International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation: Thoracic Cancer

Clinical and Dosimetric Predictors of Radiation Pneumonitis in a Large Series of Patients Treated With Stereotactic Body Radiation Therapy to the Lung

Ryan Baker, BS,* Gang Han, PhD,† Siriporn Sarangkasiri, MS,‡ MaryLou DeMarco, MS, CMD,‡ Carolyn Turke, CMD,‡ Craig W. Stevens, MD, PhD,‡ and Thomas J. Dilling, MD‡

**University of South Florida School of Medicine, Tampa, Florida; and Departments of †Biostatistics and ‡Radiation Oncology, Moffitt Cancer Center, Tampa, Florida*

Received Nov 30, 2011, and in revised form Mar 5, 2012. Accepted for publication Mar 13, 2012

Summary

Few studies describe factors predictive of radiation pneumonitis in lung SBRT patients. We report an analysis of 240 patients (263 isocenters) treated in 5-8 fractions. Female gender was predictive in univariable and multivariable analysis. In univariable analysis some dosimetric factors were predictive (V_5, V_{13}, $V_{prescription}$ [when dose = 60 Gy]), as well as Charlson Comorbidity Index. However, in multivariable analysis dosimetric factors were eliminated; pack-years smoking and larger GITV and PTV were predictive.

Purpose: To report clinical and dosimetric factors predictive of radiation pneumonitis (RP) in patients receiving lung stereotactic body radiation therapy (SBRT) from a series of 240 patients.
Methods and Materials: Of the 297 isocenters treating 263 patients, 240 patients (n = 263 isocenters) had evaluable information regarding RP. Age, gender, current smoking status and pack-years, O_2 use, Charlson Comorbidity Index, prior lung radiation therapy (yes/no), dose/fractionation, V_5, V_{13}, V_{20}, $V_{prescription}$, mean lung dose, planning target volume (PTV), total lung volume, and PTV/lung volume ratio were recorded.
Results: Twenty-nine patients (11.0%) developed symptomatic pneumonitis (26 grade 2, 3 grade 3). The mean V_{20} was 6.5% (range, 0.4%-20.2%), and the average mean lung dose was 5.03 Gy (0.547-12.2 Gy). In univariable analysis female gender ($P = .0257$) and Charlson Comorbidity index ($P = .0366$) were significantly predictive of RP. Among dosimetric parameters, V_5 ($P = .0186$), V_{13} ($P = .0438$), and $V_{prescription}$ (where dose = 60 Gy) ($P = .0128$) were significant. There was only a trend toward significance for V_{20} ($P = .0610$). Planning target volume/normal lung volume ratio was highly significant ($P = .0024$). In multivariable analysis the clinical factors of female gender, pack-years smoking, and larger gross internal tumor volume and PTV were predictive ($P = .0094$, .0312, .0364, and .052, respectively), but no dosimetric factors were significant.
Conclusions: Rate of symptomatic RP was 11%. Our mean lung dose was <600 cGy in most cases and V20 <10%. In univariable analysis, dosimetric factors were predictive, while tumor size (or tumor/lung volume ratio) played a role in multivariable and univariable and analysis, respectively.

Reprint requests to: Thomas J. Dilling, MD, Moffitt Cancer Center, 12902 Magnolia Dr, MCC-Rad Onc, Tampa, Florida 33612. Tel: (813) 745-2612; Fax: (813) 745-5625; E-mail: Thomas.Dilling@Moffitt.org

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 85, No. 1, pp. 190–195, 2013
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2012.03.041

Introduction

Stereotactic body radiation therapy (SBRT) to the lung is an emerging clinical paradigm in the treatment of patients with early-stage lung cancers or small lung metastases, particularly in patients who are not surgically resectable. However, this extreme hypofractionation represents a significant break from prior radiobiological understanding and experience in regard to normal tissue toxicity. Although the reported toxicities of lung SBRT have, for the most part, been minor, the dose constraints to use during treatment planning are based on extremely limited clinical data and mostly are not validated (1). Even the recent QUANTEC lung article devoted only 1 paragraph to pneumonitis risk in lung SBRT patients (2).

To date we have treated more than 300 lesions at our institution with SBRT. In nearly all patients we have prospectively gathered toxicity data throughout therapy and at all follow-up examinations (see below). We also retrospectively gathered dosimetric data from the dose-volume histogram curves of the individual treatment plans, as well as a variety of clinical factors for each patient. From this information, we have gained knowledge of new predictors of symptomatic radiation pneumonitis (RP) when treating with (typically) 5-fraction SBRT. This article outlines these findings.

Methods and Materials

We retrospectively gathered information on all patients treated with lung SBRT at our institution between September 2006 and July 2011. This review was approved by the institutional review board (IRB# 105996).

Since early 2008 we have prospectively recorded relevant toxicity data using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 (and more recently, version 4), including RP, at each on-treatment visit and all subsequent follow-ups for all thoracic patients treated with radiation therapy at our institution. For the comparatively few patient visits before implementation of this system, data were retrospectively gathered from the clinic notes, when available. For this analysis, other relevant clinical information was also recorded, including smoking history, gender, age at diagnosis, previous treatment information and malignancies, tumor location, current smoking status, and comorbidity (recorded as an age-adjusted Charlson Comorbidity Index score for each patient at the time of initial presentation to a radiation oncologist). We collected dosimetric information from the treatment plans, including mean lung dose (MLD), V_5, V_{13}, V_{20}, $V_{prescription}$, and Conformality Index (CI), defined as the volume (in cubic centimeters [cm^3]) enlosed by the prescription isodose line divided by the volume enclosed by the planning target volume (PTV) (cm^3). Last, we gathered information regarding the size (cm^3) of the internal gross tumor volume (IGTV) and PTV, as well as of normal lung (defined as total lung volume − IGTV).

All patients were immobilized for treatment using a BodyFix double-vacuum cradle (Elekta, Stockholm, Sweden). To minimize respiratory excursion of the diaphragm, patients typically underwent abdominal compression. We used a weightlifter's belt in 120 cases, and in 110 cases a custom-built external compression device that placed external force onto a plate on the patient's abdomen. The remainder (n = 33) did not undergo abdominal compression, either owing to poor tolerance or because a CT simulation without abdominal compression demonstrated minimal respiratory motion of the tumor. All patients were simulated using a 4-dimensional CT scan. The IGTV was derived from (at minimum) the mathematical union of the 2 extreme phases of the respiratory scan and the free-breathing scan. The standard PTV expansion was 5 mm axially and 7 mm superiorly and inferiorly. Initially (n = 152 isocenters), patients were treated on a Novalis treatment machine. Daily image guidance was performed using steroscopic imaging of the bony anatomy before each treatment, with implanted fiducials to verify positioning. Plans were calculated using BrainLab treatment planning software. Dose calculation used a pencil beam algorithm with heterogeneity corrections turned on. More recently (n = 111 isocenters), patients were treated on either a Varian (Palo Alto, CA) Trilogy or TrueBeam machine. All plans were calculated using Pinnacle treatment planning software, version 9.0 (Philips, Amsterdam, The Netherlands), using a collapsed cone convolution dose calculation algorithm. All patients were imaged daily before treatment and repositioned accordingly using a cone-beam CT scan, which was aligned to the patients' tumors on the simulation CT. Regardless of the treatment machine used, all patients were treated on consecutive weekdays.

In the statistical analysis, descriptive statistics were calculated for discrete variables (frequency and percentage) and continuous variables (mean, variance, 25% and 75% quantiles, and histogram). Radiation pneumonitis grade was treated as an ordinal variable with 4 possible values—0, 1, 2, and 3 (National Cancer Institute Common Terminology Criteria for Adverse Events)—and also coded as a dichotomous variable with 2 levels (values {0, 1} vs {2, 3}). The analysis of the ordinal values of pneumonitis grade included testing the independence between pneumonitis values and categoric variables according to Pearson's χ^2 test and Fisher's exact test, and quantifying the correlation between pneumonitis and continuous measurements using Spearman correlation coefficients. The analysis of the dichotomized pneumonitis grade included Pearson's χ^2 test of independence, as well as univariable and multivariable logistic regression analyses. The backward elimination procedure was implemented for variable selection. A significance level of .05 was used in all tests. This analysis was conducted in SAS software, version 9.2 (Cary, NC).

Results

From September 2006 through July 2011 we treated 263 patients to 297 separate isocenters using SBRT. Of these 263, 236 had 6 or more months of follow-up regarding pneumonitis in the treatment of 263 isocenters. Twenty-six patients developed grade 2 pneumonitis, and 3 patients developed grade 3 pneumonitis. Various demographic and health-related characteristics of these 236 patients and their tumors are in Tables 1 and 2. For patients treated multiple times, performance status and other demographic characteristics were re-evaluated at the time of presentation for treatment of the subsequent isocenter. The median follow-up on this patient cohort is 15.6 months (range, 3.0-58.7 months). As of the time of preparation of this article, 75.7% of patients are alive and 24.3% are deceased.

In 31 cases the previous treatment plans were electronically corrupt or otherwise not obtainable, leaving 232 evaluable plans. For 121 of these, the MLD was not available (not a readily

Table 1 Demographic characteristics of patients

Characteristic	n	%*
Gender		
Male	133	50.6
Female	130	49.4
Performance status		
0	94	35.7
1	131	49.8
2	30	11.4
3	8	3.0
Current smoker		
No	218†	83.5
Yes	43†	16.5
O_2 dependent		
No	219	83.2
Yes	44	16.7
Prior lung radiation therapy		
No	191	72.6
Yes	72	27.4
Worst pneumonitis grade		
0	65	24.7
1	169	64.2
2	26	9.9
3	3	1.1
Age (y)		
Mean ± SD	71.4 ± 10.5	
Median (range)	72 (37.0-93.0)	
Pack-years tobacco		
Mean ± SD	53.5 ± 40.6	
Median (range)	50 (0.0-200.0)	
Charlson Comorbidity Index (age-adjusted)		
Mean ± SD	6.2 ± 2.8	
Median (range)	6 (0.0-16.0)	

Values are number and percentage except where noted. Patients treated multiple times were re-evaluated at time of subsequent treatment (236 patients treated to 263 isocenters).

* May not add to 100% because of rounding.

† Smoking status unknown in 1 patient (treated twice).

Table 2 Demographic characteristics of tumors

Characteristic	n	%*
T-Stage (AJCC 7th ed)		
T1a	150	57.0
T1b	73	27.8
T2a	37	14.1
T2b	2	0.8
T3	1	0.4
Lobe of lung		
RUL	77	28.9
RML	21	7.9
RLL	66	24.8
LUL	59	22.2
LLL	40	15.0
Histology		
No biopsy	14	5.3
Adenocarcinoma	81	30.8
Squamous cell carcinoma	47	17.9
Bronchoalveolar carcinoma	21	8.0
NSCLC (NOS)	61	23.2
SCLC/mixed histology	7	2.7
Large-cell carcinoma	1	0.4
Carcinoid	2	0.8
NOS/other	5	1.9
Metastatic (non-lung primary)	24	9.1
IGTV (cm^3)		
Mean ± SD	22.5 ± 37.1	
Median (range)	12 (0.8-148.0)	
PTV (cm^3)		
Mean ± SD	53.7 ± 44.3	
Median (range)	37.6 (5.0-266.7)	
Normal lung volume (cm^3)†		
Mean ± SD	3437.2 ± 1176.7	
Median (range)	3259.7 (1220.9-8089.6)	

Abbreviations: AJCC = American Joint Committee on Cancer; IGTV = internal gross tumor volume; LLL = left lower lobe; LUL = left upper lobe; NOS = not otherwise specified; NSCSC = non-small cell lung cancer; PTV = planning target volume; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.
Values are number and percentage except where noted. A total of 236 patients were treated to 263 isocenters.

* May not add to 100% because of rounding.

† Defined as: total lungs − IGTV.

calculable value in that version of the treatment planning software). In 20 cases the total lung volume was not recorded. The dosimetric characteristics analyzed are summarized in Table 3.

The following discrete variables were analyzed as predictive factors of pneumonitis: T stage, lobe of lung, patient gender, current smoking status, O_2 dependence before SBRT, prior lung radiation therapy, treating radiation oncologist, treatment machine (Novalis vs Trilogy and TrueBeam), and use of abdominal compression (Table 4). Female gender was highly significant in univariable logistic regression analysis in developing RP ($P = .0296$) (Table 4). No other discrete variables were significant.

We also analyzed a number of continuous variables such as pack-years tobacco history, age-adjusted Charlson Comorbidity Index at presentation, radiation dose, radiation dose per fraction, V_5, V_{13}, V_{20}, MLD, $V_{prescription}$, CI, IGTV volume (cm^3), PTV volume (cm^3), total lung volume (cm^3), and PTV volume/total lung volume ratio, as well as the the $V_{prescription}$ (volume of normal lung receiving the prescribed dose). For results, see Table 4. The V_5 and V_{13} were both statistically significant under univariable logistic regression analysis ($P = .0186$ and .0438, respectively). Note, too, that the PTV volume/total lung volume ratio was highly significant under logistic regression analysis ($P = .0024$). The $V_{prescription}$ was not statistically significant ($P = .2960$ and .9403 under regression analysis and Wilcoxon t test, respectively). To investigate this further, we divided these patients into 2 subgroups, analyzing the V_{50} for the patients receiving 50 Gy (n = 187) and V_{60} in the 60-Gy patients (n = 40). (The few remaining isocenters were treated to other doses and were excluded from this subgroup analysis.) The V_{50} in the 50-Gy patients was not significant ($P = .7041$), whereas the V_{60} was highly so ($P = .0197$). In these latter 40 patients, 19 received 7.5 Gy × 8 fractions, 20 received 12 Gy × 5 fractions, and 1 received 10 Gy × 6 fractions. None of the other factors were statistically relevant under univariable analysis.

Under multivariable analysis, nearly all factors were removed via backward elimination (Table 5). Interestingly, the only factors

Table 3 Treatment characteristics

Characteristic	n	%*
Total treatment dose (Gy)		
40	12	4.6
48	13	4.9
50	187	71.1
60	40	15.2
Other	11	4.2
No. of fractions		
4	17	6.5
5	226	85.9
6	1	0.4
7	2	0.8
8	17	6.5
Dose per fraction (Gy)		
7.5	19	7.2
8	9	3.4
10	191	72.6
12	35	13.3
Other	9	3.4
Treatment machine		
Novalis	152	57.8
Trilogy	110	41.8
TrueBeam	1	0.4
Abdominal compression†		
Weight belt	120	45.6
External compression device	110	41.8
None	33	12.5
Dosimetric parameters		
V_5 (%)		
Mean ± SD	22.6 ± 10.3	
Median (range)	20.8 (6.2-59.4)	
V_{13} (%)		
Mean ± SD	10.5 ± 5.3	
Median (range)	9.7 (1.4-32.2)	
V_{20} (%)		
Mean ± SD	6.5 ± 3.6	
Median (range)	6.0 (1.1-22.6)	
$V_{precription}$ (%)		
Mean ± SD	1.4 ± 1.4	
Median (range)	1.0 (0.1-16.0)	
Mean lung dose (cGy)		
Mean ± SD	528.3 ± 208.0	
Median (range)	511.0 (144.7-1226.2)	
Conformality Index		
Mean ± SD	1.4 ± 0.3	
Median (range)	1.4 (0.9-3.4)	

Values are number and percentage except where noted. Total of 263 isocenters.

* May not add to 100% because of rounding.

† See text for discussion.

that remained in the final multivariable model were female gender, pack-years smoking, IGTV (cm^3), and PTV (cm^3) ($P = .0094$, .0312, .0364, and .0052, respectively) (Table 6).

The treatment machine used (Novalis vs Trilogy/TrueBeam) was not significant under univariable or multivariable analysis. There were 15 events of symptomatic RP in each treatment machine subgroup. Because of the small number of events in these subgroups, further subgroup analysis was not performed.

Table 4 Univariable analysis of factors predicting radiation pneumonitis

Variable	*P* value*	*P* value†
Discrete variables		
T stage	.8209	.7446
Lobe	.1666	.0646
Gender	.0296	.0257
Current smoker: 0, no; 1, yes	.9061	.8764
O_2 dependent	.6541	.6533
Prior lung radiation therapy	.6399	.6395
Treating attending	.1068	.0893
Treatment machine	.2737	.2712
Abdominal compression	.2193	.1760
Continuous variables		
Pack-years	.8910	.7754
Charlson Comorbidity Index	.0334	.0366
Conformality Index	.9535	.3372
Dose	.9887	.9200
Dose per fraction	.4109	.4959
V_5	.0186	.1343
V_{13}	.0438	.0893
V_{20}	.0610	.2074
Mean lung dose	.8346	.9743
IGTV (cm^3)	.9930	.8252
PTV (cm^3)	.1512	.3887
Total lung volume (cm^3)	.1514	.1828
PTV (cm^3)/total lung volume (cm^3)	.0024	.0602
$V_{prescription}$	.2960	.9403
$V_{prescription}$, where dose = 50 Gy	.7041	.4268
$V_{prescription}$, where dose = 60 Gy	.0197	.0128

Abbreviations as in Table 2.

* For discrete variables, type 3 *P* value from logistic regression; for continuous variables, *P* value of the slope in the logistic regression.

† For discrete variables, *P* value from χ^2 test; for continuous variables, *P* value from Wilcoxon text, *t* approximation.

Discussion

Past studies have shown the risk of developing symptomatic pneumonitis to be between 5.2% and 21% when using SBRT (3-10). In our large series of patients, 11% developed symptomatic pneumonitis. It is possible that the percentage of patients developing symptomatic pneumonitis will increase with further follow-up. However, we have previously analyzed a subgroup of our patients with several years of follow-up and have found that symptomatic pneumonitis was most apt to develop at 3-4 months (data not shown).

Our reported mean V_{20} to the bilateral lungs was 6.6% (range, 1.1%-22.6%), which is slightly lower than that reported in a previous study that reported a mean V_{20} of 8.4% (3.5%-18.2%) (9). Our MLD was 5.3 Gy (range, 1.4-12.3 Gy), which is perhaps nominally lower than the 5.4 Gy (2.7-12.9 Gy) reported in that prior article. Unfortunately, those researchers did not report on the relationship of V_{20} or MLD to the development of symptomatic pneumonitis. However, the data from our center and the Japanese group demonstrate that a V_{20} <10% is generally readily achievable. Furthermore, we have shown that if such a V_{20} is achieved, pneumonitis is not statistically predictable. Analogously, an MLD of approximately 5-6 Gy is achievable and, if achieved, should not

Table 5 Summary of multivariable analysis with backward elimination (eliminated variables)

Step	Effect removed	df	Number in	Wald χ^2	Pr > χ^2
1	O_2 dependent	1	22	0.0001	0.9942
2	Charlson Comorbidity Index	1	21	0.0049	0.9443
3	Treatment machine	1	20	0.0053	0.9417
4	Dose per fraction	1	19	0.0010	0.9749
5	T stage	4	18	0.9663	0.9149
6	Conformality Index	1	17	0.0206	0.8858
7	Prior lung radiation therapy	1	16	0.0397	0.8420
8	Abdominal compression	2	15	0.5287	0.7677
9	Current smoker: 0, no; 1, yes	1	14	0.0636	0.8009
10	Mean lung dose	1	13	0.1145	0.7351
11	V_{13}	1	12	0.0985	0.7537
12	V_{20}	1	11	0.0682	0.7939
13	Lobe	4	10	20.3024	0.6803
14	$V_{prescription}$	1	9	0.4212	0.5163
15	PTV/total lung volume	1	8	0.4681	0.4939
16	Total lung volume (cm^3)	1	7	0.1794	0.6719
17	Dose	1	6	0.4935	0.4824
18	V_5	1	5	0.5850	0.4444
19	Treating attending	1	4	0.8036	0.3700

Abbreviations as in Table 2.

predict the development of pneumonitis. Therefore, dosimetric guidelines of V_{20} <10% and MLD <600 cGy seem reasonable to minimize the likelihood of developing symptomatic (grade ≥2) pneumonitis. A German article suggested that higher MLD or higher $V_{2.5}$-V_{50} ($V_{2.5}$ in particular) correlated with symptomatic RP (10). In that study, only the dose to the ipsilateral lung was analyzed, making direct comparison with our results difficult. Very recently the Mayo Clinic reported on an initial series of SBRT patients treated at their institution. They reported an incidence of grade ≥2 pneumonitis in 12.5% of patients (14.3% in patients treated to 54 Gy in 3 fractions). In univariable analysis, a PTV maximum dose ≥60 Gy was predictive of RP (P=.16), although no other factors were found to be statistically significant (11).

In a report from the Cleveland Clinic, a higher V_5, V_{10}, and CI were statistically correlated with a drop in FEV1 (forced expiratory volume in 1 second) after SBRT, whereas the V_{20} and other dosimetric parameters only showed a trend toward significance (12). It is also not readily clear how/whether a decreased FEV1 corresponds with development of symptomatic RP. Furthermore, the decline in pulmonary function seemed to be transient, similar to the initial experience at Indiana University (13). It is unclear exactly how RP correlates (or not) with changes in pulmonary function testing. This is an area requiring further research. It is interesting to note, however, that a higher V_5 and V_{10} were predictive of RP in our patients, at least under univariable analysis, which is an analogous finding to that of the Cleveland Clinic group. However, CI was not predictive under univariable or multivariable modeling.

Table 6 Analysis of maximum likelihood estimates

Parameter	df	Estimate	SE	Wald χ^2	Pr > χ^2
Intercept	1	4.4171	1.0506	17.6771	<.0001
Gender female	1	−1.3393	0.5159	6.7404	.0094
Pack-years	1	−0.0172	0.00797	4.6434	.0312
IGTV (cm^3)	1	0.0559	0.0267	4.3763	.0364
PTV (cm^3)	1	−0.0333	0.0119	7.8128	.0052

Abbreviations as in Table 2.

Very recently the Mayo Clinic reported on a small series of patients treated with consecutive daily fractions (11). The fractionation schema used was typically 48 Gy in 4 fractions for central lesions and 54 Gy in 3 fractions for peripheral lesions. They found that a PTV maximum dose >60 Gy was predictive of pneumonitis (P=0.016), although the overall number of events was small (n=4). It is intriguing that V_{60} was predictive in our 60-Gy patients; however, they were treated with 5 fractions, not 3, so this might be happenstance. Conversely, there might be some dose threshold above which lung toxicity occurs and pneumonitis risk increases. This will require further research.

Conclusions

In our series, 11.0% of patients developed symptomatic RP. In univariable analysis, female gender (P=.0257) and Charlson Comorbidity index (P=.0366) were significantly predictive of RP. Among dosimetric parameters, V_5 (P=.0186), V_{13} (P=.0438), and $V_{prescription}$ (where dose = 60 Gy) (P=.0128) were significant. There was only a trend toward significance for V_{20} (P=.0610). Planning target volume/normal lung volume ratio was highly significant (P=.0024). In multivariable analysis, female gender, pack-years smoking, and larger GITV and PTV volumes were predictive (P=.0094, .0312, .0364, and .052, respectively).

References

1. Timmerman RD. An overview of hypofractionation and introduction to this issue of Seminars in Radiation Oncology. *Semin Radiat Oncol* 2008;18:215-222.
2. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose–volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;76: S70-S76.
3. Atsuya T, Naoko S, Etsuo K, et al. Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. *Int J Radiat Oncol Biol Phys* 2009;73:442-448.
4. Borst GR, Ishikawa M, Nijkamp J, et al. Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy. *Radiother Oncol* 2009;91:307-313.
5. Bishawi M, Kim B, Moore WH, et al. Pulmonary function testing after stereotactic body radiotherapy to the lung. *Int J Radiat Oncol Biol Phys* 2012;82:e107-e110.
6. Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;70: 685-692.
7. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94-S100.
8. Takeda A, Ohashi T, Kunieda E, et al. Early graphical appearance of radiation pneumonitis correlates with the severity of

radiation pneumonitis after stereotactic body radiotherapy (SBRT) in patients with lung tumors. *Int J Radiat Oncol Biol Phys* 2010; 77:685-690.

9. Yamashita H, Nakagawa K, Nakamura N, et al. Exceptionally high incidence of symptomatic grade 2-5 radiation pneumonitis after stereotactic radiation therapy for lung tumors. *Radiat Oncol* 2007; 2:21.
10. Guckenberger M, Baier K, Polat B, et al. Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. *Radiother Oncol* 2010;97:65-70.
11. Stauder MC, Macdonald OK, Olivier KR, et al. Early pulmonary toxicity following lung stereotactic body radiation therapy delivered in consecutive daily fractions. *Radiother Oncol* 2011;99:166-171.
12. Stephans KL, Djemil T, Reddy CA, et al. Comprehensive analysis of pulmonary function test (PFT) changes after sterotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. *J Thorac Oncol* 2009;4:838-844.
13. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003;124:1946-1955.