Lung Adenocarcinoma: Predictive Value of *KRAS* Mutation Status in Assessing Local Recurrence in Patients Undergoing Image-guided Ablation[1]

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Purpose: To establish the relationship between *KRAS* mutation status and local recurrence after image-guided ablation of lung adenocarcinoma.

Materials and Methods: This study consisted of a HIPAA-compliant institutional review board–approved retrospective review of 56 primary lung adenocarcinomas in 54 patients (24 men, 30 women; median age, 72 years; range, 54–87 years) treated with percutaneous image-guided ablation and with available genetic mutational analysis. *KRAS* mutation status and additional clinical and technical variables—Eastern Cooperative Oncology Group (ECOG) status, smoking history, stage at diagnosis, status (new primary or not), history of radiation, history of surgery, prior systemic treatment, modality of ablation, size of nodule, ablation margin, and presence of ground-glass appearance—were recorded and evaluated in relation to time to local recurrence, which was calculated from the time of ablation to the first radiographic evidence of recurrence. Predictors of outcome were identified by using a proportional hazards model for both univariate and multivariate analysis, with death as a competing risk.

Results: Technical success was 100%. Of the 56 ablated tumors, 37 (66%) were wild type for *KRAS* and 19 (34%) were *KRAS* mutants. The 1-year and 3-year cumulative incidences of recurrence were 20% and 35% for wild-type *KRAS* compared with 40% and 63% for *KRAS* mutant tumors. *KRAS* mutation status was a significant predictor of local recurrence at both univariate (P = .05; subdistribution hazard ratio [sHR], 2.32) and multivariate (P = .006; sHR, 3.75) analysis. At multivariate analysis, size (P = .026; sHR, 2.54) and ECOG status (P = .012; sHR, 2.23) were also independent significant predictors, whereas minimum margin (P = .066) was not.

Conclusion: The results of this study show that there is a relationship between *KRAS* mutation status and local recurrence after image-guided ablation of lung adenocarcinoma. Specifically, *KRAS* mutation status of the ablated lesion is a significant predictor of time to local recurrence, independent of size and margin.

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Lung cancer is the leading cause of cancer death in male and female patients in the United States (1). Non–small cell lung cancer (NSCLC) accounts for a majority of these cases, and the standard treatment for early-stage NSCLC is surgical resection. However, 25% of these patients are not surgical candidates because of medical comorbidities (2,3). In such patients, local-directed therapies such as stereotactic body radiation therapy (SBRT) and percutaneous image-guided ablation (PIA) may be offered (4). PIA includes radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CRA), and others.

Indications for PIA for NSCLC include patients with high-risk or unresectable disease and patients with recurrent or persistent disease despite treatment with surgery, radiation, or chemotherapy. Overall 2-year survival rates of approximately 70% for PIA appear to be similar to those for SBRT (5,6) and surgery after propensity score matching. Moreover, a multicenter trial (7) demonstrated no significant worsening of pulmonary function after PIA. Ongoing prospective clinical trials comparing the efficacy of SBRT, PIA, and surgery in patients with high risk aim to improve patient selection for each modality (8).

Various predictors of PIA success have been demonstrated in the literature. These include tumor-associated features such as tumor size (9,10) and technique-associated features such as ablation margin (9). Kodama et al (11) recently demonstrated excellent local tumor control for patients with ground-glass opacity–dominant lung adenocarcinoma. Ridge et al (12) showed improved local tumor control for metachronous and synchronous tumors compared with first primary lung cancers. To our knowledge, the role of biomarkers in predicting local recurrence in PIA has not been studied.

Lung adenocarcinomas are associated with several clinically important oncogenic driver mutations, although their prognostic role remains controversial. In a large meta-analysis, *KRAS* mutation status was associated with worse survival in patients with NSCLC (hazard ratio [HR], 1.35; 95% confidence interval [CI]: 1.16, 1.56) (13). However, D'Angelo et al (14) demonstrated similar overall survival rates between patients with *KRAS* mutations and patients with wild-type *KRAS* or wild-type *EGFR*. The impact of *KRAS* mutations on recurrence and survival has also been studied in relation to surgery (15) and SBRT (16). Given the high local recurrence rates with PIA (6), the role of these driver mutations may help better define cohorts appropriate for PIA or high-risk cohorts that may require more extensive ablation.

The purpose of our study was to establish the relationship between *KRAS* mutation status and local recurrence after image-guided ablation of lung adenocarcinoma. Our hypothesis was that *KRAS* mutation status is a predictor of local recurrence, independent of established clinical and technical variables such as size and margin.

Advances in Knowledge

- *KRAS* mutation status was significantly predictive of local recurrence at univariate ($P = .05$) and multivariate ($P = .006$) analysis.
- *KRAS* mutant cumulative incidence of recurrence at 1 year was 40% (65% at 3 years), compared with 20% (35% at 3 years) for wild-type *KRAS*.
- Size ($P = .026$) and Eastern Cooperative Oncology Group status ($P = .012$) were also independently predictive of local recurrence, whereas ablation margin ($P = .066$) was not.

Implications for Patient Care

- *KRAS* mutation status should be checked in lung adenocarcinomas undergoing ablation, as these tumors are more likely to recur even if they are small.
- *KRAS* mutant tumors may require wider ablation margins or more careful monitoring after ablation.

Materials and Methods

Study Design

This was a retrospective study that included consecutive patients who underwent PIA of a lung adenocarcinoma and mutational analysis of the ablated tumor. The study was approved by the institutional review board, with a waiver of informed consent, and was compliant with the Health Insurance Portability and Accountability Act.

Patient Selection

We performed an institutional database search that included consecutive patients from January 1, 2009, through July 1, 2014. Inclusion criteria were any patients who had undergone PIA for a lung tumor and had also undergone genetic testing ($n = 291$). We excluded patients who did not have pathologically proven lung adenocarcinoma (203 patients excluded; 88 patients remaining). We excluded patients if genetic testing was performed on a tumor other than the one that was ablated (20 patients excluded, 68 remaining). Metachronous tumors

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Abbreviations:
CI = confidence interval
CRA = cryoablation
ECOG = Eastern Cooperative Oncology Group
HR = hazard ratio
MWA = microwave ablation
NSCLC = non–small cell lung cancer
PIA = percutaneous image-guided ablation
RFA = radiofrequency ablation
SBRT = stereotactic body radiation therapy

Author contributions:
Guarantors of integrity of entire study, E.Z., S.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, E.Z., H.Y., E.N.P., S.G., C.T.S.; clinical studies, E.Z., J.P.E., S.G., C.T.S., D.R.J., S.B.S.; experimental studies, S.G., S.B.S.; statistical analysis, E.Z., S.G., W.S.; and manuscript editing, E.Z., J.P.E., H.Y., F.E.B., E.N.P., S.G., C.T.S., D.R.J., C.M.R., S.B.S.

Conflicts of interest are listed at the end of this article.

Figure 1

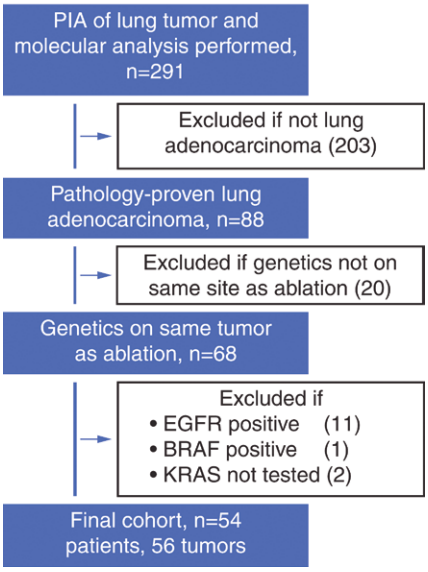

Figure 1: Flow diagram of patient selection and exclusion criteria.

were defined on the basis of published criteria (17). From among the remaining patients, we excluded those who harbored a known oncogenic driver mutation other than *KRAS* (11 patients with *EGFR* mutation excluded, one patient with *BRAF* mutation excluded) and those in whom the *KRAS* mutation was not tested (two patients excluded). The final cohort included 56 tumors in 54 patients (two patients each had two separate tumors that were ablated and analyzed for mutations). A flowchart summarizing initial patient population and each exclusion step is included in Figure 1.

Lung Ablation

The decision to perform PIA was made by the interventional radiologist in conjunction with the medical oncologist, surgeon, and radiation oncologist, who form the thoracic tumor disease management team at our institution. All lung ablations were performed with general anesthesia by using computed tomographic (CT) guidance to monitor device placement. Ablations were performed by a fellowship-trained interventional radiologist with at least 6 years of experience at the beginning of the study (including S.B.S., C.T.S., J.P.E., and H.Y.). Ablation technique, including modality (RFA, MWA, or CRA), device type, needle, and number and length of treatments, was determined by operator preference, taking into account tumor location, size, and adjacent structures. Complications were categorized by using the Society of Interventional Radiology guidelines (18). Major complications were those that increased the level of care or required that the patient be hospitalized. All other complications were considered minor. Immediate postprocedure CT and chest radiography were performed to assess technical success and postprocedure complications, respectively.

Tissue Acquisition and Mutational Analysis

Patients with lung adenocarcinomas have their tumor(s) tested for multiple oncogenic mutations at our institution as part of the standard of care. The spectrum of genes tested has increased over time but has consistently included *KRAS*. Tumor specimens were obtained either through biopsy or from a surgical specimen. After microscopic examination results confirmed the diagnosis of adenocarcinoma, tissue was sent to a molecular diagnostic laboratory in the Department of Pathology for extraction of genomic DNA. All samples were determined to have adequate DNA quality prior to testing. *KRAS* mutations of codons 12 and 13 were detected by means of direct sequencing or mass spectrometry–based genotyping (Sequenom) (19–21).

Assessment of Tumor Recurrence

Postprocedural CT was performed according to standard guidelines (22), with baseline imaging typically performed at 1 month and follow-up imaging performed at regular intervals after that (typically 3, 6, and 12 months, and yearly after that). Positron emission tomography (PET)/CT surveillance was performed for tumors that were fluorine 18 fluorodeoxyglucose avid before the ablation, according to the operator and referring clinician preference, and in the setting of suspected local recurrence on the basis of CT findings. One of the investigators (E.Z.) reviewed the imaging studies in all patients to determine tumor size at time of ablation, margin size after ablation, and local recurrence. Local recurrence was defined by imaging criteria as the appearance of tumor foci within or at the edge of the ablation zone, according to previously published standard reporting guidelines (22). Distant metastases were not included in our definition.

Covariates

Patient clinical characteristics were collected (E.Z., E.N.P., and S.G., in consensus) and included age, smoking status (measured in pack-years), sex, Eastern Cooperative Oncology Group (ECOG) performance status (0 or > 0), clinical stage at the time of original diagnosis, new primary tumor versus recurrence, prior treatment with radiation at ablated site, prior surgery at ablated site, treatment with systemic chemotherapy, treatment modality (RFA, MWA, or CRA), tumor size (using a 2-cm threshold), margin ablation (using a 5-mm threshold), and presence of a ground-glass appearance in the tumor prior to treatment. Clinical stage was defined by the tumor, node, metastasis classification system, according to the 7th edition of the American Joint Committee on Cancer staging manual (23). We used the Martini and Melamed criteria (17) to distinguish between de novo primary tumors and recurrent or metastatic tumors (12). We also enhanced these criteria by using mutation data (presence or absence of driver mutation), when available, to help either confirm or refute similar histologic types. A ground-glass appearance of the tumor at CT imaging prior to ablation was defined as either completely ground glass or as mixed solid and ground glass). None of the ablated lesions were purely ground glass in appearance.

Statistical Analyses

For the 54 patients, clinical characteristics were compared among wild-type

and *KRAS* mutant tumors by using the Fisher exact test for categoric variables and the Mann-Whitney *U* test for continuous variables. Analysis of data in the two patients who had undergone PIA of two metachronous lesions was based on their first tumor. Overall survival was measured from the time of PIA to patient death or most recent follow-up and was determined on the basis of a review of patient medical records. Overall survival rates were estimated by using the Kaplan-Meier method. For the 56 tumors, time to local recurrence was calculated from the time of PIA to the first radiologic evidence of progression at the ablation site. Our primary interest was to evaluate the association between *KRAS* and local recurrence. However, to determine which variables to include in the multivariate analysis, we needed to test multiple potential confounders. We used a standard competing-risks proportional hazards model (24) to analyze time to local recurrence with death as a competing risk and to obtain a predicted cumulative incidence function. Clustering was used to account for within-patient correlations. Univariable analysis was performed by using this model, and covariates with $P < .25$ were included in the multivariable analysis. Backward selection with a cutoff of $P = .05$ was performed to select significant predictors of outcome in multivariable analysis. Competing risk analysis was performed by using Stata12 software, while all the other analyses were performed by using SAS9.3 software. Tumor size (20 mm) and ablation margin (5 mm) were analyzed as categoric variables by using clinically well-established thresholds. Additional continuous variables, including age and smoking status, were analyzed as continuous variables to avoid imposing arbitrary thresholds.

Results

Technical success was 100%. Patient and tumor characteristics are summarized in Table 1. There were 54 patients, with a median age of 72 years (range, 54–87 years) and a median number of pack-years of smoking of 40 (range, 0–120 pack-years). There were 24 men and 30 women; 40 patients had an ECOG status of 0, and 13 had an ECOG status of 1 or 2. There were 56 ablated tumors: Forty-four (79%) were stage I, and 12 (21%) were stage II–IV; 32 (57%) were new primary cancers and 24 (43%) were recurrences. Nine (16%) tumors had previously been treated with radiation, 18 (32%) had previously been treated with surgical resection, and 27 (48%) had been treated with systemic chemotherapy; 43 (77%) tumors were treated with RFA, 10 (18%) were treated with MWA, and three (5%) were treated with CRA. The average tumor size was 17 mm (range, 8–39 mm), and 42 tumors were smaller than or equal to 20 mm, while 14 were larger than 20 mm. The average minimum margin was 4 mm (range, 0–11 mm), and 37 tumors had less than a 5-mm minimum margin, while 19 had a 5-mm or greater minimum margin. There were 15 tumors that demonstrated some ground-glass appearance. There

Table 1

Patient, Tumor, and Treatment Characteristics

A: Patient Characteristics

Characteristic	All Patients ($n = 54$)	Patients with *KRAS* Mutation ($n = 17$)	Patients with Wild-type *KRAS* ($n = 37$)	*P* Value
Age (y)*	72 (54–87)	73 (61–87)	72 (54–85)	.602
Pack-years*	40 (0–120)	40 (0–120)	40 (0–120)	.716
Sex				.153
Female	30 (56)	12 (71)	18 (60)	
Male	24 (44)	5 (29)	19 (40)	
ECOG status				.511
0	40 (74)	14 (82)	26 (70)	
>0	13 (24)	3 (18)	10 (27)	

B: Tumor and Treatment Characteristics

Characteristic	All Tumors ($n = 56$)	*KRAS* Mutants ($n = 19$)	Wild-type *KRAS* ($n = 37$)	*P* Value
Stage at diagnosis				>.99
I	44 (79)	15 (79)	29 (78)	
>I	12 (21)	4 (21)	8 (22)	
Status				.566
New primary	32	10	22	
Recurrence	24	9	13	
Radiation	9 (16)	3 (16)	6 (16)	>.99
Surgery	18 (32)	7 (37)	11 (30)	.763
Chemotherapy	27 (48)	9 (47)	18 (49)	>.99
Modality				.241
RFA	43 (77)	17 (89)	26 (70)	
MWA	10 (18)	2 (11)	8 (22)	
CRA	3 (5)	0	3 (8)	
Margin				.772
<5 mm	37 (66)	12 (63)	25 (68)	
≥5 mm	19 (34)	7 (37)	12 (32)	
Size				.106
≤20 mm	42 (75)	17 (89)	25 (68)	
>20 mm	14 (25)	2 (11)	12 (32)	
Ground-glass appearance	15 (27)	2 (11)	13 (35)	.061

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Data are medians, with ranges in parentheses.

Figure 2

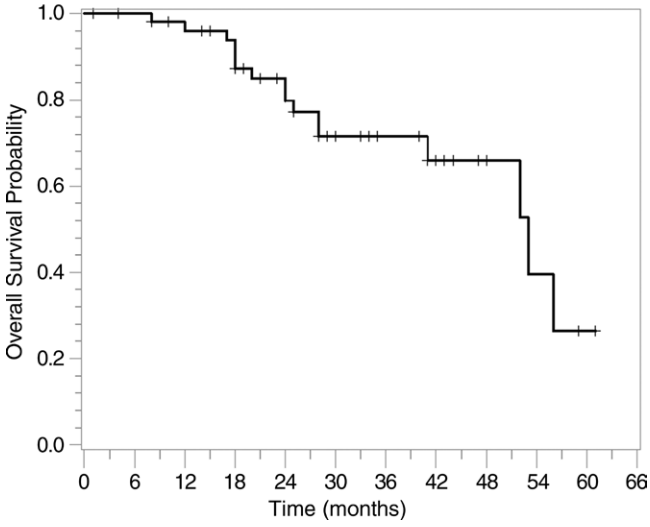

Figure 2: Graph shows overall survival for all patients. The overall survival rate was 96% at 1 year, 80% at 2 years, and 72% at 3 years.

were 19 (34%) tumors with *KRAS* mutations. Table 1 also summarizes associations between *KRAS* status and the rest of the covariates. There were no statistically significant associations, although there was a trend for *KRAS* mutant tumors to be less likely to have a ground-glass component ($P = .061$). There was no difference between the groups in terms of size or margin achieved. There was a trend for *KRAS* mutant tumors to be smaller ($P = .106$).

Complications were recorded as follows: There were 14 (25%) pneumothoraces that required chest tubes. There was one (2%) bronchopleural fistula, which was managed with a chest tube and antibiotics, and one (2%) abscess, which was managed with surgical débridement at video-assisted thoracoscopic surgery. No procedure-related deaths were recorded. There were no deaths recorded within 30 days.

Figure 2 displays the Kaplan-Meier curve for overall survival for the 54 patients. The median overall survival probability was 53 months. The overall survival rate was 96% (95% CI: 85%, 99%) at 1 year, 80% (95% CI: 65%, 89%) at 2 years, and 72% (95% CI: 55%, 83%) at 3 years.

Results of univariate analysis of time to local recurrence are summarized in Table 2. Presence of *KRAS* mutation was associated with shorter time to local recurrence ($P = .05$; subdistribution HR, 2.32; 95% CI: 1.00, 5.39). The cumulative incidence function generated from the competing risk univariate analysis is presented in Figure 3. The 1-, 2-, and 3-year cumulative incidences of recurrences were 20%, 31%, and 35% for wild-type tumors, compared with 40%, 58%, and 63% for *KRAS* mutants, respectively. The presence of a ground-glass appearance in the nodule was associated with longer time to local recurrence ($P = .04$; subdistribution HR, 0.31; 95% CI: 0.01, 0.95). ECOG status, minimum margin, and tumor size were marginally associated with time to local recurrence ($P < .25$) and were thus included in the multivariate analysis.

Table 3 lists results from the multivariate competing-risks proportional hazards model of time to local recurrence using the five covariates identified as either significant or marginally significant in the univariate analysis. *KRAS* mutation remained statistically significant ($P = .006$; subdistribution HR, 3.75; 95% CI: 1.46, 9.64). ECOG status and tumor size were also statistically significant in the multivariate analysis. Presence of ground-glass appearance and minimum margin were not significant in the multivariate analysis.

Discussion

Local recurrence after PIA in patients with lung adenocarcinoma remains an unresolved issue. In our series of patients, we found that *KRAS* mutation status was an independent predictor of time to local recurrence, with a significantly decreased cumulative incidence of recurrence (20% for wild-type *KRAS* tumors vs 40% for *KRAS* mutants at 1 year). Of note, the *KRAS* mutants were not more likely to be larger or to have smaller margins, suggesting an inherent aggressiveness of these tumors.

There has been much attention focused on the prognostic impact of *KRAS* mutation status for lung adenocarcinoma, largely focusing on overall survival. D'Angelo et al (14) reported similar overall survival in patients with and those without *KRAS* mutation with stage I–III lung adenocarcinoma, although *KRAS* mutations did predict shorter survival in a different study (25) in patients with advanced (stage IV) lung adenocarcinoma. Similar to our results, one report in the radiation oncology literature identified an association between *KRAS* mutation and lower freedom from recurrence (16), although these results are difficult to interpret because genotyping was performed in only 10 of 75 patients and likely included a biased subpopulation.

The predictive and prognostic role of other oncogenic driver mutations, including *EGFR*, has been well studied. Patients with *EGFR* mutation have a better prognosis than patients without *EGFR* mutation and are more likely to benefit from treatment with tyrosine kinase inhibitors (14,26,27). In the surgical literature, *EGFR* mutation did confer a benefit in overall survival over *KRAS* mutation that was independent of pathologic stage (15). One may make the conjecture that in our population, *EGFR* mutants may have better results because they may be candidates for

Table 2

Univariate Analysis of Time to Local Recurrence with Death as Competing Risk

Parameter	*P* Value	Subdistribution HR	95% CI
Age	.493	1.019	0.964, 1.077
Pack-years of smoking	.758	1.003	0.985, 1.021
Sex			
Female	…	…	…
Male	.688	1.186	0.514, 2.735
ECOG status	.103	1.707	0.897, 3.248
Stage			
I	…	…	…
>I	.299	1.578	0.668, 3.731
Status			
De novo primary	…	…	…
Recurrence	.732	1.154	0.508, 2.620
Radiation	.867	1.086	0.416, 2.830
Surgery	.487	0.730	0.300, 1.773
Chemotherapy	.929	0.963	0.424, 2.185
Modality	.301	0.662	0.303, 1.447
Margin			
>5 mm	…	…	…
≤5 mm	.206	1.906	0.701, 5.182
Size			
<20 mm	…	…	…
≥20 mm	.215	1.819	0.707, 4.677
Ground-glass appearance	.040	0.308	0.010, 0.948
Gene			
Wild type	…	…	…
KRAS	.050	2.322	1.000, 5.387

Table 3

Multivariate Analysis of Time to Local Recurrence with Death as Competing Risk by Using Backward Selection with $P < .05$ as Cutoff

Parameter	*P* Value		95% CI
ECOG status	.012	2.225	1.192, 4.154
Margin			
>5 mm	…	…	…
≤5 mm	.066		
Size			
<20 mm	…	…	…
≥20 mm	.026	2.540	1.120, 5.758
Ground-glass appearance	.334		
Gene			
Wild type	…	…	…
KRAS	.006	3.753	1.462, 9.635

Figure 3

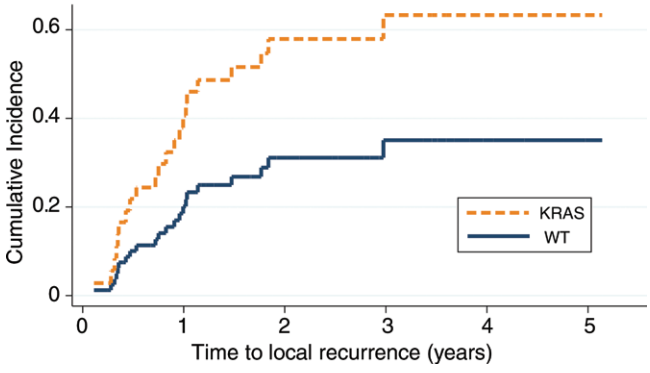

Figure 3: Graph shows cumulative incidence function of time to local recurrence, with death as competing risk ($P = .05$), for wild-type *(WT) KRAS* versus *KRAS* mutation.

tyrosine kinase inhibitor therapy. On the other hand, many of these tumors may have developed acquired resistance and failed tyrosine kinase inhibitor therapy. Because the natural history and treatment algorithms of these other mutants are so different, we chose to exclude patients with these mutations from our analysis. Subsequent analyses of other driver mutations, including *EGFR,* may yield further insight into these questions.

Many predictors of tumor response after lung ablation have been proposed. Traditional predictors of local recurrence in PIA include tumor size and ablation margin (28–30). We saw a significant association between tumor size and local recurrence. There was no significant association with minimum margin (9), although our study was small. Other markers of tumor biology may also be useful to assess. Sofocleous et al (31) have previously reported Ki-67 as a predictive biomarker after RFA. In their cohort of 47 lung tumors, 13 were known to represent primary lung cancers. Additionally, multiple reports establish the prognostic role of histologic subtype in lung adenocarcinoma (32). Because histologic subtyping is now performed in routine practice, future analysis should include this as an additional covariate.

Kodama et al (11) reported excellent local recurrence rates and overall survival in patients with ground-glass opacities who underwent RFA. Purely ground-glass opacities may actually represent adenocarcinoma in situ or minimally invasive adenocarcinoma (33,34). However, all of our nodules with a ground-glass appearance had at least partially solid components.

Interestingly, we also saw a trend toward an association between ground-glass appearance and mutation status—*KRAS* mutant tumors were less likely to have a ground-glass component (P = .06). This finding is supported by recent work correlating CT imaging features with mutation status (35,36). This may also explain why the presence of a ground-glass appearance in the nodule was significant in the univariate analysis but not in the multivariate analysis.

Our overall survival rates at 1 year (96%) and 3 years (72%) are comparable with rates in the SBRT and surgery literature (37) and are in keeping with rates in a recently published report (6) that demonstrated comparable overall survival rates for RFA, SBRT, and surgery. These results support the need for prospective comparative trials between the three modalities. Interestingly, the presence of local recurrence after ablation does not appear to affect overall survival in primary lung cancer (6) but does affect overall survival in lung metastases (28).

There were several important limitations to our study. First, this was a retrospective study with a relatively small number of patients. We note that our multivariate model was at risk for overfitting and emphasize that this result is exploratory and should be validated in a separate cohort. The population was, moreover, heterogeneous and included tumors originally diagnosed as stage I–IV disease, although most were stage I (76%). Treatment was also heterogeneous and included RFA, MWA, and CRA. Additionally, there was an inherent bias in our population because patients were identified on the basis of molecular testing at a single institution. Although molecular analysis has become the standard of care for lung cancer, not all nodules are sampled for biopsy and not all biopsy samples are genetically evaluated, so our patients may not be representative of a general population. Additionally, genetic assays have evolved, so some driver mutations may have not been identifiable with earlier versions of the assay. Despite these limitations, the findings of our study support further prospective studies validating the role of *KRAS* as a prognostic biomarker of local recurrence and further explorative studies to identify additional potential biomarkers.

In conclusion, the presence of *KRAS* mutation in lung adenocarcinoma tumors predicts a shorter time to local recurrence after ablation that is independent of tumor size and ablation margin. Our study supports the utility of *KRAS* status as a prognostic indicator for local recurrence and, more broadly, underscores the importance of biomarkers in assessing outcomes and stratifying risk. Such information can be useful in identifying appropriate patients for PIA and establishing well-matched cohorts for future prospective comparison trials between PIA and SBRT or surgery. The importance of oncogene driver mutation status has not been well established in the PIA literature. Further prospective studies will enable better understanding of these potential prognostic markers in the setting of PIA.

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