Predictors of Respiratory Decline Following Stereotactic Ablative Radiotherapy to Multiple Lung Tumors

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Abstract

The safety and efficacy of stereotactic ablative radiation therapy to multiple lung tumors remains unclear. We retrospectively reviewed a total of 86 patients treated with stereotactic ablative radiation therapy to 203 lung tumors. We observed excellent local control and low rates of conventional metrics of toxicity, but there was a high rate of respiratory decline after treatment that warrants further study.

Introduction: Stereotactic ablative radiotherapy (SABR) is highly effective at controlling early stage primary lung cancer and lung metastases. Although previous studies have suggested that treating multiple lung tumors with SABR is safe, post-treatment changes in respiratory function have not been analyzed in detail. **Patients and Methods:** We retrospectively identified patients with 2 or more primary lung cancers or lung metastases treated with SABR and analyzed clinical outcomes and predictors of toxicity. We defined a composite respiratory decline endpoint to include increased oxygen requirement, increased dyspnea scale, or death from respiratory failure not owing to disease progression. **Results:** A total of 86 patients treated with SABR to 203 lung tumors were analyzed. A total of 21.8% and 41.8% of patients developed composite respiratory decline at 2 and 4 years, respectively. When accounting for intrathoracic disease progression, 12.7% of patients developed composite respiratory decline at 2 years. Of the patients, 7.9% experienced grade 2 or greater radiation pneumonitis. No patient- or treatment-related factor predicted development of respiratory decline. The median overall survival was 46.9 months, and the median progression-free survival was 14.8 months. The cumulative incidence of local failure was 9.7% at 2 years. **Conclusion:** Although our results confirm that SABR is an effective treatment modality for patients with multiple lung tumors, we observed a high rate of respiratory decline after treatment, which may be owing to a combination of treatment and disease effects. Future studies may help to determine ways to avoid pulmonary toxicity from SABR.

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Introduction

Stereotactic ablative radiotherapy (SABR) or stereotactic body radiation therapy utilizes highly precise radiation delivery to treat targets with a small number of large doses.[1] Excellent outcomes with SABR for early stage non–small-cell lung cancers in nonoperative patients have led to the application of SABR for oligometastatic disease to the lungs.[2,3] Treatment of solitary primary lung cancers and metastatic lung tumors is associated with a low risk of toxicity and excellent local control rates of greater than 85% at 2 years, which is comparable to surgery.[4-6] However, patients with metastatic disease often present with multiple lung tumors or later progress at other sites in the lung, and the frequency of synchronous primary lung tumors at presentation has been reported as up to 8% of patients with lung cancer.[7] With emerging data demonstrating a progression-free survival (PFS) benefit for SABR in patients with oligometastatic disease[8,9] and multiple additional clinical trials underway (NCT03808662 and NCT03137771 for example),

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the use of SABR to multiple lung tumors will likely continue to grow. However, which patients should be considered for treatment of multiple lung lesions remains a topic of ongoing debate.[10]

As SABR causes long-term fibrosis and dysfunction of the portion of the lung around the target,[11,12] it is possible that treatment of multiple lung lesions with SABR could cause gradual respiratory decline as fibrosis develops. Retrospective studies have suggested that SABR to more than 1 lung tumor is feasible, provides excellent rates of local control, and offers a possibility of long-term cure in a subset of patients.[13,14] However, little has been reported on patients undergoing SABR to more than 2 lesions, and the patient characteristics and treatment-related factors that determine the risk of treatment related toxicity are unclear.[15] Recently, a large retrospective registry study reported no difference in overall survival (OS) or death within 6 months of treatment in patients who received SABR to multiple lung metastases compared with patients treated with SABR to a single lung metastasis.[16] However, a detailed analysis of changes in respiratory function following multiple lung SABR treatments has not been reported. Although respiratory decline may not affect the decision to administer SABR to multiple lung tumors if a survival benefit exists, a better understanding of potential toxicity will be critical when weighing the risks and benefits of treatment. Here, we report one of the largest series of patients treated with SABR to multiple lung lesions to date and analyze factors that may predict for pulmonary toxicity. Because respiratory decline could be owing to other factors such as chronic obstructive pulmonary disease (COPD) or intrathoracic disease progression, we attempted to account for multiple causes in the analysis.

Patients and Methods

Patient Selection

This study was approved by the Stanford Institutional Review Board under protocol 29374. We retrospectively identified patients who received SABR to 2 or more lung tumors at Stanford University from 2006 to 2017 using 2 institutional databases encompassing patients with lung cancer seen in consultation in the radiation oncology department and all patients treated with radiation therapy at Stanford University. SABR was defined as 8 or fewer fractions of radiation therapy to a total dose of 18 Gy or greater at a dose per fraction of at least 7.5 Gy. Two identified patients were excluded on further review because there was insufficient information available in our institutional databases and clinical charts.

Treatment and Follow-up

We have previously reported the technical details of the SABR treatments.[17] The volume of the lung excluding the gross tumor volumes receiving 20 Gy (V20 Gy) was ideally kept below 10% for each treatment course, but a V20 Gy of up to 15% was accepted. From 2006 to 2009, patients were treated with noncoplanar beams using the CyberKnife treatment system with Synchrony dynamic tumor tracking (Accuray). From 2010 to 2017, patients were treated with coplanar arcs using the Trilogy or TrueBeam treatment systems (Varian) with daily pre-treatment cone beam computed tomography (CT) and respiratory gating when necessary. Patients were seen in follow up 2 to 3 months after radiation treatment and every 3 months for the first year, every 4 months for the second year, every 6 months for the third year, and yearly thereafter with a CT of the thorax and/or positron emission tomography (PET)-CT at each appointment.

Toxicity and Composite Respiratory Decline

Acute and late toxicities were recorded with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Dyspnea was scored using clinical notes for each follow visit based on the modified Medical Research Council (mMRC) dyspnea scale (see Supplemental Table 1 in the online version).[18] We defined a composite respiratory decline endpoint to include any increase in oxygen requirement, an increase in the modified mMRC dyspnea scale by at least 2 points, or death from respiratory failure not attributable to cancer progression.

Dosimetric Analysis

Cumulative biologically effective doses expressed as 2 Gy per fraction equivalents (EQD2) were calculated using MIM software, version 6.6 (Cleveland, OH). The linear quadratic equation was applied voxelwise with an alpha/beta of 3. Treatment planning CT scans for each SABR course were aligned with deformable registration, and all doses were transferred to the most recent scan. Doses were accumulated to generate dose-volume histograms to calculate the mean lung dose and V20 Gy.

Statistics

The median follow-up was calculated from the first date of treatment for the most recent course of SABR to the last clinical follow-up or date of death. OS, PFS, and intrathoracic failure were calculated from the first date of treatment for the most recent course of SABR. PFS was defined as the time to disease progression anywhere in the body or death owing to any cause. Intrathoracic failure was defined as disease progression within the lungs, pleura, or mediastinum. Local failure was defined as tumor recurrence within the planning target volume, and local control was calculated from the first date of treatment for each lesion. We aimed to exclude a 20% or greater risk of composite respiratory decline after SABR to multiple lung lesions at 2 years after SABR. We expected the observed rate of composite respiratory decline to be 7.5% or less, requiring a sample size of at least 40 patients to exclude a true rate of $> 20\%$ using the binomial test with alpha $= 0.05$. The cumulative incidence function adjusted for the competing risk of death was used to measure the incidence of composite respiratory decline, grade 2 or greater pneumonitis, intrathoracic failure, and local failure. A second analysis was performed to measure the incidence of composite respiratory decline adjusting for both death and intrathoracic disease progression as competing risks or both death and administration of systemic therapy after SABR as competing risks.

We performed competing-risks survival regression to assess predictors of composite respiratory decline and grade 2 or greater pneumonitis. Death was treated as a competing risk. Patients were censored at the time of last follow-up or the next radiation treatment course, whichever was sooner. Treatment courses were included in the analysis if 2 or more lesions were treated cumulatively at the time of course completion. Courses were excluded from analysis if the toxicity endpoint had already occurred. If a patient had more than one treatment course eligible for this analysis, each course was

Table 1 Patient Characteristics

Characteristic	Number or Median	% or Range
Age, y	71	19-93
Gender		
Male	38	44.2
Female	48	55.8
SABR courses	1	1-3
Lesions treated[a]	2	2-5
COPD		
Yes	36	41.9
No	50	58.1
Smoker		
Yes	55	64.0
No	31	36.0
Prior lung resection		
Yes	27	31.4
No	59	68.6
Prior systemic therapy		
Yes	40	46.5
Cytotoxic	35	87.5
Targeted	4	10.0
Immunotherapy	1	2.5
No	46	53.5
Systemic therapy after SABR		
Yes	23	26.7
Cytotoxic	13	56.5
Targeted	5	21.7
Immunotherapy	5	21.7
No	63	73.3
Synchronous lesions		
Yes	46	53.5
No	40	46.5
Lung primary		
Yes	60	69.8
No	26	30.2
Total	86	

Abbreviations: COPD = chronic obstructive pulmonary disease; SABR = stereotactic ablative radiotherapy.
[a]Across all courses.

Table 2 Lesion Characteristics

Characteristic	Number or Median	% or Range
Tumor volume, mL	3.21	0.09-72.13
PTV volume, mL	15.65	2.57-140.01
Central location		
Yes	53	26.1
No	150	73.9
Retreatment		
Yes	11	5.4
No	192	94.6
Dose, Gy	25	18-60
Fractions	1	1-8
20 Gy in 1 fraction	12	5.9
25 Gy in 1 fraction	89	43.8
40 Gy in 4 fractions	16	7.9
50 Gy in 4 fractions	49	24.1
50 Gy in 5 fractions	14	6.9
Other	23	11.3
Histology		
Lung adenocarcinoma	79	38.9
Lung squamous cell carcinoma	41	20.2
Colorectal adenocarcinoma	19	9.4
Sarcoma	13	6.4
Head and neck squamous cell carcinoma	8	3.9
Non–small-cell lung cancer[a]	6	3.0
Hepatocellular carcinoma	5	2.5
Breast adenocarcinoma	4	2.0
Thymoma	4	2.0
Lung large-cell carcinoma	3	1.5
Lung adenosquamous carcinoma	3	1.5
Other	18	8.9
Total	203	

Abbreviation: PTV = planning target volume.
[a]Presumed non-small cell lung cancer based on imaging without biopsy.

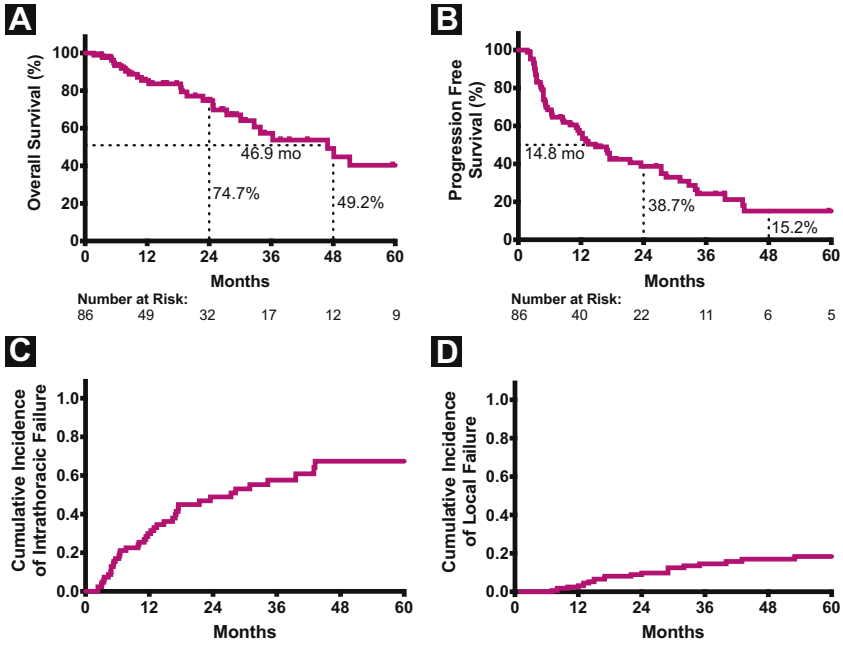
included separately. Because treatment courses were clustered within patients, the independence assumption of standard survival analysis would be violated. Therefore, a competing risks regression method that accounts for clustered data was used.[19] An alternative approach would have been to use time-varying covariates in the competing risks regression, but that approach was not chosen because it would make it more challenging to predict future patients' outcomes, for instance, by using a set of predictor values to generate a predicted survival curve. All statistical analyses were performed using R software version 3.4.3 with the *survival, cmprsk,* and *crrSC* packages. All plots were generated using GraphPad Prism version 7. All statistical tests were 2-sided, and significance was assumed at $P < .05$.

Results

Patient Characteristics

A total of 86 patients (Table 1) with 203 lung tumors (Table 2) were included in the analysis. The median follow up was 15.4 months. Patients underwent a median of 1 course of SABR (range, 1-3 courses) to a median of 2 lung tumors (range, 2-5 lung tumors). Twenty-three patients underwent SABR to more than 2 lung lesions. The most common treatment regimen was 25 Gy in 1 fraction followed by 50 Gy in 4 fractions. A total of 69.8% of patients were treated for multiple primary lung cancers, with adenocarcinoma being the most common lung primary histology. A total of 30.2% of patients were treated for multiple metastases to the lung, and colorectal cancer was the most common metastatic histology. The percentage of patients who received prior systemic

Figure 1 Outcomes for Patients Treated With Stereotactic Ablative Radiotherapy (SABR) to Multiple Lung Lesions. Overall Survival (A) and Progression-free Survival Anywhere in the Body (B) for Patients Treated with SABR to Multiple Lung Tumors. Median, 2-year, and 4-year Survival Are Indicated on Each Graph. C, Cumulative Incidence of Intrathoracic Failure for Patients Treated With SABR to Multiple Lung Tumors Adjusting for Death as a Competing Risk. D, Cumulative Incidence of Local Failure for the 203 Lesions Treated With SABR Adjusting for Death as a Competing Risk



therapy was 46.5%, and 26.7% of patients received systemic therapy after undergoing SABR to multiple lung tumors. The most common last prior systemic therapy was cytotoxic chemotherapy (87.5%), followed by targeted therapies (10%) and immunotherapy (2.5%). After SABR, the most common first administered systemic therapy was cytotoxic chemotherapy (56.5%), then targeted therapies (21.7%) and immunotherapy (21.7%). Of the patients, 64.0% had at least a 5 pack-year history of smoking, and 41.9% were diagnosed with COPD. Only 1 patient was diagnosed with interstitial lung disease. The median baseline mMRC dyspnea scale was 1 in patients with COPD and 0 in patients without COPD (on a scale of 0-4, with 0 indicating dyspnea only with strenuous exercise and 4 indicating too dyspneic to leave their house or breathless when dressing) (see Supplemental Table 2 in the online version).

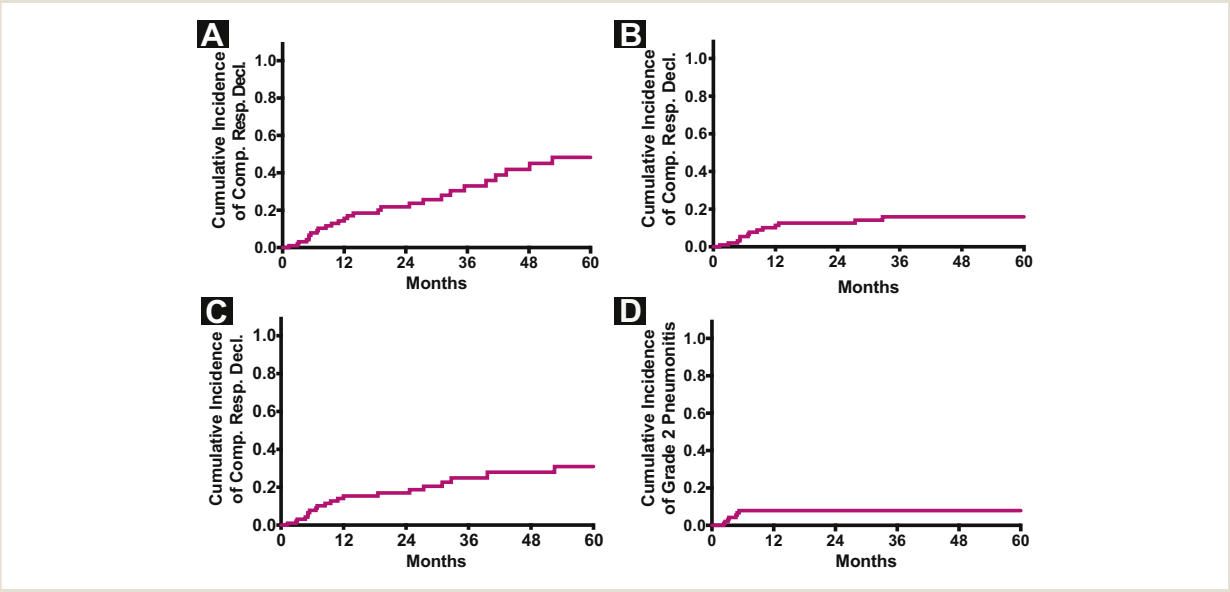
Patient Outcomes

The median OS from last eligible treatment course was 46.9 months, and the median PFS anywhere in the body was 14.8 months (Figure 1). OS and PFS anywhere in the body were 74.7% and 38.7% at 2 years and 49.2% and 15.2% at 4 years. The 2-year and 4-year cumulative incidences of intrathoracic failure were 48.9% and 67.4%, respectively. The 2-year and 4-year lesion-based cumulative incidences of local failure were 9.7% and 17.0%, respectively. Two patients developed grade 3 or greater toxicity potentially related to SABR. One patient developed a right phrenic nerve palsy 1 year after SABR that was managed with diaphragmatic plication. A second patient developed a left pneumothorax 3 months after ipsilateral SABR and ultimately died after deciding not to pursue thoracic surgery. The cumulative incidence of composite respiratory decline was 21.8% at 2 years and 41.8% at 4 years (Figure 2). When including intrathoracic disease progression as a competing risk, the cumulative incidence of composite respiratory decline was 12.7% at 2 years and 15.9% at 4 years. When including the administration of systemic therapy after SABR as a competing risk to account for the possibility that systemic therapy could contribute to respiratory decline, the cumulative incidence of composite respiratory decline was 17.0% at 2 years and 27.9% at 4 years. The cumulative incidence of grade 2 or greater radiation pneumonitis was 7.9% at 2 years and 4 years.

Predictors of Respiratory Decline and Radiation Pneumonitis

The cumulative number of lesions treated correlated weakly with cumulative mean lung dose ($R^2 = 0.04$) (see Supplemental Figure 1 in the online version), so both were included in the multivariable analysis. Cumulative mean lung dose, diagnosis of COPD, cumulative number of lesions treated, cumulative number of central lesions treated, age at treatment, and prior systemic therapy did not significantly predict the development of composite respiratory decline (Table 3) or grade 2 or greater radiation pneumonitis (Table 4). Similar results were obtained when cumulative mean lung dose was replaced with cumulative lung V20 Gy (data not shown). Composite respiratory decline and radiation pneumonitis occurred

Figure 2 Respiratory Decline and Pneumonitis After Treatment of Multiple Lung Lesions With Stereotactic Ablative Radiotherapy (SABR). A, Cumulative Incidence of Composite Respiratory Decline (Increase in Modified Medical Research Council [mMRC] Dyspnea Scale of at Least 2, Increase in Oxygen Requirement, or Death Owing to Respiratory Failure) After Treatment of Multiple Lung Tumors With SABR Adjusting for Death as a Competing Risk. B, Cumulative Incidence of Composite Respiratory Decline Adjusting for Both Death and Intrathoracic Disease Progression as Competing Risks. C, Cumulative Incidence of Composite Respiratory Decline Adjusting for Both Death and Administration of Systemic Therapy as Competing Risks. D, Cumulative Incidence of Grade 2 or Greater Pneumonitis Adjusting for Death as a Competing Risk



Abbreviation: Comp. Resp. Decl. = composite respiratory decline.

at all cumulative dose ranges and was not dependent on the number of lesions treated (Figure 3A-D). Similarly, smokers and nonsmokers and patients with/without COPD were all at risk for composite respiratory decline (see Supplemental Figure 2 in the online version).

Discussion

In this large single institution retrospective review, we observed a low rate of grade 3 or greater toxicities and grade 2 or greater radiation pneumonitis despite the high cumulative lung dose over multiple treatment courses similar to prior studies (Table 5). However, this is the first study to provide a detailed analysis of changes in respiratory function following multiple courses of SABR or multiple lung resections. We observed a higher than expected rate of composite respiratory decline, with 21.8% of patients meeting this endpoint at 2 years. Notably, respiratory function continued to decline up to 5 years after treatment, suggesting most patients experience some decline in their respiratory function at later time points. It is difficult to tease out the relative contribution of disease progression and treatment toxicity on our composite respiratory decline endpoint because most patients eventually developed progressive disease. After adjusting for intrathoracic disease progression, 12.7% of patients still developed respiratory decline at 2 years.

No patient- or treatment-related factor predicted the development of respiratory decline. This could be because of limited statistical power, or because there are unmeasured biological factors

Table 3 Multivariable Analysis of Composite Respiratory Decline

Predictor Variable	Subdistribution HR (95% CI)	*P* Value
Mean lung dose, EQD2Gy	1.03 (0.96-1.12)	.38
COPD	1.46 (0.64-3.33)	.37
Cumulative # treated lesions	0.89 (0.39-2.05)	.79
Cumulative # treated central lesions	0.90 (0.47-1.73)	.76
Age at treatment	1.02 (0.99-1.05)	.21
Prior systemic therapy	0.67 (0.28-1.58)	.36

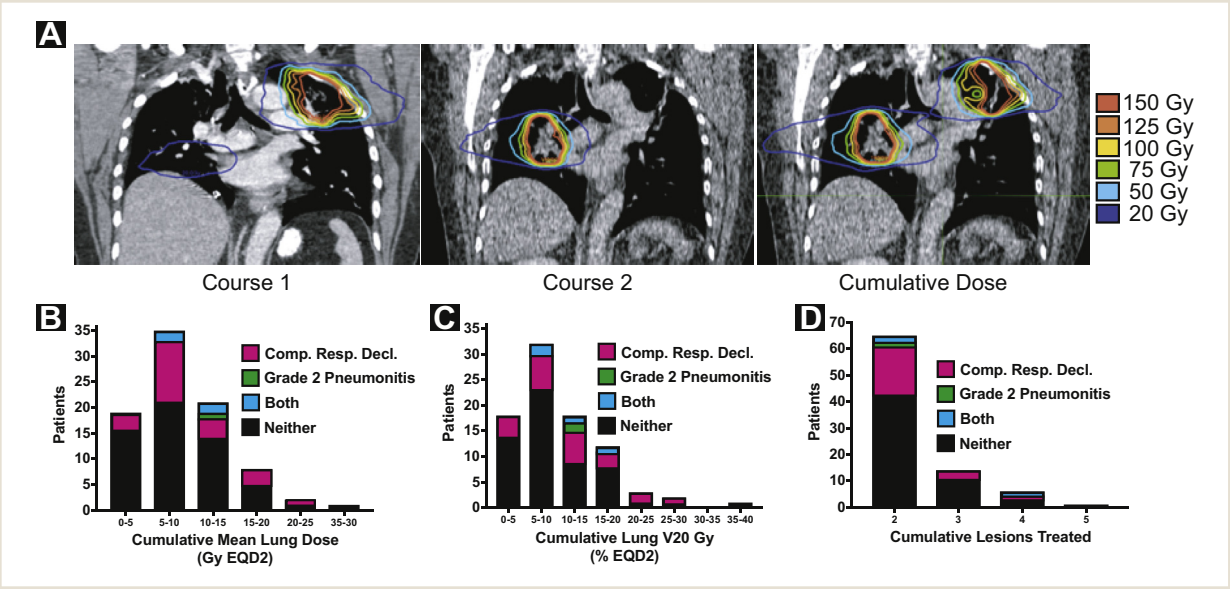
Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

Table 4 Multivariable Analysis of Grade 2 or Greater Radiation Pneumonitis

Predictor Variable	Subdistribution HR (95% CI)	*P* Value
Mean lung dose, EQD2Gy	1.10 (0.95-1.27)	.19
COPD	0.63 (0.09-4.69)	.66
Cumulative # treated lesions	0.66 (0.05-8.43)	.75
Cumulative # treated central lesions	0.63 (0.21-1.92)	.42
Age at treatment	1.00 (0.94-1.05)	.92
Prior systemic therapy	1.81 (0.27-12.22)	.54

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

Figure 3 **Dosimetric Analysis of Toxicity After Treatment of Multiple Lung Lesions With Stereotactic Ablative Radiotherapy (SABR). A, Example of the Methodology for Measuring Cumulative Radiation Dose in a Patient Treated With SABR to Left Upper Lobe and Right Lower Lobe Lung Tumors in Course 1 Followed by SABR to a New Right Lower Lobe Lung Tumor in Course 2. Dose for Each Course Was Converted to 2 Gy Per Fraction Equivalents Using the Linear Quadratic Formula. The Computed Tomography Scans From Each Course Were Deformably Registered, and the Previous Dose Was Transferred to the Most Recent Computed Tomography Where the Dose From Both Courses Was Accumulated. Distribution of Patients Who Developed Composite Respiratory Decline, Grade 2 Pneumonitis, or Both After SABR to Multiple Lung Tumors Based on Cumulative Mean Lung Dose (B), Cumulative Lung Volume Receiving At Least 20 Gy (C), and Cumulative Lesions Treated Across All Courses of SABR (D). Composite Respiratory Decline and Radiation Pneumonitis Were Not Dependent on Cumulative Dose or Number of Lesions Treated**



Abbreviation: Comp. Resp. Decl. = composite respiratory decline.

that predispose specific patients to toxicity. One previous study also reported worsening dyspnea following SABR to a single non–small-cell lung cancer and similarly found no dose-volume predictor of this outcome.[26] However, that study attributed dyspnea to exacerbations of COPD, and we did not observe a significant association between COPD and composite respiratory decline on multivariable analysis. Previous longitudinal studies of patients with COPD have found either no or minimal changes in the mMRC dyspnea scale over the follow-up period of this study.[27-29] For example, one study reported a mean increase in the mMRC dyspnea scale of 0.14 per year, which would be insufficient to meet our composite respiratory decline endpoint of an increase in mMRC scale of 2 or greater.[28]

Table 5 **Previous Studies Reporting SABR to Multiple Lung Lesions**

Reference	Lung Primary or Metastasis	Patients With > 1 SABR	Patients With > 2 SABR	Median Follow-up, mos	Overall Survival	Progression-free Survival	Local Control	Grade 3+ Toxicity
Sinha et al[20]	Lung	10	0	18.5	100% (crude)	80% (crude)	95% (crude, lesion)	0%
Peulen et al[21]	Both	3	0	12	43% (2 y)	NR	52% (5 m, patient)	37.9%
Creach et al[22]	Lung	13	0	24	58.5% (2 y)	41.7% (2 y)	92.1% (crude, lesion)	0%
Matthiesen et al[23]	Lung	10	1	15.5	60% (crude)	50% (crude)	95.2% (crude, lesion)	0%
Chang et al[24]	Lung	29	0	36	47.5% (4 y)	58% (4 y)	95.7% (4 y, lesion)	10.9%
Griffioen et al[13]	Lung	56	0	44	56% (2 y)	62% (2 y)	78% (3 y, lesion)	4.8%
Kilburn et al[25]	Both	7	0	17	45% (2 y)	16 mo (med)	67% (2 y, patient)	6.1%
Owen et al[14]	Both	63	9	12.6	85% (1 y)	10.7 mo (med)	95.3% (crude, lesion)	6.3%
Klement et al[16]	Metastasis	145	45	13	33.8% (3 y)	NR	NR	1%
This study	Both	86	23	12.2	74.7% (2 y)	38.7% (2 y)	90.3% (2 y, lesion)	2.3%

Abbreviations: med = median; NR = not reported; SABR = stereotactic ablative radiotherapy.

Temporary dyspnea secondary to reversible radiation pneumonitis did not appear to play a major role in composite respiratory decline because only 4 (14.8%) of the patients with composite respiratory decline were diagnosed with grade 2 or greater radiation pneumonitis, and 3 (75%) of these patients had persistent dyspnea at last follow-up.

We observed excellent rates of local control for SABR to multiple lung tumors and promising OS given the comorbidities of patients with multiple primary lung tumors and poor prognosis of patients with multiple lung metastases. Despite including 23 patients who received SABR to 3 or more lung tumors, our results are comparable with previous studies adding further evidence that SABR can be an effective treatment approach for these patients.

Although local control was excellent in this study, most patients ultimately developed progressive disease outside of the radiation field. The high rate of new lesions highlights the need for better predictors of prognosis when selecting patients to treat with ablative doses of radiation therapy to multiple lung tumors.[10] However, a median PFS anywhere in the body of 14.8 months suggests that SABR to multiple lung tumors could lead to a meaningful progression-free interval in patients who would otherwise require surgical resection or continued systemic therapy. Our rates of OS and PFS are comparable with retrospective reviews of repeat metastasectomy for pulmonary metastases.[30,31]

Our study was limited by the retrospective nature of our analysis and acquisition of toxicity information from clinical notes. Patients did not routinely undergo pulmonary function testing prior to and following treatment, so tests such as spirometry or lung diffusion capacity were not available for analysis. However, the mMRC dyspnea scale has previously been shown to correlate with physiologic parameters of lung function,[18] and has been used previously to evaluate dyspnea in patients with lung cancer.[32-34] Objective measures of respiratory function such as spirometry or pulmonary scintigraphy should be incorporated into future prospective trials in combination with clinical measures such as the mMRC dyspnea scale.

Conclusion

In summary, we observed excellent rates of local control and promising OS following SABR to multiple lung tumors. Typical metrics of toxicity were low in our cohort, but we observed a higher than expected rate of respiratory decline. Future studies will be critical to clarify the contribution of multiple SABR treatments to respiratory function and identify predictors of decline. We are currently investigating strategies to reduce pulmonary fibrosis and toxicity from SABR, such as the addition of anti-TGF-β therapy to radiation (NCT02581787).

Clinical Practice Points

- Patients often present with multiple lung tumors owing to synchronous primary lung cancers or lung metastases. Previous studies have suggested that treating multiple lung tumors with SABR is safe. However, post-treatment changes in respiratory function have not been analyzed in detail.
- In this study, we evaluated the long-term impact of SABR to multiple lung tumors on respiratory function as measured by dyspnea, oxygen requirement, and death owing to respiratory failure. We observed a high rate of respiratory decline after treatment, which may be owing to a combination of treatment and disease effects.
- Future studies will be helpful to clarify the contribution of multiple SABR treatments to respiratory function and identify predictors of decline. Currently, the potential impact of multiple SABR treatments on respiratory function should be considered when evaluating treatment options for patients with multiple lung tumors.

Disclosure

MFG reports grant funding from Varian Medical Systems and Philips Healthcare. BWL reports grant funding from Varian Medical Systems and RaySearch, speaking honoraria from Varian Medical Systems, and is a board member of TibaRay. MD reports research funding from Varian Medical Systems, ownership interest in CiberMed, patent filings related to cancer biomarkers, and paid consultancy from Roche, AstraZeneca, and BioNTech. All other authors state that they have no conflicts of interest.

Supplemental Data

Supplemental figures and tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2019.05.015.

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Supplemental Data

Supplemental Table 1 Modified Medical Research Council (mMRC) Dyspnea Scale

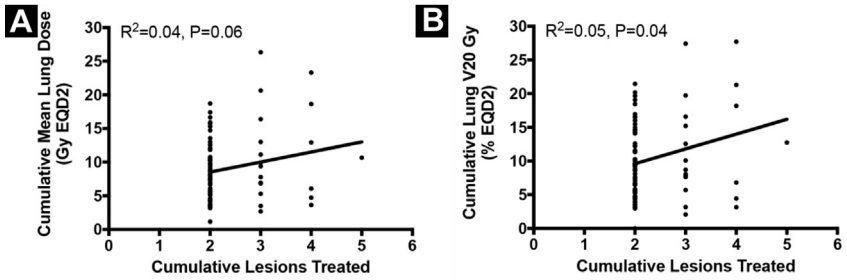
Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on level ground or walking up a slight hill
2	Walks slower than people of the same age on level ground because of breathlessness or has to stop for breath when walking at own pace on level ground
3	Stops for breath after walking about 100 yards or after a few minutes on level ground
4	Too breathless to leave the house or breathless when dressing or undressing

Supplemental Table 2 Baseline mMRC Dyspnea Score in Patients With and Without COPD

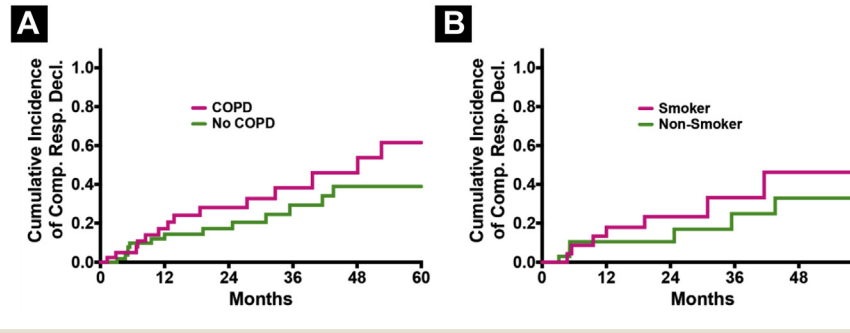
Baseline mMRC Dyspnea Score	COPD, n (%)	No COPD, n (%)
0	8 (22.9)	37 (72.5)
1	22 (62.9)	12 (23.5)
2	4 (11.4)	1 (2.0)
3	1 (2.9)	1 (2.0)
4	0 (0.0)	0 (0.0)
Mean	0.9	0.3
Median	1	0
Total	35	51

Abbreviations: COPD = chronic obstructive pulmonary disease; mMRC = modified Medical Research Council.

Supplemental Figure 1 **Relationship Between Mean Lung Dose or Lung V20 Gy With Number of Lesions Treated. Correlation of Cumulative Lesions Treated and Cumulative Mean Lung Dose (A) or Cumulative Lung V20 Gy (B) in Patients Who Received Stereotactic Ablative Radiotherapy to Multiple Lung lesions**



Supplemental Figure 2 **Effect of COPD Diagnosis and Smoking History on Development of Composite Respiratory Decline After Treatment of Multiple Lung Lesions With Stereotactic Ablative Radiotherapy. Cumulative Incidence of Composite Respiratory Decline (Increase in Modified Medical Research Council Dyspnea Scale of at Least 2, Increase in Oxygen Requirement, or Death owing to Respiratory Failure) After Treatment of Multiple Lung Tumors With Stereotactic Ablative Radiotherapy in Patients With and Without a Diagnosis of COPD (A) and Patients With and Without a Greater than 5-year Smoking History (B)**



Abbreviations: Comp. Resp. Decl. = composite respiratory decline; COPD = chronic obstructive pulmonary disease.