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Clinical Investigation

Tumor Volume-Adapted Dosing in Stereotactic Ablative Radiotherapy of Lung Tumors

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Summary

Previous studies of stereotactic ablative radiotherapy for lung tumors have suggested that small tumors might be controlled with lower doses than those needed for larger tumors. This study

Purpose: Current stereotactic ablative radiotherapy (SABR) protocols for lung tumors prescribe a uniform dose regimen irrespective of tumor size. We report the outcomes of a lung tumor volume-adapted SABR dosing strategy.

Methods and Materials: We retrospectively reviewed the outcomes in 111 patients with a total of 138 primary or metastatic lung tumors treated by SABR, including local control, regional control, distant metastasis, overall survival, and treatment toxicity. We also performed subset analysis on 83 patients with 97 tumors treated with a volume-adapted dosing strategy in which small tumors (gross tumor volume <12 mL) received single-fraction regimens with biologically effective doses (BED) <100 Gy (total dose, 18–25 Gy) (Group 1), and larger tumors (gross

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retrospectively evaluated a volume-adapted dosing strategy in which small tumors received single fraction regimens with lower doses while larger tumors were treated with multifraction regimens and higher doses. Oncologic outcomes were equivalent in the two groups but less toxicity was observed in the low dose group.

tumor volume ≥12 mL) received multifraction regimens with BED ≥100 Gy (total dose, 50−60 Gy in three to four fractions) (Group 2).

Results: The median follow-up time was 13.5 months. Local control for Groups 1 and 2 was 91.4% and 92.5%, respectively ($p = 0.24$) at 12 months. For primary lung tumors only (excluding metastases), local control was 92.6% and 91.7%, respectively ($p = 0.58$). Regional control, freedom from distant metastasis, and overall survival did not differ significantly between Groups 1 and 2. Rates of radiation pneumonitis, chest wall toxicity, and esophagitis were low in both groups, but all Grade 3 toxicities developed in Group 2 ($p = 0.02$).

Conclusion: A volume-adapted dosing approach for SABR of lung tumors seems to provide excellent local control for both small- and large-volume tumors and may reduce toxicity.

Keywords: Stereotactic ablative radiotherapy, Stereotactic body radiation therapy, Lung cancer, Metastases, Biologically effective dose

Introduction

Lung cancer is the leading cause of cancer mortality worldwide, accounting for over 1.3 million deaths each year, largely because it is most often diagnosed at advanced stages. However, early-stage non-small-cell lung cancer (NSCLC) is often surgically curable with the appropriate resection, preferably lobectomy. Unfortunately, a significant fraction of patients with early-stage NSCLC cannot tolerate surgery, owing to medical comorbidities. Similarly, although patients with pulmonary oligometastasis from malignancies at other sites may benefit from surgical resection (1), many have medical or technical contraindications to pulmonary resection (2). In such patients, stereotactic ablative radiotherapy (SABR), also called stereotactic body radiation therapy (SBRT), has recently emerged as an important treatment option (3−5). A landmark prospective Phase II clinical trial conducted by the Radiation Therapy Oncology Group, RTOG 0236, found that SABR resulted in outstanding local control (LC) and overall survival (OS) rates of 98% and 56% at 3 years in a cohort of strictly medically inoperable patients with peripherally located Stage I NSCLC (6). Although treatment was well tolerated overall, there was nevertheless a moderate incidence of significant (grade 3−4) toxicities. A prospective multi-institutional Phase I/II trial of SABR for patients with one to three pulmonary metastases demonstrated similarly excellent 2-year LC of 96% (7).

Analyses of the dose−response relationships in SABR for both primary and metastatic lung tumors have demonstrated the importance of dose intensity (8−10), identifying a biologically effective dose (BED) of ≥100 Gy as a factor for achieving high rates of LC. In general, these dose−response analyses have not been stratified by tumor volume. An earlier report from our institution of the initial results of a Phase I dose escalation study using single-fraction SABR for primary and metastatic lung tumors demonstrated 1-year LC of 91% with doses of >20 Gy (11). A subsequent expanded analysis revealed that the critical factor for LC was tumor volume, such that in the dose range of 15 to 30 Gy in a single fraction, 11-month LC was 93% to 100% for tumors with gross tumor volumes (GTVs) up to 12 mL but only 47% for tumors with GTVs >12 mL (12). On the basis of these observations, we adopted a volume-adapted dosing strategy for lung tumor SABR in which patients with small tumors (GTV <12 mL) were treated with single-fraction regimens with BED <100 Gy, and larger tumors (GTV ≥12 mL) were treated with more dose-intensive multifraction regimens with BED ≥100 Gy. The goal of this approach was to maintain equivalent LC while potentially reducing toxicities and improving convenience for patients with smaller tumors. Here we report our initial results using this approach.

Methods and Materials

Patients

We conducted a retrospective review of our institutional database of all patients treated with lung tumor SABR at Stanford Cancer Center, with institutional review board approval. We included adult patients treated from September 2005 to December 2009 who had biopsy-confirmed primary or metastatic lung tumors and who were assessable for LC by at least 3 months of imaging follow-up. We excluded from this analysis patients who had undergone previous radiation therapy to the treated tumor. We also performed subset analysis of patients treated by use of tumor volume-adapted dosing, consisting of two groups: patients in Group 1 had GTVs of <12 mL and were treated in a single fraction with prescription BED <100 Gy (18−30 Gy in 1 fraction, the majority receiving 25 Gy); patients in Group 2 had GTVs ≥12 mL and were treated with multifraction regimens with prescription BED ≥100 Gy (50−60 Gy in three to five fractions). Most of the remaining patients in the overall cohort had tumors with GTV <12 mL treated with multifraction regimens with prescription BED ≥100 Gy (Group 3). The range of doses reflected the regimens used in our institutional experience and in the published experiences of other institutions (6, 11, 13). BED was calculated by using the standard formula $D^*(1+d/(\alpha/\beta))$, where D represents total dose, d represents dose per fraction, and $\alpha/\beta = 10$ was used for acute (tumor) effects.

Stereotactic ablative radiotherapy

We implanted peritumoral metallic fiducial markers for image-guided tumor localization as needed, generally for lower lobe locations, where the magnitude of tumor motion tended to be greatest (14). During radiotherapy simulation, customized immobilization devices were formed for each patient, and four-dimensional computed tomography (CT) and positron emission tomography (PET)-CT images were acquired with the patient in the treatment position. The treating physicians contoured the

gross tumor volume (GTV) on axial CT slices using lung windows for visualizing tumor/lung interfaces and mediastinal windows for tumor/soft tissue interfaces, with the aid of fused PET. No explicit expansion for microscopic extension was added to form the clinical target volume (CTV) (*i.e.*, CTV = GTV). Breathing-induced tumor motion was assessed using the four-dimensional CT data and managed by respiratory gating, dynamic tumor tracking, or motion-inclusive technique, and the internal target volume was designed accordingly to incorporate margin for residual motion. A 0.5-cm setup margin was added to the internal target volume to form the final planning target volume (PTV).

Treatment was delivered in one to five fractions using 6-MV photons on one of two image-guided SABR treatment systems, the CyberKnife (Accuray Inc., Sunnyvale, CA) using the Synchrony dynamic tumor tracking system, and the Trilogy (Varian Medical Systems, Palo Alto, CA), using daily kilovoltage (kV) x-ray portal imaging and cone-beam CT for anatomy-based matching. Treatment planning goals included covering at least 95% of the PTV with the prescription dose, and centering the point of maximum dose, typically at least 120% of the prescription dose, inside the GTV. Heterogeneity corrections were used routinely for dose calculations. On the CyberKnife platform, plans consisted of generally ≥100 noncoplanar beams. A pencil-beam (effective path length) dose calculation algorithm was used before May 2008, after which time a Monte Carlo algorithm was adopted. On the Trilogy platform, the analytic anisotropic algorithm was used, and treatments were delivered by either dynamic conformal arc therapy or volumetric modulated arc therapy (RapidArc, Varian).

Follow-up and outcomes assessment

We routinely evaluated patients in follow-up and obtained diagnostic CT of the thorax and/or PET-CT at 2 months after SABR, then every 3 months for the first year, every 4 months for the second year, every 6 months for the third year, and yearly thereafter. Failure of LC was defined as recurrence within the PTV. Failure of regional control (RC) was defined as progression outside the PTV but in the same lobe of the lung, or in regional lymph nodes. Distant metastasis (DM) was defined as progression beyond these sites. Progression was documented by biopsy or, if biopsy was not feasible, was defined as radiographic or clinical evidence of progression that led to a change in management, including institution of chemotherapy, reirradiation, or surgical resection of the treated tumor. The date of progression was backdated to the first evidence of radiographic or clinical progression as determined by the treating physicians. OS was assessed by review of patients' records and the Social Security Death Index. We graded adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.02. Specifically, we scored any incidence of esophageal injury, radiation pneumonitis, and chest wall toxicity.

Statistical analyses

We compared LC, RC, freedom from DM (FFDM), and OS using the Kaplan-Meier method. Statistical significance was assessed with the log-rank test. Potential toxicity differences between the two treatment groups were assessed with the chi-square test. Statistical analysis was performed with GraphPad Prism software (version 5.04 for Windows, GraphPad Software, San Diego, CA).

Results

Patient and tumor characteristics

Patient, tumor, and treatment characteristics are shown in Table 1. A total of 111 patients with 138 lung tumors met the criteria for this analysis. The majority of the cohort comprised an elderly population with medically inoperable Stage I NSCLC, and a minority had metastatic lung tumors. Twenty patients had multiple tumors (range, 2–4) treated during the same course. The median follow-up time was 13.5 months (range. 3–54 months). The median follow-up time for surviving patients was 16 months. Patient, tumor, and treatment characteristics for the tumor volume-adapted dosing subgroup are shown in Table 2. This subgroup comprised 103 patients with 124 treated tumors, with characteristics quite similar to those of the overall cohort. Five patients had one or more tumors treated within each group during the same course. Compared with those in Group 2, tumors in Group 1 had a higher proportion of Stage T1 primary tumors, as expected, and also a higher proportion of metastatic tumors and nonsquamous histology. The overall median follow-up time was 13 months. The prescribed BED at the PTV margin ranged from 50.4 to 87.5 Gy for Group 1 (single fractions of 18, 20, 25, or 30 Gy, with the

Table 1 Patient, tumor, and treatment characteristics (all patients)

Parameter	Total (%)
Patients	111
Total no. of tumors	138
Median follow-up time (range)	13.5 (3–54) months
Age (y)	Median = 75 y
≥70	69 (62)
<70	42 (38)
Sex	
M	50 (45)
F	61 (55)
Patients with >1 tumor treated	20 (18)
Location	
Right	77 (56)
Left	61 (44)
Central	22 (16)
Peripheral	116 (84)
Metastatic	38 (28)
Primary lung	100 (72)
T stage (of primary lung tumors, n = 100)	
T1	62 (62)
T2	29 (29)
Other	9 (9)
Histology (of primary lung tumors, n = 100)	
Adenocarcinoma	59 (59)
Squamous	25 (25)
NSCLC, NOS	16 (16)
Median GTV (mL)	6.7
Median PTV (mL)	29.5
Median dose, Gy (range)	40 (18–60)

Abbreviations: NSCLC = non-small-cell lung cancer; NOS = not otherwise specified; GTV = gross tumor volume; PTV = planning target volume.

Table 2 Patient, tumor, and treatment characteristics for tumor volume-adapted subgroup receiving stereotactic ablative radiotherapy

Parameter	Total	Group 1 no. (%)	Group 2 no. (%)	Group 3 no. (%)	*p* value (Group1 vs. Group 2)
No. of tumors	124	62 (50)	35 (28)	27 (22)	
Patients	103	48 (47)	35 (34)	25 (24)	
Median follow-up time (mo)	13	13	13	14	
Patients with >1 tumor treated	13 (16)				
Patients with tumors in both groups	5 (6)				
Location					
Right	52 (54)	31 (50)	21 (60)	16 (59)	0.16
Left	45 (46)	31 (50)	14 (40)	11 (41)	
Central	12 (12)	7 (11)	5 (14)	4 (15)	0.52
Peripheral	85 (88)	55 (89)	30 (86)	23 (85)	
Tumor type					
Metastatic	30 (31)	26 (42)	4 (11)	3 (11)	0.002
Primary lung	67 (69)	36 (58)	31 (89)	24 (89)	
T stage (of primary lung tumors, $n = 91$)					
T1	62 (68)	29 (81)	11 (35)	22 (92)	0.0002
T2	22 (24)	2 (6)	20 (65)	0	0.000003
Other	7 (8)	5 (14)	0 (0)	2 (8)	0.03
Histology (of primary lung tumors, $n = 91$)					
Adenocarcinoma	56 (62)	25 (69)	18 (58)	13 (54)	0.33
Squamous	21 (23)	4 (11)	11 (36)	6 (25)	0.017
NSCLC, NOS	14 (15)	7 (19)	2 (7)	5 (21)	0.12
Median GTV (mL)	6.6	3.2 (range, 0.2−10.6)	22.7 (range, 2.7−44.5)	5.6 (range, 0.9−11.3)	
Median PTV (mL)	28.2	15.9 (range, 12.7−80)	60.5 (range, 30.0−224.4)	22.1 (range, 10.4−43.2)	
Median dose, Gy (range)	25	25 (18−30)	50 (50−60)	50 (30−60)	

Abbreviations: NSCLC = non-small-cell lung cancer; NOS = not otherwise specified; GTV = gross tumor volume; BED = biologically effective dose; PTV = planning target volume.
Group 1 = GTV <12 mL, single fraction, BED <100 Gy.
Group 2 = GTV ≥12 mL, multiple fractions, BED ≥100 Gy.
Group 3 = GTV <12 mL, multiple fractions, BED ≥100 Gy.
Listed *p* values represent a comparison between Groups 1 and 2. There were significantly more lung primary tumors in Group 3 than in Group 1 ($p = 0.004$), otherwise there were no significant differences between these subgroups.

majority receiving 25 Gy), and 100 to 180 Gy for Groups 2 and 3 (doses of 50 to 60 Gy over three to four fractions, with the majority receiving 50 Gy in four fractions). The median BED was 87.5 for Group 1 and 112.5 Gy for Groups 2 and 3.

Outcomes

The Kaplan-Meier−estimated LC and OS for all treated tumors is shown in Fig. 1A. Twelve-month actuarial LC was 94.1%, and

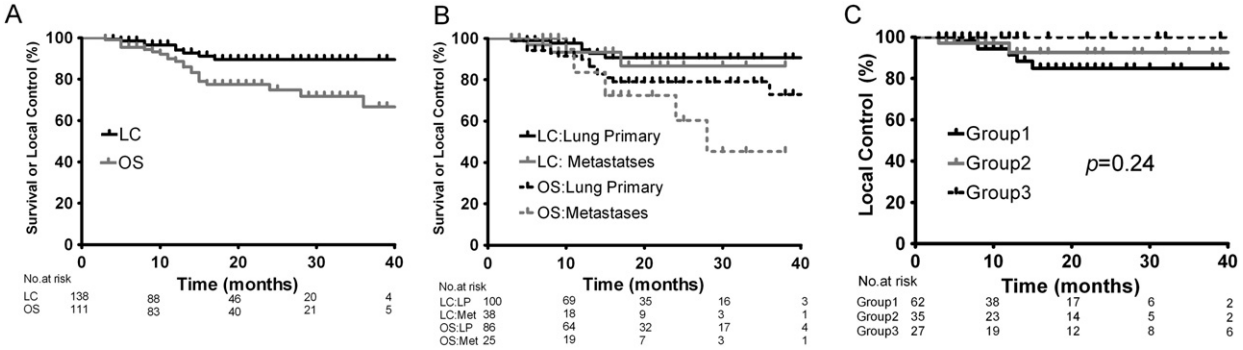

Fig. 1. Outcomes in the entire cohort. (A) Kaplan-Meier estimates of local control and overall survival for all treated tumors and patients, respectively. (B) Outcomes in all lung primary tumors and lung metastases. Kaplan-Meier estimates of local control and overall survival for lung primary tumors and metastases and lung tumor and metastatic patients. (C) Local control for all tumors by treatment type. Kaplan-Meier estimates of local control for tumors <12 mL treated with a single fraction, biologically effective dose (BED) <100 Gy (Group 1), tumors ≥12 mL treated with multiple fractions, BED ≥100 Gy (Group 2), and lesions <12 mL treated with multiple fractions, BED ≥100 Gy (Group 3).

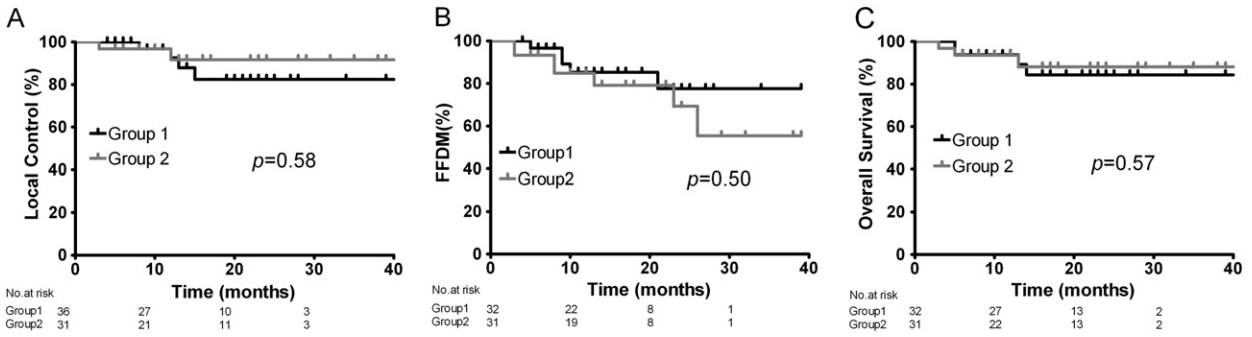

Fig. 2. Outcomes in primary lung tumors treated with the tumor volume-adapted approach. (A) Kaplan-Meier estimates of local control for primary lung tumors <12 mL treated with a single fraction, (BED) <100 Gy (Group 1) or primary lung tumors ≥12 mL treated with multiple fractions, BED ≥100 Gy (Group 2). (B) Kaplan-Meier estimates of freedom from metastasis for primary lung tumor patients in Group 1 vs. Group 2. (C) Kaplan-Meier estimates of overall survival for primary lung tumor patients in Group 1 vs. Group 2.

12-month actuarial OS was 88.6%. There was no significant difference in 12-month actuarial LC between primary lung tumors and metastases, at 94.5% and 93.4%, respectively ($p = 0.57$). Patients with metastases had lower OS than did those with primary lung tumors, with 12-month actuarial OS of 83.6% and 89.9% and median survival times of 28 months and 51 months, respectively, but this did not reach statistical significance ($p = 0.23$) (Fig. 1B). There was no significant difference in 12 month LC between tumors with GTV <12 mL treated with a single fraction to BED <100 (Group 1), tumors with GTV <12 mL treated with multiple fractions to BED ≥100 Gy (Group 3), or tumors with GTV≥ 12 mL treated with multiple fractions to BED ≥100 Gy (Group 2) at 91.4%, 100%, and 92.5%, respectively ($p = 0.24$) (Fig. 1C).

In the tumor volume-adapted SABR subgroup, the 12-month LC considering only primary lung tumors was 91.7%, and there were no significant differences in 12-month LC between primary tumors in Group 1 and those in Group 2, at 92.6% and 91.7%, respectively ($p = 0.58$) (Fig. 2A). The 12-month actuarial rate of RC was 97.1% for Group 1 and 100% for Group 2 ($p = 0.10$, not shown).

Among the primary lung cancers, FFDM and OS also did not differ significantly between Group 1 and Group 2 (Figs. 2B and 2C). In Group 1, the 12-month actuarial rates of FFDM and OS were 85.4% and 93.8%, respectively. In Group 2, the 12-month actuarial rates were 84.8% and 93.5%, respectively ($p = 0.50$ and 0.57).

Treatment-related toxicity

Table 3 outlines the clinically significant toxicities we observed in the two volume-adapted dosing groups, defined as grade 3 or above. In all, 4 patients (4.8%) experienced such treatment-related toxicity, all in Group 2 (11.4%), a statistically significant difference ($p = 0.02$). Three of these documented grade 3 toxicities involved the chest wall. There were no reported grade 4 toxicities and no treatment-related deaths. Figure 3 demonstrates an example of clinically significant chest wall toxicity.

Discussion

We retrospectively compared the outcomes in patients with lung tumors who were treated with a volume-adapted dosing strategy for lung tumor SABR. On the basis of our previous experience, we adopted a tumor volume-adapted dosing approach in late 2005, in which for the majority of patients we treated small-volume tumors with moderate dose-intensity single fraction regimens (mainly 25 Gy in one fraction) and used higher dose-intensity regimens for larger tumors (mainly 50 Gy in four fractions). Because of other treatment protocols during this time period, both on and off clinical trials, a few patients with small-volume tumors were treated with more intensive regimens as well. In this exploratory analysis, we demonstrate the potential clinical utility of a tumor volume-adapted SABR dosing strategy. The 12-month LC rates of greater than 90% that we observed in both treatment groups are consistent with those in other published series of lung tumor SABR (6, 10, 15, 16). Furthermore, in primary lung cancer, we found DM to be the primary mode of failure, consistent with published reports (6, 17).

The minimum dose required to achieve adequate LC for lung tumors has been examined previously, and several studies have found tumor volume to be a critical determinant of LC, both

Table 3 Treatment-related clinically significant toxicity by tumor/treatment type in the subgroup receiving tumor volume-adapted receiving stereotactic ablative radiotherapy

Toxicity	Grade 3 *n*	Grade 4–5 *n*	Total *n* (%)
Pneumonitis: total	1	0	1 (1.2)
Group 1	0	0	0 (0)
Group 2	1	0	1 (2.9)
$p = 0.24$			
Chest wall toxicity: total	3	0	3 (3.6)
Group 1	0	0	0 (0)
Group 2	3	0	3 (8.6)
$p = 0.04$			
Esophagitis	0	0	0 (0)
Group 1	0	0	0 (0)
Group 2	0	0	0 (0)
All toxicity			4 (4.8)
Group 1			0 (0)
Group 2			4 (11.4)
$p = 0.02$			

Abbreviation: BED = biologically effective dose.
Group 1 = GTV <12 mL, single fraction, BED <100 Gy.
Group 2 = GTV ≥12 mL, multiple fractions, BED ≥100 Gy.

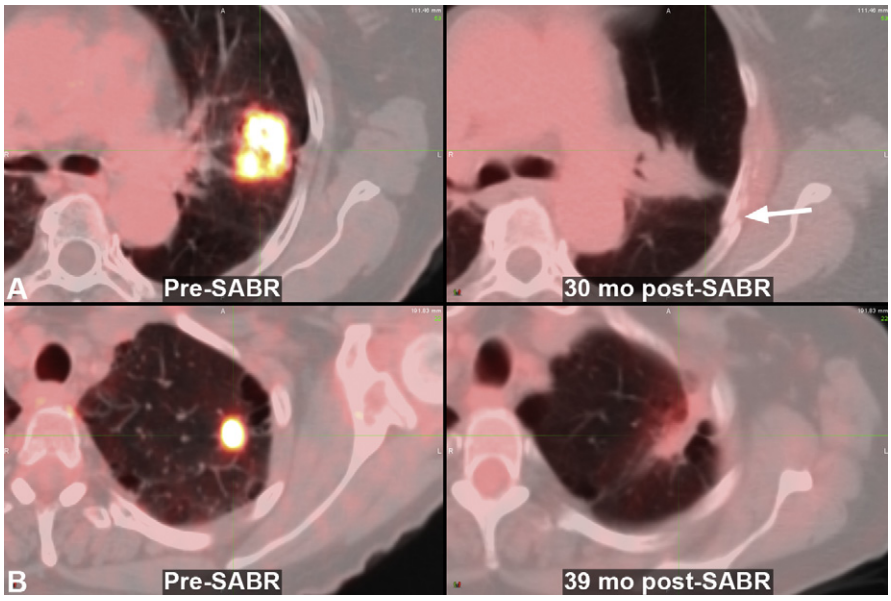

Fig. 3. Two patients treated with the tumor volume-adapted approach. (A) Tumor (19.9 mL) treated with 50 Gy in four fractions (biologically effective dose 112.5 Gy) before (left) and 30 months after stereotactic ablative radiotherapy (SABR) (right). Arrow denotes rib fracture. (B) Tumor (2.7 mL) in a similar location treated with 25 Gy (BED 87.5 Gy) in a single fraction before (left) and 39 months after SABR (right). Both tumors were locally controlled.

in conventionally fractionated radiotherapy (18) and in SABR (8, 9, 11, 12, 15). The various dose and fractionation combinations commonly used in lung tumor SABR are most easily compared by the use of BEDs, although it must be recognized that standard linear quadratic modeling is less accurate at high doses per fraction (19). Onishi *et al.* (9) demonstrated increased local failure and diminished survival for patients treated with isocenter BED $<$100 Gy compared with those treated with BED $\geq$100 Gy in a multi-institutional analysis of patients with early-stage NSCLC. Similarly, Onimaru *et al.* (15) demonstrated significantly decreased LC in patients with Stage IB NSCLC when treated with 40 Gy in four fractions (BED $<$100 Gy) compared with patients receiving 48 Gy in four fractions (BED $>$100 Gy). However, there was no significant difference in LC when Stage IA tumors were considered separately, which suggests that smaller tumors can be effectively controlled at lower BEDs. Our findings add further evidence in support of this hypothesis.

A recently published study by Baba *et al.* also analyzed the outcomes of treating smaller tumors with lower-intensity treatments (20). In this study, BED at the PTV margin ranged from $\sim$74 Gy for the smallest tumors to $\sim$96 Gy for the largest tumors. All tumors were treated with four-fraction regimens. LC was somewhat lower than in similar series, at $\sim$80%, but no differences were observed between smaller and larger tumors. Our volume-adapted dosing strategy both decreases the intensity of therapy for smaller tumors and also adds the convenience of completing the treatment for smaller tumors in a single fraction. The advantages of single-fraction treatment include decreased cost, increased patient convenience, and decreased overall treatment times.

One of the main potential benefits of using lower-intensity treatments for smaller tumors is a potential decrease in toxicity. Indeed, we found significantly less grade 3 toxicity in the small-volume, single-fraction cohort, as might be expected given the larger treatment volumes and higher doses that were used for the larger tumors. Although lung tumor SABR is generally well tolerated, decreasing clinically significant toxicities remains an important goal. In addition to decreasing toxicities related to an initial course of SABR, lower-intensity treatment also potentially allows for more aggressive reirradiation in patients who experience local recurrence or a new tumor near the initial target volume. With improvements in systemic treatments, this issue will likely become increasingly important.

The limitations of this study are its retrospective nature and its somewhat limited follow-up time. The study is also limited by heterogeneity in tumor type because it included both metastatic tumors and primary lung tumors. Of note, there was a larger percentage of metastatic lesions in the group with low tumor volume. However, our results held, even when we considered only primary lung tumors in subgroup analysis. It should also be noted that the majority of patients in this study had peripheral tumors, so care should be exercised when applying our results to centrally located tumors.

In conclusion, our study establishes the feasibility of using a volume-adapted dosing strategy for lung SABR. We found that volume-adapted dosing is both effective and safe. Patients with smaller tumors treated with single fractions to BED $<$100 Gy had equivalent LC and lower treatment-related toxicity in comparison with patients with larger tumors treated with multiple fractions to BED $\geq$100 Gy. Longer-term follow-up will be needed confirm these results. Our findings suggest that it would be valuable to design prospective studies testing tumor volume-adapted dosing strategies for lung tumor SABR.

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