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Clinical Outcomes of Stereotactic Body Radiation Therapy for Early-stage Non-small Cell Lung Cancer

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Abstract. *Background/Aim: To investigate the clinical outcomes of stereotactic body radiotherapy (SBRT) in patients with early-stage non-small cell lung cancer (NSCLC). Patients and Methods: Among consecutive patients with early-stage NSCLC who received SBRT between November 2009 and September 2019, those with cT1-2N0M0 staged by the UICC TNM classification and staging system for lung cancer were retrospectively analyzed. Results: Fifty-three patients with early-stage NSCLC received SBRT. The median follow-up period was 29 months (range=2-105 months). Twenty-one lung tumors were clinically diagnosed as early-stage primary lung cancers without histological confirmation. Histological examinations revealed adenocarcinoma in 24 patients and squamous cell carcinoma in 8. Two- and 5-year local control, cancer-specific survival, progression-free survival (PFS), and overall survival (OS) rates were 94.4 and 94.4%; 94.6 and 90.8%; 69.0 and 43.3%; and 80.0 and 59.3%, respectively. In a univariate analysis, the T stage, histology, and type of pulmonary nodule correlated with PFS and OS. Conclusion: Good clinical outcomes were achieved by patients with early-stage NSCLC who received SBRT.*

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Lung cancer accounts for the highest number of cancer deaths worldwide including the United States and Japan (1, 2). Surgical intervention is the gold standard treatment for patients with stage I/IIA non–small-cell lung cancer (NSCLC) (3). Population aging has resulted in a steady increase in the number of patients with comorbidities (4), and, as a result, stereotactic body radiotherapy (SBRT) is now the treatment of choice for patients with early-stage NSCLC. SBRT is able to deliver a very high dose of radiation over a small number of fractions while minimizing the dosage to the surrounding normal tissues. Previous studies demonstrated that the local control (LC) rate of SRBT was high and the incidence of severe toxicities was low (5-8); therefore, SRBT is a viable option with curative intent for inoperable cases (9). However, there is a significant lack of homogeneity in the dose fractionation schedules used by different institutions, ranging from 20 to 60 Gy and from 1 to 15 fractions. In the present study, we retrospectively investigate the clinical outcomes and prognostic factors of early-stage NSCLC patients treated with SBRT using common doses and fractionations.

Patients and Methods

Patients. Among consecutive patients with early-stage NSCLC who received SBRT between November 2009 and September 2019, those with cT1-2N0M0, staged by the 8th edition of the UICC TNM classification and staging system for lung cancer (10), were retrospectively analyzed. The absence of a previous history of lung cancer treatment (surgery, radiation, or chemotherapy) and a performance status of 0-2 were also used as selection criteria in the

present study. Patients lost to the follow-up within 1 month were excluded from the analysis. Biopsy is a standard diagnostic protocol at our institution; however, some patients refused to provide consent, while others were unable to undergo the procedure due to technical or clinical difficulties. Since these patients underwent examinations without histological confirmation, the lung cancer board clinically diagnosed NSCLC based on the clinical data obtained, including an elevated maximum standardized uptake value measured on (^{18}F) fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), continual increases in tumor volumes on CT images, and increases in tumor marker levels. Carcinoembryonic antigen, carbohydrate antigen 19-9, sialy1 Lex-I antigen, squamous cell carcinoma (SCC)-related antigen, and cytokeratin 19 fragment levels were monitored in all patients. The ground-glass nodule (GGN) type of pulmonary nodules on thin-section computed tomography (TSCT) was defined as a pure ground-glass opacity (GGO) or GGO in which the maximum diameter of the consolidation to the tumor diameter ratio (C/T ratio) of the solid component was <0.5. The solid nodule type was defined as a purely solid tumor or GGO in which the C/T ratio of the solid component was ≥0.5. The type of pulmonary nodule on TSCT was evaluated by one experienced radiologist. Written informed consent was obtained from all patients prior to the initiation of treatment. The present study was approved by the National Hospital Organization Nagasaki Medical Center Review Board (No.2021123).

Treatment. All patients were treated in the supine position using a customized vacuum Vac-Lok™ immobilization device. During treatment planning, we performed deep-inspiration breath-holding CT of the chest to decrease the internal target volume (ITV). Among patients unable to perform a sufficient deep inspiration breath hold, abdominal compression was utilized to minimize the range of tumor motion. Assessments of the planning target volume (PTV) were conducted by the addition of a 6- to 8-mm margin to the ITV. SBRT was delivered using three-dimensional (3D) non-coplanar beams until March 2018, after which intensity-modulated radiotherapy (IMRT) was performed. Regarding dose prescriptions, 48-52 Gy at the isocenter in 5 fractions was prescribed for peripherally located lesions and 60 Gy at the isocenter in 10 fractions for centrally located lesions until March 2018. Since April 2018, 40-42 Gy to 95% of the PTV in 5 fractions has been prescribed for peripherally located lesions and 50 Gy to 95% of the PTV in 10 fractions for centrally located lesions.

Follow-up. Patients were followed up 1, 3, 6, 9, and 12 months after SBRT in the first year, every 3 months between years 2 and 5, and then every 6 months. Chest CT was performed every 3 months for the first 12 months. Recurrence within the PTV, in the ipsilateral hilar or mediastinal lymph nodes, or at sites other than the PTV or ipsilateral hilar and mediastinal lymph nodes was classified as local, regional, or distant, respectively.

LC was defined as the absence of local recurrence. Cause-specific survival (CSS) accounted for deaths due to lung cancer. Progression-free survival (PFS) was defined as the time from SBRT to the last day of the follow-up or the date of death or tumor progression (local-regional recurrence and/or distant metastases). Overall survival (OS) was calculated from the first day of SBRT to the day of death or final clinical follow-up. Tumor progression was detected in each case based on histological or radiological features, including continual increases in tumor volumes on CT images and/or increases in standard uptake values on ^{18}F-FDG PET/CT.

Toxicity data were prospectively collected and evaluated according to the National Cancer Institute Common Terminology Criteria Version 5.0. The follow-up period was defined as the first day of SBRT to the day of death or the final clinical follow-up.

Statistical analysis. LC, CSS, PFS, and OS rates were calculated using the Kaplan–Meier method. Univariate analyses using the Cox proportional hazards model were performed to identify which of the following factors influenced LC, CSS, PFS, and OS rates after SBRT: age (<81 or ≥81 years), sex (male or female), T stages (T1a/1b or T1c/2a), histology [SCC, adenocarcinoma (ADC), or

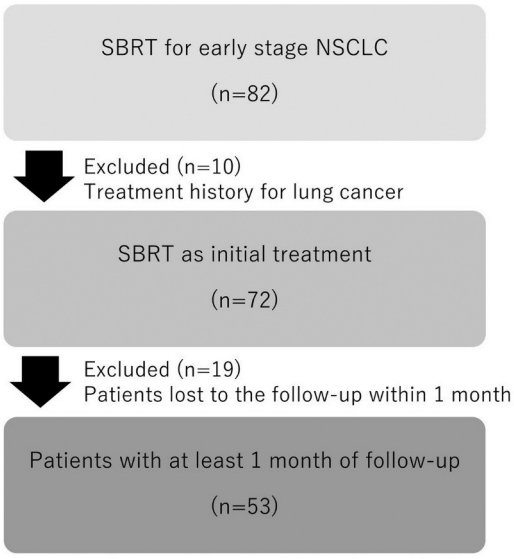

Figure 1. *Flow diagram of the selection process*.

Table I. *Patient and tumor characteristics*.

Patient and tumor characteristics	n=53
Median age (range)	81 (58-90)
Sex	
Male, n (%)	36 (67.9)
Female, n (%)	17 (32.1)
Clinical T stage	
1a, n (%)	7 (13.2)
1b, n (%)	17 (32.1)
1c, n (%)	22 (41.5)
2a, n (%)	7 (13.2)
2b, n (%)	0 (0)
Histology	
Squamous cell carcinoma, n (%)	8 (15.1)
Adenocarcinoma, n (%)	24 (45.3)
Histologically unproven, n (%)	21 (39.6)
Median follow-up duration (month) (range)	29 (2-105)

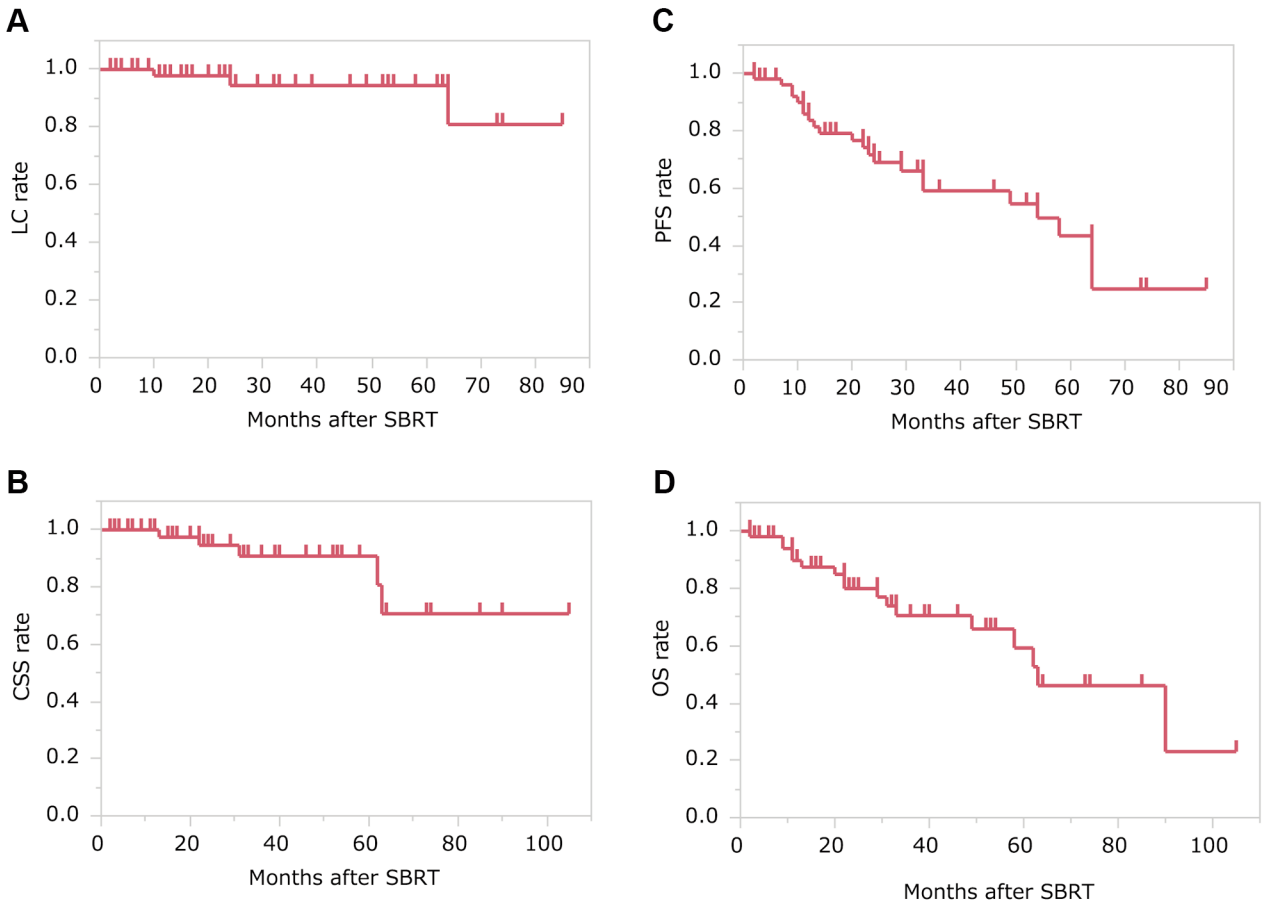

Figure 2. *Kaplan–Meier plot for the local control (LC) (A), cause-specific survival (CSS) (B), progression-free survival (PFS) (C) and overall survival (OS) (D).*

histologically unproven], histological confirmation (histologically proven NSCLC or histologically unproven NSCLC), the type of pulmonary nodule on TSCT, and external beam radiotherapy techniques (3D non-coplanar beams or IMRT). Categorical variables were described as absolute values and percentages, which were compared with Fisher's exact test. All statistical analyses were performed with the software JMP (SAS Institute, Cary, NC, USA), and a p-value <0.05 was considered to be statistically significant.

Results

Eligible patients and tumors. Eighty-two early-stage NSCLC patients who received SBRT were retrospectively enrolled. Ten patients with a previous history of lung cancer treatment were excluded. Among the remaining patients, 53 patients were followed up for at least 1 month. Figure 1 shows a flow diagram of the selection process, and Table I patient and tumor characteristics. Twenty-one patients were clinically diagnosed with early-stage primary lung cancer without histological confirmation. Regarding the type of pulmonary nodule on TSCT, the GGN type was observed in 16 patients and the solid nodule type in 37.

Treatment outcomes. Tumor progression was detected in 11 patients during the follow-up period: local recurrence in 3, regional recurrence in 2, and distant metastases in 6. Two- and 5-year LC, CSS, PFS, and OS rates were 94.4 and 94.4%, 94.6 and 90.8%, 69.0 and 43.3%, and 80.0 and 59.3%, respectively (Figure 2).

In univariate analyses, the T stage, histology, and type of pulmonary nodule were significant factors affecting PFS and OS (Table II). Five-year PFS and OS rates were 61.2 and 79.6% for T1a/1b, 21.1 and 27.5% for T1c/2a, 0 and 0% for SCC, 42.3 and 53.3% for ADC, 58.3 and 75.6% for historically unproven NSCLC, 69.3 and 69.3% for the GGN type, and 25.1 and 52.2% for the solid nodule type, respectively.

Toxicities. Three patients developed grade 3 radiation pneumonitis after SBRT. Neither grade 4 nor 5 radiation pneumonitis was detected.

Table II. *Univariate analysis of progression-free survival (PFS) and overall survival (OS).*

	PFS			OS		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age						
<81	1			1		
≥81	0.88	0.35-1.84	0.60	0.87	0.32-2.35	0.78
Sex						
Male	1	-	-	1	-	-
Female	0.44	0.17-1.13	0.09	0.45	0.14-1.39	0.16
Tumor diameter						
1a/1b	1	-	-	1	-	-
1c/2a	2.94	1.20-7.24	0.02	3.88	1.28-11.8	0.02
Radiotherapy technique						
3D non-coplanar beams	1	-	-	1	-	-
IMRT	0.92	0.21-4.13	0.92	1.56	0.33-7.44	0.58
Histology						
Squamous cell carcinoma	1	-	-	1	-	-
Adenocarcinoma	0.31	0.11-0.89	0.03	0.26	0.07-0.90	0.03
Histologically unproven NSCLC	0.21	0.06-0.60	0.01	0.26	0.07-0.91	0.04
Histological proof						
Histologically proven NSCLC	1	-	-	1	-	-
Histologically unproven NSCLC	0.46	0.18-1.14	0.09	0.64	0.22-1.85	0.41
Type of pulmonary nodule						
GGN type	1	-	-	1	-	-
Solid nodule type	4.5	1.51-13.3	0.01	3.58	1.02-12.5	0.04

HR: Hazard ratio; CI: confidence interval; IMRT: intensity-modulated radiotherapy; NSCLC: non-small cell lung cancer; GGN: ground-glass nodule.

Table III. *Summary of recent studies on stereotactic body radiotherapy for patients with early-stage non-small cell lung cancer.*

Author	Year	Prescription dose	2-year LC rate	2-year OS rate
Temming *et al*. (5)	2018	51 Gy/3 fr. (Median)	88%	77%
Hiroshima *et al*. (6)	2022	55 Gy/4 fr. for peripheral tumors 60 Gy/10 fr. for central tumors	100%	54.6%
Hayashi *et al*. (7)	2022	52 Gy/4-10 fr. (Median)	91.9%	84.8%
Iwata *et al*. (8)	2017	45 Gy, 50 Gy or 55 Gy/4 fr.	97%	82%
Present study		40-52 Gy/4 fr. for peripheral tumors 50 or 60 Gy/10 fr. for central tumors	94%	80%

LC: Local control; OS: overall survival; fr.; fractions.

Discussion

SBRT for NSCLC. Recent studies that have employed common doses and fractionations have reported mature follow-up data on SBRT for early-stage NSCLC, the findings of which are summarized in Table III. Two-year LC and OS rates in these studies were 91.9-100 and 54.6-84.8%, respectively (5-8). Two-year LC and OS rates in the present study were 94.4 and 80.0%, which are consistent with these findings.

In the present study, two patients developed local recurrence or new primary lung cancer and lung metastasis or new primary lung cancer, respectively, and were treated with repeat SBRT. Subsequently, they were diagnosed with grade 5 and 3 radiation pneumonitis, respectively (11). Radiation pneumonitis is frequently observed after repeat SBRT. Watanabe *et al*. previously showed that a mean lung dose and lung volume spared from low-dose irradiation may be useful in predicting radiation pneumonitis after repeat SBRT (12). Therefore, we plan to introduce deformable image registration and perform cumulative dose summation to evaluate the safety of the reirradiation.

Prognostic factors. Tumor size has been identified as an important prognostic factor in patients with lung cancer. The

UICC TNM classification uses a cut-off diameter of 30 mm to differentiate between T1 and T2. T1 and T2 in the 8th edition of the UICC TNM classification for lung cancer are divided into the following subgroups: T1a (≤10 mm), T1b (10-20 mm), T1c (20-30 mm), T2a (30-40 mm), and T2b (40-50 mm). Tumors with diameters >50 mm are classified as T3. Factors affecting the prognosis of patients with clinical stage I NSCLC who underwent complete resection were examined by The Japanese Joint Committee of Lung Cancer Registry (13). Clinical stage IA patients with tumor diameters ≤20 mm had a better prognosis, based on which tumor size was considered to be an independent prognostic factor in these patients. Kameyama *et al*. previously investigated 1,532 patients who underwent surgical interventions for NSCLC (14). Five-year OS rates significantly differed between T1a/1b and T2c (82.6% *vs*. 73.3%, respectively). In the Nordic SBRT trial, the 3-year failure rate in T1a/1b patients was 0%, which was significantly better than that in T1c/2a/2b patients (40.8%) (15). Tumor diameter was also identified as a significant prognostic factor after SBRT in the present study, with 20 mm being a better threshold for a good prognosis following the completion of SBRT than 30 mm.

In the present study, tumor histology was identified as a significant prognostic factor. SCC was previously identified as a poor prognostic factor and histologically unproven NSCLC as a good prognostic factor (16, 17). This difference has been attributed to SCC being radioresistant and histologically unproven NSCLC including benign lesions. In the present study, PFS and OS were worse in patients with SCC than in those with ADC and histologically unconfirmed NSCLC. No significant differences were observed between histologically confirmed and unconfirmed NSCLC, suggesting that the clinical diagnosis by the tumor board in our institution was correct.

The type of pulmonary nodule on TSCT was also a significant prognostic factor, with the GGN type having a better prognosis than the solid nodule type, which may have been due to ADC being more common in the GGN type and SCC in the solid nodule type. Except for histologically unproven NSCLC, the numbers of SCC with the GGN type and solid nodule type were 0 (0%) and 8 (100%), respectively, whereas these numbers were 11 (45.8%) and 13 (54.2%), respectively (p=0.03), in ADC.

In the present study, we report the clinical outcomes of SBRT for early-stage primary lung cancer. Additionally, SBRT is also performed for lung metastases. Previous studies have reported that SBRT administered for a limited number of lung metastases results in an excellent long-term LC rate (18). However, the LC rate following SBRT for lung metastases from colorectal cancer appears to be less favorable when compared to those for early-stage primary lung cancer or for lung metastases from other types of cancer (19).

Limitations. The limitations of this study were its small sample size and the retrospective nature of the analysis, which may have a selection bias.

Conclusion

Good clinical outcomes were achieved in patients with early-stage NSCLC who received SBRT, which is consistent with previous findings. The present study identified tumor diameter, histology, and the type of pulmonary nodule as significant prognostic factors after SBRT.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Yutaro Tasaki: Conceptualization, formal analysis, writing. Kazuto Ashizawa: Validation, writing. Daisuke Nakamura: Software. Tatsuya Takeda: Methodology, investigation. Takashi Mizowaki: Formal analysis. Seiji Nagashima: Validation. Toshifumi Fujimoto: Validation. Masataka Uetani: Formal analysis, resources, supervision, validation, investigation. All Authors have read and agreed to the published version of the manuscript.

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