Original Article

Clinical impact of *EGFR* and *KRAS* mutations in surgically treated unifocal and multifocal lung adenocarcinoma

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Background: Epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma (KRAS) are the two most common oncogenic drivers in lung adenocarcinoma, and their roles still need further exploration. Here we aimed to compare the clinical impact of *EGFR* and *KRAS* mutations on disease progression in resected unifocal and multifocal lung adenocarcinoma.

Methods: Clinicopathologic and genomic data were collected for patients who underwent resection of lung adenocarcinoma from 2008 to 2022 at Stanford University Hospital. Retrospective review was performed in 241 patients whose tumors harbored *EGFR* (n=150, 62.2%) or *KRAS* (n=91, 37.8%) mutations. Clinical outcome was analyzed with special attention to the natural history of secondary nodules in multifocal cases wherein the dominant tumor had been resected.

Results: We confirm that compared with *EGFR* mutations, patients with *KRAS* mutations had more smokers, larger tumor size, higher TNM stage, higher positron emission tomography (PET)/computed tomography (CT) standard uptake value max, higher tumor mutation burden, and worse disease-free survival and overall survival on univariate analysis. For patients with multifocal pulmonary nodules, the median follow-up of unresected secondary nodules was 55 months. Secondary nodule progression-free survival (SNPFS) was significantly worse for patients with *KRAS* mutations than those with *EGFR* mutations (mean 40.3±6.6 *vs.* 67.7±6.5 months, P=0.004). Univariate analysis showed tumor size, tumor morphology, pathologic TNM stage, and *KRAS* mutations were significantly associated with SNPFS, while multivariate analysis showed only *KRAS* mutations were independently associated with worse SNPFS (hazard ratio 1.752, 95% confidence interval: 1.017–3.018, P=0.043).

Conclusions: Resected lung adenocarcinomas with *KRAS* mutations have more aggressive clinicopathological features and confer worse prognosis than those with *EGFR* mutations. Secondary pulmonary nodules in multifocal cases with dominant *KRAS*-mutant tumors have more rapid progression of the secondary nodules.

Keywords: Epidermal growth factor receptor (EGFR); Kirsten rat sarcoma (KRAS); lung adenocarcinoma; multifocal pulmonary nodules

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Introduction

Epidermal growth factor receptor (EGFR) mutations and Kirsten rat sarcoma (KRAS) are the two most common oncogenic drivers of lung adenocarcinoma. Patients with *EGFR*-mutant tumor have a better prognosis than wild-type, while those with KRAS tumors have a poorer prognosis than wild-type (1,2). Despite recent advances in targeting *EGFR* mutations, the treatment of patients whose tumors bear *KRAS* mutations has not been similarly transformed (3,4). Although extensive research on *EGFR* and *KRAS* mutations has established that patients with *EGFR* mutant tumors have better overall survival (OS) than those with *KRAS* mutant tumors (5-8), much remains unknown about the impact of these mutations in resectable disease—particularly with regard to the natural history of progression of secondary nodules in the setting of multifocal lung adenocarcinomas.

Multiple primary lung adenocarcinomas are increasingly common (9), and they often present as multiple ground-glass or part-solid pulmonary nodules, commonly in the setting of *EGFR* or *KRAS* mutations. Understanding the natural history of multifocal nodules is key to allow timely intervention before they progress to invasive adenocarcinomas that have metastatic potential. The impact of *EGFR* and *KRAS* mutations on the natural history of multifocal pulmonary nodules has not been studied. Mutations in *EGFR* or *KRAS* play an important role in the tumorigenesis of lung adenocarcinoma by promoting cell division and growth, as well as enhancing the ability of cancer cells to invade surrounding tissues and spread (10-14). We hypothesized that in multifocal adenocarcinoma, dominant KRAS tumors would demonstrate more rapid growth of secondary nodules. Establishing this would have implications for the conduct of surveillance and interventions in these patients.

We therefore performed a retrospective analysis comparing the clinical impact of *EGFR* and *KRAS* mutations in surgically resected lung adenocarcinoma, with special attention to the growth of residual secondary pulmonary nodules after resection of dominant tumor in patients with multifocal pulmonary nodules. We present this article in accordance with the REMARK reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-165/rc).

Highlight box

Key findings

- Patients with resected lung adenocarcinoma with Kirsten rat sarcoma (*KRAS*) mutations have worse prognosis than those with epidermal growth factor receptor (*EGFR*) mutations.
- Resected lung adenocarcinomas with *KRAS* mutations have more aggressive clinicopathological features than those with *EGFR* mutations.
- The presence of a *KRAS* mutation in the dominant tumor is independently associated with more rapid progression of secondary pulmonary nodules.

What is known and what is new?

- Lung adenocarcinoma patients with *EGFR* mutant tumors have a better overall survival than those with *KRAS* mutant tumors. However, much remains unknown about the impact of these mutations in the natural history of progression of secondary nodules in the setting of multifocal lung adenocarcinomas.
- Here we found secondary pulmonary nodules in multifocal cases with dominant *KRAS*-mutant tumors have more rapid progression of the secondary nodules.

What is the implication, and what should change now?

- It is likely that patients with KRAS lung adenocarcinomas should be followed with postoperative computed tomography scans particularly closely given the faster rate at which secondary nodules progress to the point at which they are invasive and threatening.

Methods

Study population and data collection

We retrospectively reviewed records of patients with lung adenocarcinoma with *EGFR* or *KRAS* mutations who underwent surgical resection at Stanford University Hospital from July 2008 to April 2022. *EGFR* and *KRAS* mutations were identified by the Stanford Solid Tumor Actionable Mutation Panel (STAMP), which is a next generation sequencing method using target enrichment to capture genomic regions of interest. Exclusion criteria were as follows: co-mutations with EGFR and KRAS, incomplete resection of the dominant tumor, no available chest computed tomography (CT) follow-up, and death from causes other than lung cancer. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research received ethical approval from the Stanford University Institutional Review Board (protocol #21285). The requirement for informed consent was waived given the retrospective nature of the research.

Clinicopathologic data collected included demographics, imaging, clinical and pathologic tumor node metastasis (TNM) staging [AJCC (American Joint Committee on Cancer) 8th edition], recurrence and metastases, and

Table 1 Patient, tumor, and surgery characteristics

Factors	No. of patients (n=241)	Percent (%)
Age, years		
Mean ± SD	67.9±10.5	
Range	20–90	
Gender		
Male	78	32.4
Female	163	67.6
Smoking		
Yes	127	52.7
No	114	47.3
AJCC 8th TNM stage		
Ia	102	42.3
Ib	54	22.4
IIa	11	4.6
IIb	37	15.4
IIIa	35	14.5
IIIb	2	0.8
Surgical resection		
Lobectomy	207	85.9
Segmentectomy	11	4.6
Wedge resection	23	9.5

SD, standard deviation; AJCC, American Joint Committee on Cancer; TNM, tumor node metastasis.

subsequent therapies. Histologic subtypes were classified as either lepidic, acinar, papillary, micropapillary, solid, or mucinous. Routine follow-up was CT and office visit in accordance with National Comprehensive Cancer Network guidelines.

Multiple pulmonary nodules were defined as two or more pulmonary nodules found on preoperative CT in a patient with at least one proven adenocarcinoma, whether in the same lobe or in different lobe. The literature is clear that when multiple subsolid nodules are present in the setting of EGFR and KRAS tumors, these almost always behave as separate primary tumors and not as satellite nodules or metastases, which would upstage the patient. Secondary pulmonary nodules were defined as nodules other than the dominant tumor which were not resected at the first surgery but needed follow-up. Secondary nodule progression was defined as growth (nodule diameter increased by 2 mm or more) of a secondary nodule, development of a new solid component in a previously pure ground glass opacity (GGO) nodule, enlargement of a solid component (2 mm or more) in a part-solid nodule, or development of a new pulmonary nodule. In the disease-free survival (DFS) analysis, disease progression was defined as local recurrence or metastasis due to the dominant tumor, excluding progression of secondary nodules.

Statistical analysis

Continuous data are presented as mean and standard deviation. Baseline characteristics between groups were compared with the Wilcoxon rank sum test for continuous variables and Pearson χ^2 test for discrete variables. Kaplan-Meier analysis was used to estimate the OS, DFS, and secondary nodule progression-free survival (SNPFS). Univariate and multivariate logistic regression results were presented as odds ratios and 95% confidence intervals (CIs). Differences between curves were evaluated using log-rank tests. Statistical analyses were conducted using SPSS 20.0 (IBM, SPSS Inc.). Statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Clinical and pathologic differences between lung adenocarcinoma patients with EGFR vs. KRAS mutations

We performed 1,325 adenocarcinoma lung resections at our center during this study period and 241 lung adenocarcinoma patients met inclusion criteria and were studied (*Table 1*). Mean age at resection was 67.9 years, and 67.6% of patients were women (n=163). About half of patients (n=127, 52.7%) had a history of smoking, with a median of 20 pack-years. In total, 156 (64.7%) of patients were in pStage I, 48 (19.9%) pStage II, and 37 (15.4%) pStage III. Most patients underwent lobectomy at the initial surgery (n=207, 85.9%) and the remainder underwent segmentectomy or wedge resection. A total of 150 (62.2%) had *EGFR* mutations and the remaining 91 (37.8%) had *KRAS* mutations.

Compared with *EGFR* mutations, patients with *KRAS* mutations presented more smokers (85.7% *vs.* 32.7%, P<0.001), larger tumor size (3.7±2.5 *vs.* 2.6±1.4 cm, P<0.001), later TNM stage (47.3% *vs.* 28.0% stage II to III *vs.* I, P=0.003), higher positron emission tomography

Table 2 Clinicopathologic factors associated with *EGFR* and *KRAS* mutations

Factors	*EGFR* mutation (n=150)	*KRAS* mutation (n=91)	P
Age, years			
Mean ± SD	67.3±10.9	68.9±9.7	0.27
Gender, n			0.20
Male	44	34	
Female	106	57	
Smoking, n			<0.001
Yes	49	78	
No	101	13	
Dominant tumor size, cm			
Mean ± SD	2.6±1.4	3.7±2.5	<0.001
AJCC 8th TNM stage, n			0.003
I	108	48	
II–III	42	43	
Tumor morphology on CT scan, n			<0.001
Pure solid	38	57	
Part solid	106	28	
Pulmonary nodule, n			0.68
Unifocal	64	34	
Multifocal	84	51	
SUVmax in PET/CT*			
Mean ± SD	4.7±3.9	8.0±6.2	<0.001
PD-L1 expression**, n			<0.001
No	55	19	
Low and high	17	27	
TMB, MPMB***			
Mean ± SD	3.9±2.7	8.4±5.5	<0.001

*, n=214; **, n=118; ***, n=51. EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma; SD, standard deviation; AJCC, American Joint Committee on Cancer; TNM, tumor node metastasis; CT, computerized tomography; SUVmax, standard uptake value max; PET, positron emission tomography; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden; MPMB, mutations per megabase.

(PET)/CT standard uptake value max (SUVmax) (8.0±6.2 *vs.* 4.7±3.9, P<0.001), and higher tumor mutation burden (8.4±5.5 *vs.* 3.9±2.7, P<0.001) (*Table 2*).

For *EGFR* mutations, L858R and exon 19 deletion were the two most common mutation types, accounting for 46.0% (n=69) and 36.7% (n=55) of the *EGFR* mutations, respectively. Patients with EGFR exon 19 deletion were younger than those with L858R mutations, while other factors such as gender, smoking status, tumor grade and tumor size were not significantly different between groups (Table S1). For *KRAS* mutations, G12C was the most common mutation type, accounting for 49.5% (n=45) of *KRAS* mutations. Patients with *KRAS* G12C mutations had more smokers and more solid tumors than those with *KRAS* non-G12C mutations, while other factors such as gender, age, smoking status, tumor grade and tumor size were not

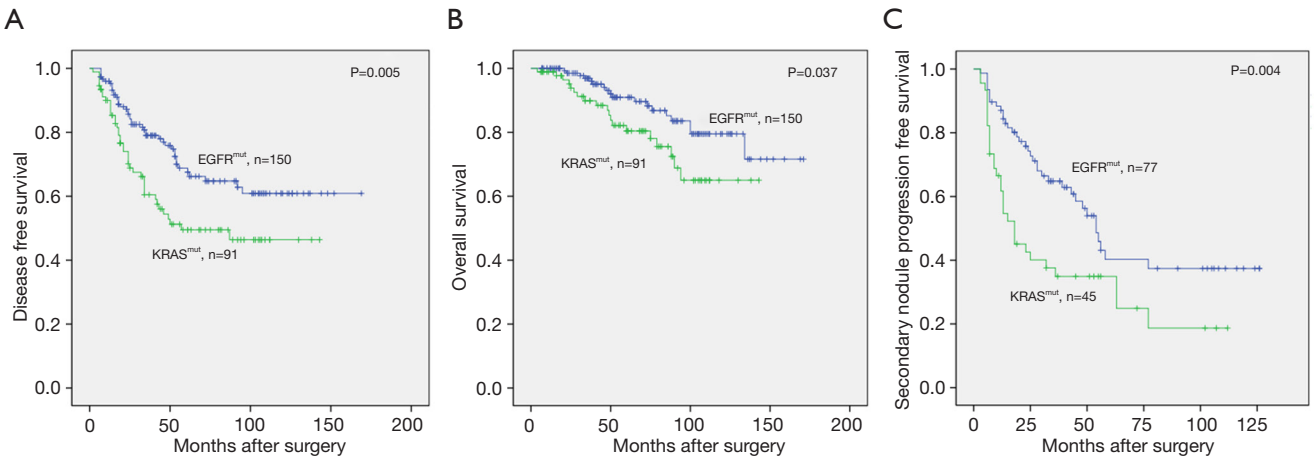

Figure 1 Survival of *EGFR* and *KRAS* mutations in lung adenocarcinoma. Patients with lung adenocarcinoma with *KRAS* mutations had worse disease-free survival (A) and overall survival (B) than those with *EGFR* mutations. (C) Secondary nodule progression-free survival for patients with multifocal pulmonary nodules. Secondary nodule progression-free survival was significantly worse for patients with *KRAS* mutations than for those with *EGFR* mutations. *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma.

significantly different between groups (Table S1).

Clinicopathologic factors associated with disease-free and OS

The median follow-up time overall was 70 months. Kaplan-Meier analyses were performed comparing lung adenocarcinoma patients with *EGFR* mutations *vs.* *KRAS* mutations. DFS was substantially worse for patients with *KRAS* mutations (mean 81.5±6.9 months, 95% CI: 67.9–95.0) than for those with *EGFR* mutations (mean 118.4±6.4 months, 95% CI: 106.0–130.9) (*Figure 1A*). OS was also significantly worse for patients with *KRAS* mutations (mean 113.3±5.8 months, 95% CI: 102.0–124.6) than for those with *EGFR* mutations (mean 146.3±5.4 months, 95% CI: 135.7–156.9) (*Figure 1B*). Among patients with *EGFR* mutations, neither DFS nor OS was significantly different between those with L858R and exon 19 deletion mutations (Figure S1A,S1B). Similarly, among patients with *KRAS* mutations, neither DFS nor OS was significantly different between those with G12C and non-G12C mutations (Figure S1C,S1D).

On univariate analysis, smoking status, tumor size, tumor morphology, tumor grade, pleural invasion, vascular invasion, pathologic TNM stage and *KRAS* mutations were significantly associated with shorter DFS (P<0.1, *Table 3*). On multivariate analysis, only pathologic TNM stage was independently associated with worse DFS [hazard ratio (HR) 3.352, 95% CI: 1.869–6.011, P<0.001; *Table 3*]. On univariate analysis, the following factors were significantly associated with OS: smoking status, lobar resection, tumor size, tumor grade, pleural invasion, pathologic TNM stage, and *KRAS* mutations (P<0.1, *Table 4*). On multivariate analysis, only pathologic TNM stage (HR 2.270, 95% CI: 1.078–4.781, P=0.03) and tumor grade (HR 4.450, 95% CI: 1.534–12.911, P=0.006) were independently associated with worse OS (*Table 4*).

Stratified analysis of clinicopathological factors associated with DFS and OS

Stratified analyses were performed with regard to gender, smoking status, tumor morphology, lung nodule number, tumor size and pathologic TNM stage to further compare lung adenocarcinoma patients with *EGFR* mutations *vs.* *KRAS* mutations. The results showed that patients with *KRAS* mutations had significantly worse DFS than those with *EGFR* mutations in female patients (P=0.006), patients with subsolid tumors (P=0.01), patients with multiple lung nodules (P=0.02), and patients with smaller tumor (<3 cm; P=0.047). DFS was not significantly different between groups in male patients, solid tumor patients, single lung nodule patients, larger tumor (diameter more than 3 cm), TNM stage I and stage II–III patients (Figure S2A). There was no significant difference in OS between groups in the stratified analysis (Figure S2B). We further compared the survival of the KRAS and EGFR groups according to early

Table 3 Univariate and multivariate analysis of factors associated with disease-free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (female *vs.* male)	1.277 (0.815–2.002)	0.29	–	
Smoking (yes *vs.* not)	0.650 (0.417–1.013)	0.057	0.976 (0.552–1.726)	0.93
Tumor size (≤3 *vs.* >3 cm)	2.446 (1.578–3.791)	<0.001	1.412 (0.849–2.349)	0.18
Tumor morphology in CT scan (pure solid *vs.* part solid)	0.485 (0.310–0.760)	0.002	1.023 (0.599–1.747)	0.93
Lobar *vs.* sublobar resection	0.775 (0.400–1.502)	0.45	–	
Pleural invasion (yes *vs.* not)	0.642 (0.409–1.008)	0.054	1.184 (0.708–1.979)	0.52
Vascular invasion (yes *vs.* not)	0.446 (0.240–0.829)	0.01	0.943 (0.473–1.883)	0.87
Tumor grade (well *vs.* moderate and poor)	1.955 (1.226–3.119)	0.005	1.310 (0.783–2.191)	0.30
AJCC 8th TNM stage (I *vs.* II–III)	3.647 (2.342–5.681)	<0.001	3.352 (1.869–6.011)	<0.001
PD-L1 expression (no *vs.* low and high)	1.173 (0.538–2.558)	0.69	–	
EGFR vs. KRAS mutations	1.839 (1.192–2.837)	0.006	1.542 (0.853–2.788)	0.15

HR, hazard ratio; 95% CI, 95% confidence interval; CT, computerized tomography; AJCC, American Joint Committee on Cancer; TNM, tumor node metastasis; PD-L1, programmed death-ligand 1; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma.

Table 4 Univariate and multivariate analysis of factors associated with overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (female *vs.* male)	1.578 (0.823–3.026)	0.17	–	
Smoking (yes *vs.* not)	0.523 (0.262–1.045)	0.07	0.752 (0.337–1.679)	0.49
Tumor size (≤3 *vs.* >3 cm)	2.413 (1.261–4.618)	0.008	1.288 (0.635–2.611)	0.48
Lobar *vs.* sublobar resection	0.144 (0.020–1.053)	0.056	0.403 (0.052–3.106)	0.38
Tumor morphology in CT scan (pure solid *vs.* part solid)	0.585 (0.292–1.171)	0.13	–	
Pleural invasion (yes *vs.* not)	0.521 (0.271–0.999)	0.050	0.880 (0.444–1.744)	0.71
Vascular invasion (yes *vs.* not)	0.523 (0.203–1.352)	0.18	–	
Tumor grade (well *vs.* moderate and poor)	6.734 (2.379–19.061)	<0.001	4.450 (1.534–12.911)	0.006
AJCC 8th TNM stage (I *vs.* II–III)	3.784 (1.950–7.343)	<0.001	2.270 (1.078–4.781)	0.03
PD-L1 expression (no *vs.* low and high)	0.829 (0.152–4.535)	0.83	–	
EGFR vs. KRAS mutations	1.964 (1.027–3.755)	0.041	1.162 (0.547–2.465)	0.70

HR, hazard ratio; 95% CI, 95% confidence interval; CT, computerized tomography; PD-L1, programmed death-ligand 1; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma.

Table 5 Univariate and multivariate analysis of factors associated with secondary nodule progression-free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (female *vs.* male)	0.859 (0.504–1.461)	0.57	–	
Smoking (yes *vs.* not)	0.786 (0.485–1.274)	0.33	–	
Tumor size (≤3 *vs.* >3 cm)	1.742 (1.057–2.871)	0.03	1.365 (0.792–2.353)	0.26
Tumor morphology in CT scan (pure solid *vs.* part solid)	0.617 (0.379–1.003)	0.051	1.088 (0.596–1.984)	0.78
Pleural invasion (yes *vs.* not)	0.677 (0.416–1.101)	0.12	–	
Tumor grade (well *vs.* moderate and poor)	1.007 (0.616–1.646)	0.98	–	
AJCC 8th TNM stage (I *vs.* II–III)	2.036 (1.252–3.313)	0.004	1.705 (0.994–2.924)	0.052
EGFR vs. KRAS mutations	1.982 (1.224–3.210)	0.005	1.752 (1.017–3.018)	0.043

HR, hazard ratio; 95% CI, 95% confidence interval; CT, computerized tomography; AJCC, American Joint Committee on Cancer; TNM, tumor node metastasis; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma.

stage (stage I) and late stage (stages II–III) and found no significant differences using that stratification (Figure S3).

Impact of primary tumor characteristics on progression of secondary nodules in multifocal disease

At presentation, 135/241 (56.0%) of patients had multiple pulmonary nodules. Of these, 13 patients had no available follow-up CT scans and were therefore excluded from this analysis, while in 122 (50.6%) nodules could be tracked on serial CT scans. Kaplan-Meier analyses were performed to analyze SNPFS for patients with traceable multiple pulmonary nodules. The median follow-up of secondary nodules was 55 months. SNPFS was significantly and markedly worse for patients with *KRAS* mutations (mean 40.3±6.6 months, 95% CI: 27.3–55.3) than for those with *EGFR* mutations (mean 67.7±6.5 months, 95% CI: 55.0–80.4) (P=0.004, *Figure 1C*).

Univariate analysis showed tumor size, tumor morphology, pathologic TNM stage and *KRAS* mutations were significantly associated with SNPFS (P<0.1, *Table 5*). Multivariate analysis showed that only *KRAS* mutation was independently associated with worse SNPFS (HR 1.752, 95% CI: 1.017–3.018, P=0.043; *Table 5*).

Discussion

We directly compared the clinical impact of *EGFR* and *KRAS* mutations in surgically resected lung adenocarcinoma, with a special interest in multifocal primary tumors. *KRAS* and *EGFR* mutations are the most frequent mutations identified in patients with subsolid and multifocal disease, and we had suspected from our clinical practice that secondary nodules in KRAS patients with multifocal disease progress more rapidly. We therefore set out to examine this, as well as studying EGFR and KRAS tumors more broadly.

We confirm that lung adenocarcinomas with *KRAS* mutations have more aggressive clinicopathological features including larger tumor size, higher TNM stage, higher PET SUVmax, higher programmed death-ligand 1 (PD-L1) expression and higher tumor mutation burden than those with *EGFR* mutations. On stratified prognostic analysis, we found that the negative prognostic impact of KRAS over *EGFR* mutations is indeed particularly strong in female patients with multifocal pulmonary nodules and small, subsolid dominant tumors. Further, we demonstrate that in these patients with multifocal disease, secondary nodules progress more frequently and more rapidly in patients with KRAS tumors than EGFR tumors.

Among *EGFR* mutations, L858R and exon 19 deletion are the two most common (15). The two subgroups had similar clinicopathological features, other than that patients with exon 19 deletion were younger than those with L858R mutation, and there was no significant difference in DFS and OS between the groups after resection. As for the *KRAS* mutations, G12C is the most common mutation subtype. In general, tumors with KRAS G12C mutation are felt to be more aggressive than tumors with other *KRAS* mutations

(16,17). In our study, indeed *KRAS* G12C mutation tumors exhibited more aggressive clinicopathologic features. However, both DFS and OS were not significantly different between the two groups.

Multiple primary lung adenocarcinomas are increasingly encountered in clinical practice, particularly in the setting of part-solid and ground glass nodules (18,19). Predicting the progression of unresected pulmonary nodules in the multifocal setting has been difficult but could be used to impact intensity of postoperative surveillance and patient selection for surgery. There is limited understanding of factors that predict progression of unresected nodules. Our group has shown that risk factors for progression of secondary nodules include larger size of the dominant, resected tumor and presence of a secondary nodule over 1 cm in size (20). An influence of EGFR *vs. KRAS* mutations (the most common mutations in part-solid nodules) has not to our knowledge been demonstrated. Given the overall more aggressive features of KRAS tumors, one might even think it possible that multifocal disease in patients with *KRAS* mutations is in fact true metastatic disease, and that perhaps it should not be approached surgically.

The findings of this study establish that this is not the case. While there is a significant difference in DFS between patients harboring *EGFR* and *KRAS* mutations in subgroups of multifocal patients on our stratified analysis, the OS is not significantly different, and even among the higher risk subgroups, both DFS and OS are far better than one would expect with actual metastatic disease (21). We show here that several features of the dominant tumor including size, tumor morphology, pathologic TNM stage and *KRAS* mutation were significantly associated with secondary pulmonary nodule progression, but only the presence of a *KRAS* mutation was an independent prognostic factor for secondary pulmonary nodule PFS. Patients with KRAS dominant tumors in a multifocal setting should still undergo surgical therapy, but patients should be counseled that there is a high chance of progression of secondary nodules to the point that they will require eventual intervention. This has significant implications for how these patients should be managed. First, surgeons should likely be more aggressive in KRAS than in EGFR tumors in attempting to resect, at the initial operative procedure, as many as possible of the nodules that are ipsilateral to the dominant tumor. One might, for example, perform a bilobectomy rather than an upper lobectomy alone when there is a KRAS-mutated dominant tumor in the right upper lobe and a small nodule in the center of the middle lobe that is not amenable to wedge resection; whereas one would likely not do this for a small subsolid *EGFR*-mutant secondary nodule in the central right middle lobe. Further, it is likely that patients with KRAS tumors should be followed with postoperative CT scans particularly closely given the faster rate at which secondary nodules progress to the point at which they are invasive and threatening.

There are some limitations of this study. First, this is a single-center, retrospective analysis, so the conclusions may be subject to selection bias; multi-center, prospective data would be needed to verify results. Secondly, the study period is long, from 2008 to 2022. Lung cancer treatment has evolved significantly during this period, which may affect the interpretation of the results. In addition, the (by necessity) lack of direct biological characterization of the secondary nodules may have had an impact on the conclusions regarding secondary nodule progression in multifocal disease. Finally, the rare occurrence of simultaneous *EGFR* and *KRAS* mutations could also be taken into account in larger patient series.

Conclusions

Our findings confirm that patients with lung adenocarcinoma with *KRAS* mutations have more aggressive clinicopathological features and worse DFS and OS than those with *EGFR* mutations. Our novel findings regarding KRAS *vs.* EGFR tumors are that in the multifocal setting, only the presence of a *KRAS* mutation is independently associated with more rapid progression of secondary pulmonary nodules. These results suggest that while patients with a resectable, dominant KRAS tumor with multifocal secondary nodules should still typically be considered strongly for surgical management, one should anticipate a high risk of progression of those secondary nodules to the point of requiring subsequent intervention.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research received ethical approval from the Stanford University Institutional Review Board (protocol #21285). The requirement for informed consent was waived given the retrospective nature of the research.

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