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Scientific Article

Clinical and Dosimetric Risk Factors Associated With Radiation-Induced Lung Toxicities After Multiple Courses of Lung Stereotactic Body Radiation Therapy

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Purpose: Data are limited on radiation-induced lung toxicities (RILT) after multiple courses of lung stereotactic body radiation therapy (SBRT). We herein analyze a large cohort of patients to explore the clinical and dosimetric risk factors associated with RILT in such settings.
Methods and Materials: A single institutional database of patients treated with multiple courses of lung SBRT between January 2014 and December 2019 was analyzed. Grade 2 or higher (G2+) RILT after the last course of SBRT was the primary endpoint. Composite plans were generated with advanced algorithms including deformable registration and equivalent dose adjustment. Logistic regression analyses were performed to examine correlations between patient or treatment factors including dosimetry and G2+ RILT. Risk stratification of patients and lung constraints based on acceptable normal tissue complication probability were calculated based on risk factors identified.
Results: Among 110 eligible patients (56 female and 54 male), there were 64 synchronous (58.2%; defined as 2 courses of SBRT delivered within 30 days) and 46 metachronous (41.8%) courses of SBRT. The composite median lung V20, lung V5, and mean lung dose were 9.9% (interquartile range [IQR], 7.3%-12.4%), 32.2% (IQR, 25.5%-40.1%), and 7.0 Gy (IQR, 5.5 Gy-8.6 Gy), respectively. With a median follow-up of 21.1 months, 30 patients (27.3%) experienced G2+ RILT. Five patients (4.5%) developed G3 RILT, and 1 patient (0.9%) developed G4 RILT, and no patients developed G5 RILT. On multivariable regression analysis, female sex (odds ratio [OR], 4.35; 95% CI, 1.49%-14.3%; $P = .01$), synchronous SBRT (OR, 8.78; 95% CI, 2.27%-47.8%; $P = .004$), prior G2+ RILT (OR, 29.8; 95% CI, 2.93%-437%; $P = .007$) and higher composite lung V20 (OR, 1.18; 95% CI, 1.02%-1.38%; $P = .030$) were associated with significantly higher likelihood of G2+ RILT.
Conclusions: Our data suggest an acceptable incidence of G2+ RILT after multiple courses of lung SBRT. Female sex, synchronous SBRT, prior G2+ RILT, and higher composite lung V20 may be risk factors for G2+ RILT.

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Introduction

Stereotactic body radiation therapy (SBRT) has become a standard-of-care treatment option for early stage non-small cell lung cancer (NSCLC) with excellent local control rates and overall survival.[1-5] SBRT has also been increasingly used in the setting of oligometastatic disease, with recent phase II trials showing promising survival benefits.[6,7] Furthermore, SBRT may be used to salvage locoregional failure after primary lung cancer treatment or to address a second primary NSCLC.[8,9]

SBRT to a single pulmonary lesion is generally considered safe based on experience from multiple trials, with 10% to 15% of patients experiencing symptomatic radiation-induced lung toxicities (RILT), which are the most common toxicities after lung SBRT.[1,2,10-12] However, data are quite limited regarding the pulmonary toxicities after multiple courses of SBRT, either in a synchronous fashion for multiple primary lung cancers or oligometastatic disease or in a metachronous fashion for second primary or disease recurrence and progression. Previous series reporting toxicities after multiple courses of lung SBRTs were limited by small numbers, wide range of SBRT doses (including palliative doses), and limited information on dosimetric parameters, precluding a comprehensive analysis of risk factors associated with RILT in such scenarios.[13-22]

We herein report a large cohort of patients treated with multiple courses of definitive-dose lung SBRT, including detailed cumulative dosimetry data, to explore the clinical and dosimetric risk factors associated with RILT after multiple courses of lung SBRT.

Methods and Materials

Patient cohort

We defined multiple-course lung SBRT as SBRT (3-8 fractions [fx]) delivered to ≥2 isocenters in the lung encompassing ≥2 lesions. We retrospectively reviewed all consecutive adult patients (≥18 years) who were treated with multiple-course lung SBRT at a multisite academic cancer center between January 2014 and December 2019. We excluded patients who had previous or synchronous conventionally fractionated thoracic radiation therapy (RT), who received an SBRT course with equivalent dose in 2 Gy fx (equivalent dose in 2 Gy fraction [EQD2] with α/β = 10 Gy, or $EQD2_{10}$) <60 Gy or who were lost to follow-up after the last course of SBRT (Fig. 1). This study was approved by the institutional review board and follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational cohort studies.[23]

Radiation treatment

The SBRT technique has been previously described elsewhere.[5] Briefly, radiation simulation was performed with patients in the supine position in a customized immobilization device. Four-dimensional computed tomography (CT)[13] or CT with deep inspirational breath hold were performed as part of the simulation to account for respiratory motion. Target volumes were created with an internal target volume to account for respiratory motion, if necessary, a 0 to 2-mm clinical target volume margin at the treating physician's discretion, and an additional 5-mm planning target volume margin. SBRT prescription dose ranged between 40 Gy to 60 Gy in 3 to 8 daily fx delivered every other day. Treatment was delivered by intensity modulated RT or volumetric modulated arc therapy with cone beam CT verification at each fx. Tissue inhomogeneity correction was used. The organ-at-risk constraints used in the planning process are listed in Table E1. Our institution does not have separate lung dose constraints for reirradiation scenarios; therefore, lung doses were constrained according to the "as low as reasonably achievable" principle. Patients were followed as clinically indicated with imaging according to the National Comprehensive Cancer Network guidelines.[24]

Toxicity and dosimetry analyses

Clinicopathologic data, radiation treatment records, treatment-related toxicities including RILT, and follow-up data were manually retrieved from electronic medical records using a uniform data abstraction form. RILT was defined as radiation pneumonitis or radiation pulmonary fibrosis within 12 months after the last course of lung SBRT, consistent with the consensus statement from the HyTEC group.[12] Our specific grading matrix for RILT is listed in Table E2. The primary endpoint was grade 2 or higher (G2+) RILT after the last course of lung SBRT. The end date of follow-up period was June 30, 2022.

Synchronous courses of SBRT were defined as ≥2 courses of SBRT delivered within 30 days interval. The rest of the patients were considered to have received metachronous courses of SBRT. Most synchronous SBRT courses were planned based on a single-simulation CT, although occasionally 2 simulation CTs were obtained when 1 of the isocenters was more suitable for treatment with deep inspirational breath hold (n = 2). For metachronous SBRT courses, the simulation CT scans underwent rigid registration in the Eclipse planning system (Varian Medical Systems, Palo Alto, CA) as well as deformable registration using a customized protocol in the Computational Environment for Radiologic Research[25] to generate composite plans based on the most recent simulation CT

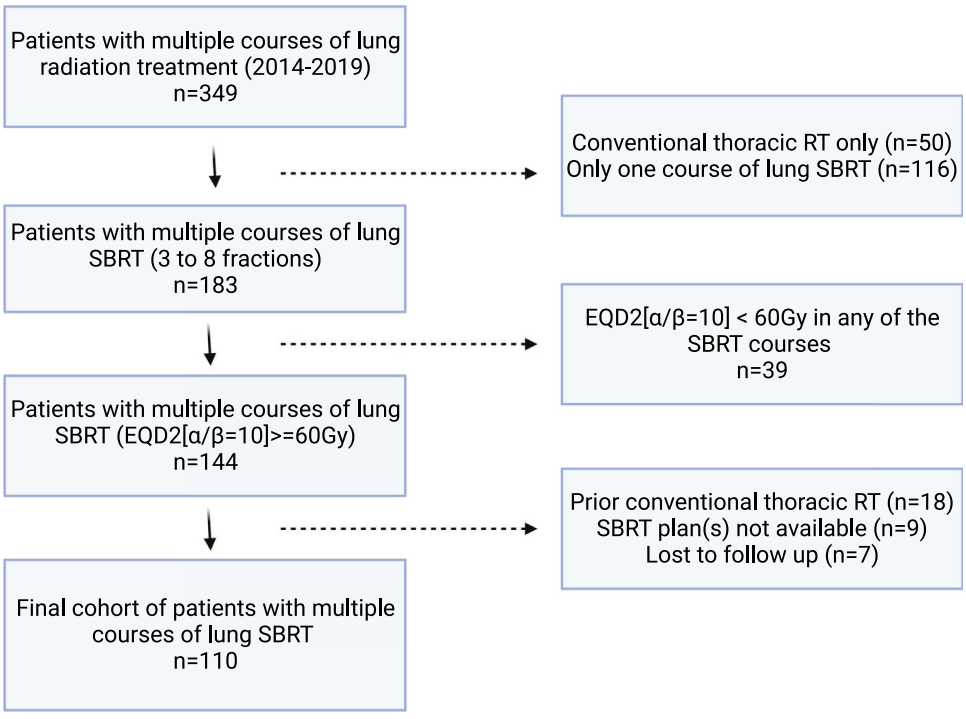

Figure 1 Patient selection flowchart.

scan. The cumulative dose-volume histogram was then generated and lung dosimetry metrics were collected including the percentage of normal lung tissue receiving ≥20 Gy (V20) or ≥5 Gy (V5) and the mean lung dose (MLD). We also converted the cumulative dose in composite plans to EQD2 using the linear quadratic model with $\alpha/\beta = 3$ Gy ($EQD2_3$) and calculated the dose-volume histogram parameters accordingly to adjust for the different dose fractionation regimens used in lung SBRT.

Statistical methods

The clinicopathologic characteristics and treatment parameters for SBRT courses were summarized and any comparison between groups was done by a χ^2 test or Fisher exact test for categorical covariates and Wilcoxon rank-sum test or Kruskal-Wallis test for continuous variables. Association between G2+ RILT and potential risk factors was evaluated by univariable logistic regression. Clinical and dosimetric variables found to be significant at a predetermined level ($P < .20$) as well as predetermined clinical variables (age, sex, performance status, chronic obstructive pulmonary disease [COPD], prior thoracic surgery, and systemic therapy use within 3 months of SBRT) were entered into a multivariable logistic regression model. The model was then assessed for interaction and any significant interaction term was added back to construct the final model. Multicollinearity was assessed by variance inflation factor testing. Model performance was evaluated by the area under the receiver operating characteristic curve. Variables found to be significantly associated with increased risks of G2+ RILT were then separately included in a multivariable analysis for risk modeling. The risk vector based on the multivariable analysis model was used to separate patients by median split. Kaplan-Meier method was used to generate and compare G2+ RILT−free survival curves between high-risk and low-risk groups with log-rank test for significance.

All tests were 2-sided, and $P < .05$ was considered statistically significant. All analyses were performed using R software, version 4.0 (R Core Team).

Results

Patient and treatment characteristics

The patient selection process is illustrated in Fig. 1. The patient and treatment characteristics are listed in Table 1. We analyzed a total of 231 lesions from 110 eligible patients (56 female, 50.9%; 54 male, 49.1%; median age at most recent SBRT: 73.6 years, interquartile range [IQR]: 67.8-79.4 years). The majority of patients (81, 73.6%) were current or former smokers, and 44 patients (40.0%) reported a history of COPD. The percentage of patients who had prior lung surgery or systemic therapy within 90 days of last SBRT course were 39.1% and

Table 1 Clinical factors and association with G2+ radiation-induced lung toxicities

Variables	Overall N = 110* (%)	G2+ RILT (n, %)	Odds ratio (95% CI)	*P* value†
Sex				
Male	54 (49.1)	9 (16.7)	Reference	-
Female	56 (50.9)	21 (37.5)	3.03 (1.25, 7.69)	.016
Age at last SBRT	73.6 (67.8, 79.4)	-	1.02 (0.98, 1.06)	.42
Age ≥70				
No	38 (34.5)	8 (21.1)	Reference	-
Yes	72 (65.5)	22 (30.6)	1.65 (0.67, 4.37)	.29
KPS				
80 or lower	52 (47.3)	15 (28.8)	Reference	-
90-100	58 (52.7)	15 (25.9)	0.86 (0.37, 2.00)	.73
Smoking status				
Never	29 (26.4)	7 (24.1)	Reference	-
Former	68 (61.8)	21 (30.9)	1.4 (0.54, 4.01)	.50
Current	13 (11.8)	2 (15.4)	0.57 (0.08, 2.86)	.53
Smoker, pack-years	45 (25, 60)	-	-	-
COPD				
No	66 (60.0)	16 (24.2)	Reference	-
Yes	44 (40.0)	14 (31.8)	1.46 (0.62, 3.42)	.38
Prior thoracic surgery				
No	67 (60.9)	17 (25.4)	Reference	-
Yes	43 (39.1)	13 (30.2)	1.27 (0.54, 2.99)	.58
Systemics‡ within 90 d of last SBRT				
No	90 (81.8)	24 (26.7)	Reference	-
Yes	20 (18.2)	6 (30.0)	1.18 (0.38, 3.31)	.76

Abbreviations: COPD = chronic obstructive pulmonary disease; G2+ = grade 2 or higher; KPS = Karnofsky performance status; SBRT = stereotactic body radiation therapy.
*Statistics presented: n (%); median (25%, 75%).
†*P* value for the odds ratio is from univariable analysis.
‡Systemics included: chemotherapy, immunotherapy, or antivascular endothelial growth factor inhibitors.

18.2%, respectively (Table 1). Six metachronous patients had prior G2+ RILT between previous and the last course of SBRT.

The majority of patients (101, 91.8%) received 2 courses of SBRT, and 9 (8.2%) received ≥3 courses (7 with 3 courses, 2 with 4 courses). Most of the SBRT targets were primary NSCLC (138, 60.0%), with 19 (8.3%) locally recurrent NSCLC and 74 (31.7%) lung metastases. At the time of the last course of SBRT, 62 patients (56.4%) had primary NSCLC, whereas 48 patients (43.6%) were treated for recurrent or metastatic cancer in the lung. The majority of SBRT courses were delivered to peripheral lung tumors (179, 77.5%). In combination, 66 patients (60.0%) received SBRTs to only peripheral lung tumors, whereas only 7 patients (6.4%) received SBRTs to only central lung tumors (Tables 2 and E3).

The most common SBRT regimens were 50 Gy/5 fx (100, 43.3%), 48 Gy/4 fx (68, 29.4%), and 54 Gy/3 fx (48, 20.8%), with a median biologically effective dose with α/β = 10 Gy of 105.6 Gy (IQR, 100-105.6). There were more synchronous (64, 58.2%) than metachronous (46, 41.8%) courses (Table 2). The lung dosimetry data from composite plans is presented in Table 3. The median composite lung V20, lung V5, and MLD were similar from composite plans based on either rigid registration or deformable registration.

Toxicity endpoint

With a median follow-up of 21.1 months (IQR, 13.3-31.2), 30 patients (27.3%) experienced G2+ RILT after the

Table 2 Treatment characteristics and association with G2+ RILT

Variables	Overall N = 110* (%)	G2+ RILT (n, %)	Odds ratio (95% CI)	*P* value†
Disease status at last course of SBRT				
Primary NSCLC	62 (56.4)	18 (29.0)	Reference	-
Recurrent/metastatic disease	48 (43.6)	12 (25.0)	0.81 (0.34, 1.90)	.64
Courses of SBRT per patient				
2	101 (91.8)	29 (28.7)	Reference	-
3 or 4	9 (8.2)	1 (11.1)	0.31 (0.02, 1.80)	.28
Location of SBRT in each patient				
Only peripheral	66 (60.0)	19 (28.8)	Reference	-
Only central	7 (6.4)	5 (71.4)	6.18 (1.22, 45.9)	.038
Mixed	37 (33.6)	6 (16.2)	0.48 (0.16, 1.28)	.16
Lobar distribution of SBRT				
Only mid/lower lobes	30 (27.3)	9 (30.0)	Reference	-
Only upper lobes	39 (35.5)	9 (22.0)	0.66 (0.22, 1.94)	.44
Mixed	41 (37.3)	12 (30.8)	1.04 (0.37, 2.98)	.95
SBRT by interval				
Metachronous (>1 mo)	46 (41.8)	9 (19.6)	Reference	-
Synchronous (≤1 mo)	64 (58.2)	21 (32.8)	2.01 (0.84, 5.11)	.13
Prior G2+ RILT				
No	104	26 (25.0)	Reference	-
Yes	6	4 (66.7)	6.00 (1.11, 45.1)	.045

Abbreviations: CI = confidence interval; G2+ = grade 2 or higher; NSCLC = non-small cell lung cancer; RILT = radiation-induced lung toxicities; SBRT = stereotactic body radiation therapy.
*Statistics presented: n (%); median (25%, 75%).
†*P* value for the odds ratio is from univariable analysis.

last course of SBRT. There were 5 patients (4.5%) who developed grade 3 RILT and 1 (0.9%) patient that developed grade 4 RILT, with no grade 5 RILT (Table E2). The median time to development of G2+ RILT was 3.1 months (IQR, 2.2-5.2). Of the 6 patients who developed grade 3 or 4 RILT, 6 patients required hospitalization, and 3 patients required supplemental oxygen (1 at home and 2 in the hospital). The patient with grade 4 RILT developed symptoms 2 months after SBRT. This patient was a nonsmoking woman, with right lower lobe and left lower lobe peripheral lung metastases from pancreatic cancer, which were both treated to 50 Gy in 5 fx synchronously. The EQD2 converted lung dosimetry in this patient showed lung V20 = 3.46%, V5 = 10.88%, and MLD = 2.46 Gy. Of note, this patient received gemcitabine and nab-paclitaxel chemotherapy within 90 days of the SBRT. She was hospitalized and treated with both steroids and antibiotics, then died, likely due to hospital-acquired pneumonia.

Clinical and dosimetric factors associated with G2+ RILT

Among the clinical factors, female sex, central tumor location, and prior G2+ RILT were significantly associated with higher risk of G2+ RILT, with odds ratio (OR) of 3.03 (female vs male; 95% CI, 1.25-7.69; $P = .016$), OR of 6.18 (central location only vs peripheral only; 95% CI, 1.22-45.9; $P = .038$), and OR of 6.00 (prior G2+ RILT vs no prior G2+ RILT; 95% CI, 1.11-45.1; $P = .045$; Tables 1 and 2). Age, performance status, smoking status, COPD, prior thoracic surgery, or systemic therapy within 90 days of last SBRT course were not significantly associated with risk of G2+ RILT. Numerically, more patients (21/64, 32.8%) who received synchronous courses of SBRT developed G2+ RILT compared with patients who received metachronous courses of SBRT (9/46, 19.6%), although the difference was not statistically significant (OR, 2.01; 95% CI, 0.84-5.11; $P = .13$).

Table 3 Lung dosimetry and association with G2+ RILT

Dosimetric parameter	Overall N = 110* (%)	G2+ RILT (%)	Odds ratio (95% CI)	*P* value†
Lung V20	9.9 (6.9, 12.6)	-	1.11 (1.00, 1.24)	.048
<9.9	55	12/55 (21.8)	Reference	-
≥9.9	55	18/55 (32.7)	1.74 (0.75, 4.17)	.20
Lung V5	33 (24, 40)	-	1.00 (0.96, 1.04)	.99
MLD	7.1 (5.3, 8.5)	-	1.00 (1.00, 1.00)	.22
Lung V20, DR	9.9 (7.3, 12.4)	-	1.12 (1.01, 1.25)	.043
<9.9	55	12/55 (21.8)	Reference	-
≥9.9	55	18/55 (32.7)	1.74 (0.75, 4.17)	.20
Lung V5, DR	32 (25, 40)	-	1.00 (0.96, 1.04)	.99
MLD, DR	7.0 (5.5, 8.6)	-	1.00 (1.00, 1.00)	.23
Lung V20, DR, EQD2	12.7 (9.9, 16.0)	-	1.09 (1.00, 1.20)	.065
<12.7	55	13/55 (23.6)	Reference	-
≥12.7	55	17/55 (30.9)	1.45 (0.62, 3.41)	.39
Lung V5, DR, EQD2	28 (22, 35)	-	1.00 (0.95, 1.05)	.92
MLD, DR, EQD2	11.2 (8.9, 13.8)	-	1.00 (1.00, 1.00)	.16

Abbreviations: DR = deformable registration; EQD2 = equivalent dose in 2 Gy fraction; α/β = 3 Gy; G2+ = grade 2 or higher; MLD = mean lung dose; RILT = radiation-induced lung toxicities.
*Statistics presented: n (%); median (25%, 75%).
†Statistical tests performed: χ^2 test of independence; Fisher exact test; Wilcoxon rank-sum test.

We analyzed the association between composite dosimetric factors including lung V20, V5, and MLD and the risk of G2+ RILT (Table 3). Univariable analyses were performed using either continuous numerical variables or binary variables split at the median value. We found that higher composite lung V20 based on either rigid registration or deformable registration were significantly associated with G2+ RILT on univariable analysis with OR of 1.11 (95% CI, 1.00-1.24; P = .048) and OR of 1.12 (95% CI, 1.01-1.25; P = .043), respectively. After EQD2 conversion, the composite lung V20 was associated with numerically higher risk of G2+ RILT, which was close to statistically significant (OR, 1.09; 95% CI, 1.00-1.20; P = .065)

We then performed a multivariable regression analysis, including clinical and dosimetric factors that were associated with higher rate of G2+ RILT at a predetermined level (P < .20), as well as other clinical variables that were found in previous literature to be associated with the development of RILT. The multivariable regression model included age, sex, performance status, COPD, prior thoracic surgery, systemic therapy use within 90 days of last SBRT, synchronous versus metachronous SBRT, location of SBRT (peripheral only vs central only vs mixed), prior G2+ RILT, and composite lung V20 (Table 4). In this model, female sex (OR, 4.35; 95% CI, 1.49-14.3; P = .01), synchronous SBRT (OR, 8.78; 95% CI, 2.27-47.8; P = .004), prior G2+ RILT (OR, 29.8; 95% CI, 2.93-437; P = .007), and higher composite lung V20 (rigid registration; OR, 1.18; 95% CI, 1.02-1.38; P = .030) were associated with significantly higher likelihood of G2+ RILT. The model reported a satisfactory area under the curve of 0.80. When substituting the composite lung V20 derived from rigid registration with lung V20 from deformable registration or lung V20 from deformable registration with EQD2 conversion, higher composite V20 was consistently associated with higher risks of G2+ RILT (Table 4).

Predicting G2+ RILT probability and G2+ RILT−free survival

When including only the statistically significant factors associated with G2+ RILT, a multivariable model was constructed to calculate the predicted risk (Y) of G2+ RILT:

$$Y = (-2.89) - 1.28 \times (1\ \textit{if male},\ 0\ \textit{if female}) + 1.47 \times (1\ \textit{if synchronous},\ 0\ \textit{if metachronous}) + 13 \times V20 + 2.78 \times (1\ \textit{if prior G2 + RILT},\ 0\ \textit{if no prior G2 + RILT})$$

For example, a male patient being treated in a synchronous fashion, without prior G2+ RILT, with a composite V20 of 15% would have a roughly 45% chance of

Table 4 Multivariable analyses for factors associated with G2+ RILT

	Multivariable analysis*,†		
Variable	**OR**	**95% CI**	***P* value**
Age at SBRT	1.06	1.00, 1.14	.08
Sex			
Male	Reference	-	-
Female	4.35	1.43, 14.28	.01
KPS			
80 or lower	Reference	-	-
90-100	0.79	0.22, 2.78	.70
COPD			
No	Reference	-	-
Yes	1.11	0.30, 4.04	.90
Prior thoracic surgery			
No	Reference	-	-
Yes	1.55	0.54, 4.54	.43
Systemics			
No	Reference	-	-
Yes	1.95	0.37, 10.62	.36
SBRT by interval			
Metachronous (>1 mo)	Reference	-	-
Synchronous (≤1 mo)	8.78	2.27, 47.80	.004
Location of SBRT in each patient			
Only peripheral	Reference	-	-
Only central	8.66	0.96, 104.05	.063
Mixed	0.29	0.07, 1.02	.067
Prior G2+ RILT			
No	Reference	-	-
Yes	29.8	2.93, 437	.007
Lung V20	1.18	1.02, 1.38	.030
Lung V20, DR	1.19	1.03, 1.39	.022
Lung V20, DR, EQD2	1.13	1.01, 1.29	.044

Abbreviations: COPD = chronic obstructive pulmonary disease; DR = deformable registration; EQD2 = equivalent dose in 2 Gy fraction; α/β = 3 Gy; G2+ = grade 2 or higher; KPS = Karnofsky performance status; MLD = mean lung dose; OR = odds ratio; RILT = radiation-induced lung toxicities; SBRT = stereotactic body radiation therapy.

*Variables with $P < .20$ on univariable analysis was entered into the multivariable logistic regression model.

†Multivariable regression models were constructed separately for V20, V20 (DR), and V20 (DR, EQD2).

developing G2+ RILT. In comparison, a male patient being treated in a metachronous fashion, without previous G2+ RILT, with a composite V20 of 5% would have only 4.5% chance of developing G2+ RILT. For a high-risk treatment condition, such as a female patient receiving synchronous SBRTs, with prior G2+ RILT, the risk of developing G2+ RILT is 72% when composite V20 is 5% versus 93% when composite V20 is 15%. When controlling all other clinical variables, each 1% increase in the composite lung V20 appears to be associated with an approximate 1% to 4% increase in risk of G2+ RILT, with the steepest increase occurring in female patients receiving synchronous treatment.

Using the median split based on the Y value, the patients were divided in 2 groups: high-risk and low-risk for developing G2+ RILT. G2+ RILT−free survival was then calculated for each group and plotted using Kaplan-Meier curves. Figure 2 illustrates the difference in G2+ RILT−free survival (1-year G2+ RILT−free survival in low-risk group [87.2%; 95% CI, 78.7%-96.5%] vs 1-year

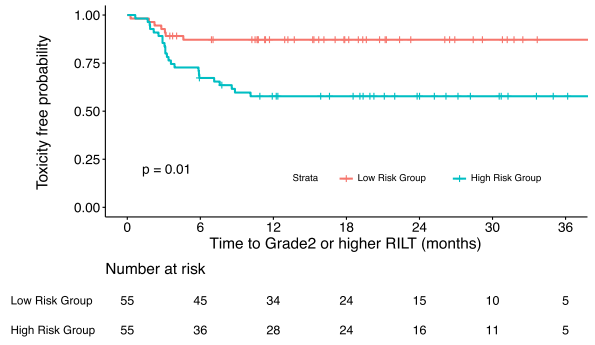

Figure 2 Grade 2 or higher radiation-induced lung toxicity−free survival with risk stratification.

G2+ RILT−free survival in high-risk group [57.8%; 95% CI, 46.0%-72.5%; log rank $P = .001$]).

Additionally, the composite V20 reirradiation constraint based on acceptable normal tissue complication probability (NTCP), assuming NTCP = exp(Y) / (1 + exp (Y)), can be calculated as:

$$V20 = (2.89 + Ln[NTPC/(1 - NTCP)] + 1.28 \times Sex - 1.47 \times S - 2.78 \times P)/13$$

where Sex = 1 if male, 0 if female; S = 1 if synchronous, 0 if metachronous; $P = 1$ if prior G2+ RILT, 0 if otherwise).

Based on this formula, a matrix table has been generated to illustrate the composite V20 constraints for 10%, 20%, and 33% of NTCP under different clinical scenarios (Table E4).

Discussion

To our knowledge, this is one of the largest analyses investigating both clinical and dosimetric risk factors for RILT in patients treated with multiple courses of definitive-dose lung SBRT. In our study, we were able to demonstrate a statistically significant association between several clinical and dosimetric risk factors and the development of G2+ RILT, including female sex, synchronous SBRT treatments, prior G2+ RILT, and higher composite lung V20. Additionally, an innovative G2+ RILT−risk stratification model was constructed to predict G2+ RILT −free survival.

RILT is the most frequent toxicity associated with lung SBRT, and high-grade RILT may lead to hospitalization, intubation, or even death. In our study, the actuarial G2+ RILT rate was 27.3%, with only 5G3 RILT, 1 G4 RILT, and no G5 adverse events noted. Previous data on the risk of clinically meaningful RILT in the setting of multiple courses of lung SBRT is limited. A series of 9 patients treated with repeat SBRT to the same or adjacent lung lesions after previous SBRT reported 33% G2+ RILT.[26] Another series with 29 patients treated with repeat lung SBRT reported 14 counts of grade 3 to 4 adverse events in 8 patients and 3 patient deaths due to massive pulmonary hemorrhage.[20] A series from the Mayo Clinic of 63 patients with 128 metachronous and synchronous lung nodules treated with SBRT reported 46% of patients experiencing any late toxicities, with the majority being dyspnea, including 3 G3 and 1 G5 radiation pneumonitis.[19] A Japanese series of 31 patients treated with repeat lung SBRT reported only 4 of 31 G2 radiation pneumonitis and no G3 adverse events.[18] A recent series focusing on SBRT for synchronous lung tumors analyzed 60 patients (126 lesions) who received SBRT treatment with median biologically effective dose with $\alpha/\beta = 10$ Gy of ≥100 Gy (except for 4 lesions) and found 23% rate of G2 or higher toxicities including just 2 cases (3%) of G3 lung toxicities.[27] Finally, a study in lung SBRT of 145 patients treated for multiple pulmonary oligometastases based on a multi-institution registry had limited toxicity analyses and reported no G4 or 5 toxicities.[17] Overall, the G2+ RILT rate in our study seems to be consistent with previous studies of multiple courses of lung SBRT, with no treatment-related death.

Risk stratification based on clinical factors was limited in most previous studies regarding multiple lung SBRTs due to the small sample sizes. In our study of over 100 patients with detailed clinical annotation, we found female sex, synchronous lung SBRT (interval <1 months), prior G2+ RILT, and increased composite lung V20 to be associated with increased risks of G2+ RILT. These findings are generally consistent with clinical risk factors identified in single-course lung SBRT series. For example, in a large series of 240 patients treated with SBRT (263 isocenters), female sex was significantly associated with symptomatic radiation pneumonitis ($P = .0094$).[28] It was speculated that the higher pneumonitis risk in female patients could be due to smaller lung volumes compared with male patients. However, in our study, female sex remained a significant risk factor in multivariable modeling, which included lung dosimetry that accounts for lung volume. Therefore, it is possible that other biologic factors associated with sex differences are contributing to the increased risks of RILT in female patients. Interestingly, older age has been reported in other series to be a risk factor for developing RILT, likely due to age-related changes in baseline lung function as well as inflammatory responses after lung SBRT.[11] In our study, however, increasing age only trended toward significance ($P = .20$). It is likely that because our cohort consisted of primarily elderly patients (median age, 74 years; 65% >70 years) a difference in RILT risks due to age would be difficult to demonstrate.

We did not identify other studies that reported differences in toxicity profile between synchronous courses versus metachronous courses of lung SBRT. Our study found that synchronous courses (using 30 days interval as the cutoff) of multiple lung SBRT were associated with higher

risks of G2+ RILT compared with metachronous courses. The main contributing factor is the potential normal tissue repair during the interval between 2 metachronous SBRT courses, although in our analysis, we did not apply a tissue repair factor in calculating cumulative lung doses from metachronous courses.

Dosimetric analyses of multiple courses of lung SBRTs based on composite plans have rarely been done. Additionally, many previous studies on SBRT reirradiation included patients who were initially treated with conventionally fractionated RT or received lower-dose SBRT (BED < 100) for reirradiation. In our study, we selected patients with no prior conventional thoracic RT who received multiple courses of lung SBRTs in the definitive dose range. In addition, we used 3 methods to generate the composite lung dosimetry, including rigid registration, deformable registration to account for changes in lung volumes between multiple courses, and EQD2 conversion to account for BED differences between various SBRT regimens. We found that higher composite lung V20 (based on either of the 3 methods) was associated with increased risks of G2+ RILT, consistent with previous findings from studies of single course lung SBRT. For example, in a pooled analysis of 88 studies of lung SBRT, the authors found a significantly higher V20 ($P = .019$) in patients with G2+ RILT compared with that of G0 to 1 RILT.[11] In the setting of multiple courses of lung SBRT, 1 study of 84 patients with synchronous SBRT courses showed that the G2 or higher radiation pneumonitis was best predicted by a composite lung V35 of ≥6.5% (in 2 Gy/fx equivalent) ($P = .007$).[29] The Mayo Clinic study of metasynchronous or synchronous lung SBRT also performed composite dosimetry analysis, but it did not find correlations between lung dosimetric parameters and the development of G2+ RILT.[19] Recently, another group of investigators studied 44 patients who received multiple courses of lung SBRT with analyses including composite dosimetry. They were able to demonstrate a correlation between multiple composite dosimetric factors (V5, V10, V20, V40, and MLD) and the development of radiation pneumonitis; however, likely due to the limitation of small sample size, none of these remained significant on multivariable analyses.[30] The expert opinion from the HyTEC lung group acknowledged the lack of dosimetric analyses in the setting of prior thoracic RT and recommended comprehensive assessment of lung dosimetry with SBRT treatment, including V20 and MLD of the composite plan.[12] To this end, we did not find significant correlations between MLD and the risks of G2+ RILT. Meanwhile, based on American Association of Physicists in Medicine TG101 and expert consensus, the United Kingdom Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy made specific recommendations regarding dose constraints to consider when treating multiple lung targets (for 3-8 fx SBRT/stereotactic ablative radiotherapy, with an endpoint of G3+ pneumonitis). They recommended a composite lung V20 of <10% for 1 lesion and optimally <12.5% (<15% acceptable) for 2 to 3 lesions.[31] Patients with composite lung V20 >12.5% are in the top quartile of our cohort but did not have significantly higher risk of G2+ RILT compared with the bottom three-quarters (data not shown). Overall, we believe that a multivariable model that incorporates both clinical and dosimetric risk factors could better risk stratify these patients than a single metric (Fig. 2).

This study is limited by its retrospective nature despite our efforts to address potential selection biases with multivariable regression models and interaction analyses. There were very few cases of G3+ toxicities, which made it impractical to perform meaningful analysis for risk factors associated with G3+ RILTs. Although our data set is among the largest series, we were unable to separate the cohort into testing and validation sets due to limited statistical power. Until recently, we have been treating patients with lung SBRT in an every-other-day (EOD) fashion. In this cohort, all patients were treated in an EOD fashion; therefore, we could not assess whether daily versus EOD treatment would confer different risks of RILT. Although our results did not show a difference in the correlations of toxicity with the composite V20 based on 3 different methods, the use of deformable registration may be necessary in other settings of lung irradiation, especially when the change in lung volumes may be more significant or when the tumor volume is larger. Finally, only 18% of patients in our study had systemic therapies including chemotherapy, antivascular endothelial growth factor inhibitors, immune checkpoint inhibitors, or tyrosine kinase inhibitors close to the delivery of the last course of lung SBRT. With more trials reporting positive results supporting the use of local ablative therapies in oligometastatic and/or oligoprogressive diseases, the effect of systemic therapy on multiple courses of lung SBRT will be important in the future analyses of such cases.

Conclusion

We selected a large modern cohort of patients who received multiple courses of definitive dose lung SBRT without prior thoracic radiation. We comprehensively generated composite SBRT plans for each patient with multiple approaches, including rigid registration, deformable registration, and EQD2 conversion. Overall, multiple courses of lung SBRT were well tolerated. We identified several clinical or dosimetric factors associated with higher risk of developing G2+ RILT including female sex, synchronous SBRT treatments, prior G2+ RILT, and higher composite lung V20. Such findings could facilitate better patient selection, safer treatment planning, more targeted posttreatment monitoring, and the expansion of indications of multicourse lung SBRT in appropriate clinical scenarios.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101284.

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