Dual-energy spectral CT characteristics in surgically resected lung adenocarcinoma: comparison between Kirsten rat sarcoma viral oncogene mutations and epidermal growth factor receptor mutations

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Abstract

Background: Kirsten rat sarcoma viral oncogene homolog (KRAS) and epidermal growth factor receptor (EGFR) are the two most frequent and well-known oncogene of lung adenocarcinoma. The purpose of this study is to compare the characteristics measured with dual-energy spectral computed tomography (DESCT) in lung adenocarcinoma patients who have KRAS and EGFR gene mutations.

Methods: Patients with surgically resected lung adenocarcinoma (n = 72) were enrolled, including 12 patients with KRAS mutations and 60 patients with EGFR mutations. DESCT quantitative parameters, including the CT number at 70 keV, the slopes of the spectral attenuation curves (slope λ HU), normalized iodine concentration (NIC), normalized water concentration (NWC), and effective atomic number (effective Z), were analyzed. A multiple logistic regression model was applied to discriminate clinical and DESCT characteristics between the types of mutations.

Results: The KRAS mutation was more common in people who smoked than the EGFR mutation. Nodule type differed significantly between the KRAS and EGFR groups (P = 0.035), and all KRAS mutation adenocarcinomas were solid nodules. Most DESCT quantitative parameters differed significantly between solid nodules and subsolid nodules. CT number at 70 keV, slope λ HU, NIC, and effective Z differed significantly between the KRAS and EGFR groups (P = 0.006, 0.017, 0.013 and 0.010) with solid lung adenocarcinoma. Multivariate logistic analysis of DESCT and clinical features indicated that besides smoking history, the CT value at 70 keV (OR = 0.938, P = 0.009) was significant independent factor that could be used to differentiate KRAS and EGFR mutations in solid lung adenocarcinoma.

Conclusions: DESCT would be a potential tool to differentiate lung adenocarcinoma patients with a KRAS mutation from those with an EGFR mutation.

Keywords: Dual-energy spectral computed tomography, Adenocarcinoma of lung, Solid nodule, Subsolid nodule, EGFR mutation, KRAS mutation
Introduction

Lung cancer is the leading cause of cancer deaths worldwide, and adenocarcinoma is its most common histologic form [1, 2]. Lung adenocarcinoma is considered a highly molecular heterogeneous disease [3]. In recent years, interest in the key role of proto-oncogenes in lung adenocarcinoma has been growing because of the rapid advances in molecularly targeted therapies. Kirsten rat sarcoma viral oncogene (KRAS) and epidermal growth factor receptor (EGFR) are the most frequent and well-known mutated oncogenes in adenocarcinoma of the lung. Compared with other types of lung adenocarcinoma, lung adenocarcinoma with EGFR mutation shows a good response to treatment with EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib [4, 5]. However, KRAS is still considered a nondrug target, and efforts to therapeutically target KRAS mutations have proved unsuccessful [6]. Indeed, KRAS has been proven to be a biomarker of resistance to EGFR-TKI treatment. In addition, previous studies have indicated that KRAS mutations are associated with worse survival, and these mutations are thought to be a negative prognostic marker in patients with lung cancer, especially patients with adenocarcinoma and early stage disease [7–11]. In the latest guideline (2018) from the College of American Pathologists/International Association for the Study of Lung Cancer/Association of Molecular Pathology, EGFR is indicated as a necessary testing gene for lung adenocarcinoma, and KRAS is a recommended testing gene, especially in cases where routine tests for EGFR show negative results [12].

Medical imaging – particularly computed tomography (CT) – is an essential noninvasive procedure for lung cancer diagnosis, staging and therapeutic response evaluation. The relationship between CT characteristics and lung cancer gene phenotypes has been a research area of particular interest, especially in relation to EGFR mutation [13, 14]. However, only a few studies have examined the correlation between the CT findings of lung adenocarcinoma and KRAS mutational status [15–18]. These studies showed that no or few inconsistent CT characteristics were associated with KRAS mutations. Furthermore, conventional CT imaging signs lack quantitative evaluation, making them vulnerable to subjective judgment. As a new, revolutionary CT imaging method, dual-energy spectral CT (DESCT) can improve material differentiation by using two different X-ray energy spectra [19, 20]. Compared to conventional mix-energy CT, DESCT scan can use a single tube with fast and dynamic kVp switching between 80 and 140 kVp X-rays during a single rotation and generates 101 monochromatic CT images in the range of 40 to 140 keV, as well as iodine/water-based density and effective atomic number images [21, 22]. Therefore, DESCT can provide multiple quantitative measurements, including the monochromatic CT number, the slope of the spectral Hounsfield unit (HU) curve (slope λ HU) based on monochromatic images, the iodine concentration (IC) based on iodine-based density images, the water concentration (WC) based on water-based density images, and the effective atomic number (effective Z) based on effective atomic number images. It has been proven that DESCT has potential applications in various clinical areas, including diagnostics in oncology [20, 23, 24]. Regarding lung cancer, DESCT has been employed in the differential diagnosis of cancers from benign lung nodules and the identification of lymph node metastases and has been used to distinguish histologic subtypes, such as adenocarcinoma and squamous cell carcinoma [25–31].

The occurrence of KRAS and EGFR mutations is mutually exclusive, and they exhibit many contrasting characteristics, such as clinical background and prognostic implications. To our knowledge, there has been scarce previous description of the DESCT characteristics of tumors with a KRAS mutation. We hypothesized that DESCT features can be used to distinguish KRAS mutations from EGFR mutations in lung adenocarcinoma. Therefore, we aimed to retrospectively explore potential differences in DESCT features between KRAS and EGFR mutations in a cohort of Chinese patients with lung adenocarcinomas.

Materials and methods

Patient selection

The study population was retrospectively selected from a prospectively collected and recorded database of information from patients who had lung nodules and masses and were undergoing pretreatment chest spectral DESCT from May 2013 to December 2015 at our institution. Inclusion criteria included being diagnosed with a cell type adenocarcinoma and having testing performed for EGFR and KRAS mutations after radical surgery at our institution (Fig. 1). The institutional ethics committee approved this study of prospectively collected data. Written informed consent for the use of clinical and imaging data for scientific and/or educational purposes was waived for this retrospective study.

DESCT examination

All patients received a DESCT (Discovery CT 750 HD, GE Healthcare, USA) enhanced chest scan from the apex of the lung to the adrenal gland before treatment. The scan applied gemstone spectral imaging (GSI) mode protocol, whose tube voltage fast switching between 80 keV and 140 keV with a cycle of 0.5 ms. The other scanning parameters were as follows: tube current of 550 mA, tube rotation time of 0.6 s, collimator of 40 mm, helical mode with a pitch of 0.984, field of view (FOV) of large body, and slice thickness and interval for axial images of 1.25 mm and 0.8 mm. All patients were intravenously injected with
Consecutive patients underwent chest DESCT scan from May 2013 to December 2015 with pathological diagnosis (n = 1010)

Lung adenocarcinoma patients with both EGFR and KRAS gene mutation tests confirmed by radical surgery (n = 106)

Lung adenocarcinoma patients with EGFR mutations (n = 60)

Lung adenocarcinoma patients with KRAS mutations (n = 12)

Fig. 1 Flowchart depicting the patient selection

**DESCT image analysis**

The CT of all lung nodules was evaluated visually by two experienced radiologists. The morphological nodule type included solid nodule (SN), part-solid nodule (PSN) or mixed ground-glass opacity (GGO), and nonsolid nodule (NSN) or pure GGO; NSN was defined as a hazy increased opacity of lung, with preservation of bronchial and vascular margins; PSN was defined as a combination of ground glass and solid attenuation, which obscures the underlying lung architecture on CT; NSN and PSN were both referred to as subsolid nodules (SSN) [32–34].

The original data acquired were reconstructed into monochromatic images. The reconstructed images were sent to a post processing workstation (Advantage Workstation 4.6, GE Healthcare, Milwaukee, WI), where GSI Viewer software was used to analyze the enhanced monochromatic data and determine quantitative parameters. For the axial image, a radiologist with 10 years of experience in CT diagnosis of chest tumors selected the axial CT slice that depicted the maximum diameter of the primary tumor and positioned the region of interest (ROI) at the center of the lesion manually. The ROI range was drawn with no less than 2/3 of the area of the lesion. Cavities, vacuoles, calcification, blood vessels and pulmonary atelectasis were avoided. Quantitative parameters measured included IC, WC, effective Z and slope $\lambda$ HU, which was calculated as the difference between the CT number at 40 keV and that at 100 keV divided by the energy difference of 60 keV [$slope \lambda = (CT_{40keV} - CT_{100keV})/60$]. The enhanced CT number at 70 keV was selected because the 120 kVp scanning in conventional polychromatic images has an average energy of approximately 70 keV in the GSI mode. To minimize the variations caused by the patient’s circulation status and the scanning times, the IC and WC of each lung lesion were normalized to the IC and WC of the descending aorta, respectively, at the T6 level to calculate a normalized IC (NIC; NIC = IC_{lesion} / IC_{aorta}) and a normalized WC (NWC; NWC = WC_{lesion} / WC_{aorta}). Finally, five types of quantitative data were obtained: CT number at 70 keV, slope $\lambda$ HU, NIC, NWC and effective Z.
Tumor pathologic characteristics and mutation analysis

All patient pathologies were confirmed by radical operative pathological examinations. All histologic and mutation analyses were performed on surgical specimens. Tumor histologic characteristics were classified on the basis of the 2015 World Health Organization criteria. The mutation status of KRAS and EGFR was examined by molecular pathological analysis.

Statistical analysis

The patient clinical and DESCT characteristics of the study population are expressed as the means and standard deviations. The association of CT texture type and DESCT features were assessed using a two-tailed Mann-Whitney U test. The differences were considered significant if the probability value (P) was less than 0.05.

Table 1 Comparison between clinical and CT texture with KRAS and EGFR mutation status in lung adenocarcinoma

| Characteristics | Total | KRAS | EGFR | P value |
|-----------------|-------|------|------|---------|
| No. of patients | 72    | 12   | 60   |         |
| Age (y)         | 56.75 ± 10.13 | 58.75 ± 7.53 | 56.35 ± 10.58 | 0.458   |
| Sex             |       |      |      | 0.054   |
| Female          | 42 (58.3) | 4 (33.3) | 38 (63.3) |         |
| Male            | 30 (41.7) | 8 (66.7) | 22 (36.7) |         |
| Smoking         |       |      |      | 0.002   |
| Never smoked    | 55 (76.4) | 4 (33.3) | 47 (78.3) |         |
| Smoker          | 17 (23.6) | 8 (66.7) | 13 (21.7) |         |
| Location        |       |      |      | 0.521   |
| Central         | 2 (2.8) | 0 (0.0) | 2 (3.3) |         |
| Peripheral      | 70 (97.2) | 12 (100.0) | 58 (96.7) |         |
| T stage         |       |      |      | 0.066   |
| T1–2            | 68 (94.4) | 10 (83.3) | 58 (96.7) |         |
| T3–4            | 4 (5.6) | 2 (16.7) | 2 (3.3) |         |
| N stage         |       |      |      | 0.702   |
| N0              | 47 (65.3) | 9 (7.5) | 38 (63.3) |         |
| N1–2            | 25 (34.7) | 3 (2.5) | 22 (36.7) |         |
| Maximum diameter | 2.89 ± 1.29 | 3.17 ± 1.38 | 2.83 ± 1.29 | 0.666   |
| CT texture feature |     |      |      | 0.035   |
| SN              | 56 (77.8) | 12 (100.0) | 44 (73.3) |         |
| SSN (PSN and NSN) | 16 (22.2) | 0 (0.0) | 16 (26.7) |         |

Note. Values are mean ± standard deviation or number (percentage)

aQuantitative data exhibited normal distribution and T test was applied
bQuantitative data did not exhibit normal distribution and Mann-Whitney U test was applied
p < 0.05 indicates significant difference. Significant P values are in bold
SN solid nodule, SSN Subsolid nodule, NIC Normalized iodine concentration, NWC Normalized water concentration, Slope λ HU the slope of the spectral Hounsfield unit curve, Effective Z effective atomic number

Table 2 Association of CT texture type and DESCT features

| Characteristics | Total | SN | SSN | P value |
|-----------------|-------|----|-----|---------|
| No. of patients | 72    | 56 | 16  |         |
| DESCT quantitative parameter | | | | |
| CT number at 70 keV | −5.25 ± 139.64 | 47.39 ± 23.04 | −189.49 ± 209.28 | 0.000 |
| Slope λ HU | 1.95 ± 1.03 | 1.71 ± 0.92 | 2.78 ± 0.98 | 0.000 |
| NIC | 0.22 ± 0.12 | 0.19 ± 0.12 | 0.28 ± 0.11 | 0.004 |
| NWC | 0.93 ± 0.14 | 0.99 ± 0.02 | 0.74 ± 0.19 | 0.000 |
| Effective Z | 8.06 ± 1.82 | 8.45 ± 0.43 | 6.69 ± 3.53 | 0.866 |

Note. Values are mean ± standard deviation or number

aQuantitative data did not exhibit normal distribution and Mann-Whitney U test was applied
| P < 0.05 indicates significant difference; Significant P values are in bold
SN solid nodule, SSN Subsolid nodule, NIC Normalized iodine concentration, NWC Normalized water concentration, Slope λ HU the slope of the spectral Hounsfield unit curve, Effective Z effective atomic number
deviations (X ± S) for continuous variables and as frequency or percentage for categorical variables. The normality of continuous variables was analyzed using one-sample Kolmogorov-Smirnov Z tests (K-S tests). Univariate analyses were performed to assess the difference in clinical and DESCT characteristics between patients with KRAS mutations and patients with EGFR mutations. A t test was used if the continuous data exhibited a normal distribution; the Mann-Whitney U test was used if the continuous data did not have a normal distribution. Categorical data were compared using chi-square (X²) tests or Fisher’s exact tests. The significant factors in univariate analyses were identified as candidate covariates in logistic regression models with backward elimination of covariates, and the odds ratios (OR) were calculated. A receiver operating characteristic (ROC) curve was generated for KRAS mutation prediction according to each significant factor. Diagnostic capability was assessed by calculating the area under curve (AUC). P values < 0.05 were considered significant. The statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL) statistical software package.

Results
A total of 72 patients with lung adenocarcinoma (30 males and 42 females; age 55.9 ± 11.6 years old) who underwent DESCT scanning and EGFR and KRAS testing were included in this study. According to the outcomes of gene testing, 60 patients had EGFR mutations (the EGFR group) and 12 patients exhibited KRAS mutations (the KRAS group).

Clinical and nodule type of patients with KRAS mutations compared to those with EGFR mutations in lung adenocarcinomas

Patient clinical and DESCT characteristics are reported in Table 1. KRAS mutations were less common in non-smoking people than EGFR mutations (33.3% vs 78.3%).

Table 3 Comparison between clinical and DESCT characteristics with KRAS and EGFR mutation status in solid lung adenocarcinoma

| Characteristics                  | Total | KRAS  | EGFR    | P value |
|----------------------------------|-------|-------|---------|---------|
| No. of patients                  | 56    | 12    | 44      |         |
| Age (y)                          | 55.98 ± 10.37 | 58.75 ± 7.53 | 55.23 ± 10.97 | 0.301   |
| Sex                              |       |       |         | 0.149   |
| Female                           | 29 (51.8) | 4 (33.3)   | 25 (56.8) |         |
| Male                             | 27 (48.2) | 8 (66.7)   | 19 (43.2) |         |
| Smoking                          |       |       |         | 0.012   |
| Never smoked                     | 36 (64.3) | 4 (33.3)   | 32 (72.7) |         |
| Smoker                           | 20 (35.7) | 8 (66.7)   | 12 (27.3) |         |
| Location                         |       |       |         | 0.452   |
| Central                          | 2 (3.6)  | 0 (0.0)   | 2 (4.5)   |         |
| Peripheral                       | 54 (96.4) | 12 (100.0) | 42 (95.5) |         |
| T stage                          |       |       |         | 0.148   |
| T1–2                             | 52 (92.9) | 10 (83.3)  | 42 (95.5) |         |
| T3–4                             | 4 (7.1)   | 2 (16.7)   | 2 (4.5)   |         |
| N stage                          |       |       |         | 0.158   |
| N0                               | 32 (57.1) | 9 (7.5)    | 23 (52.3) |         |
| N1–2                             | 24 (42.9) | 3 (2.5)    | 21 (47.7) |         |
| Maximum diameter                 | 3.15 ± 1.32 | 3.17 ± 1.38 | 3.14 ± 1.32 | 0.742   |
| DESCT quantitative parameter     |       |       |         |         |
| CT number at 70 keV              | 47.39 ± 23.04 | 31.52 ± 22.26 | 51.71 ± 21.51 | 0.006   |
| Slope λ HU                       | 1.71 ± 0.92  | 1.17 ± 0.77  | 1.85 ± 0.91  | 0.017   |
| NICb                             | 0.198 ± 0.12 | 0.14 ± 0.09  | 0.21 ± 0.12  | 0.013   |
| NWCb                             | 0.989 ± 0.02  | 0.98 ± 0.02  | 0.99 ± 0.02  | 0.239   |
| Effective Z                      | 8.45 ± 0.43  | 8.17 ± 0.39  | 8.52 ± 0.41  | 0.010   |

Note. Values are mean ± standard deviation or number (percentage)

aQuantitative data exhibited normal distribution and T test was applied
bQuantitative data did not exhibit normal distribution and Mann-Whitney U test was applied

P < 0.05 indicates significant difference; Significant P values are in bold

NIC Normalized iodine concentration, NWC Normalized water concentration, Slope λ HU the slope of the spectral Hounsfield unit curve, Effective Z effective atomic number
Nodule type was significantly different between the two mutations \((P = 0.035)\), and all KRAS mutation adenocarcinomas were SN tumors.

**Influence of nodule type on the quantitative parameters from DESCT**

The mean values of the CT number at 70 keV, slope \(\lambda\) HU, NIC, NWC, and effective Z were significantly different in SN tumors compared to SSN tumors, as shown in Table 2. There was no statistically significant difference in the effective Z between SN and SSN tumors, although the mean value in SSN was lower than that in SN (6.69 vs. 8.45).

**Clinical and quantitative DESCT parameters of patients with KRAS mutations compared to those with EGFR mutations in solid lung adenocarcinoma**

Because nodule type has obviously impact on DESCT quantitative parameters and all KRAS mutation adenocarcinomas were SN tumors, to make the measurement comparable, we deleted imaging data of the EGFR mutation group with SSN tumors before comparing differences between the two groups \((n = 12\) to \(n = 44)\). The clinical and DESCT characteristics of solid lung adenocarcinoma are reported in Table 3. For DESCT quantitative parameters, the CT number at 70 keV, slope \(\lambda\) HU, NIC, and effective Z values differed significantly between the KRAS and EGFR groups \((P = 0.006, 0.017, 0.013\) and 0.010, respectively) (Figs. 2, 3).

Multivariate analyses evaluating smoking, sex, CT number at 70 keV, NIC, effective Z, and slope \(\lambda\) HU showed that smoking \((OR = 7.421, P = 0.016)\) and CT number at 70 keV \((OR = 0.938, P = 0.009)\) were two independent prognostic factors for KRAS mutations compared to EGFR mutations in solid lung adenocarcinoma (Table 4). The AUC of CT number at 70 keV is 0.771 (95% CI: 0.597–0.945, \(P = 0.004\)) with the cutoff point of 38.47 HU. Based on this multivariate analysis, the two significant factors (CT number at 70 keV and smoking history) were combined to determine the predictive value to differentiate KRAS and EGFR mutations. The AUC of combining the two factors was 0.841 (95% CI: 0.717–0.965, \(P < 0.001\)) with the cutoff point of 2.72 (Fig. 4).

**Discussion**

Few studies have investigated conventional CT features and KRAS mutations in lung adenocarcinoma. Previous studies by Glynn et al. [15] did not find any conventional CT characteristics associated with KRAS mutations in...
patients with lung adenocarcinoma. Although some other studies showed that size, spiculation sign, and air bronchogram sign may be related to KRAS mutations, the results were quite inconsistent [16–18]. These negative or inconsistent results may reflect the limitations of conventional CT imaging signs, which lack a quantitative index and are unstable due to subjective judgment. In contrast, it is now widely recognized that the GGO ratio is significantly higher in tumors with EGFR mutations [13, 35, 36]. This phenomenon may be because EGFR mutations appear more frequently in lepidic predominant adenocarcinomas, which are associated with better outcomes [35, 37]. In this study, the SSN rate in tumors with EGFR mutations was higher than that in KRAS mutations (26.7% vs. 0%), and all KRAS mutation tumors were solid.

Given the difference in SSN that was observed between the KRAS and EGFR groups, we also studied the relationship between nodule type and DESCT quantitative parameters, which also has scarce been reported previously. Our results showed that all DESCT quantitative parameters, except effective Z, differed between SSN tumors and SN tumors. Effective Z was lower in SSN than SN, and although no statistically significant difference was observed, more sample size research is needed. The SSN contains an extremely low air attenuation, which result in low CT number at 70 keV. It is worthwhile to note that NIC and Slope λ HU of SSN were higher than SN on the contrary. This results suggest that NIC and Slope λ HU can hardly be affected by the low air attenuation in SSN, and the reason maybe the relatively small size and rich blood vessels or volume in the early stage tumor [38].

To eliminate the impact of SSN on DESCT quantitative parameters, and since the KRAS mutation adenocarcinoma are all SN as well, we deleted imaging data of SSN and then compared the difference between the two groups (KRAS n = 12 to EGFR n = 44). The results

Table 4 Multivariable Analysis of DESCT and Clinical Features Predicting the Presence of KRAS Mutation Compared to EGFR Mutation in Solid Lung Adenocarcinoma

| Characteristics                  | OR   | 95% CI       | P value |
|---------------------------------|------|--------------|---------|
| Smoking                         |      |              | 0.016   |
| Never smoked                    | 7.421| 1.451–37.948 |         |
| Smoker                          | 0.938| 0.894–0.984  | 0.009   |

Note. NA not applicable. OR odd ratio. CI confidence interval
showed that the CT number at 70 keV, slope $\lambda$ HU, NIf, and effective $Z$ were significantly different between solid lung adenocarcinomas with $KRAS$ and $EGFR$ mutations. $KRAS$ mutations in lung adenocarcinoma have special pathological features. In terms of the histological type, $KRAS$ mutations are associated more with mucinous adenocarcinoma or lung cancer with goblet cell morphology than with nonmucinous adenocarcinoma [39–42]. On the other hand, studies have shown that in addition to cancer genesis and development, $EGFR$ also plays important roles in stimulating angiogenesis through very complicated biological processes [43, 44]. We speculate that the DESCT findings might correlate with the underlying pathologic appearance. The mucus produced in $KRAS$ mutation lung adenocarcinoma and the rich blood supply of $EGFR$ mutation lung adenocarcinoma may result in the lower quantitative value with $KRAS$ mutations compared to $EGFR$ mutations.

A relationship between $KRAS$ mutational status and lung CT image features could improve the accuracy of medical decisions. Multivariate logistic analysis combining clinical and DESCT characteristics showed that CT value at 70 keV and smoking were the two independent factors potentially able to predict the presence of $KRAS$ mutations from $EGFR$ mutations in solid lung adenocarcinomas. The combination of CT number at 70 keV with smoking history was a powerful tool to differentiate $KRAS$ and $EGFR$ mutations, which could be used to aid in clinical diagnosis in the future. The ROC obtained by combining these significant factors also showed a relatively high predictive value for identifying $KRAS$ mutations (AUC = 0.841, 95% CI: 0.717–0.965). This finding suggests that combining clinical and DESCT characteristics can be recommended for use to differentiate $KRAS$ and $EGFR$ status in solid lung adenocarcinomas.
The prevalence of KRAS mutations is much lower in East Asian patients than in Western patients (8.3% vs. 32%, respectively) [45, 46]. Our study showed a KRAS mutation prevalence of 11.3% (12/106) in this population. In a previous study, KRAS mutations were more frequent in smokers and male patients than EGFR mutations [47]. In the same study, smoking history was found to be a significant determinant, while gender was a confounding factor [47]. In this study’s analysis of clinical characteristics, smoking history was significant factor in both univariate and multivariate analyses, which is consistent with previous work. The KRAS mutation was also more frequent in males than the EGFR mutation, but this gender difference was not significant ($P = 0.054$).

Although histological and immunohistochemical analyses have been accepted as the reference standard, identification of the relationship between DESCT quantitative measurements and KRAS status could help determine the molecular categories of lung adenocarcinoma. First, histological and immunohistochemical analyses of biopsies or surgical specimens is an invasive method, and it has also been well documented that diagnostic errors are common [48, 49]. Hence, additional diagnostic information can help improve accuracy. Second, 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 much less invasively. This benefit is even more critical in larger tumors, which can exhibit intratumor genomic heterogeneity [50]. Third, the relationship may suggest a greater need for blinded targeted therapies for the patients who cannot undergo histological sampling.

This study is the first to describe the imaging differences between lung cancer patients with KRAS and EGFR mutations using DESCT according to our knowledge. The present study also has several limitations. First, the retrospective single-center design has various potential biases. Second, the enrolled sample size was relatively small, especially for patients with KRAS mutations. Therefore, studies should be conducted with larger sample sizes to examine the precise characteristics of these mutations in the future.

**Conclusions**

In conclusion, the SN proportion was higher with KRAS than EGFR mutations and all KRAS mutation adenocarcinomas were SN tumors. DESCT features, especially CT number at 70 keV, can be an image biomarker to help distinguish KRAS and EGFR mutations in solid lung adenocarcinoma. Combining DESCT-based features with clinical variables – such as CT value at 70 keV with smoking history – is a promising approach for improving the discrimination of KRAS mutations from EGFR mutations in solid lung adenocarcinoma.

**Abbreviations**
- DESCT: Dual-energy spectral computed tomography; Effective Z: Effective atomic number; EGFR: Epidermal growth factor receptor; FISH: Fluorescence in situ hybridization; GGO: Ground-glass opacity; GS1: Gemstone spectral imaging; IHC: Immunohistochemistry; KRAS: Kirsten rat sarcoma viral oncogene homolog; NIC: Normalized iodine concentration; NSN: Nonsolid nodule; NWC: Normalized water concentration; Slope A: HU: Slope of the spectral Hounsfield unit curve; SN: Solid nodule; SSN: Subsolid nodule

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**Authors’ contributions**
ML and NW conceived and designed the study. WT, Y-JJ and L-LQ contributed data collection. ML and LZ contributed to data interpretation and statistical analysis. ML and J-CJ prepared the manuscript. NW revised the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**
The study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences (NCC2016G-029).

**Consent for publication**
All the authors have consented to the publication of this manuscript.

**Competing interests**
The authors declare that they have no competing interests.

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