For the evaluation of RILI after SBRT, dose distribution and fractionation should be considered. Compared with conventional radiotherapy, SBRT allows high doses to be delivered to a confined area around the tumor. Therefore, the dose distribution of SBRT is greatly different from that of conventional radiotherapy. Concerning fractionation, 60–66 Gy in 2-Gy fractions is commonly used in conventional radiotherapy for lung cancer. On the other hand, SBRT is performed with a much higher dose per fraction. For example, 48 Gy in 4 fractions at the isocenter is used for primary lung cancer at our institution. With respect to the correlation between the regional dose and the CT appearance of RILI, Levinson et al.[10] and Rosen et al.[11] suggested a threshold dose of 30 Gy. Using a linear-quadratic model,[12,13] with an alpha-beta ratio of 3 Gy for the evaluation of normal lung injury, 16 Gy in 4 fractions corresponds to approximately 24 Gy in 2-Gy fractions. Indeed, all of the RILI consolidations in our study appeared within the 16-Gy isodose curves.

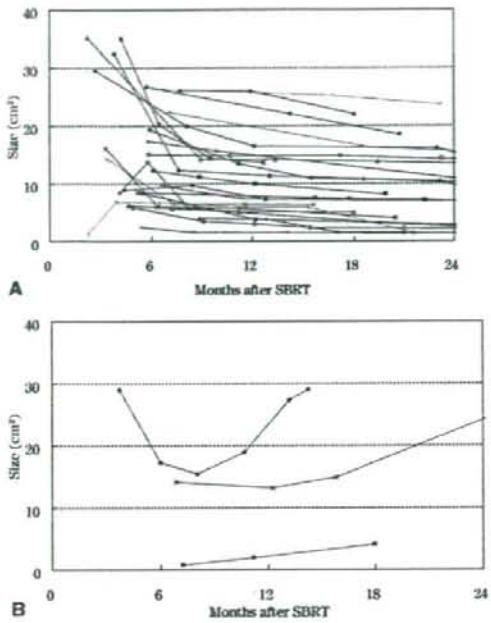

Fig. 4A,B. Serial changes in the sizes of mass-like consolidations in cases diagnosed as RILI (**A**) and cases diagnosed as local recurrence (**B**)

Several authors have reported RILI after SBRT and its classification on CT images (Table 1). Koenig et al.[14] observed modified conventional fibrosis and mass-like fibrosis in 68% cases. Aoki et al.[15] reported patchy consolidation or discrete consolidation in 74% of cases during the first 6 months after SBRT. Takeda et al.[16] reported that dense consolidation was observed in 73% of cases. Assuming that these manifestations on CT correspond to our "mass-like consolidation", our results, that mass-like consolidation appeared in 68% of tumors treated with SBRT, are in accordance with these previous results. The frequency of mass-like consolidations could be important in the evaluation of follow-up CT images after SBRT. In our study, although most of the mass-like consolidations represented RILI, a few of the mass-like consolidations turned out to represent local recurrence.

There have been a few reports on the CT differentiation of local recurrence from RILI after radiotherapy. Bourgouin et al.[17] compared CT manifestations of RILI and local recurrence after conventional radiotherapy. They suggested that RILI was consolidation with a straight lateral margin and ectatic air-containing bronchi, and that local recurrence was a soft-tissue mass with a convex lateral border and without air-containing bronchi. However, these descriptions did not always apply to our SBRT cases. Because of the differences in dose distribution described above, RILI after SBRT did not show straight lateral borders, but showed a mass-like shape. With regard to ectatic bronchi, we could not detect significant findings for the early detec-

Table 1. Summary of previous reports about radiation-induced lung injury after SBRT

	Doses	Materials	Results	Notes
Koenig et al.[14]	69.6–90.3 Gy in 33–58 fr	19 Lesions of 19 patients	Modified conventional fibrosis 26% Mass-like fibrosis 42% Scar-like fibrosis 32%	Two cases with tumor progression were excluded
Aoki et al.[15]	40–60 Gy in 4–5 fr	31 Lesions of 31 patients	≤6 Months Homogeneous pattern 26% Patchy consolidation 68% Discrete consolidation 6% >6 Months Patchy consolidation 8% Discrete consolidation 27% Solid consolidation 65%	Tumor shrank for 2–15 months after SBRT. Two cases showed tumor progression
Takeda et al.[16]	40–50 Gy in 5–8 fr	22 Lesions of 20 patients	Ground-glass opacity 33% (3–6 months) Dense consolidation 73% (3–8 months)	Dense consolidations fixed at 12 months. Four cases showed local recurrence
Present study	40 or 48 Gy in 4 fr, or 60 Gy in 5 fr	40 Lesions of 37 patients	Mass-like consolidation 68% (2–9 months)	Three cases turned out to be local recurrence

fr, fraction

tion of local recurrence. Thus, we focused attention on serial changes in the sizes of the mass-like consolidations and found a difference in enlargement 12 months or more after SBRT. Our findings were not sufficient for the early detection of local recurrence after SBRT. Further studies are required to establish a method for determining whether mass-like consolidations are RILI or local recurrence soon after SBRT.

In conclusion, mass-like consolidations were observed in 68% of cases at a median of 5 months after SBRT. Although most of the mass-like consolidations were RILI, local recurrence was observed in a few cases. Early detection of local recurrence after SBRT was difficult.

Acknowledgments This work was supported by Grants-in-Aid No. H18-014 of the Ministry of Health, Labour, and Welfare in Japan and No. 18390333 of the Japan Society for the Promotion of Science. This work was presented in part at the 90th scientific assembly and annual meeting of the RSNA in Chicago, November 28 to December 3, 2004. The authors gratefully acknowledge Mr. Daniel Mrozek for editorial assistance.

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Review

Stereotactic body radiation therapy (SBRT) for early-stage lung cancer

Radiothérapie stéréotaxique pour cancer bronchique localisé

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Available online 08 December 2006

Abstract

Stereotactic body radiation therapy (SBRT) is a new treatment modality for early-stage non-small-cell lung cancer, and has been developed in the United States, the European Union, and Japan. We started a feasibility study of this therapy in July 1998, using a stereotactic body frame. The eligibility criteria for primary lung cancer were: 1) solitary tumor less than 4 cm (T1-3N0M); 2) inoperable, or the patient refused operation; 3) no necessity for oxygen support; 4) performance status equal to or less than 2; 5) the peripheral tumor which dose constraints of mediastinal organs are maintained. A total dose of 48 Gy was delivered in four fractions in 2 weeks in most patients. Lung toxicity was minimal. No grade II toxicities for spinal cord, bronchus, pulmonary artery, or esophagus were observed. The 3 years overall survival for 32 patients with stage IA, and 13 patients with stage IB were 83% and 72%, respectively. Only one local recurrence was observed in a follow-up of 6–71 months. We retrospectively analyzed 241 patients from 13 Japanese institutions. The local recurrence rate was 20% when the biological equivalent dose (BED) was less than 100 Gy, and 6.5% when the BED was over 100 Gy. Overall survival at 3 years was 42% when the BED was less than 100 Gy, and 46% when it was over 100 Gy. In tumors, which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients. Long-term results, in terms of local control, regional recurrence, survival, and complications, are not yet evaluated. However, this treatment modality is highly expected to be a standard treatment for inoperable patients, and it may be an alternative to lobectomy for operative patients. A prospective trial, which is now ongoing, will, answer these questions.

Résumé

La radiothérapie stéréotaxique extracérébrale est une nouvelle modalité thérapeutique du carcinome bronchique non à petites cellules localisé. Cette technique a été développée aux États-Unis, en Europe et au Japon. Nous avons débuté en juillet 1998 une étude de faisabilité de ce traitement avec l'aide d'un cadre stéréotactique corporel. Les critères d'éligibilité pour le cancer bronchique primitif étaient : 1) tumeur isolée de moins de 4 cm (T1-3N0M0) ; 2) tumeur non résécable ou patient refusant la chirurgie ; 3) pas de nécessité d'avoir recours à une oxygénothérapie ; 4) indice de performance égal ou inférieur à 2 ; 5) tumeur périphérique n'entraînant pas une irradiation à dose très importante du médiastin. Une dose totale de 48 Gy a été délivrée en quatre fractions et deux semaines. Chez la plupart des patients, la toxicité pulmonaire a été minimale. Aucune toxicité de grade II n'a été observée pour la moelle épinière, les bronches, les artères pulmonaires ou l'œsophage. Les taux de survie globale à trois ans des 32 patients atteints d'un cancer de stade IA et 13 de stade IB étaient respectivement de 83 et 72 %. Une seule récidive locale a été observée pendant une période de suivi de 6 à 71 mois. Nous avons par ailleurs, rétrospectivement, analysé les résultats obtenus dans une série de 241 patients traités dans 13 institutions japonaises. Le taux de récidive local était de 20 % quand la dose biologique équivalente (BED) était inférieure à 100 Gy, et de 6,5 % quand elle était supérieure à 100 Gy. Le taux de survie à trois ans était de 42 % quand la BED était inférieure à 100 Gy et 46 % quand elle était supérieure. Lorsque la BED était supérieure à 100 Gy, le taux de survie à trois ans était de 91 %, pour les patients atteints d'une tumeur résécable, et 50 % pour les patients inopérables. Les résultats à long terme, en termes de contrôle local, récidive locale, survie et complications ne sont pas encore évalués. Cependant, cette modalité thérapeutique est d'ores et déjà considérée comme le traitement standard pour les patients inopérables et sera une possible alternative à une lobectomie pour les patients opérables. Un essai prospectif en cours permettra de répondre à ces questions.

Keywords: Non-small-cell lung cancer; Stereotactic body radiation therapy

Mots clés : Cancer bronchique non à petites cellules ; Irradiation stéréotactique extracrânienne

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Stereotactic body radiation therapy (SBRT) for early-stage non-small-cell lung cancer (NSCLC) is a new treatment modality, and Japan is one of the leading countries in this three-dimensional radiation therapy. The background of this treatment is the great success of stereotactic irradiation for intracranial tumors, in terms of the technologies used, quality assurance (QA) and quality control (QC), and clinical outcomes. That is, a high local control rate has been shown with minimal toxicities. The success has caused much interest in the application of this treatment for extracranial regions [1,5,13]. Why use stereotactic radiation irradiation (SRI) for lung cancer? The number of patients detected at an early-stage has been increased by screening examinations. Accordingly, the number of older patients with early-stage lung cancer who are not amenable to operation has increased, and the clinical results of conventional radiation therapy are not satisfactory. In regard to technical aspects, the application of this new technique is easier for lung cancer, because it is visible on fluoroscopy and because normal tissue toxicities to radiation are relatively well described compared with other normal tissues.

For the management of stage I NSCLC, surgical resection alone is the standard treatment, and lobectomy is generally accepted as the optimal surgical procedure. Survival outcomes of surgical treatment has recently been reported by the Japanese Association for Chest Surgery. According to these data, the overall survival of patients in clinical stage IA is 81.3% at 3 years, and 71.5% at 5 years, and that of patients in clinical stage IB is 62.9% at 3 years, and 50.1% at 5 years.

What about radiation therapy alone for stage I NSCLC? As is known, radiation therapy has been used primarily for those patients who are not considered to be surgical candidates; that is, those who refuse surgical intervention, and those who are medically inoperable. The reported 5 years survival rate is around 8–27%, and is not satisfactory. Several prognostic factors, such as T stage and total dose, have been reported, and doses higher than 65 Gy did show higher survival rates, which can be a rationale for dose escalation (Table 1).

However, there remain several problems with stereotactic radiation therapy for lung cancer compared to its use in intracranial tumors:

- How should the body be fixed with high accuracy?
- How do we cope with the movement of the tumor caused by respiration?
- What are the optimal treatment regimens?
- Toxicities to normal tissue caused by large-fraction size irradiation have not been examined.
- Fractionated stereotactic radiation therapy is considered to be appropriate for lung cancer, but the optimal fractionation scheme has not yet been decided.

We started a feasibility study of this SBRT for small lung tumors in July 1998 [7,8]. The treatment planning with multiple non-coplanar beams is shown in Fig. 1. The patient was placed in this body frame, and immobilized. We used both X-ray and computed tomography (CT) simulators, with the same table, to improve the accuracy of the setup. The movement of the tumor caused by respiration was estimated using fluoroscopy, and if that movement in the craniocaudal (CC) direction was greater than 8 mm, a diaphragm control was employed to suppress the movement of the chest wall. Then the three-dimensional treatment planning was carried out. We verified the tumor location in each treatment. As regards the movement of the tumor caused by respiration, the largest movement was in the CC direction. It was 0–22 mm, and

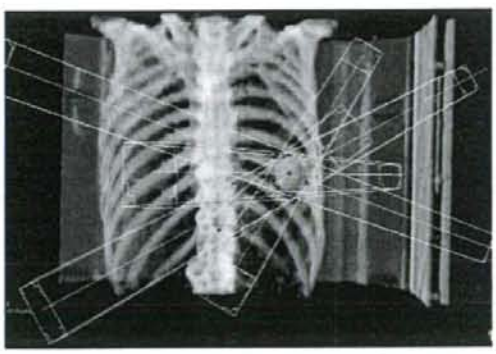

Fig. 1. SBRT for stage I lung cancer.

Table 1
Summary of the results on SBRT for primary lung cancer

Author (Refs.)	Year	Number of patients	Median follow-up (months)	Prescribed dose	Reference point	Isocenter dose (Gy)	BED[a] (Gy)	Overall survival rate (%)	Local control rate (%)
Uematsu et al. [14]	2001	50	36	50–60 Gy/5–10 fr.	Isocenter	50–60	96–100	66 (3 years)	94
Fukumoto et al. [3]	2002	22	24	48–60 Gy/8 fr.	Isocenter	48–60	76.8–105	NA	94
Hof et al. [4]	2003	10	15	19–26 Gy/1 fr.	Isocenter	19–26	55.1–93.6	64	80
Wulf et al. [15]	2004	20	11	30–37.5 Gy/3 fr.	Periphery	45–56.25	113–162	32	92
Onishi et al. [11]	2004	35	13	60 Gy/10 fr.	Periphery	70–75	119–131	58	94
McGarry et al. [6]	2005	47	27 (T1), 19 (T2)	24–72 Gy/3 fr.	Periphery	30–90	60–360	NA	79
Zimmermann et al. [17]	2005	30	18	37.5 Gy/3 fr.	Periphery	62.5	193	75	87
Nagata et al. [7]	2005	45	30	48 Gy/4 fr.	Isocenter	48	106	83 (T1), 72 (T2)	98
Nyman et al. [9]	2006	45	43	45 Gy/3 fr.	Periphery	63	195	71	80
Beitler et al. [2]	2006	75	17	40 Gy/5 fr.	Periphery	47	91.2	45	NA

[a] Biologically effective dose at the isocenter with α/β ratio of 10.

movement of less than 15 mm occurred in 90% of all tumors. When that movement was over 20 mm, we used the diaphragm control, and, with the use of this device, the movement of the respiration decreased significantly. The set-up error with patients was greater than 3 min in at least one direction. Patient repositioning had to be undertaken in 21.6% of all treatments.

The eligibility criteria for primary lung cancer were as follows: solitary tumor less than 4 cm; inoperable, or the patient refused operation; histologically confirmed malignancy; no necessity for oxygen support; performance status equal to or less than 2; and the tumor was not close to spinal cord.

The eligibility criteria for metastatic lung cancer were as follows: one to two tumors less than 4 cm each, primary tumor controlled, no other metastasis, no necessity for oxygen support, performance status less than 2, and tumors not close to the spinal cord. Between July 1998 and November 2005, a total of 147 patients received this treatment modality. Their ages ranged from 17 to 87 years, with a mean of 74 years. Seventy-nine patients had primary tumors, and 54 patients had secondary tumors. In 115 tumors, a total dose of 48 Gy was delivered, in four fractions in 2 weeks. Twenty-seven tumors were treated with a total dose of up to 60 Gy in five fractions. In the initial three tumors, a total dose of 40 Gy was administered.

Survival curves for 32 patients with stage IA, T1N0M0 NSCLC are shown in Fig. 2. One local recurrence was observed in a follow-up of 6–71 months (median, 30 months). Intrapulmonary recurrence developed in four patients, regional lymph node recurrence developed in two patients, and bone metastases developed in one patient.

Survival curves for 13 patients with stage IB, T2N0M0 NSCLC are shown in Fig. 3. No local recurrence was observed at a follow-up of 6–64 months (median, 22 months). Intrapulmonary recurrence developed in four patients, liver and brain metastases developed in one patient each.

We examined the toxicity by National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2. Lung toxicity was grade II in 4% and grade I in 96%. No grade II toxicities for spinal cord, bronchus, pulmonary artery, or esophagus were observed. The clinical course of one patient who responded well to this treatment is shown in Fig. 4.

We retrospectively analyzed data from 241 patients from 13 Japanese institutes [10]. Their ages ranged from 35 to 92 years, with a median of 76 years. Histology was squamous cell carcinoma in 106 patients, adenocarcinoma in 102 patients, and "others" in 33 patients. As regards clinical stage, 153 patients were stage IA, and 88 patients were stage IB. Tumor diameter ranged from 7 to 58 mm, with a median of 28 mm. One hundred and sixty-one patients were inoperable, and 80 patients were operable. The biological equivalent dose (BED) was 57–180 Gy, with a median of 108 Gy.

Lung toxicities were minimal, with grade II in only 2.2% and no grade III. Local response to the treatment was complete response (CR) in 23%, and partial response (PR) in 62%. The local recurrence rate was 20% when BED was less than 100 Gy, and 6.5% when BED was over 100 Gy, at follow-up periods of 4–72 months (median, 18 months). Overall survival at 3 years was 42% when BED was less than 100 Gy, and 46% when BED was over 100 Gy. For tumors, which received a BED of more than 100 Gy, overall survival at 3 years was 91% for operable patients, and 50% for inoperable patients.

Based upon several good clinical results [2,3,6,12,14–17], we have started a prospective multiinstitutional phase II study with a grant from the Health and Welfare Ministry of Japan. The target is stage IA NSCLC. A total dose of 48 Gy in four fractions will be delivered in 4–8 days. Entry of 165 patients from 16 institutes in 3 years is expected. By the end of May 2006, 85 patients were entried. The primary endpoint is survival. This is the first trial of the Radiation Therapy Study Group (RTSG), which is the newest group in the Japanese Clinical Oncology Group (JCOG). We hope that this trial will provide more conclusive data on stereotactic body irradiation for early-stage NSCLC.

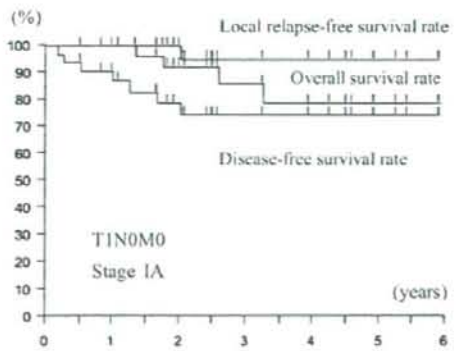

Fig. 2. Survival curves of patients with stage IA: T1N0M0 NSCLC treated with SBRT.

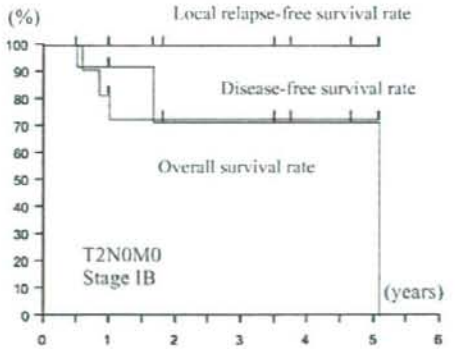

Fig. 3. Survival curves of patients with stage IB: T2N0M0 NSCLC treated with SBRT.

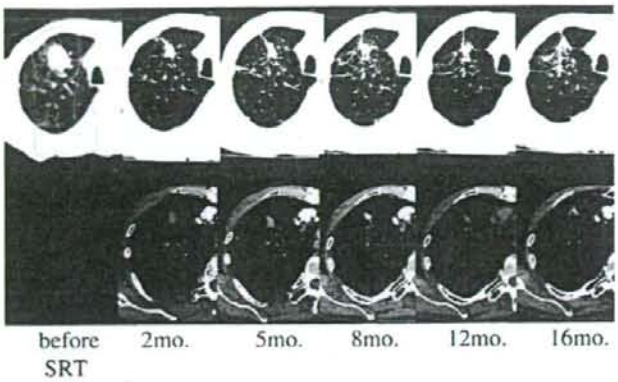

Fig. 4. Clinical course of a patient treated with SBRT. The patient, a 71-year-old man, had primary lung cancer (squamous cell carcinoma; T2N0M0).

In summary, regarding SBRT for early-stage NSCLC:

- long-term results, in terms of local control, regional recurrence, survival, and complications are not yet evaluated;
- technologies to cope with tumor movement, gauging tracking, need to be improved;
- this treatment modality is highly expected to be a standard treatment for inoperable patients, and may be an alternative to lobectomy for operative patients.

A prospective trial ongoing is expected to resolve these matters.

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A Japan Clinical Oncology Group Trial for Stereotactic Body Radiation Therapy of Non-Small Cell Lung Cancer

Masahiro Hiraoka, MD, PhD, and Satoshi Ishikura, MD, PhD†*

Stereotactic body radiation therapy (SBRT) is a new treatment modality. To confirm the safety and efficacy, the Radiation Therapy Study Group of the Japan Clinical Oncology Group (JCOG) has started a phase II study of SBRT for stage IA non-small cell lung cancer (JCOG 0403). This study is ongoing with a strict quality control and quality assurance program, and the results will indicate whether a future phase III trial comparing SBRT with surgery is warranted. In addition, international collaboration will be critical to establish the role of SBRT in the treatment of lung cancer.

Key Words: Stage I non-small cell lung cancer, Stereotactic body radiation therapy, Clinical trial.

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Lung cancer is the leading cause of cancer-related death for men and the second for women in Japan. During 2003, approximately 57,000 patients died of lung and bronchus cancer,[1] and the number is not decreasing. Because of the application of spiral computed tomography (CT) for lung cancer screening, the number of patients with early-stage non-small cell lung cancer (NSCLC) has increased recently. The number of elderly patients who are not suitable for surgery has also increased. Although surgery is the accepted standard of care for stage I NSCLC, conventional radiotherapy has been applied for these frail patients with inferior survival compared with surgery.

Stereotactic body radiation therapy (SBRT) is a new treatment modality based on the same principles and the great success of stereotactic radiosurgery/radiotherapy for intracranial tumors. The success and high local control with minimal toxicity have drawn much interest in the application of this treatment for extracranial regions, and there are several single institutional retrospective reports.[2–8]

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Although there is no large-scale prospective trial confirming the safety and efficacy of SBRT for early-stage NSCLC, it has been widely used in Japan. Onishi et al. have reported the results of a multicenter retrospective survey.[9] Data from 245 patients from 13 institutions were analyzed. There was a large variation in the dose schedule used (18-75 Gy in 1-22 fractions), and they used a biologically effective dose (BED) to account for it. With a median follow-up of 24 months, local recurrence occurred in 8% for BED $\geq$100 Gy and 26% for BED $<$100 Gy. The 3-year overall survival for medically operable patients treated with BED $\geq$100 Gy was 88%. Onishi et al. claimed that SBRT may achieve equivalent local control and survival compared with surgery; however, as in any retrospective study, it has many inherent limitations: relatively short follow-up with many censored cases, which leads to the overestimation of local control and survival; patient selection because SBRT is more often applied at a higher dose to a peripheral lesion that has favorable outcome compared with a central lesion; migration between operable and inoperable because advanced age was considered to be inoperable, which may lead to Will Rogers phenomenon; and a limited number of patients in subgroup analyses.

Therefore, we decided to develop a prospective trial to evaluate the safety and efficacy of SBRT for stage IA NSCLC.

JAPAN CLINICAL ONCOLOGY GROUP TRIAL OF SBRT FOR STAGE IA NSCLC

The Japan Clinical Oncology Group (JCOG) 0403 is a single-arm phase II study. This study was planned to determine whether SBRT is superior to conventional radiotherapy for medically inoperable patients and to explore whether SBRT can achieve survival comparable to that with surgery for operable patients with clinical stage IA NSCLC. The primary endpoint is 3-year overall survival, and the planned accrual was 100 inoperable and 65 operable patients. Local progression-free survival, patterns of failure, and toxicity were included as secondary endpoints.

Eligibility criteria included previously untreated patients with pathologically proven NSCLC; age $\geq$20 years; performance status (based on Eastern Cooperative Oncology Group scale) 0 to 2; $PaO_2 \geq 60$ torr; and $FEV_{1.0} \geq 700$ ml. All patients signed written informed consent in accordance with each institutional review board.

Patients were stratified into two groups after consultation with an experienced thoracic surgeon: 1) operable pa-

tients with postoperative predicted $FEV_{1.0}$ ≥800 ml, PaO_2 ≥65 torr, absent severe cardiac/heart disease, and absent severe diabetes mellitus; 2) inoperable patients who do not satisfy the criteria for operable patients.

The treatment consists of 48 Gy in four fractions over 4 to 8 days. The prescription point is the isocenter, and the monitor units are calculated with heterogeneity correction. The Clarkson integration algorithm is used, and the convolution-superposition algorithm is not allowed in this study.

In treatment planning, the clinical target volume (CTV) was defined as the gross tumor volume (GTV). An internal margin according to each institution was added to the CTV to define the internal target volume (ITV). The planning target volume (PTV) was defined as the ITV plus 5 mm of setup margin. The radiation ports were set to the PTV with 5 mm of leaf margin. Non-coplanar static beams (5 to 10 ports) or multiple-arc beams (in total ≥400 degrees) with 4 to 10 MV X-rays are allowed. Dose constraints to normal tissues, i.e. the lung, the esophagus, the bronchial tree, the great vessels, the spinal cord, are also defined.

QUALITY CONTROL AND QUALITY ASSURANCE

Quality control (QC) and quality assurance (QA) for radiotherapy in multicenter clinical trials are vital to evaluate new investigational treatments. In contrast to the United States, where a QC/QA program was developed in the late 1960s, it was not developed in the 20th century in Japan. In 2001, we performed a retrospective final review using a JCOG trial for the first time,[10,11] and it revealed that protocol compliance was very poor, with a protocol violation rate of 60%. After these results, we developed the Radiotherapy Quality Assurance Center (RTQAC) in the JCOG and started a comprehensive QC/QA program, including individual case reviews (initial and final reviews). The first trial with a QC/QA program was opened for accrual in 2002. Protocol violation has been decreasing yearly, and it is now less than 5%.

In the JCOG 0403 study, we asked the National Cancer Institute and the Advanced Technology Consortium (ATC) to support this trial in developing a QC/QA program. The digital data of each case from radiotherapy planning systems are submitted to the Image Guided Therapy QA Center (ITC) at Washington University in St. Louis, and the final review is being performed using the Remote Review Tool provided by the ITC.

In 2004, we also developed a non-profit organization, the Radiotherapy Support Center (RSC) to support QC/QA activities in clinical trials. The RSC, instead of the RTQAC, is now charged with radiotherapy QC/QA in JCOG trials.

CREDENTIAL PROCESS

Participating institutions in the JCOG 0403 study must pass through the following requirements: 1) a survey of institutional personnel, equipment, and treatment techniques; 2) dry run; and 3) phantom dosimetry test. An institutional survey includes immobilization/localization precision. They are required to present a document that shows the setup reproducibility for their choice of immobilization and/or localization equipment.

A dry run must be performed to reduce inter-institutional variations of treatment planning in compliance with the protocol and to check the institutional capability of digital data submission to the ATC. The results of the dry run performed before the JCOG 0403 study will be reported elsewhere. The overall coefficient of variation of the target volumes was approximately 17%, and the inter-institutional variations in target delineation were acceptable.

Phantom dosimetry test was also performed before starting the JCOG 0403 study to evaluate the accuracy of dosimetry in participating institutions to minimize inter-institutional variations. A lung phantom for SBRT was developed and used for this purpose. The absolute doses at the center of a simulated spherical tumor with a diameter of 3 cm in the lung were measured and compared with the calculated doses on-site by the responsible physicist.[12] The use of heterogeneity correction and different calculation algorithms both significantly influenced the accuracy of the absolute dose. The differences between the calculated doses with heterogeneity correction and measured doses were 4% for the Clarkson integration algorithm and 1% for the convolution-superposition algorithm. However, the Clarkson integration algorithm was selected for the JCOG 0403 study because the convolution-superposition algorithm was not available in some participating institutions at the beginning of this study.

CURRENT STATUS AND FUTURE DIRECTIONS

As of January 12, 2007, 111 patients were enrolled in this study. The accrual of operative patients has been completed, and that of inoperable patients will be completed in 2008. The final results for operable patients will be available in 3 years. At that time, we will be able to decide whether a randomized trial comparing SBRT to surgery is warranted or whether SBRT should be regarded as an alternative option for patients who refuse standard surgery. We also expect that CT criteria will be established to define local control by analyzing the serial CT data sets mandated in this study, because the response evaluation criteria in solid tumors (RECIST) are difficult to apply to see whether the tumor is eradicated because of secondary changes such as radiation fibrosis.

Another concern is the optimal dose schedule for this patient population. We selected 48 Gy in four fractions over 4 to 8 days based on retrospective data using BED formula; however, it has not been validated to be used in hypofractionated SBRT with a larger dose per fraction. Without a dose-finding phase I study, it is also hypothetical that 48 Gy in four fractions is enough to eradicate the tumor.

In the United States, prospective phase I and phase II studies have been performed at Indiana University.[13,14] Based on the results, they selected 60 Gy in three fractions over 1.5 to 2 weeks in the following RTOG trial, a phase II trial of SBRT in patients with medically inoperable stage I/II NSCLC (RTOG 0236). Not only is the dose schedule different from the Japanese schedule, but the target delineation, margins around the PTV, dose prescription (60% to 90%

isodose line vs. isocenter), and use of heterogeneity correction (uncorrected vs. corrected) are also different. These differences make it difficult to compare the results between these studies. Recently, the RTOG and JCOG have both decided to use an up-to-date and more accurate convolution-superposition algorithm with heterogeneity correction in the coming studies. The JCOG is now developing a dose-escalating phase I study for T2N0M0 NSCLC, and the RTOG is also developing a phase II study for operable patients with stage I NSCLC. We hope that these studies will define the optimal dose schedule and lead to standardization of the SBRT technique. Furthermore, international collaboration will be critical to establish the role of SBRT in the treatment of lung cancer.

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Lung cancer SBRT

A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer

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Abstract

***Background and purpose*:** The outcome of stage I non-small cell lung cancer (NSCLC) patients treated with conventional radiotherapy is inferior to that of patients treated surgically. We aimed to evaluate the clinical outcome of stereotactic body radiotherapy (SBRT) in the treatment of stage I NSCLC.

***Materials and methods*:** We performed SBRT for 31 stage I NSCLC patients. Of these, 20 were medically inoperable, and 11 refused surgery. Nineteen tumours were T1-stage masses, and 12 tumours were T2. Median tumour size was 25 mm. SBRT was administered as 45 Gy/3 fractions; however, when the tumour was close to an organ at risk, 60 Gy/8 fractions were used. These doses were prescribed at the centre of the tumours.

***Results*:** The median duration of observation for all patients was 32 months (range, 4–87 months). In 9 of the 31 cases, local recurrence was observed. The 3-year local control rates of T1 and T2 tumours were 77.9% and 40.0%, respectively. The 3-year overall and cause-specific survival rates were 71.7% and 83.5%, respectively. Although the symptoms improved with medical treatment, 5 patients developed acute pulmonary toxicity ⩾grade 2.

***Conclusions*:** SBRT is safe and effective for stage I NSCLC patients. However, a more intensive treatment regimen should be considered for T2 tumours.

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Keywords: Stereotactic body radiotherapy; Non-small cell lung cancer; Stage I; Phase II study; On-board imaging

Since 1998, lung cancer has been the leading cause of cancer death in Japan. In recent years, the number of cases diagnosed at an early stage has increased. This is most likely due to the widespread use of computed tomography (CT) screening [26]. Many lung cancers, however, continue to be detected at an advanced stage. Presently, the first treatment choice for early-stage lung cancer is surgical resection. However, non-small cell lung cancer (NSCLC) frequently occurs in people with an extensive smoking history and other smoking-related diseases, including coronary disease and chronic obstructive pulmonary disease. Accordingly, such patients may be declared medically inoperable and may be referred for radiotherapy. The local tumour control rate for such patients has been 30–60% [12,21,25], which is inferior to that achieved by surgical resection that has a local tumour control rate higher than 90% [15]. Recently, hypofractionated stereotactic radiotherapy, in particular stereotactic body radiotherapy (SBRT), has achieved excellent tumour control in stage I NSCLC [19,22,32]. However, there are insufficient clinical data to determine the optimal SBRT dose and delivery method. In 1998, we initiated a phase II study using SBRT for stage I NSCLC. The aim of this study was to evaluate the local control, survival, and toxicity of SBRT for stage I NSCLC.

Materials and methods

Patient eligibility

All patients included in this study had histological or cytological diagnoses of NSCLC and were staged as Union International Contre le Cancer (UICC) stage IA or IB (up to 5 cm) after appropriate staging studies. All the patients had either a medical contraindication to surgery or refused surgery. Further, all had a performance status of ⩽2 according to the World Health Organization guidelines. Patient eligibility was not restricted on the basis of tumour location, unless a part of the oesophagus, heart, main bronchi, hilus, or skin would be exposed to high-dose radiation of >20 Gy/3 fractions or >40 Gy/8 fractions. For the spinal cord, the restrictive dose was <15 Gy/3 fractions or <30 Gy/8 frac-

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tions. If the treatment plan included these organs in the high-dose areas, the patients were treated with conventional radiotherapy or modified SBRT with a moderate irradiation dose; these patients were excluded from this study. The present study was approved by the Tohoku University Hospital Institutional Review Board, and informed consent was obtained from all patients.

Radiotherapy

The tumours were fluoroscopically observed prior to treatment planning. In cases in which tumour identification was impossible by imaging in 2 directions, a gold marker (Hakko guiding marker system) sized 3.0 × 0.8 mm was transcutaneously inserted in or around the tumour under CT guidance to maintain accuracy and reproducibility throughout the treatment period.

Patients were immobilised in the supine position with an individually fashioned half-body vacuum cast [27]. Both the upper extremities were immobilised in the raised position unless the tumour was located at the apex of the lung, in which case both the upper extremities were immobilised beside the body.

The criterion for using a respiratory-gated system was if fluoroscopic imaging revealed that the tumour moved more than 15 mm. Using the respiratory-gated irradiation system with active breathing control that we developed reduced the range of tumour movement to <5 mm [13].

To determine the extent of tumour movement and establish an individual internal margin (IM), all patients were placed in a simulator for fluoroscopic examination just prior to CT scanning for treatment planning. Serial CT scans were performed at intervals of 3 mm in the target area and 5 mm in the remaining area. When the range of tumour movement was >1 cm, a CT scan with an acquisition time of 4 s that included internal motion was performed to accurately define the IM. When this type of CT scanning was performed, the breathing rate was confirmed to be >15 breaths/min. In the case of respiratory-gated irradiation, CT images for treatment planning were obtained using the respiratory-gated system.

Gross tumour volume (GTV) was defined as the visible extent of the tumour on the CT image at the lung window. The clinical target volume (CTV) was set equal to the GTV. The internal target volume (ITV) was defined by adding the IM to the CTV corresponding to the tumour movement. For CT scanning with an acquisition time of 4 seconds, the ITV was set equal to the CTV. The planning target volume (PTV) was determined by allowing for a set-up margin of 5 mm beyond the ITV.

Treatment planning was performed with non-coplanar multi-dynamic arcs and/or multi-static beams by using a three-dimensional radiotherapy treatment planning system (CADPLAN and Eclipse, Varian Medical Systems, Palo Alto, CA). The modified Batho power law was used as the tissue heterogeneity correction algorithm. The target reference point dose was defined as the centre of the tumour, and the PTV was encompassed by the minimum 90% dose line of the reference point dose. The high-dose area should not include the risk organs previously described. X-rays of 6 MV were used in all treatments.

SBRT requires stricter patient positioning and tumour reproducibility than conventional radiotherapy. This methodology is essential for avoiding the cold regions in the tumour and hot regions in the risk organs. At our institute, SBRT has been performed since 2000 using a unique on-board imaging system, namely, the dual fluoroscopy and flat panel system (DFFP) [28,29,34] to verify the tumour or the implanted gold marker (Fig. 1). This system comprises two conventional diagnostic X-ray tubes that have been mounted directly onto the gantry of the accelerator (Clinac 23EX, Varian Medical Systems, Palo Alto, CA) and two sets of amorphous-silicon (a-Si) flat panel X-ray sensors (PaxScan 2520, Varian Medical Systems, Palo Alto, CA) that are mounted opposite the X-ray tubes. The focal spots of the tubes are located ±45° to the accelerator target, and two sets of a-Si flat panel are located at a gantry position of ±135°on retractable arms that extend from the lower part of the accelerator gantry. The accuracy and stability of this system have been discussed in previous reports [28,29]. The patient's treatment position was confirmed in three perpendicular directions at each treatment session using this system, and the set-up and inter-fractional errors were corrected (less than 1 mm). Before introducing this system, the patient's treatment position was verified using portal films in two directions at each treatment session.

The patients were treated with a radiation schedule of 45 Gy/3 fractions/1 week. However, when the tumour was close to a risk organ, a schedule of 60 Gy/8 fractions/2 weeks was used to reduce the risk of serious toxicity due to set-up error or internal movement.

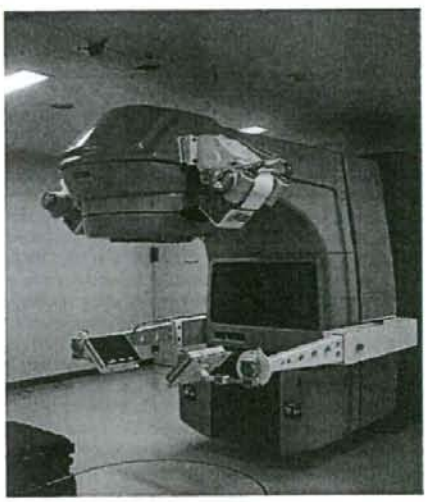

Fig. 1. Dual fluoroscopy with an amorphous-silicon flat panel (DFFP) system.

Follow-up

The first examination, including a clinical examination and CT scanning, was performed 4–6 weeks after treatment to assess the pulmonary reaction. Thereafter, the patients underwent follow-up examinations every 3 months for 2 years following treatment. After 2 years, the follow-up examinations were performed every 3–6 months.

Statistics

Follow-up was determined from the date of the first SBRT to determine the median follow-up and Kaplan–Meier time-to-event estimates of survival and local control data.

Results

Patients

Between March 1998 and December 2004, 34 patients with stage I NSCLS were registered with this study. However, 3 patients were excluded due to dose constraints related to the heart, hilus, and oesophagus, respectively. We treated 31 patients with stage I NSCLC with hypofractionated high-dose SBRT at Tohoku University Hospital (Table 1). Of the 31 patients, 20 were medically inoperable and 11 refused surgery. Further, 25 patients were men and 6 were women. Their median age was 77 years (range, 60–83 years). Their histologies were squamous cell carcinoma (15 patients), adenocarcinoma (12 patients), large cell carcinoma (2 patients), and unclassified NSCLC (2 patients). The median tumour size was 25 mm. Based on the UICC-based TNM classification system, 19 tumours were T1 masses, and 12 were T2. We treated 20 patients with a radiation schedule of 45 Gy/3 fractions/1 week, and 11 patients with a schedule of 60 Gy/8 fractions/2 weeks. The minimal and maximal PTV percent doses per fraction were 90.0% and 109.9%, respectively. The percent doses to 95% of the PTV were 95.8 ± 1.1% (mean ± standard deviation). The respiratory-gated system was used for only 2 patients. The others were irradiated with normal breathing. The median internal motions of the tumours under normal breathing were 11 mm (range, 0–15 mm), 1 mm (range, 0–5 mm), and 3 mm (range, 0–12 mm) in cranio-caudal, medial–lateral, and anterior–posterior directions, respectively. Of the 31 patients, 9 received a gold marker since their tumours were not fluoroscopically observed.

Table 1
Patient and tumor characteristics

Patient's characteristics	
Patients (*n*)	31
Age	
Range	60–83
Median	77
Gender	
Male	25
Female	6
Indication	
Refuse operation	11
Medically inoperable	20
Performance status	
0	18
1	10
2	3
Tumour characteristics	
Histology	
Squamous cell carcinoma	15
Adenocarcinoma	12
Large cell carcinoma	2
Unclassified NSCLC	2
T classification	
T1	19
T2 (≤5 cm)	12
Tumour size (mm)	
Range	10–48
Median	25
Tumour site	
Peripheral	30
Central	1
Radiotherapy	
Prescribed dose	
45 Gy/3 fractions/1 week	20
60 Gy/8 fractions/2 weeks	11
PTV (cm^3)	
Range	4.3–156.9
Median	62.4
Respiratory-gated irradiation	
Yes	2
No	29

PTV, planning target volume.

Local control and patterns of failure

All tumours showed partial or complete response to the SBRT, although it was difficult to determine if the tumour disappeared completely due to the pulmonary fibrosis that developed around it. Of the 31 patients, 9 showed evidence of local recurrence (Table 2). The 3-year local control rates for T1 and T2 tumours were 77.9% and 40.0%, respectively (Fig. 2). The median time to recurrence was 16.2 months (range, 12.7–27.6 months). Local recurrence was defined as local progression that was 1.5 times the dimensions of the original tumour. Some patients underwent positron emission tomography examination to distinguish a local recurrence from localised pulmonary fibrosis due to SBRT.

The recurrence patterns are shown in Table 3. Of the 9 patients with local recurrence, 6 had isolated local failures and the other 3 had simultaneous nodal and/or distant failures. Isolated distant metastases developed in 5 patients.

Survival

All the patients tolerated SBRT very well. The median follow-up period from the time of completion of SBRT was 32 months (range, 4–87 months). Of the 31 patients, 7 died of NSCLC and 5 of intercurrent causes. Of the 7 patients who died with NSCLC, 1 died of an isolated local disease, 1 of a local disease and regional lymph node metastases, 2 of local disease and distant metastases, and 3 of distant metastases. The 3-year overall survival rates were 71.7%, and the cause-specific survival rates after 3 years were 83.5% (Fig. 3).

Table 2
Characteristics of 9 patients with local recurrence

Age (Sex)	Operability	Tumour size (mm)	Histology	PTV (cm^3)	Prescribed dose	Period after treatment (months)
74 (Man)	Yes	35	Adeno	49.7	60 Gy/8 Fr	27.6
66 (Woman)	No	40	SqCC	155.3	60 Gy/8 Fr	24.7
73 (Man)	No	15	Adeno	39.9	45 Gy/3 Fr	22.5
82 (Man)	No	32	SqCC	89.5	45 Gy/3 Fr	12.6
71 (Man)	Yes	23	Adeno	54.5	45 Gy/3 Fr	16.2
80 (Man)	No	22	SqCC	78.7	45 Gy/3 Fr	12.7
80 (Man)	Yes	48	SqCC	156.9	60 Gy/8 Fr	17.0
60 (Man)	No	25	Large	86.6	45 Gy/3 Fr	15.4
82 (Man)	No	35	SqCC	111.7	60 Gy/8 Fr	15.9

PTV, planning target volume; Adeno, adenocarcinoma; SqCC, squamous cell carcinoma; Large, large cell carcinoma; Fr, fractions.

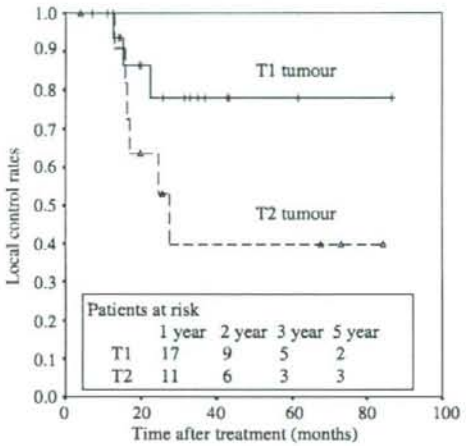

Fig. 2. Local control rates of T1 tumours (n = 19) and T2 tumours (n = 12) treated with stereotactic body radiotherapy. Patients at risk for local failure are given for 1-, 2-, 3-, and 5-year time periods.

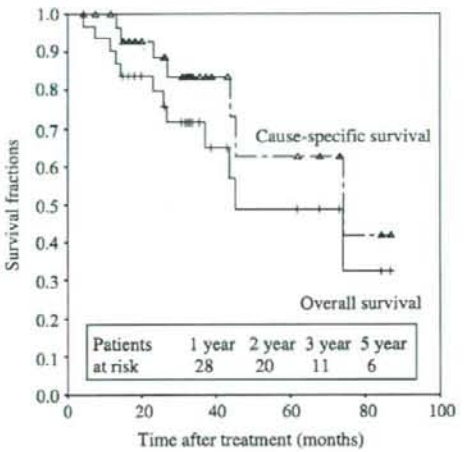

Fig. 3. Overall and cause-specific survival rates in 31 stage I non-small cell lung cancer patients. Patients at risk for failure are given for time periods up to 5 years.

Table 3
Patterns of failure

		T1	T2
Total	31	19	12
Recurrence	14	7	7
Isolated local	6	3	3
Local + L/N	2	0	2
Local + distant	1	0	1
Isolated distant	5	4	1
No recurrence	17	12	5

L/N, regional lymph node.

Toxicity

Acute adverse events were graded using the National Cancer Institute's Common Toxicity Criteria for adverse events version 3.0. Grade 1 acute pneumonitis developed in 24 patients. Grade 2 acute pneumonitis developed in 3 patients, and grade 3 in 1 patient. Two patients did not develop radiation-induced pneumonitis. Patients with grade 2 pneumonitis improved immediately after receiving steroid treatment. The patient with grade 3 acute pneumonitis was treated with oxygen before SBRT due to severe emphysema and needed to increase the flow of oxygen after SBRT. One patient with a tumour that invaded a sub-bronchus needed oxygen treatment temporally due to obstruction in the right upper bronchus that was estimated to be grade 3. No grade 2 or greater toxicity was observed outside the lungs.

Discussion

The optimum protocol of SBRT for NSCLC has not been established, although several protocols and clinical results have been previously reported [16,19,32]. When we de-

signed this protocol, 2 clinical results of SBRT had been reported for stage I NSCLC [1,31]. Both reported excellent local control rates of >90% using 50 Gy/5 fractions [31] and 60 Gy/8 fractions [1]. We calculated biologic effective dose (BED) as $nd[(1 + d/\alpha/\beta)$, where n is the number of fractions, d is the fraction size, and α/β is assumed to be 10 Gy; 50 Gy/5 fractions and 60 Gy/8 fractions were equal to BEDs of 100 Gy and 105 Gy, respectively. Therefore, we used 45 Gy/3 fractions and 60 Gy/8 fractions in this study that were equal to BEDs of 113 Gy and 105 Gy, respectively.

Onishi et al. [22] recently concluded that a BED of $\geqslant$100 Gy was necessary for optimal control in their retrospective multi-institutional study. Hoyer et al. [9] and Baumann et al. [2] reported that SBRT with a BED similar to ours resulted in favourable local control compared with conventional radiotherapy; however, Baumann et al. [2] also showed that the local control rate of T1 tumours was significantly higher than that of T2 tumours. In our study, the local control rate for T1 tumours was 77.9%. Therefore, SBRT at 45 Gy/3 fractions or 60 Gy/8 fractions for T1 tumours is more effective than conventional radiotherapy. However, for T2 tumours, the local control rate was 40.0%, which was lower than expected. However, verification by the log-rank test showed no significant difference between the local control rate of T1 and T2 tumours ($p = 0.111$). Wada et al. [33] analysed the tumour control rate of 42 pulmonary or liver tumours treated with SBRT at 45 Gy/3 fractions and concluded that the tumour control rate for tumours >3 cm in diameter was significantly lower than that for tumours with diameters <3 cm. Fowler et al. [5] suggested that the increase in the hypoxic cell population in lung tumours might correlate with the irradiation dose needed for tumour control. They reported that 3 doses of 23 Gy are required to reduce the surviving population to 10^{-11} if 1% of tumour cells is hypoxic. The increase in the hypoxic cell population due to tumour growth might decrease the control rate of T2 tumours after SBRT. Regarding the total dose of SBRT for NSCLC, it has also been suggested that the total dose delivered in 3 fractions to achieve 80% local control is between a marginal dose of 50 and 72 Gy [16]. Timmerman et al. [30] also reported that the maximal tolerated dose for stage I NSCLC is a marginal dose of more than 60 Gy administered in 3 fractions. In a review of 156 patients with stage I NSCLC, Sibley et al. [25] reported that high-dose radiotherapy showed better local control and survival rates than low-dose radiotherapy. A more intensive treatment regimen should be considered for T2 tumours because no severe toxicity occurred in this study.

Conventional radiotherapy for stage I NSCLC has been reported to achieve a 6–30% 5-year overall survival rate [8,11,12,14,17,21,23,25]. The actual overall survival rate in our study exceeded that reported with conventional radiotherapy; in our study, we achieved 3- and 5-year overall survival rates of 71.7% and 48.9%, respectively, although the median follow-up period was 32 months. In contrast, the 5-year survival rate for stage I patients after surgery has been reported to be approximately between 50% and 80% [4,7,18,20]. Most of our patients were of advanced age (median age, 77 years) and were contraindicated for surgery due to severe complications. Five intercurrent deaths (16.1% of all patients) occurred. These patients died as a result of cerebral infarction, arrhythmia, traffic accident, non-pathological femoral neck fracture or bacterial pneumonia of the non-irradiated lung.

It is reported that the incidence of pneumonitis $\geqslant$grade 3 is less than 10% for patients with stage I NSCLC administered a total dose of 60–70 Gy by conventional fractionation or hyperfractionation [11,24]. However, the rate of grade 3 or higher pneumonitis in SBRT is 5% or less [19,22]. Further, in the present study, only 1 patient (4.3%) developed grade 3 acute pneumonitis. However, the patient with grade 3 acute pneumonitis was not treated with steroids because there was no obvious radiological reason for the shortness of breath. The shortness of breath may have been caused by emphysema progression and not by the SBRT. However, Fujino et al. [6] examined the risk factors for symptomatic radiation pneumonitis ($\geqslant$grade 2) in 156 patients with stage I NSCLC after SBRT and determined that pre-treatment pulmonary function tests (percent vital capacity, forced expiratory volume in 1 second) and dose volume statistics (the percent of the total lung volume exceeding 20 Gy, total dose, BED, dose per fraction, peripheral dose) were not predictive of pneumonitis requiring steroid intake.

One patient developed grade 3 pulmonary toxicity due to an obstruction in the upper bronchus. The upper bronchus was included in the PTV because the tumour was located on and invaded the upper sub-bronchus. Although we excluded patients with a lung tumour on the hilus or main bronchus, SBRT must be carefully administered for patients with a lung tumour at the bronchus level.

The accuracy of tumour verification is crucial for SBRT because hypofractionated high-dose radiation is used and the organ at risk is often close to the tumour. In our study, all tumours were strictly verified. Patients were immobilised in the supine position with an individually fashioned half-body vacuum cast. Skin markers were also referred to for the verification. The X-ray images in 2 directions from a DFFP system were compared with CT planning pictures in the same 2 directions. Verification of the patient's treatment position was performed at each treatment session. Abdominal pressures or respiratory patterns cause interfractional errors for lung tumours when verification is performed on the basis of bone structure [10]. However, it became possible to achieve accurate tumour positioning and reproducibility by using the DFFP system. Britton et al. [3] reported that uncertainty regarding the motion of the prostate could be considerably decreased with daily use of the DFFP system. Therefore, we set a 5-mm set-up margin which appeared to be adequate to overcome set-up errors in our treatment. This system also permitted us to observe the pattern of tumour movement immediately before treatment; this was useful in confirming the coverage of the IM.

In conclusion, current data support the use of SBRT for stage I NSCLC. SBRT for T1 tumours administered in 45 Gy/3 fractions or 60 Gy/8 fractions is safe and effective. However, an appropriate treatment protocol is required, particularly for T2 tumours. Further works regarding SBRT will be necessary.

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Hypofractionated Stereotactic Radiotherapy (HypoFXSRT) for Stage I Non-small Cell Lung Cancer: Updated Results of 257 Patients in a Japanese Multi-institutional Study

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Introduction: Hypofractionated stereotactic radiotherapy (HypoFXSRT) has recently been used for the treatment of small lung tumors. We retrospectively analyzed the treatment outcome of HypoFXSRT for stage I non-small cell lung cancer (NSCLC) treated in a Japanese multi-institutional study.

Methods: This is a retrospective study to review 257 patients with stage I NSCLC (median age, 74 years: 164 T1N0M0, 93 T2N0M0) were treated with HypoFXSRT alone at 14 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. A total dose of 18 to 75 Gy at the isocenter was administered in one to 22 fractions. The median calculated biological effective dose (BED) was 111 Gy (range, 57–180 Gy) based on $\alpha/\beta = 10$.

Results: During follow-up (median, 38 months), pulmonary complications of above grade 2 arose in 14 patients (5.4%). Local progression occurred in 36 patients (14.0%), and the local recurrence rate was 8.4% for a BED of 100 Gy or more compared with 42.9% for less than 100 Gy ($p < 0.001$). The 5-year overall survival rate of medically operable patients was 70.8% among those treated with a BED of 100 Gy or more compared with 30.2% among those treated with less than 100 Gy ($p < 0.05$).

Conclusions: Although this is a retrospective study, HypoFXSRT with a BED of less than 180 Gy was almost safe for stage I NSCLC, and the local control and overall survival rates in 5 years with a BED of 100 Gy or more were superior to the reported results for conventional radiotherapy. For all treatment methods and schedules, the local control and survival rates were better with a BED of 100 Gy or more compared with less than 100 Gy. HypoFXSRT is feasible for curative treatment of patients with stage I NSCLC.

Key Words: Stereotactic radiotherapy, Non-small cell lung cancer, Stage I, Hypofractionated.

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In Japan, due to the routine use of computed tomography (CT), detection of early-stage lung cancer is increasing. For patients with stage I (T1 or 2, N0, M0) non-small cell lung cancer (NSCLC), full lobar or greater surgical resection and regional lymphadenectomy is the standard treatment choice; the local control rates exceed 80% and the overall 5-year survival rates surpass 50%.[1] However, surgical resection is often not feasible or involves a high risk for lung cancer patients with tobacco-related pulmonary illnesses, severe cardiovascular disease, or other medical conditions. Moreover, a small proportion of the patients who are fit for surgery may refuse it for personal reasons.

Radiotherapy (RT) can offer a therapeutic alternative in these cases, but the outcome with conventional RT is unsatisfactory.[2] The reason for the poor survival with conventional RT is thought to be that the dose of conventional RT is too low to control the local tumor. To give a higher dose to the tumor without increasing the adverse effects, hypofractionated high-dose stereotactic RT (HypoFXSRT) has recently been used to treat small cell lung tumors, particularly in Japan.[3–6] Although the optimal treatment technique and

schedule of HypoFXSRT for stage I NSCLC are unknown, the nationwide number of Japanese patients with stage I NSCLC who are treated with small-volume stereotactic RT (SRT) has increased rapidly.

Therefore, it is meaningful to investigate the results of SRT for stage I NSCLC from many institutions, even in a retrospective manner, despite the large differences in treatment protocols. Previously, we reported the result of a Japanese multi-institutional review of 300 patients with stage I NSCLC treated with SRT.[7] We concluded that SRT with a biological effective dose (BED) of less than 150 Gy is effective for the curative treatment of patients with stage I NSCLC and that the local control and survival rates are better with a BED of 100 Gy or more compared with less than 100 Gy.

The survival rates in selected medically operable patients with a BED of 100 Gy or more were promising and potentially comparable with those of surgery. These results for SRT were encouraging for stage I NSCLC patients; however, the 300 subjects in that report included 17 patients irradiated with comparatively small fractions (<4 Gy) and 26 patients irradiated in combination with conventional RT. This article presents the results for patients irradiated with HypoFXSRT alone in a multi-institutional study. In this study, we compared the reported results for surgery and conventional RT with those for HypoFXSRT.

PATIENTS AND METHODS

Eligibility Criteria

This was a retrospective study to review patients who were treated by HypoFXSRT for their stage I NSCLC in 14 different hospitals in Japan.

All the patients enrolled in this study satisfied the following eligibility criteria: identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdominal CT, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging; histological confirmation of NSCLC; performance status of 2 or less according to the World Health Organization (WHO) guidelines; and an inoperable tumor due to a poor medical condition or refusal to undergo surgery.

No restrictions were imposed concerning the locations of eligible tumors, irrespective of whether they were located adjacent to a major bronchus, blood vessel, chest wall, or the esophagus. Patients were informed of the concept, methodology, and rationale of this treatment, which was performed in accordance with the 1983 revision of the Declaration of Helsinki.

Patient Characteristics

The patient pretreatment characteristics are summarized in Table 1. From April 1995 to March 2004, a total of 257 patients with primary NSCLC was treated using high-dose HypoFXSRT in the following 14 institutions: Hokkaido University, Kyoto University, Cancer Institute Hospital, Tokyo Metropolitan Komagome Hospital, Kitasato University, Tohoku University, Hiroshima University, Tokyo Metropolitan Hiroo Hospital, Sapporo Medical University, Institute of Biomedical Research and Innovation, International Medical Center of Japan, Tenri Hospital, Kitami Red Cross Hospital, and University of Yamanashi. Of the 257 patients, 158 were considered medically inoperable mainly because of chronic pulmonary disease, advanced age, or other chronic illness. The remaining 99 patients were considered medically operable, but had refused surgery or had been advised to select HypoFXSRT by medical oncologists.

TABLE 1. Patient Pretreatment Characteristics

Total cases: 257
Age: 39–92 yr (median, 74)
Performance status: PS 0, 109; PS 1, 103; PS 2, 39; PS 3, 6
Pulmonary chronic disease: 168 positive, 89 negative
Histology: 111 squamous cell, 120 adenocarcinoma, 26 other
Stage: 164 IA, 93 IB
Tumor diameter: 7–58 mm (median, 28)
Medical operability: 158 inoperable, 99 operable

Treatment Methods

All the patients were irradiated using stereotactic techniques. For the purposes of this study, all the hypofractionated stereotactic techniques met five requirements: reproducibility of the isocenter of 5 mm or less, as confirmed for every fraction; slice thickness on CT of 3 mm or less for three-dimensional (3-D) treatment planning; irradiation with multiple noncoplanar static ports or dynamic arcs; dose per fraction size more than 4 Gy; and a total treatment period of fewer than 25 days. Details of the techniques and instruments used to achieve SRT in the 14 institutions were summarized in a previous report.[7] The clinical target volume (CTV) marginally exceeded the gross target volume (GTV) by 0 to 5 mm. The planning target volume (PTV) comprised the CTV, a 2- to 5-mm internal margin and a 0–5-mm safety margin. A high dose was concentrated on the tumor-bearing area, while sparing the surrounding normal lung tissues using SRT. The irradiation schedules also differed among the institutions. The number of fractions ranged between 1 and 14, with single doses of 4.4 to 35 Gy. A total dose of 30 to 84 Gy at the isocenter was administered with 6- or 4-MV x-rays within 20% heterogeneity in the PTV dose. No chemotherapy was administered before or during RT.

To compare the effects of various treatment protocols with different fraction sizes and total doses, the BED was used in a linear-quadratic model.[8] Here, the BED was defined as $nd(1 + d/\alpha/\beta)$, with gray units, where n is the fractionation number, d is the daily dose, and α/β is assumed to be 10 for tumors. The BED was not corrected with values for the tumor doubling time or treatment term. In this study, the BED was calculated at the isocenter. The median BED was 111.0 Gy (range, 57.6–180.0). The BED was 100 Gy or more in 215 patients and less than 100 Gy in 42 patients. The median BED for the less than 100 Gy and 100 Gy or more subgroups was 79.6 Gy (range, 57.6–98.6) and 117.0 Gy (range, 100.0–180.0), respectively.

Dose constraints were set for the spinal cord only. The BED limit for the spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity).

Evaluation

The objectives of this study were to retrospectively evaluate the toxicity, local control rate, and survival rate according to the BED. All patients underwent follow-up examinations by radiation oncologists. The first examination took place 4 weeks after treatment, and patients were subsequently seen every 1 to 3 months. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors by CT.[9] Chest CT (slice thickness, 2–5 mm) was usually obtained every 3 months for the first year and repeated every 4 to 6 months thereafter. A complete response (CR) indicated that the tumor had disappeared completely or was replaced by fibrotic tissue. A partial response (PR) was defined as a 30% or more reduction in the maximum cross-sectional diameter. It was difficult to distinguish between residual tumor tissue and radiation fibrosis. Any suspicious confusing residual density after RT was considered evidence of a PR, so the actual CR rate might have been higher than that given here. Local recurrence was considered to have taken place only when enlargement of the local tumor continued for more than 6 months on follow-up CT. Two radiation oncologists interpreted the CT findings. The absence of local 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

The local recurrence rates in the two groups were compared with the χ^2 test. The BED among patient groups at each pulmonary toxicity grade was compared using the Kruskal-Wallis test. The cumulative local control and survival curves were calculated and drawn applying the Kaplan-Meier algorithms with day of treatment as the starting point. Subgroups were compared using log-rank statistics. Values of $p < 0.05$ were considered statistically significant. Statistical calculations were conducted using version 5.0 StatView software (SAS Institute, Cary, NC).

RESULTS

All the patients completed the treatment with no particular complaints. The median duration of follow-up for all patients was 38 months (range, 2–128).

Local Tumor Response

Of the 257 patients evaluated using CT, CR was achieved in 66 (25.7%) and PR in 157 (61.1%). The overall response rate (CR + PR) was 86.8%. The overall response rates for tumors with a BED of 100 Gy or more ($n = 215$) or less than 100 Gy ($n = 42$) were 87.5% and 86.7% in 3 years (?), respectively. A typical case of a T1 tumor after HypoFXSRT is shown in Figure 1.

Toxicity

Symptomatic radiation-induced pulmonary complications (NCI-CTC criteria grade >1) were noted in 28 patients (10.9%). Pulmonary fibrosis or emphysema before treatment was observed in 25 (89%) of the 28 patients with pulmonary complications above grade 1. Pulmonary complications of NCI-CTC criteria above grade 2 were noted in only 14

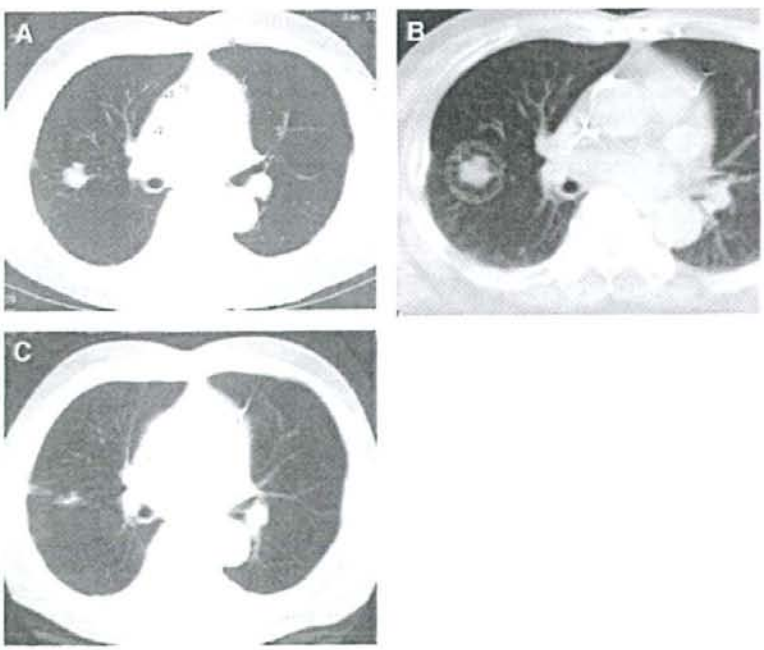

FIGURE 1. A typical example involving SRT for a 76-year-old man with T1N0 adenocarcinoma. He was treated with HypoFXSRT. (*A*) Before hypofractionated stereotactic radiotherapy (HypoFXSRT). (*B*) The calculated dose distribution. The isocenter dose was 75 Gy/10 fractions/5 days, and the tumor was fully enclosed with the 90% dose line. (C) Twelve months after HypoFXSRT, a scarred tumor is rated as a partial response.

TABLE 2. Recurrence Rate According to the BED and Stage

	Total cases	BED <100 Gy	BED ≥100 Gy	p	Stage IA	Stage IB	p
Local tumor	36/257 (14.0%)	18/42 (42.9%)	18/215 (8.4%)	<0.01	20/164 (12.2%)	16/93 (17.2%)	0.21
Regional nodal metastasis	29/257 (11.3%)	9/42 (21.4%)	20/215 (9.3%)	<0.05	17/164 (10.4%)	12/93 (12.9%)	0.54
Distant metastasis	51/257 (19.8%)	11/42 (26.2%)	40/215 (18.6%)	0.3	32/164 (19.5%)	19/93 (20.4%)	0.87

BED, biological effective dose.

patients (5.4%). The pulmonary symptoms resolved in most patients without steroid therapy, but six patients who had very poor respiratory function or severe pulmonary fibrosis before irradiation needed continuous oxygen. Chronic segmental bronchitis and wall thickening causing atelectasis in the peripheral lung was observed in one patient (0.4%). Transient grade 3 esophagitis was observed in two patients (0.8%) with tumors adjacent to the esophagus. Grade 3 or 4 dermatitis was observed in three patients (1.2%) with tumors adjacent to the chest wall. Rib fracture adjacent to the tumor was found in four patients (1.6%). No vascular, cardiac, or bone marrow complications had been encountered as of the last follow-up.

Recurrence

The recurrence rates of local, regional nodal, and distant lesions according to the BED and stage are listed in Table 2. The local recurrence rate was significantly lower for a BED of 100 Gy or more compared with a BED of less than 100 Gy (8.4 versus 42.9%, $p < 0.01$). For greater BED subgroups, the local recurrence rate was 11.8% for a BED of 120 Gy or more ($n = 93$) and 8.1% for a BED of 140 Gy or more ($n = 37$). The local recurrence rates for adenocarcinoma and squamous cell carcinoma were 13.3% (16/120) and 17.1% (19/111), respectively in 3 years. The cumulative local control rate curves according to BED subgroup are shown in Figure 2. The 5 (3? according to Table 2)-year local control rates of the BED of 100 Gy or more and less than 100 Gy subgroups were 84.2% (95% confidence interval [CI]: 77.7%–90.8%) and 36.5% (95% CI: 10.4%–62.6%), respectively. According to subgroup analysis, stage IB patients had a significantly higher rate of local recurrence than stage IA patients. The nodal and distant recurrence rates were almost identical in the stage IA and IB subgroups.

In the patients with regional nodal recurrence, nodal failures overlapped local failure in 3.1%, distant metastases in 3.9%, or both in 0.8% of the patients. Isolated local, nodal, and distant recurrences were observed in 8.6%, 5.1%, and 13.6% of the patients, respectively.

Survival

The overall 3- and 5-year survival rates for all patients were 56.8% (95% CI: 50.2%–63.5%) and 47.2% (95% CI: 38.7%–53.5%), respectively. The cause-specific 3- and 5-year survival rates were 76.9% (95% CI: 70.6%–83.2%) and 73.2% (95% CI: 66.1%–80.2%), respectively. The overall survival rates differed significantly according to medical operability, with intercurrent death in 36.8% of inoperable patients and 10.3% of operable patients. The overall 5-year survival rates of medically operable and inoperable patients (Figure 3) were 64.8% (95% CI: 53.6%–75.9%) and 35.0% (95% CI: 25.9%–44.1%), respectively. The overall survival rates according to the BED in all patients differed significantly between the BED of less than 100 Gy and 100 Gy or more subgroups. The overall 5-year survival rates of the BED 100 Gy or more and less than 100 Gy subgroups were 53.9% (95% CI: 46.0%–61.8%) and 19.7% (95% CI: 5.9%–33.4%), respectively. For the subgroup of medically operable patients with a BED of 100 Gy or more, the 3- and 5-year overall survival rates were 80.4% (95% CI: 71.0%–89.7%) and 70.8% (95% CI: 59.3%–82.2%), respectively (Figure 2). The overall 5-year survival rate according to stage in the operable patients irradiated with a BED of 100 Gy or more was 72.3%

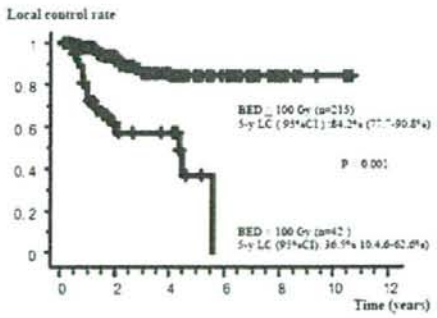

FIGURE 2. Cumulative local control rate according to the biological effective dose (BED). LC, local control rate; CI, confidence interval.

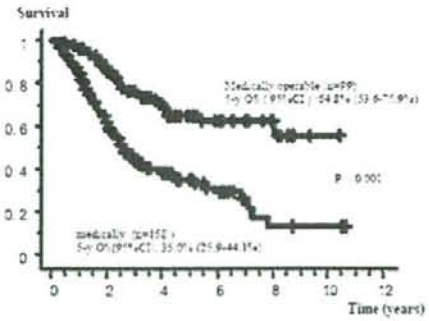

FIGURE 3. Overall survival rate according to medical operability. OS, overall survival rate; CI, confidence interval.

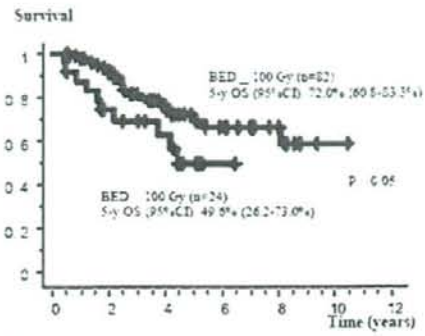

FIGURE 4. Overall survival rate in operable patients according to the biological effective dose (BED). OS, overall survival rate; CI, confidence interval.

(95% CI: 59.1%–85.6%) for stage IA and 65.9% (95% CI: 43.0%–88.9%) for stage IB patients (Figure 4).

Reproducibility of the Data Among Institutions

Table 3 compares the irradiation method and results for three major institutions enrolled in this study. These institutions used a BED of 100 Gy or more. The local control and 3-year survival rates were almost identical.

DISCUSSION

At present, surgery is the standard treatment for stage I NSCLC. RT is offered to patients who are unsuitable for surgery because of medical problems and to patients who refuse surgery. Most information on the results of RT for stage I NSCLC is based on retrospective studies of RT-treated inoperable NSCLC cases. Therefore, the role of RT for stage I NSCLC, as a curative modality, has not yet been established.

Qiao et al. summarized 18 papers on stage I NSCLC treated with conventional RT alone published between 1988 and 2000.[10] Local recurrence was the most common reason for treatment failure of stage I NSCLC with conventional RT, but the frequency of recurrence varied considerably according the report (between 6.4% and 70%). The 3-year recurrence rate was approximately 60%,[11–13] with a median time to relapse that ranged from 21 to 30 months.[12,14,15] Generally, smaller tumor size, low T stage, and increased dose had a favorable impact on local control, and increased local control was followed by increased survival.[14,16] However, the overall treatment results were disappointing. The median survival in these studies ranged from 18 to 33 months. The 3- and 5-year overall survival rates were 34 ± 9% and 21 ± 8% (mean ± 1 SE), respectively. The cause-specific survival rates at 3 and 5 years were 39 ± 10% and 25 ± 9% (mean ± 1 SE), respectively. Regarding treatment toxicity, severe (grade 3 or above) radiation esophagitis[14] and pneumonitis[11] occurred in 4.1% and 6.1% of the cases, respectively. Better local control may be achieved when the total dose is increased,[15,16] and a trend has been growing toward seeking better local control by increasing the BED[13–15] for a relatively limited span of doses (BED 59–76 Gy). Dose escalation has been the focus of developmental therapeutic strategies for inoperable stage I NSCLC to improve local control and survival.

Mehta et al.[17] provided a detailed theoretical analysis regarding the responses of NSCLC to RT and a rationale for dose escalation. They concluded that a greater BED irradiated during a short period must be given to gain local control of lung cancers. Giving a higher dose to the tumor without increasing the adverse effects was shown to be possible using the SRT technique; this is now feasible due to the technological progress that allows increasing the accuracy of localization to the tumor-bearing area using various imaging tools. SRT can also reduce the overall treatment time substantially, from several weeks for conventional RT to a few days, offering an important advantage to the patient.

After Uematsu et al.[18] reported a landmark study on SRT for stage I NSCLC using a CT-linac system, SRT has been actively investigated for stage I NSCLC in Japan and the United States. In the reports listed in Table 4,[3–6,19–21] the local control rates of primary lung cancer with SRT ranged from 87% to 97% when the BED exceeded 100 Gy. Uematsu et al.[3] showed excellent survival rates for medically operable patients, approximating those for full lobar surgical resection; however, they studied only a few patients, and it is not known whether the result is reproducible. Table 5 compares the results of Uematsu et al.[3] with the HypoFXSRT results presented here. These results suggest that the local control and survival rates of HypoFXSRT for stage I NSCLC are promising and reproducible when the BED exceeds 100 Gy.

In Japan, we consider a BED greater than 100 Gy to be a satisfactory dose for HypoFXSRT of stage I NSCLC, with a local control rate better than 85%, and a further dose escalation study is not necessary for tumors smaller than 4 cm in diameter. Conversely, in the United States, Timmerman et al.[22] concluded that 60 Gy in three fractions (BED = 180 Gy) is the proper dose, and they adopted this dose and fraction protocol for their prospective study. We need to observe the

TABLE 3. Comparison of the Irradiation Methods and Results for Three Major Institutions

Institution	No. of Patients	Total Isocenter Dose (Gy)	Single Isocenter Dose (Gy)	BED (Gy)	Median Follow-up (mo)	Local Failure, %	5-yr Overall Survival, %
Kyoto	42	48	12	106	40	3	64
Cancer Institute	30	50–62.5	10–12.5	100–141	25	4	77
Kitami	27	50–60	7.5–10	100–105	71	4	63

BED, biologically effective dose (α/β = 10) recalculated at the isocenter.