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Computed Tomography-Based Anatomic Assessment Overestimates Local Tumor Recurrence in Patients With Mass-like Consolidation After Stereotactic Body Radiotherapy for Early-Stage Non-Small Cell Lung Cancer

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Summary

Distinguishing between tumor recurrence and mass-like consolidation after lung SBRT often results in a diagnostic dilemma. This retrospective study of 80 patients with peripheral stage I NSCLC attempts to improve the diagnostic accuracy of post-treatment imaging for tumor recurrence. Our data indicate that current RECIST criteria may lead to a high number of false-positive results. The specificity of CT imaging can be improved by incorporating the volume

Purpose: To investigate pulmonary radiologic changes after lung stereotactic body radiotherapy (SBRT), to distinguish between mass-like fibrosis and tumor recurrence.

Methods and Materials: Eighty consecutive patients treated with 3- to 5-fraction SBRT for early-stage peripheral non-small cell lung cancer with a minimum follow-up of 12 months were reviewed. The mean biologic equivalent dose received was 150 Gy (range, 78-180 Gy). Patients were followed with serial CT imaging every 3 months. The CT appearance of consolidation was defined as diffuse or mass-like. Progressive disease on CT was defined according to Response Evaluation Criteria in Solid Tumors 1.1. Positron emission tomography (PET) CT was used as an adjunct test. Tumor recurrence was defined as a standardized uptake value equal to or greater than the pretreatment value. Biopsy was used to further assess consolidation in select patients.

Results: Median follow-up was 24 months (range, 12.0-36.0 months). Abnormal mass-like consolidation was identified in 44 patients (55%), whereas diffuse consolidation was identified in 12 patients (15%), at a median time from end of treatment of 10.3 months and 11.5 months, respectively. Tumor recurrence was found in 35 of 44 patients with mass-like consolidation using CT alone. Combined with PET, 10 of the 44 patients had tumor recurrence. Tumor size (hazard ratio 1.12, $P = .05$) and time to consolidation (hazard ratio 0.622, $P = .03$) were predictors for tumor recurrence. Three consecutive increases in volume and increasing volume at 12 months after treatment in mass-like consolidation were highly specific for tumor recurrence (100% and 80%, respectively). Patients with diffuse consolidation were more likely to develop grade ≥ 2 pneumonitis (odds ratio 26.5, $P = .02$) than those with mass-like consolidation (odds ratio 0.42, $P = .07$).

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kinetics of mass-like consolidation.

Conclusion: Incorporating the kinetics of mass-like consolidation and PET to the current criteria for evaluating posttreatment response will increase the likelihood of correctly identifying patients with progressive disease after lung SBRT. © 2012 Elsevier Inc.

Keywords: SBRT, Lung, Mass-like consolidation, PET, RECIST

Introduction

The advent of stereotactic body radiotherapy (SBRT) provides a nonsurgical therapy for patients with early-stage non-small cell lung cancer (NSCLC) or oligometastatic lesions to the lung. Stereotactic body radiotherapy uses elements of 3-dimensional conformal radiotherapy combined with stereotactic tumor localization to deliver ablative daily doses of radiation while limiting radiation dose to the surrounding normal tissues. The Radiation Therapy Oncology Group (RTOG) recently published the results of a phase II prospective study (0236) for early-stage NSCLC showing local tumor control of 97.8% and an overall survival of 55.8% at 3 years (1).

Radiographic changes in lung tumors have been reported after lung SBRT treatment in previous studies (2, 3). Although complete response rates after treatment have been reported to range from 25% to 50% (1, 4-7), frequently the lesion is obscured by postradiation changes, making it difficult to determine local control. Specifically, dense consolidation can occur within the high-dose volume, leading to a mass-like pattern of fibrosis. Distinguishing between tumor recurrence and mass-like consolidation is problematic and often results in a diagnostic dilemma.

Classically, treatment response after radiotherapy has been assessed radiographically. One of the more common methods of assessing response is the Response Evaluation Criteria in Solid Tumors (RECIST) (8); RECIST allows for a standardized method of assessing tumor response using anatomic imaging, which is often the primary endpoint of many clinical studies. Postradiation changes in lung tissue may lead to inaccurate interpretation of tumor response, leading some authors to suggest incorporating additional diagnostic modalities to evaluate response (1, 8). The purpose of this study was to investigate pulmonary radiologic changes after lung SBRT, to distinguish between mass-like fibrosis and tumor recurrence.

Methods and Materials

Patient eligibility and characteristics

Between March 2005 and January 2010, 80 patients with peripheral primary NSCLC were treated with SBRT at the University of Virginia after institutional review board approval for an institutional protocol. Peripheral tumors were defined by RTOG protocol 0236 as the primary tumor not touching a volume 2 cm in all directions around the proximal bronchial tree (distal 2 cm of the trachea, mainstem bronchi, and lobar bronchi). The median patient age was 73 years (range, 54-87 years). All patients underwent pre-SBRT computed tomography (CT) of the chest and abdomen for clinical staging. No patients in our cohort underwent mediastinoscopy or endobronchial ultrasound. On the basis of CT imaging, patients were classified as clinical stage I (T1-2, N0) according to American Joint Committee on Cancer staging (2002). Positron emission tomography (PET) CT scans were obtained as part of the initial staging workup in all patients. Histologic confirmation of cancer was obtained in all patients by either tissue biopsy or cytology. Patients with abnormal fluorodeoxyglucose (FDG) uptake in the mediastinum, as characterized by a maximum standardized uptake value (SUV) >2.5, were not considered candidates for SBRT.

Patients were treated with lung SBRT if they were considered to be medically inoperable (n = 78) or refused surgery (n = 2). Guidelines for inoperability were determined by the thoracic surgeon and typically included a predicted postoperative forced expiratory volume in 1 second <30%, severely reduced diffusion capacity <40% predicted, a performance status of 3 or greater, or severe cardiac disease according to the New York Heart Association functional classification. No patients received prior lung irradiation.

Treatment planning and procedure

All patients underwent treatment planning scans using free-breathing helical CT imaging. Patients were immobilized using a "frameless" semi-rigid evacuated bag system (Vac-Lok; MED-TEC, Orange City, IA). An isocenter was placed in the geometric center of the tumor. The gross tumor volume (GTV) was identified on each axial CT slice using pulmonary windowing. The clinical target volume was identical to the GTV. The planning target volume (PTV) was created by expanding the GTV volume 0.5 cm in the radial direction and 1.0 cm in the cranial−caudal direction to account for tumor motion during a normal respiratory cycle, as determined by RTOG 0236. Normal tissue dose constraints, as recommended by RTOG 0236, were followed.

Treatment planning was coordinated with both the thoracic surgeons and the radiation oncologists and performed using either the Hi-Art Helical TomoTherapy inverse planning software (Tomotherapy, Madison, WI) or the Varian Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). Patients treated using the Eclipse treatment planning system were treated with static field intensity-modulated radiotherapy with a 7 to 9 noncoplanar beam arrangement. Both lung and bone density corrections were used for planning. The dose was prescribed such that 100% of the dose covered 95% of the PTV volume. The median prescribed dose in our cohort was 60 Gy (range, 42-60 Gy) in 3 to 5 fractions. The median biologic equivalent dose (BED) for the cohort was 150 Gy (range, 78-180 Gy). Seventy percent of patients received a BED of 150 Gy. The selection of total dose and fractionation to the primary tumor was determined by constraints to the adjacent normal tissues. The prescribed dose was not dictated by T stage or tumor size.

Follow-up and evaluation

After SBRT, follow-up was performed approximately 4-8 weeks after treatment and approximately every 3 months thereafter. Computed tomography of the chest was routinely obtained at

3-month intervals from the completion of radiotherapy. PET-CT was reserved to evaluate progressive changes on CT scans that were considered worrisome for local failure. Lobar recurrences were defined as local recurrences. Local tumor progression was defined as a 20% increase in the smallest diameter of the lesion with at least a 5-mm increase in diameter, as specified by RECIST 1.1 (8). Tumor progression based on CT imaging was confirmed by PET, as defined by ≥20% increase in the maximum SUV from the pretreatment value. Biopsy was performed as a confirmatory test for local recurrence in select patients. Nodal recurrence was defined as regional recurrence. Metastatic recurrence was defined as distant systemic metastases.

The CT appearance of the consolidation was classified as either diffuse or mass-like. Diffuse consolidation was defined as consolidation occurring outside of the 50% isodose line in a manner similar to but less extensive than classic radiation fibrosis. Mass-like consolidation was defined as a new or enlarging solid opacity occurring within or directly adjacent to the PTV. The long-axis diameter and the volume of the solid opacity were measured on the pretreatment CT scan and all subsequent CT images obtained at follow-up. Positron emission tomography scans were retrospectively reviewed in patients thought to have tumor recurrence and used as an adjunct diagnostic instrument to determine local tumor recurrence. Biopsy was attempted to confirm tumor recurrence, although most patients were deemed high risk for biopsy by the referring thoracic surgeon and/or pulmonologist.

Statistical analysis

The follow-up was determined from the date of the final SBRT treatment to calculate median follow-up and Kaplan-Meier outcome data, including local control and overall survival. SPSS (Chicago, IL) was used for statistical analysis. A Cox regression analysis was performed to adjust outcomes according to patient-specific data using multiple variables analyzed simultaneously.

Results

Patient characteristics and treatment parameters

All patients received the prescribed dose. The median follow-up time for the entire cohort from the end of treatment was 24 months (range, 12.0-36.0 months). The median tumor size was 20 mm (range, 9-50 mm) with 53 patients (66%) and 27 patients (34%) having T1 and T2 tumors, respectively. According to the RTOG criteria, 85% of patients met plan criteria for conformality, with an index (CI) <1.2. Ten patients (12%) were considered to have minor deviations (CI 1.2-1.4). The mean (±SD) CI was 1.18 ± 0.12. The mean V20 for the cohort was 8.1% ± 3.2%. There was no difference in plan quality when comparing treatment modality.

Response and patterns of consolidation

The median time to maximal response of the tumor after SBRT was 6.2 months (range, 1.8-24.0 months). Response rate was assessed at 6 months after treatment. Twenty-one patients (26%) within the cohort had a radiographic complete response, whereas 50 patients (63%) had a partial response. Abnormal mass-like consolidation was identified in 44 patients (55%) at a median time from end of treatment of 10.5 months (range, 4.3-34.1 months). Of those patients with an initial radiographic complete response, ultimately 8 patients developed mass-like consolidation. The volume of mass-like consolidation was found to be substantial, with a median percentage increase in volume from the nadir size of 189% (range, 21%-602%). Diffuse consolidation, on the other hand, was identified in 15 patients (19%) at a median time from end of treatment of 11.5 months (range, 5.2-20.7 months), of whom only 2 patients had an initial radiographic complete response. Examples of mass-like consolidation and diffuse consolidation are shown in Fig 1.

Multivariate analysis was performed to determine potential factors for the development of mass-like consolidation including PTV volume, location of lesion, distance from chest wall, smoking status, chronic obstructive pulmonary disease, and BED (Table 1). The PTV volume was the only predictor for the development of mass-like consolidation (odds ratio [OR] 1.21, 95% confidence interval 1.01-1.17). Although BED as a continuous variable did not correlate with mass-like consolidation, there seemed to be a higher incidence with BED values >130 Gy ($P = .012$). Surrogates for low-dose spillage were incorporated into the multivariate analysis for diffuse consolidation, including maximum dose 2 cm from the PTV (D2 cm) and the ratio of the volume of the 50% isodose line to the volume of the PTV (R50). No significant predictive factors for diffuse consolidation were identified (Table 2).

Radiographic tumor response

Contrast-enhanced thoracic CT using RECIST 1.1 predicted tumor recurrence in 35 of 44 patients (80%) with mass-like consolidation. When thoracic contrast-enhanced CT was combined with PET, 10 of 44 patients were judged to have tumor recurrence (23%). All 10 patients with tumor recurrence showed an increase in the maximum SUV ≥20%. Five of the radiographic recurrences with PET abnormality were confirmed with biopsy, whereas the remaining patients were deemed high-risk biopsy. Patients not undergoing biopsy continued to demonstrate radiographic progressive disease on serial imaging. Multivariate analysis was performed to identify risk factors for tumor recurrence. Tumor size (hazard ratio [HR] 1.12, $P = .05$) and time to the development of mass-like consolidation from end of treatment (HR 0.622, $P = .03$) both predicted tumor recurrence (Table 3).

Mass-like consolidation kinetics

The kinetics of mass-like consolidation after SBRT was assessed in an attempt to improve the specificity of CT-based imaging alone in predicting tumor recurrence after treatment. Differences in the kinetics of the development of mass-like consolidation existed between patients ultimately found to have no tumor recurrence vs. those with tumor recurrence (Fig 2). The median latency time for the development of mass-like consolidation in patients with tumor recurrence vs. no tumor recurrence was 7.0 and 12.0 months, respectively ($P = .03$). In the 34 patients with mass-like fibrosis who did not develop local failure, serial CT imaging showed stabilization or resolution of mass-like consolidation. Ten patients had complete radiographic resolution of the consolidation, whereas the remainder were stable for >6 months. In the 10 patients with tumor recurrence, all patients experienced consecutive rises in the volume of mass-like consolidation on serial imaging at 3-month intervals. In our patient cohort, CT-based imaging was highly sensitive for detecting tumor recurrence, but

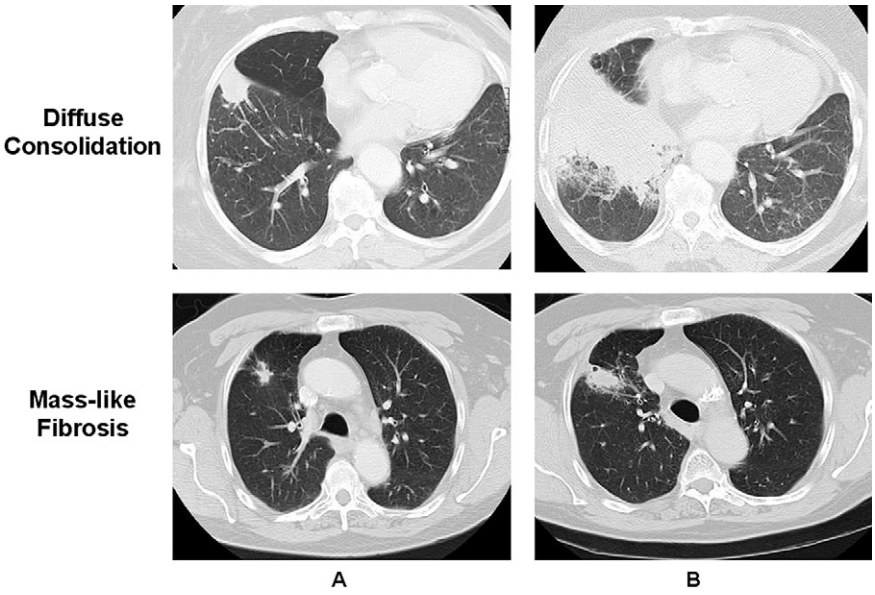

Fig. 1. Representative examples of patients with both diffuse consolidation and mass-like fibrosis before (A) and after (B) stereotactic body radiotherapy.

specificity was generally low. Different CT imaging criteria were examined to determine how best to maximize the specificity of thoracic CT as a lone modality for predicting tumor recurrence (Table 4). Three consecutive rises at 3-month intervals in the volume of mass-like consolidation had the highest specificity for tumor recurrence (100%), and increasing volume at 12 months from the end of treatment was also highly specific (80%).

Clinical symptoms and outcome as a function of radiation fibrosis patterns

Of the 80 patients treated in our cohort, symptomatic pulmonary complications (grade >1) occurred in 21 patients, with 5 patients developing grade 3 pneumonitis and no patients experiencing grade 4 or 5 pulmonary toxicity. No treatment-related deaths occurred. Patients with diffuse consolidation were more likely to develop grade ≥2 pneumonitis (OR 26.5, $P=.02$). There was a trend toward a lower risk of symptomatic pneumonitis with the development of mass-like consolidation (OR 0.42, $P=.07$). The mean recurrence-free survival for the entire cohort was 25.2 months (95% confidence interval 21.4-31.6). The median survival for the entire cohort was 19.5 months (95% confidence interval 16.2-28.4). There was no correlation between the development of mass-like consolidation (HR 2.562, $P=.945$) or diffuse consolidation (HR 1.127, $P=.938$) and risk of death.

Discussion

The ability to distinguish between local tumor recurrence and mass-like fibrosis after lung SBRT is a significant clinical problem. In our study, mass-like consolidation occurred in 55% of patients, of which 23% were found to be local tumor recurrence.

Table 1 Cox regression analysis adjusting for patient- and tumor-specific factors for predicting the risk of developing mass-like consolidation

Factor	Odds ratio	95% confidence interval	*P*
PTV volume	1.21	1.01-1.17	.037
Tumor size	1.71	0.25-2.03	.520
Tumor location			
Upper lobe	0.09	0.006-1.40	.085
Middle lobe	0.187	0.012-2.810	.225
Lower lobe	0.315	0.017-6.014	.443
Distance from chest wall	1.16	0.503-1.673	.984
Smoking status	0.499	0.260-1.12	.214
COPD	0.529	0.222-1.25	.146
Dose (BED)	1.039	0.910-1.185	.573

Abbreviations: BED = biologic equivalent dose; COPD = chronic obstructive pulmonary disease; PTV = planning target volume.

Table 2 Cox regression analysis adjusting for patient- and tumor-specific factors for predicting the risk of developing diffuse consolidation

Factor	Odds ratio	95% confidence interval	*P*
PTV volume	1.437	0.749-2.755	.275
Tumor size	1.185	0.414-3.398	.752
Tumor location			
Upper lobe	3.099	0.290-33.161	.350
Middle lobe	0.571	0.054-6.065	.642
Lower lobe	0.561	0.351-4.814	.538
Distance from chest wall	0.964	0.195-3.064	.841
Smoking status	0.499	0.158-1.577	.236
COPD	1.437	0.749-2.755	.275
Dose (BED)	1.023	0.900-1.163	.726
R50	2.215	0.982-1.236	.082
D2 cm	1.252	0.852-1.698	.102

Abbreviations as in Table 1.

Table 3 Cox regression analysis adjusting for patient- and tumor-specific factors for distinguishing between tumor recurrence and mass-like fibrosis

Factor	Hazard ratio	95% confidence interval	*P*
Tumor size/volume	1.12	1.013-1.099	.05
Time to consolidation from end of treatment	0.622	0.462-0.982	.03
Time to maximal response from end of treatment	0.901	0.855-1.034	.06
Percentage increase volume of consolidation from maximal response	1.09	0.921-1.127	.21
Percentage maximal size decrease from original tumor volume	0.922	0.901-1.042	.33

Previous studies have shown that mass-like consolidation after lung SBRT can occur in more than 50% of cases, with only a few ultimately proving to represent a local recurrence. Takeda et al (2) reported that dense consolidation was observed in 74% of patients treated with SBRT, with only 11% being local recurrences. Matsuo et al (3) reported an incidence of 68%, with 30% found to be tumor recurrence. An increased incidence of mass-like consolidation seems to have a dose-volume effect, but a larger patient cohort needs to be studied to determine the underlying mechanism.

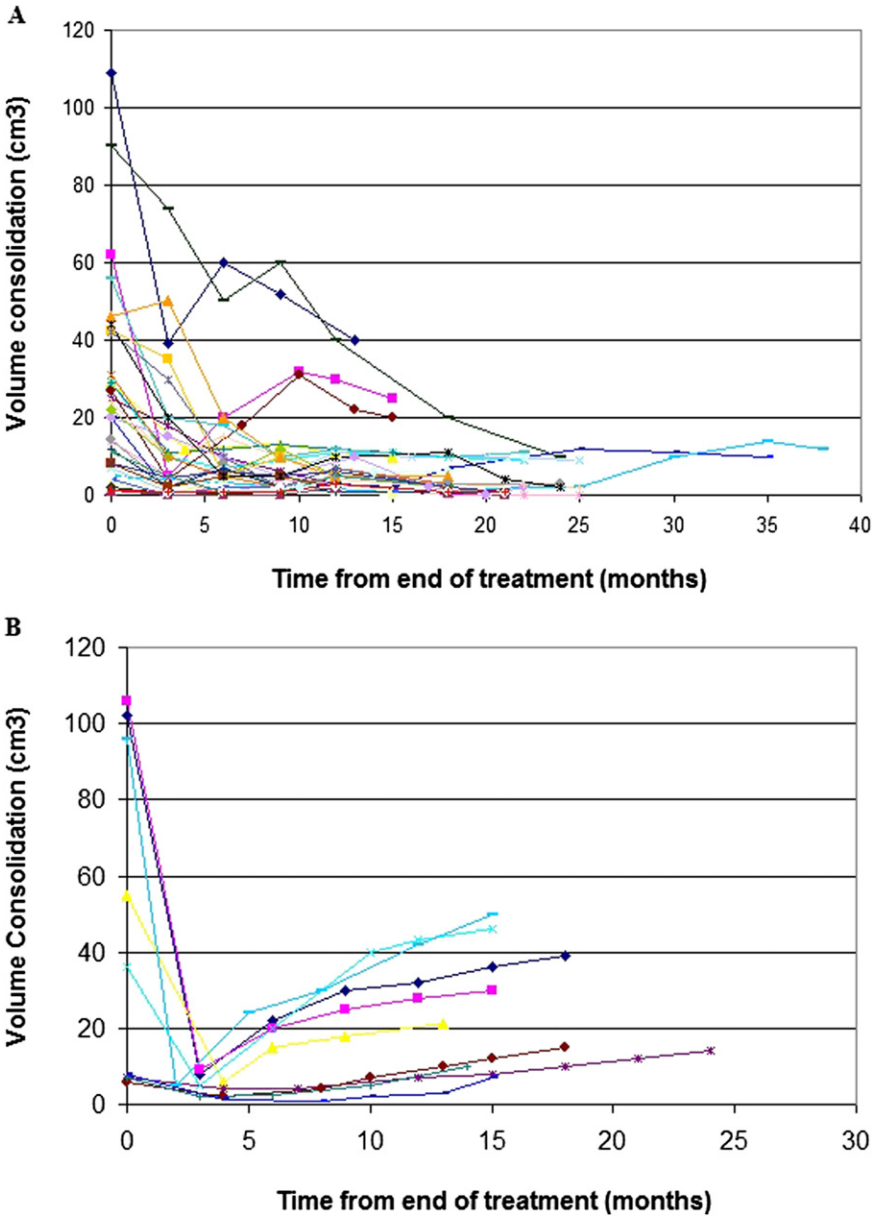

Fig. 2. Volume kinetics of mass-like consolidation on serial CT imaging in patients with local tumor recurrence (A) and mass-like fibrosis (B).

Table 4 Assessment of diagnostic accuracy for tumor recurrence by using mass-like consolidation kinetics

Factor	Three or more consecutive increases in volume	Increasing volume 6 mo after SBRT	Increasing volume 9 mo after SBRT	Increasing volume 12 mo after SBRT
Sensitivity (%)	100	100	100	100
Specificity (%)	100	26	59	80
Positive predictive value (%)	100	28	42	60
Negative predictive value (%)	100	100	100	100

RECIST 1.1 (8) has become a standard methodology for assessing tumor response after radiotherapy. The criteria specify that tumors should be evaluated with anatomic imaging, using a contrast-enhanced CT scan to assess for an interval change in the lesion. Recent phase I and phase II trials for the treatment of lung SBRT have used standardized criteria based on an interval change in size to evaluate tumor response and recurrence (1, 4-6). Applying these criteria to mass-like consolidation is very misleading and can lead to an overestimation of tumor recurrence. Our data indicate that current RECIST criteria may have positive predictive value as low as 28%, leading to a high number of false-positive results. Thus, current RECIST criteria need to be refined to evaluate local failure after SBRT.

Incorporating additional CT criteria, such as serial progression of mass-like consolidation, may improve the diagnostic accuracy of RECIST to identify progressive disease after lung SBRT. Several reports have characterized the evolution of fibrosis after fractionated radiotherapy. Solid opacity typically occurs at a minimum of 3 months after the completion of radiotherapy, followed by a period of stabilization between 9 and 12 months (9-11). In comparison, pulmonary fibrosis after SBRT occurs at a much more variable time course, with consolidation developing in as little as 5 months to longer than 2 years (2, 3, 12). Our data suggest that recurrence occurs at a shorter time interval than in those with fibrosis. Additionally, consolidation kinetics may play a role in predicting tumor recurrence by using 3 or more consecutive rises in the volume or increasing volume at 12 months after SBRT. The later observation may be a more clinically relevant endpoint for assessing recurrence, because waiting for 3 consecutive rises in volume may delay salvage therapy. A similar observation has been reported previously (3); however, late failures of >1 year were seen, and the possibility exists that with longer follow-up of our patient cohort additional local failures will be identified, making this observation invalid. Although these data seem to be promising for predicting tumor recurrence, only 5 patients had biopsy confirmation in our cohort. A larger series of patients with biopsy-proven disease should be examined to validate our findings.

The use of FDG-PET as an adjunct to anatomic imaging for evaluating lesions after lung SBRT has shown promise and may offer improved diagnostic accuracy for tumor recurrence after SBRT. The sensitivity and specificity for detecting tumor recurrence has been reported to be >97%, where tumor recurrences had significantly higher maximum SUV values than fibrotic changes (13). Recent updates to RECIST (8) highlight the potential benefit of FDG-PET as a complementary test to anatomic assessments of disease but state a lack evidence to abandon anatomic assessment of tumor burden. Moderate FDG uptake has been reported to persist up to 2 years after SBRT treatment, despite no evidence of tumor recurrence with longer follow-up (14). In our study the addition of FDG-PET to contrast-enhanced CT imaging improved diagnostic accuracy of tumor recurrence significantly, although confirmatory biopsies were only performed in 5 patients. The use of PET after lung SBRT should be further examined in a prospective setting with a larger cohort before incorporation into the standard algorithm for assessing response.

The mechanism of radiation injury that leads to the development of different consolidation patterns is not well understood. In patients with underlying emphysema, structural changes to the lung cause alterations in density and regional ventilation. These changes may affect radiation sensitivity to both high doses and low-dose spillage. The RTOG has recognized that low-dose spillage is an important factor in lung SBRT treatment planning to potentially limit symptomatic pneumonitis and has placed an emphasis on constraining the D2 cm and R50. As more prospective data is gathered, the correlation between lung density and regional ventilation abnormalities with pulmonary toxicity may be better characterized.

Conclusions

Mass-like and diffuse consolidation both occur with high frequency and a variable latency after lung SBRT. Our results suggest that the power of RECIST criteria for defining local tumor recurrence after lung SBRT may be enhanced by incorporating consolidation kinetics and PET in patients who develop mass-like consolidation. The addition of both of these changes will increase the likelihood of correctly identifying patients with progressive disease.

Finally, the development of diffuse consolidation after SBRT may predict for a higher risk of symptomatic pneumonitis. Given that the size of our series is small, all of our observations will have to be validated in prospective, randomized trials.

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