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Scientific Article

Repeat Thoracic Stereotactic Body Radiation Therapy (SBRT) for Nonsmall Cell Lung Cancer: Long-Term Outcomes, Toxicity, and Dosimetric Considerations

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Abstract

Purpose: Lung reirradiation for nonsmall cell lung cancer (NSCLC) is common for either recurrent disease or new primary cancer. Dose volume tolerance of the lung after multiple courses of radiation therapy (RT) is unknown. We review our experience with lung reirradiation for patients with NSCLC in a single community setting using stereotactic body radiation therapy (SBRT) to report lung cumulative doses, survival, and toxicity.

Methods and Materials: Forty-four patients who received at least 2 curative courses of lung RT with the second course delivered between January 2012 and December 2017 were eligible. All patients had NSCLC and were treated with SBRT for reirradiation. Cumulative lung dose volume histograms for all courses were generated, summated, and converted into cumulative equivalent dose in 2 Gy fractions (EQD2). Actuarial overall survival (OS), local control, and toxicity is reported, including a subset of patients who received more than 2 courses of SBRT.

Results: Median age of the group was 71 years (range, 51-87). Median survival of the entire group from diagnosis, first, and second courses of RT was 3.94, 3.03, and 2.03 years. Three-year actuarial OS for the entire group was 34.1% from second course of RT. The mean EQD2 Gy_3 mean lung dose for all courses was 12.35 Gy (range, 2.7-26.52). The mean EQD2 Gy_3 V5Gy, V10Gy, V20Gy, V30Gy, and V40Gy were 40.9%, 25.5%, 14.7%, 10.2%, and 7.7%. Six-year actuarial freedom from grade $\geq$3 complications was 86.3%. The rate of grade $\geq$3 lung toxicity was 4.5% (2 of 44). Other late toxicities included grade 3 recurrent laryngeal nerve damage (n = 1) and grade 3 chest wall pain/rib fracture (n = 1). Overall, 32% of patients had more than 2 courses of RT to the lung (range, 3-7).

Conclusions: Long-term OS is possible with multiple RT courses to the lung for NSCLC with low toxicity.

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Introduction

Improvements in tumor localization, treatment planning, and radiation delivery have minimized damaging effects while maximizing the therapeutic benefit of reirradiation in the treatment of intrathoracic malignancy with stereotactic body radiation therapy (SBRT).[1,2] Local and regional recurrences continue to be problematic even for early stage lung cancer, with mature follow-up of SBRT clinical trials demonstrating locoregional recurrences over 25% at 5 years.[3] In addition, there is increasing interest in the treatment of oligometastatic disease for lung cancer with SBRT and its potential to improve overall survival (OS).[4,5] Treatment options, however, after thoracic recurrence are often limited owing to patient comorbidities, underlying lung function, and previous surgical interventions.

SBRT has largely replaced conventional radiation therapy (RT) for early stage inoperable nonsmall cell lung cancer (NSCLC) and for lung oligometastases due to high rates of local control with acceptable risk of complications.[3,4,6-8] It is also an ideal therapy for reirradiation to the thorax due to highly conformal dose distributions. Retrospective studies have demonstrated that reirradiation with SBRT is feasible; however, there is paucity of data in regards to dosimetric predictors of severe toxicity.[9] The purpose of this study was to describe dosimetric parameters including V5, 10, 20, 30, 40, and mean lung dose (MLD) after reirradiation with SBRT to the lung in a large contemporary series with long follow-up.

Methods and Materials

Patient selection and data collection

Patients who had previously undergone at least 2 metachronous courses of RT to the lung parenchyma, hilar, or mediastinal lymph nodes for NSCLC with the second course of RT delivered with SBRT between January 2012 and December 2017 were included in this institutional review board–approved retrospective analysis. Patients were excluded if RT dosimetry data from any course of thoracic RT were not available for composite dose volume histogram (DVH) analysis, if follow-up imaging (positron emission tomography or computed tomography [CT]) at least 3 months after the last course of thoracic SBRT was not available, or if the intent of the repeat course of SBRT was palliative (equivalent dose in 2 Gy fractions [EQD2] $Gy_{10} < 58$ Gy). Normal tissue dose-volume constraints were used for central tumor locations, with modifications made on an individual patient basis per discretion of the treating physician after review of a cumulative composite dose plan at the time of treatment planning.

All patients were treated supine using the Accuray CyberKnife platform. CT simulation included inspiration and expiration hold CT of chest if fiducials were present or 4-dimensional CT to evaluate movement of the gross tumor volume (GTV) with respiration if no fiducials were present. kV orthogonal imaging was used for real-time target tracking with either fiducial, XSight_Lung, or XSight_Spine. An internal target volume was delineated for patients tracked with XSight_Spine, which was the minority of patients. All clinical target volumes (CTVs) had an isotropic expansion (5-8 mm) to create the planning target volume (PTV). Noncoplanar pencil beams using 6 MV photons with Monte Carlo dosimetric calculations were used for all patient treatment plans. All treatment plans were evaluated to determine whether the second course of RT was considered an "in-field recurrence" of the first RT course.

Cumulative composite plans (MIM Software Inc, Cleveland, OH) were made to combine all RT courses and generate a cumulative DVH for analysis of MLD, V5 Gy, V10 Gy, V20 Gy, V30 Gy, and V40 Gy for each patient with deformable registration on the final CT. In addition, these volumetric doses were corrected for EQD2 at an alpha-to-beta ratio of 3 (EQD2 Gy_3) for each plan and then summated with deformable registration on the final CT.

Local failure was defined as relapse within the SBRT or conventionally fractionated PTV. Response evaluation criteria in solid tumors 1.1 was used as a general guideline, and the use of positron emission tomography/CT with standardized uptake value greater than or equal to pretreatment values was considered a recurrence.[10] Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE V5.0).[11]

Pretreatment- and treatment-related variables were abstracted from various sources including electronic medical records from the hospital system, outpatient primary care, the radiation department, and specialist notes. Variables included age; sex; history of chronic obstructive pulmonary disease (COPD); use of supplemental oxygen at presentation and after SBRT; Eastern Cooperative Oncology Group performance status score; treatment with chemotherapy, targeted therapy, or immunotherapy; previous lung surgery; use of conventional RT versus SBRT; CTV for each radiation site; and time between RT courses.

Statistical analysis

Patient characteristics and dosimetric variables were described using means, standard deviations, frequencies, and percentages. OS from the second course of RT was estimated using Kaplan-Meier methodology among all patients (n = 44), patients with 2 courses of treatment (n = 30), and those with more than 2 courses (n = 14).

Table 1 Patient characteristics

Variable	All patients (n = 44)		Patients with 2 courses (n = 30)		Patients with more than 2 courses (n = 14)	
	N	(%)	N	(%)	n	(%)
Sex						
Female	27	61.36	21	70.00	6	42.86
Male	17	38.64	9	30.00	8	57.14
Previous lung surgery						
Yes	13	29.55	10	33.33	3	21.43
No	31	70.45	20	66.67	11	78.57
History of COPD						
Yes	35	79.55	27	90.00	8	57.14
No	9	20.45	3	10.00	6	42.86
Use of oxygen at presentation						
Yes	9	20.45	6	20.00	3	21.43
No	35	79.55	24	80.00	11	78.57
Use of oxygen at last F/U						
Yes	14	31.82	11	36.67	3	21.43
No	30	68.18	19	63.33	11	78.57
ECOG at presentation						
0	14	31.82	8	26.67	6	42.86
1	21	47.73	16	53.33	5	35.71
2	8	18.18	6	20.00	2	14.29
3	1	2.27	0	0.00	1	7.14
Conventional radiation to the lung						
Yes	5	13.64	5	16.67	0	0
No	39	88.64	25	83.33	14	100
Any toxicity at last F/U						
Yes	1	2.27	1	3.33	0	0.00
No	43	97.73	29	96.67	14	100.00
Toxicity at any point						
Yes	4	9.09	3	10	1	7.14
No	40	90.91	27	90	13	92.86
Number of courses to the lung						
2	30	68.18	30	100.00	0	0.00
3	10	22.73	0	0.00	10	71.43
4	2	4.55	0	0.00	2	14.29
5	1	2.27	0	0.00	1	7.14
6	1	2.27	0	0.00	1	7.14

Abbreviations: COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; F/U = follow-up.

Comparisons of OS profiles between patients with 2 versus more than 2 courses of radiation were accomplished using log-rank statistics. Time to local failure (tumor-level) and toxicity (patient-level) were estimated using Kaplan-Meier methods. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Patient characteristics

Forty-four patients were eligible and met inclusion criteria. All patients had primary NSCLC. Median age of the group was 71 years (range, 51-87). The median follow-up time after the second course of RT was 2.0 years (range, 0.3-7.0). Thirty-five patients (79.5%) had a history of COPD, 9 patients (20.4%) required supplemental oxygen, and 13 patients (29.5%) had previous lung surgery before the second course of RT. Surgical procedures included 4 unilateral wedge resections, 1 bilateral wedge resection, 6 unilateral lobectomies, and 2 wedge resections and lobectomies. Twenty-six patients (59%) received chemotherapy, 7 (15.9%) targeted therapy, and 7 (15.9%) immunotherapy at any time. Further demographic patient characteristics are described in Table 1.

The median prescription dose for the first course of RT was 54 Gy in 3 fractions (range, 45-70.2), whereas the

Table 2 EQD2 Gy10 dose per course and CTV (cm^3) of patient cohort (n = 44 at the patient level; n = 108 at the tumor level)

Variable	N	Mean	SD	Median	Interquartile range		Range	
					Q1	Q3	Min	Max
EQD2 Gy10 (tumor-level)	108	98.84	25.15	93.75	83.33	126	31.25	150
EQD2 Gy10 1st course	44	104.18	24.51	93.75	88.54	126.00	58.41	150.00
EQD2 Gy10 2nd course	44	98.54	22.5	93.75	83.33	126.00	60.00	126.00
EQD2 Gy10 3rd course	14	91.89	26.41	93.75	71.25	126.00	49.58	126.00
EQD2 Gy10 4th course	4	99.21	18.52	93.75	88.54	109.88	83.33	126.00
EQD2 Gy10 5th course	2	31.88	0.88	31.88	31.25	32.50	31.25	32.50
EQD2 Gy10 6th course	1	40.00	-	40.00	40.00	40.00	40.00	40.00
CTV (cm^3) (tumor level-all courses)	108	14.7	28.25	5.85	2.56	12.98	0.34	183.7
CTV (cm^3) from 1st course	44	18.21	29.60	8.11	3.57	20.94	0.53	154.98
CTV (cm^3) from 2nd course	44	10.34	18.97	5.48	2.22	8.91	0.61	108.40
CTV (cm^3) from 3rd course	14	19.53	47.86	4.75	1.68	12.59	0.34	183.70
CTV (cm^3) from 4th course	4	12.99	13.00	10.45	2.58	23.41	1.67	29.39
CTV (cm^3) from 5th course	1	3.54	-	3.54	3.54	3.54	3.54	3.54
CTV (cm^3) from 6th course	1	3.12	-	3.12	3.12	3.12	3.12	3.12
Combined CTV (all courses)	44	36.09	51.31	18.71	11.24	33.68	3.62	244.43

Abbreviations: CTV = clinical target volume; EQD2 = equivalent dose in 2 Gy fractions; Max = maximum; Min = minimum; SD = standard deviation.

median dose for the second course was 50 Gy in 4 fractions (range, 39-54) prescribed to the median isodose of 65% for both courses. The CTV to PTV margin was a median of 8 mm for the first course and 5 mm for the second course. The median number of radiosurgical beams was 132. Five (11.4%) patients received conventionally fractionated lung RT as first course with a median dose of 60 Gy in 30 fractions (range, 59.4-70.2 Gy). SBRT was used for all subsequent courses of reirradiation. Primarily, SBRT was recommended for development of new intrathoracic metastases or primary cancer, but 6 patients (13.6%) received reirradiation with SBRT to the same region of the lung that received an earlier course of RT for a local failure. Mean and median time between first and second course of RT was 14.6 and 7 months, respectively.

Dosimetric variables

The mean/median tumor size (CTV) for the first course was 18.2/8.1cm^3 and for the second course was 10.3/5.5 cm^3. The cumulative mean/median CTV at the patient level for all courses was 36.1/18.7cm^3 (range, 3.6-244.4). The mean EQD2 Gy_{10} for the first course of RT was 104.2 Gy and for the second course was 98.5 Gy. The mean biologically effective dose (BED) Gy_{10} for the first course of RT was 125.0 Gy and for the second course was

Table 3 Cumulative lung doses with and without conversion to EQD2 Gy_3 (n = 44 at the patient level; n = 108 at the tumor level)

Variable	N	Mean	SD	Median	Interquartile range		Range	
					Q1	Q3	Min	Max
V5 EQD2	44	40.93	17.26	37.45	28.10	50.75	14.20	78.00
V10 EQD2	44	25.49	13.26	21.70	16.70	31.20	7.40	61.70
V20 EQD2	44	14.73	9.06	13.15	8.25	17.50	3.80	46.10
V30 EQD2	44	10.23	6.48	9.70	5.75	11.95	2.60	34.40
V40 EQD2	44	7.69	4.48	7.60	4.65	9.00	2.00	26.50
V5	44	47.43	18.24	44.43	33.06	57.25	18.34	84.24
V10	44	27.26	14.98	24.39	17.74	30.62	7.01	70.66
V20	44	12.32	10.25	9.96	6.29	12.49	2.53	52.39
V30	44	7.29	7.84	5.37	3.68	7.26	1.36	44.77
V40	44	4.67	5.83	3.11	2.14	4.45	0.78	32.71
Mean lung dose EQD2	44	12.42	5.12	11.45	8.49	15.44	4.55	26.52
Mean lung dose	44	9.38	4.85	8.55	6.38	10.36	4.05	28.38

Abbreviation: EQD2 = equivalent dose in 2 Gy fractions; Max = maximum; Min = minimum; SD = standard deviation.

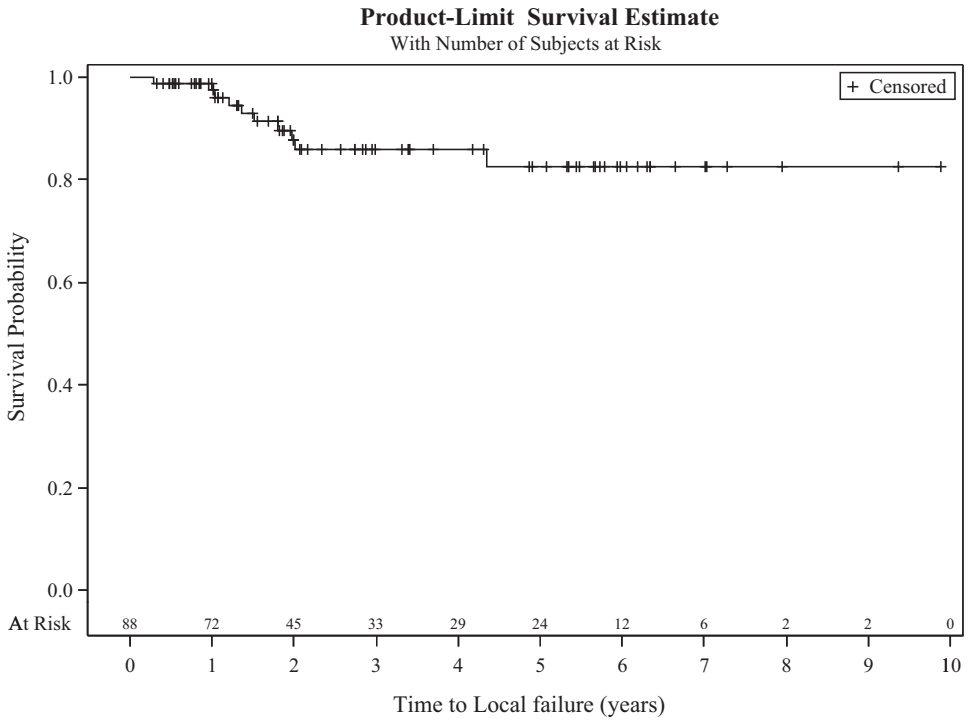

Figure 1 Time to local failure from second course of stereotactic body radiation therapy (SBRT) (n = 88; tumor level).

118.2 Gy. Tumor doses and CTV sizes stratified by course number are presented in Table 2.

The cumulative average MLD for all courses was 9.40 Gy (range, 4.05-28.38). The converted average EQD2 Gy_3 MLD for all courses was 12.42 Gy (range, 4.55-26.52). The mean V5Gy, V10Gy, V20Gy, V30Gy, and V40Gy for all courses of RT were 47.4%, 27.3%, 12.3%, 7.3%, and 4.7%, respectively. The mean EQD2 Gy_3 V5 Gy, V10 Gy, V20 Gy, V30 Gy, and V40 Gy were 40.9%, 25.5%, 14.7%, 10.2%, and 7.7%. In general, the MLD was higher with conversion to EQD2 Gy_3. In general, with EQD2 Gy_3 conversion, V5 Gy and V10 Gy were lower, V30 Gy and V40 Gy were higher, and V20 Gy was comparable to simple summation without conversion.

Only 4 patients had cumulative MLD greater than 20 Gy (20.22, 20.88, 26.52, 24.07), with the highest 2 values for 2 patients who received conventional RT at presentation. Only 6 patients had cumulative V5 > 65% (67.5, 68, 69.2, 76.5, 77.5, 78), with 3 of the 5 values and 2 of the highest for patients who received conventional RT at presentation. Only 2 patients had V20 > 37% (44.2, 46.1) with both patients receiving conventional RT at presentation. All lung specific dosimetric data are presented in Table 3.

Overall, 32% (14 patients) had more than 2 courses of RT to the lung. In this subgroup, total courses received included 6 courses (n = 1), 5 courses (n = 1), 4 courses (n = 4), and 3 courses (n = 8). Mean time between the second or third and third or fourth courses was 24 and 15

Table 4 OS from time of SBRT course

Variable	n	Mean	SD	Median	Interquartile range		Range	
					Q1	Q3	Min	Max
OS from diagnosis (years)	44	4.54	2.90	3.94	2.16	6.29	0.81	12.37
OS from 1st course (years)	44	3.84	2.57	3.03	1.83	6.08	0.40	9.88
OS from 2nd course (years)	44	2.63	1.95	2.03	0.93	4.24	0.32	7.01
OS from 3rd course (years)	14	1.9	1.48	1.38	0.95	3.04	0.00	4.45
OS from 4th course (years)	4	1.43	2.06	0.64	0.12	2.74	0.02	4.45
OS from 5th course (years)	1	3.71	-	3.71	3.71	3.71	3.71	3.71
OS from 6th course (years)	1	1.02	-	1.02	1.02	1.02	1.02	1.02

Abbreviations: Max = maximum; Min = minimum; OS = overall survival; SBRT = stereotactic body radiation therapy; SD = standard deviation.

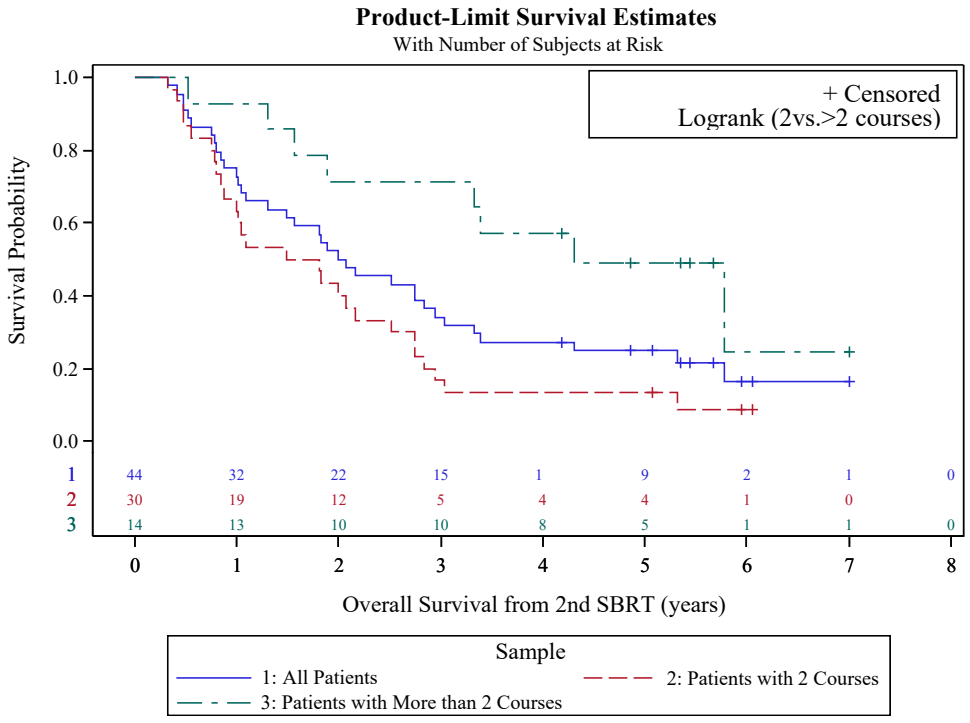

Figure 2 Overall survival from second course of stereotactic body radiation therapy (SBRT) (n = 44) by number of courses.

months, respectively. The median prescription dose for all patients from course 3 was 50 Gy (range, 35-54) and course 4 was 47.5 Gy (range, 45-54). Only 2 patients had cumulative MLD greater than 20 Gy (20.88, 26.52), with both patients receiving 3 courses. Only 4 patients had cumulative V5 > 65% (68, 76.5, 77.5, 78) with 5, 4, 3, and 6 courses, respectively. Only 1 patient had V20 > 37% (44.2), treated with 3 courses. There was only 1 patient out of the entire series who did not have more than 2 courses or conventional RT at presentation with MLD >20 and V5 greater than 65% (MLD 20.88 Gy, V5 Gy 69.2%) with V20 of 29.7%. Further details on tumor and lung doses in this subgroup can be found in Tables 2 and 3.

Local control and overall survival (OS)

Of 88 evaluable tumors from courses 1 and 2, 9 demonstrated local failure with 6-year actuarial freedom from local failure of 82.7%, with no failures after 5 years (Fig 1). Median survival of the entire group from diagnosis, first, and second courses of RT was 3.9, 3.0, and 2.0 years, respectively (Table 4). Three-year actuarial OS for the entire group was 34.1% from second course of RT. There was a significant decrease in survival for those patients treated with 2 courses (n = 30) versus greater than 2 courses of radiation (n = 14), with 3-year actuarial survival 71.4% versus 16.7%, $P = .0048$ (Fig 2).

Within the subgroup of patients who had more than 2 courses of RT to the lung (n = 14, 32%), median survival from diagnosis, first, second, third, and fourth courses of RT was 5.9, 5.7, 4.2, 1.4, and 0.6 years (Table 4). One patient who had 5 courses died with extensive metastatic disease 3.7 years from the final SBRT course. One patient who had 6 courses is alive with no evidence of disease 1 year from the final SBRT course. Three-year actuarial OS for this subgroup who had more than 2 courses was 71.4% from the second course of RT. A case presentation of the patient who received 6 courses of radiation is reviewed in Figure 3.

Toxicity

Toxicity was assessed using CTCAE V5.0.[11] Overall, toxicity was low, with 6-year actuarial freedom from CTCAE grade ≥3 complications of 86.3% (Fig 4). The rate of grade 3 RT lung toxicity requiring steroids was 4.5% (2 of 44). Case summaries of the patients with pulmonary toxicity are summarized in later paragraphs.

A 71-year-old male with a pre-SBRT forced expiratory volume in the first second of 1.12 L (41% predicted), diffusing capacity for carbon monoxide 51% predicted, and resting oxygen saturation on room air of 94% was treated with 2 SBRT courses to a right upper lobe (RUL) adenocarcinoma followed by a hilar recurrence. Cumulative EQD2 Gy_3 of both courses for MLD, V5 Gy, V10 Gy, V20 Gy, V30 Gy, and V40 Gy was 9.16 Gy, 41.1%, 20.7%, 8.5%, 5.5%, and 4.2%, respectively. Three months after treatment of first course of SBRT (54 Gy/3 fx), he required steroids and continuous oxygen for

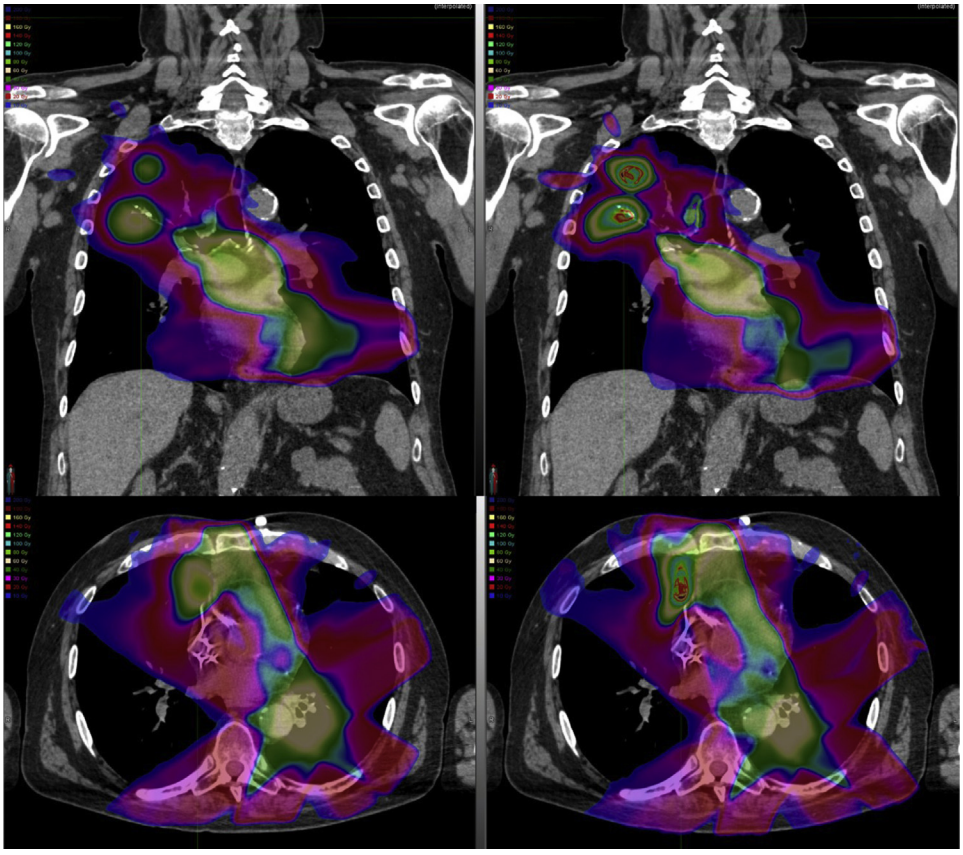

Figure 3 Case presentation: L.C. is a 69-year-old white man with past medical history of chronic obstructive pulmonary disease and 110 pack-year history of smoking who presented with a clinical stage T2aN2 (bulky subcarinal lymph node) IIIA squamous cell cancer left lower lobe (LLL) and T1aN0M0 IA adenocarcinoma of the right middle lobe (RML) status post (s/p) 4 cycles of carboplatin and paclitaxel followed by 5 field intensity modulated radiation therapy (IMRT) completing 60 Gy in 30 fractions to the LLL squamous cell cancer April 2014. He had progression to the RML mass s/p stereotactic body radiation therapy (SBRT) 50 Gy in 5 fractions September 2014. He presented with 3 metabolically active right upper lobe pulmonary nodules s/p navigational bronchoscopy and biopsy revealing adenocarcinoma. Programmed death-ligand 1 = 0, anaplastic lymphoma kinase and epidermal growth factor receptor were negative. He completed 45 Gy in 3 fractions August 2015 on the NRG Oncology BR-001 oligo-metastases trial. He subsequently received 4 cycles of pemetrexed and carboplatin. He progressed in a right level 10 lymph node s/p endobronchial ultrasound biopsy and fiducial placement confirming adenocarcinoma. He received 25 Gy in 5 fractions completed May 2016. He has been on nivolumab since May 2016. He progressed in a right level 4R lymph node s/p endobronchial ultrasound biopsy and fiducial placement confirming adenocarcinoma. He received 30 Gy in 5 fractions completed January 2019. Most recent positron emission tomography (PET)/computed tomography (CT) January 2020 was stable with no evidence of active cancer. Most recent pulmonary function testing (PFT) showed mild decrement in pulmonary function over time with moderate chronic obstructive pulmonary disease. He does not require oxygen and is not limited significantly with activity. Cumulative mean lung dose, V5Gy, V10Gy, V20Gy, V30Gy, V40Gy was 17.02 Gy, 78.0%, 56.4%, 27.6%, 15.6%, and 8.5% respectively. Most recent PFTs: forced expiratory volume in the first second = 1.43 (54% predicted), diffusing capacity for carbon monoxide 13.0 (54% predicted). The following represents a composite dose distribution of all received doses: Coronal images (left) simple summation of all dose files, (right) equivalent dose in 2 Gy fractions (EQD2) Gy_3 summation of dose, coronal plane shows right upper lobe pulmonary nodules, LLL mass, and subcarinal mass dose. Axial images (left) simple summation of all dose files, (right) EQD2Gy_3 summation of dose, axial plane shows LLL mass and RML mass doses.

radiation pneumonitis. Two years later while still requiring oxygen with exertion, he developed a right hilar recurrence, which was treated with SBRT (40 Gy/5 fx) without toxicity. He lived 3 years after the second course of SBRT and died of a COPD exacerbation/pneumonia with brain metastases.

An 80-year-old female received 2 SBRT courses to a right lower lobe/perihilar mass (50 Gy/4 fx) followed by a RUL mass (54 Gy/3 fx) 1 year later. Cumulative EQD2 Gy_3 of both courses for MLD, V5 Gy, V10 Gy, V20 Gy, V30 Gy, and V40 Gy was 10.84 Gy, 28.1%, 18.1%, 12.5%, 9.5%, and 7.6%, respectively. She developed right-sided confluent fibrosis over the next 2 years that affected her pulmonary function, requiring hospitalization and steroids. She lived 3 years after the second course of SBRT and died of unclear cause.

Other late toxicities included grade 3 recurrent laryngeal nerve damage (n = 1) and grade 3 chest wall pain/

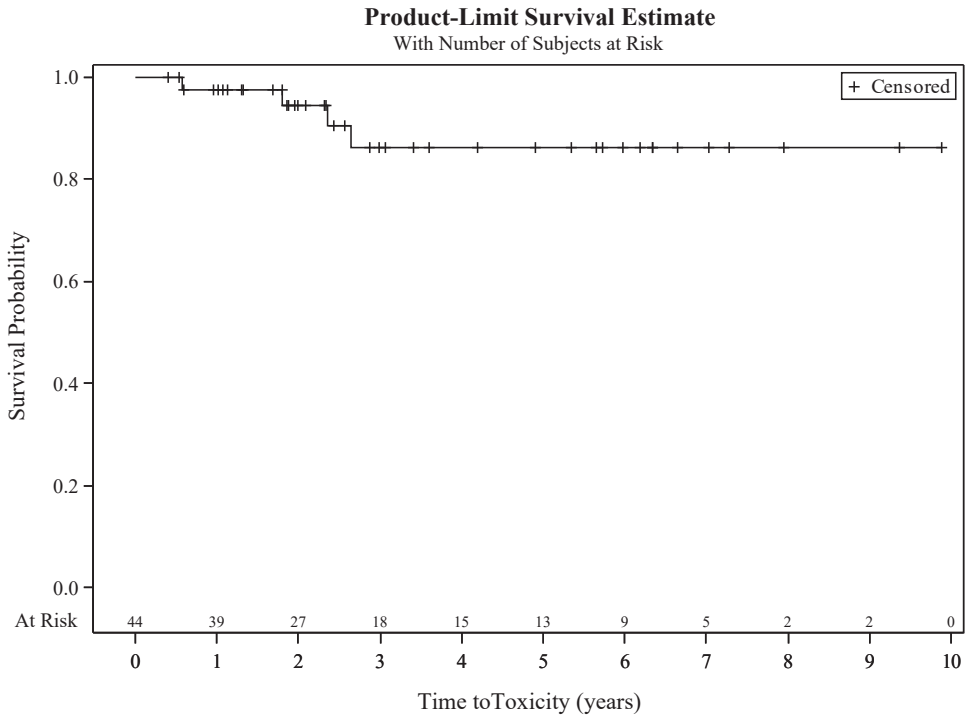

Figure 4 Actuarial freedom from Common Terminology Criteria for Adverse Events (CTCAE) grade $\geq$ 3 complications for all patients (n = 44; patient-level).

rib fracture (n = 1). All complications occurred within the first 3 years after the first course of RT. There were no cases of severe or fatal hemoptysis or other bronchial tree toxicity. The patient with grade 3 recurrent laryngeal nerve damage received 50 Gy/5 fx to a RUL mass and was retreated to an adjacent volume 2 years later with 50 Gy/5 fx. She had acute onset of hoarseness 6 months after the second course of SBRT, treated with 2 vocal cord injections with excellent clinical response and resolution of the hoarseness. She is alive without toxicity 6 years after the second course of SBRT. The patient with grade 3 chest wall toxicity with associated rib fracture presented with pain 2 years after SBRT (54 Gy/3 fx) to a left lower lobe mass adjacent to rib. In the subgroup of patients with more than 2 courses of RT, the incidence of any late CTCAE grade $\geq$3 toxicity included the single patient with grade 3 recurrent laryngeal nerve damage.

Discussion

Numerous retrospective series have demonstrated acceptable rates of local control with repeat courses of RT to the lung using SBRT. However, there remains considerable rates of acute and late toxicities of the lung, chest wall, esophagus, and bronchial tree, with at least 8 series reporting fatal grade 5 toxicities.[12-19] Correspondingly, there is a scarcity of data in regard to dose-volume constraints or guidelines for safe reirradiation in this setting.

Lung reirradiation studies are limited in their ability to draw definitive conclusions or guidelines regarding optimal dose, fractionation, and dose-volume constraints for safe lung retreatment. A major limitation to interpretation of the repeat RT literature is the wide heterogeneity within and across studies. The heterogeneity includes differences between histology (primary lung vs metastatic disease), dose, number of fractions, initial modality of treatment (3-dimensional vs intensity modulated RT vs SBRT), time interval between treatment courses, and whether reirradiation was performed in- or out-of-field. The data on reirradiation are also limited by the retrospective nature and small sample sizes, with all but 4 series having fewer than 40 patients.[9]

The current study comprises a large series with long follow-up of SBRT for NSCLC. Unlike other series, however, our cohort was a homogeneous group of patients comprised of recurrent NSCLC after initial SBRT. Acute and late toxicities were quite low, with only 2 respiratory, 1 chest wall, and 1 nerve toxicity (CTCAE grade 3 or higher), which occurred within the first 3 years after RT, with no grade 5 toxicities. Given the absolute low number of toxicity events, we were not able to determine any significant dosimetric predictors of toxicity on univariate or multivariable analysis. However, we are able to provide comprehensive cumulative lung doses that were safe with our techniques and experience with SBRT reirradiation.

In comparing the current study to the 4 largest series, our toxicity profile is quite comparable, with grade 3+

pulmonary toxicity rates of 5% to 19% (4.5% grade 3+ in current series) and grade 3+ chest wall toxicities 1% to 18% (2.3% in the current series).[12,20-22] Similar to the Horne et al[20] series involving 72 patients, we found no significant dosimetric or clinical predictors of grade 3+ toxicity. This contrasts with the Liu et al[12] and Lester et al[22] series, which found composite plan MLD and V20 > 30% to be correlated with pneumonitis risk and chest wall V30 to be correlated with chest wall toxicity. In addition, the Liu et al[12] series determined clinical factors such as performance status, baseline pulmonary function, bilateral versus unilateral treatment location, and volume of first course PTV as predictors of treatment- related pneumonitis. It should be noted that in both the Liu et al[12] and Lester et al[22] series, the majority of patients were treated either initially or during retreatment with conventionally fractionated radiation (100% and 70% of patients, respectively), which likely contributed to measurable grade 3+ pulmonary toxicities. Only 5 patients in the current series received conventionally fractionated RT at any time point. Only 2 patients in our series had a composite lung V20 > 30% without experiencing pulmonary toxicity, in contrast to the 2 previously mentioned series.[12,22]

We believe that our toxicity profile is favorable given the small 5 to 8 mm margins around GTV, and the use of SBRT exclusively for all courses of reirradiation, which led to low cumulative doses to the lung in 2 Gy per fraction. Using standard fractionation guidelines for lung tolerance (60 Gy in 2 Gy per fraction), cumulative dose constraints were achieved except for 6 patients. Five of these 6 patients ultimately exceeded constraints due to conventional fractionation at presentation or more than 2 courses of reirradiation, but none of these patients experienced grade 3+ pulmonary toxicity. Previous reirradiation studies used an internal GTV with 11 mm margin, which may have contributed to the higher grade 3+ pneumonitis rates of 19% to 28% due to higher dose to lung.[2,12] In addition, both of these series included solely patients with conventionally fractionated RT as their initial treatment, which in our series yielded the highest lung doses. A recent review showed a trend toward higher rates of grade 3+ pneumonitis after reirradiation with SBRT when starting with an initial conventionally fractionated RT course.[2,9,12]

The question remains if there is recovery of lung parenchyma over time, which allows for improved tolerance for reirradiation. Mouse models and clinical data using conventional fractionation support normal lung recovery dependent on the size of initial dose and interval between reirradiation.[23,24] Current clinical data using SBRT for reirradiation are lacking and heterogeneous. In our study we had significant time intervals between courses (mean 14, 24, and 15 months between first 2 courses, second and third courses, and third and fourth courses, respectively), which may have contributed to our low toxicity rate.

Our previous publication for reirradiation for lung cancer recurrence reports a very different population compared with the current study, where the majority of patients had conventionally fractionated RT as their first course (90%), were treated with SBRT for infield recurrence (93%), and received lower BEDs (median BED of 48 Gy_{10}).[25] Our current experience reports the majority of patients had SBRT as their first course (89%), were treated with SBRT as a subsequent course for out-of-field recurrence (86%), and received higher BEDs (median BED of >100 Gy_{10}).

Conclusions

Long-term OS and local control are possible with acceptable late toxicity with salvage repeat RT using SBRT in a large series with long-term follow-up. There were no significant predictors of toxicity, given small event rates. Prospective trials with pulmonary function tests before and after each course of radiation with DVH correlation may elucidate appropriate dose constraints for safe reirradiation to the thorax using SBRT.

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