ORIGINAL ARTICLE

Histology, Tumor Volume, and Radiation Dose Predict Outcomes in NSCLC Patients After Stereotactic Ablative Radiotherapy

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ABSTRACT

Introduction: It remains unclear if histology should be independently considered when choosing stereotactic ablative body radiotherapy dose prescriptions for NSCLC.

Methods: The study population included 508 patients with 561 lesions between 2000 and 2016, of which 442 patients with 482 lesions had complete dosimetric information. Eligible patients had histologically or clinically diagnosed early-stage NSCLC and were treated with 3 to 5 fractions. The primary endpoint was in-field tumor control censored by either death or progression. Involved lobe control was also assessed.

Results: At 6.7 years median follow-up, 3-year in-field control, involved lobe control, overall survival, and progression-free survival rates were 88.1%, 80.0%, 49.4%, and 37.2%, respectively. Gross tumor volume (GTV) (hazard ratio [HR] = 1.01 per mL, $p = 0.0044$) and histology ($p = 0.0225$) were independently associated with involved lobe failure. GTV (HR = 1.013, $p = 0.001$) and GTV dose (cutoff of 110 Gy, biologically effective dose with $\alpha/\beta = 10$ [BED10], HR = 2.380, $p = 0.0084$) were independently associated with in-field failure. For squamous cell carcinomas, lower prescription doses were associated with worse in-field control (12 Gy × 4 or 10 Gy × 5 versus 18 Gy or 20 Gy × 3: HR = 3.530, $p = 0.0447$, confirmed by propensity score matching) and was independent of GTV (HR = 1.014 per mL, 95% confidence interval: 1.005–1.022, $p = 0.0012$). For adenocarcinomas, there were no differences in in-field control observed using the above dose groupings ($p = 0.12$ and $p = 0.31$, respectively).

Conclusions: In the absence of level I data, GTV and histology should be considered to personalize radiation dose for stereotactic ablative body radiotherapy. We suggest lower prescription doses (i.e., 12 Gy × 4 or 10 G × 5) should be avoided for squamous cell carcinomas if normal tissue tolerances are met.

Keywords: Stereotactic body radiation therapy; Stereotactic ablative radiotherapy; Histology; NSCLC

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Introduction

NSCLC represents approximately 84% of lung cancer cases in the United States.[1] Approximately 30% of early-stage NSCLC patients are inappropriate for or refuse surgical resection. Historically, such patients received conventionally fractionated radiotherapy with expected 3-year overall survival (OS) rates between 20% and 35% and local failure rates between 40% and 60%.[2,3] In an attempt to improve outcomes, stereotactic ablative body radiation (SABR; also called stereotactic body radiation therapy) was initially explored in medically inoperable patients with one of the first trials originating from Timmerman et al.[4] at Indiana University. Subsequently, the Radiation Therapy Oncology Group (RTOG) conducted a phase II trial (RTOG 0236) evaluating the efficacy of SABR for patients with peripherally located tumors. The reported 3-year local control (LC) rate was 98% with a 3-year OS of 56% and a median OS of 4 years.[2] Other prospective and retrospective studies have corroborated these findings.[5-7] A pooled analysis of two prematurely closed randomized trials comparing SABR versus lobectomy for operable stage I (T1-2aN0M0) NSCLC patients suggested clinical equipoise between SABR and surgery, with a 3-year OS of 95% versus 79%, respectively.[8]

Risk factors for recurrence have been explored in surgical series, and findings suggest that outcomes are dependent on extent of resection and histology, including worse outcomes in squamous cell carcinomas and differing outcomes based on adenocarcinoma subtypes.[9-14] Similar analyses for SABR are limited. Evidence suggests that biologically effective dose ($\alpha/\beta = 10$, BED_{10}) cutoffs predict better control.[5,15-23] In addition, recent publications suggest histology may also play a role for predicting treatment response following SABR.[6,24] We aim to identify risk factors for recurrence using our institution's 16-year experience using SABR for NSCLC to allow personalization of dose prescriptions according to patient, tumor, and treatment-specific characteristics.

Materials and Methods

Study Population

This study is an Institutional Review Board–approved retrospective review of outcomes after SABR for NSCLC. We included patients treated from 2000 to 2016 who were identified by medical billing codes and relevant billing information.

Eligible patients were 18 years of age or older with histologically or clinically diagnosed early-stage NSCLC; synchronous and metachronous lesions were included, the latter of which only if a previously treated NSCLC was felt to be cured.[25] Clinical diagnosis was based on radiographic suspicion, most often via tumor board consensus.[26,27] Patients were either inoperable or had elected against surgery. Patients were excluded if they had systemic spread of lung cancer at the time of SABR.

Treatment Details

Treatment planning and delivery evolved during the study period. All patients underwent computed tomography (CT) simulation in the supine position with immobilization for stereotactic treatment. Heterogeneity corrections were taken into account starting in 2007. Radiation plans were calculated using the analytical anisotropic algorithm (AAA) (Eclipse Treatment Planning System, Varian Medical Systems, Palo Alto, California) with heterogeneity corrections, AAA (Eclipse) without heterogeneity corrections, pencil beam (Precise Plan, Elekta, Stockholm, Sweden) without heterogeneity corrections, or convolution/superposition (XiO, Elekta, Stockholm, Sweden) without heterogeneity corrections. Radiation was delivered in 3 to 5 fractions with at least 1 day between fractions. Gross tumor volume (GTV) was defined as visible tumor on CT using lung windows. Other imaging was used as needed. Internal target motion was taken into account with fluoroscopy initially and four-dimensional CT more recently to generate an internal target volume, and margins were added to generate the planning target volume (PTV). Prescriptions typically were to the 80% isodose line, and the prescription typically covered at least 95% of the PTV. More recently in the intensity-modulated radiation therapy setting, prescriptions were typically 95% of the PTV receiving 100% of the prescription and 99% of the internal target volume receiving at least 110% of the prescription. Radiation doses are represented as Gy BED_{10} except when dose is stated as "dose per fraction × # of fractions." A small proportion of the study cohort received suboptimal doses (i.e., prescription dose <100 Gy) according to current standards (n = 30 patients and lesions in the study cohort; n = 23 patients and lesions in the dosimetric cohort) as they were enrolled on dose escalation trials.

Data Collection

The date of diagnosis was defined as the date of tumor sampling for those with histologic diagnosis or the date of imaging prompting additional workup for those with clinical diagnosis. In total, 15.3% (n = 86) of lesions were diagnosed clinically, of which 12.7% (n = 71) had no biopsy and 2.7% (n = 15) had no pathology report available for review. The date of last follow-up was defined as the date the patient last visited with a radiation oncologist, medical oncologist, surgical oncologist, or pulmonologist. The T stage was updated for all lesions to be consistent with the American Joint Committee on Cancer seventh edition (AJCC 7e) staging.

Follow-up was performed at the discretion of the treating physician. Follow-up imaging most often was by CT or positron-emission tomography. Recurrences were determined by reviewing the patient's serial imaging (CT, positron-emission tomography/CT) and the clinical judgement of treating physicians. Sites of recurrences were defined as in-field (failure within or abutting the PTV), involved lobe (any failure within the treated lobe), different ipsilateral lobe, contralateral lung, regional nodes (failure within the hilum, mediastinum, and supraclavicular nodes), and distant sites (per AJCC 7e staging).[28] Synchronous tumors were staged independently and metachronous lesions were staged as new primary lung cancers.

Clinical or pathologic determination of failure took precedence for coding date of failure. If not available, the documented radiology interpretation of serial imaging was used. If radiology interpretation was equivocal, the authors (T.L., K.S., and A.C.) jointly reviewed the case and used all available imaging to determine failure. In-field failure cases were also jointly reviewed.

A subset of 442 patients with 482 lesions had treatment plans available for review. Plans that did not have heterogeneity corrections applied were recalculated with heterogeneity corrections using AAA version 11 when feasible. Recalculation was not possible for 173 plans calculated on Render or XiO systems (no heterogeneity corrections). Although the differences in calculated dose to the isocenter were reported to be 13.4% higher on average for AAA heterogeneity corrected plans as compared with non–heterogeneity corrected plans, the dose to 95% of the volume is reported to be only 2.9% greater on average for AAA versus non–heterogeneity corrected plans for the same given monitor units.[29] Because of this small difference, plans for which recalculation with heterogeneity correction was not possible were not excluded from the study population.

Statistical Analysis

OS was calculated from the date of diagnosis until death or last follow-up. Time to recurrence was calculated from the date of diagnosis until failure, death, or last follow-up. In-field control was analyzed in two different ways. First, in-field control considered in-field failure as an event and was censored only at death or last follow-up to acknowledge that treated lesion failure may still occur after a nonlocal failure, consistent with other control endpoints. Next, in-field control was reanalyzed by censoring at death, last follow-up, and first non–in-field failure to acknowledge that any failure may precipitate a change in therapy that could affect in-field control (Supplemental Fig. 1).

Multivariate models were calculated using Cox proportional hazards modeling. Survival and control were estimated using the Kaplan-Meier method. Propensity score matching was performed for in-field control to compare patients divided into different groups based on dose-fractionation schedules or (separately) histology. Patients were matched using GTV, T stage, age, and history of previous NSCLC. Nomograms were generated using logistic regression modeling with the Bioconductor/R rms (version 5.1-2) package. The performance of the model was evaluated using the receiver operating characteristic curve and areas under the curve (AUC). Logistic regression was also used to identify factors that may be predictive of long-term survival (>5 years). All statistical analyses were two-sided, and p values < 0.05 were deemed statistically significant. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used.

Results

From 2000 to 2016, 508 patients with 561 lesions met eligibility criteria and were treated with SABR. Table 1 summarizes patient demographics and baseline characteristics. The most common histologies were adenocarcinoma (36.7%), squamous cell carcinoma (31.9%), and NSCLC not otherwise specified (18.4%); 15.3% were diagnosed clinically. Overall, 28.0% of lesions were treated in the setting of previously cured lung cancers. The most common fractionation schemes were 12 Gy × 4 fractions (30.5%), 20 Gy × 3 (20.3%), 18 Gy × 3 (15.2%), and 10 Gy × 5 (12.1%) (Table 2).

The median follow-up was 6.7 years (range, 0.1 to 15.1 years); the median OS was 2.9 years (Supplemental Fig. 2) and 3-year OS was 49.4% (95% confidence interval [CI]: 44.8%–53.9%). T stage was significantly associated with OS ($p = 0.0238$); age, histology, history of previous NSCLC, and method of diagnosis were not associated with OS (Supplemental Table 1). Involved lobe failure did not seem to impact OS ($p = 0.93$). Patients with involved lobe failure lived a median of 3.2 years versus 3.0 years for patients who did not have any failure or 2.9 years for patients with noninvolved lobe failure ($p = 0.93$). Patients with distant failure lived a shorter time (median 2.1 years versus 3.0 years for no failure versus 3.9 years for nondistant failure, $p = 0.0003$) (Supplemental Fig. 3, Supplemental Table 2).

Progression-free survival at 1- and 3- years was 75.2% (95% CI: 71.3%–78.6%) and 37.2% (95% CI: 33.0%–41.4%), respectively. Involved lobe control at 3 years was 80.0% (95% CI: 75.1%–84.1%) (Supplemental Fig. 4) and in-field control at 3 years was 88.1% (95% CI: 83.8%–91.3%) (Supplemental Fig. 1). There was no significant difference in involved lobe or in-field control when comparing lesions diagnosed pathologically versus clinically when considering age, or when considering a previous diagnosis of NSCLC (Supplemental Table 3). T stage

Table 1. Patient and Lesion Characteristics

	Study Cohort (n = 561)	Dosimetric Subset (n = 482)	*p* Value[a]
Patient characteristics			
Median age (range), y[b]	72.4 (42.1-100)	72.2 (44.1-93.9)	0.74
Female (%)[b]	239 (47.1)	224 (50.7)	0.26
Lesion characteristics	n (%)	n (%)	
History of NSCLC	157 (28.0)	134 (27.8)	0.95
Histology			0.95
Adenocarcinoma	206 (36.7)	185 (38.4)	
Squamous cell carcinoma	179 (31.9)	150 (31.1)	
NSCLC NOS[c]	103 (18.4)	87 (18.1)	
Adenosquamous cell carcinoma[c]	1 (0.2)	0 (0)	
Large cell carcinoma[c]	1 (0.2)	1 (0.2)	
No pathology	71 (12.7)	59 (12.2)	
Location			0.99
Right upper lobe	174 (31.0)	155 (32.2)	
Right middle lobe	41 (7.3)	37 (7.7)	
Right lower lobe	111 (19.8)	95 (19.7)	
Left upper lobe	153 (27.3)	127 (26.4)	
Left lower lobe	82 (14.6)	68 (14.1)	
Clinicial diagnosis	86 (15.3)	71 (14.7)	0.79
Stage			0.89
T1	410 (73.1)	354 (73.4)	
T2	142 (25.3)	122 (25.3)	
T3	9 (1.6)	6 (1.2)	

[a]All *p* values are from *t* tests (continuous) or chi-square tests.
[b]These characteristics were for unique patients (n = 508 and 442, respectively) and not unique lesions.
[c]These histologies were grouped under "other histology" for analysis.
NOS, not otherwise specified.

was associated with in-field failure ($p = 0.0056$), but not with involved lobe failure ($p = 0.0773$). Prescription dose was associated with involved lobe and in-field control (Supplemental Table 3).

Cancer recurrence at one or multiple sites was observed for 224 (39.9%) treated lesions (Supplemental Table 4). No failures were observed after SABR for 337 (60.1%) lesions. First failure (often at multiple sites) (Supplemental Table 4) was in-field in 41 lesions (7.3%) and involved lobe in 73 lesions (13.0%). Other components of first failure were as follows: 50 (8.9%) in a different ipsilateral lobe, 63 (11.2%) in the contralateral lung, 62 (11.1%) in the regional nodes, and 72 (12.8%) at distant sites. Lesions that recurred in-field had a median time to in-field failure of 1.5 years. In-field failure was a first event for 4.8% of adenocarcinomas and 11.7% of squamous cell carcinomas.

Complete dosimetric information was available for a subset of 482 lesions. There was no difference between the study cohort and this dosimetric subset with respect to

Table 2. Summary of Dose-Fractionation Schemes

		Study Cohort* (n = 561)	Dosimetric Cohort* (n = 482)
# of Fractions	Dose Per fraction (Gy)	n (%)	n (%)
3	<18	45 (8.0)	27 (5.6)
	=18	85 (15.2)	78 (16.2)
	=20	114 (20.3)	90 (18.7)
	> 18 (except 20)	44 (7.8)	35 (7.3)
4	<12	2 (0.4)	1 (0.2)
	=12	171 (30.5)	158 (32.8)
	>12	15 (2.7)	12 (2.5)
5	<10	14 (2.5)	12 (2.5)
	=10	68 (12.1)	68 (14.1)
	>10	3 (0.5)	1 (0.2)

*There was no difference between the two cohorts with respect to dose-fractionation schemes ($p = 0.83$)

baseline characteristics (Table 1). Involved lobe and in-field control of the dosimetric cohort at 3 years was 80.0% (95% CI: 74.5%–84.5%) and 88.4% (95% CI: 83.6%–91.9%), respectively (Fig. 1*A* and *C*).

In this 482-lesion subset, GTV and histology were independently associated with involved lobe failure, whereas GTV and dose were independently associated with in-field failure (Table 3, Fig. 1*B*). Separate multivariate analyses were performed that included GTV, T stage, and histology as covariates. Each multivariate analysis included only one of the dosimetric variables tested (i.e., one of prescription dose as a continuous variable, prescription dose as a categorical variable, and minimum, mean, or maximum dose to the GTV) because of strong correlations between the dosimetric variables. Prescription dose as either a continuous or categorical variable (cutoff of 110 Gy) was significantly associated with in-field failure.[17] However, a cutoff of 105 Gy was significant on univariate analysis ($p = 0.0117$) but not on multivariate analysis ($p = 0.091$).[5] The other dosimetric variables analyzed (minimum, maximum, and mean dose to GTV) were all significantly associated with in-field failure (Table 3).

Within the subset with complete dosimetric information, 3-year in-field control was 89.6% (95% CI: 80.9%–94.5%), 85.0% (95% CI: 75.6%–91.0%), and 88.8% (95% CI: 74.3%–95.3%) for adenocarcinoma, squamous cell carcinoma, and other histologies, respectively (Fig. 1*D*). To understand if the association between in-field control and radiation dose was similar between histologies, subgroup analysis stratified by both histology (adenocarcinoma or squamous cell carcinoma) and prescription dose (cutoff of 110 Gy as described above) was performed and findings suggested clinically meaningful differences in in-field control between these two histologies ($p = 0.001$, Fig. 2*A*; Supplemental Fig. 5 in subgroup with minimum dose 100 Gy, $p = 0.0016$). A nomogram was constructed taking into account GTV, dose, and histology to predict 3-year in-field control (Supplemental Fig. 6*A*, AUC 0.79), provided by the following formula

$$\log \frac{p}{1-p} = \alpha + \beta_1 \times \textit{GTV volume} + \beta_2 \times \textit{Dose} + \beta_3 \times \textit{Histology}$$

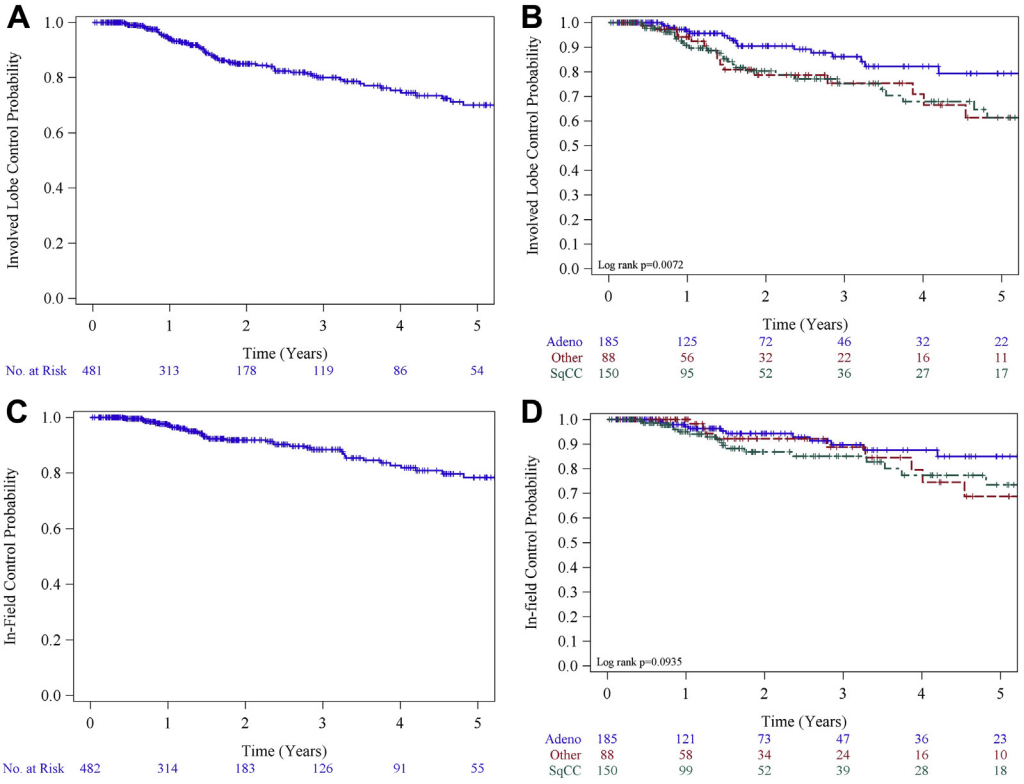

Figure 1. Involved lobe control for the dosimetric cohort (*A*) overall, and (*B*) stratified by histology. In-field control for the dosimetric cohort (*C*) overall, and (*D*) stratified by histology.

Table 3. Univariate and Multivariate Analysis for Involved Lobe and In-Field Failure in the Dosimetric Subset

	Involved Lobe Failure						In-Field Failure					
	UVA			MVA			UVA			MVA		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Previous NSCLC no versus yes	0.876	0.536-1.432	0.5972				0.803	0.433-1.488	0.4856			
Pathologic versus clinical diagnosis	1.790	0.776-4.126	0.1720				2.247	0.696-7.251	0.1756			
Age, y	1.000	0.992-1.008	0.9623				1.012	0.997-1.026	0.1140			
Prescription dose[a]	0.995	0.989-1.001	0.1087				0.987	0.979-0.996	**0.0033**	0.989	0.981-0.998	**0.0112**[b]
Prescription dose[a] $\leq$105 versus $>$ 105	1.352	0.766-2.385	0.2978				2.293	1.203-4.372	**0.0117**	1.854	0.906-3.793	0.0913[c]
Prescription dose[a] $\leq$110 versus $>$ 110	1.263	0.800-1.994	0.3166				2.355	1.273-4.356	**0.0063**	2.380	1.249-4.533	**0.0084**[d]
Minimum dose[a] to GTV	0.996	0.992-1.001	0.1452				0.991	0.984-0.997	**0.0060**	0.992	0.985-0.999	**0.0297**
Maximum dose[a] to GTV	0.997	0.993-1.001	0.1206				0.992	0.987-0.998	**0.0039**	0.993	0.987-0.998	**0.0111**
Mean dose[a] to GTV	0.997	0.993-1.001	0.1089				0.992	0.986-0.997	**0.0043**	0.993	0.988-0.998	**0.0093**
GTV	1.012	1.005-1.018	**0.0004**	1.01	1.003-1.016	**0.0044**	1.017	1.010-1.023	**<0.0001**	1.013	1.005-1.021	**0.0010**[b]
T stage			0.0527						**0.0063**			0.2879[b]
T1 versus T2	1.118	0.641-1.950					0.863	0.434-1.714		1.436	0.657-3.142	
T1 versus T3	0.247	0.077-0.797					0.144	0.044-0.475		0.501	0.118-2.129	
T2 versus T3	0.221	0.064-0.766					0.167	0.046-0.604		0.349	0.085-1.428	
Overall histology			**0.0095**			**0.0225**			0.1034			0.2314[b]
Adeno versus other	0.460	0.239-0.885		0.499	0.258-0.966		0.511	0.226-1.159		0.546	0.240-1.241	
Adeno versus SQCC	0.422	0.237-0.749		0.452	0.253-0.808		0.473	0.231-0.968		0.554	0.262-1.171	
Other versus SQCC	0.916	0.516-1.627		0.905	0.510-1.608		0.925	0.443-1.931		1.015	0.475-2.170	

Note: Bold text indicates statistically significant *p* values.

[a]Dose was converted to biologically effective dose using an α/β of 10.

[b]Multivariate models were constructed with GTV, T stage, histology, and one dosimetric factor (prescription dose [continuous], prescription dose [2 categorical cutoffs], and minimum, mean, or maximum dose to the GTV). HR and *p* value trends were similar for all MVAs performed, and only the HR, 95% CI, and *p* value for the model including prescription dose as a continuous variable are listed.

[c]The cutoff of 105 Gy was chosen based on data from Grills et al.[5]

[d]The cutoff of 110 Gy was chosen based on data from Stahl et al.[17] This cutoff also divides the four most common fractionation schedules in the study cohort into 3-fraction schedules and 4- and 5-fraction schedules.

UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval; GTV, gross tumor volume; Adeno, adenocarcinoma; SQCC, squamous cell carcinoma.

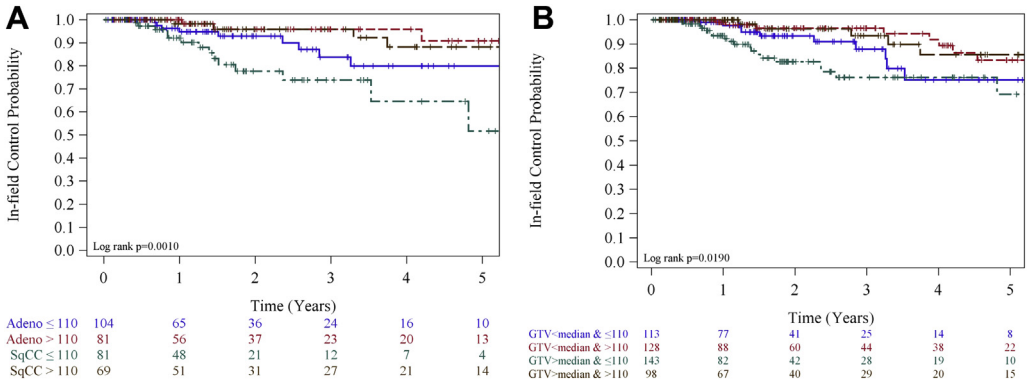

Figure 2. In-field control stratified by prescription dose (biologically effective dose, $\alpha/\beta = 10$, cutoff 110 Gy, no minimum limit) and (*A*) adenocarcinomas vs squamous cell carcinomas, or (*B*) median gross tumor volume.

where p is 3-year in-field control rate, $\alpha = -1.2542$, $\beta_1 = -0.0237$, $\beta_2 = 0.0259$, and $\beta_3 = -0.4679$. GTV volume is in milliters (mL), dose is prescription dose in BED_{10} Gy, and histology is 1 for squamous cell and 0 for adenocarcinoma. Calibration, validation, and internal validation values are summarized in Supplemental Figure 6*B–D*. A similar nomogram was built for involved lobe control (AUC 0.63).

Similar findings were noted in the entire 508-patient cohort, with 3-year in-field control of 91.0% (95% CI: 83.4%–95.2%), 85.6% (95% CI: 77.0%–91.1%), and 84.7% (95% CI: 72.2%–91.9%) for adenocarcinoma, squamous cell carcinoma, and other histologies, respectively (Supplemental Fig. 7). Within the subset of patients prescribed 12 Gy × 4 or 10 Gy × 5, in-field control was higher for adenocarcinomas than for squamous cell carcinomas (hazard ratio [HR] = 0.351, 95% CI: 0.129–0.953, $p = 0.04$), with 3-year in-field control of 88.9% and 78.5%, respectively ($p = 0.0317$). However, within the subset of patients prescribed 18 Gy or 20 Gy × 3, in-field control was not different between adenocarcinomas

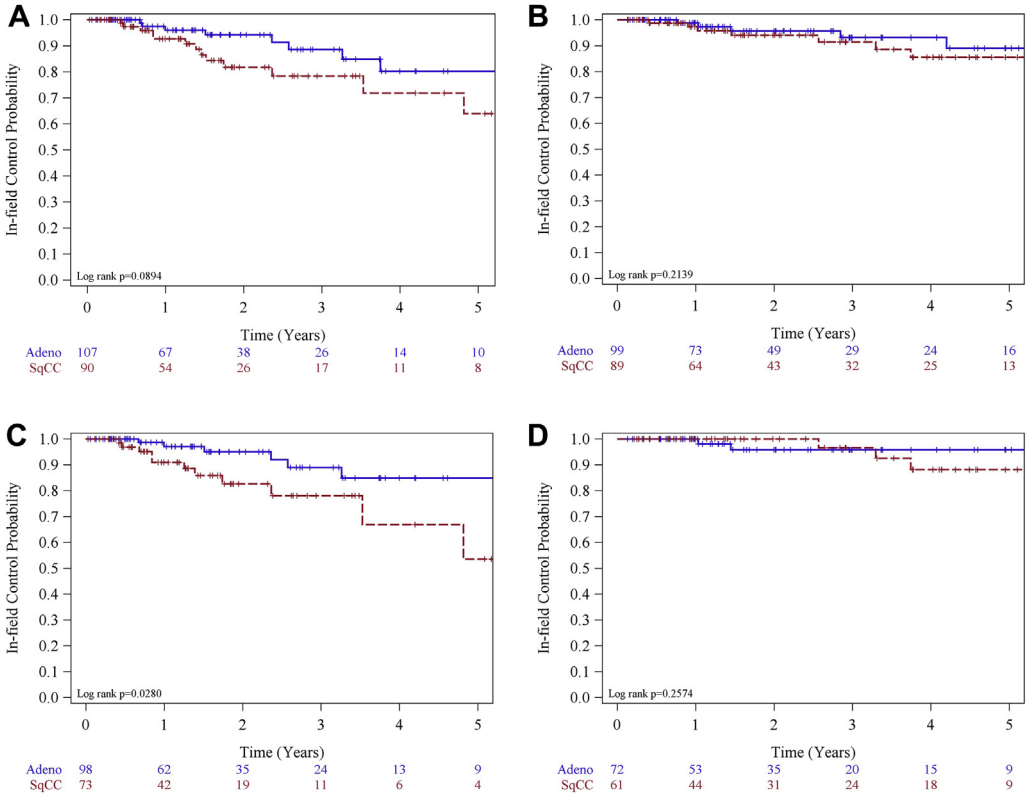

Figure 3. In-field control for adenocarcinomas versus squamous cell carcinomas in the study cohort, stratified by (*A*) 4- and 5-fraction, and (*B*) 3-fraction schedules, (*C*) 12 Gy × 4 and 10 Gy × 5 schedules, and (*D*) 18 Gy or 20 Gy × 3 schedules.

or squamous cell carcinomas (Fig. 3), suggesting the existence of a threshold dose between 105.6 Gy and 151.2 Gy (corresponding to 12 Gy × 4 and 18 Gy × 3) above which in-field control is independent of histology. These findings are further supported by propensity score matching analysis. When analyzed by histology (adenocarcinoma versus squamous cell carcinoma), in-field control did not differ by dose grouping (12 Gy × 4 or 10 Gy × 5 versus 18 Gy or 20 Gy × 3) for adenocarcinomas but was significantly worse for squamous cell carcinomas receiving 12 Gy × 4 or 10 Gy × 5 (HR = 3.96, 95% CI: 1.20–13.03, $p = 0.0238$). When analyzed by the dose groupings, in-field control did not differ by histology for 18 Gy or 20 Gy × 3 but was significantly worse for squamous cell carcinomas when treating to 12 Gy × 4 or 10 Gy × 5 (HR = 2.80, 95% CI: 1.03–7.60, $p = 0.043$).

Within the squamous cell carcinoma cohort, prescription dose was associated with worse in-field control when 110 Gy or less than when greater than 110 Gy (HR = 4.024, 95% CI: 1.468–11.031, $p = 0.0068$) (Fig. 2*A*). Multivariate analysis for in-field control confirmed the importance of prescription dose independent of GTV. Lower prescription dose (cutoff 110 Gy; HR = 3.621, 95% CI: 1.288–10.181, $p = 0.0147$) and increasing GTV (HR = 1.014 per mL, 95% CI: 1.005–1.022, $p = 0.0012$) were both independently associated with worse in-field control.[17] These results were similar when comparing outcomes after 10 Gy × 5 and 12 Gy × 4 versus 18 Gy or 20 Gy × 3 instead of using a cutoff of 110 Gy (univariate HR = 3.956, 95% CI: 1.201–13.032, $p = 0.0238$; multivariate including GTV HR = 3.530, 95% CI: 1.030–12.092, $p = 0.0447$). Within the adenocarcinoma cohort, there were no differences in in-field control according to dose using the above radiation dose groupings (cutoff 110 Gy, $p = 0.12$; 10 Gy × 5 and 12 Gy × 4 versus 18 Gy or 20 Gy × 3, $p = 0.31$).

Long-term survivors with documented follow-up of more than 5 years comprised 19.9% (n = 101) of our total study cohort. With respect to the analyzed patient, tumor, treatment, and dosimetric characteristics, long-term survivors were treated with higher doses (minimum dose to GTV $p = 0.0004$; mean dose to GTV $p = 0.0004$; and maximum dose to GTV $p = 0.0003$) as compared to the rest of the cohort. There was no difference in any of the other analyzed variables (notably GTV and histology) (Supplemental Table 5).

Discussion

This study cohort represents one of the largest series of NSCLC patients treated with SABR with one of the longest follow-ups. Our data suggests that radiation dose and GTV were independently associated with in-field failure and that histology and GTV were independently associated with involved lobe failure. Within the squamous cell carcinoma cohort, our data suggests that lower prescription dose was associated with increased in-field failure independent of GTV, a finding not observed in the adenocarcinoma cohort. To our knowledge, this is the first study to suggest a combined importance of GTV, radiation dose, and histology for local recurrence risk.

Several studies have examined the role of radiation dose in local control after SABR. Onishi et al.[21] published a retrospective series in 2007 of stage I NSCLC patients treated with SABR and identified a cutoff of 100 Gy prescription dose as associated with local failure. In this series, radiation was prescribed to isocenter and 100 Gy in this setting is more representative of a maximum dose to the GTV.[21] Grills et al.[5] reported in 2012 on patients treated with SABR that identified prescription dose and maximum dimension of the GTV to be independently predictive for local failure. Receiver operating characteristic (ROC) analysis identified the optimal predictive prescription dose cutoff as 105 Gy for local failure.[5] A similar publication also using ROC analysis by Kestin et al.[15] in 2014 identified prescription dose and mean dose to the PTV as most associated with local failure, with cutoffs of 105 Gy and 125 Gy, respectively. In 2016, Guckenberger et al.[18] reported on both patients treated for metastatic and primary NSCLC with SABR and identified that the dose to isocenter (i.e., maximum dose) to achieve 90% tumor control probability was 160 Gy and 176 Gy, respectively. Zhao et al.[22] reported in 2016 on 1092 patients with 1200 T1-T2N0M0 lesions treated with 12.5 Gy × 4 or 7 Gy × 10 fractions for those at higher risk of normal tissue toxicity. In this cohort, the 5-year in-field control rate was 93.8%, and ROC and competing risk multivariate analyses identified lower PTV dose to 95% of the volume and larger GTV as independently associated with worse in-field and involved lobe control.[22] Stahl et al.[17] reported in 2017 on 747 patients with 765 T1-T2N0M0 lung tumors treated with SABR and found that prescription dose cutoffs of both 105 Gy and 110 Gy were predictive for OS (and only 110 Gy was predictive for local failure). Most recently, Stephans et al.[23] reported that lesions treated with 3 fraction regimens (total dose 54 Gy or 60 Gy with or without heterogeneity corrections, respectively) had fewer local failures compared to lesions treated with 1, 4 to 5, or 8 to 10 fractions, at the cost of a possible crude increase in pulmonary and chest wall toxicity. This analysis did not account for differences in histology or tumor size/volume.[23]

Our study differs from the aforementioned analyses as it considers radiation dose, histology, and GTV in assessing local recurrence risk. In particular, partly based on previously discussed results, prescription dose cutoffs of 105 Gy and 110 Gy were assessed, and only a

prescription dose cutoff of 110 Gy was associated with in-field failure.[5,17] Prescription dose is not truly a continuous variable in our series given that 78.1% of the cohort received one of the four most common fractionation schedules, and 110 Gy separated the 10 Gy × 5 and 12 Gy × 4 from the 18 Gy and 20 Gy × 3 regimens. However, continuous variable analysis of minimum, maximum, and mean dose to the GTV and of prescription dose were all independently associated in separate analyses, strongly suggesting that increasing radiation dose is associated with decreasing in-field failure, independent of GTV, T stage, and histology.

In addition, data on the role of histology has only recently been published. Woody et al.[24] reported in 2017 on T1-T3N0M0 lung tumors treated with SABR and suggested that squamous histologic subtype was associated with local failure, with 3-year cumulative incidence of local failure of 18.9% versus 4.1% in squamous cell and adenocarcinoma lesions, respectively. Hörner-Rieber et al.[6] reported in 2017 on a smaller cohort with biopsy-proven T1-T3N0M0 lung tumors treated with SABR and similarly found histologic subtype to be associated with local failure. In particular, 2-year LC for adenocarcinoma and squamous cell carcinoma was greater than 96% and 81%, respectively. The most striking finding of this study was that patients with tumors treated to a total dose to the PTV isocenter of 150 Gy or greater (equivalent dose in 2 Gy fractions) did not exhibit a difference in control based on histology, suggesting that higher dose may potentially obviate the histologic impact.[6] Similarly, in our study, higher failure rates in squamous cell carcinomas are seen with lower prescription doses (i.e., $<$110 Gy), whereas such results were not observed for adenocarcinomas.

Furthermore, GTV has been reported previously in the context of dose but not histology. In particular, Modh et al.[30] reported in 2014 on a single-institution series of 125 patients treated for both primary NSCLC (n = 103) and metastatic lung tumors who received SABR for centrally located lesions and identified GTV (and not any of their dosimetric factors) as the sole factor associated with local failure. Our study suggests the importance of GTV is independent of dose, histology, and T stage in assessing recurrence risk.

Three-year involved lobe and in-field control in our study were 80.0% and 88.1%, respectively, and are comparable to other published reports, despite including 28.0% of patients treated in the setting of previously cured lung cancer.[2,7,24] Similarly, 3-year progression-free survival and OS rates were 37.2% and 49.4%, respectively, which was expected in a primarily medically inoperable patient population. The only factor associated with long-term survival beyond 5 years (19.9% of the cohort) was radiation dose (GTV minimum, mean, and maximum doses), emphasizing the importance of adequate dosing.

Limitations inherent in retrospective analyses also apply to our study. In particular, selection biases are difficult to control in the retrospective setting. Further, the execution of SABR in the Indiana University Health system evolved during the long 16-year timespan analyzed in this study. For dosimetric analysis, we attempted to control for lack of heterogeneity corrections by replanning all treatment plans that did not use a recent version of the AAA algorithm. Plans that already had been planned with an older version of AAA using heterogeneity corrections were not modified. External validation is needed for the generated nomogram. The strengths of this study include the long follow-up period and, to our knowledge, being the first study to consider GTV, dose to the GTV, and histology collectively as important factors to consider when exploring risk of recurrence.

In conclusion, to our knowledge this study is the first to suggest that GTV, dose to the GTV, and histology are all important risk factors for local recurrence after SABR. In particular, our data suggest that GTV is independently associated with both involved lobe and in-field failure, independent of T stage. Furthermore, our data suggest that radiation dose is independently associated with in-field failure, and that histology is independently associated with involved lobe failure. Our findings also suggest that patients with squamous cell carcinoma have higher failure rates at prescription doses less than 110 Gy independent of GTV and may need higher doses to achieve acceptable local control outcomes.

Our study is the third series reporting that LC for squamous cell carcinomas may be dependent on prescription dose or other dosimetric factors.[6,24] Current guidelines present common SABR prescription doses as equal options without specific preferences; in the absence of clinical trials or additional data to guide management, our series provides retrospective evidence that prescription doses of 110 Gy or more should be used, and lower prescription doses (i.e., 12 Gy × 4 or 10 Gy × 5) should be avoided for squamous cell carcinomas whenever safe. However, the optimal prescription dose remains to be determined and deserves study in a prospective trial.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of*

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