Repeated Stereotactic Body Radiotherapy With CyberKnife® in Lung Cancer: Toxicity Can Be Reduced by Sparing Irradiation to the Lungs

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Abstract

Background: Data of multiple courses of stereotactic body radiotherapy (SBRT) for lung malignancies is scarce. We aimed to investigate the efficacy and safety of repeated SBRT with CyberKnife and to identify predictors of lung toxicity.

Methods: We reviewed patients with primary or metastatic lung cancer who underwent repeated SBRT with CyberKnife® between December 2013 and April 2021. Local control (LC), overall survival (OS) and adverse events were analyzed. We generated a composite plan and investigated the mean lung dose (MLD), V5–V30 of the bilateral lungs, and absolute lung volumes spared from 5–30 Gy (VS5–VS30), based on equivalent dose in 2.0-Gy fractions ($\alpha / \beta = 3$). Clinical and dosimetric predictors of Grade 2+ radiation pneumonitis (RP) were examined.

Results: Twenty patients underwent repeated SBRT for 27 lesions. The most predominant dose fractionation was 60 Gy in five fractions. The median follow-up duration from the last SBRT was 18.0 months (range, 3–55 months). The 1-year and 2-year LC of lung lesions in repeated courses were 95.2% and 95.2%, respectively. The 1-year and 2-year OS rates after repeated SBRT were 88.4% and 49.7%, respectively. Five patients (25%) developed Grade 2+ RP, including a Grade 5 RP. There was no association between clinical factors and Grade 2+ RP. The Grade 2+ RP group showed higher composite MLD ($p = 0.042$) and lower composite VS5 ($p = 0.042$), VS10 ($p = 0.015$), VS15 ($p = 0.008$), and VS20 ($p = 0.025$), compared with the Grade 0–1 RP group.

Conclusions: Repeated SBRT with CyberKnife® showed favorable LC and OS, but a high rate of Grade 2+ RP. Analysis of the composite plans showed that MLD and VS5–VS20 may predict lung toxicity of multicourse SBRT.

Introduction

Stereotactic body radiotherapy (SBRT) for early-stage primary lung cancers and solitary lung metastases has shown excellent clinical results [1–3] and become established as a standard treatment option. However, local in-field recurrence and metachronous lung metastasis remain the common patterns of failure [1, 2]. It is also known that primary lung cancer patients have up to 10% probability of developing a secondary lung tumor within 5 years after treatment [4]. For these reasons, a significant number of patients with primary or metastatic lung cancers require repeated thoracic radiotherapy. However, patients who have previously received SBRT are often ineligible for surgery due to comorbidities. Thus, the demand for repeated thoracic irradiation is high.

Technological advancements in emerging approaches to SBRT enable repeated thoracic radiotherapy. Precise conformal dose distribution enables high dose delivery to the target, while sparing normal organs. Recent advancements in SBRT, such as volumetric modulated arc radiotherapy and robotic radiotherapy devices have led to more precise treatment, compared with conventional SBRT. It has been suggested that several organs, including the lungs, is tolerant to additional irradiation after recovery from initial radiation

damage [5, 6]. The feasibility of repeated SBRT is now being increasingly recognized. Several small, retrospective case series have illustrated the potential clinical utility of repeated SBRT [7–10]. However, optimal methods for repeated SBRT have not yet been established. Concerns about increased adverse events with subsequent irradiations have been raised by clinical data [11–13]. Furthermore, clinical and dosimetric factors that may predict lung toxicity are poorly understood in the situation of multicourse thoracic irradiation because of limited reports. Developing effective and safe procedures, and identifying indicators to avoid clinically significant toxicity, are important issues that mandate further study.

Our study aimed to investigate the clinical outcomes and dosimetric parameters of patients with primary or metastatic lung cancers who underwent repeated SBRT with CyberKnife® (Accuray, Sunnyvale, CA, USA), and to evaluate its efficacy and safety, along with predictors of lung toxicity.

Materials And Methods

Patient selection

After obtaining institutional review board approval (Approval No. ERB-c-1646), we investigated all patients with primary lung cancer or lung oligometastasis who underwent a second or third course of SBRT with CyberKnife® from October 2014 to December 2020. Patients who received their first SBRT at another institution were also included. The eligibility criterion for primary lung cancers was “clinical T1-2N0M0,” according to the Union for International Cancer Control, the eighth edition. For lung oligometastases, we included patients who had control over their primary lesion and extrapulmonary lesions before SBRT. We included those with lung lesions limited from one to three at the time of each SBRT course. Patients were excluded if radiotherapy dosimetry data from any course of lung SBRT were not available for compositing dose volume histogram (DVH) analyses, if the intent of the repeat course of SBRT was palliative (equivalent dose in 2.0 Gy fractions [EQD2] < 60 Gy), or if conventional dose fractionations (< 3.0 Gy per fraction) were used in any radiotherapy course. The associated EQD2 was then calculated using the following linear quadratic model, with an α / β ratio of 10 for tumor and 3 for normal tissue: $EQD = D (d + \alpha / \beta) / (2 + d / [\alpha / \beta])$, where D equals the total prescribed dose (Gy) and d represents the dose per fraction (Gy).

Treatment techniques

We used the CyberKnife® G4 system to perform repeat SBRT, using the following procedure. Patients were immobilized using an individually shaped body cast (ESFORM, Engineering System, Matsumoto, Japan). Four-dimensional computed tomography (CT) scanning was performed to generate contours according to the respiratory motion. Gross tumor volume (GTV) was acquired in each respiratory phase. The internal target volume (ITV) was the summed GTVs of all phases; the planning target volume (PTV) was obtained by expanding the ITV by 5 mm in all directions. We selected a collimator size and optimized the beam weight to ensure high dose conformity for PTV. The planned dose was prescribed to GTV,

covering 99% of the volume (D99). GTV at rest was used in the Monte Carlo algorithm and in normalization to avoid uncertainty of dose prescription for the lung density area. GTV D99 was required to be 70–90% isodose of the maximum dose.

Lung lesions were classified as centrally located if they were located within 2.0 cm of the proximal bronchial tree or if the PTV abutted the mediastinal or pericardial pleura [14]. Peripheral lung lesions were usually treated with 60 Gy in five fractions. For central lung lesions, dose fractionation was determined on a case-by-case basis to avoid overdosing the adjacent critical organs. Doses to critical organs were within Timmerman's constraint [15]. For more than five fractions of SBRT, the procedure was modified, based on EQD2. For five fractions, patients were irradiated once every other day. For more than five fractions, patients were irradiated over consecutive days. To assess SBRT intensity, the biological equivalent dose (BED) was calculated using the following linear quadratic model, with an α / β ratio of 10: $BED = nd (1 + d / [\alpha / \beta])$, where n equals the total number of fractions and d represents the dose (Gy) per fraction. The Xsight spine tracking system (CIRS, Norfolk, VA, USA) was used during treatment for position verification.

Analysis of dosimetric parameters

The CT scans, structure sets, and dose distributions were sent to our institution's software platform for dosimetric analysis. Composite plans were generated from each SBRT plan for all patients. We investigated cumulative DVH parameters for the bilateral lungs, including mean lung dose (MLD), bilateral lung volumes V5, V10, V15, V20, and V30, and absolute lung volumes spared from 5 Gy (VS5), 10 Gy (VS10), 15 Gy (VS15), 20 Gy (VS20), and 30 Gy (VS30). The procedure for generating a cumulative composite plan was as follows. Two CT scans were aligned rigidly by using an automatic bone match (with translation and rotations). Given the differences in dose fractionation between SBRT plans, lung doses were corrected for EQD2 ($\alpha / \beta = 3$). Finally, volumetric doses, converted to EQD2 for each plan, were summed on the CT images taken before the final course of SBRT.

Patient follow-up

Clinical response was evaluated by physical examination and chest CT scans at 1, 3, 6, 9, 12, 18, and 24 months after SBRT, then every 6 months. Local failure was defined as a 20% increase in the greatest diameter of GTV on two consecutive CT scans. If local recurrence was seen as equivocal at a given follow-up point, but later confirmed to be recurrence, the time of local failure was backdated to the time of the initial equivocal finding. Local control (LC) for second or third SBRT treatments was evaluated per lesion. The overall survival rate (OS) was calculated from the start date of the second SBRT course to the date of the last follow-up or death from any cause. Toxicities, such as radiation pneumonitis (RP), were recorded using the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

All statistical calculations were performed using SPSS version 26.0 software (IBM, Armonk, NY, USA). LC and OS were calculated using the Kaplan–Meier method. Comparative analysis was performed to identify clinical and dosimetric factors associated with the development of Grade 2+ RP. Between Grades 0–1 RP group and the Grade 2+ RP group, we compared percentage values using the chi-squared test. Discreet values were compared using the Mann–Whitney U test. All analyses used the p values of < 0.05 level of significance.

Results

Patient and tumor characteristics

Twenty patients underwent repeated lung SBRT for 27 lesions. Second course SBRT were performed on 20 patients with 23 lesions, due to local recurrence after SBRT in three patients (three lesions), second primary lung cancer in six patients (six lesions), and the appearance of newly emerged lung metastases in 11 patients (14 lesions). After the second SBRT course, four patients received the third course SBRT for four lesions because of the appearance of newly emerged lung metastases. Patient and tumor characteristics are summarized in Table 1. Our study population included more metastatic lung cancers than primary lung cancers (65.0% vs. 35.0%, respectively).

Table 1
Patient and tumor characteristics.

Characteristics		Value
Total number of patients		20
Age at last SBRT in year	Median (range)	74.5 (52–94)
Sex, n (%)	Male	14 (70.0%)
	Female	6 (30.0%)
ECOG-PS at last SBRT, n (%)	0	12 (60.0%)
	1	8 (40.0%)
Prior lung resection, n (%)	Yes	6 (30.0%)
	No	14 (70.0%)
Smoking history, n (%)	Never	6 (30.0%)
	Former	11 (55.0%)
	Current	3 (15.0%)
History of COPD, n (%)	Yes	5 (25.0%)
	No	15 (75.0%)
Interstitial change on chest CT, n (%)	Yes	3 (15.0%)
	No	17 (85.0%)
Tumor type, n (%)	Primary lung cancer	7 (35.0%)
	Metastatic lung cancer	13 (65.0%)
Primary site, n (%)	Lung	8 (40.0%)
	Colorectal	8 (40.0%)
	Gastrointestinal	2 (10.0%)
	Head and neck	1 (5.0%)
	Breast	1 (5.0%)
Histology, n (%)	Adenocarcinoma	13 (65.0%)
	Squamous cell carcinoma	2 (10.0%)
	Clinical diagnosis	5 (25.0%)
Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; SBRT, stereotactic body radiotherapy; COPD, chronic obstructive pulmonary disease; CT, computed tomography.		

Treatment details

For initial SBRT, five patients (six lesions) were treated using a conventional linear accelerator and one patient (one lesion) was treated with tomotherapy at other affiliated institutions. All patients' dosimetric data were available for analysis. Treatment details are shown in Table 2. The most predominant dose fractionation was 60 Gy in five fractions. The median BED10 was 132.0 Gy for all SBRT courses. No patient underwent concurrent systemic therapy.

Table 2
Treatment details.

Characteristics	Previous SBRT	Repeated SBRT	
		Second course	Third course
Total number of lesions, n	24	23	4
Interval from 1st SBRT, in months			
Median (range)		8.0 (3–82)	12.5 (7–82)
SBRT for local recurrence, n (%)			
Yes		3 (13.0%)	0 (0.0%)
No		20 (87.0%)	4 (100.0%)
Tumor location, n (%)			
Central	3 (%)	6 (%)	0 (%)
Peripheral	21 (%)	17 (%)	4 (%)
Dose fractionation, n (%)			
48 Gy in 4 fractions	2 (8.3%)	0 (0.0%)	0 (0.0%)
50 Gy in 5 fractions	2 (8.3%)	1 (4.3%)	0 (0.0%)
60 Gy in 20 fractions	0 (0.0%)	1 (4.3%)	0 (0.0%)
60 Gy in 15 fractions	1 (4.2%)	0 (0.0%)	0 (0.0%)
60 Gy in 10 fractions	3 (12.5%)	0 (0.0%)	0 (0.0%)
60 Gy in 5 fractions	14 (58.3%)	18 (78.3%)	4 (100.0%)
65 Gy in 10 fractions	0 (0.0%)	2 (8.7%)	0 (0.0%)
69 Gy in 23 fractions	1 (4.2%)	0 (0.0%)	0 (0.0%)
70 Gy in 10 fractions	0 (0.0%)	1 (4.3%)	0 (0.0%)
71.5 Gy in 13 fractions	1 (4.2%)	0 (0.0%)	0 (0.0%)
Prescribed dose, BED10 (Gy)			
Median (range)	132.0 (84.0–132.0)	132.0 (78.0–132.0)	132.0 (132.0–132.0)

Abbreviations: SBRT, stereotactic body radiotherapy; LINAC, conventional linear accelerator; BED, biologically effective dose; DVH, dose-volume histogram; GTV, gross tumor volume; PTV, planning target volume; MLD, mean dose of the bilateral lung; Vxx, the volume received by xx Gy of the bilateral lung.

Characteristics	Previous SBRT	Repeated SBRT	
		Second course	Third course
Systemic therapy, n (%)			
None	20 (83.3%)	19 (82.6%)	2 (50.0%)
Neoadjuvant	3 (12.5%)	2 (8.7%)	1 (25.0%)
Concurrent	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adjuvant	1 (4.2%)	2 (8.7%)	2 (50.0%)
Abbreviations: SBRT, stereotactic body radiotherapy; LINAC, conventional linear accelerator; BED, biologically effective dose; DVH, dose-volume histogram; GTV, gross tumor volume; PTV, planning target volume; MLD, mean dose of the bilateral lung; Vxx, the volume received by xx Gy of the bilateral lung.			

Local control and survival

The median follow-up duration after the second SBRT was 18.0 months (range, 3–55 months). Among second or third course SBRT patients, local recurrence was observed in one lesion (3.8%). The 1-year and 2-year LC of lung lesions in repeated courses of SBRT (with 95% confidence interval) were 95.2% (86.2–104.2%) and 95.2% (86.2–104.2%), respectively (Fig. 1). The Kaplan–Meier OS curves are shown in Fig. 2. During the observation period, death from any cause occurred in eight patients: tumor progression in four patients, treatment-related in one patient, and other cause in four patients. The estimated median survival time of the entire cohort was 23.0 months (7.1–38.9 months). The 1-year and 2-year OS rates were 88.4% (73.1–103.7%) and 49.7% (21.9–77.5%), respectively. The 1-year and 2-year OS rates of patients with primary lung cancer were 64.3% (23.1–105.5%) and 42.9% (0.0–86.8%), respectively. In patients with lung oligometastases, the 1-year and 2-year OS rates were 100.0% and 50.5% (13.5–87.5%), respectively.

Adverse events

Six patients (30.0%) experienced at least one Grade 2 or higher toxicity after repeat SBRT. One patient experienced Grade 2 chest wall pain, with Grade 2 rib fractures, which was likely attributable to SBRT. Grade 2+ RP was observed in five patients (25.0%), including one Grade 3 and one Grade 5. All Grade 2+ RP occurred after the last course of SBRT. Four patients had Grade 2+ RP after the second SBRT and one patient after the third SBRT. The median time between the last SBRT and the onset of RP was 4.0 months (range, 2–11 months). There was no case with Grade 2+ RP in the interval between initial SBRT and second SBRT.

One Grade 5 patient received second SBRT for a newly emerged primary lung cancer 28 months after initial SBRT. Notably, this patient had a slight interstitial shadow on pretreatment chest CT. The patient developed Grade 3 RP at 11 months after second SBRT. They were administered steroids but died due to an exacerbation of RP (Fig. 3).

Predictors for radiation pneumonitis

An analysis of clinical predictors for Grade 2+ RP are summarized in Table 3. The presence of a history of lung resection was the only factor to show a (weak) trend. No factors were significantly associated with the development of Grade 2+ RP. An analysis of the dosimetric predictors for Grade 2+ RP is summarized in Table 4. For the composite plan, MLD ($p = 0.042$), VS5 ($p = 0.042$), VS10 ($p = 0.015$), VS15 ($p = 0.008$), and VS20 ($p = 0.025$) in the Grade 2+ RP group were significantly lower than in the Grade 0–1 RP group. Fig. 4 shows the correlation between composite MLD, VS5, VS10, VS15, VS20, and the development of Grade 2+ RP.

Table 3
Clinical predictors for Grade 2+ radiation pneumonitis.

Factors	Grade 0–1 RP (n = 15)	Grade 2+ RP (n = 5)	<i>p</i> -value
Age at last course SBRT in years, n (%)			
<75	7 (46.7%)	3 (60.0%)	0.606
≥75	8 (53.3%)	2 (40.0%)	
ECOG-PS at last SBRT, n (%)			
0	9 (60.0%)	3 (60.0%)	1.000
1	6 (40.0%)	2 (40.0%)	
Prior lung resection, n (%)			
Yes	3 (20.0%)	3 (60.0%)	0.091
No	12 (80.0%)	2 (40.0%)	
History of COPD, n (%)			
Yes	4 (26.7%)	1 (20.0%)	0.766
No	11 (73.3%)	4 (80.0%)	
Interstitial change on CT, n (%)			
Yes	2 (13.3%)	1 (20.0%)	0.718
No	13 (86.7%)	4 (80.0%)	
Tumor type, n (%)			
Primary cancer	5 (33.3%)	2 (40.0%)	0.787
Metastatic cancer	10 (66.7%)	3 (60.0%)	
Systemic therapy, n (%)			
Combined	2 (13.3%)	1 (20.0%)	0.718
None	13 (86.7%)	4 (80.0%)	

A *p*-value indicates a statistically significant association.

Abbreviations: RP, radiation pneumonitis; SBRT, stereotactic body radiotherapy; ECOG-PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; CT, computed tomography.

Factors	Grade 0–1 RP (n = 15)	Grade 2+ RP (n = 5)	<i>p</i> -value
Repeat SBRT for central lesion, n (%)			
Yes	5 (33.3%)	1 (20.0%)	0.573
No	10 (66.7%)	4 (80.0%)	
Repeat SBRT for local recurrence, n (%)			
Yes	2 (13.3%)	1 (20.0%)	0.718
No	13 (86.7%)	4 (80.0%)	
Interval between courses in months			
Median (range)	7.0 (3.0-82.0)	15.0 (9.0-53.0)	0.497
A <i>p</i> -value indicates a statistically significant association.			
Abbreviations: RP, radiation pneumonitis; SBRT, stereotactic body radiotherapy; ECOG-PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; CT, computed tomography.			

Table 4
Dosimetric predictors for Grade 2+ radiation pneumonitis.

Composite plan parameters	Grade 0–1 RP (n = 15)		Grade 2+ RP (n = 5)		p-value
	Median (range)				
Lungs volume (cc)	3092.3	(1699.2–4998.4)	2429.0	(1658.1–2989.2)	0.119
MLD (Gy)	9.3	(5.9–20.5)	14.6	(7.7–19.5)	0.042
V5 (%)	30.0	(14.4–61.6)	41.6	(29.3–70.9)	0.197
V10 (%)	17.5	(10.1–42.2)	24.3	(15.9–44.1)	0.142
V15 (%)	11.7	(7.9–31.7)	18.5	(9.7–29.8)	0.119
V20 (%)	8.2	(6.0–25.1)	14.6	(6.9–21.5)	0.142
V30 (%)	5.9	(4.1–17.5)	10.3	(5.0–14.5)	0.066
VS5 (cc)	2023.9	(906.4–3845.8)	1258.1	(871.3–1419.3)	0.042
VS10 (cc)	2481.3	(1366.3–4416.6)	1670.0	(1394.3–1838.3)	0.015
VS15 (cc)	2664.0	(1528.6–4603.5)	1972.3	(1497.1–2099.0)	0.008
VS20 (cc)	2771.9	(1560.5–4699.5)	2073.7	(1543.1–2348.0)	0.025
VS30 (cc)	2887.3	(1595.0–4791.5)	2179.3	(1576.1–2555.4)	0.066
A <i>p</i> -value in bold indicates a statistically significant association.					
Abbreviations: RP, radiation pneumonitis; MLD, mean dose of the bilateral lung; Vxx, the volume received by xx Gy of the bilateral lung; VSxx, bilateral lung volume spared from xx Gy.					

Discussion

We investigated the clinical outcomes and dosimetric parameters of patients with primary or metastatic lung cancer who received multiple courses of SBRT, to evaluate its efficacy and safety, along with predictors of lung toxicity. The second and third courses of SBRT (performed using the CyberKnife®) showed favorable LC and OS, which suggests the effectiveness of such treatment. After repeated SBRT, Grade 2+ RP was frequently observed; a fatal case was experienced. We showed that the MLD and absolute lung volume spared from low-dose irradiation can predict lung toxicity by analyzing composite plans based on EQD2.

In a review by De Bari et al., the 1-year and 2-year LC rates after second thoracic SBRT for primary or metastatic cancer ranged between 59–95% and 50–92%, respectively [16]. A large case series reported that a second course of radiotherapy with 50 Gy in four fractions (BED10, 112.5 Gy) showed a 1-year LC of 95.0% [11]. We performed repeated SBRT (median BED10, 132.0 Gy) and demonstrated excellent LC,

which indicated that CyberKnife® -based SBRT, as a repeated radical treatment, provides durable tumor control. The 1-year and 2-year OS rates following the last course of SBRT for patients with primary or metastatic cancer, have been reported to be in the range of 59–80% and 29–74%, respectively [16], which is comparable with our results.

Lung SBRT has been considered a safe treatment with minimal toxicity. For single course SBRT, the rates of Grade 2+ and Grade 3+ lung toxicity have been reported to be 9.1% (7.15–11.4%) and 1.8% (1.3–2.5%), respectively [17]. However, the safety of multicourse SBRT is not well understood. Several retrospective studies of thoracic re-irradiation have reported high rates of Grade 2+ and Grade 3+ RP, of 13.6–50.0% and 3.0–28.0%, respectively [7, 10, 12, 16, 18]. In our study, Grade 2+ and Grade 3+ pulmonary toxicity after repeated SBRT was observed in 25.0% and 8.0% of patients, respectively, which is consistent with previous reports. Our data also suggest a concern for increased pulmonary toxicity with multiple courses of lung SBRT, compared with single course SBRT.

We experienced a fatal RP that developed after repeated SBRT. Previous reports have identified few Grade 5 RPs in patients who received SBRT after previous conventional fractionated radiotherapy [11, 13]. There are no previous reports of fatal RP following multicourse SBRT. Analysis of a large case series reported that Grade 5 RP after a single course of SBRT occurred very rarely (1.3%) [19]. In that study, interstitial changes were observed retrospectively in 73.7% of Grade 5 RP patients, indicating a potential risk factor for fatal pulmonary toxicity. In our study, Grade 5 RP occurred in one of three patients with interstitial shadow; it was not observed in patients without interstitial shadow (33.3% vs. 0.0%; $p = 0.015$). Even in the context of multicourse SBRT, interstitial changes may be a risk factor for fatal toxicity.

Several risk factors for pulmonary toxicity in repeated thoracic radiotherapy have been identified. Out-of-field relapse [7], short interval between initial radiotherapy and second SBRT [18], poor performance status, impaired lung function, and initial PTV location in the bilateral mediastinum [11] have been indicated as risk factors for RP. In our study, there was no significant association between clinical factors and lung toxicity. Other similar studies have used different population backgrounds and clinical scenarios, which makes it difficult to obtain consistent results.

There are several reports on the correlation between RP and lung DVH parameters in the context of a second course of thoracic radiotherapy using SBRT. Liu et al. reported the dosimetric predictors of lung toxicity in 72 patients who underwent SBRT after conventional fractionated irradiation [11]. The composite V10, V20, V30, V40, and MLD were significantly correlated with the development of Grade 3+ RP. High composite MLDs were correlated with lung toxicity, which is consistent with our study. Muller et al. analyzed the DVH parameter associated with RP after multiple courses of SBRT, using a composite plan based on EQD2 ($\alpha / \beta = 3$) [18]. In multivariate analysis, a trend was observed between composite lung V5 and the development of Grade 2+ RP (hazard ratio, 1.157; $p = 0.058$). Among the irradiated relative lung volumes that we investigated, composite V30 showed a weak trend of association with Grade 2+ RP. The accumulated lung dose may have a clinical impact on patients receiving multiple courses of SBRT.

In previous SBRT studies, lung dose has been assessed using irradiated relative volume (%). Our report is the first to show a significant association between absolute lung volume spared from low-dose irradiation and SBRT-induced lung toxicity. A correlation between decreased VS5 (<1,500 cc) and the development of Grade 3+ RP in conventional fractionated irradiation for primary lung cancer has been previously shown by Tsujino et al. [20]. Our entire cohort of Grade 2+ RP had VS5 < 1,500 cc; reduced VS5 correlated with the development of Grade 2+ RP. However, among the DVH parameters we examined, VS15 was the most strongly associated with RP. Due to SBRT's unique fractionation scheme and dose distribution, the DVH parameter that predicts RP in SBRT may differ from that of conventional fractionated radiotherapy.

This study has several limitations. Due to it being a retrospective analysis at a single institute, there are inherent biases, a small number of events, and an inhomogeneous study population. This may limit the power of the analyses and cause under-reporting of adverse events. Also, we included patients with primary lung cancer and with metastatic lung cancer, which makes it difficult to draw reliable conclusions about survival. Prospective studies with larger populations are needed for more precise assessment. Moreover, deformable image registration (DIR) was not available for generating the composite plans of our study. DIR is an image processing technique that can provide a more accurate assessment of the cumulative radiation doses to the lungs by accounting for anatomical changes [21, 22].

Conclusions

Lung SBRT using CyberKnife® was effective as a repeated treatment option for primary or metastatic lung cancer. High rates of lung toxicity were observed, including fatal cases. By analyzing composite plans, we showed that MLD and absolute lung volume spared from low-dose irradiation may be useful in predicting lung toxicity.

Abbreviations

SBRT: Stereotactic body radiotherapy

DVH: Dose volume histogram

EQD2: Equivalent dose in 2.0 Gy fractions

CT: Computerized tomography

GTV: Gross tumor volume

ITV: Internal target volume

PTV: Planning target volume

BED: Biologically effective dose

MLD: Mean lung dose

LC: Local control

OS: Overall survival

RP: Radiation pneumonitis

DIR: Deformable image registration.

Declarations

Ethics approval and consent to participate:

Written informed consent was obtained for the research from all patients. This retrospective study was approved by the ethics committee of our institution (Approval No. ERB-C-1646) and was conducted in accordance with the Declaration of Helsinki.

Consent for publication:

We obtained written informed consent from patients to publish the article.

Availability of data and materials:

The datasets generated and/or analyzed during the current study are not publicly available due to the institutional ethics committee regulations.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

SW, HY, TK and GS were involved in study concepts and design.

SW and HY interpreted and analyzed the patient data.

SW participated in drafting the manuscript.

HY, TK, GS, and KY critically reviewed and edited the manuscript.

All authors read and approved the final manuscript.

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Figures

Figure 1.

Figure 1

Kaplan–Meier curve of local control rate

Figure 2.

Figure 2

Kaplan–Meier curve of overall survival rate

Figure 3.

Figure 3

Computed tomography images from a 78-year-old man who developed fatal RP after a second course of SBRT. The patient had a 50 pack/year smoking history but quit before the initial SBRT; his respiratory status was satisfactory. A slight interstitial shadow was observed at the base of lung (arrow) on the chest CT taken before the second SBRT. The primary tumor in the left upper lobe, which had been treated 28 months before the second SBRT, represented scar-like fibrosis (arrowhead). Eleven months after the second SBRT for newly emerged primary lung cancer in the right upper lobe, the patient developed RP with hypoxemia. In-hospital pulse steroid therapy resolved the symptoms and pulmonary shadow, but a relapse of RP occurred during steroid tapering, which resulted in the appearance of diffuse interstitial infiltration and severe hypoxemia. No specific infectious cause was identified. The patients died from respiratory failure 13 months after the second SBRT.

Abbreviations: CT, computed tomography; RP, radiation pneumonitis; SBRT, stereotactic body radiation therapy.

Figure 4.

Figure 4

Box plot showing composite MLD, VS5, VS10, VS15, VS20, and VS30 in patients who did and did not experience Grade 2+ radiation pneumonitis. Within each box, bold black lines denote median values. Collared boxes extend from the 25th to the 75th percentile of each group's distribution of values. Vertical extending lines denote whiskers, indicating the maximum and minimum values. White dots denote observations outside the range of adjacent values.

Abbreviations: RP, radiation pneumonitis; MLD, mean dose of the bilateral lung; VSxx, bilateral lung volume spared from xx Gy.