

Correlation between high-resolution computed tomography lung nodule characteristics and EGFR mutation in lung adenocarcinomas

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Background: The aim of this study was to investigate the correlation of EGFR mutation on the high-resolution computed tomography (HRCT) features in lung adenocarcinoma.

Patients and methods: A total of 121 patients were diagnosed with lung adenocarcinoma from January 2014 to December 2016. The correlation of indexes (gender, age, tumor diameter, and EGFR mutation) was analyzed based on the HRCT characteristics of lung adenocarcinoma.

Results: There were 73 cases of EGFR mutation and 48 cases of wild-type EGFR. One hundred and three cases had pleural indentation that was significant in patients with EGFR mutation than those with wild-type EGFR ($P=0.038$). Forty-two out of 121 cases exhibited the bronchus cutoff sign. Patients with EGFR mutation were likely to develop the bronchus cutoff sign ($P=0.017$). Sixty-one out of 121 cases exhibited the lobulation sign, which was significant in patients with EGFR mutation than those with wild-type EGFR ($P<0.001$). A significant correlation was found between lobulation sign and tumor diameter ($P=0.024$). Forty-eight out of 121 and 23 out of 121 cases showed the vessel and vacuole signs, respectively. However, patients with EGFR mutation did not exert a significant correlation on either of these signs ($P=0.555$ and $P=0.372$, respectively). A statistical significance was not observed in indexes such as age, gender, and tumor diameter on pleural indentation, bronchus cutoff sign, vessel sign, and vacuole sign ($P>0.05$). Age and gender did not vary significantly in the lobulation sign ($P>0.05$).

Conclusion: HRCT characteristics such as pleural indentation, bronchus cutoff sign, and lobulation sign in lung adenocarcinoma with EGFR mutation were significantly greater than those with wild-type EGFR; however, further study is essential in determining the predictive ability of computed tomography (CT) for EGFR mutations in lung adenocarcinoma.

Keywords: computed tomography, EGFR mutation, lung adenocarcinoma, pleural traction, bronchus cutoff sign

Introduction

The incidence of lung cancer is continually increasing; currently, it is 54.8/100,000 with a 26.9% rate of increase in China from 1972 to 2006. However, the effect of treatment on the disease is not improved substantially, and the overall survival rate is 10%–15%.¹ High-resolution computed tomography (HRCT) is primarily used for the early detection of lung adenocarcinoma. Due to the prolonged doubling time of the lesion and since the altered diameter and volume of the lesion cannot be observed in a short period, the assessment of invasiveness mainly relies on the characteristics of HRCT.² The common computed tomography (CT) signs include pleural traction, lobulation sign, vessel sign, vacuole sign, and bronchus cutoff sign. Early peripheral adenocarcinoma is mainly treated by surgery. When the lesion diameter is small,

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the pathological diagnosis before an operation, using bronchoscopy or percutaneous pulmonary biopsy, is challenging. In this case, the HRCT characteristics are crucial reference indicators that can impact the early diagnosis, treatment, and prognosis of lung adenocarcinoma.^{3,4} The rate of EGFR mutation is up to 60% in lung adenocarcinoma in the Asian population, and patients with the mutation exhibit significant invasiveness and poor prognosis.⁵ Previous studies have shown that patients with EGFR mutation are susceptible to recurrence and distant metastasis after operation.⁶ Chao et al⁷ found that the EGFR mutation in Chinese patients was correlated with the recent pathological classification and prognosis of lung adenocarcinoma. The present study aimed to employ a 64-slice CT examination to find lesions, followed by a 0.625 mm reconstruction for evaluating the relationship between the invasiveness of lung adenocarcinoma on the peripheral structures and EGFR mutation. This correlation would elucidate the effect of EGFR mutation on early HRCT imaging characteristics, thereby guiding the clinical treatment.

Patients and methods

General data

Ethics statement

This study was approved by the medical ethical committee of Linyi City People's Hospital as a retrospective study. The requirement for patient informed consent was waived by the ethical committee because of the retrospective nature of this study, but patient data confidentiality was protected. The ID of ethical approval was 30009 with confirmation of compliance with the Declaration of Helsinki.

Methods

A total of 121 patients diagnosed with lung adenocarcinoma in Linyi People's Hospital from January 2014 to December 2016 were analyzed retrospectively. All patients had undergone a 64-slice enhanced CT scanning. The HRCT characteristics, including pleural indentation, bronchus cutoff sign, vessel sign, vacuole sign, and lobulation sign, were observed. Moreover, statistical analysis was performed to analyze the effect of EGFR mutation, gender, age, and tumor diameter (largest diameter on axial, sagittal, and coronal sections) on the imaging characteristics. All patients were diagnosed by bronchoscopy biopsy, percutaneous pulmonary biopsy, or postoperative pathology, and the EGFR mutation was detected. All patients were diagnosed with lung adenocarcinoma stage I–IIIA for the first time and did not undergo radiotherapy, chemotherapy, or

targeted therapy. The absence of metastasis was confirmed by positron emission tomography-CT or cerebral magnetic resonance imaging, bone emission computed tomography, and abdominal ultrasound.

1. 64-slice CT examination

1) All patients underwent 64-slice unenhanced and post-contrast CT scanning (Light Speed VCT 64; GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA) with layer thickness and interval of 0.625 mm. The CT scanning ranged from the superior aperture of the thorax to the costophrenic angle. First, the unenhanced scanning was performed, followed by the bolus injection of contrast agent using a high-pressure syringe (iopromide 300, 300 mgI/mL; flow rate, 3 mL/s; total amount, 80 mL; cubital vein injection). The post-contrast scanning was conducted at the delayed stage (30 seconds after venous stage). Three-dimensional reconstruction was performed if necessary, wherein the horizontal plane was considered as the routine layer. Thin-section CT was performed to evaluate the entire lung with a collimation of 0.625 mm. The lung was imaged with a window of -500 to -700 Hounsfield units (HU) and width of 1,500–2,000 HU as the lung window.

2) Evaluation of HRCT characteristics

Two radiologists (10 years of experience in chest imaging, respectively), who were blinded to the histological result of the lesion, assessed the HRCT images on both mediastinal (width, 350 HU; level, 40 HU) and lung (width, 1,450 HU; level, -520 HU) windows. The findings were inferred by a consensus. The HRCT findings of each nodule were analyzed as follows: 1) shape (round or oval, lobulated, or irregular); 2) margin (spiculated or smooth); 3) diameter (the largest diameter on axial, sagittal, and coronal sections); 4) bronchus cutoff sign (the responsible bronchus clearly reached the inside of the target lesion); 5) vascular changes (dilated, rigid, convergent, and tortuous). The vessel from the nodule to the hilum was traced to determine its source, which might be pulmonary or bronchial and artery or vein; 6) pleural indentation (indentation of the pleura toward the tumor), including visceral pleura, interlobar fissure pleura, and mediastinal pleura; 7) vacuole, the presence of air in the tumor at the time of diagnosis prior to biopsy or treatment.

3) HRCT reconstructed images (Figure 1)

2. EGFR gene detection

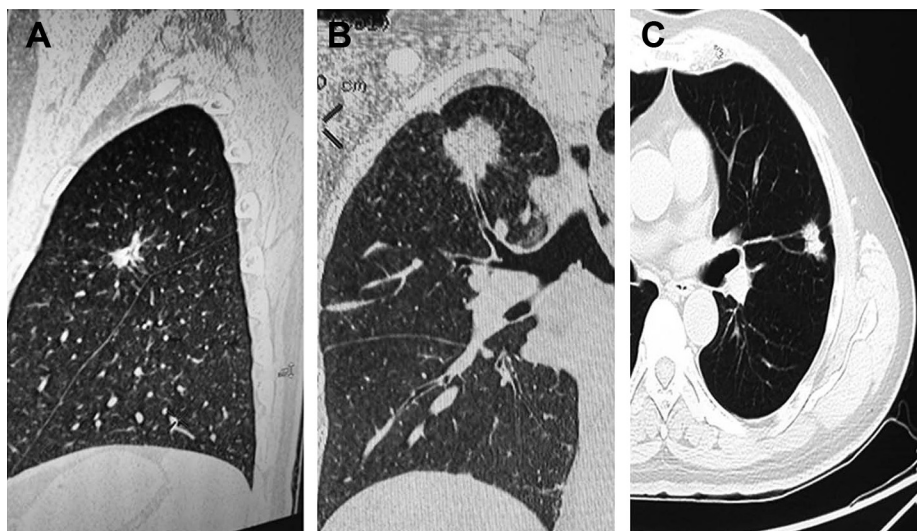


Figure 1 A 0.625 mm thin layer was reconstructed to observe the lesion in the sagittal, coronal, and horizontal positions on a lung window image. **Notes:** (A) Sagittal position: interlobar fissures and pleural indentation. (B) Coronal position: bronchus cutoff sign. (C) Horizontal position: vessel sign.

Pathological sections were used to assess the mutation on exons 18, 19, 20, and 21 by scorpion amplification-refractory mutation system-polymerase chain reaction (ARMS-PCR). The gene mutation detection kit was purchased from Amoy Diagnostics Co., Ltd. (Xiamen, China).

Statistical analyses

Statistical analysis was performed using the SPSS19.0 software package (IBM Corporation, Armonk, NY, USA). Continuous data were analyzed by unpaired *t*-test and categorical data by chi-squared test ($P < 0.05$). Multivariate analyses were performed by a logistic regression analysis. ORs and 95% CI were calculated. In all the tests, two-sided *P*-values of < 0.05 were considered statistically significant.

Results

A cohort of 121 patients with peripheral lung adenocarcinoma included 41 males and 80 females. All patients exhibited a single lesion in the lungs. A total of 23 cases were diagnosed using BF260 electronic bronchoscopy biopsy (Olympus Corporation, Tokyo, Japan), 27 cases by percutaneous pulmonary biopsy, and 71 cases by postoperative specimens. All specimens were wrapped in paraffin, followed by conventional pathological examination and evaluation of the EGFR mutation. Seventy-three out of 121 cases harbored the EGFR mutation (60.33%), whereas 48 were wild-type EGFR (39.67%). The HRCT characteristics were as follows: 103/121 cases exhibited pleural indentation (85.12%), 42/121 cases showed the bronchus cutoff sign (34.71%), 61/121 cases presented the lobulation sign (50.41%), 48/121

cases showed the vessel sign (39.67%), and 23 cases exhibited the vacuole sign (19.01%). The correlation of indexes such as EGFR mutation, gender, age, and tumor diameter with the characteristics of HRCT was analyzed statistically.

HRCT characteristics and EGFR mutation

A total of 103 cases exhibited pleural indentation, which included 66 patients with and 37 patients without EGFR mutation, 90.41% sensitivity and 22.92% specificity. Pleural indentation was found to be excessive in patients with EGFR mutation than those with wild-type EGFR (OR = 3.193 [95% CI 1.067–9.558], $P = 0.038$). Moreover, 42 cases, including 31 cases of mutation and 11 cases of wild-type EGFR, exhibited the bronchus cutoff sign. Moreover, the bronchus cutoff sign was significantly greater in patients with EGFR mutation than those with wild-type EGFR (OR = 2.836 [95% CI 1.20–6.692], $P = 0.017$), 42.47% sensitivity and 77.08% specificity. A total of 61 cases, including 45 patients with mutation and 16 patients with wild-type EGFR, presented the lobulation sign. The lobulation sign was observed to a greater extent in patients with EGFR mutation as compared to those with wild-type EGFR (OR = 4.638 [95% CI 1.963–10.960], $P = 0.000$), 61.64% sensitivity and 66.67% specificity. A significant correlation was found between lobulation sign and tumor diameter (OR = 1.036 [95% CI 1.005–1.068], $P = 0.024$). A total of 48 cases, including 30 patients with mutation and 18 patients with wild-type EGFR, demonstrated the vessel sign. The EGFR mutation did not exhibit any effect on the vessel sign (OR = 1.266 [95% CI 0.578–2.773], $P = 0.555$). Furthermore, 23 patients,

including 16 patients with EGFR mutation and 7 patients with wild-type EGFR, presented the vacuole sign. However, the EGFR mutation did not exhibit a significant effect on the vacuole sign (OR =1.584 [95% CI 0.557–4.352], $P=0.372$). Parameters such as age, gender, and tumor diameter did not vary significantly with respect to pleural indentation, bronchus cutoff sign, vessel sign, and vacuole sign ($P>0.05$); however, age and gender did not vary significantly on the lobulation sign ($P>0.05$; Tables 1–6).

A 0.625 mm reconstruction of HRCT characteristics is shown in Figures 2 and 3.

Discussion

Up to 60% EGFR mutation occurs in lung adenocarcinoma in the Asian population and is closely related to the invasiveness of the cancer. Although the doubling time of lung adenocarcinoma lesion is prolonged, it significantly increases the invasiveness in the patients with EGFR mutation.^{8–10} The early detection and diagnosis, as well as, invasiveness are primarily dependent on the characteristics observed on the HRCT.^{11,12} The pathological diagnosis is challenging when the lesion diameter is small. The correlation between the imaging features and genetic mutations indicates the physiological characteristics of the tumor at an early stage,^{13,14} which provides an insight into the appropriate treatment.¹⁵

The early invasiveness of lung adenocarcinoma primarily includes the invasion of the peripheral structures, such as intra-alveolar invasion, interlobular septal invasion, pleural invasion, and local bronchial lumen invasion.^{16,17} Common HRCT signs include pleural indentation, vacuole sign, lobulation sign, vessel sign, bronchial stiffness, traction, narrowing, and truncation.¹⁸ The present study used a 0.625 mm thin-layer CT and reconstructions at sagittal,

coronal, and horizontal positions. Thus, the characteristics of CT images, especially the visceral pleural indentation, interlobar fissure pleural indentation, and mediastinal pleural indentation, were observed from multiple views along with the bronchus cutoff sign. The thin-layer CT illustrates the vessel sign, vacuole sign, and lobulation sign rather adequately.¹² The present study found that age, gender, and tumor diameter did not vary significantly on pleural indentation, bronchus cutoff sign, vessel sign, and vacuole sign ($P>0.05$). Age and gender did not vary significantly on the lobulation sign ($P>0.05$); however, the lobulation signs are prone to appear in tumors of larger diameters (OR =1.036 [95% CI 1.005–1.068], $P=0.024$). Intriguingly, the EGFR mutation was significantly correlated with the characteristics of some HRCT images. The invasion of tumor on the peripheral structures led to pleural indentation or direct invasion.^{19,20} Pleural invasion affected the prognosis of the patients,^{21,22} and the HRCT-based reconstruction demonstrated 103 cases with visceral pleura, interlobular pleura, and mediastinal pleural indentation. The pleural indentation signs were found to be more in patients with EGFR mutation (OR =3.193 [95% CI 1.067–9.558], $P=0.038$); Smits et al²³ reported that the patients with EGFR mutation were prone to pleural metastasis; Rizzo et al²⁴ found an association between EGFR mutation and pleural retraction. Bronchus cutoff sign suggested that the cancer cells invaded along the alveolar structure and peripheral bronchiole. The tumor tissue was exposed to the bronchial cavity resulting in the bronchus cutoff at the edge of the tumor.¹⁷ Hsu et al²⁵ reported that air bronchograms were more common in the tumors with EGFR mutation, and the participation of bronchial wall and HRCT reconstruction identified the bronchial imaging features including the expansive and tractive bronchioles around the tumor. Our study

Table 1 CT features and correlation factors

CT features	Mutant EGFR	Wild-type EGFR	Male	Female	Age (years)	Diameter (mm)
Pleural traction (103)	66	37	36	67	60.53±10.318	29.13±11.966
Without pleural traction (18)	7	11	5	13	58.22±12.298	24.67±18.088
Bronchus cutoff sign (42)	31	11	15	27	60.19±9.971	29.71±12.607
Without bronchus cutoff sign (79)	42	37	26	53	60.19±10.999	27.80±13.328
Lobulation sign (61)	45	16	23	38	59.89±11.625	30.70±12.06
Without lobulation sign (60)	28	32	18	42	60.50±9.561	26.18±13.732
Vessel sign (49)	30	19	18	31	58.22±11.461	27.80±12.588
Without vessel sign (72)	43	29	23	49	61.53±9.851	28.92±13.442
Vacuole sign (23)	16	7	8	15	61.57±9.600	26.26±7.806
Without vacuole sign (98)	57	41	33	65	59.87±10.856	28.98±13.993

Abbreviation: CT, computed tomography.

Table 2 Correlation of EGFR, gender, age, and diameter on pleural indentation

Variables	Pleural traction (103)	Without pleural traction (18)	P-value	OR	95% CI	P-value
Mutant EGFR	66	7	0.044	3.193	1.067–9.558	0.038
Wild-type EGFR	37	11				
Male	36	5	0.553	1.745	0.519–5.868	0.368
Female	67	13				
Age (years)	60.53±10.318	58.22±12.298	0.396	1.008	0.957–1.062	0.764
Diameter (mm)	29.13±11.966	24.67±18.088	0.183	1.032	0.989–1.076	0.828

Table 3 Correlation of EGFR, gender, age, and diameter on bronchus cutoff sign

Variables	Bronchus cutoff sign (42)	Without bronchus cutoff sign (79)	P-value	OR	95% CI	P-value
Mutant EGFR	31	42	0.027	2.836	1.20–6.692	0.017
Wild-type EGFR	11	37				
Male	15	26	0.756	1.438	0.618–3.346	0.400
Female	27	53				
Age (years)	60.19±9.971	60.19±10.999	1.000	0.990	0.953–1.028	0.316
Diameter (mm)	29.71±12.607	27.80±13.328	0.445	1.015	0.986–1.046	0.306

Table 4 Correlation of EGFR, gender, age, and diameter on lobulation sign

Variables	Lobulation sign (61)	Without lobulation sign (60)	P-value	OR	95% CI	P-value
Mutant EGFR	45	28	0.002	4.638	1.963–10.960	0.000
Wild-type EGFR	16	32				
Male	23	18	0.371	2.271	0.941–5.484	0.068
Female	38	42				
Age (years)	59.89±11.625	60.50±9.561	0.751	0.977	0.941–1.018	0.232
Diameter (mm)	30.70±12.061	26.18±13.732	0.057	1.036	1.005–1.068	0.024

Table 5 Correlation of EGFR, gender, age, and diameter on vessel sign

Variables	Vessel sign (49)	Without vessel sign (72)	P-value	OR	95% CI	P-value
Mutant EGFR	30	43	0.760	1.266	0.578–2.773	0.555
Wild-type EGFR	19	29				
Male	18	23	0.585	1.506	0.668–3.397	0.323
Female	31	49				
Age (years)	58.22±11.461	61.53±9.851	0.093	0.965	0.930–1.001	0.059
Diameter (mm)	27.80±12.588	28.92±13.442	0.645	0.994	0.966–1.023	0.687

Table 6 Correlation of EGFR, gender, age, and diameter on vacuole sign

Variables	Vacuole sign (23)	Without vacuole sign (98)	P-value	OR	95% CI	P-value
Mutant EGFR	16	57	0.314	1.584	0.557–4.352	0.372
Wild-type EGFR	7	41				
Male	8	33	0.919	1.087	0.401–2.949	0.870
Female	15	65				
Age (years)	61.57±9.600	59.87±10.856	0.492	0.982	0.945–1.022	0.571
Diameter (mm)	26.26±7.806	28.98±13.993	0.371	0.123	0.945–1.022	0.377

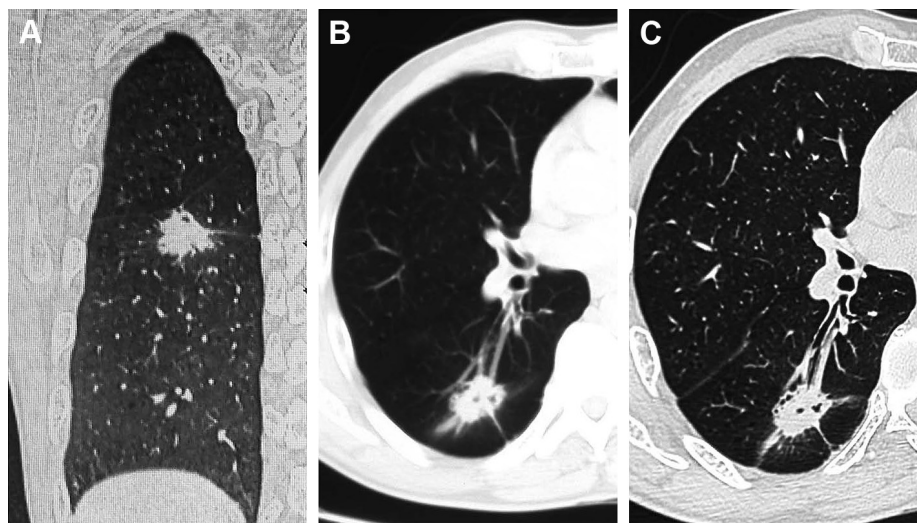


Figure 2 HRCT characteristics of the 60-year-old male patient.

Notes: (A) Sagittal position showed an interlobar fissure and visceral pleural indentation. (B and C) CT vessel sign, bronchus cutoff sign, and vacuole sign in the horizontal level. The size was 2.7×2.5 cm, and the pathological results showed a moderately differentiated adenocarcinoma, which did not invade the pleura and lymphatic vessels. The evaluation of EGFR revealed the mutation on exon 19.

Abbreviations: CT, computed tomography; HRCT, high-resolution computed tomography.

suggests that bronchus cutoff sign is correlated with EGFR mutation (OR =2.836 [95% CI 1.20–6.692], $P=0.017$). Moreover, patients with EGFR mutation were susceptible to the lobulation sign as compared to those with wild-type EGFR (OR =4.638 [95% CI 1.963–10.960], $P=0.000$), common lobulation sign is primarily moderate or deep, and the tumor with the lobulation sign indicated significant growth

and irregular shape, thereby leading to a poor prognosis.²⁶ Hasegawa et al²⁷ reported that EGFR-mutated adenocarcinoma showed significantly higher frequencies of the lobulation sign at HRCT compared to the non-EGFR-mutated type. The CT vessel sign indicated the potential increase in cancerogenesis of the lung nodules significantly.²⁸ Henschke et al⁴ reported that the lesion hyperplasia with vessel sign was accelerated, which was also a piece of evidence identifying the benign and malignant nodules. This study revealed that the CT vessel sign was not significantly correlated with the EGFR mutation. Furthermore, the vacuole sign indicated that the alveolar structure was not distorted, and the alveolar inflation or some necrosis tissues were discharged. This phenomenon was observed frequently in adherent growth or acinar adenocarcinoma, suggesting early invasion.^{29,30} This study concluded that there is no significant correlation between vacuolar sign and EGFR gene mutation (OR =1.584 [95% CI 0.557–4.352], $P=0.372$), and Zaibo et al³¹ reported similar findings.

The HRCT characteristics were manifested as single existence or coexistence of pleural indentation, bronchus cutoff sign, and lobulation sign that might indicate the putative increase in the EGFR mutation significantly. Moreover, the invasiveness of adenocarcinoma was strong, and the prognosis was poor.^{27,28} These three phenomena were correlated pathologically.¹² A timely surgery could improve the treatment effect in such patients.¹⁵ The EGFR mutation and different invasive structures would result in the surgical approaches affecting the survival and possibility

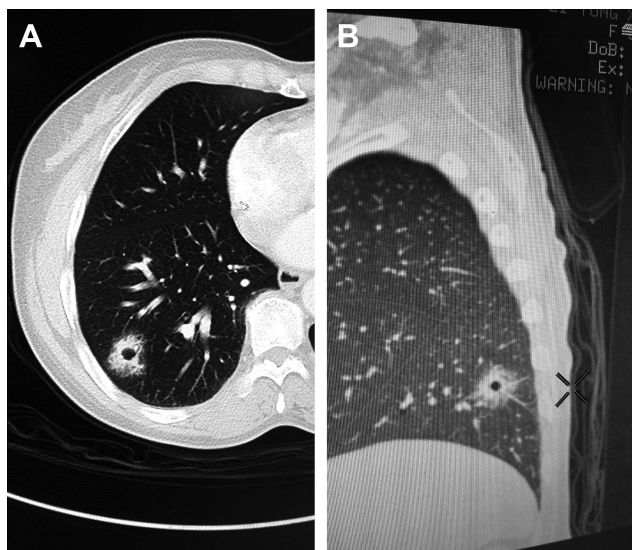


Figure 3 HRCT characteristics of the 55-year-old female patient.

Notes: The vacuole sign was visible on the horizontal (A) and sagittal positions (B); however, there was no significant bronchus cutoff sign (A and B). Pleural interlobar fissure and visceral pleura showed no significant indentation (A and B). The size of the lesion was 2.5×1.8 cm. The pathological diagnosis was invasive mucinous adenocarcinoma, which did not invade the pleura and lymph node. EGFR detection did not find any mutation.

Abbreviation: HRCT, high-resolution computed tomography.

of recurrence.³² The pulmonary wedge resection might face local or distant recurrence, whereas segmentectomy and pulmonary lobectomy might reduce the recurrence.^{33–35}

Disadvantages of the present study are as follows: our study mainly ascertained the HRCT imaging characteristics of lung adenocarcinoma and evaluated the mutant state of EGFR. However, we did not collect all the CT characteristics of non-small-cell lung cancer as well as other related genes. Therefore, further studies using large sample size and multicenter data are essential. In addition, this study was a retrospective analysis that might lead to selection bias.

Conclusion

Patients with lung adenocarcinoma underwent 0.625 mm thin-layer CT and reconstruction and displayed HRCT signs. Statistical analysis obtained the imaging characteristics of patients with EGFR mutation: pleural indentation, lobulation sign, and bronchial truncation sign that were significantly greater than those with wild-type EGFR. These phenomena can provide the reference for clinical treatment. The pleural indentation sign, lobulation sign, and bronchus cutoff sign occurring alone or coexisting with multiple CT signs suggested a putative EGFR mutation. In this case, the invasiveness was enhanced that necessitated appropriate clinical treatment at the earliest. Thus, further studies are essential to predict the EGFR mutations in lung adenocarcinoma using CT.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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