Clinical Investigation: Thoracic Cancer

# Dose–Volume Metrics Associated With Radiation Pneumonitis After Stereotactic Body Radiation Therapy for Lung Cancer

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## Summary

To identify dose–volume factors associated with radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for lung cancer, this study analyzed 74 patients who underwent SBRT for primary lung cancer. RP grade 2 or worse was observed in 15 patients (20.3%). Lung V25 and PTV volume were significant factors. SBRT with PTV ≥37.7 ml and lung V25 ≥4.2% indicated a 50% risk of RP grade 2 or worse.

**Purpose:** To identify dose–volume factors associated with radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for lung cancer.

**Methods and Materials:** This study analyzed 74 patients who underwent SBRT for primary lung cancer. The prescribed dose for SBRT was uniformly 48 Gy in four fractions at the isocenter. RP was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.3. Symptomatic RP was defined as grade 2 or worse. Optimal cut-offs dividing the patient population into two subgroups based on the incidence of symptomatic RP were sought using the following dose–volume metrics: PTV volume (ml), mean lung dose (Gy), and V5, V10, V15, V20, V25, V30, V35, and V40 (%) of both lungs excluding the PTV.

**Results:** With a median follow-up duration of 31.4 months, symptomatic RP was observed in 15 patients (20.3%), including 1 patient with grade 3. Optimal cut-offs for pulmonary dose–volume metrics were V25 and V20. These two factors were highly correlated with each other, and V25 was more significant. Symptomatic RP was observed in 14.8% of the patients with V25 <4.2%, and the rate was 46.2% in the remainder ($p = 0.019$). PTV volume was another significant factor. The symptomatic RP rate was significantly lower in the group with PTV <37.7 ml compared with the larger PTV group (11.1% vs. 34.5%, $p = 0.020$). The patients were divided into three subgroups (patients with PTV <37.7 ml; patients with, PTV ≥37.7 ml and V25 <4.2%; and patients with PTV ≥37.7 ml and V25 ≥4.2%); the incidence of RP grade 2 or worse was 11.1%, 23.5%, and 50.0%, respectively ($p = 0.013$).

**Conclusions:** Lung V25 and PTV volume were significant factors associated with RP after SBRT. © 2012 Elsevier Inc.

**Keywords:** Radiation pneumonitis, Stereotactic body radiation therapy, Dose—volume analysis

## Introduction

Stereotactic body radiation therapy (SBRT) consists of two key features. One is its high degree of accuracy, which allows delivery of a high dose to a very limited volume while limiting the dose to normal tissues. The other key feature is hypofractionation. With conventional radiotherapy, schedules of 30 to 40 fractions are commonly used, with a total dose of 60 to 74 Gy for lung cancer. SBRT is usually performed in a single fraction or two to five fractions with a much higher fractional dose (6—20 Gy). These key features of SBRT lead to high control rates of local tumors (1, 2). Use of SBRT should improve the prognosis for inoperable or elderly patients with early stage non-small-cell lung cancer (NSCLC) (3).

The safety of SBRT is being confirmed in multi-institutional Phase II trials for peripheral lung cancer in both inoperable patients (1, 4) and operable patients (2). In the Radiation Therapy Oncology Group (RTOG) trial 0236 (1), protocol-specified treatment-related grade 3 and 4 adverse events occurred in 12.7% and 3.6%, respectively; no grade 5 adverse events were reported. In the Nordic Phase II study of SBRT (4), grade 3 toxicity was seen in 21%; no grade 4 or 5 toxicity was reported. Nagata *et al.* reported grade 3 toxicity in 6.2% of operable patients in the Japan Clinical Oncology Group (JCOG) 0403 (2).

Radiation pneumonitis (RP) is one of the most common toxicities after SBRT, as well as after conventional radiotherapy to the lung. The reported rates of symptomatic RP after SBRT range from 9% to 28% (5—11). Although most of the RP was grade 2 and manageable, a few cases were severe, and there is a potential risk of mortality (5). It is very important to develop a method to predict the risk of RP after SBRT for the lung.

The dose—volume metrics from a treatment plan might be a predictor for RP. In conventional radiotherapy for the lung, many dose—volume data are available, and dose constraints have been proposed to reduce the risk of pneumonitis. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommended a lung V20 $\leq$30% to 35% and mean lung dose (MLD) $\leq$20 to 23 Gy to limit the risk of RP to $\leq$20% in definitive radiotherapy for NSCLC with conventional fractionation (12). However, there are no established criteria regarding dose—volume factors in hypofractionated SBRT. Therefore, we searched for dose—volume factors associated with RP after SBRT for lung cancer.

## Methods and Materials

This study analyzed consecutive 74 patients who underwent SBRT for pathology-proven NSCLC from September 2003 to March 2008. All patients were diagnosed with Stage I lung cancer based on CT. The eligibility criteria for SBRT for Stage I lung cancer were as follows: surgery was contraindicated or refused; maximal tumor diameter was 40 mm or less; the tumor was not adjacent to mediastinal organs (spinal cord, esophagus, heart, and main bronchus); the patient could remain stable for longer than 30 min

with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; the patient had no active interstitial pneumonitis; and written informed consent was obtained. Patient characteristics are shown in Table 1. For these patients, the prescribed dose of SBRT was uniformly 48 Gy in four fractions at the isocenter. A median in overall treatment time was 5 days (range, 4—12 days). Chemotherapy was not administered unless disease progression was confirmed.

### SBRT procedure

Details of our SBRT procedure have been described in our previous reports (13, 14). The patient was immobilized with a stereotactic body frame (Elekta AB, Stockholm, Sweden). Irradiation was performed with 6-MV x-ray beams from a linear accelerator (Clinac 2300 C/D; Varian Medical Systems, Palo Alto, CA) with multiple non-coplanar static ports (range, five to eight ports). The beams were shaped into a planning target volume (PTV) plus 5-mm margins using multi leaf collimators.

The SBRT was planned with the Eclipse (Varian Medical Systems) treatment planning system. An internal target volume (ITV) was determined using computed tomography (CT) with a slow-scan technique, considering tumor motion assessed by x-ray fluoroscopy. The PTV was defined as the ITV with a 5-mm margin for setup uncertainty. To delineate lung volumes, the segmentation wizard in Eclipse was applied to the slow-scan CT images with a threshold value of −300 Hounsfield units (HU). The lung

| Table 1 | Patient characteristics |
| --- | --- |
| Sex | |
|   Male | 55 |
|   Female | 19 |
| Age (y) | |
|   Median (range) | 77 (63—88) |
| ECOG performance status | |
|   0 | 37 |
|   1 | 30 |
|   2 | 7 |
| Operability | |
|   Operable | 24 |
|   Inoperable | 50 |
| Histology | |
|   Adenocarcinoma | 36 |
|   Squamous cell carcinoma | 30 |
|   Other* | 8 |
| T-stage (7th UICC staging) | |
|   T1a | 26 |
|   T1b | 27 |
|   T2a | 21 |

*Abbreviation:* UICC = Union for International Cancer Control.

* Other included three large-cell carcinomas and five non-small-cell carcinomas not otherwise specified.

volumes were then trimmed manually to remove overlapping regions involving the PTV and bronchi.

## RP grading

The patients were followed up 1, 2, 4, 6, 9, and 12 months after the SBRT, then every 3 months for Years 2 to 5, and then every 6 months thereafter. CT was performed every 2 to 4 months in the first year, every 6 months between Years 1 and 5 after the treatment, and annually thereafter.

Radiation pneumonitis was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v.3 for pneumonitis, which consists of the following grades: grade 1, asymptomatic with radiographic findings only; grade 2, symptomatic and not interfering with the activities of daily living (ADL); grade 3, symptomatic, interfering with the ADL and $O_2$ indicated; and grade 4, life-threatening, ventilatory support indicated. We defined symptomatic RP as grade 2 or worse.

## Statistical analysis

The dose−volume metrics were re-calculated using the Analytical Anisotropic Algorithm (AAA) with the same monitor units as used in the clinical setting. The grid size for the calculation was $2.5 \times 2.5 \times 2.5$ mm$^3$.

The following dose−volume metrics were evaluated in this study: PTV volume (ml), MLD (Gy), and V5, V10, V15, V20, V25, V30, V35, and V40, where V$d$ is the relative volume of normal lung (%) that received more than a threshold dose of $d$ Gy. We defined normal lung as both lungs excluding the PTV.

The optimal cut-offs dividing the patient population into two subgroups based on the incidence of symptomatic RP were searched using the recursive partitioning method. After dividing the groups, the occurrence rates for symptomatic RP were compared using Fisher's exact test. R version 2.13.1 with the rpart package (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses. Statistical significance was defined as $p < 0.05$.

## Results

With a median follow-up duration of 31.4 months (range, 4.2−65.0 months), symptomatic RP was observed in 15 patients (20.3%), consisting of 14 patients with grade 2 and 1 patient with grade 3. RP was diagnosed based on symptoms with radiologic findings. The median time to symptomatic RP was 4.5 months (range, 1.1−16.1 months).

Table 2 summarizes the dose−volume metrics of the PTV and normal lung. The PTV ranged from 9.9 to 86.6 ml (median, 32.5 ml). The median MLD was 3.2 Gy (range, 1.6−7.6 Gy). The median lung V20 and V25 were 4.4% and 2.9%, respectively. The lung metrics (MLD and V5−40) were highly correlated with each other, with correlation coefficients ($R$) of 0.61 to 0.99. In contrast, the correlations between the PTV volume and lung metrics were weak ($R = 0.37−0.59$). The PTV volume, MLD, V20, and V25 were respectively 42.1 ml, 3.7 Gy, 5.4%, and 3.8% in mean for patients with grade 2 RP. Those values were respectively 38.1 ml, 4.0 Gy, 5.0%, and 3.3% for a patient with grade 3 RP.

The optimal cut-offs for the dose−volume metrics are shown in Table 3. Lung V25 and V20 were significant factors, and V25

**Table 2**  Dose−volume metrics

| | | Median (range) |
|---|---|---|
| PTV | Volume (ml) | 32.5 (9.9−86.6) |
| Lung | Mean dose (Gy) | 3.2 (1.6−7.6) |
| | V40 (%) | 0.7 (0−2.9) |
| | V35 (%) | 1.4 (0.2−4.8) |
| | V30 (%) | 2.0 (0.5−6.6) |
| | V25 (%) | 2.9 (0.9−9.5) |
| | V20 (%) | 4.4 (1.7−13.1) |
| | V15 (%) | 6.7 (2.6−18.2) |
| | V10 (%) | 10.3 (4.4−25.1) |
| | V5 (%) | 16.7 (7.1−37.3) |

*Abbreviation:* PTV = planning target volume.

was more significant. The rate of symptomatic RP was 14.8% in the patients with V25 <4.2%, whereas the rate was 46.2% in the remainder ($p = 0.019$). The PTV volume was another significant factor. The symptomatic RP rate was significantly lower in the group with PTV <37.7 ml compared with the larger PTV group (11.1% vs. 34.5%, $p = 0.020$). On classifying the patient population into three subgroups (patients with PTV <37.7 ml, $n = 45$; patients with PTV ≥37.7 ml and V25 <4.2%, $n = 17$; and patients with PTV ≥37.7 ml and V25 ≥4.2%, $n = 12$), the incidence of symptomatic RP was 11.1%, 23.5%, and 50.0%, respectively ($p = 0.013$).

## Discussion

We investigated the dosimetric factors associated with symptomatic RP (≥grade 2) after SBRT, and found that PTV and lung V25 were significant factors. The optimal cut-offs for these factors (PTV <37.7 ml and V25 <4.2%) were much lower than prespecified constraints that other SBRT trials used to mainly limit the risk of grade 3 toxicities (e.g., MLD <18 Gy, lung V40 <100 ml, V15 <25%, and V20 <20% for the JCOG 0403 trial; and lung V20 <10% for RTOG 0236). As only 1 patient in our cohort had grade 3 RP, it was difficult to build a model for predicting severe RP (e.g., grade 3 or worse). Severe RP is uncommon after SBRT for the lung. Grade 3 RP was observed in 3.6% of the patients in RTOG

**Table 3**  Optimal cut-off values and crude rates of symptomatic RP

| | Cut-off values | Symptomatic RP | | $p$ values |
|---|---|---|---|---|
| | | <Cut-off | ≥Cut-off | |
| PTV (ml) | 37.7 | 11.1% | 34.5% | 0.020* |
| MLD (Gy) | 4.7 | 17.2% | 40.0% | 0.110 |
| V40 (%) | 1.6 | 17.6% | 50.0% | 0.093 |
| V35 (%) | 1.9 | 15.3% | 40.0% | 0.066 |
| V30 (%) | 2.8 | 15.3% | 40.0% | 0.066 |
| V25 (%) | 4.2 | 14.8% | 46.2% | 0.019* |
| V20 (%) | 5.8 | 15.0% | 42.9% | 0.030* |
| V15 (%) | 4.9 | 5.3% | 25.5% | 0.096 |
| V10 (%) | 10.1 | 11.4% | 28.2% | 0.089 |
| V5 (%) | 26.8 | 17.9% | 42.9% | 0.143 |

*Abbreviations:* MLD = mean lung dose; PTV = planning target volume; RP = radiation pneumonitis.
* Statistically significant.

**Table 4** Summary of reports on dose–volume factors associated with radiation pneumonitis grade 2 or worse after stereotactic body radiation therapy

| First author, reference | Year | n | Dose fractionation (total dose/fractions) | Heterogeneity correction algorithm | PTV volume (ml), median (range) | RP grade 2 or worse (crude rate) | Scoring system | Suggested factors |
|---|---|---|---|---|---|---|---|---|
| Yamashita (5) | 2007 | 25 | 48 Gy/4–6 fr | CC | 43.9 (7.5–239.4) | 28.0% | CTCAE v3 | CI |
| Ricardi (6) | 2009 | 60 | 45 Gy/3 fr or 26 Gy/1 fr | CC | NA | 14.3% | RTOG | MLD† (ipsilateral lung-CTV) |
| Borst (7) | 2009 | 128 | 35–60 Gy/4–8 fr | CS | 9.6 (0.2–106.9) in GTV | 10.9% | CTC v2 | MLD† (bilateral lung-GTV) |
| Guckenberger (8) | 2010 | 59 | 26 Gy/1 fr or 37.5 Gy/3 fr | AAA | 33 (2–236) | 18.6% | SWOG | MLD† and V2.5–50 (ipsilateral lung-CTV) |
| Ong (9) | 2010 | 18 | 55 Gy/5 fr or 60 Gy/8 fr | AAA | 137 (87–286) | 27.8% | CTCAE v4 | V5 (contra-lateral lung) |
| Barriger (10) | 2010 | 251 | 24–66 Gy/3–5 fr | NA* | 48.3 (8–401) | 9.4% | CTC v2 | MLD and V20 (bilateral lung-GTV) |
| Stauder (11) | 2011 | 84 | 32–60 Gy/3–5 fr | NA* | 42.9 (5.3–321.5) | 12.5% | CTCAE v3 | PTV maximal dose |
| Present study | | 74 | 48 Gy/4 fr | AAA | 32.5 (9.9–86.6) | 20.3% | CTCAE v3 | PTV volume and V25 (bilateral lung-PTV) |

*Abbreviations:* AAA = analytical anisotropic algorithm; CC = collapsed cone convolution superposition; CI = conformity index; CS = convolution–superposition; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; fr = fractions; MLD = mean lung dose; NA = not available; RP = radiation pneumonitis; RTOG = Radiation Therapy Oncology Group; SWOG = Southwest Oncology Group.

\* Authors reported that tissue heterogeneity was corrected in some patients, but information on heterogeneity correction algorithm was not available.

† MLD was evaluated using normalized total dose, which is the equivalent dose in 2-Gy fractions.

0236 (1) and in 3.1% of the operable patients in JCOG 0403 (2). Baumann *et al.* reported that no one developed grade 3 pneumonitis in their Phase II trial of SBRT (4).

Table 4 summarizes published reports that focused on the dose–volume metrics associated with RP grade 2 or worse after SBRT. The RP rates varied from 9.4% to 28.0%, and the suggested dose–volume factors for RP differed among the reports. This variation might be caused by differences in the PTV volume, dose fractionation schedule, and RP scoring system.

The scoring criteria for RP differ among toxicity grading systems. Steroid use for pneumonitis is scored as grade 3 in the RTOG system, whereas the Common Toxicity Criteria (CTC) v.2 scores symptomatic patients requiring steroids as grade 2. CTCAE v.3 removed steroid use from the pneumonitis scoring system. From CTCAE v.3 to v.4, the pneumonitis score was modified slightly. Grade 2 pneumonitis in CTCAE v.4 was defined as "symptomatic, medical intervention indicated or limiting instrumental ADL." The number of patients considered to have RP depends on which system is used to evaluate RP. Tucker *et al.* retrospectively evaluated 442 patients who received definitive radiotherapy for NSCLC using the three RP grading systems: RP grade 2 or worse was observed in 129 (29%), 109 (25%), and 195 (44%) patients according to RTOG, CTC v.2, and CTCAE v.3, respectively (15). The rate of grade 2 to 3 RP according to CTCAE v.3 seemed to be slightly higher (20.3%) in our study compared with other studies that evaluated it using CTC v.2 or the RTOG system. Nevertheless, we administered steroids to 6 patients (8.1%) only. Scoring systems should be considered when interpreting the results regarding RP.

This study indicated that a large PTV is a significant risk factor for symptomatic RP after SBRT. Ong *et al.* treated large tumors in 18 patients with a PTV >80 ml (median, 137 ml) with SBRT using volumetric modulated arc therapy (9). The investigators reported 5 patients (27.8%) with RP grade 2 to 3. We speculate that the large PTV volume was one of the reasons for their relatively high risk of pneumonitis. From our results, minimizing the PTV is one way to limit the RP risk. When a lung tumor has large respiratory motion, respiration management will contribute to the prevention of RP by reducing the PTV.

To correct for differences in dose fractionation, three reports (6–8) in Table 4 used normalized total doses (NTD), which were equivalent doses in 2-Gy fractions in terms of pulmonary toxicity. Borst *et al.* evaluated the relationship between the MLD and the incidence of RP after SBRT (7). They calculated the MLD in the NTD form using the linear-quadratic model with an $\alpha/\beta$ ratio of 3 Gy. A significant dose–response relationship was found between RP and MLD. We used a uniform dose fractionation of 48 Gy in four fractions for all of our patients, and we evaluated dosimetric factors in the form of a nominal dose. Although we cannot apply normalization to our data exactly, the median MLD was roughly estimated to be 3.7 Gy in NTD. The usefulness of NTD evaluation for pulmonary toxicity after SBRT should be validated in future studies.

Heterogeneity correction and the definition of lung volume may influence the dose–volume factors of the lung. De Jaeger *et al.* evaluated differences between the equivalent–pathlength and convolution–superposition algorithms in MLD and V20 for 68 patients treated with conformal radiotherapy for NSCLC (16). MLD and V20 differed between the two algorithms by 16.9% and 12.0% on average, respectively. The $TD_{50}$ for RP grade 2 or worse in MLD was estimated to be 34.1 Gy with the equivalent-pathlength algorithm, whereas the value was 29.2 Gy with the

convolution—superposition algorithm. Because most related reports have used convolution—superposition algorithms, we applied the AAA, which is a convolution—superposition algorithm, to recalculate the dose—volume data so as to limit the influences of heterogeneity correction.

Our definition of lung volume was both lungs segmented with a threshold value of −300 HU on slow-scan CT from which PTV was excluded. Lung volume can vary depending on which lung is evaluated (ipsilateral, contralateral, or bilateral), exclusion of tumor volume (GTV or PTV), type of planning CT (slow-scan CT, 4D CT, or breath-hold CT), and the threshold HU for segmentation. When the PTV is subtracted from the lung volume, a high-dose volume within the PTV margin is not evaluated as dose—volume factors for the lung. These conditions were not always stated in the previous papers, and future articles should include this information.

Factors other than the dose—volume metrics also affect the occurrence of pneumonitis after SBRT. The serum level of Krebs von den Lungen-6 (KL-6) is a predictor of RP. Hara et al. evaluated 16 patients who received single-fraction SBRT with 20 to 35 Gy (17). The relative increase in the serum KL-6 between before and at 2 months after SBRT was significantly correlated with the occurrence of grade 3 RP by the RTOG criteria. Iwata et al. reported that the pretreatment serum KL-6 levels, gender, and PTV volume were correlated with symptomatic RP in a univariate analysis, and the pretreatment KL-6 levels remained significant in a multivariate analysis (18). They concluded that patients with a pretreatment KL-6 level ≥300 U/ml should be followed carefully for the occurrence of RP. CT or x-ray imaging before and after SBRT should help to predict severe RP. Yamashita et al. recommended prescreening of interstitial pneumonitis on CT, in addition to checking the serum KL-6 and surfactant protein-D (SP-D) levels to limit the risks of severe RP (19). They reported that after introducing the prescreening, the occurrence rate of RP grade 4 to 5 decreased from 18.8% to 3.5%. Takeda et al. reported that the early appearance of RP on chest x-ray after SBRT was correlated with the severity of RP (20). The radiographic appearance of RP during the initial 2 months indicated a 40% risk for grade 3 RP, whereas the risk was only 1.2% when the radiologic change appeared 3 months after SBRT. Considering biomarkers (KL-6 and SP-D) and radiologic imaging as well as dose—volume factors helps us to limit the risks for severe pneumonitis after SBRT.

Our study has several limitations. First, this study was based on a retrospective review; thus, it was prone to selection bias. Second, the number of RP events was limited in the present study. Third, that clinical factors other than dose—volume metrics were not taken into consideration. Prospective data are awaited to investigate a correlation between pulmonary toxicities and dosimetric factors.

## Conclusion

In conclusion, this study found that the lung V25 and PTV volumes were significant factors associated with RP after SBRT. Use of SBRT with PTV ≥37.7 ml and lung V25 ≥4.2% indicated a 50% risk of RP grade 2 or worse.

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