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# Analysis of the Correlation between Biological Effects of EGFR Exon 19 and 21 Mutations and Clinical and Imaging Features in Lung Adenocarcinoma

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**Abstract:** ***Objective:*** *To analyze the correlation between Biological Effects of EGFR Exon 19 and 21 Mutations and Clinical and Imaging characteristics in Lung Adenocarcinoma.* ***Methods:*** *The clinical and imaging data of patients with lung adenocarcinoma who had undergone genetic testing in Baotou Cancer Hospital from July 2021 to May 2024 were retrospectively collected, and chest CT examination was performed before treatment to evaluate the EGFR mutant wild type and subtype (exon 19 and 21) of lung adenocarcinoma patients clinical and imaging features, and the characteristics were compared between groups. Univariate analysis was used to analyze the differences and statistically significant indicators into binary logistic regression analysis to screen out independent predictors.* ***Results:*** *Compared with wild-type EGFR19 mutations, females, small lesions with maximum diameter, spiculation, pleural indentation, and low INCTR were more common in the EGFR 19 mutation group, and males, larger lung lesions with maximum diameter, no spiculation, no pleural indentation, and higher INCTR were more common in wild-type (all p <0.5). stic regression analysis showed that the diameter of small lesions (OR=90.825, 95%CI 2.023-4078.299, P=0.020) and INCTR (OR=0.692, 95%C 0.516-0.927, P=0.014) was a risk factor for EGFR19 mutation. In the comparison of EGFR21 mutation and wild-type, female, non-smoking patients, vessel convergeence sign, and low INCTR were more common in the EGFR 21 mutation group, and binary logistic regression analysis showed vessel convergeence sign (OR=18.582, 95%CI 1.848-186.870, P=0.013) and INCTR (OR=0.793, 95%CI 0.687-0.915, P=0.002) were risk factors for EGFR21 mutation.*

**Keywords:** Lung adenocarcinoma, EGFR mutation, Chest CT, Imaging Features.

## 1. Introduction

Lung cancer is the most common malignant tumor in China and the leading cause of death 8 [1]. With the rapid development of molecularly targeted therapy, Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors (TKIs) are used to treat nonsmall cell lung cancer (NSCLC) patients with positive epidermal growth factor receptor mutations is the preferred approach [2][3]. Among them, exon 19 deletion and exon 21 missense mutation are the two most common mutation subtypes of the EGFR gene, which are known as classical mutations [4]. EGFR Exon 19 and 21 Mutations exhibit different characteristics in terms of molecular structure and biological behavior, which have an impact on the treatment and prognosis of tumors [5][6]. Hypoxia is a common feature inside tumors [7], particularly in fast-growing tumors, where there is an imbalance between the low oxygen supply due to abnormal vascularization and the hyperoxygen consumption of tumor cells, resulting in so-called hypoxic necrotic zones, which appear as low-density areas on contrast-enhanced CT images. The hypoxic environment inside the tumor is one of the important factors that promote its malignant progression [8][9]. Hypoxia can lead to changes in the metabolic mode of tumor cells, such as enhancing glycolytic activity, which in turn produces large amounts of lactate, leading to acidification of the tumor microenvironment, this acidic environment not only favors the survival and proliferation of tumor cells, but may also enhance their aggressiveness and metastasis [10]. Contrast-enhanced CT can make the tumor and the surrounding tissues form a better contrast by injecting contrast medium, which can better reflect the internal structure and blood supply of the tumor, and can quantitatively analyze the density and area of the ischemic necrosis area. Lung adenocarcinoma (LADC) is the most common pathological type of NSCLC [11]. Therefore, this study focused on comparing the clinical and imaging characteristics of patients with lung adenocarcinoma with EGFR exon 19 and 21 mutations with wild-type patients, so as to provide important clues for in-depth understanding of the biological characteristics of lung cancer, in order to assist in the individualized treatment of patients with unknown EGFR gene mutation status.

## 2. Study Subjects and Research Methods

### 2.1 Subjects of the Study

The clinical and imaging data of lung adenocarcinoma patients who underwent genetic testing in Baotou Cancer Hospital from July 2021 to May 2024 were retrospectively collected. A total of 76 patients were present. Among them, there were 35 male patients and 41 female patients. Age 42~84 (61.16±9.66) years old; There were 27 cases with a history of smoking and 49 cases without a history of smoking. Inclusion criteria: (1) The patient's intact chest contrast-enhanced CT scan images were stored on the PACS system of our hospital. (2) Confirmed by pathological diagnosis of LAD. (3) Wild-type, EGFR19, exon 21 mutations were genetically detected.

(4) There are complete clinical data. Exclusion criteria: (1) Pathological testing of non-adenocarcinoma or no genetic testing. (2) The patient has undergone radiotherapy, chemotherapy, radiofrequency ablation, immunotherapy, targeted therapy and other anti-tumor treatments that affect the internal metabolism of the tumor before chest CT examination. (3) The basic condition of the lung field of the patient caused by various underlying diseases is poor, and there is a large-scale infection or respiratory motion artifacts in the CT image. (4) People with iodine allergy.

### 2.2 Instruments and Inspection Methods

Using Philips BrillianceCT (16 slices), the patient was instructed to hold his breath at the end of deep inspiration followed by a contrast-enhanced CT scan of the chest. The scanning time was 8.517s, the tube voltage was 120kV, the tube current was 30mA, the layer thickness was 3mm, the interval was 3mm, and the scanning range was from the thoracic entrance to the diaphragmatic plane. After the noncontrast scan, 65~75mL of iodophorol was injected into the median elbow vein at a rate of 1.5~2.0mL/s, and the contrast medium was injected for 50 seconds after the enhanced scanning.

### 2.3 CT Image Analysis

CT images of all patients were qualitatively performed by 2 experienced radiologists blinded to the EGFR genome classification. Under the conditions of lung window (window width: 1400 Hu, window position: -500 Hu) and mediastinal window (window width: 350 Hu, window position: 40 Hu), the differences in image CT image characteristics were discussed and explained until a consensus was reached. Based on the clinical features and the date of the CT examination, images of each patient were extracted from the medical record. For each patient, the radiological features of CT examination were recorded on an Excel file (Microsoft Office Excel 2016). (1) The maximum diameter of the lesion: the maximum size is measured in the multi-plane reconstruction image under the condition of the lung window, and the maximum diameter of the largest tumor is taken when there are multiple tumors in the lung; (2) Spiculation: linear shadows radiating from the edge of the tumor;(3) Lobulation: a wavy or scalloped configuration of tumour's surface; (4) Air-containing cavity: an area filled with gas inside the tumor, including vacuoles and cavities; (5) Calcification: the inside of the tumor is characterized by high-density shadows; (6) Air Bronchogram: translucent bronchial shadows inside the tumor; (7) Pleural Indentation: the tumor is close to the edge of the pleural surface with sharp strips and dense lines; (8)Vessel convergeence sign: the blood vessels around the tumor show abnormal aggregation or concentration; (9) Whether there is pleural effusion: (10) Whether there is brain, liver, and bone metastases, which needs to be confirmed by CT, MRI or bone ECT at the corresponding site; (11) Ischemia necrosis CT relative value (INCTR) measurement: exported from the hospital PACS workstation in DICOM format, and the images were imported into the 3D Slicer software, in order to avoid partial volumetric effects, two experienced radiologists measured the area Si of the 1~n layer of the tumor (the tumor is visible in the n layer) and the total area △Si of the low-density area (ischemic necrosis area) of the 1~n' layer of the tumor at the maximum level of the lesion in the axial, coronal and sagittal positions of the 3mm layer thickness of the enhancement sequence, respectively. The lesion INCTR was calculated according to the following formula, $\mathrm{INCTR} = \frac{\sum_{i=1} n' \triangle S_i \triangle N_i}{\sum_{i=1} n S_i N_i} \times 100\%$,which was measured independently by two radiologists, image was measured twice, and if the difference between the two results was < 10%, the average of the two measurements was taken as the result. The above work is checked by at least one radiologist with the title of deputy director or above.

### 2.4 Statistical Analysis

SPSS25.0 software was used to analyze the data, for the counting data, such as gender, lobulation, burr, etc., the number of cases (percentages) was expressed, the comparison between the two groups was analyzed by $\chi 2$ or Fisher's exact test, and for the continuous data, the normal test was carried out, and the data conforming to the normal were ± standard deviation (x±s), comparisons between the two groups were performed using an independent-samples t-test, and data that did not conform to normality were expressed as medians (upper and lower quartiles) and analyzed using the Mann-Whitney U nonparametric rank-sum test. The univariate significant variables were included in the binary logistics regression for model analysis, and the ROC curve was used to further analyze the significant variables in the multivariate analysis, and the AUC value was calculated, and P<0.05 was used as the statistical difference marker.

## 3. Results

### 3.1 Comparison and Multivariate Analysis of Clinical and Imaging Characteristics of EGFR19 Exon Mutation and Wild-type

Among the clinical features, there were significant differences in gender between the two groups, among which females were more common in the EGFR 19 mutation group and males were more common in the wild-type group (P<0.05), while there was no statistical difference in smoking history and age between the two groups (P>0.05).Among the imaging features, the maximum diameter of the lesion, spiculation, pleural Indentation, and low INCTR were more common in the EGFR 19 mutation group, while the maximum diameter of larger lung lesions, spiculation, no pleural Indentation, and higher INCTR were more common in wild-type (both p < 0.05) Table 1. Multivariate logistic regression analysis was performed on the meaningful variables of univariate analysis, and the results showed that small lesion diameter (OR=90.825, 95%CI 2.023-4078.299, P=0.020) and INCTR (OR=0.692) were performed, (95%CI 0.516-0.927, P=0.014) was a risk factor for EGFR19 mutation. Table 2.

### 3.2 Comparison and Multivariate Analysis of Clinical and Imaging Characteristics of EGFR21 Exon Mutation and Wild-type

Among the clinical characteristics, there were significant differences in gender and smoking history between the two groups, among which female and non-smoking patients were more common in the EGFR 21 mutation group, males and

smokers were more common in the wild-type group (P <0.05), and there was no statistical difference in age between the two groups (P>0.05). Among the imaging features, Vessel convergeence sign and low INCTR were more common in the EGFR 21 mutation group, while non-vessel convergeence sign n and high INCTR were more common in wild type (both p<0.5) Table 3. Multivariate logistic regression analysis of these meaningful univariate variables showed that vessel convergeence sign (OR=18.582, 95%CI 1.848-186.870, P=0.013) and INCTR (OR=0.793) were performed, 95%CI 0.687-0.915, P=0.002) was the risk factor for EGFR21 mutation in Table 4.

**Table 1:** Comparison of clinical and imaging characteristics of EGFR19 exon mutations and wild-type

| | EGFR19 mutations | Wild-type | t/χ2 | P |
|---|---|---|---|---|
| Gender (examples) | | | 16.307 | <0.001 |
| man | 3(15.8) | 25(73.5) | | |
| woman | 16(84.2) | 9(26.5) | | |
| Age (years) | 61.47±6.54 | 61.91±11.69 | -0.175 | 0.862 |
| Smoking history (examples) | | | 2.816 | 0.093 |
| not | 14(73.7) | 17(50.0) | | |
| Yes | 5(26.3) | 17(50.0) | | |
| The maximum diameter of the lesion (cm). | 3.00±0.49 | 3.67±0.60 | -4.13 | <0.001 |
| Spiculation (examples) | | | 4.300 | 0.038 |
| not | 5(26.3) | 19(55.9) | | |
| Yes | 14(73.7) | 15(44.1) | | |
| Lobulation (example) | | | 0.221 | 0.638 |
| not | 1(5.3) | 3(8.8) | | |
| Yes | 18(94.7) | 31(91.2) | | |
| Air-containing cavity (examples) | | | 0.875 | 0.349 |
| not | 17(89.5) | 27(79.4) | | |
| Yes | 2(10.5) | 7(20.6) | | |
| Calcification (examples.)) | | | 0.181 | 0.671 |
| not | 18(94.7) | 33(97.1) | | |
| Yes | 1(5.3) | 1(2.9) | | |
| Air Bronchogram (examples) | | | 0.570 | 0.450 |
| not | 19(100.0) | 33(97.1) | | |
| Yes | 0(0.00) | 1(2.9) | | |
| Pleural Indentation (examples) | | | 4.269 | 0.039 |
| not | 4(21.1) | 17(50.0) | | |
| Yes | 15(78.9) | 17(50.0) | | |
| Vessel convergeence sign (examples) | | | 0.011 | 0.916 |
| not | 16(84.2) | 29(85.3) | | |
| Yes | 3(15.8) | 5(14.7) | | |
| Pleural effusion (examples) | | | 0.573 | 0.449 |
| not | 8(42.1) | 18(52.9) | | |
| Yes | 11(57.9) | 16(47.1) | | |
| Brain metastases (examples) | | | 0.009 | 0.925 |
| not | 18(94.7) | 32(94.1) | | |
| Yes | 1(5.3) | 2(5.9) | | |
| Liver metastases (examples) | | | 0.181 | 0.671 |
| not | 18(94.7) | 33(97.1) | | |
| Yes | 1(5.3) | 1(2.9) | | |
| Bone metastases (examples) | | | 1.203 | 0.273 |
| not | 6(31.6) | 16(47.1) | | |
| Yes | 13(68.4) | 18(52.9) | | |
| INCTR | 45.40±4.55 | 55.57±6.00 | -6.417 | <0.001 |

**Table 2:** EGFR19 exon mutations and wild-type binary logistics regression

| | B | SE | Wald | df | P | OR (95%CI) |
|---|---|---|---|---|---|---|
| gender | 4.509 | 1.941 | 5.396 | 1 | 0.020 | 90.825(2.023-4078.299) |
| The maximum diameter of the lesion | -5.272 | 2.568 | 4.212 | 1 | 0.040 | 0.005(0.000-0.789) |
| Spiculation | -1.092 | 1.540 | 0.503 | 1 | 0.478 | 0.335(0.016-6.857) |
| Pleural Indentation | 4.351 | 2.311 | 3.543 | 1 | 0.060 | 77.538(0.836-7192.886) |
| INCTR | -0.369 | 0.149 | 6.098 | 1 | 0.014 | 0.692(0.516-0.927) |

Note: P value: P> 0.05 No significant difference P <0.05 with significant difference P <0.01 with very significant difference P <0.001 with extremely significant difference.

**Table 3:** Comparison of clinical and imaging features of EGFR21 exon mutations and wild-type

| | EGFR21 mutations | Wild-type | t/χ2 | P |
|---|---|---|---|---|
| Gender (examples) | | | 10.348 | 0.001 |
| man | 7(30.4) | 25(73.5) | | |
| woman | 16(69.6) | 9(26.5) | | |
| Age (years) | 59.78±8.64 | 61.91±11.69 | -0.745 | 0.459 |
| Smoking history (examples) | | | 4.623 | 0.032 |
| not | 18(78.3) | 17(50.0) | | |
| Yes | 5(21.7) | 17(50.0) | | |
| The maximum diameter of the lesion (cm). | 3.34±0.83 | 3.67±0.60 | -1.752 | 0.085 |
| Spiculation (examples) | | | 0.076 | 0.783 |
| not | 12(52.2) | 19(55.9) | | |
| Yes | 11(47.8) | 15(44.1) | | |
| Lobulation (example) | | | 0.00 | 0.987 |
| not | 2(8.7) | 3(8.8) | | |

| | | | | |
|---|---|---|---|---|
| Yes | 21(91.3) | 31(91.2) | | |
| Air-containing cavity (examples) | | | 0.540 | 0.462 |
| not | 20(87.0) | 27(79.4) | | |
| Yes | 3(13.0) | 7(20.6) | | |
| Calcification (examples.) | | | 0.689 | 0.407 |
| not | 23(100.0) | 33(97.1) | | |
| Yes | 0(0.0) | 1(2.9) | | |
| Air Bronchogram (examples) | | | 0.080 | 0.777 |
| not | 22(97.1) | 33(97.1) | | |
| Yes | 1(4.3) | 1(2.9) | | |
| Pleural Indentation (examples) | | | 0.234 | 0.629 |
| not | 10(43.5) | 17(50.0) | | |
| Yes | 13(56.5) | 17(50.0) | | |
| Vessel convergeence sign (examples) | | | 9.202 | 0.002 |
| not | 11(47.8) | 29(85.3) | | |
| Yes | 12(52.2) | 5(14.7) | | |
| Pleural effusion (e.g) | | | 0.144 | 0.705 |
| not | 11(47.8) | 18(52.9) | | |
| Yes | 12(52.2) | 16(47.1) | | |
| Brain metastases (examples) | | | 0.065 | 0.799 |
| not | 22(95.7) | 32(94.1) | | |
| Yes | 1(4.3) | 2(5.9) | | |
| Liver metastases (examples) | | | 0.689 | 0.407 |
| not | 23(100.0) | 33(97.1) | | |
| Yes | 0(0.0) | 1(2.9) | | |
| Bone metastases (examples) | | | 1.824 | 0.177 |
| not | 15(65.2) | 16(47.1) | | |
| Yes | 8(34.8) | 18(52.9) | | |
| INCTR | 44.91±4.47 | 54.75±7.39 | -5.712 | <0.001 |

**Table 4:** EGFR21 exon mutations and wild-type binary logistics regression

| | B | SE | Wald | df | P | OR (95%CI) |
|---|---|---|---|---|---|---|
| Gender | 2.922 | 1.178 | 6.157 | 1 | 0.013 | 18.582(1.848-186.870) |
| Smoking history | -1.547 | 1.169 | 1.753 | 1 | 0.186 | 0.213(0.022-2.103) |
| Vessel convergeence sign | 2.876 | 1.243 | 5.355 | 1 | 0.021 | 17.747(1.553-202.811) |
| INCTR | -0.232 | 0.073 | 10.071 | 1 | 0.002 | 0.793(0.687-0.915) |

Note: P value: P> 0.05 No significant difference P <0.05 with significant difference P <0.01 with very significant difference P <0.001 with extremely significant difference.

## 4. Analysis

Currently, we are entering the era of precision medicine for cancer treatment. The core mechanism of lung adenocarcinoma is the somatic mutation of the epidermal growth factor receptor, which leads to the sustained activation of the EGFR tyrosine kinase domain in tumor tissues, and the therapeutic effect of the targeted therapy tyrosine kinase inhibitor is closely related to the type of mutation in the EGFR gene [12] [13]. Therefore, studying the clinical and imaging characteristics of patients with EGFR subtypes can provide important guidance for treatment selection and individualized decision-making.

From the perspective of clinical characteristics, the study found that the incidence of EGFR exon 19 and 21 mutations in women was higher than that of wild type, and the results of multivariate logistic regression analysis showed that gender waspredictors of mutations in EGFR19 and 21, which are consistent with previous studies [14] [15]. The incidence of non-smoking status in patients with EGFR exon 21 mutations is higher than that of wild type, suggesting that the association of non-smoking states is more relevant than that of EGFR exon 19 mutations. The same result was found in the study by Zhang Shi et al. [14]. EGFR19 mutations may be more related to endogenous or non-smoking-related exogenous factors, while EGFR21 mutations may be more susceptible to the effects of smoking, which requires further research.

From the perspective of imaging characteristics, in the comparison of EGFR19 mutation and wild-type lung cancer patients in the two groups, this study found that the maximum diameter of the lesion, spiculation, pleural indentation, low INCTR were associated with EGFR19 mutations, and small lesion diameter, INCTR is a risk factor. Zhang Shi et al. [14] [16] found that EGRF exon 19 mutations were associated with tumor maximum diameter and pleural indentation. Xu J et al. [17] found that patients with EGFR 19-mutated lung cancer had smaller lesion diameters and higher rates of spiculation. Tumor growth and invasion are inseparable from angiogenesis, and increased vascular endothelial growth factor (VEGF) secretion in EGFR-mutant tumors can induce more neovascularization compared with wild-type tumors [18] [19], resulting in a change in the mode of tumor metabolism, a small area of hypodensity within the tumor, and an abnormal distribution of neovascularization may also limit the further expansion of the tumor, keeping the diameter of the lesion in a small range. However, these blood vessels are often irregular and immature, resulting in burr-like changes at the tumour margins. In terms of imaging, the spiculation of lung cancer is due to the infiltration and growth of tumor tissue along the bronchi, blood vessels, or interlobular septum, and the pleural depression sign refers to the strip-shaped image changes between the lesion located around the lung and the visceral pleura, both of which are related to the aggressive and proliferative characteristics of tumor cells to some extent. These aggressive growth patterns are closely related to changes in cell biology that may be associated with EGFR 19 mutations.

Compared with wild-type patients, this study found that patients with EGFR exon21 mutations had higher rates of vessel convergeence sign and INCTR, and which were predictors of EGFR21 mutations. The vessel convergeence

sign shows one or more vascular shadows being stretched, converging to the lesion, interrupted, or penetrating through the lesion on CT, which is consistent with the Zhao FN study [20]., which is usually associated with the active and aggressive angiogenesis of the tumor. The area of intratumoral necrosis is related to the size of the tumor lesion, so the quantitative value INCTR is used to represent the ischemic area within the tumor to a certain extent. EGFR21 mutant tumors have a richer blood supply and are more likely to form new blood vessels than wild-type tumors, and EGFR21 mutant tumor cells may have different biological behaviors. As a result, it exhibits unique characteristics in angiogenesis and tissue structure. This hypothesis is also supported by studies [21] of significantly longer OS in patients with EGFR 21 L858R mutations who received anti-angiogenic therapy during treatment compared with patients who have never been treated with antiangiogenic agents. Hypoxia significantly enhances the aggressiveness of tumors through a variety of mechanisms, such as metabolic reprogramming of tumor cells under hypoxic conditions, and tumor cells produce a large amount of lactate by enhancing glycolysis, resulting in acidification of the extracellular matrix, thereby inhibiting the activity of immune effector cells and reprogramming the effect on immunotherapy [22], accelerating tumor progression. This has certain guiding significance for the tumor and prognosis of wild-type patients. The INCTR of EGFR19 and exon 21 was lower than that of the wild type, indicating that the blood supply of tumors with common mutations in EGFR was more abundant than that of the wild type, which was also confirmed by the relevant literature [18].

There are some limitations to this study. First, we studied a small sample of patients with EGFR 19 and 21 mutant subtypes, and a larger patient cohort study is needed to confirm our observations. Second, this study does not include patients with other EGFR mutant subtypes or other driver genes for lung cancer, and only includes patients with EGFR 19, 21 mutant subtypes. Thirdly, this study only used enhanced CT image features, and multimodal imaging (such as PET/CT) can provide more lesion features. We will make up for the above shortcomings in follow-up studies.

## 5. Conclusion

In summary, there are certain differences in the clinical and imaging characteristics of patients with EGFR19 and 21 mutations and wild-type lung adenocarcinoma, and familiarity and mastery of these differences will help to understand the biological effects of EGFR mutant subtypes of tumors and better provide individualized treatment for patients with lung adenocarcinoma with unknown gene mutation status.

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