Original Article

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Prognostic Factors for Overall and Disease-specific Survival of Stage I Non-Small-Cell Lung Cancer after Stereotactic Body Radiotherapy: A Retrospective Analysis

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Abstract

Background: The purpose of this study was to investigate the prognostic factors of stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer (NSCLC) to improve outcomes.

Materials and methods: Between 2008 and 2016, 71 patients with medically inoperable stage I NSCLC were treated at our hospital with SBRT (48–55 Gy in 4–5 fractions for peripheral lesions or 60–64 Gy in 8–10 fractions for central lesions). Survival outcomes were analyzed using Kaplan-Meier and cumulative incidence methods. Factors including sex, age, tumor location, tumor size, BED (biologically effective dose) 10, and maximum standardized uptake value (SUVmax) were evaluated with regard to overall survival (OS) and disease-specific survival (DSS) using Cox proportional hazard regression.

Results: The median follow-up duration of surviving patients was 33 months (range, 6–81 months). Two-year OS and DSS were 78.5% and 91.5%, respectively. Two-year cumulative local recurrence rate, regional recurrence rate, and distant metastasis rate were 6.8%, 10.9%, and 7.3%, respectively. Multivariate analysis revealed that BED10 and SUVmax were prognostic factors for DSS.

Conclusion: Lower BED10 and higher SUVmax were predictors of significantly worse DSS. A higher SUVmax may be considered for intensive treatment to improve outcomes.

Key words

Stereotactic body radiotherapy, inoperable, non-small-cell lung cancer, prognostic factor

Introduction

Stereotactic body radiotherapy (SBRT) for extracranial lesions was developed by Blomgren et al.[1] and Uematsu et al.[2]. SBRT is a highly precise hypofractionated radiotherapy technique in which large doses of radiation are administered to small tumors of the lung and liver for short periods. Overall survival (OS) and disease-specific survival (DSS) with SBRT have been found to be significantly better than those achieved with conventional radiotherapy (60–66 Gy in 30–33 fractions) for stage I non-small-cell lung cancer (NSCLC)[3].

The standard treatment for stage I NSCLC is surgical resection. However, there are numerous patients for whom surgery is contraindicated, such as the elderly and those in poor general condition or with decreased cardiorespiratory function. Compared to surgical resection, SBRT is minimally invasive, and a complete cure can be expected. As such, it may be appropriately indicated for inoperable stage I NSCLC[4]. Furthermore, OS comparable to that achieved with surgical resection was reported in a prospective study including operable cases[5]. These results will likely expand the scope of indications of SBRT. At this institution, the use of SBRT for stage I

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NSCLC was begun in November 2008, and by December 2016, 71 cased had been recorded. The aim of the present study was to investigate the prognostic factors associated with survival time in medically inoperable stage I NSCLC to improve treatment outcomes.

Materials and Methods

Patients

Study subjects were 71 patients with inoperable NSCLC who received SBRT at this institution between November 2008 and December 2016 (**Table 1**). Median age was 80 years (range, 56–93 years). The ratio of men to women was 45/26. Performance status was 0–2 for 69 patients, but 3 and 4 for 1 patient each. Cancer was pathologically proven in 40 patients. Among these patients, adenocarcinoma was shown to be present in 29, squamous cell carcinoma in 10, and unclassified NSCLC in 1. For the remaining 31 patients, transbronchial or percutaneous biopsy was difficult owing to the anatomical position of the tumor and respiratory dysfunction. Therefore, cancer was diagnosed based on changes over time in computed tomography (CT) or 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) findings. The median tumor size was 2.4 cm (1–4.3 cm). Clinical disease stage was T1-2aN0M0 (International Union Against Cancer, TNM Classification of Malignant Tumours, 7th edition[6]), and the breakdown of the T-stage was T1a, T1b, and T2a in 27, 23, and 21 patients, respectively. Prior to treatment, 58 patients underwent FDG-PET. The median maximum standardized uptake value (SUVmax) of the tumor was 3.5 (0.7–22.8). When the tumor was close to the mediastinum, the position was considered central, whereas when it was far from the mediastinum, the position was considered peripheral. Eighteen patients had central tumors and 53 had peripheral tumors.

This study was performed retrospectively following approval from the ethics committee of this institution (approval number 3650), and all patients provided written informed consent.

Treatment

When the tumor was positioned toward the head from the level of the tracheal bifurcation, there was less respiratory displacement of the tumor. Therefore, the body was immobilized using an Esform soft shell (Engineering System Co., Ltd., Nagano, Japan) and the treatment was performed while the patients breathed freely. When the tumor was positioned toward the feet from the level of the tracheal bifurcation, abdominal compression was applied with the body immobilized using Esform body immobilizing system ESN-100 (Engineering System Co., Ltd.). Al-

Table 1. Patient, Tumor and Treatment Characteristics

Characteristic	Value
Sex (male/female)	45/26
Age (years), median (range)	80 (56- 93)
Operability, no	71
ECOG perfomance status	
0	15
1	47
2	7
3	1
4	1
Tumor size (cm), median (range)	2.4 (1- 4.3)
T-stage (1a/1b/2a)	27/23/21
Pathology	
Pathologically proven	
Adenocarcinoma	29
Squamous cell carcinoma	10
Unclassified NSCLC	1
Pathologically unproven	31
Location (central /peripheral)	18 /53
SUVmax (n=58), median (range)	3.5 (0.7-22.8)
BED10 (Gy), median (range)	105.6 (78.4-130.6)

NSCLC: non-small-cell lung cancer, SUVmax: maximum standardized uptake value, BED10: biologically effective dose (α/β=10)

ternatively, irradiation was applied with indrawn air held using the Abches device (APEX Medical Inc., Tokyo, Japan). In either case, treatment was applied while 2–3 L of oxygen was administered transnasally. The planned treatment CT imaging was performed at a thickness of 2 mm. For the 3D treatment-planning system, XiO, version 5.10 (Elekta, Stockholm, Sweden) or Pinnacle^3, version 9.10 (Philips Healthcare, Amsterdam, Netherlands) was used. Planning treatment volume was a 3–5 mm margin from the gross tumor volume area of the tumor. The crossfire technique with a combination of coplanar and non-coplanar beams, 5–12 fixed portals, and a 6-MV X-ray beam were used. A Primus High-Energy KD2-7467 (Toshiba Medical Systems Corp., Tochigi, Japan) or Elekta Synergy (Elekta) was used as the linear accelerator. Prior to the irradiation, cone-beam CT or CT on rail imaging was performed each time with position correction. Treatment of the central tumor was performed with 60–64 Gy in 8–10 fractions, and that of the peripheral tumor was with 48–55 Gy in 4–5 fractions. To compare the treatment efficacy of the irradiation schedule with differing daily doses and the total dose, the biologically effective dose (BED) based on a linear quadratic model was used, where

BED (Gy) = total dose × (1 + $^{\text{daily dose}}/_{\alpha/\beta}$), and $\alpha/\beta = 10$ was set for the tumor. The median value for BED10 was 105.6 Gy (78.4–130.6 Gy). Combined administration of chemotherapy was not performed.

Evaluation

Post-radiotherapy follow-up was performed at intervals of 1–3 months. CT imaging was performed at 1 month after the completion of treatment and at intervals of 3–4 months thereafter. It was difficult in many cases to use the Response Evaluation Criteria in Solid Tumors (RECIST) criteria[7] to evaluate efficacy for the primary tumor. With the exclusion of patients with serious emphysema, measurement of tumor size was difficult in most patients owing to the appearance of an organizing shadow (the so-called tumor-like shadow) that matched the irradiation field. Therefore, cases in which the tumor-like shadow persisted and enlarged were defined as local recurrences. In addition, FDG-PET was performed if necessary. SUVmax was calculated by: [(maximum activity in VOI)/(volume of VOI)]/[(injected FDG dose)/(patient weight)]. A receiver operating characteristic curve was constructed from the SUVmax and DSS outcomes. From this curve, the SUVmax cut-off point was set at 3.5.

The primary endpoints were OS and DSS. For determination of OS, all deaths were considered as events. For determination of DSS, deaths from lung cancer or treatment-related deaths were considered as events. The secondary endpoints were local recurrence (LR), regional recurrence (RR), and distant metastasis (DM). The factors investigated were sex, age (≤ 80 years vs. > 80 years), tumor location (central vs. peripheral), tumor size (≤ 3 cm vs. > 3 cm), BED10 (≤ 100 Gy vs. >100 Gy) and SUVmax (≤ 3.5 vs. > 3.5).

Statistical analysis

The day of initiation of radiotherapy was set as the starting point, and survival rate was calculated using the Kaplan-Meier method. Recurrence rate was determined using the cumulative incidence method. The log-rank test was used for intergroup comparison of survival rate. Fine and Gray's model was used for intergroup comparison of cumulative recurrence rate. The Cox proportional hazard model was used in the analysis of prognostic factors. Multivariate analysis was performed for factors found by univariate analysis to have a p value < 0.5. Finally, a p value < 0.05 was considered statistically significant. The statistical analysis software used was R (ver.3.4.1).

Results

Outcomes

The median follow-up period of the survivors was 33 months (range, 6–81 months). Two patients were lost to follow-up, and there were 18 intercurrent deaths and 12 disease-specific deaths. Two-year OS was 78.5% (95% confidence interval [CI]: 69.0%–89.2%), and 2-year DSS was 91.5% (95% CI: 84.7%–99.0%) (**Fig. 1**). Two-year LR was 6.8%, 2-year RR was 10.9%, and 2-year DM was 7.3%.

Univariate and multivariate analysis (**Table 2**)

First, upon univariate analysis of OS, age, BED10, and SUVmax, p values of < 0.5 were obtained, whereas upon multivariate analysis, none of these factors had a p value < 0.05. Next, upon univariate analysis of DSS, age, tumor size, BED10, and SUVmax, p values of < 0.5 were obtained, whereas upon multivariate analysis, only BED10 and SUVmax showed a p value of < 0.05. The factors that affected DSS were BED10 > 100 Gy (hazard ratio [HR] 0.20, 95% CI; 0.04–0.84, p = 0.02) and SUVmax > 3.5 (HR 6.96, 95% CI; 1.06–45.58, p = 0.04).

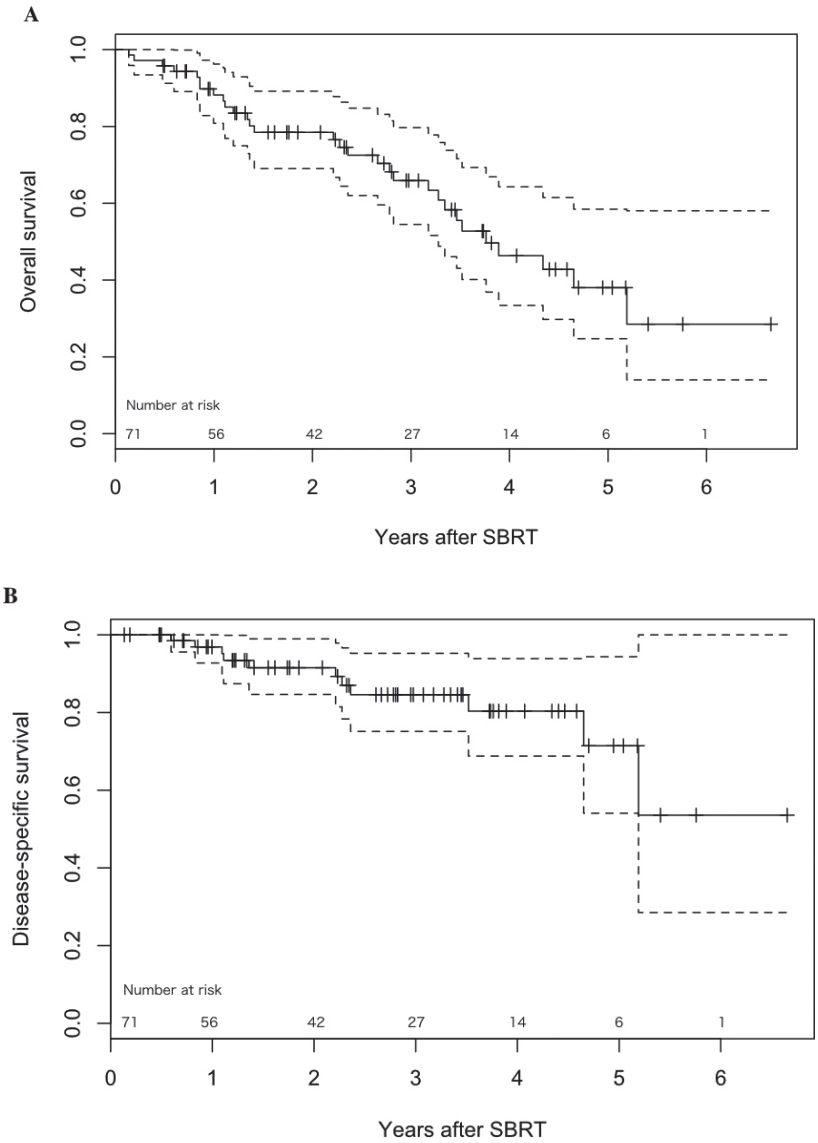

Fig. 1. Kaplan-Meier estimates of (**A**) overall survival and (**B**) disease-specific survival after SBRT.

The DSS curves for BED10 ≤ 100 Gy vs. > 100 Gy and for SUVmax ≤ 3.5 vs. > 3.5 are shown in **Fig. 2**.

Effects of BED10 and SUVmax on LR, RR, and DM **(Fig. 3)**

At BED10 > 100 Gy, LR decreased significantly. At BED10 ≤ 100 Gy, the 2-year LR was 24.2%, whereas it was 2.3% at BED10 > 100 Gy (p = 0.01). The 2-year LR was not significantly affected by SUVmax: it was 3.8% at SUVmax ≤ 3.5 and 8.8% at SUVmax > 3.5 (p = 0.53).

RR decreased significantly at BED10 > 100 Gy and SUVmax ≤ 3.5. The 2-year RR at BED10 ≤ 100 Gy was 27.1%, whereas at BED10 > 100 Gy, it was 6.2% (p = 0.02). The 2-year RR was 0.0% at SUVmax ≤ 3.5 and 19.6% at SUV max > 3.5 (p = 0.03).

DM was not affected by BED10. The 2-year DM was 14.2% at BED10 ≤ 100 Gy and 5.8% at BED10 >100 Gy (p = 0.47). However, the 2-year DM increased significantly to 20.2% at SUVmax > 3.5, whereas at SUVmax ≤ 3.5, it was 0% (p < 0.01).

Discussion

In a meta-analysis by Grutters et al.[3], the 2-year

Table 2. Univariate and Multivariate Analysis for Overall and Disease-specific Survival

	Overall survival			Disease-specific survival		
	HR	95% CI	p Value	HR	95% CI	p Value
Univariate analysis						
Sex (male vs. female)	0.92	0.43-1.97	0.83	1.06	0.31-3.65	0.92
Age (≤80 vs. >80)	1.41	0.68-2.90	0.34	3.92	1.03-14.94	0.04*
Tumor location (central vs. peripheral)	0.89	0.39-2.02	0.79	0.86	0.22-3.25	0.82
Tumor size (≤3 vs. >3 cm)	1.08	0.46-2.54	0.84	2.88	0.87-9.51	0.08
BED10 (≤100 vs. >100 Gy)	0.69	0.30-1.58	0.38	0.34	0.10-1.14	0.08
SUVmax (≤3.5 vs. >3.5)	1.39	0.61-3.15	0.42	5.62	1.15-27.28	0.03*
Multivariate analysis						
Sex (male vs. female)	-	-	-	-	-	-
Age (≤80 vs. >80)	1.42	0.63-3.21	0.39	5.87	0.92-37.48	0.06
Tumor location (central vs. peripheral)	-	-	-	-	-	-
Tumor size (≤3 vs. >3 cm)	-	-	-	1.01	0.20-5.02	0.99
BED10 (≤100 vs. >100 Gy)	0.64	0.23-1.78	0.4	0.20	0.04-0.84	0.02*
SUVmax (≤3.5 vs. >3.5)	1.41	0.62-3.22	0.4	6.96	1.06-45.58	0.04*

HR: hazard ratio, CI: confidence interval, SUVmax: maximum standardized uptake value, BED10: biologically effective dose (α/β=10)
* $p < 0.05$

OS of SBRT for stage I NSCLC was 70% (95% CI: 63–77%), and the 2-year DSS was 83% (95% CI: 75–92%). In the present study, the 2-year OS was 78.5% (95% CI: 69.0–89.2%), and the 2-year DSS was 91.5% (95% CI: 84.7–99.0%), indicating equivalent outcomes.

Multivariate analysis revealed that BED10 and SUVmax were the prognostic factors for DSS. No prognostic factors were found for OS, a result that may be explained by the fact that 60% of overall deaths were attributed to other diseases. The breakdown of other disease is as follows: 3 cases of aortic dissection; 2 cases of cerebral infarction; 2 cases of renal failure; 1 case each of chronic obstructive pulmonary disease (COPD), chronic pyothorax, and pneumonia; 1 case of myocardial infarction; 1 case of valvular heart disease; 1 case of uterine cervical cancer; 1 case of senility; and 4 unknown cases.

Zhang et al.[8] investigated the optimal BED10 of SBRT for stage I NSCLC by meta-analysis. When OS was the endpoint, the optimal BED10 was in the 83–146 Gy range. Thus, it is natural for tumor size and radiation sensitivity to affect the range of optimal BED10. To date, there have been many reports describing improvements in local control and OS with BED10 ≥ 100 Gy[9][10]. The guidelines for radiotherapy with curative intent in patients with early-stage medically inoperable NSCLC recommend BED10 ≥ 100 Gy[4]. Even in the present study, decreases in LR and RR and improvement in DSS were observed with BED10 > 100 Gy. The improvement in local control found with BED10 > 100 Gy was related to the decrease in RR and the improvement in DSS.

FDG-PET is used extensively, such as in the disease classification of many malignant tumors and in the assessment of treatment outcomes. SUVmax is one of the most commonly used PET parameters and an important prognostic factor for NSCLC survival. Liu et al.[11] performed a meta-analysis of 36 studies on NSCLC in which resection was performed. The median value of the SUVmax cut-off point was 5.9 (range, 2.4–20). Compared to lower SUVmax, the HR of primary disease deaths with higher SUVmax was 2.74 (95% CI: 2.33–3.24). Moreover, compared to a lower SUVmax, the HR for overall deaths with a higher SUVmax was 2.54 (95% CI: 1.86–3.49). SUVmax strongly influenced the survival of even patients with SBRT-treated NSCLC. Takeda et al.[12] reported that the threshold of SUVmax for LR, RR, DM, DSS, and OS was in the 2.47–3.64 range and that it was 2.55 for both DSS and OS. Compared to the lower SUVmax, the HR for primary disease death with the higher SUVmax was 5.94 (95% CI: 1.58–22.35, $p < 0.01$) and that for overall deaths with the higher SUVmax was 2.46 (95% CI: 1.03–5.91, $p = 0.04$).

In this study, the cut-off point of SUVmax was 3.5. Compared to the lower SUVmax, the primary disease death HR with the higher SUVmax was 6.96 (95% CI: 1.06–45.58, $p = 0.04$). On FDG-PET, SUV displayed high glucose metabolic activity similar to that of tumors with a high SUVmax, suggesting that

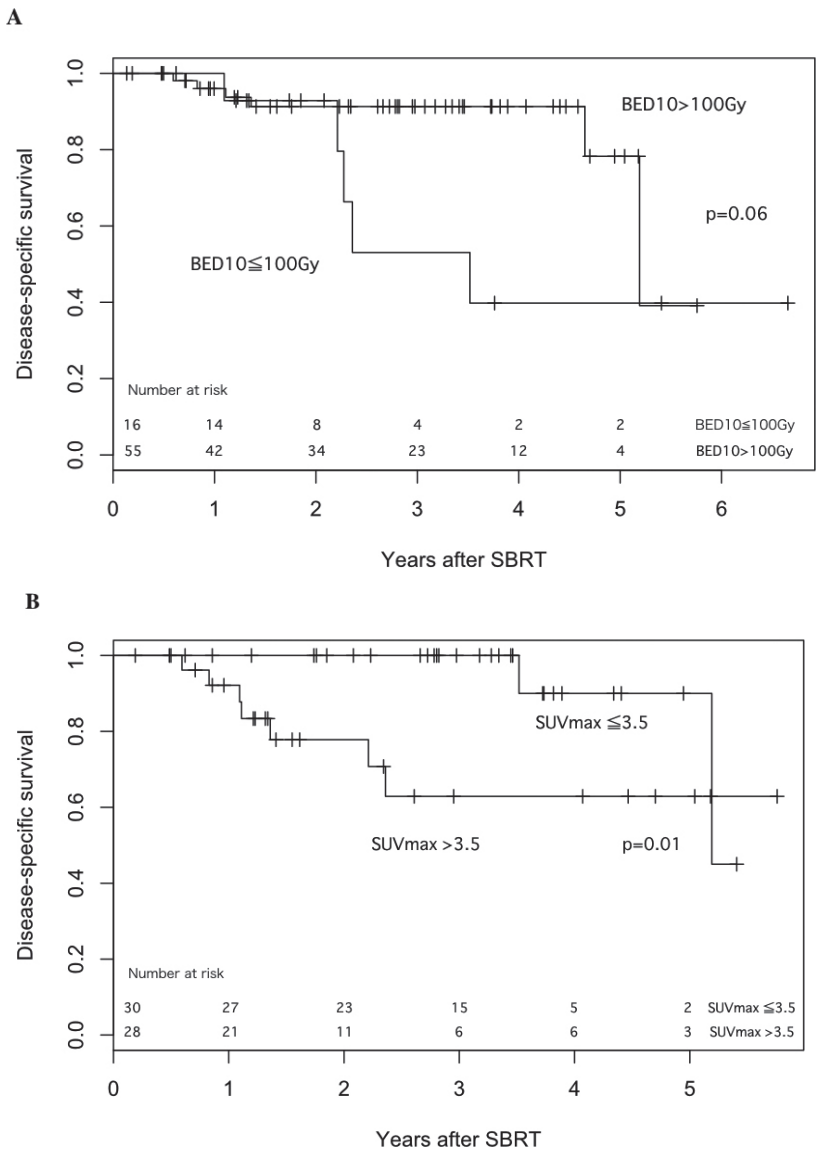

Fig. 2. Disease-specific survival after SBRT as stratified by (**A**) BED10 of ≤100 Gy or >100 Gy and (**B**) pre-treatment SUVmax of ≤3.5 or >3.5.

the degree of malignancy is high and metastasis occurs readily[10)12)]. Thus, the higher the SUVmax, the higher the RR and DM will become, which results in a decrease in DSS.

Two potential recommendations may be considered based on the results of this study and in cases in which SBRT is performed for medically inoperable stage I NSCLC. The first is that if the normal organs in the vicinity of the irradiation site can tolerate the treatment, the preferable radiation dose is BED10 > 100 Gy. The second relates to measures for regional lymph nodes and distant metastasis of patients with higher SUVmax values. The types of patients for whom SBRT is indicated are mostly the elderly and those with poor performance status, such as patients with respiratory dysfunction. Therefore, the use of potent systemic chemotherapy to prolong life is questionable. However, what about the efficacy of mild chemotherapy? Kato et al.[13)] performed a prospective randomized trial that investigated the efficacy of postoperative uracil-tegafur treatment in resectable stage I adenocarcinoma. The OS of the patients in stage T2 in the uracil-tegafur group improved significantly. Atagi et al.[14)] performed a randomized controlled

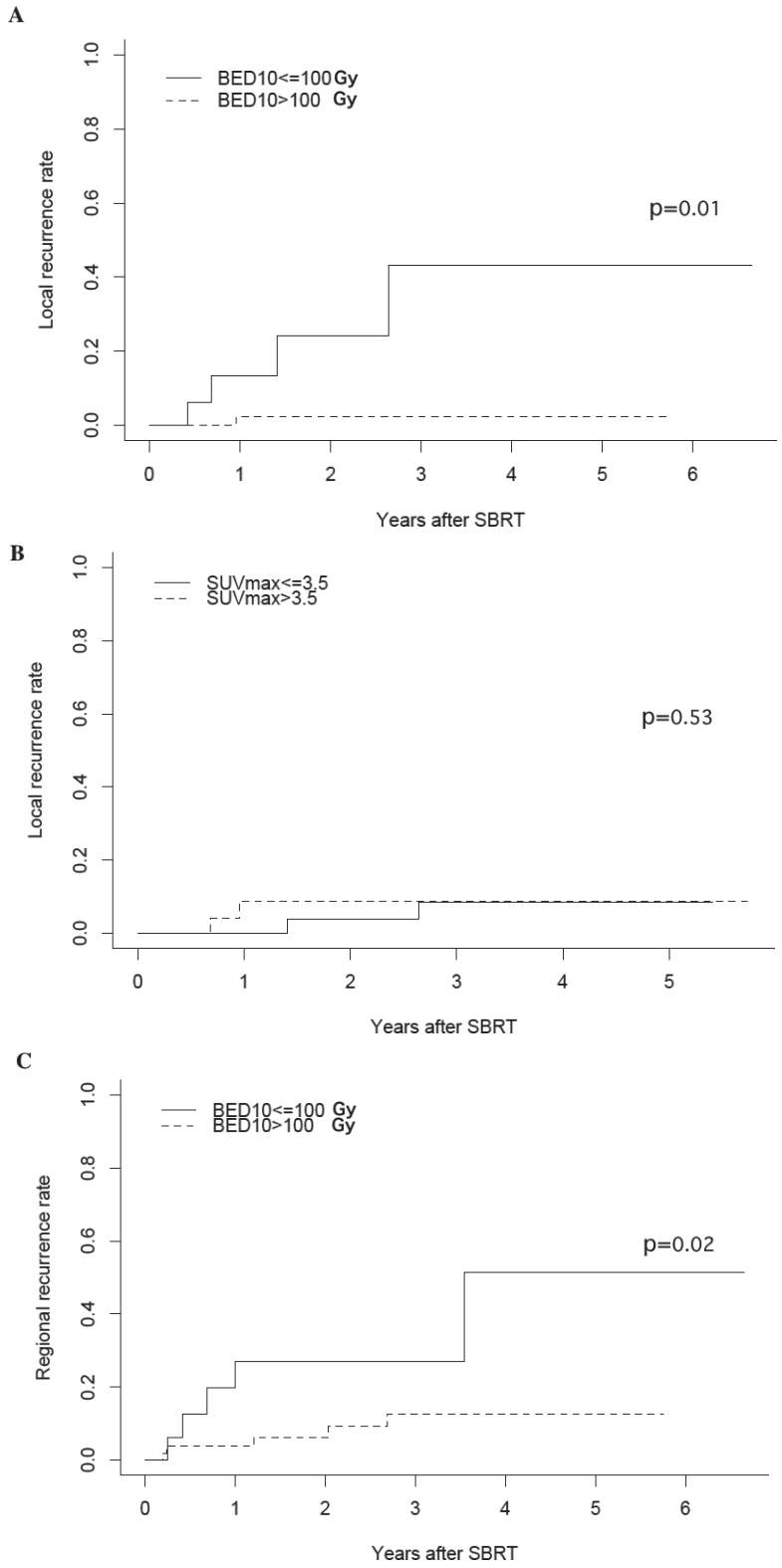

Fig. 3. Local recurrence rate after SBRT as stratified by (**A**) BED10 of ≤100 Gy or >100 Gy and (**B**) pre-treatment SUVmax of ≤3.5 or >3.5.

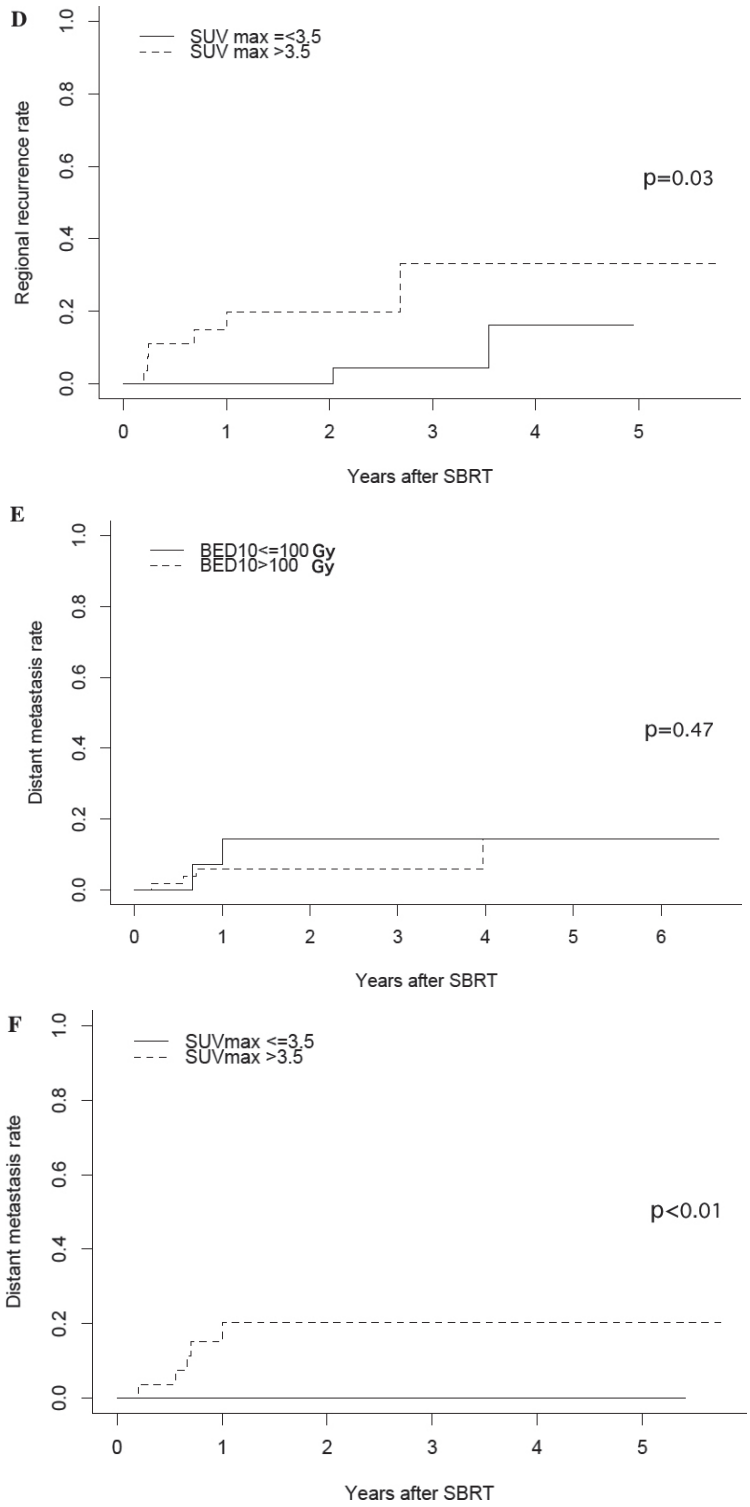

Fig. 3. Regional recurrence rate after SBRT as stratified by (**C**) BED10 of ≤100 Gy or >100 Gy and (**D**) pre-treatment SUVmax of ≤3.5 or >3.5.
Distant metastasis rate after SBRT as stratified by (**E**) BED10 of ≤100 Gy or >100 Gy and (**F**) pre-treatment SUVmax of ≤3.5 or >3.5.

phase 3 study that compared radiation therapy alone and chemoradiation (radiation + low-dose carboplatin) in elderly patients with locally advanced NSCLC. The OS of the chemoradiation group improved significantly. These mild systemic chemotherapies have comparatively few adverse effects; therefore, they may become indicated for patients in the high-risk group with regional lymph node and distant metastasis who have a comparatively good performance status.

There are some limitations to the present study. The period of observation of progression is short, the sample size is small, and the study is retrospective in nature. Among the subjects, 43.6% had no conclusive pathological evidence of tumor. The presence of such evidence would certainly be ideal. However, if biopsy per se is associated with a high risk, considering that lung cancer is highly malignant, treatment based on a clinical diagnosis should be permitted.

In conclusion, prognostic factors were analyzed from the treatment outcomes of patients with medically inoperable Stage I NSCLC in whom SBRT was performed. BED10 > 100 Gy and SUVmax > 3.5 were prognostic factors for DSS. With BED10 > 100 Gy, LR and RR improved. With SUVmax > 3.5, RR and DM increased.

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