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Predicting Radiation Pneumonitis After Stereotactic Ablative Radiation Therapy in Patients Previously Treated With Conventional Thoracic Radiation Therapy

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Abstract

Purpose—To determine the incidence of and risk factors for radiation pneumonitis (RP) after stereotactic ablative radiation therapy (SABR) to the lung in patients who had previously undergone conventional thoracic radiation therapy.

Methods and Materials—Seventy-two patients who had previously received conventionally fractionated radiation therapy to the thorax were treated with SABR (50 Gy in 4 fractions) for recurrent disease or secondary parenchymal lung cancer (T <4 cm, N0, M0, or Mx). Severe (grade 3) RP and potential predictive factors were analyzed by univariate and multivariate logistic regression analyses. A scoring system was established to predict the risk of RP.

Results—At a median follow-up time of 16 months after SABR (range, 4–56 months), 15 patients had severe RP (14 [18.9%] grade 3 and 1 [1.4%] grade 5) and 1 patient (1.4%) had a local recurrence. In univariate analyses, Eastern Cooperative Oncology Group performance status (ECOG PS) before SABR, forced expiratory volume in 1 second (FEV1), and previous planning target volume (PTV) location were associated with the incidence of severe RP. The V₁₀ and mean lung dose (MLD) of the previous plan and the V₁₀–V₄₀ and MLD of the composite plan were also related to RP. Multivariate analysis revealed that ECOG PS scores of 2–3 before SABR ($P=.009$), FEV1 <65% before SABR ($P=.012$), V₂₀ >30% of the composite plan ($P=.021$), and an initial PTV in the bilateral mediastinum ($P=.025$) were all associated with RP.

Conclusions—We found that severe RP was relatively common, occurring in 20.8% of patients, and could be predicted by an ECOG PS score of 2–3, an FEV1 <65%, a previous PTV spanning the bilateral mediastinum, and V₂₀ >30% on composite (previous RT + SABR) plans. Prospective studies are needed to validate these predictors and the scoring system on which they are based.

Introduction

Technologic advances in the past decade have made radiation therapy (RT) an option for the definitive treatment of early and advanced thoracic cancers (1). However, despite improvements in tumor control associated with precise tumor localization and dose escalation, the rates of recurrent disease after RT still remain high (2). Moreover, survivors of thoracic cancer are at a 14% higher risk for the development of a new cancer than the general population (3, 4). Thus, despite the success of thoracic RT for first cancers, the treatment and management of second cancers remains challenging, particularly in terms of the efficacy and toxicity of the retreatment method.

Few effective treatment modalities are available for patients who develop recurrent or secondary lung tumors after previous thoracic RT. Such patients are rarely eligible for surgery. Because of the toxicity associated with thoracic RT and the resistance of thoracic cancers to conventional RT and chemotherapy, retreatment is often palliative, and the outcomes remain poor (5-7). Studies of second-line chemotherapy for recurrent lung cancer have shown objective response rates of 15%-25%, median survival times of 4-8 months, and uncommon durable control (8-10).

Image-guided stereotactic ablative RT (SABR), also known as stereotactic body RT, delivers ablative doses to tumors with less toxicity to normal lung tissue (11-14). Published studies have demonstrated the effectiveness of SABR for managing early-stage non-small cell lung cancer (NSCLC) (11, 13) and recurrent or metastatic pulmonary lesions (13, 14). Our previous results suggest that SABR could yield promising in-field control rates when administered to patients with solitary lung lesions who had previously received thoracic RT, and the 2-year overall survival (OS) rate, 59%, was much higher than that achieved with palliative chemotherapy (15). However, the risk of radiation pneumonitis (RP), a relatively common and potentially lethal side effect of any thoracic RT, is of particular concern for patients who receive SABR after having received conventional RT.

The purpose of this study was to determine the incidence of and risk factors for severe (grade 3-5) RP among patients undergoing SABR who had previously undergone conventional thoracic RT, with the goal of defining a scoring system that can be used to stratify the risk of severe RP after SABR for such patients.

Methods and Materials

Acquisition of clinical data

This retrospective review was approved by the appropriate institutional review board of The University of Texas MD Anderson Cancer Center. We reviewed the records of 386 consecutive patients treated with SABR for lung cancer between October 2004 and September 2010 at MD Anderson. From this group, we identified 72 patients who had previously received conventional RT to the thorax and subsequently underwent SABR targeted to lung lesions within the thorax. Each patient had an isolated pulmonary lesion <4 cm in diameter and N0M0 or N0Mx disease. All patients had been judged ineligible for surgery after examination by thoracic surgeons, and all were fully informed of the risks of the SABR procedure. SABR (50 Gy in 4 fractions prescribed to the planning target volume [PTV]) was delivered over 4 consecutive days.

Clinical data collected for each patient included age; sex; history of chronic obstructive pulmonary disease (COPD); previous thoracic surgery; previous chemotherapy (no induction or adjuvant chemotherapy was used during SABR); Eastern Cooperative Oncology Group performance status (ECOG PS) before SABR; interval between previous

conventional RT and SABR; pre-SABR pulmonary function; previous PTV location (unilateral or bilateral mediastinum [restricted to 1 side vs crossing the midsagittal plane, respectively]); and location of recurrent lesion (central [defined as within 2 cm of the proximal bronchial tree, major vessels, esophagus, heart, trachea, pericardium, brachial plexus, or vertebral body, but more than 1 cm from the spinal canal] or peripheral [all others; (15)] and in-field or out-of-field [within an area that had received ≥ 30 Gy vs <30 Gy during the initial conventional RT, respectively; (15)]). Dose-volume histogram data were also extracted from the previous conventional RT, SABR, and composite plans.

Treatment

Techniques for immobilization and treatment planning have been described elsewhere (15). All patients received SABR while supine and immobilized in a BodyFIX cradle (Dlekta, Stockholm, Sweden). Gross tumor volume (GTV) was delineated on a maximal intensity projection of 4-dimensional computed tomography (CT) and modified according to its movement in different breath phases to create the internal gross tumor volume (iGTV). The clinical target volume (CTV) was created by expanding the iGTV by an 8-mm isotropic margin. A 3-mm margin (to account for setup error) was added to the CTV to create the planning target volume (PTV). 6-MV x-rays were used. Patients were positioned each day by using either CT-on-rail or cone-beam CT. The dose-volume constraints used for critical organs were consistent with previous guidelines (15). Composite plans were generated for all patients by identifying the prior isocenter from the conventional RT plan, recalculating it on the CT images generated for SABR, and combining the dose distributions of the 2 treatment plans.

Follow-up

Patients received chest CT scans every 3 months for the first 2 years after SABR and then every 6 months for the next 3 years. RP was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Effects version 3. Briefly, RP was scored as grade 1 (asymptomatic, radiographic findings only), grade 2 (symptomatic, not interfering with activities of daily living), grade 3 (symptomatic, interfering with activities of daily living, O₂ indicated), grade 4 (life-threatening, ventilator support indicated), or grade 5 (death). Rates and times of OS, progression-free survival (PFS), RP, relapse (central or peripheral, in-field or out of field), and distant metastasis were recorded. The follow-up period began at the last day of SABR.

Statistical analysis

Continuous variables such as forced expiratory volume in 1 second (FEV1), interval between previous conventional RT and SABR, V₁₀-V₄₀, and mean lung dose (MLD) from all 3 sets of plans were dichotomized according to the sample median and then analyzed as nominal categorical variables. All variables were analyzed with Pearson's χ^2 or Fisher's exact tests. *P* values of less than .05 were considered statistically significant. Characteristics found to be significant on univariate analysis were then entered in a stepwise method in a binary logistic regression analysis to develop a multivariate model of independent factors predicting severe (grade ≥ 3) RP. The ratio of regression coefficients of the final model was determined and was rounded to whole digits for convenience. Scores for the independent factors were summed to obtain a total score for each patient. Receiver-operator curve analysis was used to evaluate accuracy of the scoring system. SPSS 17.0 software (Chicago, IL) was used for all statistical analyses.

Results

Patient/tumor characteristics and clinical outcomes

Patient characteristics are listed in Table 1. The median follow-up time after SABR was 16 months (range, 4-56 months). The study population included 72 patients (25 women and 47 men). Thirty-two patients (44.4%) had a history of COPD, and the median FEV1 was 65% of predicted values. Most patients treated with conventional RT (57, or 79.2%) had had NSCLC. The median dose of the previous RT plan was 63 Gy (range, 30-79.2 Gy), and the median interval between conventional RT and SABR was 21 months (range, 0-106 months). Chemotherapy was not given during or after SABR, but 58 patients received chemotherapy for the prior thoracic tumor (19 as induction therapy and 39 concurrent with radiation). The regimens most often given for NSCLC (42 of 43 patients) were taxanes (paclitaxel or docetaxel) and carboplatin or cisplatin. Nine patients with previous esophageal cancer received concurrent cisplatin and fluorouracil, and 5 patients with previous SCLC received concurrent or induction etoposide and cisplatin. No patients received consolidation chemotherapy after previous conventional RT. No patient developed severe (grade 3-5) RP after the initial (conventional) RT.

All patients experienced a radiographic response to radiation; the 2-year OS and PFS rates were 74.4% and 41.8%, respectively. Only 1 patient (1.4%) experienced local recurrence within the SABR field; 8 patients (11.1%) (7 with previous NSCLC and 1 with previous esophageal cancer) had regional lymph node recurrence; and 15 patients (20.8%) (12 with previous NSCLC and 3 with previous esophageal cancer) developed distant metastasis after SABR.

Severe (grade 3-5) RP

Fifteen patients (20.8%) experienced severe RP (14 grade 3 and 1 grade 5), which was diagnosed at a median of 4 months after SABR completion (range, 1-15 months). The median previous RT dose for those patients had been 50 Gy (range, 30-70 Gy). The patient with grade 5 RP had had a significant history of chronic infectious pulmonary disease in the 6 years before SABR, including fungal pneumonia, chronic bronchiectasis, and mycobacterial infection. The median MLDs were 12.4 Gy for the previous conventional RT plans, 4.2 Gy for the SABR plans, and 16.5 Gy for the composite plans. The median V_{20} were 23% for the previous conventional RT plans, 6% for the SABR plans, and 30% for the composite plans.

Risk factors for grade 3-5 RP

Univariate analysis of patient characteristics (Table 2) and dosimetric factors (Table 3) revealed that pre-SABR ECOG PS, FEV1, previous PTV location (unilateral vs bilateral), the V_{10} and MLD of the previous plans, and the V_{10} - V_{40} and MLD of the composite plans were significantly associated with the incidence of grade 3-5 RP ($P < .05$). The interval between previous conventional RT and SABR, the V_{30} and V_{40} of the previous RT plans, and the V_{10} - V_{40} and MLD of the SABR plans tended to associate with grade 3-5 RP, but these apparent associations were not statistically significant.

All of the variables showing significant associations in univariate analysis were then evaluated in a multivariate analysis with stepwise variable selection. In that analysis, having a pre-SABR ECOG PS 2-3 ($P = .008$), a pre-SABR FEV1 65% ($P = .012$), a V_{20} 30% in the composite plan ($P = .020$), and previous bilateral mediastinal PTV ($P = .024$) were associated with grade 3-5 RP.

Beta coefficients associated with each characteristic in the multivariate model and the assigned score for each risk factor for predicting the incidence of grade 3-5 RP are shown in Table 4. To simplify the scoring system, scores were assigned to each factor according to the standardized regression coefficient in the final multivariate model, and the predictive score was defined as the sum of each score. The scores for the independent factors were added to generate a final score, which ranged from 0-4. The incidence, sensitivity, specificity, and positive and negative predictive values associated with each possible score are shown in Table 5. The median score was 2. None of the patients with a score = 1 had grade 3-5 RP after SABR. Conversely, 4 of 5 patients with a score = 4 had grade 3-5 RP (Fig.).

Discussion

Our study demonstrated the overall outcomes and incidence of RP after SABR in patients who had previously received conventional thoracic RT. Although 15 of 72 patients (20.8%) had severe RP (1 grade 5), SABR did yield durable in-field control and promising long-term survival rates. Pre-SABR ECOG PS, FEV1, previous PTV location (unilateral vs bilateral mediastinum), and V_{20} of the composite plan were predictors of grade 3-5 RP. Our scoring system based on these factors may be helpful for predicting the risk of RP and thus for identifying which patients would benefit from SABR. To our knowledge, this is the first study to analyze predictive factors for RP in patients undergoing SABR who had previously undergone conventional thoracic RT and to develop a scoring system to evaluate the risk of SABR-induced RP in this setting.

Consistent with previous reports of early-stage NSCLC, we found SABR to yield a high local control rate (>95%) as a retreatment option for solitary lung tumors after previous RT. In our previous study of 37 patients with recurrent/secondary NSCLC previously treated with conventional thoracic RT, the 2-year actuarial OS and PFS rates after SABR were 59% and 26%; 3 patients (8.1%) had local failure, but less than 5% had local failure when 50 Gy was delivered in 4 fractions. In that study, 26 patients were treated with 50 Gy in 4 fractions, and 6 were treated with 40 Gy in 4 fractions (15). In the current study, all patients received 50 Gy in 4 fractions, and only 1 patient (1.4%) developed local recurrence after SABR. Both 2-year OS and PFS were favorable in this study as well, leading us to conclude that 40 Gy delivered in 4 fractions is associated with higher local recurrence rates.

Retreatment with conventional RT has been regarded as a palliative option for in-field relapse of NSCLC. Tada et al (6) reported that 14 of 19 patients treated with 50 Gy in 25 fractions in 5 weeks were able to tolerate the full course of radiation and had a response rate of 43% and a 2-year survival rate of 11%. In the subset of patients in our study who underwent re-irradiation for in-field relapse of NSCLC (n=19), only 1 patient had local failure. Although this result undoubtedly reflects some form of radiation resistance, the local control rate for in-field relapse of NSCLC (18/19, 94.7%) was still promising with SABR delivered at 50 Gy in 4 fractions.

The overall rate of grade 3-5 RP (20.8%) was higher in the current study than in previous studies of palliative retreatment with RT (6, 7). In our univariate analysis of risk factors for RP, pre-SABR ECOG PS and FEV1, the interval between previous conventional RT and SABR, and the location of the previous PTV (unilateral vs bilateral) were significant. Interestingly, the incidence of grade 3-5 RP seemed to be higher among patients with longer intervals between treatments, but multivariate analysis did not show longer intervals to be an independent risk factor. Of the 36 patients whose interval between RT and SABR was ≥ 21 months, 16 had a history of COPD, 21 had FEV1 $\geq 65\%$ (median value), 28 had a PTV that included the bilateral mediastinum, and 11 had a $V_{20} \geq 39\%$ (75th percentile value) in their composite plans. One might assume that patients with longer intervals between RT and

SABR might have poorer pulmonary function because of the natural progression of COPD over the interval. One might also assume that patients with larger previous PTVs might also have poorer pulmonary function.

Hayakawa et al (16) reported that of 5 patients with lung cancer treated with 80 Gy in 40 fractions to the hilar region, 4 developed marked stenosis of proximal bronchi and subsequently died of pulmonary insufficiency within 3 years after RT. In a phase II study of SABR, Timmerman et al suggested that patients with perihilar/central tumors had an increased risk of experiencing severe toxicity than those with more peripheral tumors (12). In our study, 36 patients had a previous PTV that included the bilateral mediastinum; among them, 9 had received prior preoperative or postoperative RT. Twelve of the 36 patients in this subgroup (33%) developed grade 3-5 RP after retreatment with SABR. Moreover, the median previous RT dose in these 12 patients, 50.4 Gy, was lower than the median previous dose of 63 Gy in the whole group. Although the SABR-treated lesions in these patients were peripheral rather than central, the perihilar/central region could have received a high composite irradiation dose. Our findings suggest that the location of both the SABR-treated lesions and the previous PTV are important for predicting the risk of severe RP in patients who undergo retreatment with SABR. Moreover, previous studies suggest that patients retreated for infield relapses experienced lower rates of pneumonitis than did those given SABR to targets outside the previous treatment field (15). In our study, most of the patients with grade 3-5 RP (12/15, 80%) had been treated for out-of-field relapses, but only 12 of the 53 patients who received SABR for out-of-field relapses had grade 3-5 RP (23%).

Dosimetric factors are also important for evaluating retreatment plans. Detailed dosimetric data from previous conventional RT, SABR, and composite plans were available for all 72 patients in this study. Dosimetric data from the SABR plans seemed to be associated with the risk of severe RP in our study, but these apparent associations were not significant in univariate analysis. This finding might be attributed to the small volume of the SABR target: the median GTV was 4.23 cm³, the median PTV was 46.21 cm³, and the median V₂₀ was <10%. Some dosimetric data from the previous RT plans (eg, V₂₀ and V₃₀) were not related to RP risk, but V₁₀ and MLD were. This finding suggests that the volume of lung exposed to low radiation doses might contribute to the incidence of RP. We did find that the dosimetric data from the composite plans were more predictive than were those from the previous RT or the SABR plans; in composite plans, both V₁₀-V₄₀ and MLD were related to severe RP, but only a V₂₀ > 30% in the composite plan was significant in multivariate analysis. Thus, composite plans should be considered as an important option for evaluating retreatment with SABR, even though the dose distributions in such plans are subject to uncertainty because of the potential for lung distortion from previous irradiation.

We further found that our scoring system, in which the beta coefficients for each significant variable were added to produce a total score, can predict the likelihood of the incidence of grade 3-5 RP in retreated patients. However, the small number of patients and the variability in their medical histories require that this model be tested in a larger independent group of patients. Although the sensitivity associated with a score ≥ 3 was 93.3%, the positive predictive value was relatively low because 5 patients with a score ≥ 3 had grade 0-2 RP. Of the 5 patients with a score ≥ 4, 4 developed grade 3-5 RP. The remaining patient in that group had tumors in both lungs; the left lung lesion involved the hilar region and was treated with conventional RT, and the right lung lesion was treated with SABR. That patient had significant symptoms including chest pain, cough, and fatigue, all of which improved after treatment; this might explain why this patient had grade 2 RP with a score of 4. Of the 31 patients who had a score ≤ 1, only 1 developed grade 3-5 RP. That patient had stage IV lung cancer and developed grade 3 RP with pulmonary thromboembolism and progression of distant metastasis. In general, we recommend forgoing retreatment if the patient has 3 or

more of the following factors: poor performance status (ECOG PS 2 or 3); poor lung function (FEV1 < 65%); large tumor volume with a composite lung $V_{20} > 30\%$; or a previous PTV that included the bilateral mediastinum.

Finally, when obtaining dosimetric data from the composite plans, we did not use a biologically equivalent dose model to convert the SABR dose to 2-Gy equivalents because the reliability of conversion models is controversial (17) and the process remains impractical. In addition, the genetic backgrounds of individual patients can also affect the toxicity profile. Because of the small sample size, the retrospective nature of the study, and the lack of biologically equivalent dose conversion and genetic information, the scoring system reported in the current study needs to be validated and improved to enable the development of a more comprehensive and reliable predictive model. The current scoring system should be used as a reference for clinical consideration and future study.

Conclusions

Stereotactic ablative RT can be used to achieve long-term local control for patients with isolated pulmonary recurrent disease who received prior chest radiation. At 21%, the incidence of RP was significant and could be predicted by poor PS (pre-SABR ECOG PS 2-3), FEV1 < 65%, a previous PTV that spanned the bilateral mediastinum, and $V_{20} > 30\%$ on the composite RT + SABR plan. Prospective studies are needed to validate these predictive factors.

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References

1. Chang JY, Dong L, Liu H, et al. Image-guided radiation therapy for non-small cell lung cancer. *J Thorac Oncol.* 2008; 3:177–186. [PubMed: 18303441]
2. Blackstock AW, Govindan R. Definitive chemoradiation for the treatment of locally advanced non small-cell lung cancer. *J Clin Oncol.* 2007; 25:4146–4152. [PubMed: 17827465]
3. Jeremic B, Shibamoto Y, Acimovic L, et al. Second cancers occurring in patients with early stage non-small cell lung cancer treated with chest radiation therapy alone. *J Clin Oncol.* 2001; 19:1056–1063. [PubMed: 11181669]
4. Fraumeni, JF., Jr.; Curtis, RE.; Edwards, BK., et al. New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000. Curtis, RE.; Freedman, DM.; Ron, E., et al., editors. National Cancer Institute; Bethesda, MD: 2006. p. 1-7.
5. Kramer GWPM, Gans S, Ullmann E, et al. Hypofractionated external beam radiotherapy as retreatment for symptomatic non-small-cell lung carcinoma: an effective treatment? *Int J Radiat Oncol Biol Phys.* 2004; 58:1388–1393. [PubMed: 15050314]
6. Tada T, Fukuda H, Matsui K, et al. Non-small-cell lung cancer: reirradiation for loco-regional relapse previously treated with radiation therapy. *Int J Clin Oncol.* 2004; 10:247–250. [PubMed: 16136369]
7. Okamoto Y, Murakami M, Yoden E, et al. Reirradiation for locally recurrent lung cancer previously treated with radiation therapy. *Int J Radiat Oncol Biol Phys.* 2002; 52:390–396. [PubMed: 11872284]

8. Socinski MA, Shcell MJ, Bakri K, et al. Second-line, low-dose, weekly paclitaxel in patients with stage III/A/IV nonsmall cell lung carcinoma who fail first-line chemotherapy with carboplatin plus paclitaxel. *Cancer*. 2002; 95:1265–1273. [PubMed: 12216094]
9. Gonzalez CM, Aramendia JM, Salgado E, et al. Second-line chemotherapy with irinotecan and vinorelbine in stage IIIB and IV non-small-cell lung cancer: a phase II study. *Am J Clin Oncol*. 2002; 25:480–484. [PubMed: 12393989]
10. Serke M, Schoenfeld N, Loddenkemper R, et al. Weekly docetaxel as second-line chemotherapy in advanced non-small cell lung cancer: phase II trial. *Anticancer Res*. 2004; 24:1211–1216. [PubMed: 15154649]
11. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010; 303:1070–1076. [PubMed: 20233825]
12. Timmerman RD, Kavanagh BD, Cho LC, et al. Stereotactic body radiation therapy in multiple organ sites. *J Clin Oncol*. 2007; 25:947–952. [PubMed: 17350943]
13. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2008; 72:967–971. [PubMed: 18954709]
14. Loo BW, Chang JY, Dawson L, et al. Stereotactic ablative radiotherapy: what's in a name? *Practical Radiat Oncol*. 2011; 1:38–39.
15. Kelly P, Balter PA, Rebueno N, et al. Stereotactic body radiation therapy for patients with lung cancer previously treated with thoracic radiation. *Int J Radiat Oncol Biol Phys*. 2010; 78:1387–1393. [PubMed: 20381271]
16. Hayakawa K, Mitsuhashi N, Saito Y, et al. Short communication: adverse chronic effects of high-dose irradiation on proximal bronchus in patients treated for bronchogenic carcinoma. *Br J Radiol*. 1993; 66:477–479. [PubMed: 8319074]
17. Wennberg BM, Baumann P, Gaqliardi G, et al. NTCP modeling of lung toxicity after SBRT comparing the universal survival curve and the linear quadratic model for fractionation correction. *Acta Oncol*. 2011; 50:518–527. [PubMed: 21198416]

Summary

We analyzed the incidence and severity of radiation pneumonitis (RP) after receipt of stereotactic ablative radiation therapy (SABR) for isolated lung recurrences after previous conventional radiotherapy and developed a scoring system to predict the risk of grade 3-5 RP after SABR. Severe RP (rate, 21%) could be predicted by a combination of clinical and dosimetric factors (eg, performance status and lung function before SABR, V₂₀, and bilateral [vs unilateral] initial planning target volume).

Fig.
Distribution of scores predicting radiation pneumonitis of grade 0-2 or grade 3-5 after retreatment with stereotactic ablative radiation therapy.

Table 1

Patient characteristics *

Characteristic	n [†] (%)
Sex	
M	47 (65.3%)
F	25 (34.7%)
Age (y)	
Median	67
Range	(44-89)
Median dose of previous RT, Gy (range)	63 (30-79.2)
Median interval between previous RT and SABR, mo (range)	21 (0-106)
Median FEV1, % predicted (range)	67 (14-114)
Median DLCO, % predicted (range) (n=65)	58 (20-153)
History of COPD	
Yes	31 (43.1%)
No	41 (56.9%)
Prior thoracic surgery	
Yes	14 (19.9%)
No	58 (80.1%)
Prior chemotherapy	
Induction chemotherapy	19 (26.4%)
Concurrent chemotherapy	39 (54.2%)
No chemotherapy	14 (19.4%)
ECOG PS score before SABR	
0-1	54 (75.0%)
2-3	18 (25.0%)
Type of previous cancer	
Non-small cell lung cancer	57 (79.2%)
Small-cell lung cancer	5 (6.9%)
Esophageal cancer	9 (12.5%)
Unknown primary	1 (1.4%)
T status of previous lung cancer (n=62)	
T1-2	37 (59.7%)
T3-4	25 (40.3%)
N status of previous lung cancer (n=62)	
N0-2	48 (77.4%)
N3	14 (22.6%)
Histology of lesions treated with SABR	
Adenocarcinoma	31 (43.0%)
Squamous cell carcinoma	20 (27.8%)
NSCLC, NOS	20 (27.8%)

Characteristic	n [†] (%)
Other	1 (1.4%)

Abbreviations: COPD = chronic obstructive pulmonary disease; DLCO = diffusion capacity of the lung for carbon monoxide; ECOG PS = Eastern Cooperative Oncology Group performance status; FEV1 = forced expiratory volume in 1 second; NSCLC, NOS = non-small cell lung cancer, histology not otherwise specified; RT = radiation therapy; SABR = stereotactic ablative radiation therapy.

*
n=72 unless otherwise noted.

[†]
Denotes number of patients unless otherwise noted.

Table 2

Univariate analysis of associations between patient characteristics and RP (n=72)

Variable	RP grade 0-2 (n=57)	RP grade 3-5 (n=15)	P value
Sex			.553
M	36 (63.2%)	11 (73.3%)	-
F	21 (36.8%)	4 (26.7%)	-
Age (y)			.846
67	32 (56.1%)	8 (53.3%)	-
<67	25 (43.9%)	7 (46.7%)	-
History of COPD			.244
Yes	23 (40.4%)	9 (60.0%)	-
No	34 (59.6%)	6 (40.0%)	-
Prior thoracic surgery			.471
Yes	10 (17.5%)	4 (33.3%)	-
No	47 (82.5%)	11 (66.7%)	-
Prior chemotherapy			.273
Yes	44 (77.2%)	14 (93.3%)	-
No	13 (22.8%)	1 (6.7%)	-
ECOG PS before SABR			.000
0-1	49 (86.0%)	5 (33.3%)	-
2-3	8 (14.0%)	10 (66.7%)	-
Interval between RT and SABR (mo)			.079
21	25 (43.9%)	11 (73.3%)	-
<21	32 (56.1%)	4 (26.7%)	-
FEV1 before SABR			.008
>65%	35 (61.4%)	3 (20.0%)	-
65%	22 (38.6%)	12 (80.0%)	-
DLCO before SABR (n=65)			.131
>58%	28 (54.9%)	4 (28.6%)	-
58%	23 (45.1%)	10 (71.4%)	-
Previous PTV location			.018
Bilateral mediastinum	24 (42.1%)	12 (80.0%)	-
Unilateral mediastinum	33 (57.9%)	3 (20.0%)	-
SABR lesion location			.833
Central	3 (5.3%)	1 (6.7%)	-
Peripheral	54 (94.7%)	14 (93.3%)	-
SABR lesion status			.744
In-field relapse	16 (28.1%)	3 (20.0%)	-
Out-field relapse	41 (71.9%)	12 (80.0%)	-

Abbreviations: COPD = chronic obstructive pulmonary disease; DLCO = diffusing capacity of the lung for carbon monoxide; ECOG PS = Eastern Cooperative Oncology Group performance status; RP = radiation pneumonitis; RT = radiation therapy; SABR = stereotactic ablative radiation therapy.

Table 3

Univariate analysis of associations between dosimetric factors and RP (n=72)

Variable	RP grade 0-2 (n=57)	RP grade 3-5 (n=15)	P value
V ₁₀ (previous RT plan)			.019
33%	26 (44.1%)	12 (80.0%)	-
<33%	31 (55.9%)	3 (20.0%)	-
V ₂₀ (previous RT plan)			.082
23%	26 (44.1%)	11 (73.3%)	-
<23%	31 (55.9%)	4 (26.7%)	-
V ₃₀ (previous RT plan)			.082
16%	26 (44.1%)	11 (73.3%)	-
<16%	31 (55.9%)	4 (26.7%)	-
V ₄₀ (previous RT plan)			.088
11%	27 (45.8%)	11 (73.3%)	-
<11%	30 (54.2%)	4 (26.7%)	-
MLD (previous RT plan)			.019
12.4 Gy	25 (42.4%)	12 (80.0%)	-
<12.4 Gy	32 (57.6%)	3 (20.0%)	-
V ₁₀ (SABR plan)			.082
12%	26 (44.1%)	11 (73.3%)	-
<12%	31 (55.9%)	4 (26.7%)	-
V ₂₀ (SABR plan)			.082
6%	26 (44.1%)	11 (73.3%)	-
<6%	31 (55.9%)	4 (26.7%)	-
V ₃₀ (SABR plan)			.082
3%	26 (44.1%)	11 (73.3%)	-
<3%	31 (55.9%)	4 (26.7%)	-
V ₄₀ (SABR plan)			.088
2%	27 (45.8%)	11 (73.3%)	-
<2%	30 (54.2%)	4 (26.7%)	-
MLD (SABR plan)			.082
4.2 Gy	26 (44.1%)	11 (73.3%)	-
<4.2 Gy	31 (55.9%)	4 (26.7%)	-
V ₁₀ (composite plan)			.003
43%	24 (40.7%)	13 (86.7%)	-
<43%	33 (59.3%)	2 (13.3%)	-
V ₂₀ (composite plan)			.003
30%	24 (40.7%)	13 (86.7%)	-
<30%	33 (59.3%)	2 (13.3%)	-
V ₃₀ (composite plan)			.022
22%	26 (44.1%)	12 (80.0%)	-

Variable	RP grade 0-2 (n=57)	RP grade 3-5 (n=15)	P value
<22%	31 (55.9%)	3 (20.0%)	-
V ₄₀ (composite plan)			.019
15%	25 (42.4%)	12 (80.0%)	-
<15%	32 (57.6%)	3 (20.0%)	-
MLD (composite plan)			.022
16.5 Gy	26 (44.1%)	12 (80.0%)	-
<16.5 Gy	31 (55.9%)	3 (20.0%)	-

Abbreviations: MLD = mean lung dose; RP = radiation pneumonitis; RT = conventional radiation therapy; SABR = stereotactic ablative radiation therapy; V_x = percent volume of lung exposed to at least x Gy.

Table 4

Multivariate binary logistic regression analysis of risk factors for severe RP

Characteristic	P value	Relative risk (95% CI)	Beta coefficient	Assigned score
ECOG PS before SABR	.009	10.40 (1.81-59.78)	2.34	1
FEV1 before SABR	.012	12.01 (1.72-84.03)	2.49	1
V ₂₀ (composite plan)	.021	11.58 (1.45-92.42)	2.45	1
Location of previous PTV	.025	10.79 (1.35-86.44)	2.38	1

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FEV1 = forced expiratory volume in 1 second; PTV = planning target volume; RP = radiation pneumonitis; SABR = stereotactic ablative radiation therapy; V₂₀ = percent volume of lung exposed to at least 20 Gy.

Table 5

Predictive value of scoring system

Predictive score	No. of patients experiencing grade 3-5 RP	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
1	15	100.0	17.5	24.2	100.0
2	14	93.3	54.4	35.0	96.9
3	14	93.3	91.2	73.7	98.1
4	4	26.7	98.2	80.0	83.6

Abbreviation: RP = radiation pneumonitis.