Original Article

Depicting growth characteristics with computed tomography for KRAS-mutated lung adenocarcinoma

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Background: Kirsten rat sarcoma viral oncogene homolog (KRAS) is a key oncogenic driver in lung adenocarcinoma (LUAD). The correlation between KRAS mutations and the computed tomographic (CT) texture features in LUAD patients is not well established. This study aimed to investigate the relationship between the CT texture features of LUAD and the KRAS mutation.

Methods: This study included 808 LUAD patients who were diagnosed with the KRAS mutation and underwent surgical resection at the Huadong Hospital. Of the 808 patients, 720 had preoperative chest CT data, which were collected for retrospective analysis. Further, all the CT images of lesions were classified into different categories based on the CT texture features. Moreover, the association between KRAS status and the clinical features and CT texture features was evaluated.

Results: The results revealed that KRAS mutations were more common in the male patients than the female patients [8.5% (29/341) *vs.* 2.4% (11/467), P<0.0001] and were more frequent in the older patients than the younger patients [6.5% (29/448) *vs.* 3.1% (11/360), P=0.02]. The CT texture feature of mixed ground-glass opacity (mGGO) indicated a lower incidence of KRAS mutations than the CT texture features of pure ground-glass opacity (pGGO) [1.3% (3/232) *vs.* 6.7% (15/225), P=0.0032] and pure solid opacity (pSO) [1.3% (3/232) *vs.* 6.1% (16/263), P=0.0056]. Moreover, a comparison of the frequency of pGGOs and pSOs ≤1 cm showed that the frequency of PGOs was higher than that of pSOs for KRAS mutations *vs.* wild type, but the statistical significance was marginal [12.0% (11/92) *vs.* 0% (0/27), P=0.05].

Conclusions: This study revealed that KRAS mutations were more common in male and older LUAD patients. Further, in most LUAD patients with KRAS mutations, pGGOs changed into pSOs at the size of >1 cm at least.

Keywords: Lung adenocarcinoma (LUAD); Kirsten rat sarcoma viral oncogene homolog (KRAS); computed tomography (CT); texture; smoking

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Introduction

In recent years, several non-small cell lung cancer (NSCLC) associated oncogenes have been identified (1-3), including the mutated epidermal growth factor receptor (EGFR) gene, rearranged anaplastic lymphoma kinase (*ALK*) gene, and mutated Kirsten rat sarcoma viral oncogene homolog (KRAS) (4). Mutations in driver genes have been shown to be significantly related to the prognosis of patients (5-7). Further, it has been estimated that 5–15% of NSCLC patients in Asian populations have the KRAS mutation (8). The KRAS is either present in the rat sarcoma (RAS)-guanosine triphosphate bound active state, or the RAS-guanosine diphosphate bound inactive state (9).

Computed tomography (CT) is the optimal modality for detecting and characterizing pulmonary tumors (10,11). In lung adenocarcinoma (LUAD), pulmonary nodules are categorized into the following three groups based on their consolidation-to-tumor (C/T) ratios, which are determined using CT images obtained within one month before surgery: the pure ground-glass opacity (pGGO) type (C/T ratio: 0); the partial-solid tumor type (0< C/T ratio <1); and the solid tumor type (C/T ratio: 1) (12). Due to it high-density resolution, lung CT scans can help to investigate the growth of LUAD.

This study analyzed 808 LUAD patients with KRAS mutations and their preoperative CT scans to evaluate the growth characteristics of LUAD in patients with KRAS mutations. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1880/rc).

Methods

Patients

This study was approved by the Ethics Review Board of the Huadong Hospital, Fudan University (No. 20230108), and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The requirement of informed consent was waived for this study due to its retrospective nature.

This study included 808 histologically confirmed LUAD patients with primary lung cancer at the Huadong Hospital, who were enrolled from January 2018 to December 2023. The patients were selected consecutively. To be eligible for inclusion in the study, the patients had to meet the following inclusion criteria: (I) have been pathologically diagnosed with LUAD; (II) have single lesions on CT scans; (III) have undergone KRAS mutation tests; and (IV) have clinical data, including age, sex, and smoking history data, available.

Of the 808 patients, 720 had preoperative CT scans, which were used to evaluate the CT features of the lesions. The medical record analysis revealed that 68 patients had no record of the size of the specimen, and 740 patients had pathological data available.

CT assessment

Preoperative chest CT scans were performed using three scanners: GE Discovery CT750 HD, 64-slice Light Speed volume CT (GE Medical Systems, GE Healthcare, Chicago, IL, USA), and Somatom Definition Flash (Siemens Healthcare, Forchheim, Germany). The following scanning parameters were used: 120 kVp, 100–200 mAs, 0.75–1.5 pitch range, and 1–1.25 mm collimation widths. A medium sharp reconstruction algorithm was used for all the imaging data and provided images of 1–1.25-mm thickness.

Interpretation of CT images

The CT images were independently reviewed by two radiologists with 10 to 12 years of experience in chest CT diagnosis. The radiologists were aware that the patients had undergone surgical resection for LUAD; however, they were blinded to clinical data, as well as gene expression and mutational status data. Both mediastinal [width =350 Hounsfield unit (HU); level =40 HU] and lung (width =1,500 HU; level =–650 HU) window settings were employed for the CT image analysis. Further, lesion location, size, and texture were retrospectively analyzed, with the long-axis diameter measured at the largest section. The lesions with 100% ground-glass opacity (GGO) were categorized as pGGO, those with 1% and 100% GGO were as classified mixed ground-glass opacity (mGGO), and those lacking GGO (0%) were classified as pure solid opacity (pSO).

Mutation analysis

To analyze the mutation status of the patients, samples were subjected to amplification refractory mutation system quantitative polymerase chain reaction analysis.

Statistical analysis

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was

Table 1 Correlation between the clinical features and KRAS status

Groups	KRAS mutation	KRAS wild type	P value
Sex, n			<0.0001
Male	29	312	
Female	11	456	
Age (years), n			0.02
≤60	11	349	
>60	29	419	
Smoking, n			
Yes	7	65	
No	33	703	0.05
No[¶]	29	312	0.74[†]
Yes[‡]	3	35	0.90[§]
[#]T stage, n			
T1a	11	198	0.59
≥T1b	23	508	
[#]N stage, n			
N0	32	675	0.68
≥ N1	2	31	

[†], only includes males; [‡], smoking index >400; [§], between males with a "never-smoking status" and those with a smoking index >400; [¶], only including males; [#], 68 of 808 patients had no corresponding records. KRAS, Kirsten rat sarcoma viral oncogene homolog.

employed for all the statistical analyses. The distribution differences in the categorical variables were assessed using the chi-square (χ^2) test, while differences in the continuous variables were evaluated using the independent *t*-test. A P value of <0.05 was considered statistically significant.

Results

Patient demographics

The study included 808 patients, 341 men and 467 women, who had an average age of 61.4 years (range, 16–86 years). Among the patients, 40 (4.9%) had KRAS mutations, and 65 had a history of smoking.

Correlation between KRAS status and clinical factors

The results of the statistical analysis (*Table 1*) indicated that the incidence of the KRAS mutation was higher in the male patients than the female patients [8.5% (29/341) *vs.* 2.4% (11/467), P<0.0001], and in the older patients than the younger patients [6.5% (29/448) *vs.* 3.1% (11/360), P=0.02].

The correlation analysis revealed a marginally statistically significant association between the KRAS mutation and smoking in the overall cohort [9.7% (7/72) *vs.* 4.5% (33/736), P=0.05]. However, when excluding the female cohort, which had no smokers, no significant difference was observed between the smokers and non-smokers. The smoker group included patients with a smoking index of >400, and this group was compared with the never-smoking group to assess the incidence of the KRAS mutation, but no statistically significant difference was found.

The LUAD patients were also classified into T1a and ≥T1b stages, but no correlation was found between the KRAS mutation and T stage. Moreover, no correlation was found between lymph node status and the KRAS mutation in the LUAD patients.

Comparison of CT texture nodules between the patients with the KRAS mutation and KRAS wild-type lesions

Of the 720 patients with CT scans, 34 had KRAS mutations. The results indicated that the incidence of the KRAS mutation was statistically lower in the mGGO group than the pGGO group [1.3% (3/232) *vs.* 6.7% (15/225), P=0.0032 females] and pSO group [1.3% (3/232) *vs.* 6.1% (16/263), P=0.0056]. However, no statistically significant difference was found between the pGGO and pSO groups in terms of the KRAS mutation (P=0.79) (*Table 2* and *Figures 1*,*2*).

Comparison of pGGO and pSO rates in different sizes of lesions between the KRAS mutation and KRAS wild-type lesions

The pGGO and pSO rates of lesions ≤1 cm were compared. The frequency of ≤1 cm pGGO was higher than that of ≤1 cm pSO, but the level of statistical significance was marginal [12.0% (11/92) *vs.* 0 (0/27), P=0.05) (*Table 3*).

Discussion

The literature suggests that approximately 5–15% of NSCLC patients in Asian populations carry KRAS mutations (8), which is consistent with the results of this study, which had a KRAS mutation rate of 4.9%. Further, this study showed that KRAS mutations were more common in male and older LUAD patients, which is also in line with the findings of previous studies (13-15). For example,

Table 2 Comparison of the incidence rate of the KRAS mutation and KRAS wild type between different LUAD nodules in 720 patients with CT scans

CT texture	KRAS mutation	KRAS wild type	P value
pGGO, n	15	210	0.0032[†], 0.0056[‡], 0.79[§]
mGGO, n	3	229	
pSO, n	16	247	

[†], mGGO *vs.* pGGO; [‡], mGGO *vs.* pSO; [§], pGGO *vs*. pSO. CT, computed tomography; KRAS, Kirsten rat sarcoma viral oncogene homolog; LUAD, lung adenocarcinoma; mGGO, mixed ground-glass opacity; pGGO, pure ground-glass opacity; pSO, pure solid opacity.

Table 3 Comparison of the frequency of pGGO and pSO for a lesion size of ≤1 cm between the KRAS mutation and wild-type LUAD patients

CT textures and size	KRAS mutation	KRAS wild type	P value
pGGO ≤1 cm	11 (12.0)	81	0.05[†]
pSO ≤1 cm	0 (0.0)	27	

[†], Fisher's exact test of probability. The number in parentheses is the percentage of the corresponding lesions in a total of the same column. KRAS, Kirsten rat sarcoma viral oncogene homolog; LUAD, lung adenocarcinoma; pGGO, pure ground-glass opacity; pSO, pure solid opacity.

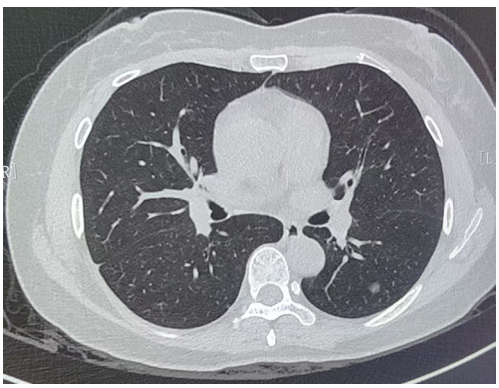

Figure 1 CT image of a 53-year-old female LUAD patient with the KRAS mutation. CT scan showed a pGGO with a diameter of 7 mm in the left inferior lobe. CT, computed tomography; KRAS, Kirsten rat sarcoma viral oncogene homolog; LUAD, lung adenocarcinoma; pGGO, pure ground-glass opacity.

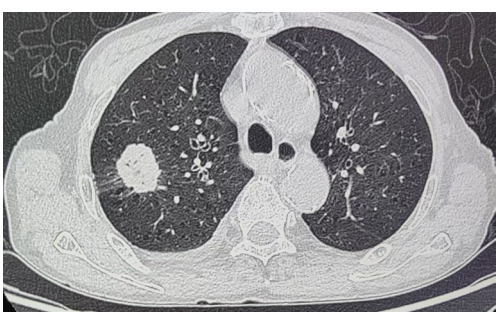

Figure 2 CT image of a 71-year-old male LUAD patient with the KRAS mutation. The CT scan showed a pSO with a diameter of 2.8 cm in the right upper lobe. CT, computed tomography; KRAS, Kirsten rat sarcoma viral oncogene homolog; LUAD, lung adenocarcinoma; pSO, pure solid opacity.

one study (16) reported that 275 of 3,829 LUAD patients had KRAS mutations. KRAS mutations have also found to be correlated with a male gender but not age (17-22). Conversely, other studies have reported that the KRAS mutation is not associated with sex or age (13-23). These conflicting results can be attributed to the scarcity of KRAS mutations and ethnic differences; thus, further research needs to be conducted.

A few studies (13,23) have reported that smoking is not associated with the KRAS mutation; however, the most studies, including one meta-analysis (24), have reported that the KRAS mutation is correlated with smoking (14,15,17-19,21,24-27). The present study found a marginal correlation between smoking and the KRAS mutation when both females and males were included in the cohort (P=0.05). However, this correlation disappeared when the females were excluded from the cohort, which is significant, as most females in China are non-smokers. Further, the comparison of the incidence of the KRAS mutation between heavy smokers (those with a smoking index >400) and never smokers revealed no significant difference. Zhu *et al.* (16) studied 275 patients with the KRAS mutation, and found that the KRAS mutation was more common in smokers before propensity score matching, but found no correlation after propensity score matching. In general, the prevalence of smoking is higher in men than women worldwide (28-33). A meta-analysis of 68,868 lung cancer cases reported that the prevalence of smoking in men ranged from 11.7% to 97.5%, while in women, it ranged from 5.9% to 67.7% (34). However, previous studies did not distinguish between males and females when evaluating the effect of smoking on KRAS mutations. Thus, further research needs to be conducted to determine whether the correlation between the KRAS mutation and smoking is due to the prevalence of smoking or ethnic differences.

In this study, no correlation was found between the T and N stages, and the KRAS mutation, which is consistent with the findings of previous studies (16,21,35).

Research on CT texture features is scarce. Some studies have found no significant association between KRAS mutations and the presence of any GGO (36-38) or the GGO ratio (35); however, these studies cannot be compared with the present study, as they did not distinguish between pGGO and mGGO. Notably, Wang *et al.* (39) revealed that KRAS mutations were more common in lesions with a lower GGO proportion, while Park *et al.* (40) found that KRAS mutations were associated with solid tumors. However, these studies are not comparable with the present study, as the sample size of Wang *et al.*'s (39) study was relatively small, and the Park *et al.*'s (40) study only included advanced LUAD patients.

This study found that the KRAS mutation lesions had a CT texture feature that could be described as "more at the two ends and less in the middle" (i.e., a dumbbell shape). Further, the frequency of mGGOs was significantly lower than that of pGGOs and pSOs. The incidence rates of pGGOs, mGGOs, and pSOs in LUAD have been reported to range from 17.1–39.2%, 28.5–28.8%, and 32.0–54.3%, respectively (16,26,39), while in the present study, the rates were 31.3%, 32.2%, and 36.4%, respectively. These results fall within the range of previous findings, suggesting that they were not influenced by interpretive bias.

It may be that the CT texture features of pGGO, mGGO, and pSO present in a dumbbell shape because the initial increase in the size of the GGO nodule is followed by the appearance and gradual enlargement of a solid portion within the lesion (41). Lesions transitioning from pGGO to mGGO, or from mGGO to pSO have shown a rapid increase in size (10,42,43). Overall, it can be inferred that the mGGO associated with the KRAS mutation is a distinct type. If pGGO lesions of this type transition to mGGO, the solid components in the mGGO increase rapidly, resulting in a rapid change to pSO. Therefore, in LUAD, the mGGO of the KRAS period is very short, resulting in reduced frequency of visible mGGOs.

To validate this hypothesis, the frequency of ≤1 cm pGGO and pSO LUAD were compared between the KRAS mutation and KRAS wild-type lesions. The results showed that the frequency of pSO was less than that of pGGO [0% (0/27) *vs.* 12.0% (11/92), P=0.05], but the P value was only marginally significant. Studies have found that the presence of a solid portion (an mGGO or pSO) is a risk factor for a significant size increase (10,44). Thus, it can be inferred that most KRAS mutation lesions change into pSOs at a size of at least >1 cm, but as stated above, the statistical significance was marginal. This showed that the speed at which pGGO changes into pSO in KRAS mutation lesions was slower than that of KRAS wild-type lesions in LUAD.

Limitations

This study had a number of limitations. First, the sample size was relatively small; therefore, the stratification of smokers by KRAS status was not possible. Second, the majority of the Chinese female patients had no history of smoking due to cultural factors. Therefore, it was not appropriate to compare smoking with the KRAS mutation in this group. Third, only patients with single lesions were included in the study, and patients with multiple lesions were not included in the study. Fourth, due to the inherent limitations of a retrospective analysis, this study only provides preliminary data on the CT texture features of LUAD for the KRAS mutation. Fifth, as the patients lacked CT scans, an analysis of the progression characteristics of LUAD with and without the KRAS mutation could not be conducted; therefore, the progression characteristics are speculative, which weakens our hypothesis. Further studies need to be conducted to gather evidence in support of our hypothesis. Sixth, the identification of the progression feature of LUAD with the KRAS mutation was based on a comparison between LUAD with or without the KRAS mutation, and no comparisons with other kinds of mutations (e.g., EGFR and ALK) were made. In the future, we intend to conduct analyses of other types of mutations in LUAD.

Conclusions

The results showed that the incidence of the KRAS mutation was higher in male and older LUAD patients. Further, smoking was not found to be associated with the KRAS mutation. Moreover, in KRAS-mutant LUAD, mGGO was observed less frequently than pGGO and pSO, and most lesions that transitioned from pGGO to pSO were at least >1 cm in size. Further large-scale studies and investigations need to be conducted to verify these findings, especially for the marginally statistically significant results.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1880/coif). The authors have no conflicts of interest to declare.

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. This retrospective study was approved by the Ethics Review Board of the Huadong Hospital, Fudan University (No. 20230108), and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The requirement for informed consent was waived for this study due to its retrospective nature.

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