Scientific Article

T Stage and Pretreatment Standardized Uptake Values Predict Tumor Recurrence With 5-Fraction SABR in Early-Stage Non-Small Cell Lung Cancer

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Abstract

Purpose: Five-fraction stereotactic ablative radiotherapy (SABR) regimens are frequently used to treat centrally located early-stage non-small cell lung cancer or disease in the proximity of the chest wall as a means of optimizing tumor control and reducing treatment toxicity. However, increasing these SABR regimens to 5 fractions may reduce tumor control outcomes. We sought to identify the clinical parameters predictive of treatment failures with these 5-fraction courses.

Methods: Ninety patients with T1-2 non-small cell lung cancer were treated with 50 or 60 Gy in 5 fractions. Failure over time was modeled using cumulative incidences of local, regional, or distant failure, with death as a competing risk. Cox proportional hazards analysis for incidences of failure was performed to control for patient variables.

Results: Of 90 patients, 24 of 53 patients with T1 tumors and 19 of 37 patients with T2 tumors received 50 Gy SABR, and the other 47 patients received 60 Gy. Two-year overall survival and progression-free survival for the whole cohort were 75.8% and 59.3%, respectively. Total SABR dose (50 vs 60 Gy) did not influence survival nor failure rates at 2 and 5 years. Within 2 years of treatment, 7.8% of all patients developed local failure. For all patient and tumor characteristics evaluated, only T stage and pretreatment positron emission tomography standardized uptake values served as predictors of local, regional, and distant failure at 2 and 5 years posttreatment on univariate and multivariable analysis.

Conclusions: Five-fraction SABR provides excellent in-field control. T2 and high fluorodeoxyglucose uptake tumors have increased failure rates, suggesting the potential need for adjuvant therapies, which are being assessed in randomized phase 3 trials.

Introduction

Surgical lobectomy is considered the standard-of-care for operable patients with early-stage non-small cell lung cancer (NSCLC), but many of these patients exhibit comorbidities that preclude them from surgery.[1] In these patients, stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT), has become a standard treatment option for early-stage NSCLC. Medicare defines that a course of SABR uses as few as 1 and as many as 5 fractions, with daily radiation treatment as a stand-alone therapy.[2] In this fashion, SABR boasts high efficacy with 2-year local control rates exceeding 90%.[3,4] However, several studies have shown significant rates of grade 3+ toxic effects in patients, especially in those with tumors centrally located near primary airways.[5,6]

In an effort to reduce toxicity for centrally located tumors and those near the chest wall, clinicians commonly use 5-fraction SABR regimens rather than more hypofractionated regimens. In the Radiation Therapy Oncology Group (RTOG) 0813 multicenter phase 1/2 clinical trial evaluating the role of SABR in patients with centrally located tumors, dose escalation from 50 Gy in 5 fractions to 60 Gy in 5 fractions resulted in a limited increase in toxicity (2.0%-7.2%) and 1 instance of a grade 5 toxic effect, while preserving high rates of local control (87.9% at 2 years).[7]

With lower toxicity from increased fractionation SABR regimens, 5-fraction SABR has become a commonly selected treatment for both central and chest wall tumor locations. However, few studies have directly addressed the clinical risk factors that contribute to patient response and overall efficacy. Therefore, in this study, we investigated patterns of failure in patients treated with 5-fraction SABR and used multivariable regression to identify the patient characteristics that predict for recurrence.

Methods and Materials

We retrospectively reviewed a database of 90 patients with T1-T2 NSCLC treated with SABR at our institution between July 2008 and July 2017. Patient tumors were defined as either located near central airways (denoted as central) or close to the chest wall (denoted as peripheral).[6] Patient disease was staged using positron emission tomography (PET)/computed tomography (CT) (97.8% of all cases) and/or mediastinal lymph node biopsy (26.7% of all cases). Staging was defined according to the American Joint Committee on Cancer eighth edition, with T1 being no greater than 3 cm and T2 being greater than 3 cm.[8] Patients were treated with definitive 5-fraction SABR

regimens, receiving either 50 or 60 Gy in 5 fractions as defined in RTOG 0813.[7] The study was approved by the UT Southwestern Medical Center institutional review board (No. STU 052012-019).

Patients underwent CT simulation with a Vac-Lok bag within a stereotactic frame in the supine position with arms up. Tumor motion during respiration was assessed via fluoroscopy (if visible) or mini 4-dimensional CT, which samples and sorts CT images over a patient's entire breathing cycle. If tumor motion was greater than 1 cm in any direction, abdominal compression or breath hold was used to minimize motion. An internal target volume (ITV) was delineated, and a uniform 5-mm expansion around the ITV was used to generate the planning target volume (PTV). Biological effective dose (BED) was calculated as the product of relative effectiveness and total dose.[9]

Clinical response was evaluated using Response Evaluation Criteria in Solid Tumor 1.1 criteria.[10] Local failure was defined as a 20% or more increase in the maximum dimension of the treated tumor, positron emission tomography (PET) with maximum standardized uptake values (SUV) >5, or biopsy-proven progression.[11,12] Regional failure was defined as PET-positive or biopsy-proven evidence of lymph node involvement. Distant metastasis included PET-proven evidence of new lesions in uninvolved lobes of the lung or other organs.

Statistics

The incidence of local, regional, and metastatic recurrence was estimated using cumulative incidence statistics, with death as a competing risk. A failure for progression-free survival (PFS) was defined as any incidence of recurrence or any cause of death starting from initiation of treatment. Overall survival (OS) and PFS were estimated using the Kaplan-Meier method. Patients who were alive without evidence of recurrence were censored at the date of last follow up. *P* values were calculated from incidence of failure, and survival curves were created with Cox proportional hazards tests.

Cox proportional hazards regression was used to determine the effect of patient covariates on incidence at 2 years. A regression model was fit using treatment dose, age, sex, smoking history, tumor histology, tumor location, pretreatment maximum SUV, and tumor stage. The median value of 9 was selected as the cutoff between low and high pretreatment maximum SUV values. Patients who died before evidence of recurrence before 2 years, who were lost to follow-up before 2 years, or who did not receive biopsy/PET scans were excluded from multivariable analysis. Hazard ratios (HRs) and confidence

intervals (CIs) were calculated for each variable. Five-year analyses were also conducted in a similar manner.

Results

Of the 90 patients treated with 5-fraction SABR, 43 received 50 Gy in 5 fractions and 47 received 60 Gy in 5 fractions prescribed to the 66% to 98% isodose (67 cases <85%, 23 cases >85%), with a combined median elapsed treatment time of 13 days. The median age of all patients was 74 years, and the majority (65.6%) had an Eastern Cooperative Oncology Group performance status of 0. All tumors were either stage T1 (53 tumors) or T2 (37 tumors). Of the 43 patients treated with 50 Gy, 24 had

stage T1 tumors and 19 had stage T2 tumors. Of the 47 patients treated with 60 Gy, 29 had stage T1 tumors and 18 had stage T2 tumors. Median pretreatment maximum SUV was 9 (range, 1.0-32.0). With the exception of tumor location and tumor histology, patient characteristics were relatively balanced in both cohorts (Table 1). Median follow-up for all patients was 31.6 months (range, 2.9-148.4 months). The mean ITV BEDs for the 50-Gy and 60-Gy cohorts were 144.3 Gy and 192.4 Gy, respectively.

For the entire cohort, 2-year OS and PFS were 75.8% and 59.3%, respectively. Five-year OS and PFS were 44.7% and 32.8% (Fig 1A), respectively. Throughout the duration of the study, the cumulative incidences of local failure, regional failure, and distant failure were respectively 21.1%, 30.0%, and 28.9% after definitive treatment

Table 1   Patient characteristics

Characteristic	Cohort	50 Gy in 5 fractions	60 Gy in 5 fractions
Total number of patients	90	43	47
Age (y)			
Median	74	72	75
Range	54-93	58-91	54-93
ECOG performance status			
0-1		28	31
2+		15	16
Sex			
Male	44	22	22
Female	46	21	25
Smoking	57	31	26
Tumor stage			
T1	53	24	29
T2	37	19	18
Pathology			
Adenocarcinoma	45	16	29
SCC	32	18	14
NSCLC	7	3	4
No biopsy	6	6	0
Tumor location			
Central	22	16	6
Peripheral	68	27	41
Pretreatment maximum SUV			
<9	40	17	23
≥9	40	23	17
Treatment duration			
Median	13	12	13
Range	9-19	9-19	9-17

Abbreviations: central = located centrally; ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; peripheral = located close to the chest wall; SCC = squamous cell carcinoma; SUV = standardized uptake values.
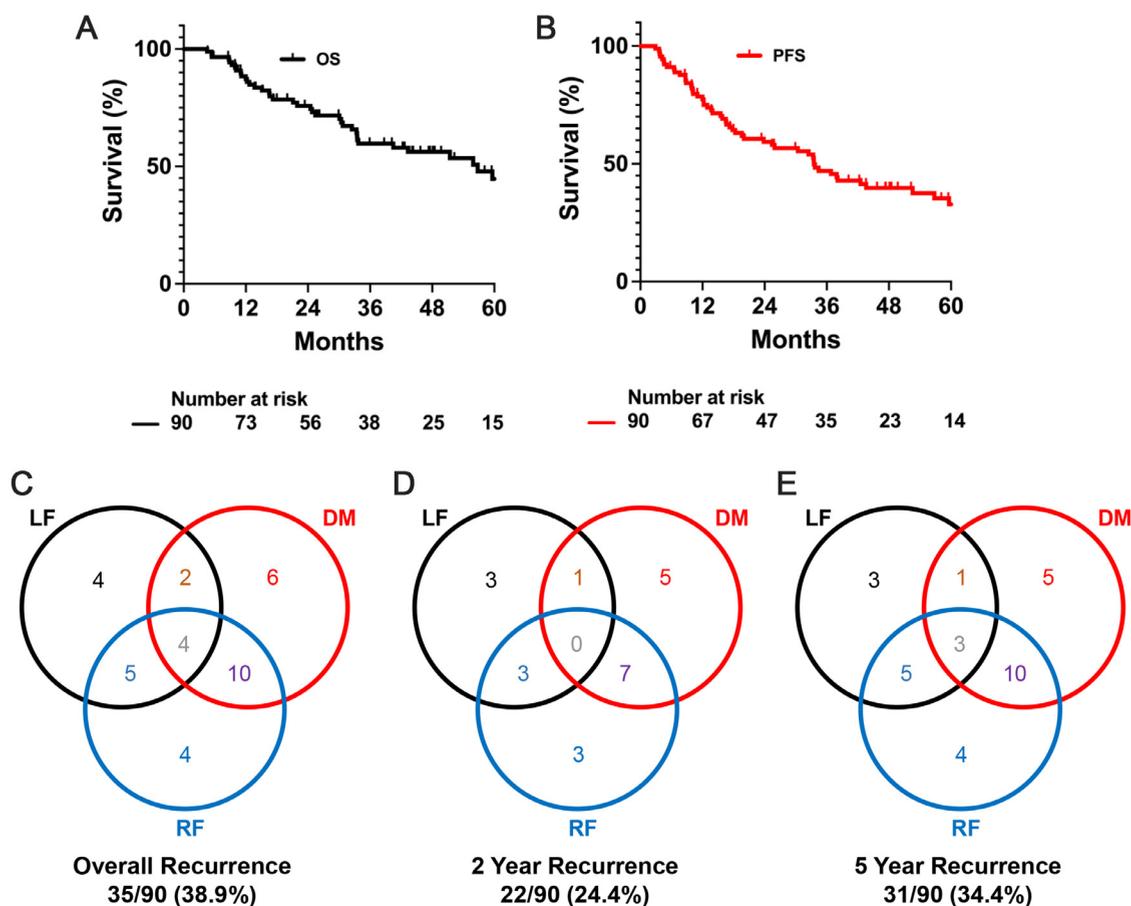
Fig. 1 Outcomes for whole patient cohort. A, Kaplan-Meyer plot of overall survival and progression-free survival. C-E, Total instances of each type of recurrence over the whole time scale of the study within 2 and 5 years of treatment. *Abbreviations:* DM = distant metastasis; LF = local failure; OS = overall survival; PFS = progression-free survival; RF = regional failure.

with SABR (Fig 1B). For all incidences of local failure, 80% of patients were categorized as having a >20% increase in tumor size, 66.7% had evidence of fluorodeoxyglucose avidity of maximum SUV >5, and 33.3% underwent biopsy confirmation of disease. From the whole patient population, 24.4% developed local failure, regional failure, or distant metastasis within 2 years, with 7.8% of all patients having local failure, 14.4% having regional failure, and 14.4% having distant metastases (Fig 1C). Similarly, 34.4% of all patients showed evidence of recurrence by 5 years, with similarly scaled proportions of patients exhibiting each type of failure (Fig 1D).

Univariate analysis of the cumulative incidence for combined local, regional, and distant recurrence demonstrated that patients with stage T1 tumors exhibited a decreased incidence of recurrence levels at 2 years (18.8% vs 44.0% for T2; HR, 2.68; 95% CI, 1.16-6.22) (Fig 2A, Table 2). This was also observed in patients with low pretreatment maximum SUV (19.4% vs 42.6% for maximum SUV ≥9; HR, 2.80; 95% CI, 1.14-6.88) (Fig 2B, Table 2). Patients with both T2 tumors and pretreatment SUV ≥9 exhibited significantly higher rates of any recurrence at

2 years compared with patients with T1 tumors and low pretreatment SUV (15.0% vs 58.0%; HR, 5.80; 95% CI, 1.82-18.46). Patients with low T stage and high pretreatment SUV or high T stage and low pretreatment SUV exhibited a more "intermediate" rate of recurrence (Fig 2C). Univariate analysis of cumulative 5-year incidence of recurrence yielded comparable results (Table E1). Univariate analysis of any failure for all other patient characteristics was also performed. No significant differences in cumulative incidence over time were observed between patients with different age, sex, smoking history, tumor histology, or tumor location (Fig E1).

Multivariable analysis was performed to identify which patient characteristics associated with timing and pattern of failure. Because fewer than 10% of all patients developed local failure after 2 years, we chose to analyze all incidences of failure after SABR treatment. Table 2 shows the normalized HRs for each patient characteristic's association with 2-year incidence of any failure. The only statistically significant predictor of recurrence at 2 years was high pretreatment maximum SUV (greater than a median value of 9; HR, 2.93; 95% CI, 1.03-8.31; *P* = .0431). Larger
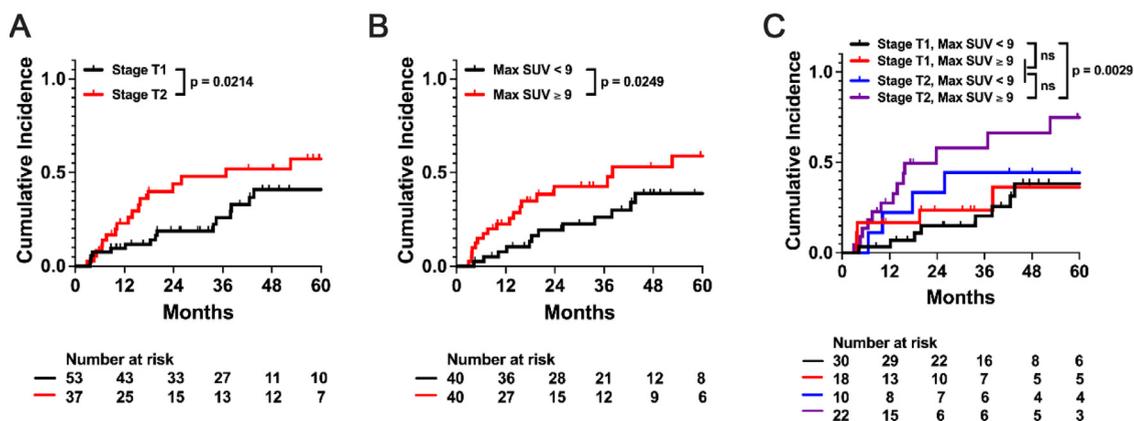
Fig. 2 A-C, Effects of T stage and pretreatment maximum standardized uptake values (SUV) on recurrence. Kaplan-Meyer plots of cumulative incidence of local, regional, or distant recurrence comparing patients with different T stage, pretreatment maximum SUV, and combined T stage/pretreatment maximum SUV. Statistical analysis was performed using Cox proportional hazards tests at 2 years posttreatment.

tumor size (T2; HR, 2.47; 95% CI, 0.93-6.58; P = .0712) also trended toward being a predictor of 2-year incidence of recurrence (Table 3). Similarly, high pretreatment maximum SUV and larger tumor size also predicted for 5-year incidence of recurrence (Table E2). These results were also observed when using other pretreatment SUV and tumor size cutoffs as well, such as those from the Southwest Oncology Group S1914 clinical trial (NCT04214262) (Fig E2, Tables E3 and E4).

In multivariable analysis, SABR total treatment dose did not significantly contribute to 2-year local, regional, or distant recurrence (P = .2339) (Table 3). As noted previously, univariate analysis also indicated that there was no significant difference in survival nor cumulative incidence between these 2 treatment groups, both at 2 years and over the entire time course of the study. Survival rates at 2 years for the 50 Gy and 60 Gy treatment groups were 76.9% and 74.9%, respectively (P = .785). Cumulative incidence of any recurrence at 2 years between these groups was also unchanged (25.9% vs 31.5%, P = .374) (Fig 3). The

5-year incidence of recurrence was also unchanged between these 2 treatment groups (Tables E1 and E2).

Discussion

As increasing numbers of patients with early-stage NSCLC receive definitive SABR to treat their primary disease, it becomes vital to determine the patient risk factors that contribute to post-SABR recurrence. Particularly compared with 3-fraction SABR regimens, 5-fraction SABR regimens are commonly used when extra care is required to mitigate toxicity due to anatomic constraints, such as with centrally located tumors or tumors close to the chest wall.[7] This reduced toxicity is based on the assumption of improved tolerance with increased fractionation.[13] Herein, we did not set out to prove that 5-fraction SABR regimens are inherently less toxic than using 1- to 4-fraction regimens. However, accepting this premise, we directed our attention to efficacy. We used multivariable and univariate analysis of patient clinical

Table 2 Univariate Cox proportional hazards regression: Effect of patient characteristics on 2-year incidence of local, regional, or distant recurrence

Variable (univariate)	Hazard ratio (unadjusted)	95% CI	P value
60-Gy dose	1.02	0.94-1.11	.671
Age ≥74 y	1.02	0.97-1.07	.482
Male sex	1.23	0.54-2.80	.617
Smoking history	0.83	0.36-1.92	.659
SCC histology	0.83	0.58-1.19	.300
Central location	0.85	0.32-2.30	.752
Max SUV ≥9	2.80	1.14-6.88	.0249
T stage T2	2.68	1.16-6.22	.0214
Abbreviations: CI = confidence interval; SCC = squamous cell carcinoma; SUV = standardized uptake value.			

Table 3   Multivariable Cox proportional hazards regression: Effect of patient characteristics on 2-year incidence of local, regional, or distant recurrence

Variable (multivariable)	Hazard ratio (adjusted)	95% CI	P value
60-Gy dose	1.06	0.97-1.15	.234
Age ≥74 y	1.03	0.98-1.09	.235
Male sex	0.90	0.36-2.29	.829
Smoking history	0.61	0.25-1.49	.274
SCC histology	0.94	0.61-1.47	.800
Central location	1.29	0.46-3.62	.624
Max SUV ≥9	2.93	1.03-8.31	.0431
T stage T2	2.47	0.93-6.58	.0712
Abbreviations: CI = confidence interval; SCC = squamous cell carcinoma; SUV = standardized uptake value.			

characteristics to help identify patients with higher recurrence risk after SABR treatment.

Consistent with other SABR regimens, 5-fraction SABR exhibited high rates of local tumor control, with more than 92% in-field, failure-free survival within 2 years of either 50 Gy or 60 Gy SABR treatment. With limited in-field failures, our primary question investigated the identification of clinical characteristics that could predict for any progression, whether locoregional or distant. Univariate and multivariable analyses yielded 2 tumor characteristics that were correlated with the incidence of recurrence within 2 or 5 years of treatment. First, we observed that patients with T2 tumors exhibited greater rates of recurrence than those with T1 tumors (Fig 2A). Even though 2-year multivariable analysis showed that T stage only modestly predicted for tumor recurrence, 5-year multivariable analysis demonstrated statistical significance, thus still identifying high T stage as an important

standalone pattern of failure. Moreover, a calculated hazard ratio of 2.47 still indicates more than double the risk of developing a recurrence in patients with T2 tumors. Second, we observed that patients with pretreatment maximum SUV levels greater than the median value of 9 also had greater rates of failure than those with lower levels (Fig 2B). This is consistent with previous studies that observed that pre-SABR maximum SUV levels were a prognostic indicator of survival and local control.[14,15] Expanding on this, we observed that more than 50% of patients with both high T stage and SUV levels experienced any recurrence within 2 years of treatment (Fig 2C). This combined stratification may provide clinicians with more confident predictions about whether certain patients may experience early treatment failure. These results were also robust when we analyzed these characteristics using different tumor size and SUV level cutoffs, such as those from the Southwest Oncology Group S1914
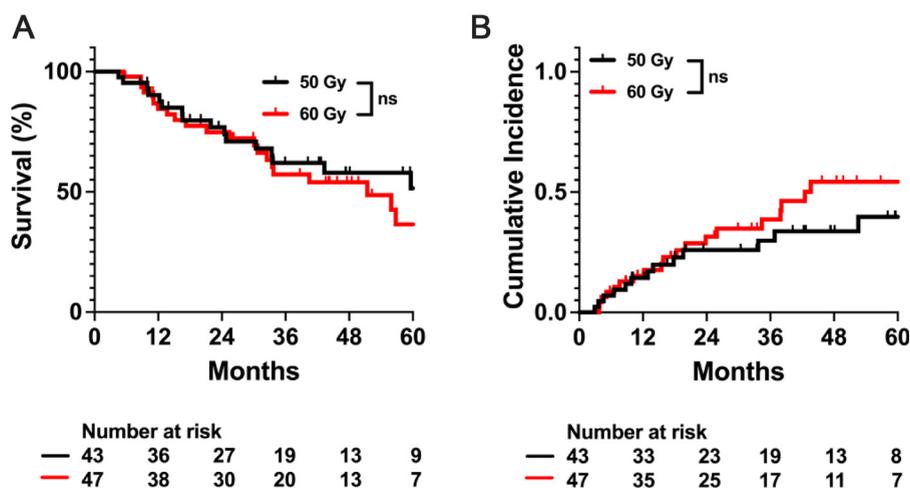
Fig. 3 A and B, Outcomes for 50 Gy and 60 Gy cohorts. Kaplan-Meyer plots of overall survival and cumulative incidence of local, regional, or distant recurrence in patients treated with either 10 Gy or 12 Gy 5-fraction SABR. Statistical analysis was performed using Cox proportional hazards tests at 2 years posttreatment. *Abbreviations:* Gy = Gray, ns = not significant.

clinical trial (NCT04214262) (Fig E2, Tables E3 and E4). Our findings suggest that these 2 tumor characteristics are robust predictors of 5-fraction SABR treatment failure.

Five-fraction SABR has been observed to exhibit antitumor efficacy similar to other ablative SABR regimens.[4,7] However, as evidenced by continued observable high-grade toxicity, the optimal 5-fraction SABR dose that provides effective local and distant control of tumors while minimizing adverse effects has not been clearly delineated.[7] Local control and survival rates have been observed to be increased with patients receiving BED >100 Gy compared with BED <100 Gy.[16] Both 50 Gy and 60 Gy provide a BED of >100 Gy. Furthermore, we observed that survival and cumulative incidence between patients who received 50 Gy or 60 Gy doses in 5 fractions did not significantly differ both 2 and 5 years after SABR treatment (Fig 3, Tables E1 and E2). Our results suggest that in early-stage NSCLC, 5 fractions of both 10 Gy and 12 Gy doses can be administered to achieve similar patient outcomes. NRG Oncology recently published the results of their phase 1/2 study of dose escalation for 5-fraction SABR for centrally located tumors to determine the maximum tolerated dose, efficacy, and toxicity. They found that 12 Gy × 5 fractions was associated with a 7.2% dose-limiting toxicity, defined as any treatment-related grade 3 or worse predefined toxic effect that occurred within the first year, and a 87.9% 2-year local control rate.[5] Furthermore, the RTOG 0236 study observed respective 5-year OS and PFS rates of 40% and 26%, with a disseminated recurrence rate of 31%.[17] Our results demonstrate similar control rates to these studies. In our study, we found a 7.8% local failure rate at 2 years, 5-year OS and PFS rates of 44.7% and 32.8%, and a disseminated recurrence rate of 21.1%. Our results demonstrate the efficacy of a 5-fraction regimen in a real-world setting.

Our study indicates that in patient characteristics with high T stage and high pretreatment maximum SUV values, 5-fraction SABR treatment alone may not sufficiently prevent tumor recurrence. This combined stratification group can help identify which patients are particularly at higher risk of failure. In such cases, further intensification of treatment with additional systemic therapy may improve patient prognosis. For example, the Durvalumab vs Placebo With Stereotactic Body Radiation Therapy in Early Stage Unresected Non-small Cell Lung Cancer (NSCLC) Patients / Osimertinib Following SBRT in Patients With Early Stage Unresected NSCLC Harboring an EGFR Mutation randomized phase 3 trial (NCT03833154) is evaluating the role of adjuvant durvalumab after receipt of SABR for patients with stage I-II lymph node−negative NSCLC. Furthermore, our study also sheds light on potential de-escalation of 5-fraction SABR doses to early-stage NSCLC. This sets the stage for new prospective studies or clinical trials that can definitively define a 5-fraction dose that still provides equivalent patient outcomes and tumor control with further reduced toxicity.

Our study had the traditional limitations that are relevant to all retrospective evaluations. These weaknesses include nonrandom treatment group allocation, selection bias, and nonrandom loss to follow-up intrinsic to any nonrandomized, nonprospective study.[18] Despite this, our study still provides patient populations that are relatively balanced across treatments, and also accounts for loss to follow-up during statistical analysis. Our study also focused on treatment efficacy and did not include a formal evaluation of toxicity, though there were no concerning adverse events associated with any of the patients in this study. Though we observed that the efficacy of 50 Gy and 60 Gy 5-fraction SABR did not significantly differ, our study did not indicate an objective measure as to whether the 50 Gy dose truly induced less toxicity than the 60-Gy dose. Therefore, this study cannot report on whether 10 Gy × 5 fraction SABR is truly less toxic without compromising antitumor efficacy. One other limitation is the limited number of patients who exhibited local failure within 2 years of treatment. As a result, we could not effectively identify statistically significant changes in local control owing to different patient and tumor characteristics.

Conclusion

Taken together, our study provides insight into the factors that contribute to the efficacy of 5-fraction SABR in treatment of early-stage NSCLC. Consistent with previous studies, 5-fraction SABR at our institution induces excellent local control, demonstrating patient outcomes similar to other SABR regimens of the same dose. We note that 2-year and 5-year incidence rates of recurrence are increased in patients who have tumors that are of higher T stage or have higher pretreatment maximum SUV values. Finally, although this study does not clearly define an optimal recommended dose of 5-fraction SABR, we report that using a potentially less toxic dose (10 Gy × 5 fractions) of SABR results in similar clinical outcomes compared with those used (12 Gy × 5 fractions) in previous large 5-fraction SABR clinical trials. Overall, this study can inform clinicians about which patients with NSCLC may respond more effectively to 5-fraction SABR.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.100995.

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