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Clinical and dosimetric factors for symptomatic radiation pneumonitis after stereotactic body radiotherapy for early-stage non-small cell lung cancer

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ABSTRACT

Background and purpose: The present study attempted to identify risk factors for symptomatic radiation pneumonitis (RP) after stereotactic body radiotherapy (SBRT) in patients with early-stage non-small cell lung cancer (NSCLC).

Materials and methods: We reviewed 244 patients with early-stage NSCLC treated with SBRT. The primary endpoint was the incidence of grade ≥2 RP. Gray's test was performed to examine the relationship between clinical risk factors and grade ≥2 RP, and the Fine-Gray model was used for a multivariate analysis. The effects of each dose parameter on grade ≥2 RP were evaluated with the Fine-Gray model and optimal thresholds were tested using receiver operating characteristic (ROC) curves.

Results: With a median follow-up period of 48 months, the 4-year cumulative incidence of grade ≥2 RP was 15.3%. Gray's test revealed that tumor size, a central tumor, interstitial pneumonia, and the biologically effective dose correlated with RP. In the multivariate analysis, a central tumor and interstitial pneumonia remained significant factors ($p < 0.001$, $p = 0.002$). Among dose parameters, the total lung volume (%) receiving at least 8 Gy (V8), V10, V20, and the mean lung dose correlated with RP ($p = 0.012$, 0.011, 0.022, and 0.014, respectively). The results of the Fine-Gray model and ROC curve analyses showed that V10 >16.7% was the best indicator of symptomatic RP among dose parameters.

Conclusion: The present results suggest that a central tumor and interstitial pneumonia are independent risk factors for symptomatic RP and lung V10 ≤16.7% is recommended as the threshold in SBRT.

Introduction

Lung cancer is the primary cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) estimated to account for 85% of all lung cancer cases. Computed tomography (CT) is now widely available for lung cancer screening. The detection rate of early-stage NSCLC has increased to approximately one in four patients [1]. Stereotactic body radiation therapy (SBRT) delivers high doses of X-rays to a planned target volume (PTV) by focusing X-rays from multiple directions with high fixed accuracy, thereby providing better local control than conventional techniques and also reducing exposure to organs at risk. SBRT is the standard treatment for patients with medically inoperable early-stage NSCLC. Recently, evidence indicates that SBRT is a treatment option for operable early-stage NSCLC and oligometastatic lung tumors [2–4].

Although SBRT is generally a safe treatment for early-stage NSCLC, this therapeutic option may result in some toxicities, with radiation pneumonitis (RP) being one of the most common. The incidence of symptomatic RP has been reported to vary from approximately 10 to 30% [5–11]. Although RP is asymptomatic (i.e., grade 1) in most patients, it may also be fatal. Therefore, minimizing the incidence of RP is crucial in SBRT for early-stage NSCLC. Although various risk factors for symptomatic RP have been reported, no clear threshold for the dose-volume level for the lung has been established. Therefore, the present study attempted to identify risk factors for grade ≥2 RP after SBRT in patients with early-stage NSCLC.

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Materials and methods

Study population

The present study examined the medical records of patients with early-stage NSCLC who were treated with SBRT between February 2004 and September 2018 at our institution. Informed consent was obtained from all patients prior to treatment. Eligibility criteria were as follows: 1) the clinical stage of Tis-T2bN0M0 according to the 8th TNM classification; 2) treatment with SBRT; 3) histologically confirmed NSCLC or clearly considered to be NSLC based on diagnostic imaging findings and the clinical course. A total of 245 patients met these criteria and were included in the study cohort. One patient was excluded from the analysis because it was not possible to accurately evaluate dose-volume histogram (DVH) data. The present study was approved by the Institutional Review Board of Nagoya City University Graduate School of Medical Sciences (approval number: 60-22-0024) and followed the ethical guidelines of the 1964 Declaration of Helsinki and its subsequent revisions. Because this study was conducted retrospectively, the requirement for written informed consent was waived, and an opt-out form was provided on the website for those who did not wish to participate. A total of 244 cases were analyzed for the study cohort.

Pretreatment evaluation

The clinical staging of patients was conducted using a combination of chest and upper abdomen CT, magnetic resonance imaging (MRI) or CT of the brain, and ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET), with bone scintigraphy used in cases where FDG-PET was not available. The eligibility of SBRT was assessed in a multidisciplinary tumor board.

SBRT methods

Previous studies provided detailed descriptions of the planning procedures [12–14]. Three-phase CT of normal breathing, the expiratory phase, and inspiratory phase was acquired at a slice thickness of 2.5 mm. The gross tumor volume (GTV) was measured based on CT and/or FDG-PET. The clinical target volume (CTV) was set to be equal to the GTV, and fluoroscopy was used to assess the respiratory motion of the tumor. An internal target volume (ITV) was created to encompass the CTV in all respiratory phases, and additional anisotropic margins of 5 mm in the lateral and anteroposterior directions and 5–10 mm in the craniocaudal direction were added to the ITV to create the PTV. In patients exhibiting significant respiratory motion, metallic markers were used during irradiation while the patients held their breath. The indication for this technique was determined when the displacement observed in fluoroscopy was ≥1 cm. The metallic markers were either Visicoil or Gold Anchor. For contouring, we predominantly utilized expiration CT scans. The PTV was created by extending a 6 mm margin in all directions from the GTV. We used this breath-hold technique for 8 patients.

The doses using a 6 MV photon beam prescribed to the isocenter of PTV were decided by the tumor diameter. SBRT was performed twice a week in four fractions, with a minimum interval of three days between treatments based on radiobiological considerations [15]. Each treatment was typically spaced at least 72 h apart; however, due to patient and machine availability, the actual treatment duration had a median of 12 days. At least 90% of the isocenter dose was recommended to cover 95% of the PTV. There were no specific rules regarding the minimum and maximum doses. However, the minimum and maximum doses of the PTV were higher than 80% and lower than 107% of the prescription doses, respectively, in most SBRT plans. Prior to November 2008, doses of 44, 48, and 52 Gy were prescribed for peripheral tumors with maximum diameters <1.5 cm, 1.5–3 cm, and >3 cm, respectively. After December 2008, the protocol was changed for dose escalations, and planned doses of 48, 50, and 52 Gy were given according to the respective tumor diameters. Doses of 60 or 64 Gy in eight fractions were used on an individual basis for cases with proximity to the pulmonary hilum or vital organs [16]. From February 2004 to November 2008, pencil beam convolution with Batho power law was used for dose calculations. The analytical anisotropic algorithm was employed from December 2008 to May 2015, and since June 2015, the collapsed cone convolution has been utilized.

Follow-up and evaluation of RP

After SBRT, patients received CT every 2 to 3 months up to 6 months. Thereafter, CT was performed at least every 6 months, and FDG-PET and MRI or CT of the brain were performed as needed. The endpoint was defined as grade ≥2 RP. RP was diagnosed based on chest X-rays, CT, blood tests, and clinical findings. The grade of RP was defined according to CTCAE v5.0.

Dose-volume analyses

Data on the DVH and dose distributions were evaluated in RayStation (RaySearch Medical Laboratories AB, Stockholm, Sweden). Vn was defined as the volume of the total lung receiving at least n Gy of SBRT. The mean lung dose (MLD), V5, V8, V10, and V20 were extracted from the DVH. The total lung volume was defined as the volume of both lungs.

Statistical analysis

Gray's test was performed to evaluate the relationship between clinical risk factors and grade ≥2 RP, and the Fine-Gray model was used in a multivariate analysis, considering death as a competing risk. The effects of each dose parameter on grade ≥2 RP were evaluated with the Fine-Gray model, with death as a competing risk. The optimal threshold for each dose parameter was verified using receiver operating characteristic (ROC) curves. The significance of differences was defined as a p-value <0.05. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [17].

Results

A total of 244 cases were analyzed. The median follow-up period was 48 months (range, 0–198) for all patients and 59 months (range, 0–198) for living patients. Patient characteristics are shown in Table 1. Median age was 77 years. A total of 177 patients (73%) were smokers (current or ex) and 11 (5%) had interstitial pneumonia. Ninety-three patients (38%) had tumors in the lower lobe of the lung and 35 (14%) had central tumors according to the definition of central lung tumors [11]. Most patients (232 patients, 95%) were treated in 4 fractions (44–52 Gy), while the remainder were treated in 6–8 fractions (54–64 Gy). In our cohort of 209 peripheral tumor cases, prescription doses were distributed as follows: 44 Gy/4fr was used in 2 cases, 48 Gy/4fr in 82 cases, 50 Gy/4fr in 68 cases, 52 Gy/4fr in 52 cases, 60 Gy/6fr in 1 case, 60 Gy/8fr in 3 cases, and 64 Gy/8fr in 1 case. The median biologically effective dose (BED) calculated with an α/β value of 10 was 112.5 (range, 92.4–120).

Grades 1, 2, 3, 4, and 5 RP developed in 168 (69%), 28 (11.5%), 8 (3.3%), 0, and one patient (0.4%), respectively. Among the 244 patients analyzed, 37 (15.2%) developed symptomatic (i.e., grade ≥2) RP. The median time for the onset of RP was 4 months (range, 2–38) after SBRT. The 4-year cumulative incidence of grade ≥2 RP was 15.3% (95% confidence interval [CI], 11.2–20.8).

Gray's test was used to examine the relationships between clinical risk factors and grade ≥2 RP. Table 2 shows differences in the 4-year incidence of grade ≥2 RP with each clinical risk factor. Tumor size, a central tumor, interstitial pneumonia, and BED correlated with the development of grade ≥2 RP (p = 0.010, <0.001, 0.002, and 0.017,

Table 1
Patient and treatment characteristics.

Characteristic	Number or median	% or range
Sex		
Male	169	69%
Female	75	31%
Age (years)	77	29–89
PS		
0	117	48%
1	101	41%
2	23	9%
Missing	3	1%
Smoke		
Current	70	29%
Ex	107	44%
Non	60	25%
Missing	7	3%
FEV1 (L)	1.66	0.55–3.25
Interstitial pneumonia		
Yes	11	5%
No	233	95%
Solid component diameter (mm)	23	0–50
Tumor location (lobes)		
Upper or middle lobes	151	62%
Lower lobe	93	38%
Tumor location (centrally)		
Peripheral	209	86%
Central	35	14%
Total dose (Gy)		
Peripheral tumors	50	44–64
Central tumors	52	48–60
Fractions		
Peripheral tumors	4	4–8
Central tumors	4	4–8
BED10	112.5	92.4–120

PS, performance status; FEV1, forced expiratory volume in one second; BED10, biologically effective dose calculated with an α/β value of 10.

Table 2
Difference in the cumulative incidence of grade ≥2 radiation pneumonitis according to patient and treatment characteristics.

Characteristics	Number	4-year incidence	95% CI	*p*-value
Age (years)				0.26
≤77	134	12.4%	7.4–18.8	
>77	110	18.1%	11.4–26.2	
Sex				0.24
Male	169	16.8%	11.4–23.0	
Female	75	11.0%	5.1–19.3	
PS				0.82
0, 1	218	14.7%	10.3–19.9	
2, 3	26	17.0%	5.3–34.3	
Smoker				0.40
No	60	11.9%	5.2–21.5	
Yes	177	16.7%	11.5–22.7	
Interstitial pneumonia				0.002
No	233	13.5%	9.4–18.4	
Yes	11	45.5%	16.7–70.7	
FEV1 (L)				0.92
≤1.5	94	14.2%	8.0–22.2	
>1.5	148	14.7%	9.4–21.0	
Solid component diameter (mm)				0.010
≤23	126	9.4%	4.9–15.6	
>23	118	20.9%	14.0–28.8	
Tumor location (lobes)				0.17
Upper or middle lobes	151	12.4%	7.7–18.3	
Lower lobe	93	19.2%	11.7–28.1	
Tumor location (centrally)				0.0002
Peripheral	209	11.5%	8.0–16.4	
Central	35	35.9%	20.3–51.9	
BED10				0.017
≤113	179	11.7%	7.4–17.0	
>113	65	24.2%	14.3–35.4	

95% CI, 95% confidence interval; PS, performance status; FEV1, forced expiratory volume in one second; BED10, biologically effective dose calculated with an α/β value of 10.

respectively). Fig. 1 shows differences in the cumulative incidence of grade ≥2 RP according to these significant factors. Table 3 shows the results of the multivariate analysis. In the multivariate analysis, a central tumor (hazard ratio [HR] 3.77, 95% CI 1.88–7.55, $p < 0.001$) and interstitial pneumonia (HR 4.88, 95% CI 1.77–13.4, $p = 0.002$) remained significant factors for grade ≥2 RP among several clinical factors.

Table 4 shows the results of the univariate analysis of dosimetric factors. V8, V10, V20, and MLD correlated with the risk of grade ≥2 RP ($p = 0.012$, 0.011, 0.022, and 0.014, respectively), whereas V5 did not ($p = 0.057$). The optimal threshold for dosimetric factors was evaluated using the receiver ROC curve. The ROC curve analysis showed that the optimal diagnostic thresholds for V5, V8, V10, V20, and MLD were 22.2% (the area under the curve [AUC], 0.606), 19.5% (AUC, 0.629), 16.7% (AUC, 0.629), 7.9% (AUC, 0.621), and 5.2 Gy (AUC, 0.623), respectively, as shown in Fig. 2.

The 4-year cumulative incidence of grade ≥2 RP was compared between values above and below the ROC threshold using Gray's test and Table 5 summarizes these results. The 4-year incidence of grade ≥2 RP in the V5 ≤22.2% vs. >22.2% groups, V8 ≤19.5% vs. >19.5% groups, V10 ≤16.7% vs. >16.7% groups, V20 ≤7.9% vs. >7.9% groups, and MLD ≤5.2 Gy vs. >5.2 Gy groups were 10.6% vs. 21.7% ($p = 0.022$), 10.6% vs. 26.2% ($p = 0.003$), 10.2% vs 26.9% ($p = 0.001$), 10.2% vs 27.0% ($p = 0.001$), and 10.6% vs 26.3% ($p = 0.003$), respectively. The results of the Fine-Gray model and ROC curve analysis showed that V10 >16.7% was the best indicator of grade ≥2 RP among dose parameters.

Discussion

We examined the incidence of grade ≥2 RP in 244 patients with early-stage NSCLC treated with SBRT and analyzed risk factors for grade ≥2 RP. The results obtained showed that the incidence of grade ≥2 RP was 15.3% over 4 years, which was consistent with reported rates of 9.4–29% [5–11]. Grade 4 RP was not observed and SBRT-related death (i.e., grade 5) occurred in one patient (0.4%). The incidence of grade ≥4 RP was lower than reported rates of 0.4–16% [5–11]. The reason for this low rate of grade ≥4 RP may be that we delivered >4 fractions and did not use an extremely high BED regimen, such as 60 Gy in 3 fractions.

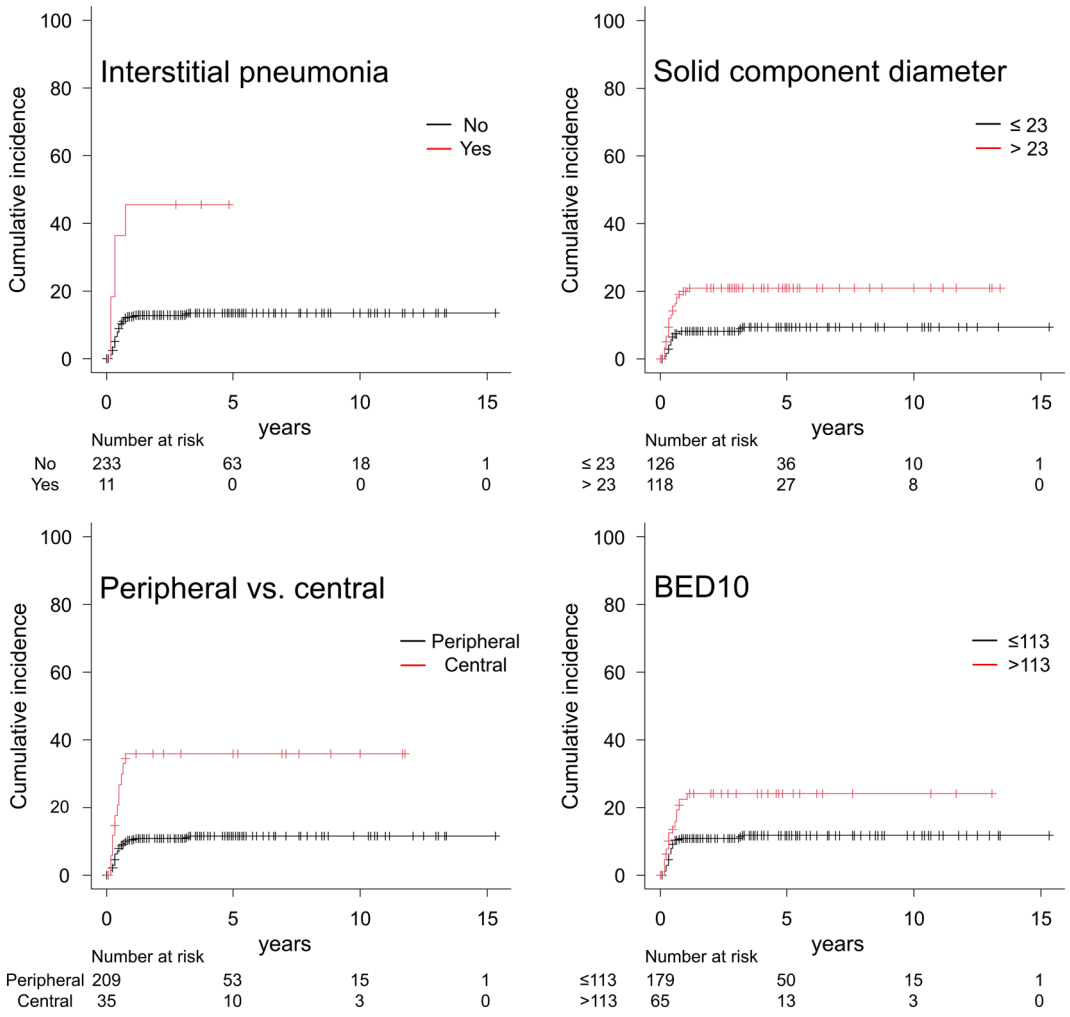

Fig. 1. Differences in the cumulative incidence of grade ≥2 radiation pneumonitis (RP) according to tumor size, a central tumor, interstitial pneumonia, and the biologically effective dose (BED).

Table 3
Multivariate analysis of clinical factors for grade ≥2 radiation pneumonitis.

Factors	HR	95% CI	*p*-value
Age (>77 vs. ≤77)	0.98	0.50–1.92	0.96
Sex (male vs. female)	1.29	0.49–3.41	0.61
PS (2, 3 vs. 0, 1)	0.58	0.16–2.12	0.41
Smoker	1.25	0.42–3.72	0.69
Interstitial pneumonia	4.88	1.77–13.4	0.002
FEV1 (L) (≤1.5 vs. >1.5)	1.04	0.55–2.00	0.90
Solid component diameter (mm) (>23 vs. ≤23)	1.98	0.84–4.65	0.12
Lower lobe vs. upper or middle lobes	1.86	0.97–3.56	0.063
Central vs. peripheral tumors	3.77	1.88–7.55	0.0002
BED10 (>113 vs. ≤113)	1.50	0.69–3.28	0.31

HR, hazard ratio; 95% CI, 95% confidence interval; PS, performance status; FEV1, forced expiratory volume in one second; BED10, biologically effective dose calculated with an α/β value of 10.

Table 4
Dosimetric analysis of grade ≥2 radiation pneumonitis.

Factors	HR	95 %CI	*p*-value
V5 (%)	1.04	1.00–1.08	0.057
V8 (%)	1.06	1.01–1.11	0.012
V10 (%)	1.07	1.02–1.13	0.011
V20 (%)	1.10	1.01–1.19	0.022
Mean lung dose (Gy)	1.26	1.05–1.51	0.014

HR, hazard ratio; 95% CI, 95% confidence interval;
Vn, volume of the lung receiving at least n Gy.

Various factors, including the dosimetric factors of SBRT and patient and tumor characteristics (e.g., the presence of interstitial pneumonia, tumor size, and tumor location), may be associated with the development of RP. The ratio of RP is also affected by the follow-up period. Since the median follow-up period was 48 months for all patients and 59 months for living patients, we consider the present study to have provided reliable data on RP.

The results obtained herein demonstrated that a central tumor and interstitial pneumonia were independent significant factors for the development of grade ≥2 RP. Side effects increase when SBRT is performed on central tumors [18,19]. This predisposition can be attributed to the fact that the treatment of central tumors of the lung often results in constriction or occlusion of the major bronchi, thereby rendering the lung more susceptible to radiation-induced toxicity [20]. Until July 2011, we treated central tumors with a 4-fraction regimen without increasing the number of fractions. Starting from August 2011, we began using dose levels such as 60–64 Gy in 8 fractions as needed depending on the case. The efficacy and safety of SBRT in patients with central tumors have been widely discussed. Bezjak et al. applied a regimen consisting of 50–60 Gy in 5 fractions to patients with central lung tumors and demonstrated good efficacy and safety [21]. Other studies examining the location of lung tumors also reported that right lobe tumors correlated with grade ≥2 RP [22]. In the present study, patients with a central

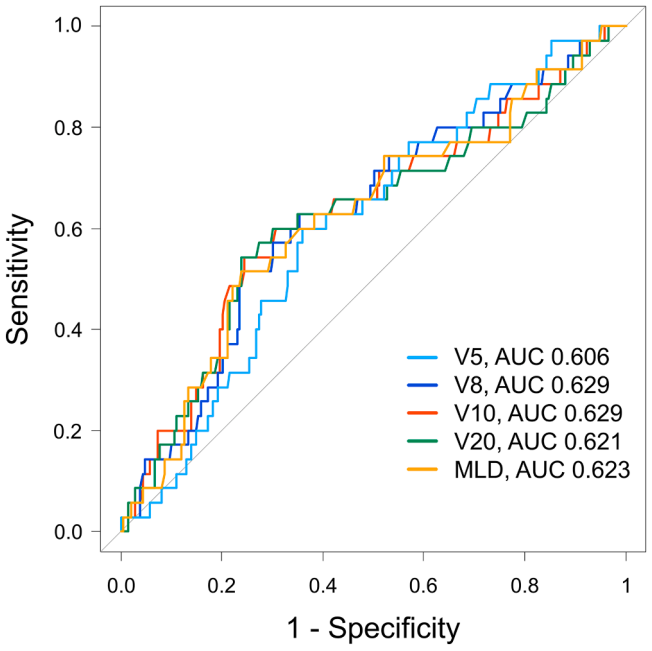

Fig. 2. Receiver operating characteristic (ROC) curves for predicting grade ≥2 radiation pneumonitis (RP) using V5, V8, V10, V20, and the mean lung dose (MLD).

Table 5
Difference in the cumulative incidence of grade ≥2 radiation pneumonitis according to dosimetric parameters.

Factors	Number	4-year incidence	95% CI	*p*-value
V5 (%)				0.022
≤22.2	149	10.6%	6.2–16.4	
>22.2	95	21.7%	13.9–30.6	
V8 (%)				0.003
≤19.5	177	10.6%	6.5–15.9	
>19.5	67	26.2%	16.2–37.4	
V10 (%)				
≤16.7	175	10.2%	6.2–15.4	0.001
>16.7	69	26.9%	16.9–37.9	
V20 (%)				
≤7.9	176	10.2%	6.2–15.4	0.001
>7.9	68	27.0%	16.9–38.0	
Mean lung dose (Gy)				
≤5.2	178	10.6%	6.5–15.9	0.003
>5.2	66	26.3%	16.2–37.4	

Vn, volume of the lung receiving at least n Gy; 95% CI, 95% confidence interval.

tumor had a higher risk of grade ≥2 RP than those with a peripheral tumor (HR 3.77, 95% CI 1.88–7.55, p < 0.001).

Regarding the risk of RP in patients with interstitial pneumonitis, previous studies reported that interstitial pneumonitis or interstitial lung disease was a significant risk factor for symptomatic and severe RP [23–25]. Onishi et al. evaluated the outcomes of SBRT for stage I NSCLC in patients with interstitial lung disease. Among 242 patients, fatal (i.e., grade 5) RP was very high at 6.9%. Ueki et al. demonstrated that prescreening for the findings of interstitial lung disease was important for predicting the risk of RP when planning SBRT. The incidence rates of grade ≥2 RP and grade ≥3 RP were significantly higher in patients with than in those without interstitial lung disease (1-year rate of grade ≥2 RP, 55.0% vs. 13.3%, p < 0.001; 1-year rate of grade ≥3 RP, 10.0% vs. 1.5%, p = 0.020). In the present study, patients with interstitial pneumonia had a higher risk of grade ≥2 RP than those without interstitial pneumonia (HR 4.88, 95% CI 1.77–13.4, p = 0.002).

Tumor size is generally regarded as a significant clinical factor associated with grade ≥2 RP [7,26–28]. The reason for this may be that a larger tumor size increases the lung dose needed. In the present study, the 4-year incidence of grade ≥2 RP in patients with tumor size ≤23 mm vs. >23 mm was 9.4% vs. 20.9% (p = 0.010), as shown in Table 2. However, the multivariate analysis showed that tumor size did not correlate with grade ≥2 RP (HR 1.98, 95% CI 0.84–4.65, p = 0.12). In conventional radiotherapy (e.g., 60 Gy in 30 fractions) for stage III NSCLC, patients with tumors in the lower lobes generally have a higher risk of symptomatic RP than patients with tumors in the upper lobes [29]. In the present study on SBRT, the multivariate analysis showed that patients with tumors in the lower lobes had a slightly higher risk of grade ≥2 RP than those with tumors in the upper and middle lobes (HR 1.86, 95% CI 0.97–3.56, p = 0.063).

The present results indicate that the optimal diagnostic thresholds for V8, V10, V20, and MLD were 19.5%, 16.7%, 7.9%, and 5.2 Gy, respectively. Based on the ROC curve analysis, the AUC for V8 and V10 was the highest at 0.629. A study by the American Association of Physicists in Medicine's Working Group on Biological Effects of SBRT indicated that 10–15% of grade ≥2 RP was acceptable from the SBRT data of 97 studies [30]. In the present study, the cumulative incidence of grade ≥2 RP in the group with V8 and V10 values below the threshold was approximately 10%, as shown in Table 5, which was within the acceptable range. Considering the effects of each dose parameter on grade ≥2 RP in Table 4 and differences in the rate of grade ≥2 RP between below and above each threshold in Table 5, we recommend using the V10 cut-off value as the threshold to predict the development of symptomatic RP. The present results suggest that maintaining the V10 value at ≤16.7% will reduce the risk of symptomatic RP to approximately 10%. There is no clear cut-off value for the lung radiation dose associated with grade ≥2 RP, and this is a topic of ongoing discussion. Matsuo et al. reported a relationship between grade ≥2 RP and lung dose parameters and proposed V25 <4.2% in SBRT [27]. Barriger et al. proposed V20 <4% and MLD <4 Gy to reduce the risk of symptomatic RP in SBRT [5]. Zhao et al. analyzed 88 studies and found that patients with grade ≥2 RP had significantly higher MLD and V20 values, but did not propose their thresholds [28]. In another review on SBRT, Kong et al. examined 97 studies and found that various dose parameters were associated with grade ≥2 RP; however, no clear threshold for the "tolerance dose-volume" level was identified [30]. However, most studies suggested that the incidence of grade ≥2 RP was lower than 10–15% when MLD was <8 Gy in 3–5 fractions and lung V20 was lower than 10–15%, indicating that this treatment is safe [30].

This study had several limitations. The protocol was changed in December 2008, resulting in an increase in the dose and the inclusion of different protocols in the analysis. Furthermore, this was a retrospective study conducted at a single institution, which has inherent biases associated with retrospective studies. Therefore, large-scale multicenter studies are needed to verify the results obtained.

Conclusion

In conclusion, we herein aimed to identify risk factors for symptomatic RP after SBRT in patients with early-stage NSCLC. Among the 244 patients analyzed, 37 developed grade ≥2 RP and the median time for onset was 4 months after SBRT. The 4-year cumulative incidence of grade ≥2 RP was 15.3%. The present study demonstrated that a central tumor and interstitial pneumonia were independent significant clinical factors associated with grade ≥2 RP. The results obtained in this study seem to suggest that V10 ≤16.7% may be the most effective indicator for preventing grade ≥2 RP among dose parameters in SBRT for early-stage NSCLC.

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Role of the funding source

The funding institutions had no role in the design or conduct of the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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