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.

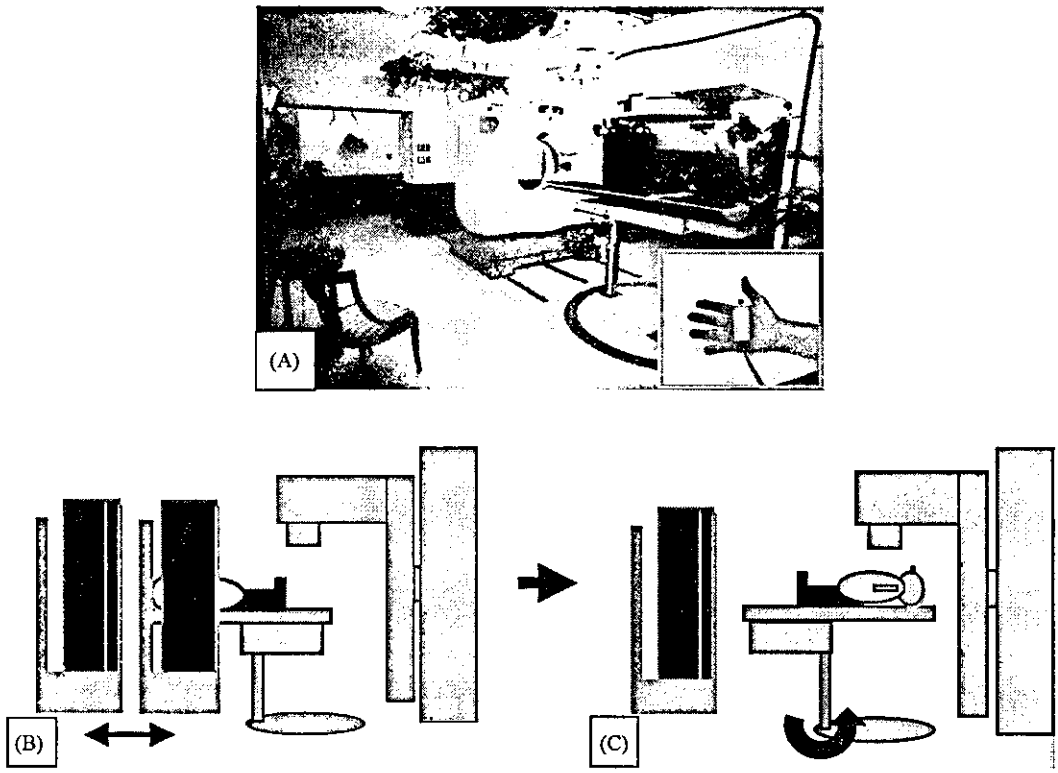

Fig. 1 Treatment room and procedure. (A) Linear accelerator coupled to CT scanner (linac/CT unit) and a patient's handheld switch for radiation beam control. (B) Isocenter of the PTV was adjusted to correspond to the planned isocenter with CT scanning under patient self-breath-hold before every radiotherapy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

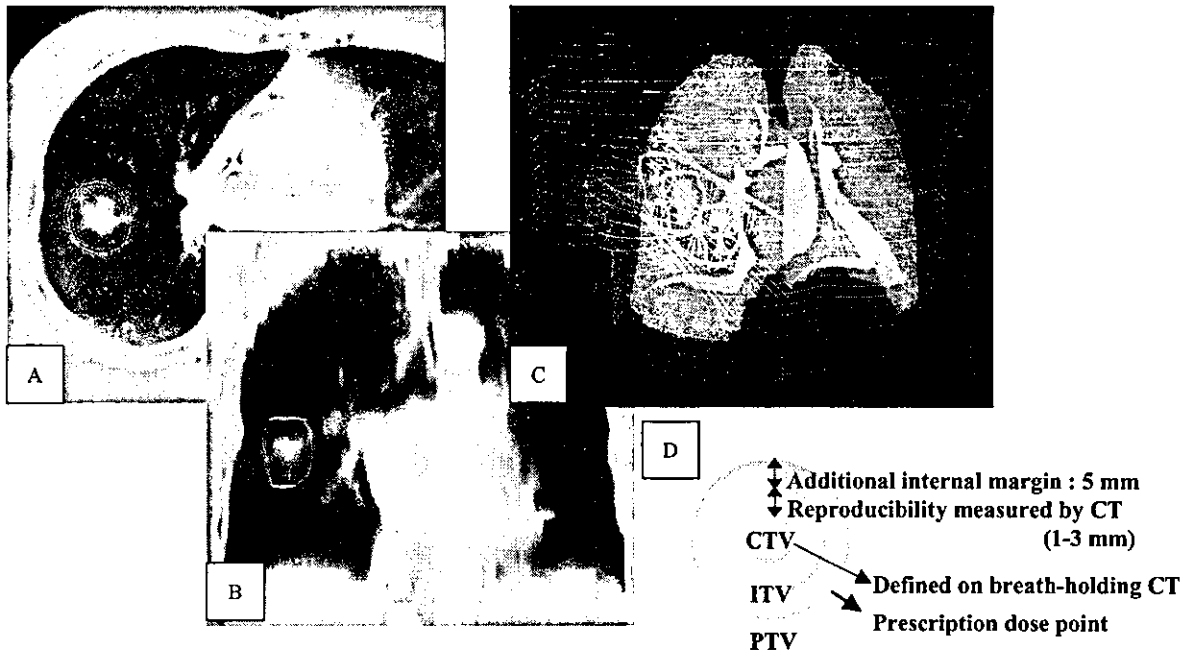

Fig. 2 Three-dimensional treatment planning. Prescribed dose was calculated at the 80% line of global maximum dose in the planning target volume. The 80% isodose line accords with the third line from inside. (A) Isodose curves on axial CT through the center of the PTV; coronal reconstructed image through 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.

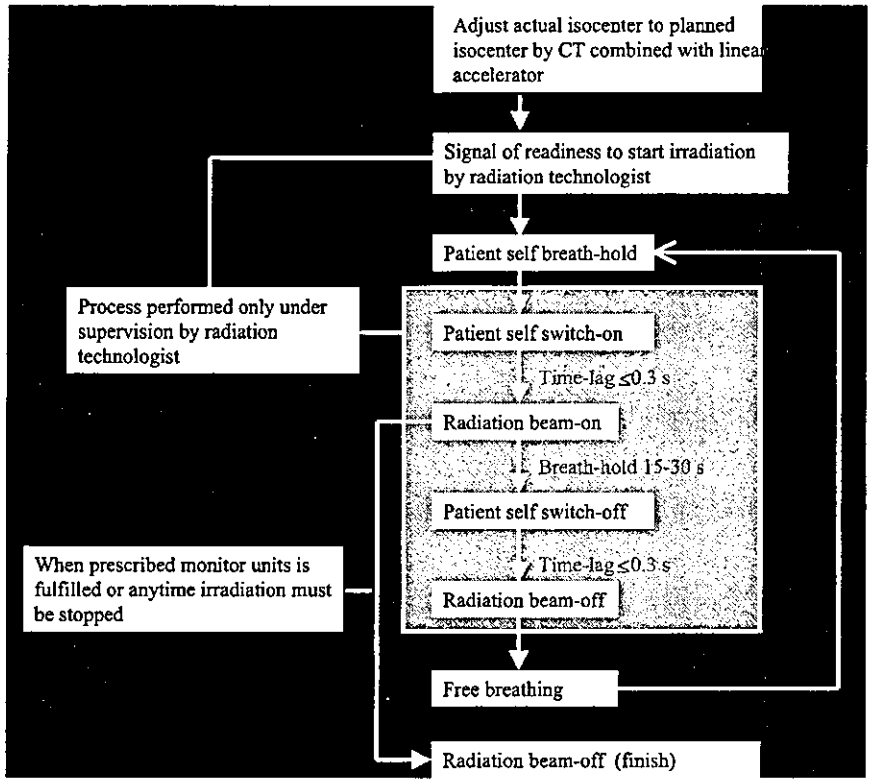

Fig. 3 Flowchart for irradiation method.

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

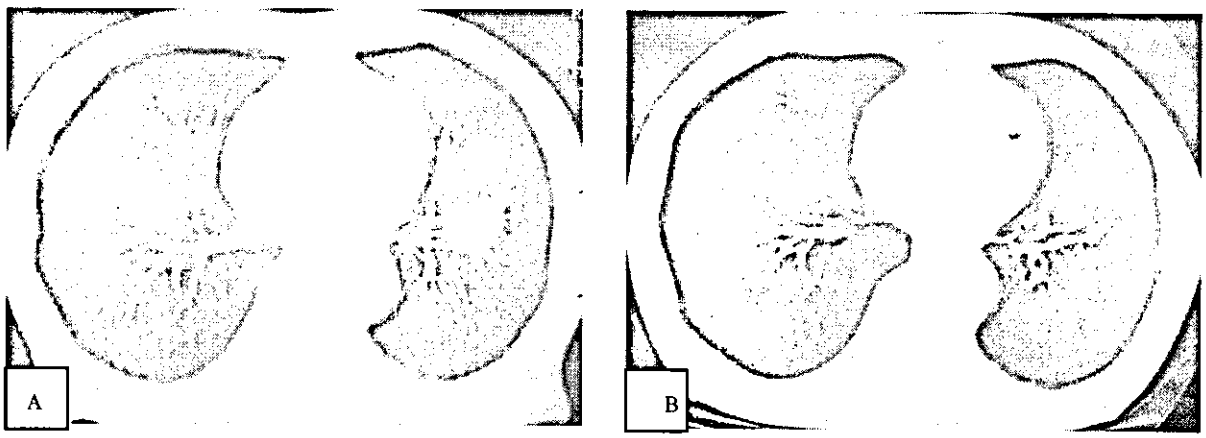

Fig. 4 An example of CR. The patient was an 80-year-old male with T2N0 adenocarcinoma: (A) CT before SRT; (B) CT 6 months after SRT.

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.

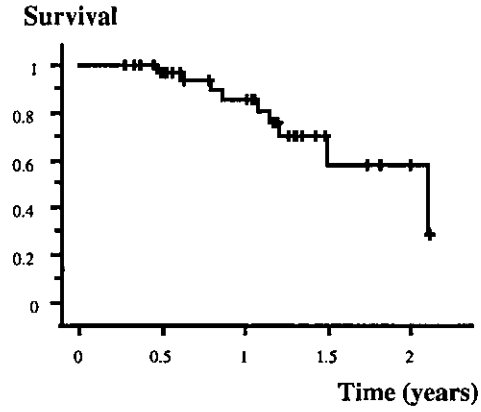

Fig. 5 Actual overall survival rate for all cases.

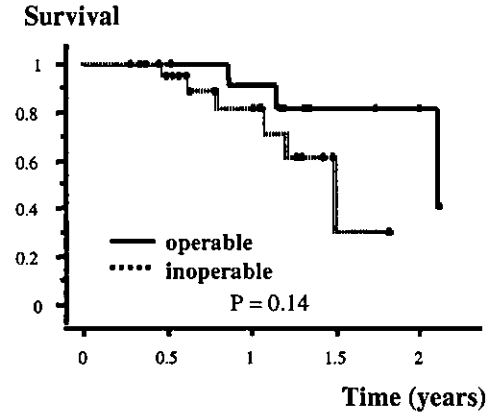

Fig. 7 Actual overall survival rates for medically operable and inoperable patients.

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.

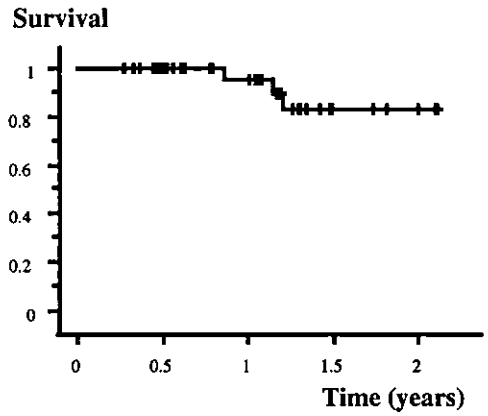

Fig. 6 Actual cause-specific survival rate for all cases.

4. Discussion

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

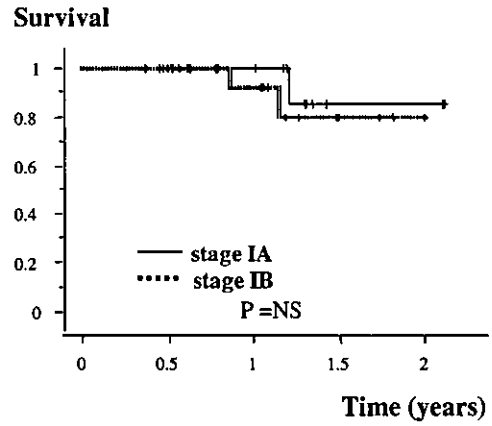

Fig. 8 Cause-specific survival rates for stages IA and IB patients.

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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Stereotactic Hypofractionated High-Dose Irradiation for Stage I Nonsmall Cell Lung Carcinoma

Clinical Outcomes in 245 Subjects in a Japanese Multiinstitutional Study

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BACKGROUND. Stereotactic irradiation (STI) has been actively performed using various methods to achieve better local control of Stage I nonsmall cell lung carcinoma (NSCLC) in Japan. The authors retrospectively evaluated results from a Japanese multiinstitutional study.

METHODS. Patients with Stage I NSCLC (n = 245; median age, 76 years; T1N0M0, n=155; T2N0M0, n=90) were treated with hypofractionated high-dose STI in 13 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. A total dose of 18–75 gray (Gy) at the isocenter was administered in 1–22 fractions. The median calculated biologic effective dose (BED) was 108 Gy (range, 57–180 Gy).

RESULTS. During follow-up (median, 24 months; range, 7–78 months), pulmonary complications of National Cancer Institute-Common Toxicity Criteria Grade > 2 were observed in only 6 patients (2.4%). Local progression occurred in 33 patients (14.5%), and the local recurrence rate was 8.1% for BED ≥ 100 Gy compared with 26.4% for < 100 Gy ($P < 0.05$). The 3-year overall survival rate of medically operable patients was 88.4% for BED ≥ 100 Gy compared with 69.4% for < 100 Gy ($P < 0.05$).

CONCLUSIONS. Hypofractionated high-dose STI with BED < 150 Gy was feasible and beneficial for curative treatment of patients with Stage I NSCLC. For all treatment methods and schedules, local control and survival rates were better with BED ≥ 100 Gy compared with < 100 Gy. Survival rates in selected patients (medically operable, BED ≥ 100 Gy) were excellent, and were potentially comparable to those of surgery. ***Cancer* 2004;101:1623–31.**

KEYWORDS: stereotactic, radiotherapy, altered fractionation, nonsmall cell lung carcinoma, Stage I, dose escalation, multicenter study, local control, survival rate.

Nonsmall cell lung carcinoma (NSCLC) represents a leading cause of mortality worldwide. Lung carcinomas are being detected increasingly early, thanks to routine use of computed tomography (CT)

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scans. For patients with Stage I (T1N0M0 or T2N0M0) NSCLC, full lobar or greater surgical resection represents a treatment choice that promises local control rates ≥ 80% and overall survival rates > 50% after 5 years.[1] However, surgical resection is often not feasible or involves excessive risk for some patients with lung carcinoma with tobacco-related illness, severe cardiovascular disease, or other medical conditions. A small proportion of patients who are eligible for surgery may refuse procedures for personal reasons. Radiotherapy can offer a therapeutic alternative for these patients, but outcomes for conventional radiotherapy are unsatisfactory, and are potentially amplified by selection bias, with local control rates of 40–70% and 5-year survival rates of only 5–30%.[2–4] Doses of conventional radiotherapy to treat NSCLC have been suggested to be too low to achieve tumor control. However, providing a higher dose to the tumor without increasing adverse effect was previously impossible, due to technical uncertainties over focusing irradiation only on the tumor-bearing area of the lung.

With the increasing accuracy of localization for tumor-bearing areas using various imaging techniques, hypofractionated or single high-dose stereotactic irradiation (STI) has been actively investigated for Stage I NSCLC in Japan.[5–8] STI can also substantially reduce overall treatment time from several weeks for a conventional radiotherapy schedule to a few days, offering important advantages to the patient. A landmark study by Uematsu et al.,[5] one of the pioneers of STI for extracranial lesions, revealed excellent survival rates for medically operable patients, approximating those for full lobar surgical resection. Under the guidelines of the Japanese Society of Radiation Oncology study group,[9] Stage I NSCLC has been treated using small-volume STI in numerous Japanese institutions since the late 1990s, with far fewer symptomatic adverse effects than conventional radiotherapy. Although optimal STI techniques and schedules for Stage I NSCLC remain unclear, the number of patients with Stage I NSCLC treated nationwide using small-volume, high-dose STI has accumulated rapidly. Although differences in techniques and schedules may vary widely, retrospective investigation of the results of STI for Stage I NSCLC from the many institutions that have used small-volume, high-dose irradiation in this short period should yield some meaningful data. The current study retrospectively evaluated Japanese multiinstitutional results for high-dose STI for Stage I NSCLC, and sought to answer the following questions: 1) What is the optimal dose to limit toxicity and still obtain local control? 2) Are the results from single-institution studies reproducible? 3) Are STI results comparable to those of surgery?

TABLE 1
Patient Characteristics

Total no. of patients	245
Age	35–92 yrs (median, 76 yrs)
PS	PS 0, 94; PS 1, 104; PS 2, 47
Pulmonary chronic disease	Positive, 196; negative, 96
Histology	Squamous cell carcinoma, 110; adeno carcinoma, 109; others, 26
Stage	Stage IA, 155; Stage IB, 90
Tumor diameter	7–58 mm (median, 28 mm)
Medical operability	Inoperable, 158; operable, 87

PS: performance status.

MATERIALS AND METHODS

Eligibility Criteria

All patients enrolled in the current study satisfied the following eligibility criteria: 1) identification of T1N0M0 or T2N0M0 primary lung carcinoma on chest and abdominal CT scans, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging scans; 2) histologic confirmation of NSCLC; 3) tumor diameter < 60 mm; 4) performance status ≤ 2 according to World Health Organization guidelines; and 5) inoperable tumor due to poor medical condition or refusal to undergo surgery.

No restrictions were utilized concerning the location of eligible tumors, irrespective of whether they were located adjacent to a major bronchus, blood vessel, chest wall, or the esophagus or spinal cord. However, the spinal cord was kept out of the high-dose area.

Patients were informed as to the concept, methodology, and rationale of this treatment. Written informed consent was obtained from all patients. The study was approved by the ethics committee of each institution and was performed in accordance with the 1983 revision of the Helsinki Declaration.

Patient Characteristics

A summary of patient characteristics is provided in Table 1. From April 1995 to February 2003, 245 patients with primary NSCLC were treated with hypofractionated high-dose STI in 13 institutions. Of the 245 patients, 158 (65%) were considered to be medically inoperable, due predominantly to chronic pulmonary disease, advanced age, or other chronic illness. The remaining 87 patients (35%) were considered to be medically operable, but had refused surgery or had been advised to select STI by medical oncologists.

Treatment Methods

All patients were irradiated using stereotactic techniques. For the purposes of the current study, all ste-

TABLE 2
Treatment Schemes

Beam energy	6-MV X-ray, 12; 4-MV X-ray, 1
Measures for respiratory motion	Respiratory gating, 5; breath hold, 2; non, 6
Fixation of patients	Vacuum pillow, 5; body frame, 4; non, 4
Irradiation port shape	Regular, 4; conformal, 9
Fraction numbers	1–25 (multiple, 11; single, 2)
Irradiation mode	Multiple (6–20) static ports, 7; dynamic arc, 6
Single dose (at the isocenter)	3–35 Gy
Total dose (isocenter) of stereotactic irradiation	20–69 Gy
Conventional radiotherapy	30–44 Gy/15–20 fractions in 27 patients; non, 218 patients
BED = nd(1+d/a/b) at the isocenter	57–180 Gy (median, 108 Gy)

BED: biologic effective dose; Gy: gray.

reotactic techniques fulfilled three requirements: 1) reproducibility of the isocenter ≤ 5 mm, as confirmed in every fraction; 2) slice thickness on CT scan ≤ 3 mm for three-dimensional (3D) treatment planning; and 3) irradiation with multiple noncoplanar static ports or dynamic arcs. Table 2 summarized various techniques and instruments introduced to achieve STI in 13 institutions. To fulfill the first requirement, a CT scan or two-directional portal graph was undertaken before every treatment regimen in 12 institutions, whereas real-time tumor tracking using a gold marker inserted around the tumor[10] was performed in 1 institution. A CT scanner sharing a common couch with the linear accelerator was placed in an irradiation room in two institutions.[11,12]

Treatment planning with irregularly shaped beams using noncoplanar multiple (3–10) dynamic arcs or multiple static ports (6–20 ports) was established with the help of a 3D treatment-planning computer. Beam shaping was performed in some institutions using an integrated motorized multileaf collimator with 0.5–1-cm leaf width at the isocenter. Furthermore, various techniques using breathing control or gating methods and immobilization devices such as a vacuum cushion with or without a stereotactic body frame were utilized to reduce respiratory internal margins. Respiratory gating or breath-hold methods were used in seven institutions.

Planning CT scans were performed with 2 or 3-mm slice thickness and displayed using a window level of −700 Hounsfield units (HU) and a window width of 2000 HU. In some institutions, irradiation and planning CT scans were performed under breath-hold conditions. In other institutions, irradiation and planning CT scans were performed under free shallow breathing, with images taken using slow scanning (4 seconds per slice).

The clinical target volume (CTV) marginally exceeded the macroscopic target volume by 0–5 mm. The planning target volume (PTV) comprised the CTV, a 2–5-mm internal margin, and a 0–5-mm safety margin. An example of an STI dose distribution for Stage I lung tumors is shown in Figure 1. A high dose was concentrated on the tumor-bearing area while sparing surrounding normal lung tissues using STI.

Irradiation schedules also differed among institutions. The number of fractions ranged between 1 and 25, with single doses of 3–12 Gy. A total dose of 18–75 Gy at the isocenter in 1–25 fractions was administered with 6-MV X-rays within 20% heterogeneity in the PTV dose. Twenty-seven patients had received conventional irradiation doses of 30–44 Gy in 15–20 fractions before STI due to physician preferences. No chemotherapy regimens were administered before or during radiotherapy.

To compare the effects of various treatment protocols with different fraction sizes and total doses, a biologic effective dose (BED) was utilized in a linear-quadratic model.[13] BED was defined as $nd(1+d/\alpha/\beta)$, with units of grays, where n is the fractionation number, d is the daily dose, and α/β is assumed to be 10 for tumors. BED was not corrected with values for tumor-doubling time or treatment term.

The median BED at the isocenter was 108 Gy (range, 57–180 Gy). BED was ≥ 100 Gy in 173 patients and < 100 Gy in 72 patients.

Dose constraints were set for the spinal cord only. The BED limitation for the spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity). This dose constraint for the spinal cord was achieved in all patients who satisfied all eligibility criteria.

Evaluation

The objectives of the current study were to retrospectively evaluate toxicity and the local control and survival rates according to BED. Follow-up examinations were performed by radiation oncologists for all patients. The first examination took place 4 weeks after treatment, and patients were subsequently seen every 1–3 months. Tumor response was evaluated using previously published National Cancer Institute (NCI) criteria.[14] Chest CT scans (slice thickness, 2–5 mm) were usually obtained every 3 months for the first year, and repeated every 4-6 months thereafter. A complete response (CR) indicated that the tumor had completely disappeared or was replaced by fibrotic tissue. A partial response (PR) was defined as a ≥ 30% reduction in the maximum cross-sectional diameter. Distinguish-

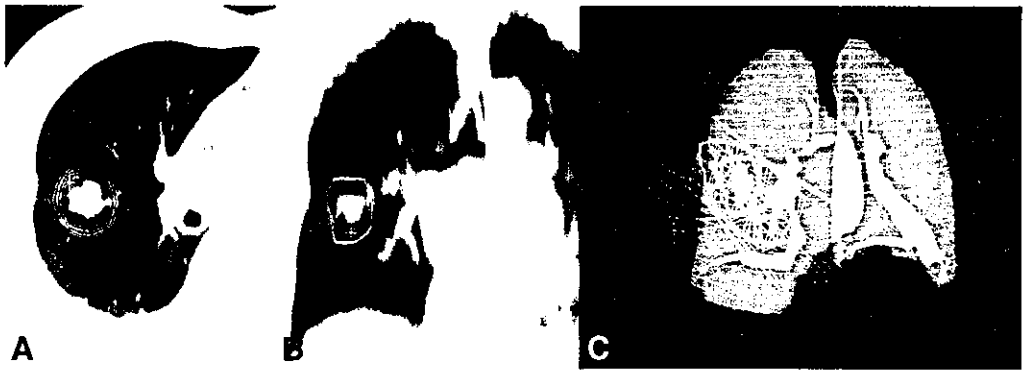

FIGURE 1. An example of three-dimensional treatment planning. (A) Isodose curves on axial CT through the center of the PTV. (B) Isodose curves on a coronal reconstructed image through the center of the PTV. (C) Three-dimensional image showing all radiotherapy arcs and isodose curves.

ing between residual tumor tissue and radiation fibrosis was difficult. Any suspicious residual confusing density after radiotherapy was considered to be evidence of PR, so the actual CR rate may be higher than presented in the current study. Local disease recurrence was considered to have occurred only when enlargement of the local tumor continued for > 6 months on follow-up CT scans. Findings on CT scans were interpreted by two radiation oncologists. Absence of local disease recurrence was defined as locally controlled disease.

Lung, esophagus, bone marrow, and skin were evaluated using Version 2 of the National Cancer Institute-Common Toxicity Criteria (NCI-CTC).

Statistical Analysis

Local disease recurrence rates in the two groups were compared using the chi-square test. BED among patient groups at each pulmonary toxicity grade was compared using Kruskal–Wallis tests. Cumulative survival curves were calculated and drawn using Kaplan–Meier algorithms with the day of treatment as the starting point. Subgroups were compared using log-rank statistics. Values of $P < 0.05$ were considered to be statistically significant. Statistical calculations were conducted using Version 5.0 StatView software (SAS Institute Inc., Cary, NC).

RESULTS

All patients completed treatment with no particular complaints. The median period of follow-up was 24 months (range, 10–78 months). BED (α/β is assumed to be 2 Gy for chronic toxicity of the spinal cord) did not exceed 80 Gy in any of the patients.

Local Tumor Response

Of the 245 patients evaluated using CT scans, CR and PR were achieved in 57 (23.3%) and 151 (61.6%) patients, respectively. The overall response rate (CR+PR) was 84.8%. Overall response rates for tumors with BED ≥ 100 Gy ($n = 173$) and < 100 Gy ($n = 72$) were 84.5% and 83.3%, respectively. An example of a CR is shown in Figure 2.

Toxicity

Treatment toxicities are summarized in Table 3. Symptomatic radiation-induced pulmonary complications (NCI-CTC criteria Grade > 1) were observed in 17 patients (6.9%). No significant differences in BED were identified among patient groups at each pulmonary toxicity grade. Pulmonary fibrosis or emphysema before treatment was observed in 15 (88%) of the 17 patients with pulmonary complications > Grade 1. Pulmonary symptoms resolved in most patients with or without steroid therapy, but continuous oxygen supply was required in three patients who displayed poor respiratory function before irradiation. Chronic segmental bronchitis and wall thickening causing atelectasis on the peripheral lung was observed in one patient. Grade 3 esophagitis was temporarily observed in two patients with tumors adjacent to the esophagus. Grade 3 or 4 dermatitis was observed in two patients with tumors adjacent to the chest wall. No vascular, cardiac, or bone marrow complications had been encountered as of the last follow-up.

Disease Recurrence

Local disease recurrence occurred in 13.5% of all patients, with rates being significantly lower for BED ≥ 100 Gy (8.1%) compared with < 100 Gy (8.1% vs. 26.4%, $P < 0.01$). Patients with Stage IB disease displayed significantly higher rates of local disease recurrence compared with patients with Stage IA disease. However, no differences in the local disease recurrence rate were observed between patients with Stage IA disease and patients with Stage IB disease for BED

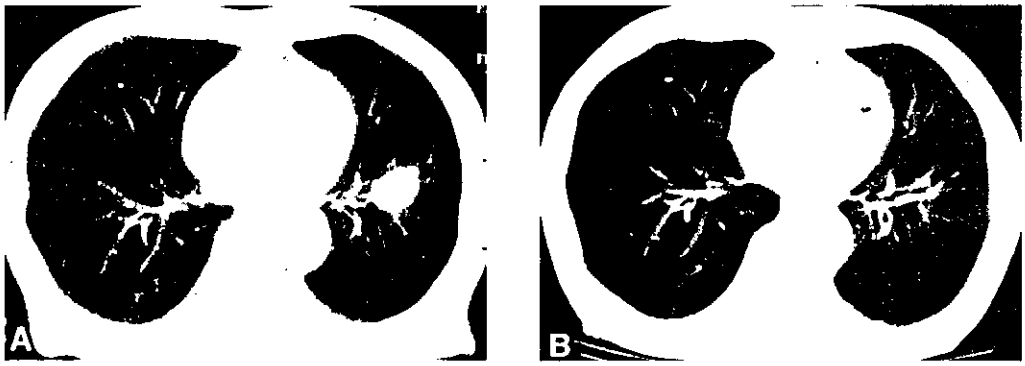

FIGURE 2. An example of a patient with a complete response (CR). The patient was an 80-year-old male with T2N0 adenocarcinoma. (A) Computed tomography scan (CT) before stereotactic irradiation (STI) of 70 gray/10 fractions/5 days. (B) CT scan 6 months after STI. CR was acquired and no radiation-induced pneumonia was apparent.

TABLE 3
Toxicity

Pneumonitis[a]	
Grade 0, 32.8%	
Grade 1, 59.6%	
Grade 2, 4.1%	
Grade 3, 1.2%	
Grage 4, 1.2%	
Esophagitis[a]	
Grade 0, 95.6%	
Grade 1, 2.4%	
Grade 2, 1.2%	
Grade 3, 0.8%	
Dermatitis[a]	
Grade 0, 98.0%	
Grade 1, 0.8%	
Grade 2, 0.4%	
Grade 3, 0.4%	
Grade 4, 0.4%	
Pleural effusion (1.6%)	
Rib fracture (0.8%)	
Bone marrow suppression (0.0%)	

[a] Graded according to National Cancer Institute-Common Toxicity Criteria (Version.2.0).

≥ 100 Gy. Rates of local disease recurrence were also significantly lower in the total group and Stage IA and Stage IB subgroups for BED ≥ 100 Gy compared with < 100 Gy. In particular, when BED was < 100 Gy, the local disease recurrence rate in patients with stage IB disease was 41.4% (12 of 29) compared with 16.3% (7 of 43) for patients with Stage IA disease. For BED ≥ 100 Gy, the local disease recurrence rate was 7.5% for BED ≥ 120 Gy (n = 80) and 9.8% for BED ≥ 140 Gy (n = 40). The local disease recurrence rates for adenocarcinoma and squamous cell carcinoma were 13.6% (15 of 110) and 13.8% (15 of 109), respectively.

The patterns of first disease recurrence are listed in Table 4. Some sites of disease recurrence overlapped, and isolated local, lymph node, and distant disease recurrences were observed in 8.6%, 3.3%, and 9.8% of patients, respectively. The local disease recurrence rate of patients with Stage IB was twice that of patients with Stage IA disease, whereas lymph node and distant disease recurrence rates were basically identical in the two subgroups.

Survival

The overall 3 and 5-year survival rates were 56% and 47%, respectively. The cause-specific 3 and 5-year survival rates were both 78%. Overall survival rates differed significantly according to medical operability. For example, intercurrent deaths occurred in 19.1% of inoperable patients and in 3.4% of operable patients (Fig. 3). Overall survival rates according to BED in all patients revealed significant differences between the subgroups for BED < 100 Gy and ≥ 100 Gy (Fig. 4). Overall survival rates according to BED in operable patients revealed identical 3 and 5-year survival rates of 88% for BED ≥ 100 Gy (Fig. 5). Overall 5-year survival rates according to stage in operable patients irradiated with BED ≥ 100 Gy were 90% for patients with Stage IA disease and 84% for patients with Stage IB disease (Fig. 6).

DISCUSSION

Surgical resection remains the standard management for patients with Stage I NSCLC. The 5-year overall survival rates for patients undergoing resection range from 55% to 72% for Stage I NSCLC.[15–17] Results for treating early-stage NSCLC using conventional radiotherapy are disappointing. Qiao et al.[18] reviewed 18 studies on Stage I NSCLC treated using conventional radiotherapy alone, and reported that the 3-year overall and cause-specific survival rates were 34 ± 9% (mean ± standard error of the mean) and 39±10%, respectively. Although CR represents an important

TABLE 4
Patterns of First Disease Recurrences According to Stage and BED

Site of disease recurrence[a]	Total no. of patients (%)	Stage IA (%)	Stage IB (%)	BED < 100 Gy (%)	BED ≥ 100 Gy (%)
Local disease recurrence	33/245 (13.5)	15/155 (9.7)	18/90 (20.0)	19/72 (26.4)	14/173 (8.1)
Regional lymph node recurrence	20/245 (8.2)	12/155 (7.7)	8/90 (8.9)	8/72 (11.1)	12/173 (6.9)
Distant metastasis	36/245 (14.7)	23/155 (14.8)	13/90 (14.4)	14/72 (19.4)	22/173 (12.7)

BED: biologic effective dose; Gy: gray.
[a] Some of the disease recurrences overlapped each other.

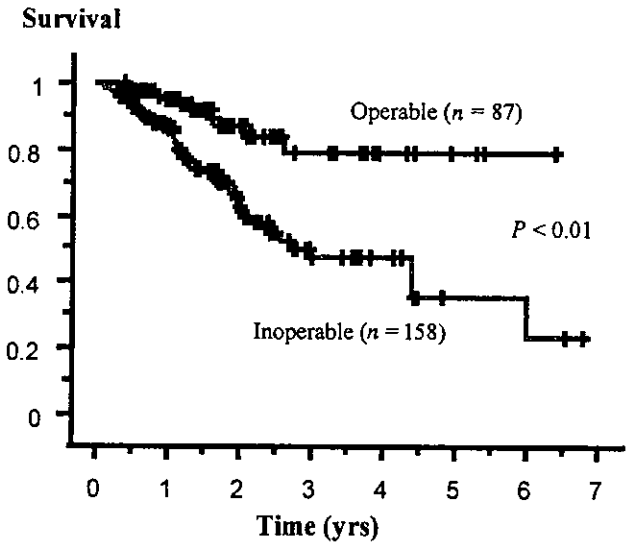

FIGURE 3. Overall survival rate according to medical operability.

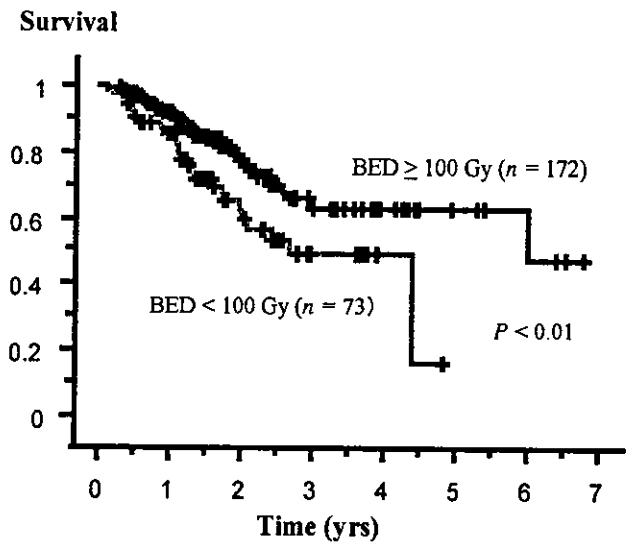

FIGURE 4. Overall survival rate according to the biologic effective dose in all patients.

prognostic factor, particularly for tumors < 5 cm in diameter,[19,20] local disease recurrence is common after conventional radiotherapy for early-stage NSCLC.[18,21,22] Several studies have shown the value of dose escalation in Stage I NSCLC.[18–20] Although increased radiation dose to the tumor is essential, escalating the dose is difficult under conventional radiotherapy techniques, given the relatively large amount of normal lung tissue enclosed in the high-dose region, including internal and safety margins to accommodate respiratory movements and daily setup errors. The most common reactions caused by radiation dose escalation are pneumonitic changes, which can induce acute symptoms of fever and cough, leading to interstitial fibrosis and subsequent reduction in lung capacity. In patients with already compromised respiratory function, such reductions can prove fatal.

Because excessive dose escalation, which improves local control in patients with NSCLC,[18,23,24] is so hard to obtain using conventional techniques, new approaches must be taken to improve outcomes. In 1995, Blomgren et al.[25] introduced a new STI technique for extracranial radiotherapy that was analogous to cranial radiosurgery. 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. The ability to concentrate radiotherapy on a small tumor while sparing surrounding tissues had already been made possible using STI. Results from treating small brain metastases are excellent, with local control rates of approximately 90%. Application of STI techniques to the treatment of small lung tumors is reasonable, as the ratio of high-dose radiation volume to normal tissue volume should be smaller than that for the brain. Moreover, the limited volume of radiation damage on the lung or adjacent structures is unlikely to result in the severity of symptoms possible with damage to cerebral tissues. The current data reveal that Grade 3 or 4 radiation pneumonitis was observed in few patients (4%). Acute esophagitis, dermatitis, and chronic bronchitis were also observed in relatively few patients for whom tumors bordered on these organs. No other life-threatening toxicities were encountered.

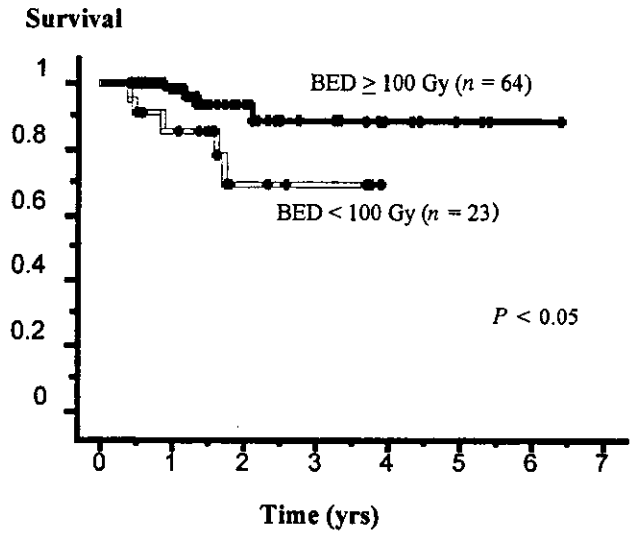

FIGURE 5. Overall survival rate according to the biologic effective dose in medically operable patients.

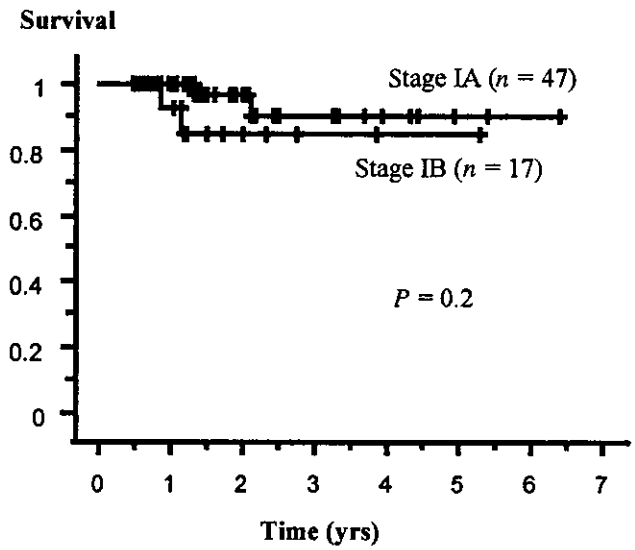

FIGURE 6. Overall survival rate according to stage in medically operable patients irradiated with biologic effective dose ≥ 100 gray.

However, the chronic effects of hypofractionated irradiation on major vessels, bronchus, esophagus, heart, and spinal cord remain unknown. Lethal pulmonary bleeding has been reported after a schedule of 24-Gy single-dose irradiation (BED = 81.6 Gy).[26] Long and careful follow-up is therefore warranted.

Recently, STI for small lung tumors using a linear accelerator has gained acceptance as an effective treatment modality. Irradiation methods and local disease recurrence rates from several institutions in which STI has been performed for primary Stage I NSCLC are listed in Table 5.[5-7,27-29] Although BED analysis using the linear-quadratic model is not quite appropriate for radiotherapy with a large single dose or short treatment period,[30] the model is useful to compare outcomes from a variety of treatment schedules using different single doses and number of fractions. Cheung et al.[31] summarized several clinical studies. In their study, crude local recurrence rates with conventional radiotherapy were 36–70%, with BED of 59.6–76.4 Gy at an α/β ratio of 10. They recommended dose escalation to increase the local control rate. STI appears to represent an ideal modality for dose escalation. Local tumor recurrence rates of Stage I NSCLC after STI with a BED of 99–137 Gy were 0–6% for a median follow-up period of 19–60 months.[5-7,27,28] The comparatively high local disease recurrence rate reported by Hof et al.[29] may be attributable to lower BED. In the current study, the local control rate was 91.9% for BED ≥ 100 Gy. For BED < 100 Gy, the local control rate was poor, particularly in patients with Stage IB disease. Given our clinical results, additional dose escalation studies may be possible. However, patients receiving BED ≥ 120 Gy or ≥ 140 Gy did not display significantly better local control rates than patients receiving lower BED, even for patients with Stage IB disease. Satisfactory BED to achieve local control for Stage I NSCLC is approximately 100 Gy. Representative examples of dose regimens performed in the current study that provided approximate BEDs > 100 Gy were 48 Gy/4 fractions or 50 Gy/5 fractions. However, treatment outcomes for patients who received conventional irradiation before STI in our study were not significantly different from those of other patients. Although a longer follow-up is necessary to determine final control rates of tumors in our study, local control rates for STI may be equivalent to surgical results, as most local disease recurrences generally occur within 3 years after treatment.[18]

In our study, the overall survival rates were excellent for limited patients considered operable before treatment and with BED ≥ 100 Gy. The 88% three-year overall survival rate in operable patients treated with BED ≥ 100 Gy was consistent with single institutional results (a 3-year overall survival rate of 88% in 29 medically operable patients) reported by Uematsu et al.[5] The patients in that study (from the Medical Defense College, Saitama, Japan) were not included in the current multiinstitutional study. Survival rates after STI for BED ≥ 100 Gy may well match those after lobectomy for Stage I NSCLC. We believe that good treatment outcomes from STI depend on a high BED, a large single dose, a short treatment period, and delivery of a modest dose to a large lung volume. STI can reduce substantially overall treatment time from

TABLE 5
Comparison of STI Methods and Local Control Rates for Stage I Nonsmall Cell Lung Carcinoma

Author	No. of patients	Total tumor dose (Gy)	Single dose (Gy)	Treatment time (days)	BED (Gy)[a]	Safety Margin (mm)[b]	Breath-hold or respiratory gating	Image-guided repositioning	Median follow-up (mos)	Local disease recurrence (%)
Uematsu et al.[5,27]	50	50–60	5–6	5–12	100–120	0	No	Yes	60	6
Nagata et al.[6,28]	27	48	12	12–13	106	0	No	Yes	19	0
Fukumoto et al.[7]	17	48–60	6–7.5	14	99–137	0	Yes	Yes	24	6
Hof et al.[29]	10	19–26	19–26	1	55–94	5	Yes	No	15	20

Gy: gray; STI: stereotactic irradiation; BED: biological effective dose (α/β = 10).

[a] BED was recalculated at the isocenter.

[b] Safety margin: subtract the clinical target volume and maximum respiratory motion from the planning target volume.

several weeks of conventional radiotherapy to a few days, offering important advantages to the patient.

In conclusion, hypofractionated high-dose STI with BED < 150 Gy represents a feasible and beneficial method for obtaining curative treatment of patients with Stage I NSCLC. Local control and survival rates were better for BED ≥ 100 Gy than for BED < 100 Gy for all treatment methods and schedules. Survival rates for STI in selected patients (medically operable and BED ≥ 100 Gy) were excellent and reproducible among institutions, irrespective of specific treatment methods, and were potentially equivalent to those of surgery. The current study was a retrospective review, and unknown selection biases for treated and analyzed patients may have been present. Moreover, treatment parameters were very heterogeneous. However, STI may become a standard radical treatment strategy for Stage I NSCLC, at least for compromised patients. More patients and longer follow-up, or a prospective Phase II study based on a single treatment schedule followed by a Phase III trial comparing surgical outcomes with those of STI, are necessary to determine standard treatments for Stage I NSCLC.

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CORRESPONDENCE

Reply to Dr. S. Senan

As Dr. Senan commented, so we are also surprised to find our presented data showing 47% of grade 3 or higher radiation pneumonits, which is in contrast to a former phase II study. We have evaluated the cause of a high frequency of severe radiation pneumonits, and combined it with the irradiation techniques (2D versus 3D) as well as the advanced age of the patients. In our results, fatal chemo-radiation pneumonitis was observed in 3 of 32 patients, and the mean dimension of their radiotherapy port was 194 cm^2. And further five patients died from infectious pneumonia which occurred outside the irradiated port. The poor respiratory function caused by previously produced chemo-radiation pneumonitis had an additional effect on the cause of death in three of these five patients, and the mean dimension of their radiotherapy port was 166 cm^2.

Certainly, we know the merits of 3D techniques, as reported in a number of papers and they are superior to 2D techniques for irradiation of lung cancer, which Senan and co-workers [1] also reported in their article. We do not quite protest that 2D techniques are always acceptable for concurrent chemo-radiotherapy schedules when portal sizes are small. In many Japanese institutions, radiotherapy is still performed using the 2D portal technique. Thus, physicians should be aware of the present results when planning therapy, and that a dose-modification of docetaxel or radiotherapy is needed when radiotherapy is performed using a 2D portal technique with a large port (dimensions >150 cm^2). Rosenman's paper [2] includes important points for concurrent chemo-radiotherapy in locally advanced non-small-cell lung cancer. However, we estimate that the resultant dose–volume histograms of normal tissue in their irradiation method are not so different from ours. The irradiation techniques solely could not account for the high frequency of severe radiation pneumonits in our results. There may be a racial difference in biological response of pulmonary normal tissue to this chemo-radiotherapy schedule between the Japanese and others; however, further research using a large number of patients or from other Japanese institutions are necessary to confirm our results.

In addition, Dr. Senan commented on a difference between our study and previous studies concerning an induced pulmonary toxicity due to the use of G-CSF. We have learned that all hematopoeitic-colony-stimulating factors should be avoided in patients receiving concurrent chemo-radiotherapy but in Japan, G-CSF is administered to not a few patients with granulocyte counts of under 1000 μl^{-1}. The reason why there were no clear relations between the use of G-CSF and the grade of chemo-radiation pneumonitis in our results was unclear; however, it may be the small number of patients enrolled in this study.

In Japan, the standard treatment methods recommended by ASCO or the National Cancer Institute are not popular enough and besides, Japanese pulmonary medical oncologists are not always know of irradiation techniques. The most important point we make in this paper is that we should not use 2D irradiation techniques and that we must pay attention to severe pulmonary toxicity caused by this chemo-radiotherapy schedule when portal sizes are large, at least in Japan.

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