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Stereotactic body radiotherapy for primary non-small cell lung cancer patients with clinical T3-4N0M0 (UICC 8th edition): outcomes and patterns of failure

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ABSTRACT

The evidence for stereotactic body radiotherapy (SBRT) is meagre for patients with clinical T3-4N0M0 non-small cell lung cancer (8th Edition of the Union for International Cancer Control (UICC)). This study retrospectively investigated clinical outcomes following SBRT for such patients. Among consecutive patients treated with SBRT, patients staged as cT3-4N0M0 by all criteria were examined, most of whom were unsuitable to chemoradiotherapy due to their fragile characters. Clinical outcomes were evaluated and factors associated with outcomes were investigated. Between 2005 and 2017, 70 eligible patients (T3: 58, T4: 12; median age 81 (63–93) years) were identified. Median follow-up duration was 28.6 (1.0–142.5) months. No adjuvant chemotherapy was administered. The 3-year local recurrence rates were 15.8% and 16.7% in T3 and T4 patients, respectively, and they were significantly lower in the high-dose group (3.1% vs 28.6%, $P < 0.01$). Multivariate analyses showed that the dose-volumetric factor was the significant factor for local recurrence. The 3-year regional and distant metastasis rates, cancer-specific mortality, and overall survival in T3 and T4 patients were 22.7% and 25.0%, 26.5% and 33.3%, 32.2% and 41.7%, and 39.5% and 41.7%, respectively. Only age was correlated with overall survival. Radiation pneumonitis ≥grade 3 and fatal hemoptysis occurred in 3 and 1 patients, respectively. SBRT for cT3-4N0M0 lung cancer patients achieved good local control. Survival was rather good considering that patients were usually frail, staged with clinical staging, and were not given adjuvant chemotherapy, and it may be comparable to surgery. To validate these outcomes following SBRT, a prospective study is warranted.

Keywords: stereotactic ablative body radiotherapy; SABR; locally advanced lung cancer; curative treatment; radical therapy

INTRODUCTION

Lung cancer is the number one cause of cancer death and the second most prevalent cancer in both men and women in the US [1]. The treatment outcomes for lung cancer have progressively improved because of increased knowledge and skills for each lung cancer treatment, and new modalities have been used clinically. Correspondingly, the staging system has been updated. In 2016, the 8th edition of the Union for International Cancer Control (UICC)

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TNM staging system for lung cancer was published. In the new staging system, T-stages are more segmentalized with primary tumor diameters based on the solid component [2, 3]. In addition, tumors 5–7 cm and >7 cm are upstaged from T2 to T3, and from T3 to T4, respectively.

Stereotactic body radiotherapy (SBRT), also called stereotactic ablative body radiotherapy (SABR), has recently been regarded as a treatment option for patients with medically inoperable cT1–2N0M0 non-small cell lung cancer (NSCLC) [4–6]. It can be given with acceptable toxicity even to patients with comorbidities or advanced age. However, the evidence for the use of SBRT for tumors > 5 cm and T3 tumors with chest wall invasion is insufficient [5, 7]. In the European Society for Medical Oncology clinical practice guidelines, conventional radical radiotherapy schemes have been recommended for such patients [8].

In our institution, we have performed SBRT for cT3-4N0M0 NSCLC in patients who were not good candidates for surgery in a proactive manner. We previously investigated the outcomes for a relatively small sample of patients staged as cT3-4N0M0 by the 7th edition TNM and treated with SBRT, and we reported good survival and low morbidity rates [9]. Tumor diameter >5 cm is the new upgraded T3 factor, and it is also a challenge for SBRT [5]. The modification of the staging system prompted us to examine outcomes of medically inoperable patients with AJCC 8th edition T3 and T4 (by size criteria) NSCLC with SBRT and to compare their outcomes with historical surgical data.

MATERIALS AND METHODS

Patients

Consecutive patients with primary NSCLC (cT3-4N0M0, UICC 8th edition) according to any of the criteria (size, invasion, and/or separate nodule factors) who were treated with SBRT with a prescribed total dose of 40–50 Gy in 5–10 fractions at Ofuna Chuo Hospital between May 2005 and February 2017 were reviewed retrospectively. The patients were usually frail, and were not given adjuvant chemotherapy. They were informed that local control after conventionally fractionated (chemo)radiotherapy is generally poor, whereas it is expected that SBRT will provide good local control, though the evidence for toxicity is poor. After obtaining their informed consent, the patients were treated with SBRT. Those who had follow-up of less than 6 months without death were excluded. A lung cancer board at our hospital, including a respirologist, thoracic surgeons, and a radiation oncologist, discussed the NSCLC diagnosis and treatment policy and assessed the cases. Table 1 shows the characteristics of the patients and their tumors. There were 70 patients in total, with a median age of 81 years (range 63–93 years); 55 were diagnosed pathologically with NSCLC, and 15 were diagnosed clinically with NSCLC based solely on clinical information, such as elevated tumor marker levels, increased maximum standardized uptake value on [^{18}F] fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), and serial enlargement on CT follow-up. No invasive procedures, such as mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration, were performed. Ten patients were considered potentially operable, but after taking into account their condition, age, and risk of surgery, SBRT was selected because it was thought to be preferable by the lung cancer board and following discussion with the patients. Two experienced radiologists (T.M. and K.Y.) determined each patient's T stage on CT images. Mediastinal staging was based on CT and ^{18}F-FDG PET/CT examinations. Written, informed consent was provided by all patients, and this study was performed with the approval of the Ofuna Chuo Hospital Review Board (No. 2017-014).

Treatment

The SBRT methods used in the present study have been described in detail previously [10]. Briefly, the internal target volume (ITV) was visualized with long-scan-time CT after the patient was immobilized with a vacuum pillow. A margin of 6–8 mm was then added to the ITV to determine the planning target volume (PTV). SBRT was delivered by dynamic conformal multiple arc therapy up to January 2012, after which non-coplanar volumetric modulated arc therapy was used. The total prescribed dose was 40 or 50 Gy with 5 or 10 fractions to the 60–80% isodose of the maximum dose, and this covered at least 95% of the PTV over 5 or 12 consecutive days. A steep dose-gradient prescription of 80% isodose line of maximum dose fitting to the PTV was used up to April 2011, after which 60% isodose was used. The doses delivered to the esophagus, trachea, and spinal cord were kept below a maximum dose of 25 Gy, and the doses for the bronchus, pulmonary artery, brachial plexus, and left ventricle were minimized to be as low as reasonably achievable. After 2014, the doses delivered to the pulmonary artery and bronchus were kept to less than a maximum dose of 50 Gy. The ratio of lung volume irradiated with 20 Gy to total lung was ≤15%. There were no specific dose limits for the heart and aorta.

Follow-up

Follow-up CT was performed 1 and 3 months after SBRT and then every 3 months for the first 2 years. Follow-up CT was then performed every 4–6 months. Pulmonary function testing was performed about 1 year after SBRT. In addition, ^{18}F-FDG PET/CT was performed about one year after SBRT and when there was high suspicion of local, regional, and/or distant recurrences. Grading of all acute and chronic toxicities was performed using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.

Statistical analysis

A cumulative incidence function was used to calculate local, regional, and distant metastasis recurrences, with death as a competing risk, as well as cancer-specific mortality (CSM), with non-specific death as a competing risk. Gray's test was then used for comparisons. The Kaplan–Meier method was used to estimate overall survival (OS) and progression-free survival (PFS), and the log-rank test was used to test differences between groups. Independent predictors of local recurrence were identified by univariate and multivariate analyses with a Fine and Gray competing risks regression model, while a Cox proportional hazards model was used for OS. To avoid including highly correlated factors in the multivariate analysis, the candidate factors were chosen taking into account each factor's importance in this study and their *P* values on

Table 1. Patients' characteristics

Age, years, median (range)	81 (63–93)	
Sex, male/female (%)	50/20	(71/29)
Median follow-up duration, months (range)	28.6 (1.0–142.5)	
Performance status, 0/1/2/3/4 (%)	27/22/18/1/2	(39/31/26/1/3)
Charlson comorbidity index, 0/1–2/3–4/5–7 (%)	8/35/20/7	(11/50/29/10))
Clinical T stage, T3/T4 (%)	58/12	(83/17)
Tumor diameter, <5 cm/≥5 cm and <7 cm/≥7 cm (%)	30/37/3	(43/53/4)
Invasion, -/T3/T4 (%)	24/36/10	(34/51/14)
T3 invasion		
Chest wall invasion (%)	25	(36)
Mediastinal pleura invasion (%)	11	(16)
T4 invasion		
Great vessels (%)	10	(14)
Mediastinum invasion (%)	3	(4)
Heart invasion (%)	1	(1)
Carina invasion (%)	1	(1)
Subnodule, -/same lobe/different ipsilateral lobe (%)	67/2/1	(96/3/1)
Location, central/peripheral (%)	29/41	(41/59)
Histology		
Squamous cell carcinoma (%)	24	(34)
Adenocarcinoma (%)	20	(29)
Non-small cell carcinoma (%)	11	(16)
Pathologically unproven (%)	15	(21)
Operability, yes/no (%)	10/60	(14/86)
PET staging, yes/no (%)	51/19	(73/27)
Median SUVmax (range)	7.8 (2.1–19.4)	
Median tumor diameter, cm (range)	5.1 (1.6–13.9)	
Median ITV, cm^3 (range)	29.3 (2.2–314.1)	
Median PTV, cm^3 (range)	84.2 (16.2–363.1)	
Dose fractionation, 40 Gy·5 fr/50 Gy·5 fr/50 Gy·10 fr (%)	21/48/1	(30/69/1)

PET = positron emission tomography, SUVmax = maximum standardized uptake value, ITV = internal target volume, PTV = planning target volume.

the univariate analyses when there was an insufficient number of events for the evaluation. The factors selected in this way were entered into the multivariate analysis.

The dosimetric parameter, the mean value of the biological effective doses (assuming $\alpha/\beta = 10$) of the ITV dose (mBED-ITV), was used in the analysis of local control. The mBED-ITV is calculated as 'mean total ITV dose' × (1+ 'mean total ITV dose'/fractions-number/10). The treatment planning system (Eclipse version 10.0; Varian Medical Systems, Palo Alto, CA) was used to calculate the 'mean total ITV doses'.

In all statistical analyses, two-sided P values <0.05 were considered significant. The statistical software package R (The R Foundation for Statistical Computing, version 3.4.3) and EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [11], a graphical user interface for R (The R Foundation for Statistical Computing, version 3.4.1), were used for the analyses.

RESULTS

For the 70 patients treated with SBRT and retrospectively diagnosed as having cT3–4N0M0 NSCLC according to the UICC 8th edition, the median follow-up durations for all patients and for survivors were 28.6 (range: 1.0–142.5) months and 55.5 (range: 8.7–95.3) months, respectively. Figure 1 shows the distributions of the factors of clinical T stage. No patient received adjuvant chemotherapy. During follow-up, 38 patients had recurrences, and 55 patients died; 28 and 27 patients died from lung cancer and non-specific other causes, respectively. When recurrences occurred, only 5 patients received chemotherapy: platinum doublet, 2 patients; docetaxel, 1 patient; pemetrexed, 1 patient; and tegafur/uracil, 1 patient.

The 3-year local recurrence rates for patients with cT3 and cT4 were 15.8% and 16.7%, respectively (Fig. 2A). On multivariate analysis for local recurrence, only two candidate factors, tumor diameter of the solid component and mBED-ITV, were included because the event number of local recurrences was as small as 11. Maximum standardized uptake value (SUVmax) ($P = 0.05$ on univariate analysis) was not included in the multivariate analysis because it was less relevant than the two factors selected. Multivariate analysis showed that the dose-volumetric factor (mBED-ITV) was the only significant factor for local recurrence (Table 2). Local recurrences in patients with mBED-ITV ≥119 Gy and <119 Gy occurred in 3.1% and 28.6%, respectively ($P < 0.01$) (Fig. 2B).

The 3-year regional and distant metastasis recurrence rates for patients with T3 and T4 were 22.7% and 25.0%, and 26.5% and 33.3%, respectively (Fig. 2C, D). On multivariate analysis for distant metastases, only three candidate factors, clinical T stage, histology, and SUVmax, were included because the event number of distant metastases was as small as 25. Operability ($P = 0.04$ on univariate analysis) was not included because it was less relevant than the three factors that were selected. The multivariate analysis showed that location and SUVmax were the significant factors for regional recurrence, and histology was the significant factor for distant metastasis recurrence (Table 2). The rates were not related to meanBED-ITV (regional <119 Gy: 28.6% vs ≥ 119 Gy: 17.5%, $P = 0.99$; distant <119 Gy: 22.9% vs ≥ 119 Gy: 32.4%, $P = 0.60$).

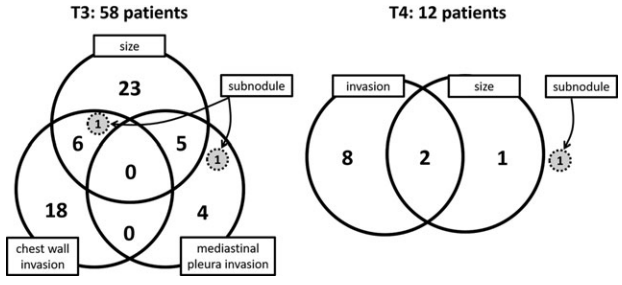

Fig. 1. Distributions of the factors determining the clinical T stage.

The 3-year CSM rates for patients with T3 and T4 were 32.2% and 41.7% ($P = 0.237$), respectively (Fig. 2E). The 3-year OS and median OS for patients with T3 and T4 were 39.5% and 41.7%, and 28.6 months and 28.2 months ($P = 0.816$), respectively (Fig. 2F). CSM and OS were also not related to meanBED-ITV (CSM < 119 Gy: 40.0% vs ≥ 119 Gy: 27.1%, $P = 0.23$; OS < 119 Gy: 37.1% vs ≥ 119 Gy: 42.7%, $P = 0.89$). Only age was correlated with OS (Table 2).

The 3-year PFS and median PFS for patients with T3 and T4 were 29.4% and 33.3%, and 13.0 months and 13.7 months ($P = 0.853$), respectively.

SBRT was well tolerated, and all patients completed the treatment course on schedule. As for toxicities, grade 0–1, grade 2, and grade 3 radiation pneumonitis occurred in 59, 8, and 3 patients, respectively. No other acute toxicities, including general fatigue, nausea, fever, and respiratory symptoms, were reported. In the chronic phase, one patient died from hemoptysis (grade 5) 13 months after SBRT. The patient had a squamous cell carcinoma, with the diameter of the solid component of 5.8 cm, located in the left lobe and invading into the mediastinum. SBRT with a prescription dose of 50 Gy/5 fractions (80% isodose) was delivered. The minimum doses delivered to 1 ml of the most irradiated part of the pulmonary artery and bronchus were 58.4 Gy and 52.0 Gy, respectively. No other chronic toxicities ≥grade 3, including rib fracture, intercostal neuralgia, brachial plexus neuropathy, or pulmonary fibrosis were reported.

DISCUSSION

In 2016, the UICC 8th edition for lung cancer was published. Of the original data creating the staging system, approximately 85% were treated with surgery, while only 1.5% were treated with radiotherapy (including SBRT) alone [3], though rates of patients treated with SBRT were increasing, reaching 25% of stage I NSCLC patients aged ≥60 years [12, 13]. Therefore, we wondered if the new staging system might not reflect the outcomes of patients treated with SBRT. This motivated us to investigate the outcomes of patients treated with SBRT for cT3–4N0M0 using the UICC 8th edition. For such patients, the American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline states [5] that hypofractionated radiotherapy utilizing 6–15 fractions or conventionally fractionated radiotherapy may be considered for central tumors for which SBRT is deemed too high-risk, and that SBRT may be an appropriate option for select tumors >5 cm in diameter with an acceptable therapeutic ratio. We have proactively treated such patients with careful attention to published evidence and our own experience. To the best of our knowledge, this is the first report of long-term follow-up after SBRT for cT3-4N0M0 using the UICC 8th edition.

OS following surgery for T3-4N0M0 using the UICC 8th edition

Surgery is recommended for patients with cT3-4N0M0 (stages IIB and IIIA) [8, 14], if possible, though these patients are heterogeneous (Table 3). In the previous studies, the outcomes of resected

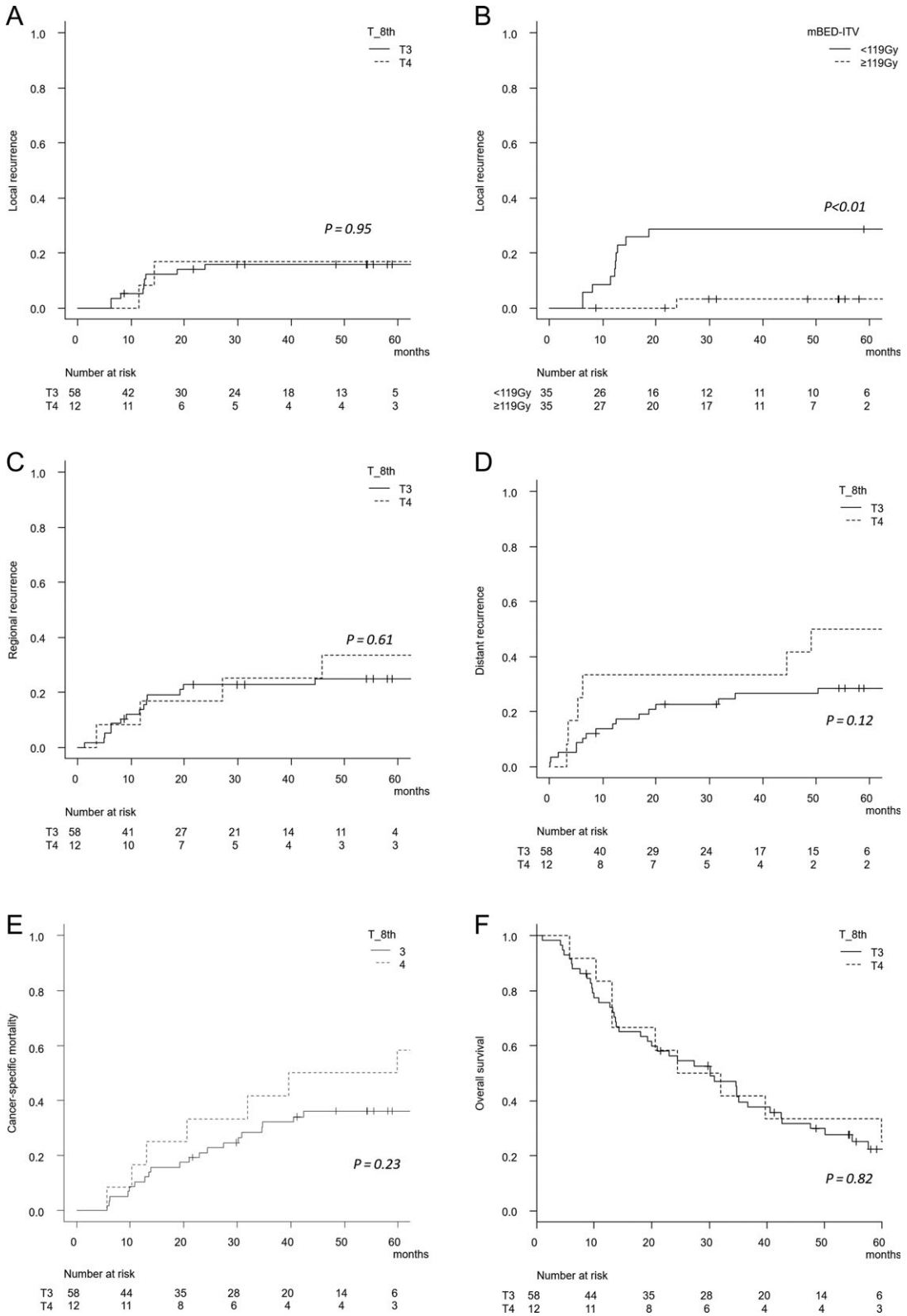

Fig. 2. Cumulative incidences. (A) **Local recurrence, T3 vs. T4.** (B) **local recurrence, mBED-ITV <119 Gy vs ≥119 Gy.** (C) **Regional recurrence, T3 vs. T4.** (D) **Distant metastasis, T3 vs T4.** (E) **Cancer-specific death, T3 vs T4.** (F) **Overall survival, T3 vs T4.**

Table 2. Univariate and multivariate analyses

	Local recurrence (Fine-Gray test)								Regional recurrence (Fine-Gray test)							
	UVA				MVA				UVA				MVA			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Age, >75 y (vs ≤75 y)	1.16	0.35	3.80	0.80					1.34	0.53	3.3	0.53				
Sex, male (vs female)	1.91	0.41	8.87	0.40					1.06	0.38	2.95	0.91				
Performance status, 2–4 (vs 0–1)	1.17	0.34	4.01	0.79					1.12	0.42	2.98	0.82				
Charlson comorbidity index, 3–7 (vs 0–2)	0.96	0.28	3.28	0.95					1.36	0.54	3.38	0.51				
Clinical T stage, T4 (vs T3)	1.05	0.22	4.87	0.94					1.34	0.46	3.85	0.58				
Tumor diameter of solid component, >5 cm (vs ≤5 cm)	3.82	0.82	17.70	0.08	2.65	0.56	12.41	0.21	1.29	0.51	3.27	0.58				
Invasion factor, none/T3/T4				0.16								0.65				
None	1.00								1.00							
T3	0.37	0.11	1.28	0.12					1.03	0.37	2.83	0.94				
T4	0.58	0.21	1.60	0.30					0.81	0.39	1.66	0.57				
Location, peripheral (vs central)	0.54	0.16	1.79	0.31					0.51	0.20	1.27	0.15	0.31	0.10	0.93	0.03
Histology				0.20								0.48				
Adenocarcinoma	1.00								1.00							
Squamous cell carcinoma	4.64	0.54	39.75	0.16					2.06	0.54	7.77	0.28				
Non-small cell carcinoma	4.04	0.36	44.62	0.25					1.91	0.96	3.79	0.06				
Pathologically unproven	4.35	0.45	41.90	0.20					1.11	0.66	1.87	0.69				
Operability, no (vs yes)	0.55	0.07	4.33	0.57					0.70	0.17	2.83	0.62				
SUVmax, ≥8 (vs <8)	3.69	0.97	13.95	0.05					2.87	1.02	8.08	0.04	2.81	1.01	7.83	0.04
BED mean ITV dose, ≥119 Gy (vs <119 Gy)	0.08	0.01	0.68	0.01	0.10	0.01	0.82	0.03	0.61	0.24	1.56	0.31				
Radiation method, VMAT (vs DCMAT)	0.26	0.03	2.07	0.20					0.75	0.25	2.20	0.60				
Isodose, 60% (vs 80%)	0.14	0.01	1.10	0.06					1.15	0.72	1.85	0.54				

	Distant metastasis (Fine-Gray test)								OS (Cox proportional hazard model)							
	UVA				MVA				UVA				MVA			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value	HR	95% CI		*P*-value	HR	95% CI		p-value
Age, >75 y vs ≤75 y	1.33	0.60	2.95	0.47					1.62	0.94	2.80	0.07	2.19	1.08	4.44	0.03
Sex, male vs female	0.53	0.24	1.17	0.12					1.36	0.74	2.51	0.31				
Performance status, 2–4 vs 0–1	1.82	0.84	3.92	0.12					1.20	0.68	2.09	0.51				

Continued

Table 2. Continued

	Distant metastasis (Fine-Gray test)								OS (Cox proportional hazard model)							
	UVA				MVA				UVA				MVA			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value	HR	95% CI		*P*-value	HR	95% CI		p-value
Charlson comorbidity index, 3–7 vs 0–2	0.70	0.30	1.59	0.40					0.76	0.43	1.35	0.36				
Clinical T stage, T4 vs T3	2.14	0.92	4.98	0.07	1.99	0.64	6.19	0.230	0.92	0.46	1.84	0.81				
Tumor diameter of solid component, >5 cm vs ≤5 cm	1.06	0.49	2.28	0.88					1.07	0.19	1.29	0.42				
Invasion factor, none/T3/T4				0.51								0.02				0.09
None	1.00								1.00				1.00			
T3	0.74	0.30	1.84	0.52					0.45	0.25	0.83	0.01	0.53	0.29	0.98	0.04
T4	1.29	0.80	2.10	0.29					0.45	0.19	1.06	0.06	0.48	0.20	1.14	0.09
Location, peripheral vs central	0.82	0.38	1.79	0.63					0.79	0.46	1.37	0.41				
Histology				0.09				0.03				0.72				
Adenocarcinoma	1.00				1.00				1.00							
Squamous cell carcinoma	0.59	0.24	1.44	0.25	0.58	0.15	2.21	0.42	1.79	0.89	3.59	0.10				
Non-small cell carcinoma	0.65	0.36	1.16	0.15	0.52	0.21	1.32	0.17	1.71	0.74	3.94	0.20				
Pathologically unproven	0.74	0.51	1.07	0.11	0.60	0.35	1.03	0.06	0.87	0.38	2.01	0.76				
Operability, no vs yes	2.51	1.01	6.17	0.04					0.88	0.38	2.08	0.78				
SUVmax, ≥8 vs <8	0.47	0.18	1.26	0.14	0.44	0.16	1.22	0.12	1.16	0.61	2.20	0.64				
BED mean ITV dose, ≥119 Gy vs <119 Gy	1.22	0.56	2.64	0.60					0.87	0.49	1.55	0.64				
Radiation method, VMAT vs DCMAT	0.74	0.27	1.98	0.55					0.80	0.41	1.57	0.52				
Isodose, 60% vs 80%	0.87	0.57	1.32	0.51					0.73	0.41	1.32	0.30				

UVA = univariate analysis, MVA = multivariate analysis, HR = hazard ratio; CI = confidence interval, SUVmax = maximum standardized uptake value, BED = biologically effective dose, ITV = internal target volume, VMAT = volumetric modulated arc therapy, DCMAT = dynamic conformal multiple arc therapy.

patients with T3-4N0M0 were analyzed with the previous staging system or each size or invasion T3-4 factors. For patients with pT3N0 and pT4N0 using the 7th UICC staging from the Japanese national survey, the 5-year OS rates were 50.6% and 45.0%, respectively [15, 16]. As to the size factors of T3-4, some studies showed that the 5-year OS was 42.0–46.6% for completely resected patients with tumors >5 cm (pT3-4), and others showed that the 5-year OS of patients with tumors >5–7 cm (pT3) and >7 cm (pT4) were significantly different (47.9% vs 21.9%) [17]. As to the invasion factors of T3-4, there is very little information on their effects on survival. According to two reports of patients with chest wall invasion, outcomes seem compromised, with the 5-year OS around 30% [18, 19].

Outcomes depend on the possibility of complete resection, invasiveness, and patient age and physical fitness. Complete resection resulted in better survival [15, 16, 20]. The 5-year OS rates of pT3 patients using the UICC 7th edition with R0 and R1+R2 resection were 47.5% and 24.2%, and those of pT4 with R0, R1, and R2 resection were 45.0%, 27.0%, and 25.0%, respectively [15, 16]. Pneumonectomy is often inevitable to achieve complete resection, and it is performed for 15–42% of patients with cT3N0 using the UICC 7th edition [18, 21, 22]. However, patients undergoing pneumonectomy had a poor prognosis because it is an invasive procedure [18]. Being elderly was in itself a risk factor for worse OS [16, 20, 23]. Therefore, pneumonectomy tended to be performed for younger patients [21]. For such patients predicted to have a poor prognosis, Lee *et al.* [18] suggested that chemoradiotherapy should be considered an alternative to surgery.

Postoperative adjuvant chemotherapy for T3-4N0M0 might provide benefits as for other stage II-III NSCLC status [14, 20].

Table 3. 6th, 7th, and 8th UICC T staging

		6th edition	7th edition	8th edition
T3	Invasion factors	Chest wall, diaphragm, phrenic nerve, mediastinal pleura	Chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium	Chest wall, phrenic nerve, mediastinal pleura, parietal pericardium
	Location factors	-	Tumor in the main bronchus <2cm distal to the carina	-
	Size factors	-	>7 cm	>5 cm
	Separate nodule factors	-	in the same lobe	in the same lobe
	Other factors	-	Associated atelectasis or obstructive pneumonitis of the entire lung	-
	N0M0 staging	Stage III	Stage IIB	Stage IIB
T4	Invasion factors	Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina	Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina	Mediastinum, diaphragm, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina
	Location factors	-	-	-
	Size factors	-	-	>7 cm
	Separate nodule factors	In the same lobe	In a different ipsilateral lobe	In a different ipsilateral lobe
	Other factors	Malignant pleural or pericardial effusions, and pleural nodules	-	-
	N0M0 staging	Stage IVA	Stage IIIA	Stage IIIA

In another study, adjuvant chemotherapy led to better OS for pT2-4N0M0 patients using the UICC 7th edition [24, 25], with more absolute benefit when the tumors were larger [25].

OS following SBRT for T3–4N0M0 using the UICC 8th edition

In the present study, the outcomes following SBRT might be comparable with the outcomes in surgical series considering the staging system, no administration of systemic chemotherapy, and patients' age and physical fitness. SBRT patients are all staged clinically, which could be more often upstaged than downstaged on pathological staging. In contrast, reports of surgical patients were usually staged with pathological staging. Therefore, SBRT cohorts may contain more advanced patients than surgical series. Furthermore, candidates for surgery were young and robust, and they were selected carefully. The median age of surgical series was around 65 years, and half of the patients received systemic chemotherapy [15, 16]. On the other hand, the present SBRT patients were frail. In fact, in this SBRT study, most patients were medically inoperable and elderly. The median age was as old as 81 years, which is almost equivalent to the average life expectancy of Japanese men, and the rate of a Charlson comorbidity index ≥1 was 89%. No patients underwent adjuvant chemotherapy because of their poor conditions. Accordingly, of the 55 patients who died during follow-up, 27 died from non-specific other causes. Non-specific death in SBRT caused OS to be relatively poorer than that reported in surgical series: 5-year OS rates in pT3 and pT4 using the UICC 7th edition in surgery, and in cT3 and cT4 using the UICC 8th edition in the present SBRT study, were 50.6% and 45.0% [15, 16], and 22.3% and 25%, respectively. On the other hand, the 5-year CSS in the present SBRT study was compatible with the 5-year OS in surgery: 5-year

CSS rates (calculated by 1-CSM) in cT3 and cT4 using the UICC 8th edition in the present SBRT study were 63.9% and 41.7%, respectively.

The present results did not show any significant differences in treatment outcomes between T3 and T4. The classification of T3 and T4 in the UICC 8th edition might not fit for SBRT outcomes, because the classification is mainly derived from surgical series. It is necessary to accumulate more data on treatment outcomes to validate the usefulness of the T3-4 classification in SBRT cases.

Local control following SBRT for T3–4N0M0 in the UICC 8th edition

In SBRT, dose prescription to the tumor is one of the most important factors for local control and subsequent survival. This may be similar to the fact that the completeness of resection was reported to be the most significant factor for better survival in surgical series [15, 16, 20]. Just as complete resection is often difficult for patients with tumors invading mediastinal organs tightly, sufficient dose administration to the tumor while sparing organs at risk adjacent to the tumor is often difficult. In the ESTRO-ACROP consensus guideline, BED10 > 100 Gy to PTV D95–99% is recommended on the basis of the dose threshold for achieving >90% tumor control probability for stage I NSCLC [6]. However, compliance with the recommendation is not enough to achieve favorable results for larger tumors, and higher doses may be needed. SBRT for T2 tumors has a worse local control and survival than for T1 tumors [26]. Another study suggested that higher doses (>150 Gy BED10) had a significant survival benefit even in patients with T2 tumors [27]. However, a sharp dose gradient within the PTV and various definitions of BED10 (e.g., prescribed to a point or a volume), and questionable validity of BED calculation with a large fraction size make such comparisons very complicated. In fact, various dosimetric parameters for tumor control were studied: ITV dose coverage (BED10 > 150 Gy) [28], maximum dose [29], and mean PTV (BED10 > 125 Gy) [30], and there is no consensus on which parameter correlates best with tumor control.

In the present study, mBED-ITV was used as a dosimetric parameter because the ITV features a high dose within the PTV. This parameter was adopted because it reflects the real dose for target volumes, even though it is rather unfamiliar. The BED calculated from the prescription dose often deviates from the real dose. It depends largely on the treatment planning strategy, including the prescription site and inhomogeneous dose distribution in the PTV. SBRT showed excellent local control, especially for patients with mBED-ITV > 119 Gy. We previously assessed the optimal prescription isodose level encompassing the PTV, and we found that the 60% isodose plan leads to lower comparative dosimetric factors in normal lung tissue, with higher mean PTV and ITV doses achieved, along with good conformity index values [31]. Volumetric modulated arc therapy (VMAT) planning can achieve more favorable target dose conformity than multiple static field planning for the treatment of early lung cancer using SBRT [32]. Consequently, these techniques enabled irradiation with high doses to the tumor in safety and achieved excellent local control.

High local control does not necessarily lead to long survival

Although high local control was achieved, the rates of regional and distant metastases following SBRT for cT3-4N0M0 were high. In the present study, 5-year regional and distant metastasis recurrence rates were 40% and 50%, respectively. For patients who could tolerate systemic chemotherapy, these high recurrence rates may be improved by administration of adjuvant chemotherapy. In a randomized, controlled study comparing chemoradiotherapy with radiotherapy alone for patients older than 70 years with unresectable stage III NSCLC, median OS and PFS were significantly better in the chemoradiation group (22.4 months vs 16.9 months, $P = 0.018$; 8.9 months vs 6.8 months, $P = 0.009$) [33] .Adjuvant chemotherapy following SBRT for patients with tumor ≥5 cm was associated with longer OS (median OS 30.6 vs 23.4 months) [34], and adjuvant chemotherapy had a significant survival benefit in surgical series [20, 24, 25]. Therefore, to achieve better survival, adjuvant chemotherapy should be carefully considered. A prospective study of SBRT with adjuvant therapy for cT3-4N0M0 is warranted.

For patients with cT3-4N0M0 lung cancer, surgery is recommended as the first treatment if feasible. However, in reality, it is not indicated for many patients. Furthermore, surgery is often conducted with a risk of incomplete treatment and invasiveness. SBRT for such patients could be applied in a clinical trial to validate its feasibility, or currently it could be used only in experienced institutions. In our institution, we have conducted SBRT widely in a proactive manner. SBRT for patients with cT3-4N0M0 NSCLC is still challenging [5]. SBRT has some favorable characteristics compared with surgery. In SBRT, the quality of life and indirect costs were significantly better and less expensive [35]. In a questionnaire investigation of patients having experienced both surgery and SBRT, SBRT was reported to satisfy patients significantly more [36].

This study has several limitations, including its small sample size and its retrospective nature with possible selection bias. Dose constraints for critical organs have not been established. There are no established dose constraints for mediastinal organs, and rather strict ones were adopted in the present study with an assumption of 5 fractions. In addition, the dose prescriptions have changed historically. In the present study, patients suitable for SBRT were selected after considering the indications for each patient. This process is presumably the same for surgery as well, because the indications for treatment are not yet evident. Long-term safety is still unclear, because more than half of the patients died within 3 years.

In conclusion, SBRT for cT3-4N0M0 using the UICC 8th edition achieved good local control using the technique of VMAT and 60% isodose prescription with enough dose to the target volume. Survival was rather good considering patients' condition and might be comparable to surgery. To validate the outcomes following SBRT, a prospective study of SBRT with or without adjuvant chemotherapy according to the patient's physical condition is warranted.

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CONFLICT OF INTEREST

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IRB APPROVAL

This study including data collection and analysis was approved by the review board of Ofuna Chuo Hospital.

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