BJR https://doi.org/10.1259/bjr.20160560

Received: 21 June 2016 | Revised: 22 September 2016 | Accepted: 4 October 2016

Cite this article as:
Nakamura M, Nishimura H, Nakayama M, Mayahara H, Uezono H, Harada A, et al. Dosimetric factors predicting radiation pneumonitis after CyberKnife stereotactic body radiotherapy for peripheral lung cancer. *Br J Radiol* 2016; **89**: 20160560.

FULL PAPER

Dosimetric factors predicting radiation pneumonitis after CyberKnife stereotactic body radiotherapy for peripheral lung cancer

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MN and HN made substantial contributions to the conception and design of the study. Masaki N aided in the collection of data, statistical analysis and drafting of the article. MN, HM, HU, AH, NH, YE and TI assisted in the acquisition of data. HN and RS helped to draft the article.

Objective: The aims of this study were to investigate the frequency of symptomatic radiation pneumonitis (RP) after CyberKnife lung stereotactic body radiotherapy (SBRT) and to evaluate predictive factors of symptomatic RP.
Methods: 56 patients with peripheral non-small-cell lung cancer were treated using the CyberKnife® VSI™ System (Accuracy Inc., Sunnyvale, CA) between May 2013 and September 2015. Total radiation doses ranged from 48 to 56 Gy, as delivered in four equal fractions. Symptomatic RP was defined as a grade of ≥2. Predictive factors for symptomatic RP were evaluated using univariate and multivariate analyses.
Results: With a median follow-up duration of 12.5 months (range, 3–27 months), symptomatic RP was observed in 6 (10.7%) of the 56 patients. In the univariate analysis, percent vital capacity ($p < 0.05$), maximum tumour diameter ($p < 0.05$), gross tumour volume ($p < 0.05$), planning target volume ($p < 0.01$), mean lung dose ($p < 0.01$) and a normal lung volume receiving 5–50 Gy of radiation (V_{5-50}) ($p < 0.01$) were identified as significant predictive factors for symptomatic RP. In the multivariate analysis, only a V_{25} >3.4% ($p = 0.011$) was identified as a significant predictive factor of symptomatic RP.
Conclusion: The incidence of symptomatic RP after CyberKnife SBRT was almost identical to the incidences reported in the linear accelerator-based SBRT. A significant association was observed between a V_{25} >3.4% and the risk of developing symptomatic RP.
Advances in knowledge: This is the first report that has investigated prognostic factors for symptomatic RP after CyberKnife SBRT for lung cancer. The newly developed scoring system may help to predict symptomatic RP.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is considered a treatment option for Stage I non-small-cell lung cancer, if patients are inoperable owing to comorbidities or refusal of surgical resection.[1,2] Recently, a meta-analytic comparison of SBRT and surgery was performed, and the indication of SBRT has broadened to include patients who are operable.[3] However, lung tumours are prone to motion (mainly caused by respiratory breathing) that affects both intrafractional and interfractional radiation delivery. The motion tends to be small in tumours located in the apex or attached to the chest wall, but can be more pronounced in smaller, peripheral tumours. These tumours frequently move >1 cm (occasionally up to 3 cm) between deep inspiration and deep expiration.[4] Covering this range of motion, conventional radiotherapy has generally been used with wide safety margins, at a cost of larger irradiated volume of healthy lung. Real-time tumour tracking system precisely identifies the tumour location and repositions the radiation beam during respiration. To use this system, CyberKnife SBRT requires smaller safety margins than conventional SBRT.[5]

Radiation pneumonitis (RP) is a major concern for patients undergoing lung radiotherapy. It is uncertain whether predictive factors of RP after conventional SBRT are the same as predictive factors of RP after CyberKnife SBRT because the dose distributions differ between these techniques. Ding et al[6] noted that while CyberKnife and conventional SBRT systems both provide adequate dose coverage for the target tumour, their plans involve different lung doses, depending on the location of the tumour. Furthermore, only a few studies have evaluated dosimetric factors of RP induced by CyberKnife SBRT, although treatment efficacy with CyberKnife has been widely discussed.[3,7] The aims of this study were to investigate the frequency of symptomatic RP after CyberKnife lung SBRT and to evaluate predictive factors of symptomatic RP.

METHODS AND MATERIALS

Patients

This study included 56 patients who had peripheral non-small-cell lung cancer who were treated using the CyberKnife® VSI™ System (Accuracy Inc., Sunnyvale, CA) between May 2013 and September 2015 at the Kobe Minimally Invasive Cancer Center (Hyogo, Japan). The study cohort included patients who had a history of interstitial pneumonia (IP) without the active condition (continuous steroids required). Patients with ≥2 lung tumours, a maximum tumour diameter (MTD) of >50 mm or a history of lung irradiation were excluded. Initial staging was performed using an ^{18}F-fludeoxyglucose positron emission tomography/CT scan. Tumour histology was proved by transthoracic or bronchoscopic biopsy. In instances where histology could not be proved, patients were treated when tumour growth was observed. A summary of the patient characteristics is provided in Table 1. The median age was 78 years (range, 41–92 years). 8 (14.3%) patients had an Eastern Cooperative Oncology Group performance status of 2. None of the patients had a performance status >2. 7 (12.5%) patients had a history of IP.

Table 1. Patient characteristics

Characteristics	All patients ($n = 56$)
Age (years)	
Median (range)	78 (41–92)
Gender	
Male	39
Female	17
ECOG PS	
0–1	48
2	8
History of IP	7
Emphysema	23
Previous lung operation	13
Operable case	18
Histologic type	
Adenocarcinoma	25
SqCC	10
Other	4
Unknown	17
Pack years	
Median (range)	40 (0–200)

ECOG, Eastern Cooperative Oncology Group; IP, interstitial pneumonia; PS, performance status; SqCC, squamous cell carcinoma.

Stereotactic body radiotherapy procedure

A spine tracking system was used during the treatment of nine tumours that were located in the apical region and exhibited small respiratory movement. The spine tracking system is able to detect and track the bony anatomy of the spine to guide beam targeting without synchronizing respiratory movement. A directed tumour tracking system was used during the treatment of 22 tumours that were >15 mm in diameter, located in the periphery and visible in the orthogonal X-ray images created by the CyberKnife VSI System. A fiducial tracking system was used during the treatment of 25 tumours. In this system, the intravascular method was used to place one fiducial marker close to the tumour. The motion of red light-emitting diodes attached to the patient chest wall was then registered and correlated to the location of the implanted fiducial, as determined by a series of orthogonal X-ray images taken during respiration. A thin-sliced four-dimensional CT scan without contrast was recorded with 1-mm slices. The organs at risk (*i.e.* the spinal cord, normal lung tissue, heart and oesophagus) were contoured on the CT scan in the resting respiratory level. Gross tumour volumes (GTVs) were contoured on each phase of the four-dimensional CT scan registered with the fiducial marker in the fiducial tracking system, the tumour itself in the tumour tracking system and the vertebral body in the spine tracking system. The internal target volume was defined as a fusion of all GTVs at each phase of the four-dimensional CT scan. The planning target volume (PTV) equalled the internal target volume plus 2–6 mm. Treatments were planned using the MultiPlan 4.6.0 treatment planning software (Accuracy Inc., Sunnydale, CA). Radiation doses were calculated using the Monte Carlo algorithm. Treatment consisted of a 6-MV radiation beam using one or two circular collimator cones. Total radiation doses ranged from 48 to 56 Gy (48 Gy: $n = 20$, 54 Gy: $n = 2$ and 56 Gy: $n = 34$), as delivered in four equal fractions. The radiation dose was prescribed to the 75–85% isodose line of the PTV, covering ≥95% volume. However, an underdosage of the PTV was permitted to protect the constraints of the organ at risk. Four-fraction radiotherapy was selected in accordance with the Japan Clinical Oncology Group 0403 study.[8]

Toxicity

Toxicity was graded according to the Common Terminology Criteria for Adverse Events, v. 4.0. RP was diagnosed with radiological findings (ground-glass opacities and/or consolidation) by agreement of radiologist and radiation oncologist.[9] Differential diagnoses, such as infection or recurrence, were excluded. Symptomatic RP was defined as a grade of ≥2. The following dose–volume metrics were assessed: the mean lung dose (MLD) and V_5, V_{10}, V_{15}, V_{20}, V_{25}, V_{30}, V_{35}, V_{40}, V_{45} and V_{50}, where V_x is defined as the normal lung volume (both lungs excluding the GTV) receiving x Gy of radiation.

Statistical analyses

All statistical analyses were conducted using R software, v. 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). The correlation coefficient was evaluated using the Spearman's rank correlation coefficient. Univariate (Fisher's exact test, two-sample *t*-test, Wilcoxon signed-rank test and receiver-operating characteristic curve analysis) and multivariate (logistic regression) analyses were performed to evaluate predictive factors for symptomatic RP. The multivariate analysis included factors that had shown significant associations ($p < 0.05$) in the univariate analyses. When faced with factors that were correlated with each other, we selected the factor with the highest area under the curve in receiver-operating characteristic (ROC) curve analyses. Cumulative incidence curves of symptomatic RP were generated using the Kaplan–Meier method. *p*-values of <0.05 were considered statistically significant.

Ethical approval

All study participants provided informed, written consent. The study protocol was approved by the research ethics committee of our institution [reference number: 2016-(kenkyu05)-03]. The research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Table 2. Patient characteristics and univariate analysis of factors related to symptomatic radiation pneumonitis (RP)

Variables	All patients ($n = 56$)	RP < Grade 2 ($n = 50$)	RP ≥ Grade 2 ($n = 6$)	*p*-value
Age (years)				
Median (range)	78 (41–92)	78 (41–92)	77 (66–85)	0.916
Gender				
Male	39	34	5	0.656
Female	17	16	1	
ECOG PS				
0–1	48	43	5	1
2	8	7	1	
History of IP	7	5	2	0.158
Emphysema	23	20	3	0.681
Previous lung operation	13	11	2	0.615
Operable case	18	17	1	0.652
Histologic type				
Adenocarcinoma	25	23	2	0.682
SqCC	10	9	1	1
Other	4	2	2	0.053
Unknown	17	16	1	0.656
Pack years				
Median (range)	40 (0–200)	40 (0–200)	50 (33–80)	0.763
Previous FEV 1.0%				
Mean (range)	76.9 (16.7–136.9)	79.9 (16.7–136.9)	59.7 (39.4–78.3)	0.1
Previous VC %				
Mean (range)	90.4 (53.5–152.2)	93.2 (58.1–152.2)	74.8 (53.5–102.3)	0.034
Tumour location				
Anterior	17	15	2	1
Posterior	39	35	4	
Superior	29	28	1	0.096
Inferior	27	22	5	
Distance between the tumour and chest wall (mm)				
Median (Range)	7.0 (0–45)	7.0 (0–45)	4.5 (0–23)	0.648

ECOG, Eastern Cooperative Oncology Group; FEV, forced expiration volume; IP, interstitial pneumonia; PS, performance status; SqCC, squamous cell carcinoma; VC, vital capacity.

RESULTS

In total, 56 patients with peripheral lung cancer were treated using the CyberKnife System and included in this study. With a median follow-up duration of 13 months (range, 3–27 months), symptomatic RP was observed in 6 (10.7%) patients, consisting of 5 patients with Grade 2 RP and 1 patient with Grade 3 RP. RP was diagnosed based on symptoms and radiological findings. Grade 1 RP (with radiological findings without symptoms) was observed in 45 (80.4%) patients. The median duration to symptomatic RP was 3 months (range, 1–8 months). Two patients developed symptomatic RP in 1 month; both of them had a history of IP. 5 (8.9%) patients complained of a Grade 1

Table 3. Dose–volume metrics and univariate analysis of factors related to symptomatic radiation pneumonitis (RP)

Metrics	All patients ($n = 56$)	RP < Grade 2 ($n = 50$)	RP ≥ Grade 2 ($n = 6$)	p-value
MTD (mm)				
Mean (range)	22.0 (5–42)	21.2 (5–37)	28.8 (15–42)	0.019
GTV (cm^3)				
Median (range)	5.8 (0.4–29)	5.35 (0.4–21.4)	13.35 (3–29)	0.016
PTV (cm^3)				
Median (range)	23.8 (2.2–59.8)	22.05 (2.2–55.0)	56.7 (15–59.8)	0.003
Total dose				
Median (range)	56 (48–56)	56 (48–56)	56 (48–56)	0.816
Maximum dose (Gy)				
Mean (range)	66.5 (57.8–77.8)	66.5 (57.8–77.8)	66.6 (59.9–70.7)	0.967
Normal lung volume (ml)				
Median (range)	2651 (1230–5383)	2655 (1612–5383)	2480.5 (1230–3825)	0.375
MLD (Gy)				
Median (range)	3.2 (1.1–8.0)	2.95 (1.1–5.6)	5.05 (3.8–8.0)	0.001
V_{50} (%)				
Median (range)	0.4 (0.1–1.2)	0.4 (0.1–1.2)	0.9 (0.4–0.8)	0.006
V_{45} (%)				
Median (range)	0.7 (0.1–1.8)	0.6 (0.1–1.8)	1.4 (0.7–1.6)	0.003
V_{40} (%)				
Median (range)	0.9 (0.2–2.4)	0.9 (0.2–2.4)	1.75 (1.1–2.2)	0.001
V_{35} (%)				
Median (range)	1.2 (0.3–3.1)	1.1 (0.3–3.1)	2.35 (1.4–3.1)	0.001
V_{30} (%)				
Median (range)	1.55 (0.4–4.3)	1.35 (0.4–3.9)	3.15 (1.9–4.3)	<0.001
V_{25} (%)				
Median (range)	2.05 (0.6–5.8)	1.80 (0.6–5.1)	4.45 (2.6–5.8)	<0.001
V_{20} (%)				
Median (range)	2.85 (0.8–8.2)	2.55 (0.8–6.9)	6.75 (3.6–8.2)	0.001
V_{15} (%)				
Median (range)	4.45 (1.1–14.3)	4.05 (1.1–11.0)	10.55 (5.3–14.3)	0.001
V_{10} (%)				
Median (range)	8.25 (1.5–31.8)	7.95 (1.5–19.7)	16.25 (9.3–31.8)	0.002
V_5 (%)				
Median (range)	18.1 (2.6–32.6)	17.3 (2.6–32.6)	26.95 (17.0–32.2)	0.008

GTV, gross tumour volume; MLD, mean lung dose; MTD, maximum tumour diameter; PTV, planning target volume; V_x, normal lung volume receiving x Gy of radiation.

cough, 4 (7.1%) patients were diagnosed with Grade 2 rib fractures and 2 (3.6%) patients exhibited signs of Grade 1 chest pain without rib fractures.

As presented in Table 2, we performed univariate analyses of various patient characteristics related to symptomatic RP. Of the patient characteristics that were assessed in the univariate analyses, percent vital capacity (VC) ($p < 0.05$) was identified as the only significant predictive factor of symptomatic RP. Tumour in the inferior lung also tended to be associated with symptomatic RP, but analysis revealed that the association was non-significant ($p = 0.096$).

A summary of the dose–volume metrics is provided in Table 3. The lung metrics (MLD and V_{5-50}) and PTV correlated with one another, with correlation coefficients of between 0.51 and 0.99. Correlations between GTV MTD and the lung metrics were relatively weak, with correlation coefficients of between 0.34 and 0.63. According to the results of the univariate analyses, MTD ($p < 0.05$), GTV ($p < 0.05$), PTV ($p < 0.01$), MLD ($p < 0.01$) and V_{5-50} ($p < 0.01$) were identified as significant predictive factors of symptomatic RP (Table 3). Among the dose–volume metrics, V_{25} exhibited the highest area under the curve value (0.923) in the ROC analyses (optimal cut-off value: 3.4%) (Table 4). Symptomatic RP was observed in 41.7% of patients with a V_{25} of >3.4% and in 2.3% of the remaining patients ($p < 0.01$) (Figure 1a).

Percent VC and a V_{25} of >3.4% were included as covariates in the multivariate analysis of symptomatic RP. Based on the results of this analysis, only a V_{25} of >3.4% ($p = 0.011$) was confirmed as an independent predictive factor of symptomatic RP.

The patients in the study cohort were scored according to following three factors: history of IP (yes: 1, no: 0), tumour location in the lung (inferior: 1, superior: 0) and V_{25} (>3.4%: 1, ≤3.4%: 0). The patients were then classified into two subgroups based on the results of the scoring system (0–1 point, $n = 46$, and 2–3 points, $n = 8$). Symptomatic RP had an incidence of 2.2% and 50.0% in the 0–1 point group and the 2–3 point group, respectively ($p < 0.001$) (Figure 1b). Although predictive factors for cough, rib fracture and chest pain were also investigated, no significant predictive factors were identified.

All 25 fiducial markers were placed using an intravascular approach. Regarding toxicities that were related to the method of fiducial marker placement, a patient was diagnosed with a Grade 1 femoral haematoma. Additional toxicities (*e.g.* cardiac arrhythmia) were not identified. No coil migration was observed.

DISCUSSION

In our study, the frequency of symptomatic RP was 10.7% (in 6/56 patients). This result is almost identical to the incidences reported in the conventional SBRT literature. Baker et al[10] reported 26 (9.9%) patients and 3 (1.1%) patients who developed Grade 2 and Grade 3 RP, respectively. Barriger et al[11] reported 42 (17%) patients who developed RP after treatment, including 19 (8%) patients with Grade 1, 17 (7%) patients with Grade 2, 5 (2%) patients with Grade 3 and 1 (0.4%) patient with Grade 4 RP. Severe RP (Grade 3 or more) was observed in 1 (1.8%) patient from our cohort. This finding is consistent with the observations made by the majority of groups practising pulmonary SBRT, for which the incidences of RP of Grade 3 or more are generally quite low (0–8%).[12,13] Table 5 summarizes

Table 4. Optimal cut-off values and area under the curve (AUC) values derived from ROC analysis

Metrics	Cut-off values	Crude incidence rate of symptomatic RP		AUC values
		≤Cut-off	>Cut-off	
MTD	27.0 mm	4.5%	33.3%	0.762
GTV	7.9 cm^3	2.6%	29.4%	0.805
PTV	41.7 cm^3	2.1%	62.5%	0.873
MLD	3.6 Gy	0.0%	30.0%	0.908
V_{50}	0.7%	2.3%	38.5%	0.843
V_{45}	1.1%	2.3%	41.7%	0.875
V_{40}	1.5%	2.2%	50.0%	0.902
V_{35}	1.9%	2.2%	45.5%	0.907
V_{30}	2.5%	2.2%	45.5%	0.918
V_{25}	3.4%	2.2%	50.0%	0.923
V_{20}	3.5%	0.0%	28.6%	0.917
V_{15}	5.1%	0.0%	26.1%	0.905
V_{10}	9.1%	0.0%	28.6%	0.89
V_5	21.5%	2.4%	33.3%	0.833

GTV, gross tumour volume; MLD, mean lung dose; MTD, maximum tumour diameter; PTV, planning target volume; ROC, receiver-operating characteristic; RP, radiation pneumonitis; V_x, normal lung volume receiving x Gy of radiation.

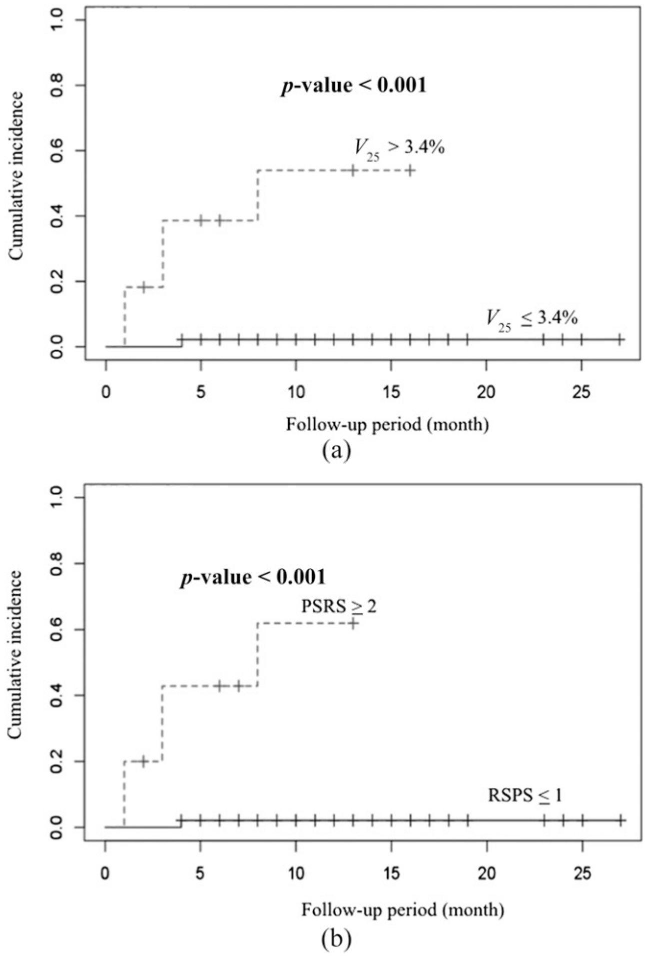

Figure 1. (a) Cumulative incidence curves of symptomatic radiation pneumonitis stratified by the normal lung volume receiving 25 Gy of radiation (V_{25}). (b) Cumulative incidence curves of symptomatic radiation pneumonitis stratified by the predictive score of symptomatic radiation pneumonitis after stereotactic body radiotherapy (PSRS).

published reports that focused on the incidence rate of ≥Grade 2 RP and its related factors.

IP is considered to be a contraindication for conventional radiotherapy because of the high frequency of acute exacerbation that has been reported following treatment.[14] SBRT is occasionally indicated for patients with IP, but the relationship between subclinical (untreated and oxygen-free) interstitial lung disease and the incidence of RP is still unclear.[15] In our study, the relationship between history of IP and incidence of symptomatic RP was not significant ($p = 0.158$). However, two patients with a history of IP developed symptomatic RP in only 1 month; one of than had severe IP (Grade 3). Therefore, special care should be continued in the treatment of patients with a history of IP, even if the condition of IP is kept stable. Kimura et al[16] reported that patients with emphysema have a lower probability of developing symptomatic RP, but this finding was not observed in our study ($p > 0.05$). Several reports have been published on lung function. Takeda et al[17] reported that a high forced expiratory volume in 1 s is significantly associated with Grade 2 RP. In our study cohort, a previous low VC % was a significant predictive factor for RP in univariate analysis. This finding has not been stated in any of the previous reports that we reviewed. There is a close connection between background lung disease and lung function, but further investigation is needed to clarify this connection. Future articles should include data on previous VC %.

Ding et al[6] noted that CyberKnife may deliver lesser dose to the lung than linear accelerator-based SBRT when treating tumours in the anterior region of the lung; however, the low-dose volume from CyberKnife delivery is significantly greater than that from linear accelerator-based delivery when treating tumours in the posterior region of the lung. This is because CyberKnife SBRT treatment plans use many more beams than conventional SBRT treatments, and because CyberKnife cannot deliver radiation from underneath the patient, as a consequence of the limited movable range of the robotic arm. However, a significant relationship between symptomatic RP and posterior tumour position was not evident in our study. Instead, inferior tumour position tended to be associated with symptomatic RP; although that association was non-significant in the present study, it has been identified as significant in some previous studies of conventional fractionated radiation therapy.[18,19] For tumours that are located in the lower thorax and move accordingly with respiratory motion, CyberKnife SBRT can deliver radiation beams with continuous tumour fiducial tracking, and internal margins for treatment planning can be minimized regardless of the tumour location in the upper or lower thorax. Further investigation is warranted about the association between tumour location and symptomatic RP.

A significant relationship has been observed between dose–volume metrics and symptomatic RP after pulmonary CyberKnife SBRT. Some studies have supported the hypothesis that the delivery of low radiation doses to the lung is predictive of RP development. Baker et al[10] reported that V_5 and V_{13} were significant predictive factors of symptomatic RP in 240 patients treated with SBRT. Moreover, several earlier articles have also reported that mid-dose parameters were predictive of the risk of symptomatic RP after pulmonary SBRT. Barriger et al[11] reported a correlation between V_{20} and the development of symptomatic RP in 251 patients with lung cancer treated with SBRT. There have also been a few published reports concerning high-dose parameters. Chang et al[20] reported a significant association between the MLD or V_{40} in the ipsilateral lung and the risk of developing symptomatic RP. In our study, lung doses (MLD and $V_{5–50}$), MTD, GTV and PTV all correlated with one another and were found to be significant predictive factors of symptomatic RP in univariate analyses. These findings were consistent with the report of Guckenberger et al,[21] which noted that the MLD and $V_{2.5–50}$ of the ipsilateral lung were correlated with the incidence of symptomatic RP.

All lung doses metrics (MLD and $V_{5–50}$) were related to symptomatic RP in our study, and we used a statistical analysis to select a V_{25} of >3.4% from among these metrics. Matsuo et al[22] reported that a V_{25} of ≥4.2% was a significant predictive factor for symptomatic RP after conventional SBRT in 74 patients with

Table 5. Summary of reports on incidence rate and predictive factors of symptomatic radiation pneumonitis (RP)

First author, reference	Year	N	Total dose/ fraction	Equipment	Algorithm	RP Grade 2	RP Grade 3 or more	Scoring system	Predictive factors
Guckenberger[12]	2010	59	26 Gy/1 fr	Linear accelerator	AAA	18.6%	0.0%	SWOG	MLD
			37.5 Gy/3 fr						$V_{2.5–50}$
Matsuo[22]	2012	74	48 Gy/4 fr	Linear accelerator	AAA	18.9%	1.4%	CTCAE3	PTV
									V_{25}
Barriger[11]	2012	251	24 72 Gy/3–5 fr	Linear accelerator	NA	7.0%	2.4%	CTC2	MLD
									V_{20}
Chang[20]	2012	130	50 Gy/4 fr	Linear accelerator	CC	9.2%	2.3%	CTCAE3	MLD
									V_{40}
Takeda[17]	2012	128	40–60 Gy/5 fr	Linear accelerator	superposition	16.4%	5.5%	CTCAE3	Female
									High FEV 1
Baker[10]	2013	263	40–60 Gy/4–8 fr	Linear accelerator	PBA	9.9%	1.1%	CTCAE3/4	V_5, V_{13}
					CC				
Bibault[25]	2012	51	45–60 Gy/3 fr	CyberKnife	PBA	3.9%	0.0%	CTCAE4	NA
Shen[26]	2015	50	48–60/3 fr	CyberKnife	NA	6.0%	4.0%	RTOG	NA
Present study		56	48–56/4 fr	CyberKnife	Monte Carlo	8.9%	1.8%	CTCAE4	VC %
									V_{25}

AAA, analytical anisotropic algorithm; CC, collapsed cone convolution superposition; CTC, Common Toxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; FEV 1, forced expiratory volume in 1 s; fr, fractions; MLD, mean lung dose; NA, not available; PBA, pencil beam algorithm; PTV, planning treatment volume; RTOG, Radiation Therapy Oncology Group; SWOG, Southwest Oncology Group; V_x, normal lung volume receiving x Gy of radiation; VC, vital capacity.

lung cancer. There is no definitive predictive parameter for symptomatic RP after CyberKnife SBRT, and V_{25} may be one of the most preferable parameters, based on these findings. To provide additional evidence, there is a need for further investigations that increase the number of case series and use prospective designs.

We have suggested a new scoring system, called predictive score of symptomatic radiation pneumonitis after stereotactic body radiotherapy (PSRS), which scores patients according to three factors (history of IP, tumour location in the lung and value of V_{25}). The symptomatic RP was significantly more common among patients with ≥2 points than that among those with <2 points. To date, there has been no definite scoring system for symptomatic RP; the PSRS could be an index for lung SBRT in the future. Verification of this scoring system is warranted in other patient cohorts, preferably using a prospective design.

One of the included patients (4.0%) exhibited an adverse event relating to fiducial marker placement (Grade 1 haematoma). No toxicity of grade ≥2 was observed. Pneumothorax is the most important event associated with the percutaneous marker placement method.[23] An alternative method for fiducial marker placement is the endobronchial placement using a bronchoscope. This method reduces the risk of pneumothorax. However, Shirato et al[24] reported that the marker dropped out of the lesion in 7.3% of patients. Because very few adverse events and no coil migration were observed in the present study, we recommend the intravascular fiducial maker placement method as a safer and more reliable option than other methods.

Our study has some limitations: first, the use of a retrospective design means that our findings may be prone to selection bias; and second, the total number of RP events in our cohort was relatively small.

CONCLUSION

In the prior literature, the incidence of symptomatic RP after CyberKnife lung SBRT had not been investigated fully and, to our knowledge, predictive factors for symptomatic RP after CyberKnife SBRT had not been reported. This is the first report that has investigated prognostic factors for symptomatic RP after CyberKnife SBRT. The incidence of symptomatic RP after CyberKnife lung SBRT was almost identical to the incidences reported in the literature on conventional SBRT. Percent VC, MTD, GTV, PTV, MLD and V_{5-50} were identified as significant predictive factors for symptomatic RP. V_{25} appears to be the most important of these parameters, and the newly developed scoring system may help to predict symptomatic RP with greater sensitivity. However, further investigation is needed because of the limitations to our study.

ACKNOWLEDGMENTS

We would like to thank Editage (www.editage.jp) for English language editing.

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