

## Scientific Article

# An Analysis of Clinical Toxic Effects and Quality of Life as a Function of Radiation Dose and Volume After Lung Stereotactic Body Radiation Therapy



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## Abstract

**Purpose:** To analyze clinical toxicity and quality-of-life (QOL) outcomes among patients with stage I non-small cell lung cancer (NSCLC) after stereotactic body radiation therapy (SBRT) as a function of radiation dose and volume parameters.

**Methods and Materials:** In this institutional review board–approved study, 55 patients with stage I NSCLC who received SBRT (12 Gy  $\times$  4) and completed QOL forms were analyzed. Clinical symptoms and QOL outcomes were measured at baseline and at 3, 6, 12, 18, 24, and 36 months after SBRT. Clinical toxicity was graded using the *Common Terminology Criteria for Adverse Events*, version 4.0. Quality of life was followed using the validated Functional Assessment of Cancer Therapy–Lung–Trial Outcome Index (FACT-L-TOI) instrument. Dosimetric parameters including the mean lung radiation dose and the volume of normal lung receiving greater than 5, 10, 13, or 20 Gy ( $V_5$ ,  $V_{10}$ ,  $V_{13}$ , and  $V_{20}$ ) were measured from the radiation treatment plan. Student *t* tests and Pearson correlation analyses were used to examine the relationships between radiation lung metrics and clinically meaningful changes in QOL and/or clinical toxic effects. The Kaplan-Meier method was used to estimate rates of local control (LC), disease-free survival (DFS), and overall survival (OS).

**Results:** With a median follow-up of 24 months, the 3-year LC, DFS, and OS were 93%, 65%, and 84%, respectively, with a 5.5% rate of grade-3 toxic effects and no grade 4 or 5 toxic effects. Clinically meaningful declines in patient-reported QOL (FACT-L-TOI, lung cancer subscale, physical well-being, and/or functional well-being) posttreatment significantly correlated with increased dosimetric parameters such as  $V_{10}$ ,  $V_{13}$ , and  $V_{20}$ .

**Conclusion:** Although lung SBRT was associated with excellent LC and minimal clinical toxic effects for early-stage NSCLC, clinically meaningful declines in QOL were significantly correlated with increasing lung dose and volume parameters.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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## Introduction

Lung cancer is the most common cause of cancer-related death worldwide, with more than 1.5 million related deaths annually.<sup>1</sup> Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers.<sup>1</sup> Although surgical resection is currently the gold standard for patients with operable early-stage NSCLC, lung stereotactic body radiation therapy (SBRT), particularly for patients who are medically inoperable, has become a new standard of care with local tumor control rates >90% and minimal clinical toxic effects.<sup>2-5</sup>

In this study, we report on a cohort of patients with stage I, medically inoperable NSCLC treated with lung SBRT with prospective follow-up for quality-of-life (QOL) and clinical toxic effects. Toxic effects were followed by using the *Common Terminology Criteria for Adverse Events*, version 4 (CTCAE)<sup>6</sup> and QOL using the validated Functional Assessment of Cancer Therapy-Lung-Trial Outcome Index (FACT-L-TOI) questionnaire, which has been associated with meaningful changes in patients with lung cancer.<sup>7,8</sup> Prior studies assessing QOL after lung SBRT suggest a minimal effect on patient QOL over time.<sup>9-12</sup> However, these studies did not fully analyze the influence of radiation dose and volume parameters on QOL. Our hypothesis was that clinically meaningful declines in QOL over time would be associated with increased radiation lung dose and volume parameters.

## Materials and Methods

### Patient population

A prospective study of 55 patients with stage I medically inoperable NSCLC treated with SBRT, who agreed to fill out a validated lung QOL questionnaire, was conducted as part of an institutional review board–approved protocol. All cases were assessed by the multidisciplinary thoracic oncology tumor board, and SBRT was the recommended treatment. The patient characteristics are listed in Table 1. Out of 54 patients who had ever smoked, 14 were current smokers and 23 had smoked more than 10 years before they received the radiation treatment.

### Treatment planning and image-guided delivery

All patients underwent a free-breathing 4-dimensional computed tomography (4DCT) planning scan using a real-time position management system (RPM [Varian Medical Systems, Palo Alto, CA] or Bellows [Philips

**Table 1 Patient characteristics**

Characteristic	Patients, no. (%) <sup>*</sup> (N = 55)
QOL compliance	
3 mo	54 (98)
6 mo	48 (89)
12 mo	43 (88)
18 mo	32 (73)
24 mo	29 (71)
36 mo	13 (34)
Median KPS (baseline)	90
Sex	
Male	29
Female	26
Race	
White	36
African American	19
Age, median, y	75
ITV, mean, cm <sup>3</sup>	19.3 ± 16.3
Lung dose, mean, Gy	3.2 ± 1.5
Lung V <sub>5</sub> , mean, %	14.7 ± 7.1
Lung V <sub>20</sub> , mean, %	4.0 ± 2.3
Total lung volume, mean, cm <sup>3</sup>	3631.1 ± 1302.3
Stage	
IA	43
IB	12
Tumor location	
Peripheral	39
Central	16
Smoking status	
Prior	40
Current	14
None	1
Abbreviations: KPS = Karnofsky Performance Status; ITV = internal target volume; QOL = quality of life; V <sub>x</sub> = percentage of volume of the normal lung receiving equal to or more than x Gy.	
<sup>*</sup> Data are presented as the number and percentage of patients unless otherwise indicated.	

Health Care, Cleveland, OH)].<sup>2</sup> The 4DCT was sorted into 4 CT phases: 0% (end-inhale), 25% (midexhale), 50% (end-exhale), and 75% (midinhale). Maximum intensity projections were created to assist in contouring. Free-breathing CT scans were also acquired for tumor localization and subsequently used for dose calculations, consistent with the institution's routine clinical practice. The CT scan allowed simultaneous view of the patient anatomy and was acquired with 2-mm to 3-mm slice thickness. The gross tumor volume (GTV) was delineated on each of the 4-dimensional phases. The clinical target volume (CTV) margin was 0; CTV = GTV. The internal target volume (ITV) was created from the composite of all clinical target volumes. All patients were treated according to the institution's standard SBRT regimen, 12 Gy × 4 fractions, to cover the planning target volume (PTV) at the 95% isodose level. The treatment plan used a 3-mm PTV margin in the axial plane and a 6-mm margin in the superior/inferior direction (around the ITV).

Normal organ dose constraints and tumor location followed protocols from Radiation Therapy Oncology Group trials (RTOG 0813 and RTOG 0915).<sup>5</sup> Doses were calculated using the anisotropic analytical algorithm in the Eclipse treatment planning system (Varian Medical Systems), which accounts for tissue inhomogeneities. The grid size of the dose calculations was 2.5 mm. In the treatment room, patients were first set up by aligning tattoos marked during simulation. For image-based localization, a full-rotation, low-dose thorax cone beam CT scan (110 kVp, 20 mA, 2-mm slice thickness) was acquired for each treatment fraction on either a Varian Trilogy or TrueBeam linear accelerator (Varian Medical Systems). Following the institution's routine clinical process, free-breathing CT was used as the reference data set for all cases. To perform image registration, automatic bony anatomy match was first applied based on alignment of the vertebral bodies and other rigid landmarks. The registration was manually adjusted, where necessary, to produce accurate bony alignment. The image data set was then viewed with a lung window to verify that the soft-tissue volume (ie, tumor) was within the ITV. Under rare circumstances, after soft-tissue matching, when the target was found to be outside of the ITV, manual adjustment was performed to shift the target into the ITV. The couch correction was then applied, and a MV/kV orthogonal image served as a verification of bony structure alignment after correction. An optical surface monitor system was part of one of the TrueBeam linac's imaging-guidance systems that detected sudden motion during delivery, such as patient coughing. Gating was not used during treatment delivery. The treatments were delivered every other day.

### Clinical evaluation and follow-up

In addition to baseline data, follow-up data were collected at 3, 6, 12, 18, 24, and 36 months posttreatment for the patients enrolled in this study. These data were assessed using the CTCAE, version 4.0,<sup>6</sup> and the FACT-L-TOI<sup>8,13</sup> scoring forms for patient-reported QOL data.<sup>14</sup>

### Toxicity and QOL statistics

Patients participated in the QOL study by completing the validated FACT-L-TOI form. For each individual patient, the QOL score (TOI) for each follow-up time point (3, 6, 12, 18, 24, or 36 months) was determined and baseline corrected using the pretreatment QOL score (eg, the pretreatment TOI score was subtracted from the 3-month TOI score). The criterion from Cella et al was used to categorize "clinically meaningful decline," defined as a

change of 5 points or less in the TOI score or a change of 2 points or less on subscales from pretreatment scores.<sup>13,14</sup> To prevent disease progression from affecting the QOL findings regarding the dosimetric parameters, the QOL score was incorporated for patients with no evidence of (or before the occurrence of) any disease progression.

### Pearson correlation, Student t test, and Kaplan-Meier analyses

Dosimetric parameters such as the mean lung dose (MLD) and lung subvolumes ( $V_5$ ,  $V_{10}$ ,  $V_{13}$ , and  $V_{20}$ ) were obtained from the treatment planning system. The MLD was defined as the delivered dose to the bilateral lungs minus the ITV. Similarly, the total lung volume (TLV) was defined as the bilateral lung volume minus the ITV. The lung subvolumes were defined as  $V_D$ , the volume of lung, minus the ITV, that received at least "D" Gy. The statistics of all indices were calculated using IBM SPSS, version 26 (IBM, Armonk, New York). Pearson correlation analysis was used to evaluate the correlation (using a 2-sided significance level of 0.05) of dosimetric parameters with toxic effects and QOL. The Student *t* test was used to determine statistically significant ( $P < .05$ ) results of dosimetric parameters with clinically meaningful decline versus no decline of QOL data. The Cohen *d* statistic was used to calculate the effect size of QOL score change between cohorts with and without a decline in QOL scores. The Kaplan-Meier method was used to estimate rates of local control, distant failure, and overall survival.<sup>15</sup> The log-rank test was used to compare variables between groups.

### Results

For the studied patient population,  $V_5$ ,  $V_{10}$ ,  $V_{13}$ , and  $V_{20}$  were  $14.7 \pm 7.1\%$ ,  $9.2 \pm 4.9\%$ ,  $7.1 \pm 3.9\%$ , and  $4.0 \pm 2.3\%$ , respectively. The MLD was distributed with an average of  $3.2 \pm 1.5$  Gy.

### Clinical toxicities

Toxic effects of grade 0, 1, 2, and 3 during the course of the study are summarized in Table 2. No toxic effects of grade 4 or greater were observed, and only 3 of the 55 patients (5.5%) overall had any grade-3 toxic effects. Ten patients (18%) experienced grade 2 fatigue, and 21 (38.2%) experienced grade 2 dyspnea. Of the 21 patients with grade 2 dyspnea, 6 (29%) already had grade 2 dyspnea at baseline before radiation therapy. One of the 55 patients (1.8%) experienced grade 3 cough and pericardial effusion, whereas 2 patients (3.6%) experienced grade 3 dyspnea (1 of these had grade 3 dyspnea before radiation therapy).

**Table 2** Summary of patients with toxic effects of grade 0, 1, 2, and 3

Toxic effect	Patients, No. (%)			
	Grade 0	Grade 1	Grade 2	Grade 3
Cough	4 (7.3)	41 (74.5)	9 (16.4)	1 (1.8)
Dyspnea	6 (10.9)	26 (47.3)	21 (38.2)	2 (3.6)
Pneumonitis	46 (83.6)	7 (12.7)	2 (3.6)	0 (0.0)
Esophagitis	52 (96.3)	2 (3.7)	0 (0.0)	0 (0.0)
Fatigue	7 (12.7)	38 (69.1)	10 (18.2)	0 (0.0)
Pericarditis	52 (94.5)	3 (5.5)	0 (0.0)	0 (0.0)
Pericardial effusion	53 (96.4)	1 (1.8)	0 (0.0)	1 (1.8)
Dermatitis	41 (74.5)	4 (7.3)	0 (0.0)	0 (0.0)

## QOL

All 55 patients reported QOL using the FACT-L-TOI questionnaire. The median QOL follow-up was 24 months (range, 3-36 months). The means and standard deviations of the baseline QOL indices were  $19.5 \pm 3.6$  for the lung cancer subscale (LCS),  $23.7 \pm 3.6$  for physical well-being (PWB),  $18.7 \pm 5.3$  for functional well-being (FWB), and  $62.0 \pm 9.6$  for TOI (TOI = LCS + PWB + FWB). Overall, through 2 years of follow-up, the QOL reporting compliance was >70% (Table 1). A summary of the statistically significant clinically meaningful results is presented in Table 3. An analysis was performed to determine whether there were any statistically significant associations between any dosimetric parameters and the development of a clinically meaningful decline in QOL. Each patient was analyzed, using the Student *t* test, as his or her own control. Lung  $V_{10}$  and  $V_{13}$  were key dosimetric parameters for which a statistically significant difference was found between the cohort with clinically meaningful decline and the cohort with no decline for the lung cancer subscale at 24 months, physical well-being at 3 and 36 months, and functional well-being at 3 months. Lung  $V_{20}$  also showed a statistically significant difference ( $P < .05$ ) between the decline and no-decline cohorts for the lung cancer subscale at 6 months, physical well-being at 3 months and 36 months, functional well-being at 36 months, and TOI at 36 months. The patients with smaller healthy total lung volumes (TLV = bilateral lung volume – ITV) showed a decline in physical well-being at 36 months (Table 3). Patients with a larger PTV and GTV experienced decline in physical well-being at 36 months. Overall, for dosimetric parameters such as the  $V_{10}$ ,  $V_{13}$ ,  $V_{20}$ , and MLD, statistically significant ( $P < .05$ ) mean differences were found between the decline and no-decline cohorts for both early and late time points of patient-reported QOL. The mean changes between the group with clinically meaningful decline and the group with no decline corresponded to moderate effect sizes (0.5-0.7) at the early QOL time points and large effect sizes (>0.8) at the later time points.

The Pearson correlation analysis showed that at the later time points (24 and 36 months), the lung cancer subscale,

functional and physical well-being, and FACT-L-TOI had statistically significant correlations with many dosimetric parameters, including  $V_{10}$ ,  $V_{13}$ ,  $V_{20}$ , MLD, or TLV, that corresponded well with *t* test analysis, as shown in Table 3. Lung  $V_{20}$  was strongly correlated ( $r > 0.5$ ) with the total FACT-L-TOI index as well as all the subscales, lung cancer subscale, physical well-being, and functional well-being at 36 months for patients with stage I NSCLC treated with SBRT. Of note, later QOL indices (18-36 months) showed a negative Pearson correlation with cough ( $P < .05$ ). Moreover, lung  $V_{10}$  was positively correlated with PTV, ITV, and the ratio of ITV to PTV ( $r > 0.5$ ;  $P < .01$ ). The mean difference of these parameters between the cohort of patients with a lung  $V_{10}$  of 10% or greater and the cohort with a  $V_{10}$  of less than 10% were statistically significant based on the Student *t* test (PTV:  $57.6 \pm 30.1 \text{ cm}^3$  vs  $31.8 \pm 21.4 \text{ cm}^3$ ; ITV:  $29.2 \pm 18.9 \text{ cm}^3$  vs  $13.2 \pm 10.8 \text{ cm}^3$ ; and ITV/PTV:  $0.48 \pm 0.10$  vs  $0.38 \pm 0.11$ ).

Figure 1 shows an average lung  $V_{10}$  as a function of the lung cancer subscale at 24 months that represents a clinically meaningful decline (a decrease of 2 or more points), no change (a difference of less than 2 points), and improvement (an increase of 2 or more points).<sup>7,13</sup> The regression analysis test indicated an  $R^2$  of 0.7. This showed an association between clinically meaningful declines in the lung cancer subscale at 24 months with increasing  $V_{10}$  levels. The error bars represent the standard error of each data point. Based on the linear fit, a clinically meaningful decline in the lung cancer subscale occurred with an increase of approximately 1% in the lung  $V_{10}$  in patients with a  $V_{10}$  greater than 10%.

## Clinical outcomes

With a median follow-up of 24 months, the 3-year local control, disease free survival, and overall survival rates were 93%, 65%, and 84%, respectively. Lung cancer stage (T1 vs T2), sex, race (White vs African American), and tumor location (central vs peripheral) were further analyzed. The log-rank test for stage T1 versus T2 showed a statistically significant difference in local control rates (97% vs 75%) and as well as disease-free survival rates (75% vs 34%), but no significant difference in the overall

**Table 3** Summary of statistically significant results of clinically meaningful decline or no decline associated with dosimetric parameters and volumes

Dosimetric parameter	Quality of life outcome					
	Mean	SD	Mean	SD	P value	Effect size
	Trial outcome index at 36 mo					
	Decline (n = 7)		No decline (n = 6)			
Lung V <sub>20</sub> , %	5.53	2.70	2.69	1.47	0.020	1.56
	Lung cancer subscale at 6 mo					
	Decline (n = 14)		No decline (n = 33)			
Lung V <sub>20</sub> , %	4.88	3.16	3.42	1.76	0.049	0.57
MLD, Gy	3.80	2.02	2.83	1.13	0.041	0.59
	Lung cancer subscale at 24 mo					
	Decline (n = 12)		No decline (n = 16)			
Lung V <sub>10</sub> , %	12.11	6.61	7.50	3.22	0.022	0.89
Lung V <sub>13</sub> , %	9.52	5.26	5.86	2.67	0.024	0.88
	Physical well-being at 3 months					
	Decline (n = 13)		No decline (n = 41)			
Lung V <sub>5</sub> , %	18.25	5.38	13.63	7.35	0.041	0.72
Lung V <sub>10</sub> , %	11.92	4.88	8.23	4.70	0.018	0.77
Lung V <sub>13</sub> , %	9.52	4.08	6.29	3.62	0.009	0.84
Lung V <sub>20</sub> , %	5.23	2.56	3.60	2.14	0.027	0.69
MLD	4.07	1.39	2.93	1.41	0.014	0.81
	Physical well-being at 36 months					
	Decline (n = 7)		No decline (n = 6)			
Lung V <sub>10</sub> , %	13.75	5.65	6.88	2.36	0.018	1.59
Lung V <sub>13</sub> , %	10.78	4.05	5.11	2.11	0.011	1.75
Total lung volume, cm <sup>3</sup>	2883.36	793.58	4736.06	880.86	0.002	2.20
PTV, cm <sup>3</sup>	52.62	25.63	24.77	11.44	0.032	1.40
GTV, cm <sup>3</sup>	16.06	11.94	4.17	4.28	0.042	1.33
	Functional well-being at 36 mo					
	Decline (n = 8)		No decline (n = 6)			
Lung V <sub>20</sub> , %	5.31	2.56	1.99	0.94	0.019	1.72
MLD	4.03	1.71	2.22	0.52	0.044	1.43

*Abbreviations:* GTV = gross tumor volume; MLD = mean lung radiation dose; PTV = planning target volume; V<sub>x</sub> = percentage of volume of the normal lung receiving equal to or more than x Gy.

survival rate was found between the 2 groups. Figure 2 shows the survival estimates for local control, disease-free survival, and overall survival. Of note, the 3-year distant disease control rate was 80%.

## Discussion

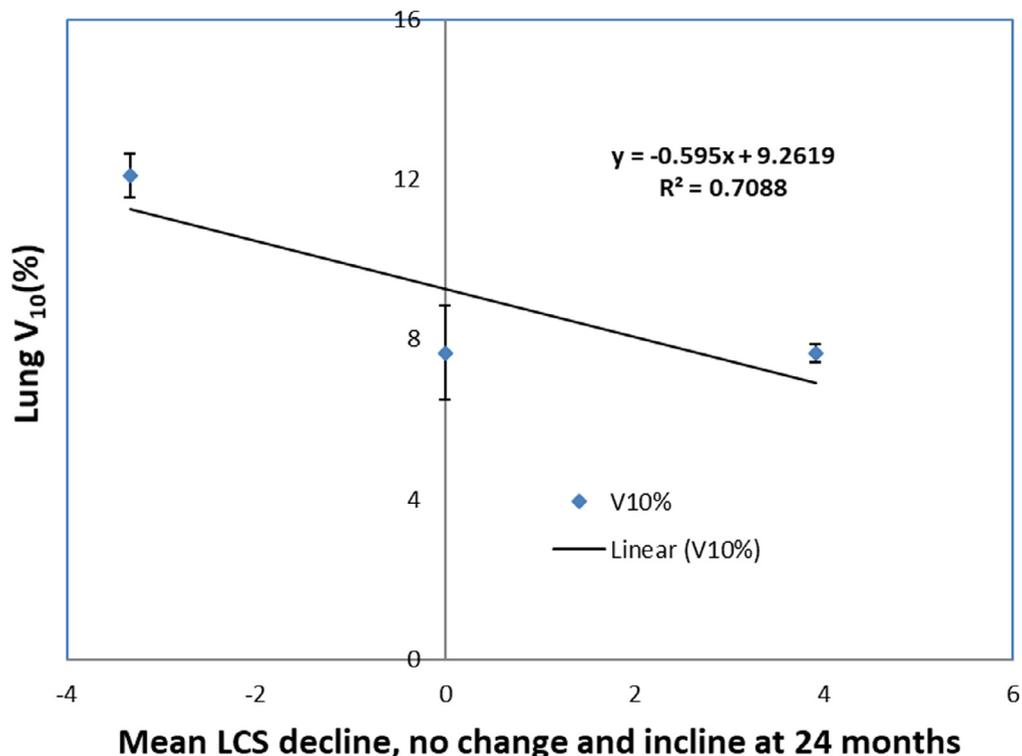
### Dosimetric outcomes for QOL

Lung SBRT has emerged as a new standard of care for patients with medically inoperable stage I NSCLC.<sup>3</sup> This noninvasive treatment has been shown to have excellent local control with minimal clinical toxicity.<sup>3,5,16-18</sup> Similarly, our experience reported here also showed excellent clinical outcomes, with a local control rate of 93% and minimal clinical toxic effects. Unlike after surgical resection,<sup>19,20</sup> studies after lung SBRT have reported overall stable QOL outcomes for patients with early-stage

NSCLC.<sup>9-12</sup> For example, Lagerwaard et al<sup>9</sup> studied more than 380 patients treated with lung SBRT and found no clinically significant worsening of any of the QOL scores even up to 2 years after SBRT. However, to our knowledge, prior studies have not directly analyzed the influence of radiation dosimetric parameters on QOL. Our hypothesis was that radiation dose and volume parameters would have clinically meaningful outcomes on QOL.

As we hypothesized, our results showed a strong association between radiation dosimetric parameters and the development of clinically meaningful changes in QOL, using the validated FACT-L-TOI instrument.<sup>8,13,14</sup> Overall, for various lung dose and volume parameters such as the V<sub>10</sub>, V<sub>13</sub>, and V<sub>20</sub>, statistically significant differences were found between patients with or without clinically meaningful declines in their QOL at both early and late time points. For example, using the V<sub>10</sub> parameter, we found a clinically meaningful decrease in lung cancer symptom scale scores with each increase of 1% of the lung V<sub>10</sub> in patients with a V<sub>10</sub> greater than 10%. These

## Lung V<sub>10</sub> vs Lung cancer subscale at 24 months



**Figure 1** Mean volume of the normal lung receiving more than 10 Gy (V<sub>10</sub>), with standard deviation, plotted against the lung cancer subscale at 24 months. The x-axis values represent the mean value of decline ( $\leq -2$ ), no change (between  $-2$  and  $2$ ), and incline ( $\geq 2$ ) of the lung cancer subscale.

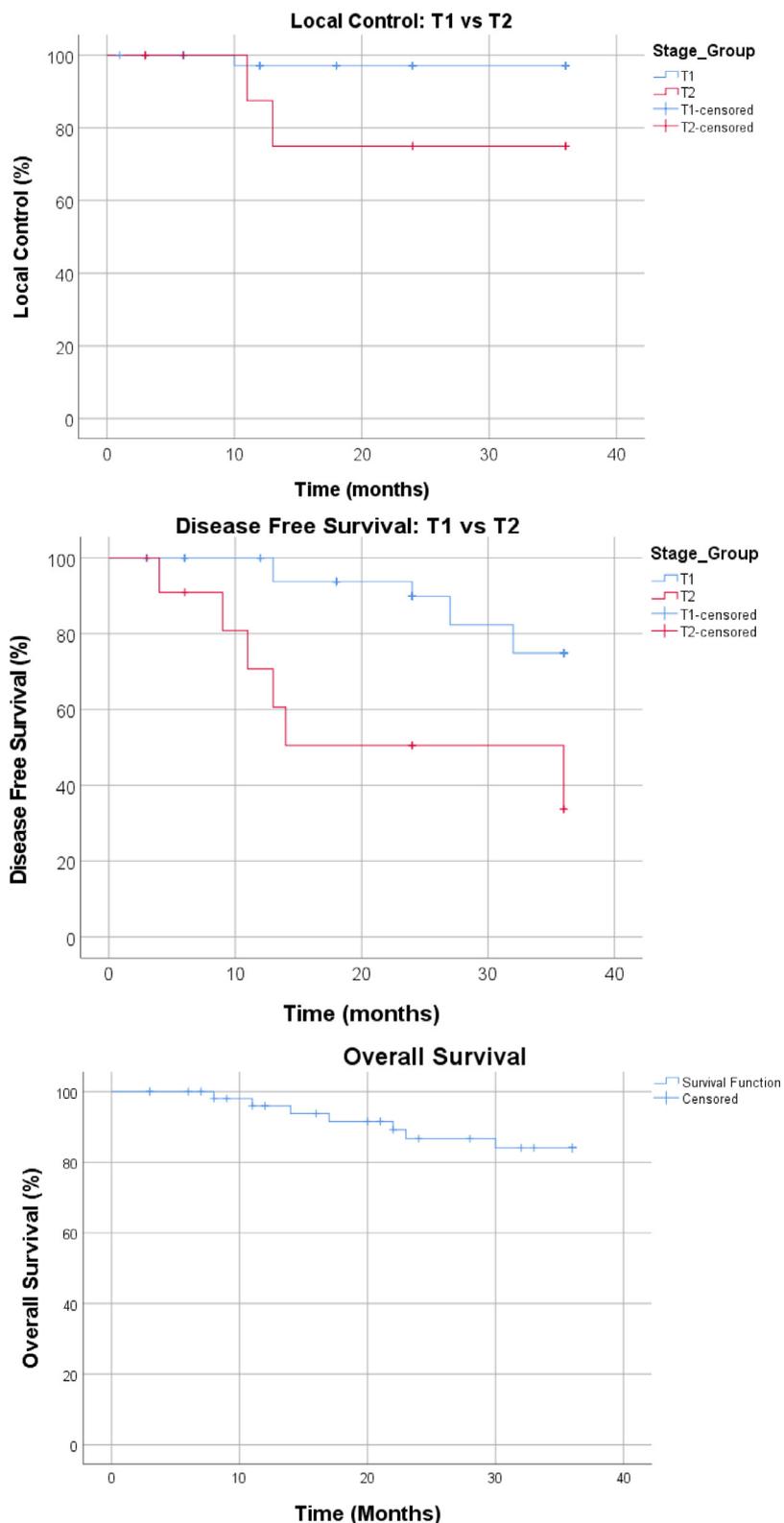
data suggest that by keeping the V<sub>10</sub> to less than 10%, the risk of a clinically meaningful decline in QOL can be minimized.

A key limitation of this analysis is the relatively small clinical experience. The conclusions need to be confirmed with a larger cohort of patients treated with lung SBRT with QOL follow-up. Despite this limitation, this study of a group of patients treated with lung SBRT in a consistent manner who had reasonable compliance with QOL reporting ( $>70\%$ ) for 2 years after SBRT showed clinically meaningful changes, all in the same direction, in QOL measures when examining multiple lung dosimetric parameters. By comparison, compliance rates of QOL reporting in the study by Lagerwaard et al were 59%, 36%, and 39% at 12, 18, and 24 months, respectively.<sup>9</sup> Of note, prior studies have shown that QOL can be sensitive in picking up clinically meaningful changes.<sup>21</sup> Prior studies have also shown that rates of clinical toxic effects reported by providers often underestimate the level of symptoms reported directly by patients.<sup>21,22</sup> This highlights the critical role of patient-reported outcomes as a part of clinical care.<sup>23,24</sup> A recent randomized study showed that monitoring of real-time patient-reported outcomes improved not only QOL but also survival.<sup>25</sup> Whereas the current

study did not incorporate pulmonary function testing, prior studies have suggested a limited effect of lung SBRT on pulmonary function tests.<sup>11</sup> To our knowledge, this is the first study to show a significant association between radiation dosimetric parameters and clinically meaningful changes in QOL after lung SBRT.

### Treatment planning implications

This study’s novel finding could have practical implications for radiation treatment planning. For example, as in this study, many centers use a free-breathing technique for lung SBRT,<sup>9</sup> creating an ITV that incorporates the entire motion of the lung nodule during the various phases of breathing. However, this ITV-based technique can lead to an increase in the overall volume of normal lung receiving radiation (eg, the V<sub>10</sub> or V<sub>20</sub>). If the ITV and subsequent V<sub>10</sub> (or V<sub>20</sub>) are relatively small (for example, V<sub>10</sub>  $< 10\%$ ), this may be acceptable. However, if the ITV is large (owing to increased respiratory motion), the current analysis suggests that this could be associated with negative clinically meaningful effects on QOL.<sup>24</sup> Indeed, in this analysis, the mean differences in the PTV,



**Figure 2** Survival curves for T1 versus T2 for local control (top), disease-free survival (middle), and overall survival (bottom) of 55 patients treated with stereotactic body radiation therapy.

ITV, and ITV/PTV among patients who received a  $V_{10}$  of 10% or greater versus less than 10% were statistically significant ( $P < .01$ ). As expected, this indicates that not only using larger margins (ie, a larger PTV) but also

creating a larger ITV (relative to the PTV) leads to a higher  $V_{10}$  (owing, for example, to respiratory motion), which has been associated with a clinically meaningful decline in QOL. In light of this, other techniques, which

are now more available, may be reasonable to consider, such as respiratory gating, abdominal compression, or real-time magnetic resonance imaging–guided radiation, which can limit the volume of irradiated normal lung tissue by reducing the PTV and/or the ITV. This study also raises a new paradigm to consider in that radiation dose and volume constraints should not simply be based on clinical toxicity alone, as in the past.<sup>26</sup> Rather, radiation dose and volume parameters should constantly be enhanced based on the more sensitive and clinically meaningful effect that they have on patients' QOL.

## Conclusions

Lung SBRT remains a standard of care for patients with early-stage medically inoperable NSCLC because it provides a noninvasive treatment option with excellent local control and minimal clinical toxic effects. The findings of this QOL analysis suggest that increased radiation dose and volume parameters are associated with clinically meaningful declines in QOL after lung SBRT. This suggests that further improvements in the techniques of lung SBRT have the potential to further enhance patients' QOL after receiving this treatment.

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## References

- Peters S, Adjei AA, Gridelli C, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23:vii56–vii64.
- Chetty IJ, Devpura S, Liu D, et al. Correlation of dose computed using different algorithms with local control following stereotactic ablative radiotherapy (SABR)-based treatment of non-small-cell lung cancer. *Radiation Oncol*. 2013;109:498–504.
- Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010;303:1070–1076.
- Stephans KL, Woody NM, Reddy CA, et al. Tumor control and toxicity for common stereotactic body radiation therapy dose-fractionation regimens in stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2018;100:462–469.
- Videtic GM, Paulus R, Singh AK, et al. Long-term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2019;103:1077–1084.
- US Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.0. Available at: [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03/Archive/CTCAE\\_4.0\\_2009-05-29\\_QuickReference\\_8.5x11.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf). Accessed October 19, 2021.
- Movsas B, Hu C, Sloan J, et al. Quality of life analysis of a radiation dose-escalation study of patients with non-small-cell lung cancer: A secondary analysis of the Radiation Therapy Oncology Group 0617 Randomized Clinical Trial. *JAMA Oncol*. 2016;2:359–367.
- Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy–Lung (FACT-L) questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. *J Clin Epidemiol*. 2002;55:285–295.
- Lagerwaard FJ, Aaronson NK, Gundy CM, et al. Patient reported quality of life after stereotactic ablative radiotherapy for early-stage lung cancer. *J Thorac Oncol*. 2012;7:1148–1154.
- van der Voort van Zyp NC, Prévost JB, van der Holt B, et al. Quality of life after stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2010;77:31–37.
- Videtic GM, Reddy CA, Sorenson L. A prospective study of quality of life including fatigue and pulmonary function after stereotactic body radiotherapy for medically inoperable early-stage lung cancer. *Support Care Cancer*. 2013;21:211–218.
- Sun V, Kim JY, Williams AC, et al. Quality of life and symptoms following stereotactic body radiotherapy in early-stage lung cancer patients. *J Community Support Oncol*. 2014;12:407–414.
- Cella DF, Bonomi AE, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy–Lung (FACT-L) quality of life instrument. *Lung Cancer*. 1995;12:199–220.
- Cella DF, Tulskey DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *J Clin Oncol*. 1993;11:570–579.
- Fleiss JL, Levin B, Paik MC. *Statistical Methods for Rates and Proportions*. Hoboken, NJ: John Wiley & Sons, Inc; 2003.
- Baumann P, Nyman J, Lax I, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer: A retrospective analysis of patients treated in the Nordic countries. *Acta Oncol*. 2006;45:787–795.
- Reyngold M, Wu AJ, McLane A, et al. Toxicity and outcomes of thoracic re-irradiation using stereotactic body radiation therapy (SBRT). *Radiat Oncol*. 2013;8:99.
- Stauder MC, Macdonald OK, Olivier KR, et al. Early pulmonary toxicity following lung stereotactic body radiation therapy delivered in consecutive daily fractions. *Radiation Oncol*. 2011;99:166–171.
- Pompili C, Brunelli A, Xiume F, et al. A. Predictors of postoperative decline in quality of life after major lung resections. *Eur J Cardiothorac Surg*. 2011;39:732–737.
- Schulte T, Schniewind B, Walter J, et al. Age-related impairment of quality of life after lung resection for non-small cell lung cancer. *Lung Cancer*. 2010;68:115–120.
- Siddiqui F, Liu AK, Watkins-Bruner D, et al. Patient-reported outcomes and survivorship in radiation oncology: Overcoming the cons. *J Clin Oncol*. 2014;32:2920–2927.
- Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: An analysis of RTOG 9801. *J Clin Oncol*. 2009;27:5816–5822.
- Basch E, Stover AM, Schrag D, et al. Clinical utility and user perceptions of a digital system for electronic patient-reported symptom monitoring during routine cancer care: Findings from the PROTECT Trial. *JCO Clin Cancer Inform*. 2020;4:947–957.
- Basch E, Charlot M, Dueck AC. Population-level evidence of survival benefits of patient-reported outcome symptom monitoring software systems in routine cancer care. *Cancer Med*. 2020;9:7797–7799.
- Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA*. 2017;318:197–198.
- Paximadis P, Schipper M, Matuszak M, et al. Dosimetric predictors for acute esophagitis during radiation therapy for lung cancer: Results of a large statewide observational study. *Pract Radiat Oncol*. 2018;8:167–173.