Pilot Study of the Safety and Efficacy of Dose Escalation in Stereotactic Body Radiotherapy for Peripheral Lung Tumors

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Abstract

This pilot study evaluated the safety and efficacy of a dose escalation method with steep dose gradients using stereotactic body radiotherapy for peripheral lung tumors. The rate of grade 2 or higher radiation pneumonitis within 1 year was almost 10%. This dose escalation method was safe and effective for peripheral lung tumors and may obtain excellent local control rates.

Background: This pilot study aimed to evaluate the safety and efficacy of a dose escalation method for the treatment of peripheral lung tumors by administrating steep dose gradients in the target volumes via stereotactic body radiotherapy (SBRT). **Patients and Methods:** Patients with peripheral lung tumors were enrolled onto this study and treated with SBRT using a total dose of 70 Gy in 4 fractions at target isocenter, covering the planning target volume surface with 70% of the isodose. The primary end point was the rate of grade 2 or higher radiation pneumonitis (RP) within 1 year. **Results:** A total of 35 patients were enrolled onto this study between September 2014 and January 2016. Thirty-two patients with primary lung cancers and 3 patients with lung metastases were treated with SBRT. Grade 2 RP was observed in 4 patients within 1 year. No severe RP (grade 3 or higher) was observed within the follow-up period. The median follow-up period was 21.2 months (range, 4.2-31.7 months). Local recurrence was observed in a single patient with lung metastasis. No local recurrence was observed within the follow-up period in the 32 patients with primary lung cancer. The local control and overall survival rates at 2 years were 95.7% (95% confidence interval, 72.9-99.4) and 85.2% (95% confidence interval, 67.8-93.6), respectively. **Conclusion:** This dose escalation method with steep dose gradients using SBRT for peripheral lung tumors was safe in the subacute phases. These results also suggest that this method can obtain excellent local control rates.

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Introduction

Stereotactic body radiotherapy (SBRT) is an important option for the treatment of solitary and oligometastatic lung tumors, especially in patients with inoperable disease. Clinical outcomes and local control rates for lung tumors after SBRT have been previously reported.[1,2]

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According to a survey of Japanese practice, a total dose of 48 Gy in 4 fractions at the isocenter has been the most widely used treatment for peripheral lung tumors in Japan.[3] However, local recurrences were observed in 12.7% to 17.4% of cases with this treatment schedule in long-term follow-up studies.[4,5] In our previous study, the 3-year local recurrence rate was 13.2%.[6] In contrast, it was reported that the higher radiation doses used in the United States resulted in lower 3-year local recurrence rates of 2.4% to 5.7%.[7,8] We hypothesized that a total dose of 48 Gy in 4 fractions is insufficient to control peripheral lung tumors. Therefore, the most promising treatment strategy to improve local control after SBRT is dose escalation.[9]

When considering dose escalation for lung tumors, it is important to maintain acceptable levels of toxicity, especially for radiation pneumonitis (RP). RP is a common adverse effect in thoracic

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radiotherapy that can lead to chronic respiratory dysfunction and occasionally death.[10] Rates of symptomatic RP after SBRT range from 2.4% to 28.0%, and the dose for normal lung tissue is associated with RP risk.[11-14] To avoid increasing the risk of RP, it is important to maintain normal lung dose as the target dose is escalated. In this study, to escalate target dose without increasing the dose to normal lung tissue, dose gradients were increased compared to those of a previous method.[13]

The purpose of this study was to evaluate the safety and efficacy of dose escalation with steep dose gradients in the target volumes treated with SBRT for peripheral lung tumors.

Methods

Patient Eligibility

The inclusion criteria of this study were as follows: (1) patient has primary or metastatic peripheral lung cancer (primary lung cancer, tumor size $\leq$ 5 cm, clinical stage IA or IB disease diagnosed according to the 7th edition of the tumor, node, metastasis classification system, metastatic lung cancer, tumor size $\leq$ 5 cm, $\leq$ 2 lung lesions, and no lesions other than lung); (2) patient not eligible for or refused surgery; (3) dose to adjacent organs estimated not to exceed constraints established using pretreatment chest computed tomographic (CT) imaging; (4) patient $\geq$ 20 years old; (5) Eastern Cooperative Oncology Group performance status of 0 to 2; and (6) patient can lay supine with arms overhead and maintain this position for at least 30 minutes. The following conditions were excluded: (1) previous irradiation around the lesion; (2) active interstitial pneumonia or pulmonary fibrosis; (3) severe diabetic mellitus or collagen disease; (4) women currently pregnant or lactating, or women who might become pregnant; (5) psychiatric illness that would impede the treatment protocol; and (6) patients considered inappropriate for this study by physicians. Informed consent was obtained from all study patients.

The treatment protocol and consent form for this pilot study were approved by the institutional review board and ethics committee of our institution. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry in Japan (UMIN000014815).

Simulation and Treatment

We have previously described our methods of SBRT delivery.[15-17] In this study, before acquiring CT images, respiratory motion was assessed using X-ray fluoroscopy. Then 10 respiratory phases of 4-dimensional (4-D) CT were acquired using a 16-slice CT scanner (Light-Speed RT16; GE Healthcare, Little Chalfont, UK), to produce the treatment-planning CT. The CT images generated by averaging the 10 respiratory phase images of the 4-D CT image set were used as the treatment-planning CT. Internal gross tumor volume (iGTV) was delineated on the treatment-planning CT by referring to the 10 respiratory phase images of the 4-D CT, as well as the tumor motion detected on X-ray fluoroscopy imaging. The internal target volume was defined as the iGTV plus 3 mm. To determine the planning target volume (PTV), we used a margin of 5 mm in all directions around the internal target volume, with the 70% isodose region encompassing the PTV. The prescription dose was 70 Gy administered in 4 fractions at the isocenter. Radiotherapy was typically delivered with 7 or 8 beams: 3 or 4 noncoplanar and 4 coplanar 6 MV X-ray beams. The dose distributions were calculated using an X-ray voxel-based Monte Carlo algorithm by running iPlan RTDose 4.5.3 (Brainlab, Munich, Germany) using the treatment-planning CT with a heterogeneity correction. The dose constraints for the organs at risk were defined to avoid serious complications, as described in Table 1. In all cases, irradiation was applied using a Vero4DRT system (MHI-TM2000; Mitsubishi Heavy Industries, Hiroshima, Japan; and Brainlab). All patients were set up for each radiotherapy session according to skeletal anatomy using the ExacTrac kilovoltage imaging system (Brainlab), and cone-beam CT. If the locational errors of the tumor were over 3 mm, we shifted the irradiation fields to fit the tumor according to the iGTV structure. A 1-week schedule (3-4 fractions per week; overall treatment time, 4-8 days) was used. After SBRT, no additional treatment was offered to the patient until disease progression was observed.

Follow-up After Treatment

Follow-up visits were planned at 1, 2, 4, 6, 9, and 12 months within the first year after SBRT and every 3 months thereafter. Chest CT imaging was performed every 2 to 3 months for the first 12 months. [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET) was performed to detect any locoregional recurrence or metastasis. Enhanced magnetic resonance imaging of the brain was also used to identify any cranial metastasis. The follow-up period was defined as the duration between the first day of treatment and the last follow-up visit or the date of death. We defined local progression as meeting either of the following criteria: exacerbation of postirradiated changes observed as positive using FDG-PET, or cancer pathologically confirmed by biopsy or surgical resection. Toxicity grading in this study was conducted according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.[18] We diagnosed grade 2 RP when a patient showed symptomatic pneumonitis or oral administration of anti-inflammatory medication, but did not require administration of oxygen or intravenous steroids at hospital admission. Every follow-up CT was evaluated regarding the presence or absence of rib fractures and chest wall edema near the irradiated tumor.

Table 1 Dose Constraints

Organ at Risk	Dose (Gy) per Fraction	Volume (mL)
Lung	MLD <18.0 Gy	—
	V15 <25%	—
	V20 <20%	—
Spinal cord	25/4	Maximum
Esophagus, pulmonary artery	40/4	<1
	35/4	<10
Stomach, intestine, colon	36/4	<10
	30/4	<100
Trachea/bronchus	40/4	<10

There were no dose constraints for rib, chest wall, or liver. Skin received 40 Gy in 4 fractions at the most (if possible).
Abbreviations: MLD = mean lung dose; Vd = lung volume (%) receiving at least d Gy of radiation.

End Points

The primary end point was the rate of grade 2 or more RP within 1 year. The secondary end points were the rates of grade 2 or more adverse events, local control, overall survival, and patterns of failure.

Statistical Analysis

Estimating the rate of grade 2 or higher RP within 1 year at 10%, the number of samples was calculated to predict a 2-sided 95% confidence interval at an accuracy of within 10%.[11,12,19] The study design called for enrollment of 35 patients.

Local control and overall survival rates were calculated by the Kaplan-Meier method. Statistical analyses were conducted by R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). Statistical significance was defined as $P < .05$.

Results

A total of 35 patients enrolled onto this study between September 2014 and January 2016. The patient and tumor characteristics are listed in Table 2. A total of 19 lung tumors were diagnosed clinically as early primary lung cancers without histologic proof, with 3 lung tumors also being diagnosed as lung metastases. The median values for iGTV and PTV were 10.8 mL (range, 1.7-49.0 mL) and 48.3 mL (range, 16.9-146.9 mL), respectively. For all study patients, the organs at risk satisfied dose constraints.

Table 2 Patient and Tumor Characteristics

Characteristics	Value
Patients	35 (100)
Age (year), median (range)	77 (58–92)
Gender	
Male	23 (66)
Female	12 (34)
ECOG performance status	
0	10 (28)
1	22 (63)
2	3 (9)
Disease	
Primary lung cancer	32 (91)
Lung metastasis	3 (9)
Histology[a]	
Adenocarcinoma	10 (28)
SCC	3 (9)
Clinically diagnosed	19 (54)
T-stage[a]	
T1a	15 (43)
T1b	11 (31)
T2a	6 (17)
Target location	
Upper/middle	26 (74)
Lower	9 (26)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; SCC = squamous-cell carcinoma.
[a]Characteristics of the primary lung cancer.

Grade 2 RP was observed in 4 patients (11.4%), without severe RP (grade 3 or higher) being observed within 1 year after SBRT. The rate of grade 2 or higher RP within 1 year after treatment was within the 95% confidence interval of the predicted incidence of RP. Grade 2 RP was observed in 1 patient (2.9%) within 18 months after treatment, with no severe RP being observed later than 1 year after SBRT within the follow-up period. The median time to symptomatic RP was 4.5 months (range, 3.0-18.7 months). All cases of RP were cured by steroid treatment or resolved after observation. Grade 2 rib fractures were observed in 5 patients (14.3%). All tumors in patients with rib fractures after SBRT were located at the edge of the lungs, close to the chest wall. The median time to rib fracture was 17.9 months (range, 12.0-20.0 months). No other grade 3 or higher toxicities were observed.

The median follow-up period was 21.2 months (range, 4.2-31.7 months). All living patients were followed for at least 1 year. At the time of analysis, disease progression had been observed in 7 patients. The first site of progression was local lesion in 1 patient, mediastinal lymph node lesion in 1 patient, and distant metastasis in 5 patients. Local recurrence was observed in the lung metastasis of a patient with primary colorectal cancer. Of the 32 patients with primary lung cancer, no local recurrence was observed within the follow-up period. One patient died of primary lung cancer, 3 died of other cancers, and 2 died of noncancer causes. Local control and overall survival at 2 years were 95.7% (95% confidence interval, 72.9-99.4) and 85.2% (95% confidence interval, 67.8-93.6), respectively.

Discussion

To improve local control after SBRT for peripheral lung tumors, we performed a pilot study of dose escalation. All toxicities were grade 2 or less during the follow-up period and were deemed acceptable. We demonstrated the safety and efficacy of this dose escalation technique in this pilot study.

After SBRT for lung malignancies, symptomatic RP is a common toxicity that is occasionally fatal. Symptomatic RP normally occurs within 1 year after SBRT.[10] In this study, we followed all living patients for at least 1 year, which is a sufficient follow-up period to evaluate the occurrence and severity of RP. The rate of symptomatic RP after SBRT has been reported to be 2.4% to 28.0% in previous studies.[11,12] The rate of RP in this study is not greater than those reported in previous studies. We compared the rates of symptomatic RP and the dose–volume metrics between the present study and our previous work.[13] Detailed comparisons are shown in the Supplemental Materials in the online version (Document S1; Supplemental Tables S1 and S2; Supplemental Figures S1 and S2). We demonstrated that the dose to the PTV can be escalated by increasing dose gradients without increasing normal lung dose. In addition, this dose escalation method did not increase the rate of symptomatic RP compared to our previous method. We concluded that this dose escalation SBRT method was safe in regard to RP.

Chest wall pain and rib fractures are also common toxicities after SBRT for lung tumors.[20] Rib fractures occur in approximately 5% of patients (range, 1.6%-8.3%).[21] The rate of rib fractures in this study was higher than previously reported rates. Asai et al[22] reported that the maximum dose and high-dose volumes delivered to the ribs were strongly correlated with rib fractures. We evaluated the relationship between rib fractures and dosimetric parameters of the ribs.

The evaluated data are described in the Supplemental Materials in the online version (Document S2; Supplemental Table S3). We demonstrated that tumor–chest wall distance and maximum dose to the ribs were significantly associated with rate of rib fractures. The maximum dose to the ribs may have increased with dose escalation, which may be responsible for the higher rate of rib fracture in this study, compared to those of previous reports. The time to occurrence of rib fracture has been reported as within 30 months after SBRT.[23,24] At the time of analysis, the median follow-up time was 21 months, and more rib fractures could be expected in this study population in the future. A longer follow-up period is required for a precise evaluation of rib fractures due to SBRT.

The optimal dose distribution for lung SBRT is unknown. A systematic review of SBRT for early-stage non–small-cell lung cancer showed a relationship between dose at isocenter and the tumor periphery, and local control rates.[1] The local control rate at higher prescribed doses was better than rates at lower prescribed doses. The review study concluded that a higher total dose is needed to achieve optimal tumor control for primary lung cancer (biologically effective dose [BED] at the tumor periphery > 100 Gy_{10} and BED at the isocenter > 140 Gy_{10}). The total dose of 48 Gy in 4 fractions (BED 106 Gy_{10} at the isocenter), which is widely used in Japan, is safe but insufficient to achieve an excellent tumor control rate. In this study, we used a total dose of 70 Gy in 4 fractions at the isocenter, covering the PTV surface with 70% of the isodose. The BEDs at the isocenter and the PTV periphery were 193 and 106 Gy_{10}, respectively. In this study, no local recurrence was observed for primary lung cancer during the follow-up period. The dose is therefore assumed to be sufficiently high to achieve an excellent tumor control rate for primary lung cancer. This proposed prescribed dose escalation method may achieve excellent local control for primary lung cancer.

In this study, local recurrence was observed in metastatic lung tumors from primary colorectal cancer. Takeda et al[25] reported that the 2-year local control rate was 73% in oligometastasis from colorectal cancer treated with SBRT at a prescribed dose of 50 Gy in 5 fractions to the PTV periphery, which was defined as 80% of the maximal dose to the PTV. The authors concluded that dose escalation should be considered to achieve sufficient local control of colorectal oligometastatic lung tumors. In our study, of 3 metastatic lung tumors, 1 developed recurrence. Therefore, additional dose escalation may be necessary for oligometastatic lung tumors.

There were several limitations to this study. First, because this study was a pilot study to evaluate toxicities within 1 year after treatment, we have not assessed late toxicities such as chest wall pain, rib fractures, or symptomatic pulmonary fibrosis. To clarify the long-term safety profile of this method, further follow-up will be required. Second, the follow-up time was quite short to evaluate the efficacy of this method. Within the follow-up period, local recurrence had not occurred in any of the 32 primary lung cancers; however, recurrence may be observed in the future. Further follow-up observations are needed to clarify the long-term efficacy of this method. Furthermore, because this was a single-arm study conducted at a single institution, we need the conduct of further clinical trials in a multicenter setting to precisely and comprehensively assess the clinical results of this dose escalation method.

Conclusion

We evaluated the safety of dose escalation in SBRT using a total dose of 70 Gy in 4 fractions at the target isocenter, covering the PTV surface with 70% of the isodose for peripheral lung tumors. We clarified that this treatment method is safe in the acute and subacute phases. The results also suggest that this method can result in excellent local control rates. Further follow-up observations will be required to assess the utility of this method.

Clinical Practice Points

- SBRT is a safe and effective local treatment option for peripheral lung tumors. However, local recurrence is occasionally observed.
- To improve local control, the most promising treatment strategy is dose escalation. When considering dose escalation for lung tumors, it is important to minimize the dose to normal lung tissue to acceptable levels of toxicity, especially for RP.
- We studied a dose escalation method with steep dose gradients in the target volume to minimize dose to normal lung tissue. The prescription dose with this method is a total dose of 70 Gy in 4 fractions at the target isocenter, covering the PTV surface with 70% of the isodose.
- A total of 35 patients were enrolled onto this study, and we evaluated the safety and efficacy of this dose escalation method.
- Grade 2 RP was observed in 4 patients within 1 year. No severe RP (grade 3 or higher) was observed within the follow-up period. Local recurrence was observed in 1 patient with lung metastasis. In the 32 patients with primary lung cancer, no local recurrence was observed within the follow-up period.
- This dose escalation method for peripheral lung tumors was safe in the acute and subacute phases. The results also suggest that this method can result in excellent local control rates.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental materials, tables, and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2017.11.008.

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Document S1

Comparison of Radiation Pneumonitis Incidence in This Study With That of Our Previous Study

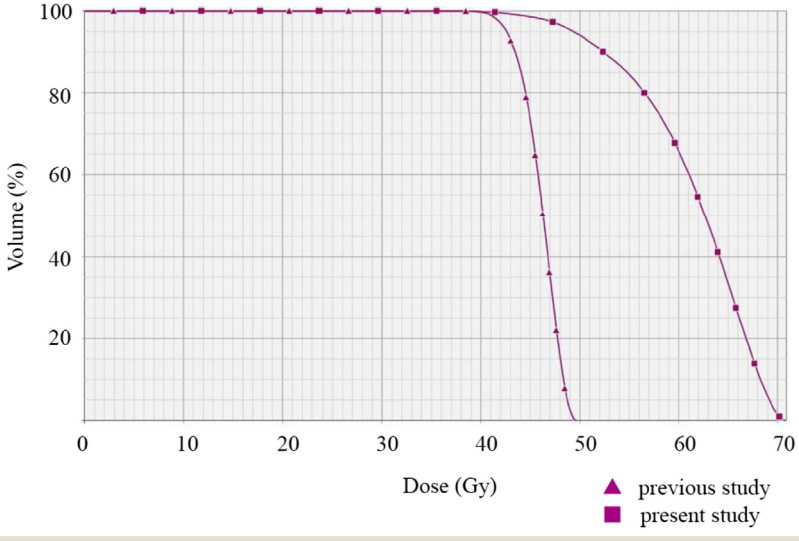
In our previous study, we analyzed the dose–volume metrics and the rates of symptomatic radiation pneumonitis (RP) in 74 patients who underwent stereotactic body radiotherapy for primary lung cancer.[1] We compared the results between the present study and our previous study. The patient and tumor characteristics in both studies are shown in Supplemental Table S1. All tumors in our previous study were primary lung tumors. Except for histology, no significant differences in patient and tumor characteristics were observed between our previous study and the present study. The patient and tumor characteristics were compared by *t* tests for continuous variables and chi-square tests for categorical variables.

The prescription dose and target definition method in our previous study were as follows: the internal gross tumor volume (iGTV) was delineated by the treatment-planning computed tomography (CT) image by referring to the 10 respiratory phase images of the 4-dimensional CT and the tumor motions detected on X-ray fluoroscopy; this was the same method used in the present study. The planning target volume (PTV) in our previous study was determined by adding a margin of 5 mm to the iGTV. The beams were conformed to the PTV plus 5 mm margins using multileaf collimators on the linear accelerator. The resulting gaps between the iGTVs and multileaf collimators were 10 mm in size. The prescription dose was 48 Gy in 4 fractions to the target isocenter. To compare the dose distributions of the targets between the present and previous studies, we needed to evaluate the structures generated by the same margins from the iGTVs. We defined the assessed target volume (ATV) in our previous study as the iGTV plus 8 mm.

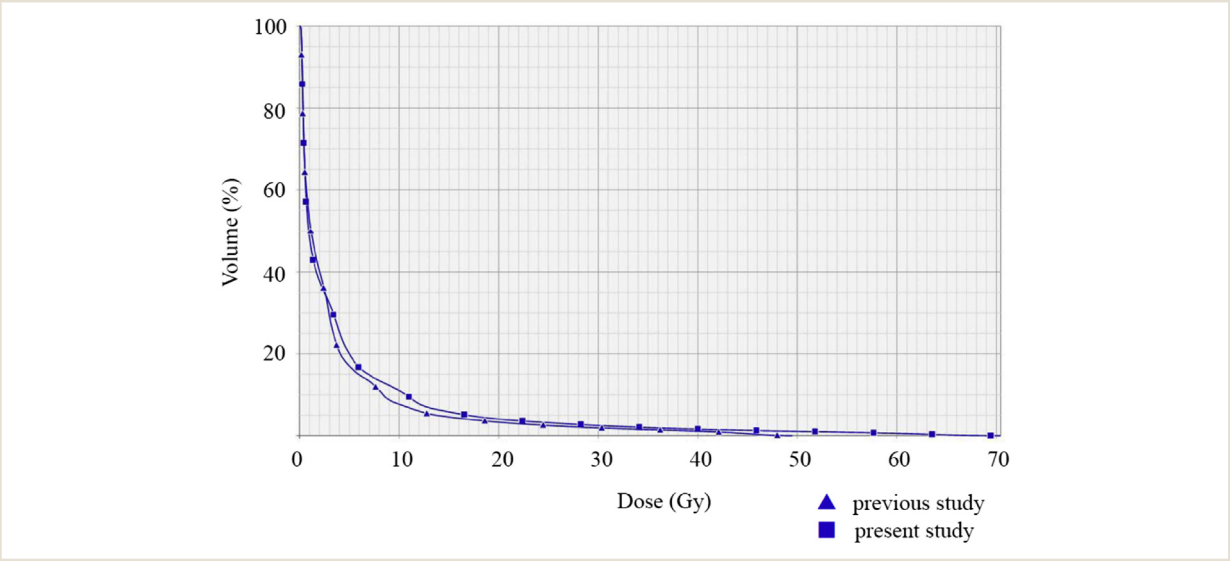
The dose–volume metrics of the iGTV, PTV or ATV, and normal lung tissue of 35 patients in the present study and 74 patients in the previous study are listed in Supplemental Table S2. The following dose–volume metrics were evaluated: iGTV volume (mL); PTV or ATV volume (mL), D2 (Gy), where D*x* is the absolute dose (Gy) that covered *x*% of the PTV or ATV; D98 (Gy); homogeneity index (HI), which was defined as the ratio of the PTV or ATV D2 to D98; lung volume (mL); mean lung dose (Gy); and lung V5–V40 (%), where V*d* was the relative volume of normal lung tissue (%) that received more than a threshold dose of *d* Gy. We defined normal lung tissue as both lungs excluding the iGTV. The dose–volume metrics were compared by *t* tests. No significant differences were observed between the target volumes in the present and previous studies. No significant difference was observed between the dose–volume metrics of normal lung. By contrast, the D2, D98 of target volumes, and HI in the present study were significantly higher than those in our previous study ($P < .01$). Supplemental Figures S1 and S2 show the dose–volume histograms of PTV and normal lung calculated with the present method or our previous method, respectively. We determined that the dose to the PTV can be escalated by increasing the dose gradients without increasing the dose to normal lung tissue.

We also compared the rates of symptomatic RP between our previous study and the present study. In our previous study, RP was observed in 15 patients (20.3%), comprising 14 patients with grade 2 and 1 patient with grade 3 RP. The rates of grade 2 or higher RP were not significantly different between the 2 studies ($P = .59$). Therefore, we concluded that this dose escalation method did not increase the rate of symptomatic RP.

Supplemental Figure S1 Dose–Volume Histograms for Planning Target Volume (PTV) or Assessed Target Volume (ATV)



Supplemental Figure S2 Dose–Volume Histograms for Normal Lung (Lung Volume Minus Internal Gross Tumor Volume)



Supplemental Table S1 Patient and Tumor Characteristics in Our Present and Previous Studies

Characteristics	Present Study (N = 35)	Previous Study (N = 74)	*P*
Age (year), median (range)	77 (58–92)	77 (63–88)	.51
Gender			.48
Male	23 (66)	55 (74)	
Female	12 (34)	19 (26)	
ECOG performance status			.08
0	10 (28)	37 (50)	
1	22 (63)	30 (41)	
2	3 (9)	7 (9)	
Disease			.03
Primary lung cancer	32 (91)	74 (100)	
Lung metastasis	3 (9)	0 (0)	
Histology[a]			<.01
Adenocarcinoma	10 (28)	36 (49)	
SCC	3 (9)	30 (41)	
NSCLC	0 (0)	8 (10)	
Clinically diagnosed	19 (54)	0 (0)	
T-stage[a]			.44
T1a	15 (43)	26 (35)	
T1b	11 (31)	27 (36)	
T2a	6 (17)	21 (29)	
Target location			.16
Upper/middle	26 (74)	43 (58)	
Lower	9 (26)	31 (32)	

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; SCC = squamous cell carcinoma; NSCLC = non–small cell lung cancer.
[a]Characteristics of the primary lung cancer.

Supplemental Table S2 Dose–Volume Metrics of iGTV, PTV and ATV, and Normal Lung Tissue of Patients in Our Present and Previous Studies

Variable	Present Study (N = 35)	Previous Study (N = 74)	*P*
iGTV			
Volume (mL)	10.8 (1.7-49.0)	12.3 (2.2-43.6)	.373
PTV (ATV)			
Volume (mL)	48.3 (16.9-146.9)	48.9 (20.7-126.4)	.936
D2 (Gy)	70.4 (66.1-73.9)	49.0 (42.9-52.2)	<.001
D98 (Gy)	48.3 (35.2-54.6)	38.8 (32.7-42.8)	< .001
HI	1.41 (1.30-1.94)	1.26 (1.16-1.52)	<.001
Lung			
Volume (mL)	2862 (1395-5131)	2992 (1270-4956)	.774
Mean dose (Gy)	3.3 (2.0-6.1)	3.2 (1.6-7.6)	.594
V40 (%)	0.9 (0.3-2.5)	0.8 (0.1-2.9)	.529
V35 (%)	1.3 (0.5-3.5)	1.4 (0.6-4.8)	.977
V30 (%)	1.9 (0.8-5.3)	2.1 (0.9-6.6)	.803
V25 (%)	2.9 (1.1-7.5)	3.0 (1.4-9.5)	.508
V20 (%)	4.6 (1.8-10.1)	4.5 (1.9-13.1)	.206
V15 (%)	7.5 (3.3-15.3)	6.7 (2.8-18.2)	.094
V10 (%)	11.7 (6.0-20.5)	10.2 (4.4-25.1)	.194
V5 (%)	18.1 (8.5-31.0)	16.5 (7.1-37.3)	.251

Data are presented as median (range).
Abbreviations: ATV = assessed target volume; D*n* = more than *n*% of target volume; HI = homogeneity index; iGTV = internal gross tumor volume; PTV = planning target volume; V*d* = lung volume (%) receiving at least *d* Gy of radiation.

Document S2

Relationships Between Incidence of Rib Fracture and Rib Dosimetric Parameters

To clarify the relationship between the incidence of rib fracture and radiation dose to the ribs, the follow-up computed tomographic (CT) scan was evaluated regarding the presence or absence of rib fractures near the irradiated tumor. Rib fracture was defined as a disruption of cortical continuity with malalignment. We contoured exclusively on the rim of the ribs and did not include the cartilage, using the bone window setting (window level, 400; window width, 2000) on the radiation treatment planning system, and we then calculated the radiation dose. Distance (mm) between the tumor and chest wall (tumor–chest wall distance) was measured on the planning CT. The following dosimetric parameters were calculated for each rib: maximum dose (Gy) of ribs (rib maximum dose [D_{max}]), or rib V30-70 (mL), where V*d* was the absolute volume of ribs (mL) that received more than a threshold dose of *d* Gy.

Grade 2 rib fractures were observed in 5 patients (14.3%) during the follow-up period. The irradiated doses to the ribs were compared between fractured and nonfractured ribs, and the statistical significance of the differences was evaluated by Student's *t* test. The tumor–chest wall distance, values of rib D_{max}, and rib V30–V70 with or without rib fracture are shown in Supplemental Table S3. The tumor–chest wall distance and rib D_{max} were significantly associated with rib fractures.

Supplemental Table S3 Comparison of Dosimetric Factors Between Fractured and Nonfractured Ribs

Parameter	Fracture (N = 5)	No Fracture (N = 30)	*P*
Tumor–chest wall distance (mm)	0	5.5 (0-29.6)	<.01
Rib			
D_{max} (Gy)	71.3 (69.3-72.8)	66.9 (30.8-72.8)	<.01
V70 (mL)	0.2 (0.0-0.6)	0.1 (0.0-1.0)	.35
V60 (mL)	2.3 (1.1-3.4)	1.3 (0.0-6.0)	.06
V50 (mL)	3.8 (1.5-5.4)	2.7 (0.0-12.4)	.30
V40 (mL)	5.2 (2.1-7.9)	4.9 (0.0-22.0)	.86
V30 (mL)	7.0 (2.7-11.5)	9.4 (0.0-37.0)	.32

Data are presented as mean (range).
Abbreviations: D_{max} = maximum dose to ribs, V*d* = rib volume (mL) receiving at least *d* Gy of radiation.

Reference for the Supplemental Data

1. Matsuo Y, Shibuya K, Nakamura M, et al. Dose–volume metrics associated with radiation pneumonitis after stereotactic body radiation therapy for lung cancer. *Int J Radiat Oncol Biol Phys* 2012; 83:e545-9.