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Outcomes by Tumor Histology and *KRAS* Mutation Status After Lung Stereotactic Body Radiation Therapy for Early-Stage Non–Small-Cell Lung Cancer

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Abstract

We analyzed outcomes after lung stereotactic body radiotherapy (SBRT) for early-stage non–small-cell lung carcinoma in patients by histology and *KRAS* mutation status. Histology was not associated with outcomes, but *KRAS* mutation was associated with lower freedom from recurrence on univariable analysis and decreased cancer-specific survival on multivariable analysis. Given the small sample sizes, these results are hypothesis generating, and further study of SBRT outcomes by tumor genotype in larger data sets is needed.

Background—We analyzed outcomes after lung stereotactic body radiotherapy (SBRT) for early-stage non–small cell lung-carcinoma (NSCLC) by histology and *KRAS* genotype.

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Disclosure

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Patients and Methods—We included 75 patients with 79 peripheral tumors treated with SBRT (18 Gy $\times$ 3 or 10 to 12 Gy $\times$ 5) at our institution from 2009 to 2012. Genotyping for *KRAS* mutations was performed in 10 patients. Outcomes were analyzed by the Kaplan-Meier method/Cox regression, or cumulative incidence method/Fine-Gray analysis.

Results—The median patient age was 74 (range, 46 to 93) years, and Eastern Cooperative Oncology Group performance status was 0 to 1 in 63%. Tumor histology included adenocarcinoma (44%), squamous cell carcinoma (25%), and NSCLC (18%). Most tumors were T1a (54%). Seven patients had *KRAS*-mutant tumors (9%). With a median follow-up of 18.8 months among survivors, the 1-year estimate of overall survival was 88%, cancer-specific survival (CSS) 92%, primary tumor control 94%, and freedom from recurrence (FFR) 67%. In patients with *KRAS*-mutant tumors, there was a significantly lower tumor control (67% vs. 96%; $P = .04$), FFR (48% vs. 69%; $P = .03$), and CSS (75% vs. 93%; $P = .05$). On multivariable analysis, histology was not associated with outcomes, but *KRAS* mutation (hazard ratio, 10.3; 95% confidence interval, 2.3–45.6; $P = .0022$) was associated with decreased CSS after adjusting for age.

Conclusion—In this SBRT series, histology was not associated with outcomes, but *KRAS* mutation was associated with lower FFR on univariable analysis and decreased CSS on multivariable analysis. Because of the small sample size, these hypothesis-generating results need to be studied in larger data sets.

Keywords

Early stage; *KRAS*; Non–small-cell lung cancer; Stereotactic body radiotherapy

Introduction

Stereotactic body radiotherapy (SBRT) has emerged as the treatment of choice for medically inoperable stage I non–small-cell lung cancer (NSCLC) in the past decade. Multiple prospective^{1–3} and retrospective^{4–6} series of different SBRT regimens have demonstrated very high local control (80% to 90% at 2 to 3 years), high overall survival (OS) (50% to 60%), and cancer-specific survival rates (60% to 70%) compared to historical series of patients treated with conventionally fractionated radiotherapy (RT). However, in these series, both regional and distant recurrences remain an issue, with reported incidences of 5% to 13% and 14% to 25%, respectively.^{1,2,4,6} Thus, developing prognostic markers that identify patients at highest risk for recurrence after SBRT remains an important area for further research.

Alongside the emergence of SBRT technology, advances in cancer genomics in the last decade have identified genetically distinct subgroups of lung adenocarcinoma defined by mutations in oncogenes such as *v-Kiras2 Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) and *epidermal growth factor receptor* (*EGFR*).⁷ The unique biology of each genotypic subgroup has led to the development of personalized, genotype-directed therapy in the stage IV setting, resulting in the widespread adoption of clinical *EGFR* mutation testing and evidence that first-line *EGFR* tyrosine kinase inhibitor therapy results in improved outcomes.^{8–10}

However, the role of tumor genotype in earlier stages of disease remains understudied and controversial. *KRAS* mutation status has been studied extensively as both a prognostic factor and predictor of response to chemotherapy in stage I NSCLC patients with conflicting, inconclusive results.^{11–17} Furthermore, the radiation responsiveness and clinical outcomes after RT for the genotypic subgroups of NSCLC have not been well elucidated. Prior studies have shown possible associations between NSCLC genotype and response to RT. For example, retrospective series have demonstrated that patients with locally advanced *EGFR* mutant NSCLC had lower risk of locoregional failure compared to *EGFR* wild-type (WT) patients after chemotherapy and conventional RT,^{18–20} while patients with *KRAS*-mutant locally advanced NSCLC had decreased OS compared to those with *KRAS* WT tumors.¹⁹ However, it remains unclear if differences in radiation response by genotype is relevant at the higher doses delivered with SBRT.

Because patients receiving SBRT for stage I NSCLC typically have substantial medical comorbidities that often preclude adjuvant chemotherapy, this patient subset provides a unique population to study *KRAS* genotype as a potential prognostic marker. In this retrospective study, we build on these prior studies by performing an analysis of patients with stage I NSCLC treated with SBRT and analyzing outcomes after SBRT by tumor histology and *KRAS* genotype.

Materials and Methods

Patients

With institutional review board approval under a waiver of consent, we reviewed the records of 75 consecutive patients with newly diagnosed early-stage NSCLC treated with SBRT from 2009 to 2012 at our institution. Patients who received SBRT for locally recurrent disease, local progression of advanced stage disease, or metastases to the lung from other sites of primary disease were excluded.

Tumor Genotyping

Ten patients had their tumors genotyped for activating *KRAS* mutations as part of routine clinical care at the discretion of the treating physician, either in our institution's pathology department or in a commercial laboratory. Briefly, in all cases, DNA was isolated from tumor in paraffin-embedded tissue specimens and polymerase chain reaction using primers specific for codons 12, 13, and 61 of the *KRAS* gene was performed.²¹ The primer extension products were then analyzed by capillary gel electrophoresis. Only 1 patient's tumor sample underwent testing for *EGFR* mutation status, and none was tested for *ALK* mutation status. Thus, these tumor characteristics were not assessed.

Covariates

Pretreatment patient characteristics were collected, including age, sex, race, Eastern Cooperative Oncology Group performance status, and smoking history. Smoking status was categorized as: (1) never smokers (< 100 cigarettes in their lifetime); 2) former smokers (quit smoking > 1 year before diagnosis), and 3) current smokers (smoking at the time of diagnosis or had quit < 1 year before). Tumor characteristics were noted, including histology

and tumor, node, metastasis classification system stage according to the 7th edition of the American Joint Committee on Cancer staging manual. Treatment characteristics including SBRT prescribed dose, SBRT technique (conformal or volumetric modulated arc therapy), and biologically effective dose delivered were collected.

SBRT Treatment and Follow-up

All patients were treated with SBRT per institutional norms, which included (1) restriction of SBRT to peripheral tumors as defined in Radiation Therapy Oncology Group (RTOG) 0236;² (2) use of abdominal compression to restrict tumor motion < 1 cm; (3) 4-D computed tomographic planning to create an internal target volume; (4) 5 mm planning target volume margin with no clinical target volume margin; (5) dose of 10 to 12 Gy $\times$ 5 fractions for tumors close to the chest wall and 18 Gy $\times$ 3 fractions for all other tumors; and (6) daily setup and image-guided treatment with Exac Trac, cone-beam computed tomography (CT), and portal imaging using a linear accelerator.

Patients were followed every 3 to 4 months after treatment for the first 2 years with a chest CT, then every 6 months for the next 3 years, and annually thereafter.

Outcomes

OS, cancer-specific survival (CSS) and patterns of failure, including local tumor control (TC; absence of tumor recurrence in-field or within 1 cm of planning target volume), lobar control (LC; including local tumor control and absence of recurrence in the same lobe), regional control (RC; absence of hilar and mediastinal recurrences), local-regional control (LRC; composite end point of lobar and regional control), freedom from distant metastases (FFDM), freedom from any recurrence (FFR), and recurrence-free survival (survival with absence of LRR or DM) were calculated from the date of completion of SBRT treatment to the time of first failure.

CSS was defined as absence of death from NSCLC, and cause of death was ascertained by death certificates when available. In cases where death certificates were not available, death with active, progressing NSCLC and/or enrollment on hospice for NSCLC before death was considered death from NSCLC. TC and LC were defined on the basis of the definitions outlined in RTOG 0236. In brief, primary tumor failure was defined as (1) local enlargement defined as at least a 20% increase in the longest diameter of the gross tumor volume per CT scan and (2) evidence of tumor viability (either positron emission tomography [PET]-CT demonstrating ¹⁸F-fludeoxyglucose uptake of similar intensity as the pretreatment staging PET, or with pathologic confirmation via biopsy). Primary tumor failure included marginal failures occurring within 1 cm of the planning target volume (1.5 to 2.0 cm from the gross tumor volume). Failure beyond the primary tumor but within the involved lobe was also ascertained, and lobar control was defined as absence of primary tumor and/or involved lobe failure. Censoring for patients without disease progression was performed at the date of the last restaging study (any chest CT or PET-CT) without evidence of progression.

Statistical Analyses

Descriptive statistics were used to characterize patients at study entry. Differences in the distribution of categorical variables and continuous variables by *KRAS* mutation status were analyzed by the Fisher exact and Wilcoxon rank sum tests, respectively.

OS and all patterns of failure outcomes were analyzed by the Kaplan-Meier method and log-rank test. For the TC and LC end points, all tumors treated were included in the analysis, whereas the other end points were analyzed on a per-patient basis.

Cox regression analysis was performed to identify predictors of each outcome. Because the risk of failure was changed as a result of the administration of systemic treatment during the follow-up period, a Cox proportional hazards regression model with systemic treatment as a time-dependent covariate was used to evaluate the associations between patient/tumor characteristics and all patterns of failures. Gray's method was used to analyze time to first recurrence with death as a competing risk, and separately CSS with death of other causes as a competing risk. Univariable analysis was performed, and covariates with a *P* value less than .10 were included in the multivariable analysis. Backward selection was performed to select significant predictors of outcome on multivariable analysis. Competing risk analysis was performed by R 2.10.0, while all the other analyses were performed by SAS software, version 9.2 (SAS Institute, Cary, NC).

Results

Patients

A total of 75 patients with 79 early-stage NSCLC tumors treated by SBRT were included in the analysis. The pretreatment patient characteristics are shown in Table 1. Tumor histology included adenocarcinoma (44.3%), squamous cell carcinoma (25.3%), and NSCLC not otherwise specified (NOS; 17.7%), with 12.7% of patients treated based on a radiographic diagnosis. Of 10 patients who had tumor genotyping, 7 had *KRAS*-mutant tumors, and 3 were *KRAS* WT, including one with an *EGFR* mutation. The *KRAS* mutations were all in codon 12, including four c.34G>T (p.Gly12Cys), two c.35G>A (Gly12Asp), and one c.35G>T (p.Gly12Val).

Treatment

As shown in Table 1, all patients were treated with SBRT to a biologically effective dose of at least 100 Gy₁₀. Only 3 patients received chemotherapy, and all of these received induction chemotherapy with platinum doublets (1 *KRAS* mutant and 2 *KRAS* WT/unknown).

Outcomes

With a median follow-up of 18.8 months among survivors, the 1-year estimates of survival are shown in Table 2. The median survival was 26.6 months in all patients, and there was no significant difference in patients with *KRAS*-mutant tumors (median not reached) versus with *KRAS*-WT/unknown tumors (median 26.6 months; *P* = .51). CSS was significantly lower in patients with *KRAS*-mutant tumors versus WT/unknown on a competing risk

analysis with death due to other causes as a competing risk (Figure 1; hazard ratio [HR], 4.6; 95% confidence interval [CI], 1.1–19.7; $P = .04$).

Patterns of Recurrence

The 1-year estimates of patterns of recurrence are shown in Table 2. There were 3 primary tumor recurrences and an additional 3 intralobar recurrences with 1-year TC estimate of 94.2% and 1-year LC estimate of 88.9%. There were 12 nodal recurrences with a 1-year RC estimate of 81.2%, and the 1-year LRC estimate was 74.3%. Seventeen patients had a distant recurrence with a 1-year FFDM estimate of 72.8%. Sites of distant recurrence included brain ($n = 3$), bone ($n = 5$), liver ($n = 2$), multifocal lung ($n = 5$), pleural effusion ($n = 1$), and abdominal lymph nodes ($n = 1$). There were a total of 22 local and/or distant recurrences with 1-year estimate of FFR of 66.7% and median time to any recurrence of 27.2 months. Three patients were diagnosed with a second primary lung tumor, with a 1-year estimate of 3.7%.

Outcomes and Patterns of Recurrence by Histology

Comparing the patterns of recurrence in tumors treated without a biopsy (ie, treated with a radiographic/clinical diagnosis alone; $n = 10$) versus those with biopsy-proven NSCLC ($n = 69$), there was no statistically significant difference in TC (100% vs. 93.3%; $P = .51$), LC (100% vs. 87.3%; $P = .35$), RC (77.1% vs. 82.0%; $P = .74$), LRC (77.1% vs. 72.4%; $P = .83$), FFDM (61.7% vs. 74.4%; $P = .66$), or FFR (61.7% vs. 67.3%; $P = .94$).

There was also no significant difference in patterns of recurrence when comparing adenocarcinoma ($n = 35$) versus squamous cell carcinoma ($n = 20$), versus NSCLC NOS ($n = 14$), histology with 1-year estimates as follows: TC (85.4% vs. 100% vs. 100%; $P = .15$), LC (82.6% vs. 85.1% vs. 100%; $P = .36$), RC (79.4% vs. 77.3% vs. 92.3%; $P = .51$), LRC (67.5% vs. 64.9% vs. 92.3%; $P = .25$), or FFDM (61.5% vs. 84.6% vs. 84.6%; $P = .32$), or FFR (59.2% vs. 64.9% vs. 84.6%; $P = .35$). Nor was there a significant difference in the pairwise comparisons between the 3 histologic groups (P values not shown).

However, in comparing tumors with adenocarcinoma histology ($n = 35$) versus those with either SCC or NSCLC NOS histology ($n = 34$), there was a trend toward decreased TC in adenocarcinomas (85.4% vs. 100%; $P = .053$), and all primary tumor failures occurred in tumors of adenocarcinoma histology. However, there was no significant difference in LC (82.6% vs. 91.5%; $P = .28$), RC (79.4% vs. 84.2%; $P = .34$), LRC (67.5% vs. 76.7%; $P = .22$), FFDM (61.5% vs. 85.6%; $P = .13$), or FFR (59.2% vs. 74.1%; $P = .23$) for adenocarcinoma versus other histologies.

Outcomes and Patterns of Recurrence by *KRAS* Mutation Status

There was no statistically significant difference in OS or recurrence-free survival when comparing *KRAS*-mutant versus *KRAS*-WT/unknown status (Table 2), but there was a difference in CSS on competing risk analysis, with more deaths due to cancer among patients with *KRAS* mutations (1-year estimate: 75.0% vs. 93.3%; $P = .05$). As shown in Table 2, there was both decreased TC ($P = .04$) and FFR ($P = .03$) for *KRAS*-mutant tumors

versus those with *KRAS*-WT/unknown status. The patterns of recurrence including sites of first recurrence are shown in Table 3.

Univariable and Multivariable Analysis

On univariable analysis, there were no clinical, pathologic nor treatment features associated with primary TC, LC, RC, or LRC. *KRAS* mutation status was not significantly associated with LC, RC, or LRC, but there was a trend for decreased primary TC (HR, 8.0; 95% CI, 0.82–78.4; $P = .07$). On multivariable analysis with backward selection, no variables were associated with any of these local and/or regional recurrence end points. Neither univariable nor multivariable analysis with backward selection identified any clinical variables associated with risk of distant recurrence.

However, univariable analysis of any recurrence demonstrated that *KRAS* mutation status was associated with increased incidence of any recurrence (HR, 3.2; 95% CI, 1.1–9.6; $P = .04$; Table 4). However, no variables were associated with FFR on multivariable analysis with backward selection.

On univariable and multivariable analysis of CSS with death of other causes as a competing risk, presence of *KRAS* mutation was associated with increased risk of death from lung cancer (HR, 10.3; 95% CI, 2.3–45.6; $P = .0022$), after adjusting for age (Table 5; Figure 1).

Discussion

In this study of patients treated with SBRT for early-stage NSCLC, we demonstrate high primary TC and OS with the predominant sites of failure in regional nodes or distant sites, which is comparable to previously published series.^{1,2,6} We performed subgroup analyses to determine whether tumor biology as reflected by tumor histology or genotype was associated with outcomes after SBRT. We demonstrated that tumor histology was not associated with local, regional or distant recurrence, but *KRAS* mutation status was associated with decreased TC and FFR on univariable analysis, and decreased CSS on multivariable analysis.

Prior SBRT series have shown an association between adenocarcinoma histology and increased risk of distant metastases,² but few have studied association between NSCLC histology and TC. In our series, there was no clear association between TC and histology, but primary tumor recurrences occurred in only patients with adenocarcinoma histology. The high biologically equivalent dose delivered with SBRT and the low incidence of local failure events likely minimizes the likelihood of detecting a histologic difference in radiosensitivity, particularly in small series. Further study of TC by tumor histology will likely require pooled analyses of larger SBRT data sets.

The most interesting finding of this study was an association between *KRAS* mutation status with FFR and CSS. The role of *KRAS* mutation status as a potential prognostic and predictive marker for early-stage NSCLC remains controversial. A recent pooled analysis of multiple adjuvant chemotherapy trials demonstrated that *KRAS* mutation status was not prognostic, but codon 13 *KRAS* mutation was possibly predictive of decreased response to

chemotherapy (HR, 5.78; 95% CI, 2.06–16.2; $P < .001$; interaction $P = .002$).¹⁵ In our study, there was no clear association between primary TC and *KRAS* mutations status, but the high dose delivered with SBRT may obscure any underlying variability in radiation responsiveness that may be imparted by tumor genotype, and the low number of primary tumor recurrence events with SBRT also reduces the power to detect any such association. However, our study demonstrated an association between *KRAS* mutation status and both CSS and risk of any recurrence. However, given the small sample size, this hypothesis-generating result must be further studied in a larger data set before *KRAS* genotype can be utilized as a prognostic biomarker among patients treated with SBRT. Because our study and other published SBRT series demonstrate that distant metastases and regional nodes are the predominant sites of failure,^{1–3,6} potential biomarkers such as *KRAS* mutation status that identify patients at high risk for such recurrence may help guide the use of adjuvant therapy, and may be particularly important in the medically ill subset of patients treated with SBRT.

One of the main limitations of this study was incomplete genotyping. There is a possibility that incomplete genotyping may introduce bias, but because *KRAS* mutations are present in approximately 20% of adenocarcinomas, it is likely that the incomplete genotyping would bias the results toward the null because there would be patients with undetected *KRAS* in the control group. Another unusual finding was the high incidence of *KRAS* mutations (70%; $n = 7$) in the subset of patients ($n = 10$) who had tumor genotyping, which may have been due to chance or possibly due to the heavy smoking history in this patient population ($> 95\%$ were smokers with median 50 pack-years' history). Thus, the association between outcomes and *KRAS* mutation status must be interpreted with caution due the potential for confounding given the unexpectedly high incidence of *KRAS* mutation in the genotyped cohort, and the association between *KRAS* mutation and larger tumor size in this study.

Additionally, less common genotypic subgroups such as patients with *EGFR*-mutant or *ALK*-translocated tumors could not be analyzed in this cohort due to small numbers and lack of testing, which was not clinically indicated due to the low incidence of alterations of these genes in a group of patients with heavy smoking. Similarly, this study was conducted in an era where clinical genotyping involved only a limited panel of genes (*KRAS*, *EGFR*, and *ALK*), and thus mutations in genes that are known to alter the underlying biology of *KRAS* mutant tumors such as *LKB1* and *p53* were not genotyped.²² Clearly, further studies analyzing outcomes after SBRT by genotyping *KRAS* and a more comprehensive set of associated genes are needed, but this attempt may be limited by the difficulty of obtaining sufficient tumor samples in the medically inoperable subset of patients with NSCLC. For instance, in this study, the majority of patients underwent fine-needle aspiration, which precluded additional genetic analyses. Additionally, as a result of concerns for significant potential biopsy-related morbidity (eg, pneumothorax) among these medically ill patients, many patients treated with SBRT do not receive a pathologic diagnosis but are treated on the basis of a radiographic diagnosis only.⁶ This underscores the need for cooperation and coordination between multiple centers to comprehensively genotype patients undergoing SBRT who have biopsy specimens available.

Conclusion

In this series of patients with medically inoperable early-stage NSCLC who were treated with SBRT, there was no significant difference in outcomes by histology. A small *KRAS*-mutant subgroup had a significantly higher risk of recurrence on univariable analysis and cancer-specific mortality on multivariable analysis compared to patients with WT or unknown *KRAS* status. Differences in outcomes after SBRT by *KRAS* genotype is worthy of further study, but further study may be limited by the difficulty of obtaining sufficient tumor samples in this medically inoperable subset of patients with NSCLC.

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Clinical Practice Points

- SBRT remains an important treatment for early-stage NSCLC.
- Tumor genotyping of patients with NSCLC may yield further insight into radiation response of molecular subtypes of NSCLC and provide information for future trials of adjuvant or salvage targeted therapies in high-risk patients.

Figure 1.

Outcomes by *KRAS* Mutation Status Including: (A) Kaplan-Meier Plot of OS; (B) Kaplan-Meier Plot of Freedom From Any Recurrence; (C) Cumulative Incidence Plot of Death Due to Cancer With Death Due to Other Causes as a Competing Risk

Table 1**Patient, Tumor, and Treatment Characteristics**

Characteristic	All Patients (n = 75)	KRAS Mutant Patients (n = 7)	KRAS WT/Unknown Patients (n = 68)	P
Age, years, median (range)	74 (46–93)	73 (46–82)	74 (51–93)	.75
Gender				.45
Male	34 (45.3%)	2 (28.6%)	32 (47.1%)	
Female	41 (54.7%)	5 (71.4%)	36 (52.9%)	
Race				.09
White	69 (92.0%)	5 (71.4%)	64 (94.1%)	
Black	5 (6.7%)	2 (28.6%)	3 (4.4%)	
Asian	1 (1.3%)	0 (0.0%)	1 (1.5%)	
Performance Status				.28
0	13 (17.3%)	2 (28.6%)	11 (16.2%)	
1	34 (45.3%)	4 (57.1%)	30 (44.1%)	
2	20 (26.7%)	0 (0.0%)	20 (29.4%)	
3–4	8 (10.7%)	1 (14.3%)	7 (10.3%)	
Smoking				.07
Current	18 (24.0%)	0 (0.0%)	18 (26.5%)	
Former	55 (73.3%)	6 (85.7%)	49 (72.1%)	
Never	2 (2.7%)	1 (14.3%)	1 (1.5%)	
Pack-years	50 (3–150)	45 (20–65)	50 (3–150)	.44
FEV ₁ , L ^a	1.45 (0.52–3.35)	1.93 (0.78–2.70)	1.42 (0.52–3.35)	.42
Predicted FEV ₁ , %	65.0% (20%–141%)	93% (30%–141%)	64% (20%–111%)	.19
DLCOb	9.51 (0.87–22.57)	15.76 (11.19–20.33)	9.34 (0.87–22.57)	.14
Predicted DLCO, %	48.0% (5.0%–142.0%)	108.0% (69.0%–142.0%)	47.0% (5.0%–125.0%)	.004

Tumor Characteristics	All Tumors (n = 79)	KRAS Mutant Tumors (n = 7)	KRAS WT/UNK Tumors (n = 72)	P
Clinical T Stage				.04
T1a	43 (54.4%)	2 (28.6%)	41 (56.9%)	
T1b	22 (27.8%)	1 (14.3%)	21 (29.2%)	
T2a	13 (16.5%)	4 (57.1%)	9 (12.5%)	
T2b	1 (1.3%)	0 (0.0%)	1 (1.4%)	
Overall Stage				.02
IA	65 (82.3%)	3 (42.9%)	62 (86.1%)	
IB	13 (16.5%)	4 (57.1%)	9 (12.5%)	
IIA	1 (1.3%)	0 (0.0%)	1 (1.4%)	
Tumor Location				.54
RUL	19 (24.1%)	2 (28.6%)	17 (23.6%)	
RML	7 (8.9%)	1 (14.3%)	6 (8.3%)	

Tumor Characteristics	All Tumors (n = 79)	KRAS Mutant Tumors (n = 7)	KRAS WT/UNK Tumors (n = 72)	P
RLL	20 (25.3%)	3 (42.9%)	17 (23.6%)	
LUL	16 (20.2%)	0 (0.0%)	16 (22.2%)	
LLL	17 (21.5%)	1 (14.3)	16 (22.2%)	
Histology				.12
Adenocarcinoma	35 (44.3%)	6 (85.7%)	29 (40.3%)	
Squamous cell	20 (25.3%)	0 (0.0%)	20 (27.8%)	
NSCLC NOS	14 (17.7%)	1 (14.3%)	13 (18.1%)	
None ^c	10 (12.7%)	0 (0.0%)	10 (13.9%)	
Tumor Grade				.005
No grade reported	56 (70.9%)	2 (28.6%)	54 (75.0%)	
1	5 (6.3%)	2 (28.6%)	3 (4.2%)	
2	10 (12.7%)	3 (42.9%)	7 (9.7%)	
3	8 (10.1%)	0 (0.0%)	8 (11.1%)	
Tumor Genotype				
KRAS mutant	7 (8.9%)	7 (100%)	0 (0.0%)	
KRAS wild type	2 (2.5%)	0 (0.0%)	2 (2.8%)	
KRAS unknown	69 (87.3%)	0 (0.0%)	69 (95.8%)	
EGFR mutant	1 (1.3%)	0 (0.0%)	1 (1.4%)	
Clinical tumor size	1.9 (0.7–5.5)	3.4 (1.2–4.2)	1.9 (0.7–5.5)	.09
Pretreatment SUV _{max} ^d	5.8 (1.0–21.7)	5.7 (1.4–21.7)	5.7 (1.0–19.0)	.79
Nodal Staging				.58
PET only	66 (83.5%)	7 (100.0%)	59 (81.9%)	
Mediastinoscopy or EBUS	13 (16.5%)	0 (0.0%)	13 (18.1%)	
Mediastinoscopy	10 (12.7%)	0 (0.0%)	10 (13.9%)	
EBUS	3 (3.8%)	0 (0.0%)	3 (4.2%)	
Treatment Characteristics				
SBRT Technique				1.0
Conformal	65 (82.3%)	6 (85.7%)	59 (81.9%)	
VMAT	14 (17.7%)	1 (14.3%)	13 (18.1%)	
Prescribed radiation dose, Gy, median (range)	54 (48–60)	54 (50–60)	54 (48–60)	1.0
Prescribed dose per fraction, Gy, median (range)	18 (10–19.7)	12 (10–18)	18 (11–19.7)	.15
Delivered BED, Gy ₁₀ , median (range)	151.2 (100–175.5)	132.0 (100–151.2)	151.2 (105.6–175.5)	.16
Chemotherapy				.25
Induction	3 (3.8%)	1 (14.3%)	2 (2.8%)	
None	76 (96.2%)	6 (85.7%)	70 (97.2%)	

Data are presented as median (range) or n (%).

Abbreviations: BED = biologically effective dose; DLCO = diffusion capacity of the lung for carbon monoxide; EBUS = endobronchial ultrasound-guided biopsy; FEV1 = forced expiratory volume in 1 second; LLL = left lower lobe; LUL = left upper lobe; NOS = not otherwise

specified; NSCLC = non-small-cell lung cancer; PET = positron emission tomography; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SUVmax = Maximum standardized uptake value; VMAT = volumetric modulated arc therapy; WT = wild type.

^a n = 71 (n = 7 and 64 for *KRAS* mutant and WT, respectively).

^b n = 45 (n = 2 and 43 for *KRAS* mutant and WT, respectively).

^c Radiographic diagnosis.

^d n = 64 (n = 5 and 59 for *KRAS* mutant and WT, respectively)

Table 2One-Year Estimates of Survival and Pattern of Recurrence by *KRAS* Mutation Status

Characteristic	All (n = 75)	<i>KRAS</i> Mutant (n = 7)	<i>KRAS</i> WT/Unknown (n = 68)	<i>P</i>
Overall survival	87.7% (28)	75.0% (2)	88.5% (26)	.51
Cancer-specific survival	92.2% (11)	75.0% (2)	93.3% (9)	.05
Recurrence-free survival	65.7% (38)	47.6% (4)	67.5% (34)	.14
Freedom from distant metastases	72.8% (17)	57.1% (2)	74.1% (15)	.37
Freedom from recurrence	66.7% (22)	47.6% (4)	68.7% (18)	.03
Regional control	81.2% (12)	85.7% (2)	81.2% (10)	.26
Locoregional control	73.0% (17)	57.1% (3)	74.2% (14)	.10
	All (n = 79)	<i>KRAS</i> Mutant (n = 7)	<i>KRAS</i> WT/Unknown (n = 72)	<i>P</i>
Primary tumor control	94.2% (3)	66.7% (1)	95.9% (2)	.04
Lobar control ^a	88.9% (6)	66.7% (1)	90.2% (5)	.27

Abbreviation: WT = wild type.

^aIncludes both primary tumor control and lack of recurrence in the originally involved lobe.

Table 3

Patterns of Recurrence

Characteristic	All Patients (n = 75)	<i>KRAS</i> Mutant (n = 7)	<i>KRAS</i> WT/Unknown (n = 68)
Site of First Recurrence			
Locoregional	7	2	5
Distant	5	1	4
Both locoregional and distant	10	1	9
Second primary lung tumor	4	0	4
Any Recurrence			
Locoregional only	5	2	3
Distant only	5	1	4
Both locoregional and distant	12	1	11

Abbreviation: WT = wild type.

Table 4

Univariable Cox Proportion Hazard Analyses for Freedom From Any Recurrence

Covariate	n	Univariable HR, (95% CI)	P
Age			
<75 year	39	1.74 (0.73–4.17)	.21
75 year	36	1.0	
Performance Status			
0–1	47	1.0	
2–4	28	0.74 (0.28–1.91)	.53
Smoking Status			
Current	18	1.11 (0.41–3.02)	.84
Former/never	57	1.0	
KRAS Status			
Mutant	7	3.22 (1.07–9.64)	.04
WT/unknown	68	1.0	
Histology (n = 65)			
Adenocarcinoma	32	1.0	
SCC/NSCLC	33	0.58 (0.23–1.44)	.24
Histology (n = 65)			
Adenocarcinoma/NSCLC	46	1.0	
SCC	19	0.94 (0.36–2.49)	.90
Tumor Grade			
1, 2, unknown	67	1.0	
3	8	2.52 (0.73–8.68)	.14
Maximum Clinical Tumor Size			
2 cm	36	0.60 (0.26–1.43)	.25
<2 cm	39	1.0	
Lower Lobe Tumor			
No	41	1.0	
Yes	34	1.10 (0.48–2.55)	.82
Pre-SBRT SUV_{max}			
>5.8	30	1.21 (0.49–2.98)	.68
5.8	30	1.0	
T Stage			
T1	62	1.0	
T2	13	1.82 (0.71–4.69)	.21
Surgical Nodal Staging			
No	63	1.0	
Yes	12	0.42 (0.10–1.82)	.25

Covariate	n	Univariable HR, (95% CI)	P
Prescribed Radiation Dose			
>54 Gy	27	0.77 (0.31–1.90)	.57
54 Gy	48	1.0	
Biologically Equivalent Dose			
151.2	47	0.88 (0.37–2.06)	.76
<151.2	28	1.0	
Radiation Technique:			
Conformal	62	1.0	
VMAT	13	0.39 (0.09–1.68)	.21

Abbreviations: CI = confidence interval; HR = hazard ratio; NSCLC = non–small-cell lung cancer; SBRT = stereotactic body radiotherapy; SCC = squamous cell carcinoma; VMAT = volumetric modulated arc therapy; WT = wild type.

Table 5
Unadjusted and Adjusted Hazard Ratios on Competing Risk Analyses for Risk of Cancer-Specific Survival

Covariate	n	Univariable		Multivariable Adjusted	
		HR, (95% CI)	P	HR, (95% CI)	P
Age					
<75 years	39	3.18 (0.87–11.6)	.08	5.08 (1.22–21.1)	.025
75 years	36	1.0 ^a	—	1.0 ^a	—
Performance Status					
0–1	47	1.0 ^a	—		
2–4	28	0.29 (0.06–1.35)	.11		
Smoking Status					
Current	18	1.02 (0.30–3.43)	.98		
Former/never	57	1.0 ^a			
KRAS Status					
Mutant	7	4.59 (1.07–19.7)	.04	10.25 (2.31–45.6)	.0022
WT/unknown	68	1.0 ^a	—	1.0 ^a	—
Histology (N = 65)					
Adenocarcinoma	32	1.0 ^a	—		
SCC/NSCLC	33	0.62 (0.17–2.26)	.47		
Histology (N = 65)					
Adenocarcinoma/NSCLC	46	1.0 ^a	—		
SCC	19	0.59 (0.14–2.53)	.48		
Tumor Grade					
1, 2, unknown	67	1.0 ^a	—		
3	8	1.35 (0.32–5.72)	.68		
Maximum Clinical Tumor Size					
2 cm	36	0.48 (0.15–1.59)	.23		
<2 cm	39	1.0 ^a			

Covariate	n	Univariable		Multivariable Adjusted	
		HR, (95% CI)	P	HR, (95% CI)	P
Lower Lobe Tumor					
No	41	1.0 ^a	—		
Yes	34	2.69 (0.82–8.8)	.1		
Pre-SBRT SUV _{max} (n = 60)					
>5.8	30	1.09 (0.31–3.92)	.89		
5.8	30	1.0 ^a	—		
T Stage					
T1	62	1.0 ^a			
T2	13	1.14 (0.25–5.22)	.87		
Surgical Nodal Staging					
No	63	1.0 ^a			
Yes	12	0.52 (0.08–3.29)	.49		
Prescribed Radiation Dose					
>54 Gy	27	0.62 (0.17–2.36)	.49		
54 Gy	48	1.0 ^a	—		
Biologically Equivalent Dose					
151.2	47	1.01 (0.30–3.42)	.99		
<151.2	28	1.0 ^a	—		
Radiation Technique					
Conformal	62	1.0 ^a	—		
VMAT	13	0.96 (0.21–4.42)	.96		

Abbreviations: CI = confidence interval; HR = hazard ratio; NSCLC = non-small-cell lung cancer; SBRT = stereotactic body radiotherapy; SCC = squamous cell carcinoma; VMAT = volumetric modulated arc therapy; WT = wild type.

^aReference group.