



# Predictive factors of symptomatic radiation pneumonitis in primary and metastatic lung tumors treated with stereotactic ablative body radiotherapy

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**Purpose:** Although stereotactic ablative body radiotherapy (SABR) is widely used therapeutic technique, predictive factors of radiation pneumonitis (RP) after SABR remain undefined. We aimed to investigate the predictive factors affecting RP in patients with primary or metastatic lung tumors who received SABR.

**Materials and Methods:** From 2012 to 2015, we reviewed 59 patients with 72 primary or metastatic lung tumors treated with SABR, and performed analyses of clinical and dosimetric variables related to symptomatic RP. SABR was delivered as 45–60 Gy in 3–4 fractions, which were over 100 Gy in BED when the  $\alpha/\beta$  value was assumed to be 10. Tumor volume and other various dose volume factors were analyzed using median value as a cutoff value. RP was graded per the Common Terminology Criteria for Adverse Events v4.03.

**Results:** At the median follow-up period of 11 months, symptomatic RP was observed in 13 lesions (12 patients, 18.1%), including grade 2 RP in 11 lesions and grade 3 in 2 lesions. Patients with planning target volume (PTV) of  $\leq 14.35$  mL had significantly lower rates of symptomatic RP when compared to others (8.6% vs. 27%;  $p = 0.048$ ). Rates of symptomatic RP in patients with internal gross tumor volume (iGTV)  $> 4.21$  mL were higher than with  $\leq 4.21$  mL (29.7% vs. 6.1%;  $p = 0.017$ ).

**Conclusions:** The incidence of symptomatic RP following treatment with SABR was acceptable with grade 2 RP being observed in most patients. iGTV over 4.21 mL and PTV of over 14.35 mL were significant predictive factors related to symptomatic RP.

**Keywords:** Lung cancer, Radiation pneumonitis, Stereotactic ablative body radiotherapy, Risk factors

## Introduction

Stereotactic ablative body radiotherapy (SABR) has been widely used in the treatment of early-stage primary lung cancers due to its high local control rates of approximately 90% or more [1]. In addition, SABR is also used to treat metastatic lung tumors in the oligometastatic setting as salvage therapy [2]. Along with increasing the application of SABR, we also need

to evaluate the factors relating to SABR associated toxicity, especially radiation pneumonitis (RP) [3,4]. However, there are limited reports on the predictive factors for developing RP after treatment with SABR for primary or metastatic lung tumors. Previous reports showed that the incidence of RP ranges from 9% to 28%, mostly of grade 2 or less [5].

Dose-volume values are potential factors that could predict the development of RP after treatment with SABR.

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In conventional fractionation, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommends a  $V_{20}$  of  $\leq 30\%$  to  $35\%$  and a mean lung dose (MLD) of  $\leq 20$  to  $23$  Gy to reduce the risks of developing RP to less than  $20\%$  [6]. In some studies, size of target,  $V_{20}$ - $V_{25}$  of bilateral lung dose or MLD has been shown as a possible predictive factor of symptomatic pneumonitis [7-11]. However, there are no clear guidelines for the dose-volume limits for treatment with SABR. As tissues irradiated with high fraction doses are expected to show different radiobiologic responses, it is difficult to predict the possibility of developing RP by using traditional dosimetric guidelines [12].

In this study, we aim to determine the clinical and dose-volume factors that affect the development of symptomatic RP after treatment of primary or metastatic lung tumors with SABR, to facilitate the application of SABR in practical settings.

## Materials and Methods

### 1. Study design

This study was approved by the Yonsei University Health System Institutional Review Board (No. 4-2017-0108).

We retrospectively reviewed data on patients with primary and metastatic lung tumors who underwent treatment with SABR from March 2012 to March 2015 in our institution. Inclusion criteria were as follows: age above 20 years, histologically confirmed primary lung cancers and histologically or radiologically diagnosed as metastatic lung tumors, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. For selection of eligible patients, we reviewed medical records, laboratory results, and imaging studies. Finally, we retrieved 72 tumors from 59 patients with primary lung cancers ( $n = 29$ ) and metastatic lung tumors ( $n = 43$ ). The locations of these lung tumors were divided into central versus peripheral lesions, according to the Radiation Therapy Oncology Group (RTOG) 0813 protocol [13]; central lesions are defined as the tumors located at  $< 2$  cm from the proximal bronchial tree, or with a planning target volume (PTV) touching the mediastinum, or both. Non-central lesions are considered as peripheral tumors. Single lesion was treated for 46 patients and 2 lesions for 13 patients. Each of 2 lesions were located in the opposite lung separately and treated with radiotherapy at the interval of 6 months or more. As SABR is characterized by steep dose fall off we decided to analyze by 72 lesions.

### 2. Procedure for SABR

All patients underwent simulation computed tomography (CT) with immobilizing devices, such as, a whole-body vacuum lock or a stereotactic body frame, and an abdominal compressor for respiration control. A shallow breathing technique using Abches (APEX Medical Inc., Tokyo, Japan) was also applicable for patients who were intolerant to the body compressor. If the respiratory diaphragm moved over 1 cm vertically, the abdominal compressor or shallow breath technique using Abches were indicated for LINAC multiport group and intensity-modulated radiotherapy (IMRT) group. All patients underwent four-dimensional CT (4D-CT) scans to track the movement of the target along the respiratory movement. For SABR, the gross tumor volume (GTV) was delineated in every phase of the 4D-CT images, and the PTV was defined as the internal gross tumor volume (iGTV) with a 5- to 10-mm margin. In patients treated with CyberKnife (Accuray Inc., Sunnyvale, CA, USA), whole-body vacuum lock was used for the stability of patients during treatment. However abdominal compressor or Abches was not indicated as CyberKnife can track the tumor along the respiratory movement. PTV for patients treated with CyberKnife group was minimized to 2-3 mm. Four dose schemes were used according to the tumor location and volume, and were administered as 48 Gy in 4 fractions (fx), 45 Gy in 3 fx, 60 Gy in 4 fx, and 60 Gy in 3 fx; these were prescribed to the volumetric PTV and the primary aim was to cover 100% volume of the PTV with 80% isodose line of the prescribed dose. When converted to biologically equivalent dose (BED), these doses are 106 Gy, 113 Gy, 150 Gy, and 180 Gy when the  $\alpha/\beta$  value of the tumor is assumed to be 10 Gy. All patients were treated every other day. Specific prescriptions of SABR doses are shown in Table 1.

Different planning systems according to treatment modality are used and specific name of planning systems are as follows; Pinnacle3 treatment planning system (Philips Radiation Oncology Systems, Milpitas, CA, USA) for LINAC multiport

**Table 1.** Characteristics of stereotactic ablative body radiotherapy ( $n = 72$ )

Dose prescription	LINAC multiport	VMAT	TomoTherapy	CyberKnife
4,800 cGy/4 fx	6	4	2	0
4,500 cGy/3 fx	22	1	2	6
6,000 cGy/4 fx	6	5	3	0
6,000 cGy/3 fx	9	0	3	3

LINAC, linear accelerator; VMAT, volume modulated arc therapy; fx, fraction.

group, RayStation (RaySearch Laboratories AB, Stockholm, Sweden) for volumetric modulated arc therapy (VMAT) group, TomoTherapy treatment planning system (Accuray Inc.) for TomoTherapy group, and Multiplan Treatment Planning System v2.05 (Accuray Inc.) for CyberKnife group.

Normal organ dose constraints for SABR are based on the report of the American Association of Physicists in Medicine Task Group 101 (AAPM TG 101) [14]. Dose constraints for specific organ are as follows: 12 Gy/3 fx and 13 Gy/4 fx for MLD,  $V_{20} < 10\%$  for bilateral lung, 39 Gy for great vessel and 15 Gy for trachea and bronchial tree.

Delivery quality assurances for each patient and each radiation treatment were done before start of treatment, and the use of 4D cone beam CT (Symmetry) or megavoltage CT for accurate delivery were also mandatory. When tumors were treated with CyberKnife (Accuray Inc.), a tracking system was applied. As we do not insert gold fiducial markers, tumors visible on either one or both X-ray cameras were indicated for treatment with CyberKnife. Patients who could not tolerate the duration of treatment and had non-trackable lesions were excluded from the indication for treatment.

### 3. Assessment of radiation pneumonitis

Patients were assessed through regular follow-up visits, and underwent chest CT scans at 1, 3, and 6 months after undergoing treatment with SABR. Per the decision of the physician, positron emission tomography-computed tomography (PET-CT) scans were also available at 3 to 6 months after treatment with SABR, particularly for metastatic lung tumors, to confirm the extent of disease. RP was graded in 5 levels per the Common Terminology Criteria for Adverse Events (CTCAE) ver 4.03 [15,16]. RP was diagnosed based on clinical symptoms and radiologic findings, which develop within 6 months after undergoing treatment with SABR [16,17]. We assessed symptomatic RP that was defined as grade 2 or worse, and analyzed the predictive factors related to symptomatic RP.

### 4. Data analysis and statistical method

We measured PTV (in mL), iGTV (in mL), tumor diameter (in cm), MLD (in Gy), bilateral  $V_5$ ,  $V_{10}$ ,  $V_{15}$ ,  $V_{20}$ ,  $V_{25}$ ,  $V_{30}$ ,  $V_{35}$ , and  $V_{40}$  (in %).  $V_d$  is defined as the volume of the bilateral normal lung that received a radiation dose of over 'd' Gy. Target volumes, lung volumes, and  $V_d$  were measured using MIM software (MIM Software Inc., Cleveland, OH, USA). Potential predictive factors for the occurrence of an RP event were: patient age, sex, the ECOG performance status, smoking history, underlying

pulmonary disease, pathology, tumor location, fraction size and total dose of SABR, PTV, the number of targets, and dosimetric parameters, such as, ipsilateral and contralateral MLD, and  $V_5$ - $V_{40}$  in increments of 5 Gy.

We used median value as the cutoff values of iGTV, PTV, tumor diameter, MLD, and  $V_d$  for statistic analysis. Chi-square test was used for univariable analysis for all variables. Characteristics which are found to be significant and  $V_{20}/V_{25}$  were entered in stepwise method in a binary logistic regression analysis to develop multivariate model. SPSS ver. 20.0 (IBM, Armonk, NY, USA) was used for the analysis, and a p-value of  $< 0.05$  was defined as statistically significant.

## Results

### 1. Characteristics of patients, tumors, and treatments

All baseline characteristics are listed in Table 2. Median duration of follow-up was 11 months (range, 6 to 31 months). Twenty-nine lesions (40.3%) were primary lung cancers, and the others were metastatic sites (59.7%). Forty-two lesions (58.3%) were on the left lung, and the remaining were on the right side. Eighteen lesions (25%) were in the central area. Forty-six patients were treated for single lesion with SABR, while 13 patients were treated for 2 lung lesions. The 2 lesions were located in the opposite lung and they were treated with SABR at intervals of more than 6 months. Median iGTV was 4.21 mL (range, 0.23 to 36.43 mL) and the PTV was 14.35 mL (range, 3.33 to 78.61 mL).

Median time of treatment was 7 days (range, 4 to 12 days). The individual radiation treatment schemes were as follows: 31 lesions treated with 45 Gy in 3 fx, 12 lesions with 48 Gy in 4 fx, 14 lesions with 60 Gy in 4 fx, and 15 lesions with 60 Gy in 3 fx. All irradiated doses to normal organs were acceptable, according to the report of AAPM TG 101.

### 2. Incidence of symptomatic RP

During the median follow-up period, symptomatic RP developed in 13 lesions (12 patients, 18.1%). Of these patients, 11 had grade 2 RP and two had grade 3 RP with a median onset of 14 weeks (range, 4 to 24 weeks) from the starting date of radiotherapy. No patients showed RP of grade 4 or higher. All patients with RP over grade 2 achieved symptomatic relief with conservative management and the use of steroid agents. One patient with grade 3 RP is shown in Fig. 1 with radiologic image.

**Table 2.** Characteristics of patients (n = 59) and tumors (n = 72)

Characteristic	Value
Age (yr)	63 (22–86)
Sex	
Male	40 (67.8)
Female	19 (32.2)
Site of primary cancer	
Lung	29 (49.2)
Colorectum	15 (25.4)
Head and neck	6 (10.2)
Hepatobiliary	4 (6.8)
Genitourinary	4 (6.8)
Malignant melanoma	1 (1.7)
Number of treated lung lesions (n = 59 patients)	
1	46 (78.0)
2	13 (22.0)
Smoking history	
Yes	33 (55.9)
No	26 (44.1)
Any pulmonary disease	
Yes	23 (39.0)
No	36 (61.0)
ILD	2 (3.4)
No ILD	57 (96.6)
Lobes of lung	
RUL	13 (18.1)
RML	7 (9.7)
RLL	10 (13.9)
LUL	24 (33.3)
LLL	18 (25)
Location of lung	
Central	18 (25)
Peripheral	54 (75)
Lung mass size profiles	
Tumor diameter (cm)	2.0 (0.8–4.1)
iGTV (mL)	4.21 (0.23–36.43)
PTV (mL)	14.35 (3.33–78.61)

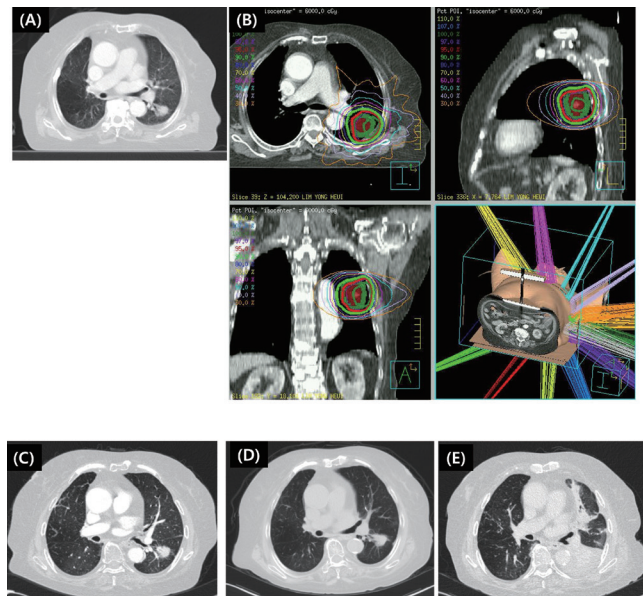
Values are presented as median (range) or number (%).

ILD, interstitial lung disease; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; iGTV, internal gross tumor volume; PTV, planning target volume.

### 3. Predictive factors for symptomatic RP

The predictive factors associated with the development of RP were analyzed, and both iGTV and PTV were established as significant predictive factors. The detailed analyses of clinical factors related to symptomatic RP are shown in Table 3, and that of dosimetric factors in Table 4.

In multivariate analysis, there were significant differences in the incidence of symptomatic RP in patients with PTV of  $\leq 14.35$  mL compared to those with PTV of  $> 14.35$  mL (8.6% vs. 27%;  $p = 0.048$ ). Additionally iGTV of  $\leq 4.21$  mL was significant cut off value for the reduced incidence of RP (6% vs. 30%;  $p = 0.017$ ) (Table 5). Other factors such as patient age, sex,



**Fig. 1.** An 82-year-old woman with asthma was diagnosed with adenocarcinoma of the left lower lung, which was classified as cT1bN0M0 per TNM system of classification (A). Due to old age and impaired cardiac function, SABR was delivered as a total dose of 60 Gy in 3 fractions, as an alternative to surgery. SABR was delivered with 14 non-coplanar beams to the lesion in the left lower lung (B). She underwent a CT scan of the chest at 1 month (C) and 3 months (D) after undergoing treatment with SABR. She had no complaints, and both CT scans showed no abnormal signs related to radiation pneumonitis. However, after 5 months of SABR, she developed dyspnea, and underwent a CT scan of her chest for the evaluation of dyspnea. Newly developed pleural effusion with consolidation was observed, and diagnosed as radiation pneumonitis of grade 3 (E). SABR, stereotactic ablative body radiotherapy; CT, computed tomography.

the ECOG performance status, smoking history, underlying pulmonary disease, pathology, tumor location, fraction size and total dose of SABR, MLD, the number of treated targets and tumor diameter did not show association with the development of symptomatic RP. Dosimetric factors, including  $V_5$ ,  $V_{10}$ ,  $V_{15}$ ,  $V_{20}$ ,  $V_{25}$ ,  $V_{30}$ ,  $V_{35}$ , and  $V_{40}$ , were not significant predictive factors that influenced symptomatic RP.

The incidence of pneumonitis between patients with single lesion and 2 lesions was not different (21.7% vs. 11.5%;  $p = 0.352$ ).

### 4. Dose-volume values and the incidence of RP according to the radiation treatment modalities

We analyzed the incidence of symptomatic RP and dose-volume factors according to the 4 treatment modalities: the

**Table 3.** Predictive factor univariate analysis of symptomatic RP

Variable	RP	No RP	p-value
Sex			0.476
Male	9 (22.5)	31 (77.5)	
Female	3 (15.8)	16 (84.2)	
Smoking history			0.488
Yes	8 (24.2)	25 (75.8)	
No	4 (15.4)	22 (84.6)	
Any pulmonary history			0.725
Yes	4 (17.4)	19 (82.6)	
No	8 (22.2)	28 (77.8)	
Lung site			0.325
Right	7 (23.3)	23 (66.7)	
Left	6 (14.3)	36 (85.7)	
Location			0.860
Central	3 (16.7)	15 (83.3)	
Peripheral	10 (18.5)	44 (81.5)	
Dose schemes			0.583
4,500 cGy/3 fx	8 (25.8)	23 (74.2)	
4,800 cGy/4 fx	1 (8.3)	11 (91.7)	
6,000 cGy/4 fx	2 (14.3)	12 (85.7)	
6,000 cGy/3 fx	2 (13.3)	13 (86.7)	
Mean lung dose (Gy)			0.541
<3.2	5 (13.9)	31 (86.1)	
≥3.2	8 (22.2)	28 (77.8)	
iGTV (mL)			0.013
≤4.21	2 (6.1)	34 (93.9)	
>4.21	11 (29.7)	25 (70.3)	
PTV (mL)			0.042
≤14.35	3 (8.6)	33 (91.4)	
>14.35	10 (27.0)	26 (73.0)	
Tumor diameter (cm)			0.131
≤2.0	4 (11.1)	32 (88.9)	
>2.0	9 (25.0)	27 (75.0)	
Number of treated lung lesions			0.352
1	10 (21.7)	36 (78.3)	
2	3 (11.5)	23 (88.5)	
Treatment modality			0.138
LINAC multiport	11 (25.6)	32 (74.4)	
IMRT (VMAT and TomoTherapy)	2 (10)	18 (90)	
CyberKnife	0 (0)	9 (100)	

Values are presented as number (%).

RP, radiation pneumonitis; fx, fraction; iGTV, internal gross tumor volume; PTV, planning target volume; LINAC, linear accelerator; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy.

LINAC multiport, VMAT, TomoTherapy, and CyberKnife with tumor tracking system. There was no difference of incidence of symptomatic RP and dosimetric values between modalities. No patients who were treated with CyberKnife suffered from symptomatic RP, although the PTV, MLD, and  $V_5-V_{40}$  in this group were not significantly different from the LINAC multiport group.

**Table 4.** Predictive factor univariate analyses of symptomatic RP according to  $V_5-V_{40}$  of bilateral normal lung parenchyme (n = 72)

Variable	RP	No RP	p-value
$V_5$ (%)			1.0
<15.00	6 (16.7)	30 (83.3)	
≥15.00	7 (19.4)	29 (80.6)	
$V_{10}$ (%)			0.541
<8.76	5 (13.9)	31 (86.1)	
≥8.76	8 (22.2)	28 (77.8)	
$V_{15}$ (%)			0.541
<5.27	5 (13.9)	31 (86.1)	
≥5.27	8 (22.2)	28 (77.8)	
$V_{20}$ (%)			0.222
<3.56	4 (11.1)	32 (88.9)	
≥3.56	9 (25.0)	27 (75.0)	
$V_{25}$ (%)			0.222
<2.58	4 (11.1)	32 (88.9)	
≥2.58	9 (25.0)	27 (75.0)	
$V_{30}$ (%)			1.0
<1.78	6 (16.7)	30 (83.3)	
≥1.78	7 (19.4)	29 (80.6)	
$V_{35}$ (%)			1.0
<1.33	6 (16.7)	30 (83.3)	
≥1.33	7 (19.4)	29 (80.6)	
$V_{40}$ (%)			1.0
<1.04	6 (16.7)	30 (83.3)	
≥1.04	7 (19.4)	29 (80.6)	

Values are presented as number (%).

RP, radiation pneumonitis;  $V_d$  (%), volume of bilateral normal lung that received a dose of over 'd' Gy.

## Discussion and Conclusion

Acute RP is a common side effect of radiation treatment that can significantly affect the quality of life of patients, by inducing chronic respiratory problems and sometimes death, therefore, many studies have reported the predictive factors related to RP [18-21]. However, in SABR or SBRT, there is no clear consensus for predicting the risk of RP in relation to the clinical and dosimetric factors. In this study, we showed that a value of iGTV of over 4.21 mL and PTV of over 14.35 mL were significant factors for developing acute symptomatic RP after treatment of primary lung cancers and metastatic lung tumors with SABR.

Some recent studies have suggested predictive factors of RP after treatment with SABR for lung tumors. We have summarized previous studies that dealt with the dose-volume factors related to RP in Table 6. A group from the Netherlands Vrije University reported that almost three times the incidence of symptomatic RP (10% vs. 28%) appeared after treatment with SABR when the PTV was over 80 cm<sup>3</sup> [22]. In 251 patients of node negative stage I-IIb non-small cell lung cancers (NSCLCs), Barriger et al. [7] reported predictive factors of grade



**Table 5.** Multivariate analysis of predictive factor analyses of symptomatic RP (n = 72)

Variable	RP	No RP	p-value
Tumor diameter (cm)			0.342
≤2.0	4 (11.1)	32 (88.9)	
>2.0	9 (25.0)	27 (75.0)	
iGTV (mL)			0.017
≤4.21	2 (6.1)	34 (93.9)	
>4.21	11 (29.7)	25 (70.3)	
PTV (mL)			0.048
≤14.35	3 (8.6)	33 (91.4)	
>14.35	10 (27.0)	26 (73.0)	
Mean lung dose (Gy)			0.754
<3.2	5 (13.9)	31 (86.1)	
≥3.2	8 (22.2)	28 (77.8)	
V <sub>20</sub> (%)			0.342
<3.56	4 (11.1)	32 (88.9)	
≥3.56	9 (25.0)	27 (75.0)	
V <sub>25</sub> (%)			0.342
<2.58	4 (11.1)	32 (88.9)	
≥2.58	9 (25.0)	27 (75.0)	
Treatment modality			0.416
LINAC multiport	11 (25.6)	32 (74.4)	
IMRT (VMAT, TomoTherapy)	2 (10)	18 (90)	
CyberKnife	0 (0)	9 (100)	

Values are presented as number (%).

RP, radiation pneumonitis; iGTV, internal gross tumor volume; PTV, planning target volume; V<sub>d</sub> (%), volume of bilateral normal lung that received a dose of over 'd' Gy; LINAC, linear accelerator; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy.

≥2 RP when treated with SABR. In this study, MLD >4 Gy and V<sub>20</sub> >4% were significant factors for RP, although PTV was not a significant risk factor for the development of symptomatic RP. In addition, Matsuo et al. [5] showed that PTV, V<sub>20</sub>, and V<sub>25</sub> were independent predictive factors of symptomatic RP for patients diagnosed with stage I NSCLCs who received SABR with 48 Gy in 4 fractions. Interestingly, there was a study of Ong et al. [23] reporting that contralateral lung V<sub>5</sub> significantly affect the development of symptomatic RP. Compared to other reported literatures in Table 6, crude rate of 18.1% of grade ≥2 pneumonitis in our study is somewhat higher. This can be explained by a strict symptom control in our clinic. All patients presenting clinical symptoms with suspicious radiologic changes at follow-up are recommended to use steroid agents and this might have resulted in an overestimation of the incidence. In agreement with other studies, there were limited incidence of grade >2 pneumonitis in our study also; two cases of grade 3 RP and no grade 4 or 5.

In our study, only tumor and target size were significant factors related to symptomatic RP. Meaning of other dose volume factors such as MLD and V<sub>5</sub>-V<sub>40</sub> (%) might have

been diluted as the prescription dose and fraction number were different for each lesion treatment modality was not a significant predictive factor for RP. PTV size between LINAC multiport group and IMRT group was significantly different (20.0 mL vs. 11.7 mL; p = 0.019) and this is the reason that more people suffered symptomatic RP in LINAC multiport group, without significance (25.6% vs. 10.9%; p = 0.19).

As we mentioned above, many studies failed to suggest common dose volume factors of cutoff values which are critical to the development of RP. Thus, in general, both the volume reduction of the target (significant predictive factor in our study) and the dose restriction for bilateral lungs after treatment of lung tumors with SABR is recommended. In practice, based on other reports including those of our study, most radiation oncologists are trying to reduce the PTV and irradiated dose to normal lungs in many aspects. Firstly, 4D-CT simulation is gaining popularity for targeting moving organs, especially the lungs. The 4D-CT leads to 10 phases of images per the respiration cycle, and it reflects the movement of the target organs. These moving images may increase the certainty of the target, and lead to a reduction of unnecessary PTV margins. To specifically reduce the respiratory movement, the use of a body compressor or shallow breathing technique with Abches is also applicable. In this study, such devices were used with the vertical movement of the respiratory diaphragm over 1 cm, for selected patients who could tolerate them. Furthermore, 4D cone beam CT was available before delivery and this makes it possible for us to reduce the PTV margins [24,25]. Finally, the technique of real-time tumor tracking was applied to the trackable tumor using CyberKnife, which can reduce the safety margins [26]. Despite the small number of cases in our study, we found that patients who are treated with CyberKnife did not suffer from symptomatic RP, even though the PTVs, V<sub>5</sub>-V<sub>40</sub> values, and small fraction numbers were comparable with those of the LINAC multiport group.

Additionally, we found that the rate of incidence of RP above grade 3 was very low (3%) within 6 months after treatment with SABR, and this rate is comparable to that observed in other studies [27,28]. When the rates of toxicities of over grade 3 are compared to other modalities of treatment, such as surgery, SABR emerges as a potentially safer and more tolerable choice for patients. Chang et al. [1] reported the occurrence of grade 3-5 toxicities corresponding to treatment methods in stage I NSCLCs. In the group of patients treated with SABR, three patients (10%) had grade 3 toxicities, two had dyspnea or cough, three had chest wall pain, and one had a rib fracture. In the group of patients that underwent

**Table 6.** Studies of RP after treatment with SABR

Author	Year	No. of patients	SBRT scheme	Incidence of RP	Factor related to RP
McGarry et al. [28]	2005	47	24–72 Gy/3 fx	8.5% 2.1% grade 2 6.4% grade 3	-
Ricardi et al. [9]	2009	60	45 Gy/3 fx or 26 Gy/1 fx	14.3% grade 2 or worse	MLD
Timmerman et al. [30]	2010	55	60 Gy/3 fx	3.6% grade 3	Central lesion
Guckenberger et al. [10]	2010	59	26 Gy/1 fx or 37.5 Gy/3 fx	18.6%	MLD and V <sub>2.5</sub> -V <sub>50</sub>
Ong et al. [23]	2010	18	55 Gy/5 fx or 60 Gy/8 fx	27.8% grade 2 or worse	V <sub>5</sub> (contralateral lung)
Stauder et al. [29]	2011	84	32–60 Gy/3–5 fx	12.5% grade 2 or worse	PTV maximal dose
Barriger et al. [7]	2012	251	24–66 Gy/3–5 fx	9.4% grade 2 or worse	MLD and V <sub>20</sub>
Matsuo et al. [5]	2012	74	48 Gy/4 fx	20.3% grade 2 or worse	PTV, V <sub>20</sub> , V <sub>25</sub>
Nagata et al. [27] (JCOG 0403)	2015	169	48 Gy/4 fx	6.5%	-
Current study	2017	59	45–60 Gy/3–4 fx	5.9% grade 3 0.6% grade 4 18.1% grade 2 or 3	iGTV, PTV

RP, radiation pneumonitis; SABR, stereotactic ablative body radiotherapy; MLD, mean lung dose; fx, fraction; V<sub>d</sub>, volume of bilateral normal lung that received a dose of over 'd' Gy; iGTV, internal gross tumor volume; PTV, planning target volume.

lobectomies, one patient died of surgical complications, and 12 (44%) developed grade 3–4 toxicities related to treatment.

This study has some limitations. Firstly, the follow-up period in this study is short. However, it appears that a median follow-up period of 11 months is enough, upon the consideration that symptoms of RP generally appear at a median time of 5 months after treatment with SABR [8,10]. Secondly, deficient data on pulmonary function tests and pre-radiotherapy interventions may have compromised the quality of our data set. We could not suggest the performance of quantitative pulmonary function tests on patients before and after undergoing SABR because the pulmonary function test is not a mandatory examination for patients with metastatic tumors and for those who do not express discomfort or other symptoms. Thirdly, we lack data on patient previous thorax area surgery history which can damage lung parenchyme and induce fibrotic changes of lung. Thus our data cannot verify whether interventions or surgeries themselves influenced the development of RP.

In conclusion, the incidence of symptomatic RP following treatment with SABR was acceptable, with most patients showing RP of grade 1 or 2; there were no patients with grade 4 RP. Additionally, we found that both the large PTV and iGTV were predictive factors related to the development of symptomatic RP after treatment with SABR. Therefore, selected patients with small volumes of lung tumors, advanced RT techniques, such as respiratory gating and tracking systems, and appropriate dose prescriptions corresponding to tumor sizes are recommended for safer treatments with SABR. In the future, clinical trials with larger number of patients or meta-analyses of previous studies would be helpful for establishing the indications of the predictive factors that affect RP in lung tumors treated with SABR.

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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