International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Local Control and Toxicity in a Large Cohort of Central Lung Tumors Treated With Stereotactic Body Radiation Therapy

Ankit Modh, MD,* Andreas Rimner, MD,* Eric Williams, PhD,† Amanda Foster, MS,* Mihir Shah, BS,* Weiji Shi, MS,‡ Zhigang Zhang, PhD,‡ Daphna Y. Gelblum, MD,* Kenneth E. Rosenzweig, MD,§ Ellen D. Yorke, PhD,† Andrew Jackson, PhD,† and Abraham J. Wu, MD*

**Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York;*
†Department of Medical Physics Memorial Sloan Kettering Cancer Center, New York, New York;
‡Department of Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York; and
§Department of Radiation Oncology, Mount Sinai Medical Center, New York, New York

Received Feb 6, 2014, and in revised form Aug 6, 2014. Accepted for publication Aug 7, 2014.

Summary

We reviewed local control and toxicity in 125 patients receiving stereotactic body radiation therapy (SBRT) for central lung tumors and attempted to identify dosimetric predictors of pulmonary toxicity. With moderate dose regimens, SBRT achieved acceptable local control with low rates of severe

Purpose: Stereotactic body radiation therapy (SBRT) in central lung tumors has been associated with higher rates of severe toxicity. We sought to evaluate toxicity and local control in a large cohort and to identify predictive dosimetric parameters.

Methods and Materials: We identified patients who received SBRT for central tumors according to either of 2 definitions. Local failure (LF) was estimated using a competing risks model, and multivariate analysis (MVA) was used to assess factors associated with LF. We reviewed patient toxicity and applied Cox proportional hazard analysis and log-rank tests to assess whether dose-volume metrics of normal structures correlated with pulmonary toxicity.

Results: One hundred twenty-five patients received SBRT for non-small cell lung cancer (n = 103) or metastatic lesions (n = 22), using intensity modulated radiation therapy. The most common dose was 45 Gy in 5 fractions. Median follow-up was

Reprint requests to: Abraham J. Wu, MD, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065. Tel: (212) 639-5257; E-mail: wua@mskcc.org

This work was presented orally at the 55th Annual Meeting of the American Society for Radiation Oncology (ASTRO), Atlanta, GA, September 22-25, 2013.

Note—An online CME test for this article can be taken at http://astro.org/MOC.

This work was supported in part by National Cancer Institute grant R01 CA129182. Weiji Shi and Zhigang Zhang's research was partly supported by NIH Core Grant P30 CA008748.

Conflict of interest: Dr Rimner has served as consultant for Varian Medical Systems and GE Healthcare and has received research support from Varian Medical Systems. Dr Wu has served as consultant for Pfizer, Inc.

Dr Modh is currently at Albany Medical College, Albany, New York.

Mihir Shah is currently at Northeast Ohio Medical University, Rootstown, Ohio.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. 90, No. 5, pp. 1168–1176, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2014.08.008

toxicity. Dosimetric analysis showed no correlations between lung, heart, or central airway dose and pulmonary toxicity. Esophagitis occurred in 13% of patients and was particularly common when the planning target volume overlapped with that of the esophagus.

17.4 months. Incidence of toxicity ≥ grade 3 was 8.0%, including 5.6% pulmonary toxicity. Sixteen patients (12.8%) experienced esophageal toxicity ≥ grade 2, including 50% of patients in whom PTV overlapped the esophagus. There were 2 treatment-related deaths. Among patients receiving biologically effective dose (BED) ≥80 Gy (n = 108), 2-year LF was 21%. On MVA, gross tumor volume (GTV) was significantly associated with LF. None of the studied dose-volume metrics of the lungs, heart, proximal bronchial tree (PBT), or 2 cm expansion of the PBT ("no-fly-zone" [NFZ]) correlated with pulmonary toxicity ≥grade 2. There were no differences in pulmonary toxicity between central tumors located inside the NFZ and those outside the NFZ but with planning target volume (PTV) intersecting the mediastinum.

Conclusions: Using moderate doses, SBRT for central lung tumors achieves acceptable local control with low rates of severe toxicity. Dosimetric analysis showed no significant correlation between dose to the lungs, heart, or NFZ and severe pulmonary toxicity. Esophageal toxicity may be an underappreciated risk, particularly when PTV overlaps the esophagus. © 2014 Elsevier Inc.

Introduction

Stereotactic body radiation therapy (SBRT) is now a well-established treatment for medically inoperable early stage non-small cell lung cancer (NSCLC), with 2-year local control rates ranging from 80% to 97% (1, 2). However, an early prospective trial indicated that patients with centrally located lung tumors were at increased risk for severe pulmonary toxicity when treated with SBRT (3). As a result, tumors within a 2-cm radius of the proximal bronchial tree (PBT), often described as the "no-fly zone" (NFZ), were excluded from the landmark Radiation Therapy Oncology Group (RTOG) 0236 trial (2) and are now being studied separately in a phase 1/2 trial (RTOG 0813) (4), which aims to determine the maximum tolerated dose for SBRT in central lung tumors.

Until data from RTOG 0813 are available, the optimal dose for SBRT in central lung tumors will remain uncertain. Most institutions, including ours, have adopted more conservative fractionation schemes for central lung tumors in the absence of prospective data that establishes the maximum tolerated dose, but substantial data for local control and toxicity with these schemes are also lacking. For this reason, we retrospectively assessed local control and toxicity in a large cohort of patients treated with SBRT for central lung tumors at our institution, where a variety of fractionation schemes have been used in an effort to balance efficacy and toxicity.

It is unclear whether the NFZ as defined by Timmerman et al (2) is itself the appropriate structure to evaluate for risk of excessive pulmonary toxicity or whether this region is simply an arbitrary surrogate for the true at-risk structure or structures. This uncertainty is reflected in the diverging definitions of central lung tumors in RTOG 0236 and RTOG 0813. We therefore also undertook dose-volume histogram (DVH) analysis to determine whether dose to the NFZ was predictive of pulmonary toxicity and whether dose to heart, esophagus, ipsilateral, or bilateral lungs might also be predictive of pulmonary toxicity.

Methods and Materials

Inclusion criteria

The Institutional Review and Privacy Boards approved this study, and patient confidentiality was maintained as required by the Health Insurance Portability and Accountability Act. We reviewed treatment plans of all patients in our institutional lung SBRT database to identify treated lung tumors within a 2-cm radius of the PBT, according to the RTOG 0236 definition of the NFZ. We also included patients whose planning target volume (PTV) intersected mediastinal structures (including heart, great vessels, vertebral bodies, esophagus, and trachea), according to the RTOG 0813 inclusion criteria for central lung tumors. Patients with prior thoracic radiation therapy or with synchronous treatment to multiple tumors were excluded. Because we wished to assess toxicity across a wide variety of fractionation schedules, we included all patients who received at least 600 cGy per fraction and 5 or fewer fractions in the toxicity analysis.

Treatment

All patients were assessed by a multidisciplinary team and were considered medically inoperable, or opted for SBRT over surgery, after consideration of the risks and benefits. No specific tumor locations were excluded from consideration of SBRT, and prescription doses were generally chosen to maintain normal tissue constraints. Patients underwent simulation with a 4-dimensional computed tomography (4DCT) scan and immobilization with an alpha cradle or other customized immobilization device. The

gross tumor volume (GTV) was contoured and expanded to generate an internal target volume (ITV) based on respiratory excursion. A clinical target volume (CTV) was generated with a 2- to 3-mm expansion of the ITV, and the CTV was expanded 5 mm in all directions to generate the PTV. All patients were treated with intensity modulated RT, and treatment plans were generated using our in-house treatment planning system. The planning system uses a pencil beam algorithm with radiological path length correction along the central ray of each pencil beam (5, 6). Dose was prescribed with the objective of achieving a dose to 95% of the organ (D95) to the PTV equal to or greater than the prescription dose; if this was not achievable due to normal tissue constraints, a lower prescription dose was selected. PTV coverage was kept as homogeneous as possible, with tolerance of a hotspot of up to 110% of the prescription dose. The PBT was defined by contouring the bilateral mainstem bronchi and lobar bronchi up to the branching of the segmental bronchi, according to RTOG 0236 criteria. The NFZ was a 2-cm expansion of the PBT in all directions. The lungs were defined as the entire lung parenchyma excluding the GTV. The heart was contoured by including the entire pericardial sac below the level where the pulmonary trunk turns across the mediastinum.

Normal tissue constraints included a 55-Gy maximum point dose for the NFZ and a 55-Gy maximum point dose for the PBT when treating with 5 fractions (all tumors near the PBT were treated with 5 fractions). Maximum point dose to the spinal cord was 25 Gy in 5 fractions or 24 Gy for 3 to 4 fractions. We attempted to limit the maximal esophageal dose to 30 Gy, but in cases where this was not realistic due to proximity of the PTV to the esophagus, a maximum point dose of 45 Gy in 5 fractions was allowed, with the exception of 4 cases in which the tumor approached the esophagus, and the physician allowed the maximum esophageal dose to be slightly higher in order to maintain adequate target coverage. During the time that most of the patients were treated, no standardized heart constraint was in place, other than to keep hotspots out. Lung constraints were 20 Gy to the target volume (V20) of $\leq$12% for both lungs and V20 $\leq$ 25% for the ipsilateral lung, which was not varied for different fraction numbers, given the lack of data that fraction number affects the V20 threshold for lung toxicity in SBRT.

Generally, patients with NSCLC within the NFZ were treated with 5 fractions of 8 to 10 Gy each. However, a variety of other schedules were also used at the discretion of the treating physician, such as for tumors outside the NFZ but approaching mediastinal structures. Patients were treated with 4 to 7 coplanar, intensity modulated 6-MV beams. After each initial setup using skin and immobilization marks, a kV cone beam CT was acquired and reviewed to refine patient setup so that the visualized tumor was no more than 2 mm from the ITV contour. Just before each treatment, orthogonal kV images were acquired to ensure that the patient had not shifted, and intrafraction motion was also monitored with infrared beacons placed on the patient surface. Treatment was given every other weekday.

Follow-up

Follow-up data were collected through April 25, 2013, from institutional records, records from referring facilities, or direct patient or family contact. Follow-up visits and imaging were obtained according to standard guidelines (7) and included a follow-up visit 1 month after treatment, and starting at 3 months after treatment, a CT scan and follow-up visit every 3 months for the first 2 years and every 6 to 12 months thereafter.

Local failure was defined as disease progression or recurrence in the originally radiated lesion, as defined by CT, PET-CT, or biopsy. Toxicity was scored using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The highest score was recorded for each patient in the following organ toxicity categories: pulmonary (including dyspnea, cough, radiation pneumonitis, and pneumonia), gastrointestinal, and cardiac.

Statistical analysis

All endpoints were calculated from the completion of SBRT. For local failure (LF), death without an event was treated as a competing risk. Patients receiving a biologically effective dose (α/β = 10 Gy) (BED_{10}) of <80 Gy (n = 17) were excluded from the LF analysis because we wished to report disease control results that were generalizable to contemporary practice, in which there is increasing consensus that higher BED regimens are necessary for durable local control. However, all 125 patients were retained in the toxicity analysis, because significant toxicity events occurred in patients treated at lower BED, as well, and such data might provide valuable information on the dose-volume dependence of those toxicity endpoints, which are dependent upon dose distribution and not directly on prescription dose. Gray (for categorical variables) and Fine-Gray competing risks methods (for continuous variables) were used for univariate analysis (UVA), and the latter was used for stepwise multivariate analysis (MVA). The Kaplan-Meier method was used to estimate overall survival (OS). Log-rank test was used to analyze categorical variables, and Cox proportional hazards regression model was used for continuous variables for UVA. Stepwise selection was also used to construct multivariate Cox models. All variables with a P value of $< .1$ on UVA were candidates for the stepwise multivariate analysis. SAS, version 9.2, software (SAS institute Inc, Cary, NC) and R, version 3.0.1, software function "cmprsk" were used for statistical analysis.

For DVH analysis of pulmonary toxicity, doses were converted to linear-quadratic equivalent doses delivered in 2-Gy fractions using α/β = 3 Gy for each dose bin in the DVH (8). Unless otherwise stated, all following normal tissue dose-volume and generalized equivalent uniform

dose (gEUD) metrics are such linear-quadratic corrected quantities. Cox proportional hazard analysis and log-rank tests were used to determine whether dose to a volume, v, of the given structure (D_v) or volume of the given structure receiving the dose d (V_d) were predictive of pulmonary toxicity. Structures analyzed in this fashion included heart, lungs, esophagus, PBT, and NFZ. Additionally, logistic models were tested using gEUD for a range of the volume parameter, a, between $\log_{10}(a) = -1$ to 1 in steps of 0.1. To account for the interaction between the inherent latency of complication onset and the variation in the follow-up times of individual patients, we used the method of Farewell (9-11). Kaplan-Meier analysis was used to assess whether there were any significant differences in the risk of pulmonary toxicity between patients with tumors (GTV) within the NFZ and patients with tumors outside the NFZ but PTV approaching mediastinal structures.

For the purposes of future data synthesis (12, 13) dose-volume atlases of the incidence of pulmonary complications $\geq$ grade 2 (14, 15) based on physical dose are provided in Excel files in Supplementary Appendix S1 for each of the anatomic structures analyzed and for each fraction number. The format of these files is described in Supplementary Appendix S2.

Results

Patient and treatment characteristics

We identified 125 patients who received SBRT between 2006 and 2011 for single lung tumors within 2 cm of the PBT (n = 81) or whose PTV intersected mediastinal structures (n = 44). Patient characteristics are detailed in Table 1. Ninety-one patients had primary NSCLC, 12 had locally recurrent NSCLC, and 22 had a metastatic tumor involving the lung. All primary NSCLC patients had early stage (I-II) disease, except for one patient with multifocal T4N0 disease, where one lesion was treated with SBRT and the other with surgery. Table 2 summarizes SBRT treatment characteristics and tumor volumes for the study population. A variety of fractionation schemes were used, with a median BED_{10} of 85.5 Gy (range, 43.2-180 Gy). The most common doses were 45 Gy in 5 fractions (n = 56), 48 Gy in 4 fractions (n = 21), or 50 Gy in 5 fractions (n = 14). Forty-nine patients received a $BED_{10} \geq 100$ Gy, whereas 76 received a $BED_{10} < 100$ Gy. Patients with $BED_{10} < 80$ (n = 17) were excluded from the LF analysis because we wished to report disease control results that were generalizable to contemporary practice, in which there is increasing consensus that higher BED regimens are necessary for durable local control. All but 2 of the patients in the LF analysis (98%) had a PTV D95 > 97% of the prescription dose.

Table 1 Patient and tumor characteristics

Characteristic	No. of patients
Patients treated	125
Primary	91
Recurrent	12
Metastatic	22
Central definition	
Within 2 cm of the PBT ("no-fly zone")	81
PTV intersecting mediastinal structure	44
Heart/pericardium	12
Aorta or great vessels	22
Vertebral Body	7
Trachea	1
Esophagus	2
Age at diagnosis, yrs	
Median (range)	76 (32-95)
Sex	
Male	62
Female	63
Smoking history	
Never	20
Former	94
Current	11
Median smoking pack years	45
Baseline KPS	
≥80	92
<80	31
Not available	2
COPD at diagnosis	
Yes	55
No	70
Histology	
Adenocarcinoma	86
Squamous cell carcinoma	30
Other	9
Stage	
IA (T1N0)	61
IB (T2aN0)	26
IIA (T2bN0)	2
IIB (T3N0)	1
III (T4N0)	1
IV (M1)	22
Recurrent	12

Abbreviations: COPD = chronic obstructive pulmonary disease; KPS = Karnofsky performance status; PBT = proximal bronchial tree; PTV = planning treatment volume.

Local control and survival

Median follow-up for living patients was 17.4 months (range, 1.6-65.4 months). Of the 108 patients who were treated with a $BED_{10} \geq 80$ Gy, the 1- and 2-year rates of LF were 14% (95% confidence interval [CI], 6%-21%) and 21% (95% CI, 12%-31%), respectively. Figure 1 shows the cumulative incidence of LF. Nineteen patients experienced LF at a median of 9 months after treatment. For patients with primary and recurrent NSCLC, the median survival was 29.1 months (95% CI,

Table 2 SBRT characteristics

Characteristic	No. of patients	Median GTV size, cm^3 (range)
$BED_{10} \geq 100$ Gy	49	11.1 (0.7-110.8)
60 Gy in 3 fx ($BED_{10} = 180$)	4	10.7 (4.5-18.6)
54 Gy in 3 fx ($BED_{10} = 151.2$)	9	10.1 (0.7-44.7)
48 Gy in 4 fx ($BED_{10} = 105.6$)	21	8.4 (1.3-110.8)
36 Gy in 2 fx ($BED_{10} = 100.8$)	1	10.6 (10.6)
50 Gy in 5 fx ($BED_{10} = 100$)	14	15.2 (0.9-49.2)
$BED_{10} < 100$ Gy	76	17.0 (0.7-195.4)
44 Gy in 4 fx ($BED_{10} = 92.4$)	1	9.9 (9.9)
45 Gy in 5 fx ($BED_{10} = 85.5$)	56	13.0 (0.6-25.9)
40 Gy in 4 fx ($BED_{10} = 80$)	2	52.7 (32.6-72.8)
36 Gy in 3 fx ($BED_{10} = 79.2$)	1*	27.3 (27.3)
40 Gy in 5 fx ($BED_{10} = 72$)	6*	49.7 (6.1-71.9)
30 Gy in 5 fx ($BED_{10} = 48$)	7*	43.7 (19.4-186.6)
Other*	3*	38.2 (5.2-105.1)
GTV size		
0-10 cm^3	46	
10-20 cm^3	36	
20-50 cm^3	27	
>50 cm^3	16	
Median BED_{10} Gy (range)	85.5 (43.2-180)	
Median PTV size, cm^3 (range)	63.0 (17.3-401.7)	
Median GTV size, cm^3 (range)	13.1 (0.6-195.4)	

Abbreviations: BED_{10} = biologically equivalent dose for an α/β of 10; fx = fraction; GTV = gross tumor volume; PTV = planning treatment volume.

* Excluded from local failure analysis.

24.0-38.4 months); their 1- and 2- year OS rates were 83% (95% CI, 73-90%) and 64% (95% CI, 52%-74%), respectively. Table 3 describes variables associated with LF. Whether patients were treated with $BED_{10} \geq 100$ Gy or <100 Gy (categorical variable) was not significantly associated with LF on univariate analysis. Of the variables analyzed, GTV size and BED_{10} (continuous variable) were candidates for stepwise MVA. Only increasing GTV size remained associated with LF on the final MVA model (hazard ratio [HR], 1.52; 95% CI, 1.05-2.20; $P = .03$) (Fig. 2). After adjusting for GTV size, increasing BED_{10} was not significantly associated with LF (HR, 0.98; 95% CI, 0.96-1.01; $P = .21$).

Toxicity

Table 4 describes patients' toxicity in this cohort. Ten patients experienced toxicity ≥ grade 3, representing 8.0% of the cohort (9.3% if patients with BED <80 are excluded). Median time to toxicity was 4 months. Four patients experienced worsening dyspnea that limited self-care and activities of daily living. Two of those patients had chronic obstructive pulmonary disease prior to treatment. One patient developed "pneumonia" 4 months after treatment, requiring hospitalization at an outside facility, which was suspicious for pneumonitis. There were 2 cases of grade 3 gastrointestinal complications: 1 patient with tumor abutting the esophagus had esophagitis 4 months after treatment, which then developed into a fistula; and the other patient (tumor, 2.1 cm from esophagus) had upper gastrointestinal bleeding that required endoscopic intervention 2 weeks after radiation. The maximum esophageal doses for these patients were 46.0 Gy and 18.0 Gy, respectively, both treated in 5 fractions. Fourteen additional cases of grade 2 esophagitis occurred, for an overall 12.8% incidence of esophageal toxicity ≥ grade 2. The median distance from PTV to esophagus for those with toxicity was 1.3 cm (range, 0-5.6 cm). The range of maximum point doses to the esophagus for patients with toxicity was 16.5 to 47.0 Gy (median, 29.5 Gy). Among the 12 patients with PTV overlapping esophagus, 6 (50%) developed ≥ grade 2 esophageal toxicity, including 1 grade 3 event. For the 28 patients with PTV <2 cm from esophagus, 4 (14%) had toxicity. Among the remaining 85 patients with PTV ≥2 cm from esophagus, only 4 patients had toxicity (4.7%).

Two patients died, likely, of treatment-related causes. The first patient was a 75-year-old woman with a history of bronchiectasis treated with 45 Gy in 5 fractions for a 2.4-cm squamous cell carcinoma in the left hilum. She developed presumed pneumonia that required intubation 1 month after treatment, recovered, then developed hemoptysis 7 months from treatment, and died. This patient had a mean bilateral lung dose of 5.7 Gy, a bilateral lung V_{20} of 9.8%, and an ipsilateral lung V_{20} of 21.2%. Maximum point doses to the PBT and NFZ were 46.5 Gy and 48.6 Gy, respectively.

The second patient was a 67-year-old man with synchronous right upper lobe and left lower lobe NSCLC. The right-sided tumor was first treated with wedge resection and then the left-sided tumor with SBRT to 45 Gy in 5 fractions. This tumor measured 4 cm and encased the left superior segmental bronchus. He developed hypoxemia 6 months after treatment and died 2 weeks later from presumed radiation-induced lung injury. This patient received a mean lung dose of 7.5 Gy, a bilateral lung V_{20} of 9.9%, and an ipsilateral lung V_{20} of 25.6%, minimally exceeding our institutional guideline of $V_{20} \leq 25\%$. Maximum point doses to the PBT and NFZ were 47.7 Gy and 48.6 Gy, respectively.

Although cardiac events were difficult to attribute to RT in this population with frequent comorbidities, we

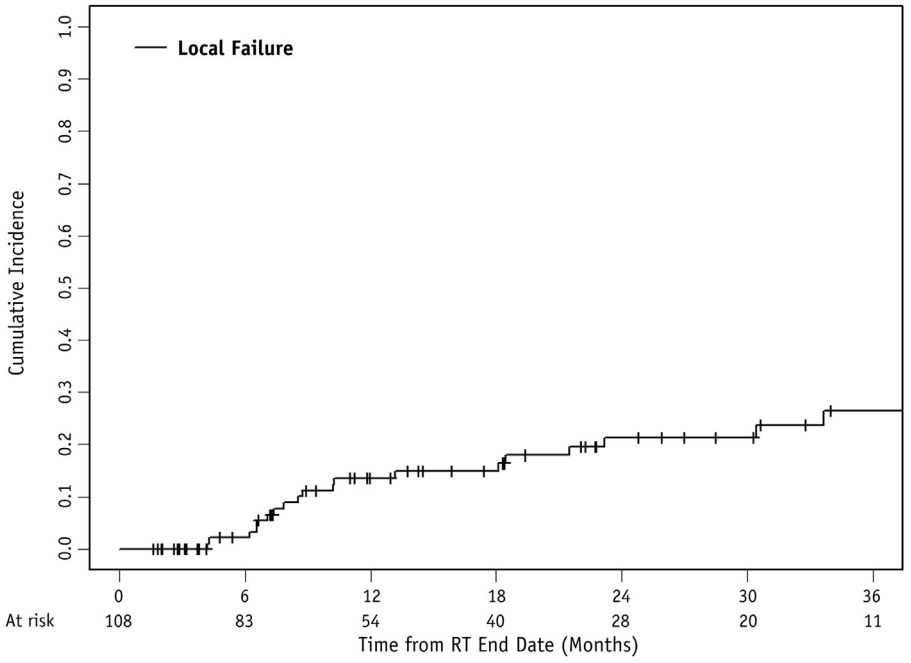

Fig. 1. Cumulative incidence of local failure for patients receiving a $BED_{10} \geq 80$ (n = 108).

identified three cases of significant cardiac toxicity possibly attributable to SBRT: 1 case of pericardial effusion, 1 case of pericarditis, and 1 case of myocardial infarction.

In the DVH analysis, no significant models were found for gEUD values of the heart, ipsilateral and bilateral lung, esophagus, PBT, and NFZ to pulmonary toxicity ≥ grade 2. Results were not significantly different when low-BED patients were excluded from the analysis. Supplementary Figure S3.1 (supplementary file EA3) shows the resulting t statistic of the logistic correlation coefficient for each structure. Similarly, Cox proportional hazards analysis and log rank tests found no significant models of pulmonary toxicity based on the dose-volume metrics D_v or V_d for any of the investigated structures. No significant difference in the incidence of pulmonary toxicity was identified between central tumors located within the NFZ and those not in the NFZ but approaching mediastinal structures.

Discussion

This is the largest series of SBRT for centrally located lung tumors reported to date. SBRT achieved local control in most patients but at lower rates than those reported in RTOG 0236 and other series of peripheral lung SBRT using high-BED regimens such as 54 Gy in 3 fractions (2). Other prospective and retrospective series have reported 2-year rates of local control for centrally located tumors ranging from as low as 60% (16) to as high as 94% (17). No significant correlation between local control and BED was

Table 3 Analysis of local failure for patients receiving a $BED_{10} \geq 80$ (n = 108), using competing risks methods

	Univariate analysis	Multivariate analysis final model	
Factor	*P* value	HR (95% CI)	*P* value
Mean ± SD age at diagnosis (yr)	.22 (HR = 1.03)		
Male (vs female)	.41		
>2 cm from PBT (yes vs no)	.27		
KPS <80 at diagnosis (yes vs no)	.75		
Tumor type	.27		
Primary NSCLC			
Recurrent NSCLC			
Metastatic NSCLC			
GTV size (continuous)	.009 (HR = 1.62)	1.52 (1.05-2.20)	.03
BED_{10} (continuous)	.15 (HR = 0.98)		
$BED_{10} \geq 100$ (yes vs no)	.22		

Abbreviations: BED_{10} = biologically equivalent dose for an $\alpha/\beta = 10$; GTV = gross tumor volume; HR = hazard ratio; KPS = Karnofsky performance status; NSCLC = non-small cell lung cancer; PBT = proximal bronchial tree; SD = standard deviation.

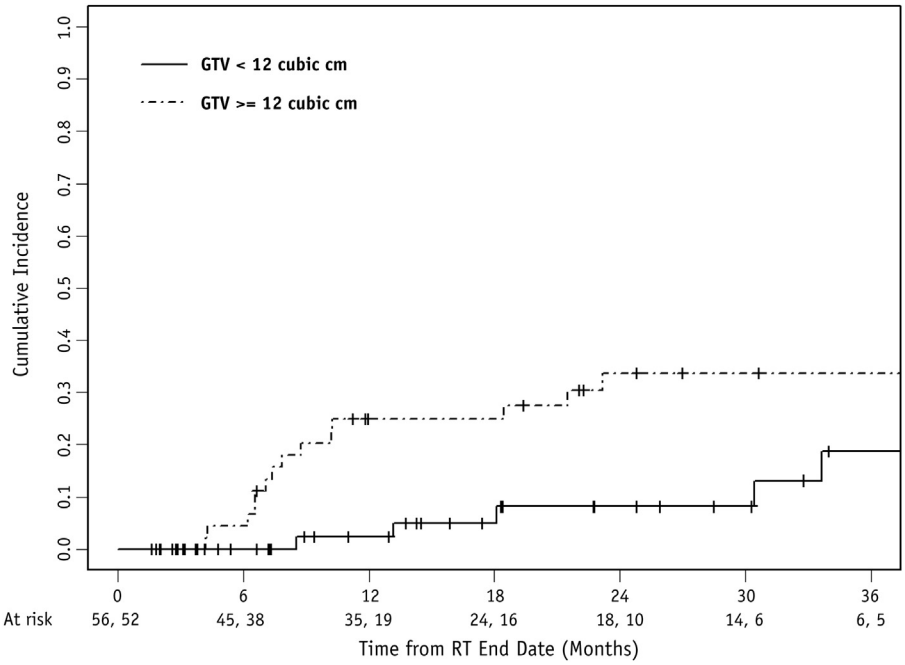

Fig. 2. Cumulative incidence of local failure stratified by gross tumor volume for patients receiving a $BED_{10} \geq 80$ (n = 108); $P = .02$ by the Gray test. The first and second number of patients at risk at each time point is for a GTV of <12 cm^3 and a GTV ≥ 12 cm^3, respectively.

found in our analysis, and a multivariate model incorporating both BED and tumor size indicated that across the dose regimens we used, only tumor size was independently correlated with local control. However, it is likely that our modest rates of local control are due to our use of relatively low-BED regimens. A clearer impact of BED on local control might have been seen if we had treated more patients with higher BED regimens, given that BED ≥ 100 has been established as a significant predictor of local control in other larger series (18). Prior tumor control probability models have suggested a correlation between BED and tumor size with respect to local control (19). It is likely that fractionation schedules such as 45 Gy in 5 fractions are inadequate to control larger tumors, and our current practice and recommendation is to prescribe 50 Gy in 5 fractions for lesions in the central lung zone. However, larger lung tumors have also been associated with increased risk of severe toxicity (20), so optimizing the therapeutic ratio remains a major challenge when treating large lesions in the central lung zone.

Table 4 Toxicity

	Grade			
Toxicity	2	3	4	5
Pulmonary				
Dyspnea	2	4		
Cough	4			
Radiation Pneumonitis	18			1
Pneumonia	2	1		1
Esophagitis	14	2		
Cardiac	2	1		
Total (%)	42 (34%)	8 (6%)	0	2 (2%)

The incidence of severe toxicity was acceptably low in this cohort at 8% overall, indicating that with the use of conservative fractionation, rates of SBRT-related toxicity in central lung tumors are comparable to those for peripheral lung lesions. Our findings are similar to the 8.6% incidence of toxicity $\geq$ grade 3 reported by Senthi et al (21) in their systematic review of outcomes after SBRT for central lung tumors. Other major series on this topic have shown comparable results. Haasbeck et al (22) found no significant differences in toxicities when comparing 63 patients with central lung tumors treated with 60 Gy in 8 fractions to peripheral tumors. A report from MD Anderson Cancer Center similarly found that SBRT can be safely delivered to these patients with excellent disease control (23). Last, Rowe et al (20) found a 94% 2-year actuarial lobar control rate in their cohort of 47 patients with central lung tumors, most of whom were treated with 62.5 Gy in 5 fractions. Our larger study contributes to the body of evidence showing that SBRT can be safely delivered to centrally located lung tumors, and ongoing studies such as RTOG 0813 should clarify the optimal dose fractionation in a prospective fashion. It is also worth noting that updated results from the seminal trial from Timmerman et al showed that longer-term rates of severe toxicity and survival were equivalent between central and peripheral tumors (1).

Two patients in our cohort died of pulmonary events likely attributable to SBRT. This incidence of treatment-related mortality (2%) is acceptable compared to that with

surgical resection in this subset of tumors, especially considering that most patients receiving SBRT are medically or technically inoperable (24). However, over 10% of patients developed clinically significant esophageal toxicity, including 50% of patients with PTV overlapping esophagus. These findings contrast with those recently reported by the MD Anderson Cancer Center, where the rate of significant esophagitis was much lower, likely because tumors approaching esophagus would have been treated with a more highly fractionated regimen (7 Gy × 10 fractions) (25). Given that the maximum esophageal dose in our series was 47 Gy in 5 fractions and that a minimum of 50 Gy in 5 fractions would be required to achieve BED of 100 to an adjacent tumor, such patients should be offered SBRT with particular caution, perhaps using more than 5 fractions. Three patients also had significant cardiac events possibly attributable to SBRT. The risk of esophageal and cardiac toxicities with lung SBRT warrants further study.

The precise mechanisms and risk factors for severe pulmonary toxicity in patients with central lung tumors remain unclear, a fact underlined by the presence of two different definitions of "central" in recent RTOG trials. Our analysis did not demonstrate a signficant difference in pulmonary toxicity according to the definition of "central" used. Previous analyses have demontrated V_{20} and mean lung dose correlated with rates of radiation pneumonitis after SBRT (26). However, we did not identify any DVH characteristics with respect to the NFZ, heart, or lungs that were predictive of significant pulmonary toxicity. It is possible that studying a larger cohort of patients may reveal clearer dosimetric predictors of toxicity. However, as this report adds to the increasing experience indicating that moderate-dose SBRT is safe and feasible in central lung tumors, it appears likely that the high rates of severe toxicity observed in the early reports from Timmerman et al (2, 3) were related to the high-BED regimens used and that central tumor location is not a predictor of enhanced pulmonary toxicity when moderate-dose SBRT is used.

In addition to the constraints of any retrospective study, our study had several limitations. Because we included patients treated over a time period when institutional standards for SBRT dose were rapidly evolving, our cohort was heterogeneous with respect to fractionation and dose. This heterogeneity was potentially valuable in trying to identify underlying dosimetric factors associated with toxicity and local control but makes it difficult to extrapolate a single recommended dose for clinical practice. Also, most patients in our cohort were treated with conservative fractionation schemes with BED <100 Gy. RTOG 0813 may eventually demonstrate that higher-BED regimens are preferable for central tumors, which could limit the clinical generalizability of our results. We also note that our SBRT technique involved prescribing to the 100% isodose line, which results in significantly lower hotspots than the RTOG technique of prescribing to the 60% to 90% isodose line and, as such, may not be a fully comparable population. Finally, because toxicity events ≥ grade 3 were rare, it was necessary to include less clinically significant grade 2 events in order to facilitate statistically meaningful analysis. Even so, no significant correlations were found.

Despite these limitations, this analysis demonstrates the feasibility and effectiveness of SBRT for central lung tumors in a large number of patients. It also represents a comprehensive attempt to identify dosimetric factors predictive of severe pulmonary toxicity, and the first attempt to determine whether a significant difference in toxicity profile exists between 2 different definitions of "central" lung tumors.

Conclusions

SBRT using attenuated fractionation schemes for central lung tumors achieves acceptable local control with low rates of severe toxicity. However, death from pulmonary complications remains a possible though rare event even with conservative fractionation such as 45 Gy in 5 fractions. Although the enhanced risk of severe pulmonary toxicity in central tumors was evident from the prior prospective experience of Timmerman et al (2, 3) comprehensive DVH analysis in this cohort failed to demonstrate any dosimetric factors predictive of pulmonary toxicity. Because dose to the NFZ as defined in RTOG 0236 did not predict for pulmonary toxicity and there were no differences in toxicity profiles between the 2 definitions of central tumor, the underlying risk factors and mechanisms of severe pulmonary toxicity in these patients remain unclear. Other significant toxicities, particularly esophageal and cardiac complications, are also possible and patients with tumors approaching the esophagus may require modified treatment approaches.

References

1. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: Four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677-682.
2. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070-1076.
3. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833-4839.
4. Bezjak A. Stereotactic body radiation therapy in treating patients with stage I non-small cell lung cancer. Available at: http://clinicaltrials.gov/show/NCT00750269. Last accessed August 4, 2014.
5. Mohan R, Barest G, Brewster LJ, et al. A comprehensive three-dimensional radiation treatment planning system. *Int J Radiat Oncol Biol Phys* 1988;15:481-495.
6. Chui CS, LoSasso T, Spirou S. Dose calculation for photon beams with intensity modulation generated by dynamic jaw or multileaf collimations. *Med Phys* 1994;21:1237-1244.

7. Ettinger DS, Akerley W, Borghaei H, et al. Non-small cell lung cancer, version 2.2013. *J Natl Compr Cancer Netw* 2013;11:645-653. quiz 653.
8. Wheldon TE, Deehan C, Wheldon EG, et al. The linear-quadratic transformation of dose-volume histograms in fractionated radiotherapy. *Radiother Oncol* 1998;46:285-295.
9. Farewell VT. The use of mixture models for the analysis of survival data with long-term survivors. *Biometrics* 1982;38:1041-1046.
10. Schultheiss TE, Thames HD, Peters LJ, et al. Effect of latency on calculated complication rates. *Int J Radiat Oncol Biol Phys* 1986;12:1861-1865.
11. Tucker SL, Dong L, Bosch WR, et al. Late rectal toxicity on RTOG 94-06: Analysis using a mixture Lyman model. *Int J Radiat Oncol Biol Phys* 2010;78:1253-1260.
12. Deasy JO, Bentzen SM, Jackson A, et al. Improving normal tissue complication probability models: The need to adopt a "data-pooling" culture. *Int J Radiat Oncol Biol Phys* 2010;76:S151-154.
13. Jackson A, Marks LB, Bentzen SM, et al. The lessons of QUANTEC: Recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. *Int J Radiat Oncol Biol Phys* 2010;76:S155-160.
14. Jackson A, Yorke ED, Rosenzweig KE. The atlas of complication incidence: A proposal for a new standard for reporting the results of radiotherapy protocols. *Semin Radiat Oncol* 2006;16:260-268.
15. Cox BW, Jackson A, Hunt M, et al. Esophageal toxicity from high-dose, single-fraction paraspinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2012;83:e661-e667.
16. Oshiro Y, Aruga T, Tsuboi K, et al. Stereotactic body radiotherapy for lung tumors at the pulmonary hilum. *Strahlenther Onkol* 2010;186:274-279.
17. Bral S, Gevaert T, Linthout N, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a phase II trial. *Int J Radiat Oncol Biol Phys* 2011;80:1343-1349.
18. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: Clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer* 2004;101:1623-1631.
19. Ohri N, Werner-Wasik M, Grills IS, et al. Modeling local control after hypofractionated stereotactic body radiation therapy for stage I non-small cell lung cancer: A report from the Elekta collaborative lung research group. *Int J Radiat Oncol Biol Phys* 2012;84:e379-e384.
20. Rowe BP, Boffa DJ, Wilson LD, et al. Stereotactic body radiotherapy for central lung tumors. *J Thorac Oncol* 2012;7:1394-1399.
21. Senthi S, Haasbeek CJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for central lung tumours: A systematic review. *Radiother Oncol* 2013;106:276-282.
22. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. *J Thorac Oncol* 2011;6:2036-2043.
23. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;72:967-971.
24. Chen C, Bao F, Zheng H, et al. Local extension at the hilum region is associated with worse long-term survival in stage I non-small cell lung cancers. *Ann Thorac Surg* 2012;93:389-396.
25. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: How to fly in a "no fly zone" *Int J Radiat Oncol Biol Phys* 2014;88:1120-1128.
26. Barriger RB, Forquer JA, Brabham JG, et al. A dose-volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2012;82:457-462.