while the table remained stationary [8]. Accuracy of matching between linac isocenter and CT image center was $\leq$0.5 mm.

In order to reproduce and maintain tumor position during irradiation, patients were trained in procedures for self-breath-holding at inspiration. Reproducibility of tumor position under self-breath-hold was measured by three repeated CT scans that were performed to obtain randomly timed images of 2 mm thickness in the vicinity of the tumor during self-breath-hold. Maximum difference in the center of tumor position for the three CT scans was then calculated. The uncertainty concerning the reproducibility of patient-controlled breath-hold has previously been presented [9]. Chest CT under self-breath-hold was performed for each patient and a plan was established with the help of a three-dimensional (3D) treatment-planning computer (FOCUS, version 3.2.1, CMS, St. Louis, MO). Patients were positioned on the CT table and a skin marker for the temporary isocenter was placed using the cross-hair laser system. An example of the 3D treatment plan is showed in Fig. 2. Clinical target volume (CTV) was equal to the gross tumor volume (GTV) delineated on CT images displayed with a window level of −300 Hounsfield units (HU) and a window width of 1700 HU. Planning target volume (PTV) was determined on CT images as the CTV plus the maximum difference of the tumor position measured on the aforementioned three repeated CT scans performed during self-breath-holding with an additional margin of 5 mm to compensate full internal margin including intra-session reproducibility. Since the tumor position was adjusted to the planned position before every session using CT images, set-up error was neglected [8]. Elective nodal irradiation to the hilar and mediastinal regions was not delivered.

A flowchart of the irradiation process is shown in Fig. 3. The isocenter of the PTV was visually adjusted with CT images of 2 mm thickness taken before every radiotherapy fraction to correspond to the planned isocenter under patient self-breath-hold using the CT scanner unified with the linac (Fig. 1B). The couch was rotated 180° so that the rotational center of the CT-gantry corresponded to the isocenter of the linac. A signal indicating readiness to start irradiation was given by a radiation technologist when alignment was obtained (Fig. 1C). Irradiation was started only when both switches for the patient and the console of the linac were turned on. The actual switching of the radiation beam was delayed $<$0.1 s behind the patient's switching. The linac delivered a maximum of 400 monitor units/min. Patients determined their breath-holding time and controlled radiation beam as often as needed until the prescribed monitor units were completed. Radiation technologists were able to stop irradiation whenever necessary.

Tumor position during each radiotherapy session was complementarily verified using an electronic portal-imaging device. Electronic portal images (EPIs) were real-time and taken every 2 s during irradiation. Whenever the tumor was visually determined to move beyond the PTV on EPI, the radiation technologist turned off the radiation beam and irradiation was restarted after realigning the tumor under patient self-breath-hold. Mean time for one radiotherapy session, including patient set-up, adjustment of the isocenter, and irradiation, was approximately 30 min.

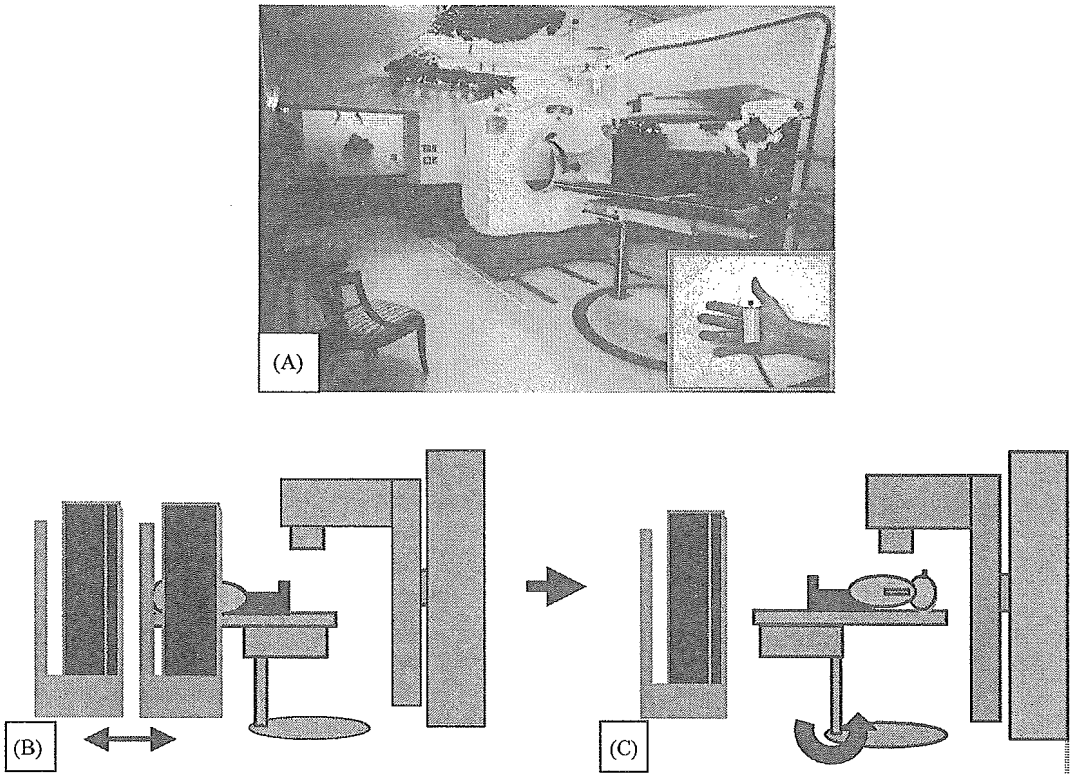

Fig. 1 Treatment room and procedure. (A) Linear accelerator coupled to CT scanner (linac/CT unit) and a patient's handheld switch for radiation beam control. (B) Isocenter of the PTV was adjusted to correspond to the planned isocenter with CT scanning under patient self-breath-hold before every radiotherapy fraction. (C) The couch was rotated 180° so that the rotational center of the CT-gantry corresponded to the isocenter of the linac.

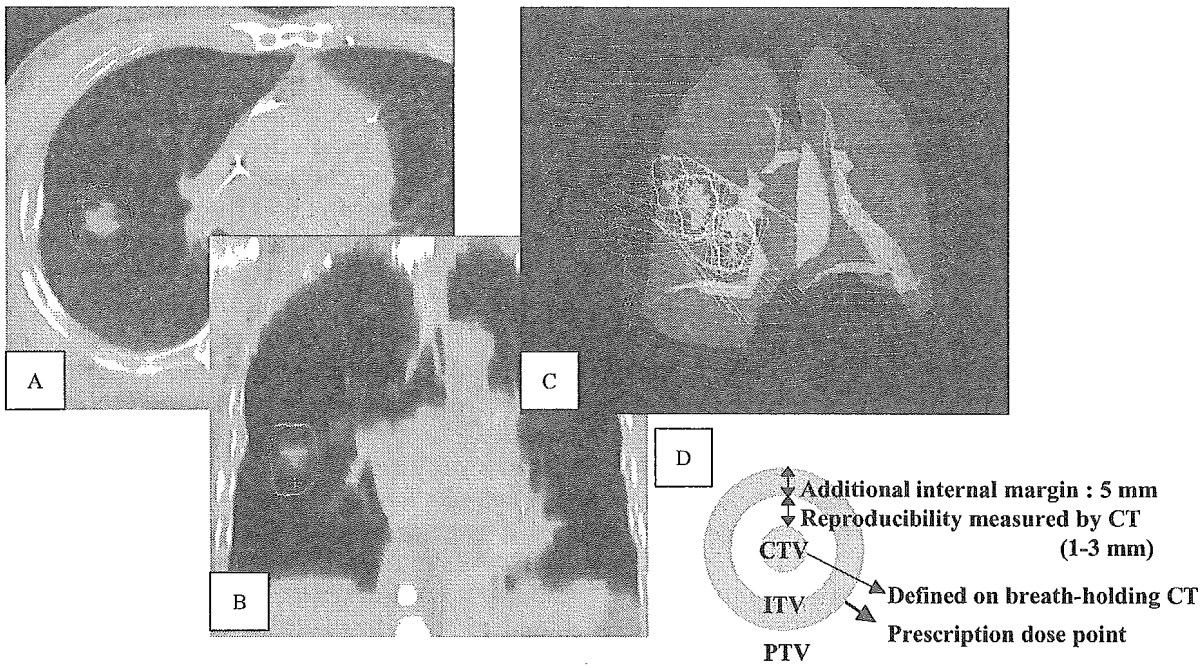

Fig. 2 Three-dimensional treatment planning. Prescribed dose was calculated at the 80% line of global maximum dose in the planning target volume. The 80% isodose line accords with the third line from inside. (A) Isodose curves on axial CT through the center of the PTV; coronal reconstructed image through the center of the PTV. (B) Isodose curves on a coronal reconstructed image through the center of the PTV. (C) Three-dimensional image showing all radiotherapy arcs and isodose curves. (D) Definitions for the internal target volume (ITV) and PTV.

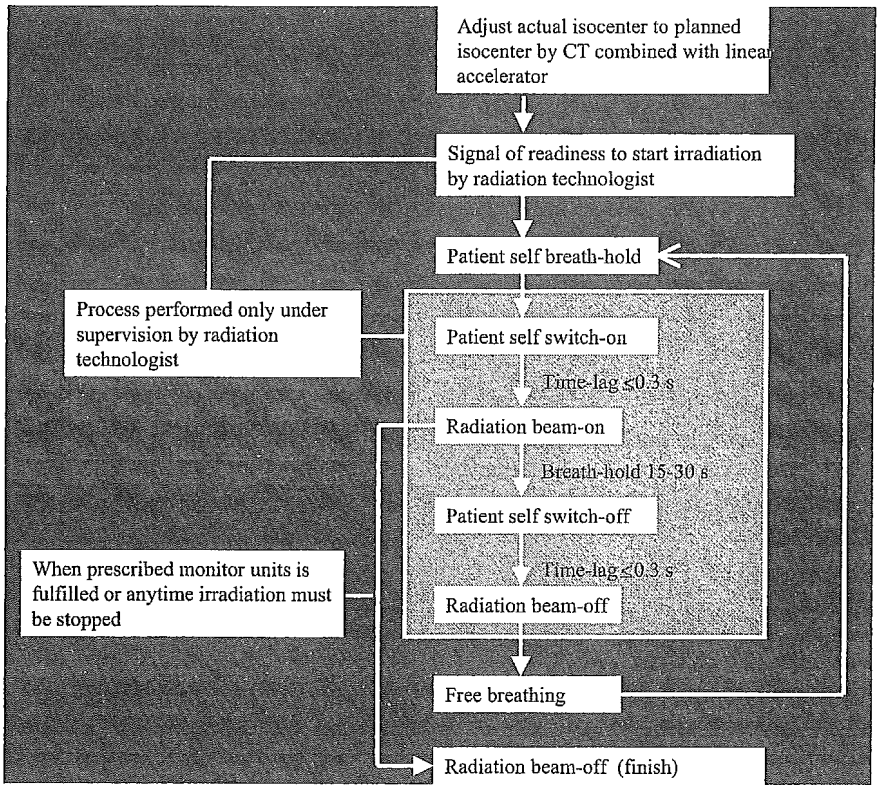

Fig. 3 Flowchart for irradiation method.

Ten different 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 border of the PTV which was almost on the 80–85% isodose line of the global maximum dose in the PTV (Fig. 2) was delivered using a 6 MV X-ray. According to the linear-quadratic model [10], the biologically effective dose (BED) at the isocenter was approximately 120 Gy. Under the patient's self-initiated breath-hold, the radiation beam was turned on and off repeatedly by the handheld switch connected to the linac console box until the full dose was obtained.

A more detailed account of treatment methods has been previously presented [11].

2.4. Evaluation

The patients were followed by the radiation oncologists. Primary and secondary end-points to be investigated were locally progression-free rate and toxicity, respectively. Tumor response was evaluated using the response evaluation criteria in solid tumors by CT. Chest CT was usually obtained every 3 months for the first year, and repeated every 4–6 months thereafter. Complete response (CR) indicated that the tumor had completely disappeared or was replaced by fibrotic tissue. Partial response (PR) was defined as a reduction of ≥30% in longest cross-sectional diameter. Local progression was judged only when the tumor displayed an increase in size on follow-up CT. Findings on CT were interpreted by two radiation oncologists. When difficulty was encountered in deciding whether the findings indicated viable tumor or secondary changes including radiation pneumonitis and fibrosis, tumor was initially presupposed, with results modified according to alterations on further follow-up. Lung, esophagus, bone marrow, and skin were evaluated using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 2.0. Dose–volume histogram (DVH) of lung was calculated with the 3D treatment-planning computer.

2.5. Statistical analysis

Statistical evaluation was performed on Statview (SAS Institute). Cumulative survival rate with the day of treatment as the starting point and analyses of differences between two groups were calculated using the Kaplan–Meier algorithms and log-rank

test. Analysis of possible correlations between patient characteristics or treatment factors and grade of radiation pneumonitis were determined using the Pearson's correlation test. Values of $P < 0.05$ were considered statistically significant.

3. Results

All patients completed the treatment as planned with no interruptions. No patients were lost to follow-up evaluation. The radiation technologist turned off the radiation beam due to misalignment in approximately 3% of all sessions. Follow-up period was 6–30 months (median, 13 months). Of the 35 patients, 18 were followed for >12 months.

3.1. Local tumor response

Rates of CR and PR were 11/35 (31%) and 22/35 (63%), respectively. Overall response rate was 94%. An example of a patient with CR is shown in Fig. 4.

3.2. Toxicity

The ratio of the lung volume irradiated >20 Gy to the whole lung on DVH distributed from 1.0 to 13.0% (median: 5.0%). Lung, esophagus, bone marrow and skin toxicities are listed in Table 2. No pulmonary complications with NCI-CTC grade >2 were noted. Five patients developed acute interstitial pneumonitis in the high-dose irradiated area and developed mild (grade 1 or 2) respiratory symptom, but conditions improved after temporary steroid therapy. There was no significant correlation between patient characteristics and grade of radiation pneumonitis. None of the patients experienced symptomatic radiation esophagitis or dermatitis.

Table 2 Radiation toxicities (NCI-CTC criteria)

	Lung	Esophagus	Bone marrow	Skin
Grade 0	5	35	35	35
Grade 1	25	0	0	0
Grade 2	5	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0

3.3. Progression

Data for progressive cases is shown in Table 3. Two patients (6%) developed local progression 9.9 and 13.5 months after completion of treatment. Both of these locally progressive cases were stage IB and had obtained CR. The other 33 patients had no locally tumor progression. Five patients (14%) developed distant or regional lymph node metastases, including the preceding two patients with local progression. One patient with stage IA adenocarcinoma developed brain and bone metastases without locoregional progression. The time interval between completion of treatment and progression ranged from 6.5 to 13.5 months. Four of the five progressive cases involved stage IB tumors. progressive cases were treated with radiotherapy or chemotherapy in four patients, and two of these were stable at the latest follow-up.

3.4. Survival

During follow-up period of 6–27 months, a total of nine patients died. Of these, six died of other disease; two of chronic liver disease, two of acute intracranial hemorrhage, one of renal dysfunction, and one of Parkinson's disease. Three patients died

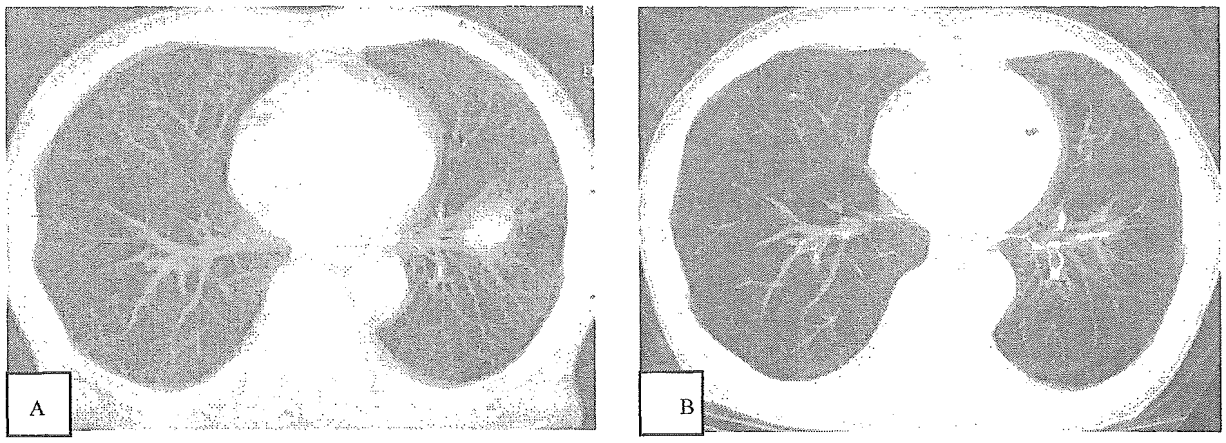

Fig. 4 An example of CR. The patient was an 80-year-old male with T2N0 adenocarcinoma: (A) CT before SRT; (B) CT 6 months after SRT.

Table 3 Summary of progressive cases

Case number	Stage	Tumor diameter (mm)	Histology	Site of progression	Progression time (months after treatment)
1	IB	37	Squamous cell carcinoma	Primary tumor, lung	9.9
2	IB	32	Adenocarcinoma	Primary tumor, lymph nodes[a]	13.5
3	IB	45	Squamous cell carcinoma	Lymph nodes[a]	10.3
4	IB	36	Adenocarcinoma	Lymph nodes[a]	7.1
5	IA	30	Adenocarcinoma	Brain, bone	6.5

[a] Regional lymph nodes: lung hilar and mediastinal lymph nodes.

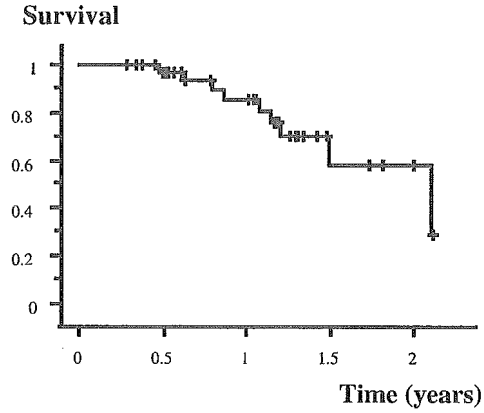

Fig. 5 Actual overall survival rate for all cases.

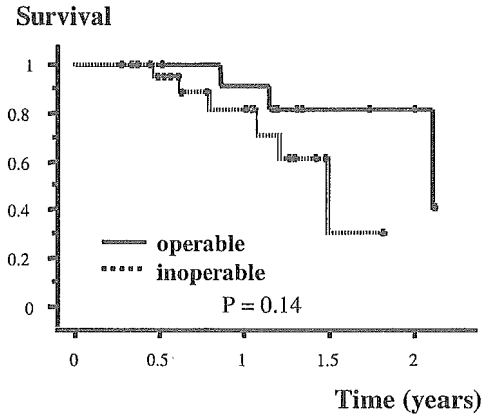

Fig. 7 Actual overall survival rates for medically operable and inoperable patients.

due to progression of metastatic lesions involving lymph nodes and distant sites. Actual overall and cause-specific survival curves are shown in Figs. 5 and 6, respectively. Two-year overall and cause-specific survival rates were 58 and 83%, respectively. Actual overall survival rates of medically operable and inoperable patients are shown in Fig. 7. Two-year overall survival rate for medically operable cases were 83%. Cause-specific survival rates for stages IA and IB patients are shown in Fig. 8. Two-year cause-specific survival rates for stages IA and IB patients were 86 and 80%, respectively, and no significant differences were observed between patients with stages IA and IB tumors.

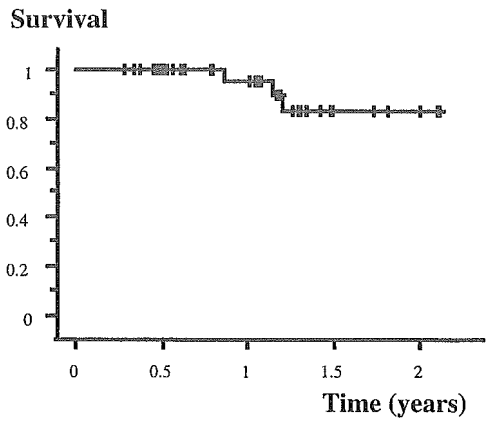

Fig. 6 Actual cause-specific survival rate for all cases.

4. Discussion

Standard management for stage I NSCLC is still surgical resection as the results of treating early

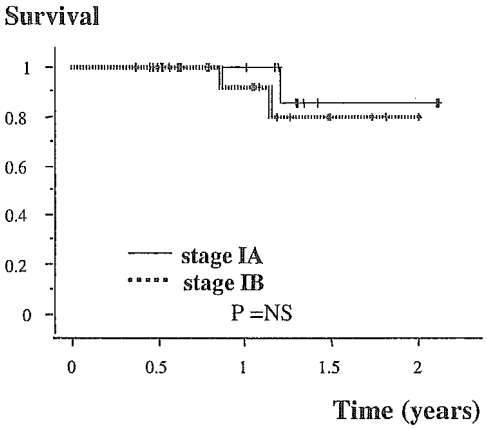

Fig. 8 Cause-specific survival rates for stages IA and IB patients.

stage NSCLC with conventional radiation therapy are disappointing. Local progression is common [12,13] and techniques are needed to increase the radiation dose to the tumor. Cheung et al. reported the results of using 48 Gy in 12 once-daily fractions delivered to an involved field with a conventional two-dimensional techniques for stage I NSCLC. At 2 years, overall and cause-specific survival rates were 46 and 54%, respectively, and local progression was reported in 29.4% of patients [14]. Acute and late skin reactions were found in 30.3 and 24.2% of patients, respectively. Maximizing tumor radiation dose while minimizing damage to adjacent tissues is difficult to achieve using conventional radiotherapy or even with 3D conformal radiation therapy [15]. The ability to concentrate radiation on a small tumor while sparing surrounding tissues has already been made possible using SRT for the treatment of brain lesions. Results from treating small brain metastases are excellent and the local control rate is approximately 90%. When planning treatment for small pulmonary lesions, the ratio of high-dose radiation volume to low-dose radiation volume should be smaller than that for the brain. Moreover, a limited volume of radiation damage in the lung is not likely to cause the severity of symptoms possible with damage to cerebral tissues. However, applying accurate irradiation techniques to an extra-cranial site is difficult, as lesions may be mobile even after bony structures are fixed.

To overcome problems with targeting and immobilizing lesions, we have developed a novel irradiation technique for stereotactic radiotherapy: patient self-controlled breath-hold and beam switching using a combined linac and CT scanner [11]. This new technique is likely to prove extremely useful for the irradiation of lung tumors with a small internal margin and for reduced proportion of high-dose irradiated normal lung to total lung volume. We believe it is useful for irradiation of any lung tumors with reduced PTV and sufficient reproducibility.

Use of CT-guided linac treatment, also called FOCAL (''fusion of CT and linear accelerator''), was pioneered by Uematsu for adjustment of tumor position [4,7,16]. The FOCAL system largely eliminates daily differences in target center attributable to tumor migration or set-up error. It was confirmed that set-up error using the FOCAL system was diminished to almost zero (within 0.5 mm) [8,16]. Use of megavoltage portal films has achieved some success in locating the treatment target. Jaffray et al. integrated a kilovoltage radiographic and tomographic imaging system with a linac to allow localization of bone and soft-tissue structures in the reference frame of the accelerator [17]. However, image quality of diagnostic CT scanners was superior to the kilovoltage radiographic and tomographic imaging systems.

In confirming the radiation field on a well-specified target volume, respiratory organ motion remains problematic. Synchronized or controlled breathing radiotherapy has therefore been receiving worldwide attention. We have implemented patient self-breath-holding in the absence of respiratory monitoring devices for irradiation of small lung tumors. We previously evaluated how precisely patients can hold deep inspiration breath-hold to reproduce the same tumor position in the absence of respiratory monitoring devices. Reproducibility of tumor position under self-breath-holding after sufficient practice was within 3 mm [9,18]. This is similar to results reported by other investigators for breath-hold or gating via respiratory monitoring devices [19,20]. In the PTV, we added 5 mm to the maximum difference of the tumor position measured on the three repeated CT scans performed during self-breath-holding to include sufficient internal margin which cover the reproducibility of the breath-hold technique and intra-session reproducibility according to ICRU 50 and 62 reports. A benefit of breath-holding during deep inspiration is the reduced density of normal lung and minimized proportion of lung volume receiving high-dose radiation, compared to total lung volume. In addition, we have recently developed a new switch, which is connected to the radiation console that enables the patient to turn the radiation beam on and off voluntarily and independently, as it is difficult for the radiation technologist to determine the timing of the patient self-breath-holding in the operating room. The switch could utilize the timing of breath-hold and breath-restart to turn the radiation beam on and off. This system improves the efficiency of irradiation treatment duration, as patients can maximize the time of irradiation during breath-holding.

SRT for small lung tumors using a linac has gained acceptance as an effective means of treatment [4–6,21–25]. The advantages of this radiotherapeutic technique include narrow X-ray beams, concentrated in such a manner as to provide intense irradiation to small lesions at high doses, and a small number of treatment fractions. Irradiation methods and local control rates from several institutions [4–6,25] in which SRT was performed for primary stage I NSCLC are listed in Table 4. Various devices have been used to reduce set-up margins and the internal margins of the radiotherapy port. In three of eight institutions, respiratory gating, active breath control, and tumor-tracking techniques using some respiratory monitoring devices have been applied

Table 4 Comparison of SRT methods and local control rates for stage I non-small cell lung cancer

Reference	Number of patients	Total tumor dose (Gy)	Single dose (Gy)	Treatment time (days)	BED[a] (Gy)	Safety margin[b] (mm)	Breath-hold or respiratory gating or etc.	Image-guided repositioning	Prescription dose point	Median follow-up (months)	Local control (%)
Uematsu et al. [4]	50	50–60	5–6	5	75–96	0	No	Yes	PTV margin	36	94
Nagata et al. [5]	27	48	12	12–13	106	0	No	No	Isocenter	16	96
Fukumoto et al. [6]	17	48–60	6–7.5	14	77–105	0	Yes	Yes	PTV margin	24	94
Hof et al. [25]	10	19–26	19–26	1	55–94	5	Yes	No	Isocenter	15	80
Onishi	35	60	6	5–8	96	5	Yes	Yes	PTV margin	12	94

[a] Biological effective dose ($\alpha/\beta = 10$).
[b] Subtract CTV and maximum respiratory motion from PTV.

to reduce the internal margin. Body frames (Stereotactic Body Frame, Elekta Corp.) and vacuum pillows have been used to control movement in several institutions. Neither body frame nor respiratory monitoring devices are necessary for our method.

Treatment-planning methods also differ among researchers. For example, the prescribed radiotherapy dose normalized to the border of the PTV including a sufficient internal margin at our institution, while it is normalized to the isocenter of the PTV or the border of the PTV without a sufficient internal margin in other institutions. Thus the dose actually delivered to the CTV with our method may be higher than with previously reported methods. In addition, inspired breath-hold was favored on DVHs of PTV relative to normal lung volume [26]. During our follow-up, no severe complications were encountered.

Local control rates presented by previous studies (Table 4) are generally satisfactory. Low local control rates from Hof et al.'s study [25] may be due to reduced irradiation doses. We set an irradiation schedule of 60 Gy twice daily 10 fractions, as BED as the isocenter >100 Gy may be effective for SRT of stage I NSCLC with local control rate >90% [5]. In our study, local relapses have been detected in two (6%) of 35 cases during the 6–30 months post-treatment period. Both of two locally progressive cases were stage IB, and no local progressions occurred among stage IA cases. Previously reported 3-year overall survival rates reached 89% in medically operable patients [4]. The reason why the 2-year overall survival rate in our results was low (58%), while the 2-year cause-specific survival rate was 83%, was that cause of death in six of nine dead cases was other disease due to very high age of patients enrolled in this study (median, 78 years) or serious comorbidity. The overall survival rate of operable cases was encouraging. Four of the total five progressive cases were stage IB, but half were salvaged with additional treatment.

We believe that SRT is a minimally invasive therapy for stage I NSCLC, and should be considered as a radical treatment for all patients. A larger population and longer follow-up period are needed to examine potential benefits to local control and survival rates using the novel SRT technique presented in this report.

5. Conclusion

In conclusion, preliminary results from CT-guided SRT with patient self-breath-hold and self-beam-control technique suggest that this method is safe and effective for treating stage I NSCLC. Advantages of this technique include reduced set-up margins and internal margins, reduced tumor motion during irradiation without the need for respiratory monitoring devices, improved DVHs due to inspired breath-hold, and reduced treatment times. The local progression rate was sufficiently low, and no severe toxicity was produced. Further follow-up and a larger population are needed to evaluate long-term outcomes.

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