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Association between computed tomographic features and *KRAS* mutations in patients with stage I lung adenocarcinoma and their prognostic value

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Abstract

Background—To investigate the association between computed tomographic (CT) features and *KRAS* mutations in patients with stage I lung adenocarcinoma and their prognostic value.

Patients and Methods—Seventy-nine patients with pathologic stage I lung adenocarcinoma, available *KRAS* mutational status, preoperative CT images, and survival data were included in the study. Seven CT features including spiculation, concavity, ground-glass opacity, bubblelike lucency, air bronchogram, pleural retraction, and pleural attachment were evaluated. The association between the clinical characteristics, CT features and mutational status was analyzed using Student's t test, Chi-square or Fisher's exact test, and logistic regression. The association between CT features, mutational status, and overall survival was analyzed using Kaplan-Meier survival curves with the log-rank test and Cox proportional hazard regression.

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Results—The prevalence of *KRAS* mutations was 41.77%. Spiculation was significantly associated with *KRAS* mutations (OR = 2.99; 95% CI = 1.16 – 7.68). While *KRAS* mutational status was not significantly associated with overall survival, presence of pleural attachment was associated with an increased risk of death (HR = 2.46; 95% CI = 1.09 – 5.53). When analyzing combined *KRAS* mutational status and pleural attachment, patients with wild-type *KRAS* and no pleural attachment had significantly better survival compared to those with wild-type *KRAS* and with pleural attachment ($p = 0.014$).

Conclusion—These data suggest that spiculation was associated with *KRAS* mutations while pleural attachment was associated with overall survival in patients with stage I lung adenocarcinoma. Combining analysis of *KRAS* mutational status and CT features could better predict survival.

Keywords

Computed tomography; Imaging; *Kirsten RAS*; Lung neoplasms; Prognosis

Introduction

Kirsten rat sarcoma viral oncogene (KRAS) mutations occur frequently in non-small cell lung cancer (NSCLC) and most commonly in adenocarcinoma. In recent years, there has been a growing interest in the role of *KRAS* in lung adenocarcinoma because of the rapid advances in molecularly-targeted therapies. Although the efforts to therapeutically target *KRAS* mutations have thus far proven unsuccessful, *KRAS* has emerged as a useful negative predictive marker because it commonly occurs in a mutually-exclusive fashion with *epidermal growth factor receptor (EGFR)* mutations – lung cancers with *KRAS* mutations are unlikely to respond favorably to *EGFR* tyrosine kinase inhibitors, such as gefitinib and erlotinib. Several studies also suggested that *KRAS* mutations may be markers of resistance to conventional cisplatin-based chemotherapy. In addition, a recent meta-analysis suggested *KRAS* mutations were associated with a worse overall survival in patients with NSCLC, especially in patients with adenocarcinoma and early stage. *KRAS* mutations also have a higher risk of post-operative recurrence in stage I lung adenocarcinoma.

Previous studies have demonstrated that preoperative computed tomographic (CT) findings are associated with pathological features and postoperative outcomes. For example, ground-glass opacity (GGO) was associated with lepidic growth pattern of lung adenocarcinoma, and correlated well with histologic prognostic factors and survival. Compared with molecular technologies, routine imaging can provide a more comprehensive view of the entire tumor and can be used on an ongoing basis to monitor relapse after surgery through a much less invasive way. There are only very few studies regarding the correlation between CT findings of lung adenocarcinoma with *KRAS* mutational status, showing that none of the CT characteristics except for tumor size were observed to be associated with *KRAS* mutations. In another study, the presence of an internal air bronchogram was only moderately associated with the overexpression of *KRAS*. Hence, there have been no published studies combining CT features and *KRAS* mutations in association with survival in lung cancer patients.

Such a relationship could have a significant impact on decision support for the lung cancer patient. First, although histology and immunohistochemical analyses of biopsies or surgical specimens are accepted as a gold standard, it is well documented that diagnostic errors are unfortunately common, and hence additional diagnostic information can improve accuracy. Additionally, for early stage resectable cancers, diagnoses are made with biopsy material that is subject to sampling artifact without image-guidance. This is even more critical in larger tumors that can exhibit intratumoral genomic heterogeneity. Further, the commonly employed Sanger-type di-deoxy sequencing can be error-prone with false negatives compared to the less common massively parallel “deep” sequencing. In contrast, radiographic images interrogate the entire tumor, are commonly obtained from patients as standard of care, and do not suffer from sampling artifact. Deep analyses of radiographic data (“Radiomics”) can thus add diagnostic power and a second opinion to standard histopathological results. We hypothesize that CT features reflect underlying pathophysiology of tumors and that these can be driven with *KRAS* mutations. If true, these radiomic features, in combination with *KRAS* mutational status, would have prognostic importance in stage I lung adenocarcinomas.

Patients and Methods

Study Population

This analysis included NSCLC patients recruited for H. Lee Moffitt Cancer Center and Research Institute's Total Cancer Care™ (TCC) protocol. The TCC protocol is a multi-institutional observational study of cancer patients that prospectively collects self-reported demographic data, clinical data, medical record information, imaging, and tissue samples for research purposes. There are no exclusion or inclusion criteria to provide consent; patients are followed for life and every patient is eligible. The lung cancer patients in this analysis consented to the TCC protocol between January 2006 and November 2009. For this analysis, we restricted lung cancer patients to pathologic stage I lung adenocarcinoma that had *KRAS* mutational status and available preoperative CT images on our picture archiving and communication system. Exclusion criteria included those cases with multiple surgeries and those with multiple lesions on CT which individually could not be conclusively correlated with the lesions documented in the pathology or mutation. The final sample for this analysis was 79 patients with overall survival data and among these, 62 patients also had available recurrence status after surgery. Of the 79 patients with *KRAS* mutations, nine also had an *EGFR* mutation and were neither excluded nor analyzed separately due to the low incidence. The University of South Florida institutional review board approved this retrospective study.

Cancer Registry Data

Data for this analysis were obtained from Moffitt's Cancer Registry. The Cancer Registry abstracts information from patient electronic medical records on demographics, history of smoking, stage, histology, and treatment. Follow-up for vital status and survival time occurs annually through active (i.e., chart review and directly contacting the patient, relatives, and other medical providers) and passive methods (i.e., matching mortality records to patients' names, gender, and addresses). Smoking status was categorized self-reported ever smoker (current- and former smokers combined) or never smoker.

KRAS Mutational Status

KRAS mutational status of Exons 2 and 3 was determined by Sanger sequencing (Functional Biosciences, Inc., Madison, WI) on the isolated tumor DNA using standard cycle sequencing using previously published primers. All sequencing traces were examined manually by two independent readers and mutant peak heights and identity determined using Mutation Surveyor (SoftGenetics, State College, PA). Mutations were called if the mutant peaks were at least 20% of the WT signal (due to tumor heterogeneity) and were present on both the forward and reverse reads. Germline SNPs were eliminated if they appeared in the 1000 Genomes Project data (www.1000genomes.org).

CT Imaging and Analysis

All CT scans were performed prior to surgery. Slice thicknesses varied between 1 to 5 mm. Sixty-seven patients underwent contrast-enhanced CT and 12 patients had non-enhanced CT.

Two radiologists with 8 and 5 years of experience in chest CT diagnosis independently reviewed all of the CT images. Both radiologists were aware that patients had surgically resected lung adenocarcinomas but were unaware of the clinical data as well as the gene expression and mutational status. The presence or absence of 7 features including spiculation, concavity, GGO, bubble-like lucency, air bronchogram, pleural retraction, and pleural attachment were used to describe the tumors.

Spiculation was defined as the presence of strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface. Concavity, also referred to as notch, was defined as V-shaped indentation of the border deeper than 3 mm. GGO was defined as hazy increased opacity of lung, with preservation of bronchial and vascular margins. Bubblelike lucency was defined as small spots of air attenuation within tumor. Air bronchogram was defined as air-filled bronchi seen as radiolucent, branching bands within tumor. Pleural retraction was defined as linear structure originating from the tumor and extending to the pleural surface, and the pleura was retracted toward the tumor. Pleural attachment was defined as tumor's margin obscured by the pleura or fissure.

Statistical Analyses

The association between the nominal clinical characteristics (including gender, race, smoking status, and pathological stage), CT features and *KRAS* mutational status was analyzed by using Chi-square or Fisher's exact test, where appropriate. The difference in age between *KRAS* mutant and wild-type group was compared by using Student's *t*-test. Univariable logistic regression analysis was performed to analyze the association between *KRAS* mutational status and the clinical characteristics and between *KRAS* mutational status and the CT features. The association between *KRAS* mutational status, CT features and recurrence status was also analyzed using Chi-square test and univariable logistic regression for 62 patients with available recurrence status. The association between CT features and *KRAS* mutational status with overall survival was analyzed by using Kaplan-Meier survival curves with the log-rank test, and Cox proportional hazard regression. All statistical analyses were performed by using commercial software packages (Stata/MP 12.1,

StataCorp LP, College Station, TX and SPSS for Windows, Version 18.0. SPSS Inc., Chicago, IL). A p value of less than 0.05 was considered statistically significant.

The agreement between the two readers was measured by Kappa. The kappa value was interpreted as follows: <0: poor agreement; 0 – 0.2: slight agreement; 0.2 – 0.4: fair agreement; 0.4 – 0.6: moderate agreement; 0.6 – 0.8: substantial agreement; > 0.8: almost perfect agreement.

Results

Clinical Characteristics by *KRAS* Mutational Status

Overall, the mean age of the patients was 69.78 years (range 49 – 88 years), 94.94% self-reported race as White, 51.90% were female, 93.67% were ever-smokers, and 67.09% had pathologic stage IA lung adenocarcinoma. The prevalence of *KRAS* mutations was 41.77% (33/79). Codon 12 mutation was most frequent (29/33, 87.88%), other mutations were located in codon 13 (1/33, 3.03%) or 61 (2/33, 6.06%), and one patient had both codon 12 and 61 mutations (1/33, 3.03%). The most common mutation type was G12C (13/29, 44.83%). The association between clinical characteristics, recurrence status and *KRAS* mutational status is shown in Table 1. There were no statistically significant differences for the clinical characteristics and recurrence status by *KRAS* mutations.

Reader Reproducibility

The agreement of the two readers, as measured by the kappa value, ranged between 0.69-0.87. Spiculation, bubble-like lucency, and air bronchogram had almost perfect agreement (kappa = 0.85, 0.87, and 0.82, respectively); concavity, GGO, pleural retraction, and pleural attachment had substantial agreement (kappa = 0.79, 0.80, 0.69, and 0.74, respectively).

CT Features by *KRAS* Mutational Status

Spiculation was significantly associated with *KRAS* mutational status ($p = 0.021$) (Table 2). Specifically, tumors harboring *KRAS* mutations had a more incidence of spiculation compared to tumors with wild-type *KRAS* (23/33, 69.7% vs. 20/46, 43.5%). None of the other CT features were significantly associated with *KRAS* mutational status. Logistic regression showed presence of spiculation was statistically significantly associated with *KRAS* mutational status (odds ratio [OR] = 2.99; 95% confidence interval [CI] = 1.16 – 7.68).

CT Features by Recurrence Status

None of the CT features were significantly associated with recurrence status (Table 3).

The Association of CT Features and *KRAS* Mutational Status with Overall Survival

CT features significantly associated with overall survival were pleural retraction (log-rank test $p = 0.032$) and pleural attachment (log-rank test $p = 0.024$) (Figure 1). As shown in Table 4, *KRAS* mutational status was not significantly associated with overall survival (log-rank test $p = 0.58$; hazard ratio [HR] = 1.24; 95% CI 0.57 – 2.69). Cox proportional hazard

regression model showed presence of pleural attachment was statistically significantly associated with an increased risk of death (HR = 2.46; 95% CI = 1.09 – 5.53).

When we combined *KRAS* mutational status and pleural attachment together to assess their association with overall survival (Table 4 and Figure 2), we found that patients with wild-type *KRAS* and no pleural attachment, PA (*KRAS*+/PA-) had better survival compared to those with pleural attachment regardless of *KRAS* status (*KRAS*+/PA+, HR = 3.86; 95% CI 1.21 – 12.34; *KRAS*+/PA+, HR = 3.17; 95% 0.93 – 10.86). There were no statistically significant associations for overall survival between the other CT features with *KRAS* status. A backward elimination approach was utilized to identify a parsimonious model that contained the most meaningful covariates associated with survival. All covariates (patient clinical characteristics, *KRAS* mutational status, and CT features) were considered for inclusion. The backward elimination approach yielded a final model that only included pleural attachment.

Discussion

In this study we investigated the association between CT features with *KRAS* mutations and their prognostic value in 79 patients with stage I lung adenocarcinoma. We found that tumors with spiculation were significantly associated with *KRAS* mutations. Pleural attachment was significantly associated with poor survival and when we analyzed the joint effects of *KRAS* mutational status and pleural attachment, patients with wild-type *KRAS* and absent of pleural attachment had the most favorable overall survival.

KRAS mutations define a molecularly distinct subgroup of lung adenocarcinoma patients. They are more common in Western patients than Asian patients (20-50% vs. 5-15%, respectively) [11]. Our study showed similar findings, with a prevalence of 41.77% in our stage I lung adenocarcinoma in a primarily Caucasian population. In prior work, *KRAS* mutations were found more frequently in smokers and male patients [12]; however, recent studies suggested that *KRAS* mutations were not rare in never smokers or in women, and several studies did not find a significant association between *KRAS* mutations and gender or smoking status [13]. There were no significant associations between *KRAS* mutations and gender ($p = 0.332$) or smoking status ($p = 0.394$) in our study. However, since most of our patients were ever smokers (93.67%), we did not find a statistically significant association between smoking and *KRAS* mutational status. A previous study reported approximately 80% of *KRAS* mutations in NSCLC involved codon 12 [14]. Recent studies showed G12C was the most frequent mutation in lung adenocarcinoma from former and current smokers [15]. Our study also observed that G12C in codon 12 was the most common mutation type, which may be associated with the high prevalence of smokers in our study population.

Previous studies have attempted to find pathologic features, which may be imageable, of lung adenocarcinomas harboring *KRAS* mutations. Several studies showed an association of *KRAS* mutations with poor differentiation [16]. *KRAS* mutations were found to be associated with a solid growth pattern and tumor-infiltrating leukocytes in lung adenocarcinoma [17], or more likely to invade visceral pleura [18]. As we know, CT findings are correlated with their underlying pathological appearance. We hypothesized that CT findings are also correlated

with *KRAS* mutations. However, prior studies by Glynn et al. did not find any imaging characteristics associated with *KRAS* mutations in patients with lung adenocarcinoma with bronchioloalveolar features, and Sugano et al. found only that tumor size was associated with *KRAS* mutations although the presence of GGO and spiculation were also evaluated. Unlike previous studies, we limited our patients to those with stage I lung adenocarcinoma who were treated surgically, and observed that spiculation was associated with *KRAS* mutations. Spiculation was usually due to a desmoplastic response, resulting in coarse fibrotic strands radiating from the tumor margin into the lung. It was also observed to be secondary to direct tumor extension along interstitial planes and to occur as a consequence of lymphangiotic spread of tumor. This finding may be explained by the pathological association of *KRAS* mutations with tumor inflammatory infiltrate reported by Rekhtman et al. However, we did not find an association of *KRAS* mutations with pleural retraction or pleural attachment, which was known to be associated with pathologically visceral pleural tumor invasion.

Although *KRAS* mutations have been shown to be associated with poor survival in NSCLC patients, the prognostic value of *KRAS* mutations remains controversial. A lack of association has been observed in several studies, even when the analysis was restricted to stage I lung adenocarcinomas. In our study, we did not find a significant association between *KRAS* mutations and recurrence status or overall survival; however, we did observe that pleural attachment was significantly associated with an increased risk of death (HR = 2.46, 95% CI = 1.09-5.53). Although CT findings of pleural attachment differ from pathologically pleural tumor invasion, this simple feature appears to have significant association with overall survival. Compared with molecular or pathological markers, CT features can predict survival without invasive biopsy or surgery. Furthermore, we found that, for patients with wild-type *KRAS*, those with presence of pleural attachment had worse survival than those without pleural attachment; however, for patients with *KRAS* mutations, there was no difference between those with and without pleural attachment. This result may suggest that *KRAS* mutations also have impact on survival. Since *KRAS* mutational status is becoming a routine test for lung adenocarcinoma, we may combine *KRAS* mutational status and pleural attachment to better predict survival. Further, knowledge of *KRAS* status by imaging (i.e. Spiculation) in addition to genomic profiling will be beneficial with the advent of *KRAS* targeted therapies.

There are several limitations in the present study. First, the sample size of our study was relatively small. Because of the relatively small sample size, we were unable to assess potential interaction between the covariates and perform stratified analyses such as by adenocarcinoma histologic subtypes. Second, the CT scanning parameters were not consistent for all the patients, and some CT scans were not performed with thin slices. While this can be problematic for extraction of higher order statistical features, such as radiomics, it is less of a concern for the semantic features described herein, as human readers can process heterogeneous data better than machine learning algorithms. Further, the excluding patients based on scanning parameters would have had a detrimental effect on the statistical power. With larger data sets, we plan to include scanning parameters as a co-variate. Third, we didn't have the exact recurrence time for the patients, so we were not able to perform analyses of time-to-recurrence or recurrence-free survival. Despite these limitations,

however, statistically significant associations between a subset of radiomic features and *KRAS* status were observed and can potentially be incorporated into clinical decision support.

Conclusion

In conclusion, these analyses suggest that spiculation was associated with *KRAS* mutations while pleural attachment was associated with overall survival in patients with stage I lung adenocarcinoma. Validation will require a larger, multi-institutional cohort. Combining analysis of *KRAS* mutational status and CT features could better predict survival. Further, a non-invasive imaging method to enrich a population with *KRAS* mutations may be useful in the future to direct the use of anti-*KRAS* therapies, as they are developed.

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Clinical Practice Points

- Previous studies have demonstrated that preoperative CT findings are associated with pathological features and postoperative outcomes. Compared with molecular technologies, routine imaging can provide a more comprehensive view of the entire tumor through a much less invasive way. We hypothesize that CT features reflect underlying pathophysiology of tumors and that these can be driven with *KRAS* mutations.
- Spiculation was associated with *KRAS* mutations while pleural attachment was associated with overall survival in patients with stage I lung adenocarcinoma. Patients with wild-type *KRAS* and absent of pleural attachment had the most favorable overall survival.
- This work may help to advance the role of imaging in personalized medicine and predict prognosis noninvasively using imaging features.

Figure 1.
Kaplan–Meier survival curve for pleural attachment.

Figure 2.
Kaplan–Meier survival curve for combined analysis of *KRAS* mutational status and pleural attachment (PA).

Table 1
Clinical characteristics by *KRAS* mutational status

Clinical characteristic	<i>KRAS</i>		<i>p</i> value ^a	uOR (95% CI)
	Mutant	Wild-type		
Gender, N (%)			0.332	
Female	15 (45.5%)	26 (56.5%)		1.00 (referent)
Male	18 (54.5%)	20 (43.5%)		1.56 (0.63 – 3.83)
Age, mean (SD)	70.8 (8.3)	69.0 (9.4)	0.374	1.02 (0.97 – 1.08)
Smoking status, N (%)			0.394	
Never	1 (3.1%)	4 (8.7%)		1.00 (referent)
Ever	32 (96.9%)	42 (91.3%)		3.05 (0.32 – 28.6)
Race, N (%)			0.636	
Other	1 (3.1 %)	3 (6.5%)		1.00 (referent)
White	32 (96.9%)	43 (93.5%)		2.23 (0.22 – 22.5)
Stage, N (%)			0.580	
IA	21 (63.6 %)	32 (69.6%)		1.00 (referent)
IB	12 (36.4%)	14 (30.4%)		1.31 (0.51 – 3.36)
Recurrence^b			0.697	
No recurrence	19 (70.4)	23 (65.7)		1.00 (referent)
Recurrence	8 (29.6)	12 (34.3)		0.81 (0.27 – 2.38)

Abbreviations: SD, standard deviation; uOR, univariable odds ratio; CI, confidence interval

^aP-value from Chi-square or Fisher's exact test

^bRecurrence status is unknown on 17 patients

Table 2
CT features by *KRAS* mutational status

CT feature	<i>KRAS</i>		<i>p</i> value ^a	uOR (95% CI)
	Mutant	Wild-type		
Spiculation, N (%)			0.021	
absent	10 (30.3%)	26 (56.5%)		1.00 (referent)
present	23 (69.7%)	20 (43.5%)		2.99 (1.16 – 7.68)
Concavity, N (%)			0.713	
absent	18 (54.5%)	27 (58.7%)		1.00 (referent)
present	15 (45.5%)	19 (41.3%)		1.18 (0.48 – 2.92)
Ground-glass opacity, N (%)			0.659	
absent	16 (48.5%)	20 (43.5%)		1.00 (referent)
present	17 (51.5%)	26 (56.5%)		0.82 (0.33 – 2.01)
Bubble-like lucency, N (%)			0.981	
absent	13 (39.4%)	18 (39.1%)		1.00 (referent)
present	20 (60.4%)	28 (60.9%)		0.99 (0.40 – 2.47)
Air bronchogram, N (%)			0.164	
absent	12 (36.4%)	24 (52.2%)		1.00 (referent)
present	21 (63.6%)	22 (47.8%)		1.91 (0.76 – 4.77)
Pleural retraction, N (%)			0.364	
absent	6 (18.2%)	4 (8.7%)		1.00 (referent)
present	27 (81.8%)	42 (91.3%)		0.42 (0.11 – 1.66)
Pleural attachment, N (%)			0.480	
absent	16 (48.5%)	26 (56.5%)		1.00 (referent)
present	17 (51.5%)	20 (43.5%)		1.38 (0.56 – 3.39)

Bold font indicates a statistically significant p-value or odds ratio

Abbreviations: uOR, univariable odds ratio; CI, confidence interval

^aP-value from Chi-square or Fisher's exact test

Table 3
CT features by lung cancer recurrence status

CT feature	Recurrence ^b		<i>p</i> value ^a	uOR (95% CI)
	No recurrence	Recurrence		
Spiculation, N (%)			0.986	
absent	19 (45.2)	9 (45.0)		1.00 (referent)
present	23 (54.8)	11 (55.0)		1.01 (0.35 – 2.94)
Concavity, N (%)			0.679	
absent	25 (59.5)	13 (65.0)		1.00 (referent)
present	17 (40.5)	7 (35.0)		0.79 (0.26 – 2.39)
Ground-glass opacity, N (%)			0.573	
absent	20 (47.6)	8 (40.0)		1.00 (referent)
present	22 (42.4)	12 (60.0)		1.36 (0.46 – 4.02)
Bubble-like lucency, N (%)			0.189	
absent	20 (47.6)	6 (30.0)		1.00 (referent)
present	22 (52.4)	14 (70.0)		2.12 (0.68 – 6.57)
Air bronchogram, N (%)			0.209	
absent	16 (38.1)	11 (55.0)		1.00 (referent)
present	26 (61.9)	9 (45.0)		0.50 (0.17 – 1.48)
Pleural retraction, N (%)			0.486	
absent	7 (16.7)	2 (10.0)		1.00 (referent)
present	35 (83.3)	18 (90.0)		1.80 (0.34 – 9.57)
Pleural attachment, N (%)			0.725	
absent	23 (54.8)	10 (50.0)		1.00 (referent)
present	19 (45.2)	10 (50.0)		1.22 (0.42 – 3.52)

Abbreviations: uOR, univariable odds ratio; CI, confidence interval

^aP-value from Chi-square or Fisher's exact test

^bRecurrence status is unknown on 17 patients

Table 4
CT features and *KRAS* mutational status associated with overall survival

CT feature and <i>KRAS</i>	uHR (95% CI)
<i>KRAS</i>	
Wildtype	1.00 (referent)
Mutant	1.24 (0.57 – 2.69)
Spiculation, N (%)	
absent	1.00 (referent)
present	1.06 (0.49 – 2.30)
Concavity, N (%)	
absent	1.00 (referent)
present	1.72 (0.80 – 3.74)
Ground-glass opacity, N (%)	
absent	1.00 (referent)
present	0.71 (0.33 – 1.53)
Bubble-like lucency, N (%)	
absent	1.00 (referent)
present	0.67 (0.31 – 1.44)
Air bronchogram, N (%)	
absent	1.00 (referent)
present	1.57 (0.72 – 3.47)
Pleural retraction, N (%)	
absent	1.00 (referent)
present	NC
Pleural attachment, N (%)	
absent	1.00 (referent)
present	2.46 (1.09 – 5.53)
Pleural attachment/<i>KRAS</i>	
Absent/Wildtype	1.00 (referent)
Present/Wildtype	3.86 (1.21 – 12.34)
Absent/Mutant	2.14 (0.56 – 7.99)
Present/Mutant	3.17 (0.93 – 10.86)

Bold font indicates a statistically significant hazard ratio

Abbreviations: uHR, univariable hazard; CI, confidence interval; NC, not calculable