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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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)
Narita shows the characteristics of the patients and T.M. and K.Y. determined each 80% isodose of the −6 150 Gy in 5 fractions at Ofuna Chuo 78 years); 55 were diagnosed pathologically values on 2N0M0 non-small cell lung cancer (NSCLC) [18]. Patients with other malignancies were excluded. A lung cancer board at our hospital, including a control, though the evidence for toxicity is poor. After obtaining informed consent, the patients were treated with SBRT. poor, whereas it is expected that SBRT will provide good local after conventionally fractionated (chemo)radiotherapy is generally described total dose of 40–50 Gy to total lung was 8th edition (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 maximum dose of 25 Gy, and the doses for the bronchus, pulmonary artery, brachial plexus, and left ventricle were minimized to be as 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 [18F] fluorodeoxyglucose positron emission tomography/computed tomography (18F-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 18F-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 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, 18F-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 nonspecific 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
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’.

Table 1. Patients’ characteristics

| Characteristic                                | Median (Range)       |
|-----------------------------------------------|----------------------|
| 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.
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) \( (P = 0.055\text{ on univariate analysis}) \) 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 \( \geq 119 \text{ Gy} \) and \( <119 \text{ Gy} \) 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 cT3 and cT4 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 \( (P = 0.04\text{ on univariate analysis}) \) 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 \( \leq 119 \text{ Gy} \): 28.6% vs \( \geq 119 \text{ Gy} \): 17.5%, \( P = 0.09 \); distant \( <119 \text{ Gy} \): 22.9% vs \( \geq 119 \text{ Gy} \): 32.4%, \( P = 0.60 \)).

The 3-year CSM rates for patients with T3 and T4 were 32.2% and 41.7% \( (P = 0.237\text{, respectively}) \) (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 \( (P = 0.816\text{, respectively}) \) (Fig. 2F). CSM and OS were also not related to meanBED-ITV (CSM \( <119 \text{ Gy} \): 40.0% vs \( \geq 119 \text{ Gy} \): 27.1%, \( P = 0.23\); OS \( <119 \text{ Gy} \): 37.1% vs \( \geq 119 \text{ Gy} \): 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 \( (P = 0.853\text{, respectively}) \).

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 \( (80\%\text{ isodose}) \) 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 \( \geq \text{grade 3} \), 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 \( \geq 60\text{ years} \) [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 \( \geq 5\text{ cm} \) 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 IIA) [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 HR 95% CI P-value             | MVA HR 95% CI P-value               | UVA HR 95% CI P-value | MVA 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 | 1.29 0.51 3.27 0.58                 |
| Invasion factor, none/T3/T4 | 0.16 0.65                      | 0.65 0.01 1.10 0.06                 |
| 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                 |
| 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 46.62 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                 |
| BED mean ITV dose, ≥119 Gy (vs <119 Gy) | 0.08 0.01 0.68 0.01 | 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 HR 95% CI P-value             | MVA HR 95% CI P-value               | UVA HR 95% CI P-value | MVA 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                 |
| 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
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 rates were 50.6% and 45.0%, respectively [15, 16]. 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].

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 |
| 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 |
| T4                       | 1.29 0.80 2.10 0.29 | 0.45 0.19 1.06 0.06 |
| 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                 | 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 |
| Non-small cell carcinoma | 0.65 0.36 1.16 0.15 | 0.52 0.21 1.32 0.17 |
| Pathologically unproven  | 0.74 0.51 1.07 0.11 | 0.60 0.35 1.03 0.06 |
| 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 |
| 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.
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 OS following SBRT for T3–4N0M0 using the UICC 8th edition

| 6th edition | 7th edition | 8th edition |
|-------------|-------------|-------------|
| **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 | - |
| **T3 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 |
|--------------|---------|---------|---------|
| **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** | - | - | - |
| **T4 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 |
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 \( \geq 5 \) 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 constraints for critical organs have not been established. There are no constraints for mediastinal organs, and rather strict constraints for critical organs have not been established. There are no constraints for mediastinal organs, and rather strict constraints for critical organs have not been established.

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**

Dr. Takeda reports the two following grants. Other authors have declared no conflicts of interest.

**IRB APPROVAL**

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

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**REFERENCES**

1. Siegel R-L, Miller K-D, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
2. Rami-Porta R, Bolejack V, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2015;10:990–1003.
3. Rami-Porta R, Bolejack V, Giroux D-J et al. The IASLC lung cancer staging project: the new database to inform the eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2014;9:1618–1624.
4. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (2017/12/26 2017, date last accessed).
5. Schneider B-J, Daly M-E, Kennedy E-B et al. Stereotactic body radiotherapy for early-stage non-small-cell lung cancer: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline. *J Clin Oncol* 2018;36:710–719.
6. Guckenberger, M, Andratschke N, Dieckmann K et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. *Radiother Oncol* 2017;124:11–17.
7. Videtic G-M-M, Donington J, Giuliani M et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. * Pract Radiat Oncol 2017;7:295–301.
8. Postmus P-E, Kerr K-M, Oudkerk M et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;28:v1–iv21.
9. Eriguchi T, Takeda A, Sanuki N, et al. Stereotactic body radiation therapy for T3 and T4N0M0 non-small cell lung cancer. *J Radiat Res* 2016;57:265–272.
10. Takeda A, Kunieda E, Sanuki N, et al. Dose distribution analysis in stereotactic body radiotherapy using dynamic conformal multiple arc therapy. *Int J Radiat Oncol Biol Phys* 2009;74:363–369.
11. Kanda Y. Investigation of the freely available easy-to-use software ‘EZT’ for medical statistics. *Bone Marrow Transplant* 2013;48:452–458.
12. Stahl J-M, Corso C-D, Verma V et al. Trends in stereotactic body radiation therapy for stage I small cell lung cancer. *Lung Cancer* 2017;103:11–16.
13. Dalwadi S-M, Szeja S-S, Bernicker E-H et al. Practice patterns and outcomes in elderly stage I non-small-cell lung cancer: A 2004 to 2012 SEER Analysis. *Clin Lung Cancer* 2018;19:e269–e76.
14. Howington J-A, Blum M-G, Chang A-C et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e278S–e313S.
15. Kawaguchi K, Miyaoaka E, Asamura H et al. Modern surgical results of lung cancer involving neighboring structures: a retrospective analysis of 531 pT3 cases in a Japanese Lung Cancer Registry Study. *J Thorac Cardiovasc Surg* 2012;144:431–437.
16. Watanabe S, Asamura H, Miyaoaka E et al. Results of T4 surgical cases in the Japanese Lung Cancer Registry Study: should mediastinal fat tissue invasion really be included in the T4 category? *J Thorac Oncol* 2013;8:759–765.
17. Suemitsu R, Ueda H, Shikada Y et al. Relationship of tumor size to survival in patients with pT2N0 lung cancer. *Asian Cardiovasc Thorac Ann* 2006;14:30–34.
18. Lee C-Y, Byun C-S, Lee J-G et al. The prognostic factors of resected non-small cell lung cancer with chest wall invasion. *World J Surg Oncol* 2012;10:9.
19. Matsuoka H, Nishio W, Okada M et al. Resection of chest wall invasion in patients with non-small cell lung cancer. *Eur J Cardiothorac Surg* 2004;26:1200–1204.
20. Ahmad U, Crabtree T-D, Patel A-P et al. Adjuvant chemotherapy is associated with improved survival in locally invasive node negative non-small cell lung cancer. *Ann Thorac Surg* 2017;104:303–307.
21. Moreno A-C, Morgensztern D, Yu J-B et al. Impact of preoperative radiation on survival of patients with T3N0>7-cm non-small cell lung cancers treated with anatomic resection using the Surveillance, Epidemiology, and End Results database. *J Surg Res* 2013;184:10–18.
22. Choi Y, Lee I-J, Lee C-Y et al. Multi-institutional analysis of T3 subtypes and adjuvant radiotherapy effects in resected T3N0 non-small cell lung cancer patients. *Radiat Oncol J* 2015;33:75–82.
23. Wisnivesky J-P, Henschke C, McGinn T et al. Prognosis of Stage II non-small cell lung cancer according to tumor and nodal status at diagnosis. *Lung Cancer* 2005;49:181–186.
24. Strauss G-M, Herndon J-E 2nd, Maddaus M-A et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043–5051.
25. Morgensztern D, Du L, Waqar S-N et al. Adjuvant chemotherapy for patients with T2N0M0 NSCLC. *J Thorac Oncol* 2016;11:1729–1735.
26. Dunlap N-E, Larner J-M, Read P-W et al. Size matters: a comparison of T1 and T2 peripheral non-small-cell lung cancers treated with stereotactic body radiation therapy (SBRT). *J Thorac Cardiovasc Surg* 2010;140:583–589.

27. Koshy M, Malik R, Weichselbaum R-R et al. Increasing radiation therapy dose is associated with improved survival in patients undergoing stereotactic body radiation therapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2015;91:344–350.

28. Shaverdian N, Tenn S, Veruttipong D et al. The significance of PTV dose coverage on cancer control outcomes in early stage non-small cell lung cancer patients treated with highly ablative stereotactic body radiation therapy. *Br J Radiol* 2016;89:20150963.

29. Guckenberger M, Klement R-J, Allgauer M et al. Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer. *Radiother Oncol* 2013;109:13–20.

30. Kestin L, Grills I, Guckenberger M et al. Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. *Radiother Oncol* 2014;110:499–504.

31. Oku Y, Takeda A, Kunieda E, et al. Analysis of suitable prescribed isodose line fitting to planning target volume in stereotactic body radiotherapy using dynamic conformal multiple arc therapy. *Pract Radiat Oncol* 2012;2:46–53.

32. Dickey M, Rao W, Drodge S et al. A planning comparison of 3-dimensional conformal multiple static field, conformal arc, and volumetric modulated arc therapy for the delivery of stereotactic body radiotherapy for early stage lung cancer. *Med Dosim* 2015;40:347–351.

33. Atagi S, Kawahara M, Yokoyama A et al. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). *Lancet Oncol* 2012;13:671–678.

34. Verma V, McMillan M-T, Grover S et al. Stereotactic body radiation therapy and the influence of chemotherapy on overall survival for large (≥5 centimeter) non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2017;97:146–154.

35. Louie A-V, van Werkhoven E, Chen H et al. Patient reported outcomes following stereotactic ablative radiotherapy or surgery for stage IA non-small-cell lung cancer: Results from the ROSEL multicenter randomized trial. *Radiother Oncol* 2015;117:44–48.

36. Shaverdian N, Wang P-C, Steinberg M et al. The patient’s perspective on stereotactic body radiation therapy (SBRT) vs. surgery for treatment of early stage non-small cell lung cancer (NSCLC). *Lung Cancer* 2015;90:230–233.