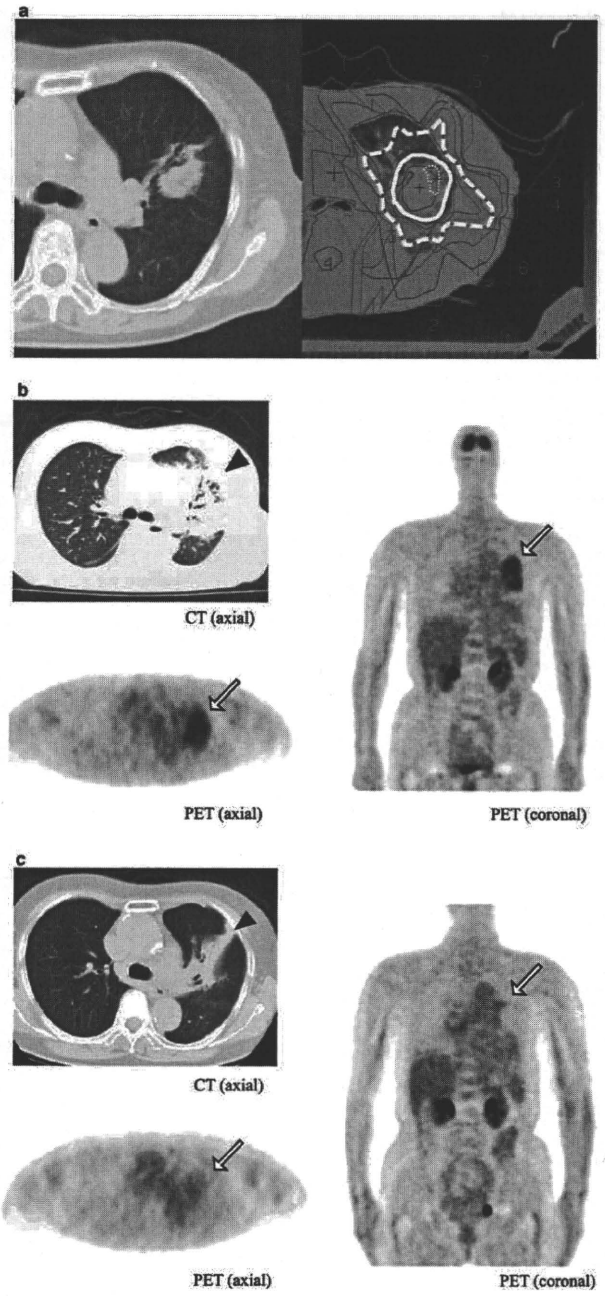

Fig. 3. 79-year-old woman (Patient D in Table 2) with cT2N0M0 primary lung adenocarcinoma, who underwent SBRT with a prescription dose of 48 Gy administered in four fractions at the isocenter. (a) CT image before treatment (left) and dose distribution of SBRT (right). The inner thin dashed, solid, and outer dashed lines indicate 48-, 40-, and 20-Gy isodose lines, respectively. (b) CT and FDG-PET images 2 months after SBRT. Radiation pneumonitis is observed upon CT (arrowhead). The FDG-PET scan shows well-defined and intense (grade 2) uptake (arrows) with the SUVmax of 7.1. (c) CT at 52 months and FDG-PET at 49 months; CT shows a scar-like shadow (arrowhead). Ill-defined and mild (grade 1) uptake is seen upon FDG-PET (arrows). The SUVmax was 3.0.

after SBRT, which is consistent with the results of Hoopes et al. [20].

It is important to detect local recurrence soon after SBRT, but this is difficult based on CT alone. We have previously evaluated post-irradiation changes and local recurrence after SBRT, based on CT [9]. However, in the previous study, we could not detect any significant CT differences between radiation-induced inflammatory changes and local recurrence. We concluded that early detection of local recurrence is difficult using CT because of the dense consolidation, called mass-like consolidation, which was observed at a median post-SBRT time of 5 months in 68% of the cases. Most cases (89%) of consolidation were confirmed as radiation-induced lung injury, although a few (11%) were local recurrence. Takeda et al. reported that 20 of 50 patients had abnormal opacity that was suspicious for local recurrence at a median of 20.7 months after SBRT [10]. However, only three patients had recurrence, and the remaining 17 patients were free from recurrence or were considered equivocal. They also concluded that it was difficult to distinguish radiation fibrosis from local tumour recurrence.

The value of FDG-PET in detecting residual or recurrent NSCLC after conventional radiotherapy has been evaluated by Frank et al. [15] and Bury et al. [16], who found a sensitivity and specificity of 100% and 89–92%, respectively. Inoue et al. have suggested a threshold SUV of 5.0 for the differential diagnosis between local recurrence of lung cancer and post-treatment changes [17]. Indeed, our study had no case in which the SUVmax was >5.0 at $\geqslant$6 months after SBRT. According to Takeda et al. [10], a patient with a SUVmax of 5.0 at 12 months after SBRT developed local recurrence, and three patients with a SUVmax of 2.2–3.13 showed no evidence of local recurrence. However, Hoopes et al. [18] reported that two patients with a SUV > 5.0 at 23–26 months were free from local recurrence. Further studies are needed to investigate an optimal SUV for distinguishing local recurrence from post-SBRT changes. As far as we are aware, there have been no studies to date regarding FDG-PET detection of local recurrence after SBRT.

The present study has some limitations. First, the study was not prospective but was a retrospective review. FDG-PET was performed in a limited number of patients, some of whom had a suspicious consolidation upon CT, which might have caused selection bias. Second, local control was not based on pathological confirmation but on CT images. Therefore, FDG uptake demonstrating recurrent tumours might have been included with that owing to inflammation caused by irradiation. However, clinically suspicious recurrent cases were not included, and a median follow-up duration of 51 months was sufficient to establish no recurrence of local tumours.

In conclusion, this study showed that FDG uptake tended to be high and well-defined during an early time period after SBRT, especially within the initial 6 months, and became lower and ill-defined during later periods. Moderate to intense FDG uptake observed during an early period after SBRT does not always indicate residual or recurrent tumour. These findings may help in interpreting FDG-PET data for follow-up in patients with NSCLC after SBRT.

Conflict of interest notification

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CLINICAL INVESTIGATION **Lung**

PROGNOSTIC FACTORS IN STEREOTACTIC BODY RADIOTHERAPY FOR NON–SMALL-CELL LUNG CANCER

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Purpose: To investigate the factors that influence clinical outcomes after stereotactic body radiotherapy (SBRT) for non–small-cell lung cancer (NSCLC).

Methods and Materials: A total of 101 consecutive patients who underwent SBRT with 48 Gy in 4 fractions for histologically confirmed Stage I NSCLC were enrolled in this study. Factors including age, maximal tumor diameter, sex, performance status, operability, histology, and overall treatment time were evaluated with regard to local progression (LP), disease progression (DP), and overall survival (OS) using the Cox proportional hazards model. Prognostic models were built with recursive partitioning analysis.

Results: Three-year OS was 58.6% with a median follow-up of 31.4 months. Cumulative incidence rates of LP and DP were 13.2% and 40.8% at 3 years, respectively. Multivariate analysis demonstrated that tumor diameter was a significant factor in all endpoints of LP, DP, and OS. Other significant factors were age in DP and sex in OS. Recursive partitioning analysis indicated a condition for good prognosis (Class I) as follows: female or T1a (tumor diameter ≤20 mm). When the remaining male patients with T1b–2a (>20 mm) were defined as Class II, 3-year LP, DP, and OS were 6.8%, 23.6%, and 69.9% in recursive partitioning analysis Class I, respectively, whereas these values were 19.9%, 58.3%, and 47.1% in Class II. The differences between the classes were statistically significant.

Conclusions: Tumor diameter and sex were the most significant factors in SBRT for NSCLC. T1a or female patients had good prognosis. © **2011 Elsevier Inc.**

SBRT, Lung cancer, Prognostic factor.

INTRODUCTION

Lung cancer is the leading cause of cancer death in Japan (1) and the United States (2). Surgery is accepted as the standard intervention for Stage I non–small-cell lung cancer (NSCLC) (3). Clinical outcomes of conventional radiotherapy for Stage I NSCLC are inferior to those of surgery. The overall survival rate of conventional radiotherapy for medically inoperable patients with Stage I NSCLC is approximately 15% (4).

Stereotactic body radiotherapy (SBRT) is a newly emerging method for treatment of extracranial lesions. Initial reports of SBRT were made by Blomgren *et al.* in 1995 (5) and by Uematsu *et al.* in 1998 (6). Initial experience and the results of Phase I trials of SBRT were reported by leading institutions in the early 2000s (7–10). The results were very promising, with excellent rates of local control, and encouraged other institutions to begin using SBRT for lung cancer. According to a survey by the Japan 3-D Conformal External Beam Radiotherapy Group, 53 institutions had already begun using SBRT in Japan by November 2005, and more than 1000 patients with histologically confirmed NSCLC were treated with SBRT (11).

Local dose is thought to be a significant factor affecting the outcome after SBRT for NSCLC. Onishi *et al.* (12) reviewed 257 patients who received SBRT for Stage I NSCLC during the period 1995–2004 at 14 institutions in Japan. Significant differences were observed according to biologically effective dose (BED) at the isocenter. The local recurrence rate was 8.4% in patients who received BED of ≥100 Gy, whereas the rate was 42.9% in patients receiving <100 Gy in BED. The 5-year overall survival rate of medically operable patients was 70.8% among those who were treated with a BED of ≥100 Gy, compared with 30.2% among those

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treated with <100 Gy. Baumann *et al.* (13) retrospectively reviewed the results of SBRT for 138 patients with medically inoperable Stage I NSCLC treated during the period 1996–2003 at five centers in Sweden and Denmark. The group receiving a dose above 55.6 Gy in equivalent dose in 2-Gy fractions (EQD2) showed a significant survival advantage. According to the authors, 55.6 Gy in EQD2 at the planning target volume (PTV) periphery corresponded to BED 100 Gy at the isocenter, as in the Onishi study.

We started using SBRT for the lung in July 1998 and have performed SBRT in more than 100 patients with histologically confirmed NSCLC using a single-fractionation schedule of 48 Gy in 4 fractions at the isocenter, which corresponds to 105.6 Gy in BED. Although we have prescribed a dose of >100 Gy in BED, the disease progressed in several cases in our 10-year experience of SBRT. Prognostic factors other than local dose should be examined to improve SBRT outcomes for NSCLC.

The present study was performed to investigate the factors that influence clinical outcome after SBRT for lung cancer.

METHODS AND MATERIALS

Patients

A total of 101 consecutive patients who underwent SBRT with 48 Gy in 4 fractions for histologically confirmed Stage I NSCLC during the period from September 1998 to December 2007 were enrolled in this study. The eligibility criteria for SBRT for Stage I lung cancer were as follows: (*1*) surgery was contraindicated or refused; (*2*) maximal tumor diameter was ≤40 mm; (*3*) the tumor was not adjacent to mediastinal organs (spinal cord, esophagus, heart, and main bronchus); (*4*) the patient could remain stable in the body frame for longer than 30 min with World Health Organization performance status of 0–2; (*5*) the patient had no active interstitial pneumonia; and (*6*) written informed consent was obtained. No adjuvant chemotherapy was administered until disease progression was confirmed.

The characteristics of the patients are summarized in Table 1. The study population consisted of 74 men and 27 women with a median age of 77 years (range, 62–87 years). Histology was adenocarcinoma in 49, squamous cell carcinoma in 44, large-cell carcinoma in 2, and NSCLC not otherwise specified (NOS) in 6 patients. The median maximal tumor diameter was 25 mm (range, 12–43 mm). Newly revised T-stage (14) was T1a (≤20 mm) in 33 patients, T1b (21–30 mm) in 40 patients, and T2a (31–50 mm) in 28 patients according to tumor diameter.

Table 1. Patient characteristics (n = 101)

Sex	
Male	74
Female	27
Age (y)	77 (62–87)
Performance status	
0	57
1	37
2	7
Operability	
Operable	37
Inoperable	64
Histology	
Adenocarcinoma	49
Squamous cell carcinoma	44
Large-cell carcinoma	2
NSCLC NOS	6
Tumor diameter (mm)	25 (12–43)
T-stage*	
T1a (≤20 mm)	33
T1b (21–30 mm)	40
T2a (31–50 mm)	28

Abbreviation: NSCLC NOS = non-small-cell lung cancer, not otherwise specified.

Values are number or median (range).

* T-stage according to the revised 7th edition of the TNM classification for lung cancer.

SBRT procedure

The details of our SBRT procedure were described previously (15). The patient's body was immobilized with a stereotactic body frame (Elekta, Stockholm, Sweden). The SBRT plan was created with commercial treatment planning systems: CADPLAN (Varian Medical Systems, Palo Alto, CA) until December 2002, and thereafter Eclipse (Varian Medical Systems). The internal target volume was determined considering computed tomography (CT) with a slow scan technique, which can visualize a major part of the trajectory of the tumor by scanning each slice for a time longer than the respiratory cycle, and tumor motion assessed by X-ray fluoroscopy. The PTV was defined as the internal target volume with a 5-mm margin for setup uncertainty.

Irradiation was performed with 6-MV X-ray beams from a linear accelerator (Clinac 2300 C/D; Varian Medical Systems) in multiple noncoplanar static ports (five to eight ports). The beams were shaped into PTV plus 5-mm margins with a multileaf collimator (Mark-II 80 until September 2006, and then Millennium 120; Varian Medical Systems). The dose was prescribed to the isocenter. Monitor units were calculated with a pencil beam convolution algorithm with heterogeneity correction using the Batho power law method.

A fractional dose of 12 Gy was irradiated within a day, and the total dose was 48 Gy in 4 fractions. A 2-week schedule (1 to 2 fractions per week; overall treatment time [OTT] 10–13 days) was applied until February 2004, and then the schedule was changed to a 1-week schedule (3 to 4 fractions per week; OTT 4–8 days).

Follow-up after SBRT

Follow-up visits were at 1, 2, 4, 6, 9, and 12 months in the initial year after SBRT, every 3 months between Years 2 and 5, and every 6 months thereafter. Computed tomography scans were performed every 2–4 months for the first year after treatment, every 6 months between Years 1 and 5, and annually thereafter. Local progression was diagnosed on the basis of histologic confirmation or enlargement of the local tumor on CT that continued for at least 6 months. ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) was recommended when local recurrence was suspected, but this was not mandatory. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 2.0. The follow-up period was defined as from the first day of SBRT to the last day of a follow-up visit or date of death.

Statistical analysis

Univariate and multivariate analyses were performed using the Cox proportional hazards model to find potential factors that affected local progression (LP), disease progression (DP), and overall survival (OS) after SBRT. The factors evaluated were age (in years), maximal diameter of tumor (in millimeters), and OTT (in days) as continuous data; and sex (male or female), performance status (0, 1, or 2), operability (operable or inoperable), and histology

(adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, or NSCLC NOS) as categoric data. In multivariate analysis, stepwise selection (16) was applied to identify potential factors. To build prognostic models, recursive partitioning analysis (RPA) was performed with the variables selected in multivariate analysis. Overall survival rate was estimated by the Kaplan-Meier method, and the differences between patient groups were assessed by the log–rank test. Rates of LP and DP were computed by the cumulative incidence function, accounting for death as a competing risk, and the differences between groups were evaluated by the Gray test.

R version 2.9.2 with the survival, cmprsk, and rpart packages (R Project for Statistical Computing, Vienna, Austria) was used for statistical analyses. Statistical significance was defined as $p < 0.05$.

RESULTS

The median follow-up period was 31.4 months (range, 4.2–118.6 months). Overall treatment time ranged from 4 to 13 days (median, 5 days). The 1-week schedule was applied in 64 patients and the 2-week schedule in 37 patients.

Disease progression was observed in 43 patients. The first site of progression was the local lesion in 14 patients, regional node metastasis in 11, and distant metastasis in 20, including 2 patients with synchronous metastasis to node and distant organ. Organs of distant metastasis were the brain in 6 patients, lung in 6, liver in 3, and bone in 5. In 1 patient, distant metastasis was followed by LP. A total of 15 patients developed LP diagnosed by salvage surgery (2 patients), transbronchial biopsy (1 patient), CT with FDG-PET (7 patients), and CT findings alone (5 patients).

Three- and 5-year OS rates were 58.6% (95% confidence interval [CI], 48.7–70.6%) and 46.7% (95% CI, 36.0–60.7%), respectively (Fig. 1a). Median survival time was 48.8 months (95% CI, 35.9–91.9 months). The cumulative incidence rates of DP were 40.8% (95% CI, 30.5–51.0%) at 3 years and 42.8% (95% CI, 32.1–53.4%) at 5 years after SBRT (Fig. 1b). The LP rate was 13.2% (95% CI, 6.2–20.3%) at both 3 and 5 years.

Toxicities

National Cancer Institutes Common Toxicity Criteria Grade 2 pneumonitis (i.e., pneumonitis requiring steroids or diuretics) was observed in 4 patients. Pneumonitis Grade 3 or worse occurred in 3 patients, including 1 patient with Grade 5. In total, the incidence rate of pneumonitis Grade 2 or worse was 6.9%. Dermatitis Grades 2 and 3 were observed in 3 and 2 patients, respectively. Four patients developed rib fractures that were caused by SBRT.

Univariate and multivariate analyses

Univariate analysis revealed the following significant factors (Table 2): tumor diameter in LP; tumor diameter, age, and histology in DP; and sex and histology in OS. The stepwise procedure selected tumor diameter and sex as potential factors affecting LP and OS, and tumor diameter, sex, age, and OTT for DP. Multivariate analysis demonstrated tumor diameter as a significant factor in all endpoints of LP, DP, and OS. Other significant factors were age in DP and sex in OS (Table 3).

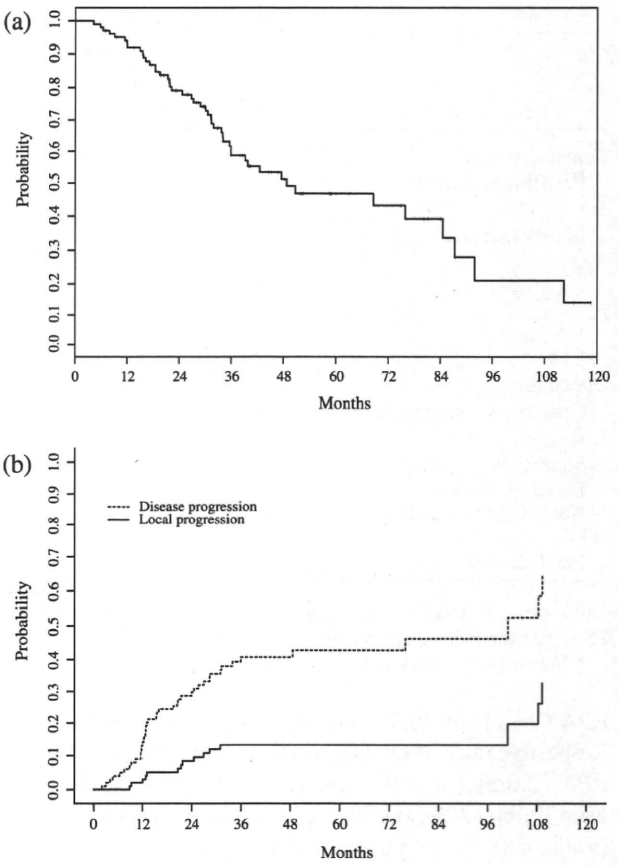


Fig. 1. Overall survival (a), local progression, and disease progression (b) in the total patient population included in this study.

Patients were divided into three groups according to tumor diameter (T1a, T1b, or T2a), and the 3-year OS rates were 69.1%, 57.2%, and 48.3%, respectively. Rates of LP were 3.6%, 15.5%, and 21.9%, and DP rates were 20.4%, 49.4%, and 53.9%, respectively (Table 4). Significant differences were observed between T1a and T2a in LP, DP, and OS, and between T1a and T1b in DP. Three-year DP rates were 46.4% and 37.0% in patients aged <77 years and ≥77 years, respectively. The difference was not statistically significant ($p = 0.096$). Women had significantly better OS rates than men (80.3% vs. 51.3% at 3 years, respectively; $p = 0.008$).

Recursive partitioning analysis

Recursive partitioning analysis was performed with potential factors found with stepwise selection: tumor diameter (T1a, T1b, or T2a) and sex (male or female) for LP and OS; and tumor diameter, sex, age (<77 or ≥77 years), and OTT (1-week or 2-week schedule) for DP. Regression trees obtained with RPA are shown in Fig. 2. Age was not significant in the RPA. The effects of OTT on DP were not uniform among T1b–2a male patients; the 1-week schedule was better for T1b but worse for T2a. Recursive partitioning analysis indicated that female gender and T1a were independently associated with good prognosis. With Class I defined as patients who were female or T1a, and with Class II defined as male and T1b–2a, 3-year LP and DP were 6.8% and 23.6% in

Table 2. Univariate analysis using the Cox proportional hazard model

	LP		DP		OS	
Parameter	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Tumor diameter		0.039*		0.001*		0.060
Per 10-mm increase	2.14 (1.04–4.40)		1.97 (1.31–2.95)		1.43 (0.98–2.07)	
Sex		0.197		0.053		0.011*
Male vs. female	2.76 (0.59–12.9)		2.25 (0.99–5.12)		2.86 (1.27–6.45)	
Age		0.304		0.009*		0.557
Per 10-y increase	0.56 (0.19–1.69)		0.46 (0.26–0.82)		0.84 (0.47–1.50)	
PS		0.717		0.147		0.146
1 vs. 0	1.57 (0.50–4.87)		1.00 (0.51–1.95)		1.17 (0.63–2.18)	
2 vs. 0	1.62 (0.19–13.6)		2.56 (0.96–6.81)		2.65 (1.00–7.02)	
Operability		0.600		0.415		0.227
Operable vs. inoperable	0.74 (0.25–2.25)		0.77 (0.40–1.45)		0.69 (0.38–1.26)	
Histology		0.440		0.023*		0.040*
Squamous vs. adeno.	2.68 (0.80–8.95)		1.72 (0.89–3.32)		2.24 (1.21–4.15)	
Large vs. adeno.	<0.01 (NA)		8.88 (1.98–39.9)		6.15 (0.79–48.1)	
NSCLC NOS vs. adeno.	2.85 (0.80–25.8)		2.46 (0.71–8.51)		2.24 (0.64–7.78)	
OTT		0.543		0.221		0.606
Per 7-day increase	0.69 (0.21– 2.26)		0.66 (0.34–1.29)		0.85 (0.49–1.60)	

Abbreviations: LP = local progression; DP = disease progression; OS = overall survival; HR = hazard ratio; CI = confidence interval; PS = performance status; adeno. = adenocarnimoa; NA = not available; OTT, overall treatment time. Other abbreviation as in Table 1.
* Statistically significant.

RPA Class I and 19.9% and 58.3% in Class II, respectively. Respective rates of OS at 3 years were 69.9% and 47.1% in RPA Classes I and II, respectively. Significant differences were observed between the classes in all endpoints of LP ($p = 0.028$), DP ($p < 0.001$) and OS ($p = 0.001$) (Fig. 3).

DISCUSSION

Matured data on SBRT for Stage I NSCLC have recently been published by several groups (17–23). Baumann *et al.* (23) reported the results of a Phase II trial of SBRT for inoperable Stage I NSCLC in Nordic countries. At a median follow-up of 35 months, 3-year local control and OS rates were 92% and 60%, respectively. Table 5 summarizes the results of these recent studies. The 3-year rates of local control and OS were 80–90% and 50–60%, respectively. The present report is an update of our previous article (24), with longer follow-up and a larger number of patients. This study demonstrated a local progression-free rate of 86.8% and OS rate of 58.6% at 3 years, consistent with recent reports. Multi-institutional Phase II trials of SBRT are currently underway in Japan (Japan Clinical Oncology Group [JCOG] Protocol 0403) and the United States (Radiation Therapy Oncology Group [RTOG] Protocol 0236). Patient enrollment for these trials has already closed, and the results are expected to be available within a few years and to validate the efficacy and safety of SBRT for NSCLC.

Tumor size is a significant prognostic factor in the treatment of lung cancer. A size criterion of 30 mm is applied between T1 and T2 in the current TNM system. The Japanese Joint Committee of Lung Cancer Registry (JJCLCR) analyzed prognostic factors in completely resected cases of clinical Stage I NSCLC (25). Patients with tumors ≤20 mm in diameter had better prognosis compared with those whose tumors were >20 mm in diameter in clinical Stage IA, and it was concluded that tumor size is an independent prognostic factor in clinical Stage I patients. In the newly revised TNM system (14), T1 and T2 are divided into subgroups:

Table 3. Multivariate analysis with variables selected by stepwise method

	LP		DP		OS	
Parameter	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Tumor diameter		0.020*		<0.001*		0.013*
Per 10-mm increase	2.30 (1.14–4.65)		2.32 (1.52–3.54)		1.60 (1.10–2.32)	
Sex		0.121		0.052		0.004*
Male vs. female	3.45 (0.72–16.6)		2.30 (0.99–5.35)		3.40 (1.48–7.82)	
Age		—		0.005*		—
Per 10-y increase	—		0.45 (0.26–0.78)		—	
OTT		—		0.086		—
Per 7-day increase	—		0.55 (0.28–1.09)		—	

Abbreviations as in Table 2.
* Statistically significant.

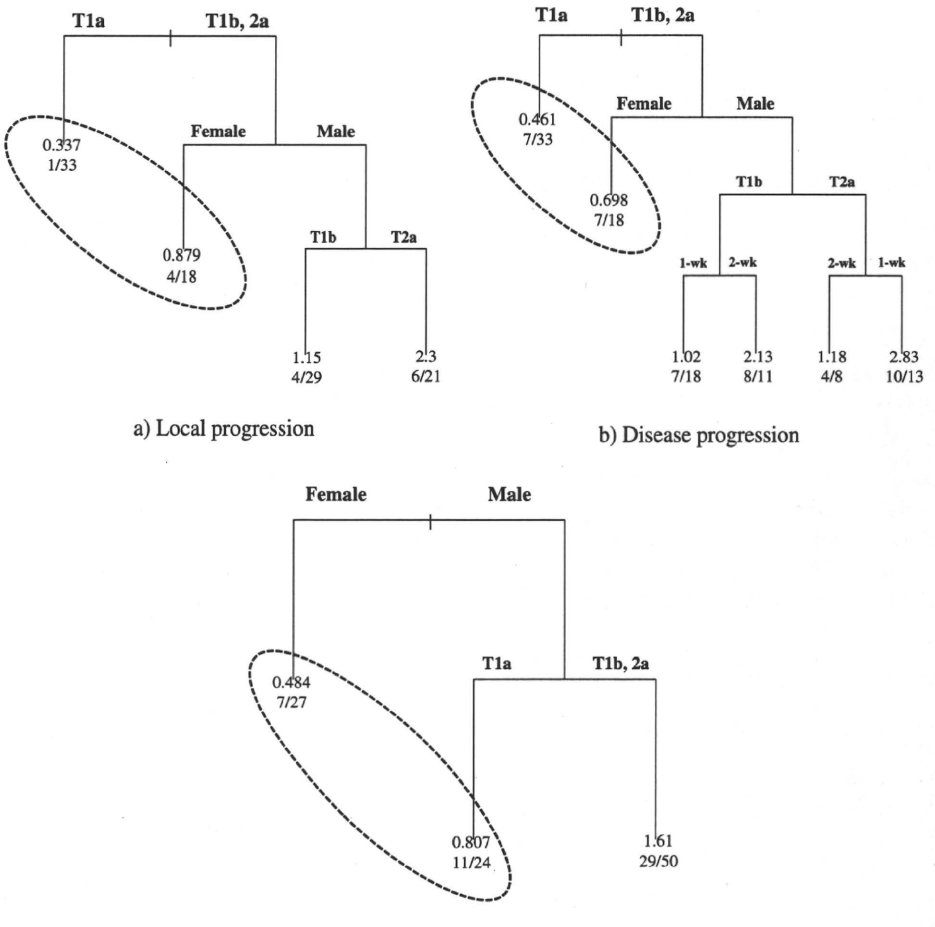
Table 4. Three-year rates of LP, DP, and OS according to the revised T-stage*

Parameter	LP	DP	OS
Rates by T-stage (%)			
T1a	3.6	20.4	69.1
T1b	15.5	49.4	57.2
T2a	21.9	53.9	48.3
P values for comparisons between T-stages			
T1a vs. T1b	0.139	0.030†	0.301
T1a vs. T2a	0.031†	0.002†	0.026†
T1b vs. T2a	0.330	0.325	0.387

Abbreviations as in Table 2.
* T1a: ≤20 mm; T1b: 21–30 mm; T2a: 31–50 mm.
† Statistically significant.

T1a (≤20 mm), T1b (21–30 mm), T2a (31–50 mm), and T2b (51–70 mm). Tumors >70 mm in diameter are classified as T3. A number of recent studies have validated the new T classification in surgical series (26–28). Kameyama *et al.* (26) evaluated 1532 patients who underwent surgery for NSCLC. A significant difference was observed in survival rate between the new T1a and T1b (82.6% vs. 73.3% at 5 years, respectively). In the Nordic SBRT trial (23), the failure rate in T1a patients was 0% at 3 years, which was significantly better than the rate of 40.8% in T2a patients. The present study also demonstrated that tumor diameter is one of the most significant factors affecting outcome after SBRT and indicated that 20 mm was a more optimal threshold than 30 mm for prognosis after SBRT with our dosage of 48 Gy in 4 fractions.

Female patients tend to show histology of adenocarcinoma at a younger age and to have better survival in studies of resected NSCLC (29–31). The patients in our study showed the same tendencies, except for age. The numbers of male patients with adenocarcinoma and others were 29 (39.2%) and 45 (60.8%), respectively, whereas the numbers in women were 20 (74.1%) and 7 (25.9%), respectively ($p = 0.004$). With regard to age, female patients tended to be slightly older than male patients (mean age, 77.4 vs. 76.0 years, respectively; $p = 0.250$). Female patients had significantly better OS after SBRT than did male patients (80.3% vs. 51.3% at 3 years, respectively). Univariate analysis indicated



a) Local progression

b) Disease progression

c) Overall survival

Fig. 2. Regression trees by recursive partitioning analysis in local progression (a), disease progression (b), and overall survival (c). "1-wk" and "2- wk" indicate 1-week and 2-week schedules of SBRT, respectively. In each terminal node, the upper row shows the hazard ratio with reference to all patients, and the lower row shows the numbers of events and patients in the node. Ellipses with dashed lines indicate groups with good prognosis.

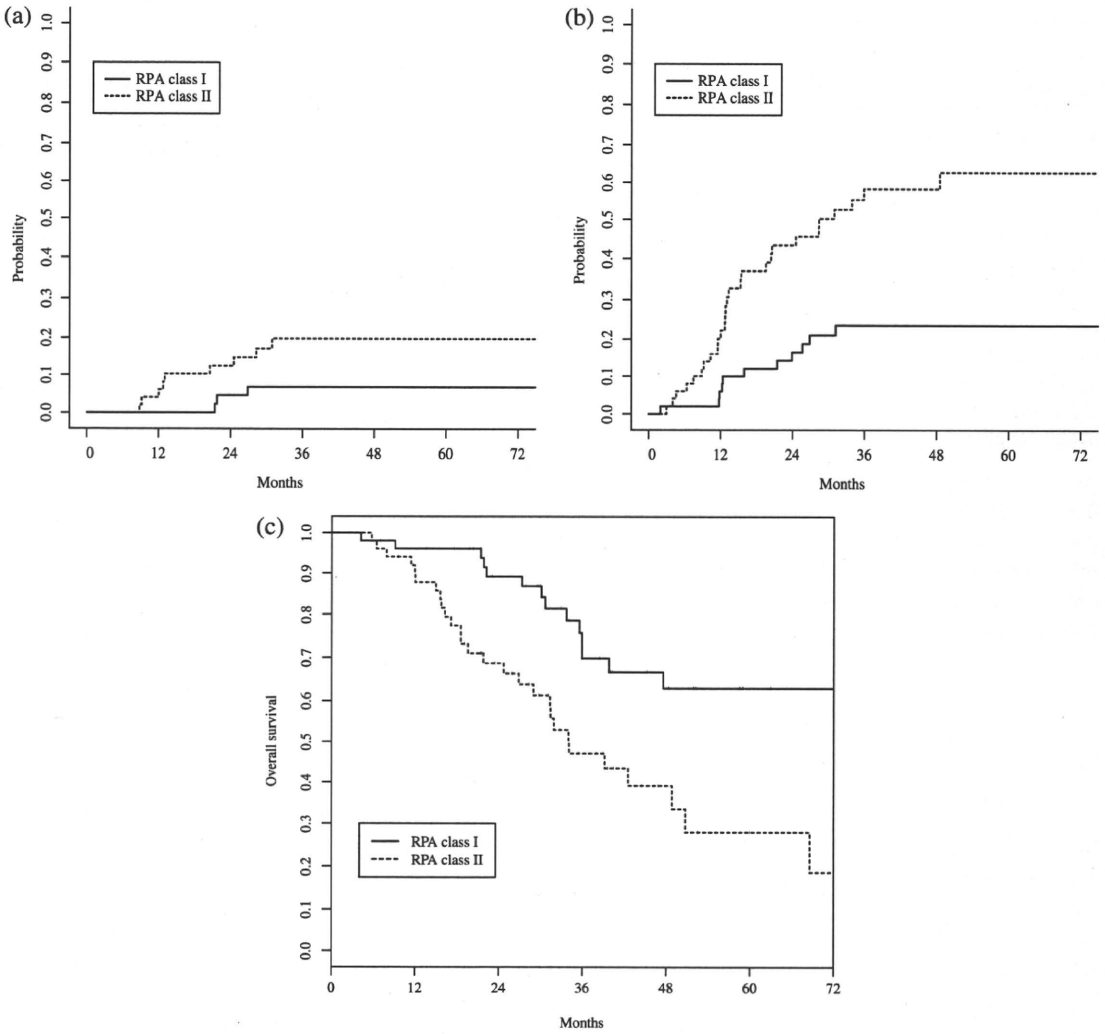


Fig. 3. Differences between the recursive partitioning analysis (RPA) classes in local progression (a), disease progression (b), and overall survival (c). RPA Class I was defined as female or T1a, and RPA Class II was male or T1b–2a.

adenocarcinoma as a favorable prognostic factor. Thus, the question arose whether adenocarcinoma histology or female gender had a more dominant effect on clinical outcome.

The prognostic effect of histology is not uniform across surgical studies. Ost *et al.* (32) analyzed survival after resection of Stage IA and IB NSCLC using the Surveillance, Epidemiology, and Results registry. In small tumors (≤20 mm), lung cancer–associated mortality was similar for adenocarcinoma when compared with squamous cell carcinoma. However, lung cancer–associated mortality was higher for

Table 5. Summary of recent reports on SBRT for Stage I NSCLC

Author (reference)	*n*	T-stage (T1/T2) (*n*)	Sex (M/F) (*n*)	Age (y)	Dose	Prescription	F/U (mo)	3-y LC (%)	3-y OS (%)	MST (mo)
Nyman (17)	45	18/27	25/20	74	45 Gy/3 fx	PTV periphery	43*	80	55	39
Hoyer (18)	40	22/18	18/22	70	45 Gy/3 fx	Isocenter	29	85 (2 y)	48 (2 y)	NA
Koto (19)	31	19/12	25/6	77	45 Gy/3 fx or 60 Gy/8 fx	Isocenter	32	77.9 (T1)	71.7	NA
Fakiris (20)	70	34/36	NA	NA	60 or 66 Gy/3 fx	PTV periphery	50.2*	88.1	42.7	32.4
Ricardi (21)	62	43/19	52/10	73.7	45 Gy/3 fx	PTV periphery	28	87.8	57.1	NA
Kopek (22)	88	51/36	45/43	73	45 or 67.5 Gy/3 fx	PTV periphery	44*	89	36	21.8
Baumann (23)	57	40/17	26/31	75	45 Gy/3 fx	PTV periphery	35	92	60	40.6
Present study	101	73/28	74/27	77	48 Gy/4 fx	Isocenter	31.4	86.8	58.6	48.8

Abbreviations: SBRT = stereotactic body radiotherapy; F/U = follow-up period; MST = median survival time; fx = fractions. Other abbreviations as in Table 2.

* The definition of follow-up period seemed to be different from that in the present study.

adenocarcinoma in large tumors (≥30 mm). The JJCLCR reported that adenocarcinoma patients tended to have a better survival in clinical Stage IA compared with those in clinical Stage IB (25). McGovern *et al.* (33) from the M. D. Anderson Cancer Center analyzed 831 patients treated with radiotherapy for NSCLC and reported that sex was an independent prognostic factor associated with outcome. Among cases of medically inoperable Stage I NSCLC, female patients had a better 5-year OS than did male patients (30.0% vs. 13.1%, respectively). In the present study, multivariate analysis and RPA indicated that sex significantly affected outcome after SBRT, and histology was less significant.

In a surgical series of Stage I NSCLC, older age was one of the factors associated with a poor prognosis. The JJCLR (25) reported that the hazard ratio (HR) for OS was 1.673 in patients aged ≥70 years compared with younger patients in resected clinical Stage I NSCLC. In multivariate analysis in the present study, older age showed a favorable impact on DP (HR = 0.41 increase per 10 years of age). However, the RPA did not indicate the importance of age in DP. The effects of age on SBRT outcome should be investigated further.

Operability is one of the well-known prognostic factors after SBRT for the lung. Onishi *et al.* (12) reported that OS rates differed significantly according to medical operability. The 5-year OS rates for medically operable and inoperable patients were 64.8% and 35.0%, respectively ($p < 0.001$). Our study also showed a tendency that operable patients have better OS than inoperable patients (66.8% vs. 52.9% at 3 years, respectively; $p = 0.225$), although uni- and multivariate analyses did not choose operability as a significant factor.

The importance of OTT is well known in conventionally fractionated radiotherapy for lung cancer (34, 35), and longer OTT has a negative impact on outcome. Chen *et al.* (35) reported that patients treated with prolonged OTT (>45 days) had a significantly poorer local progression-free survival rate compared with patients with shorter OTT (17% vs. 35% at 3 years, respectively). To our knowledge, few reports are available on OTT in a hypofractionated schedule such as that used in SBRT. Multivariate analysis in the present study showed a tendency toward poorer DP outcomes with shorter OTT. However, the effect of OTT was not uniform in the RPA in the present study. Overall treatment time is different among SBRT protocols. In the Nordic SBRT study (23), 3 fractions of 15 Gy were given every second day, and median OTT was 5 days (range, 4–15 days). In RTOG SBRT Protocol 0236, 3 fractions of 20 Gy are delivered in 1.5–2 weeks, with no more than 2 fractions given within a week. Four fractions of 12 Gy are given within 8 days in JCOG Protocol 0403, and a consecutive 4-day schedule is allowed. It will be necessary to review the SBRT treatment schedule in the near future.

The present study pointed out tumor diameter and sex as significant factors for prognosis after SBRT for NSCLC. The RPA indicated an optimal threshold between T1a and T1b, rather than between T1 and T2, for tumor diameter and built a prognostic model that combined the two factors of diameter and sex. The RPA Class I was defined as patients who were female or T1a, and Class II was as male and T1b–2a. Significant differences in outcomes were observed between the RPA classes. The RPA class would be useful to predict clinical outcomes in patients who are planned to be treated with SBRT, and to investigate the methods to improve the SBRT outcomes in patients with poor prognosis.

There are two ways that potentially improve outcomes after SBRT: escalation of local dosage and combination with chemotherapy. The dose–response relationship for local tumor control has been investigated by several authors. As described above, the two large series of multi-institutional reviews by Onishi *et al.* (12) and by Baumann *et al.* (13) showed the significance of higher BED to local tumor for better outcomes. Onimaru *et al.* (36) compared two dose regimens of 40 Gy and 48 Gy in 4 fractions for Stage I NSCLC. Local control and cause-specific survival in Stage IB patients were significantly better with the 48-Gy regimen than with 40 Gy, though the differences were not significant in Stage IA. On the basis of these reports and the present study, local BED needs to be escalated to >106 Gy for patients with large tumor, especially for the RPA Class II patients.

When considering that metastasis to regional nodes or distant organs occurred in not a few cases, combination with chemotherapy seems an attractive way for improving SBRT outcomes. However, use of adjuvant chemotherapy is controversial for postoperative Stage IB NSCLC. A Japanese group reported the survival benefit of adjuvant chemotherapy with uracil-tegafur for postoperative patients with Stage I adenocarcinoma, and the benefit was greater in Stage IB (37). On the other hand, Cancer and Leukemia Group B Protocol 9633 could not show a significant advantage of adjuvant chemotherapy with paclitaxel plus carboplatin for Stage IB NSCLC (38). Further studies are needed of combined chemotherapy and SBRT.

In conclusion, sex and tumor diameter were the most significant factors affecting clinical outcome after SBRT for NSCLC. Patients with tumor diameter ≤20 mm (T1a) or female patients had good prognosis.

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