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The study of relationship between CT features and *EGFR* gene mutation in peripheral non-small cell lung cancer.

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Abstract

Objective: To investigate the relationship between CT features of Peripheral Non-Small Cell Lung Cancer (PNSCLC) and gene mutation of Epidermal Growth Factor Receptor (EGFR).

Methods: 60 PNSCLC samples with complete clinical data and affirmed by histopathological examination in our hospital. All the histological or cytological specimens were subjected to the Amplification Refractory Mutation System (ARMS) or gene sequencing method for EGFR mutation situation. The relationship between CT features and *EGFR* gene mutation was evaluated with each patient's chest radio-graphic examination.

Results: 60 PNSCLC, 29 cases of *EGFR* gene mutation, including 53.3% of women and 55.6% of non-smokers. CT amplification of the *EGFFR* gene mutation was 49.07 ± 12.57 Hu. *Non-EGFR* gene mutation was 38.43 ± 13.93 Hu. By comparing the data, the difference was highly significant (P<0.01). With CT angiography, pleural depression and bone metastasis, gene mutation rate and non-gene mutation rate were 33.3%, 66.7%, 38.5%, 61.5%, 70.6%, 29.4%, respectively. The difference was considerable (P<0.05). With CT deep subdivision, fine short burrs, pleural effusion and other metastatic signs, the difference between gene mutation rate and non-gene mutation rate was not significant (P>0.05).

Conclusion: In PNSCLC, CT amplification of the *EGFR* gene mutation is significantly higher. The *EGFR* gene mutation with bone metastasis is higher, and *EGFR* gene mutation is low.

Keywords: Peripheral non-small cell lung cancer, *EGFR*, Gene mutation, Enhanced CT scanning.

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Introduction

Lung cancer is among the most common malignant tumors in clinical and with increased rapidly morbidity, which has become the major cause of cancer death in China [1]. With the development of molecular biology and the progress of the lung cancer molecular targeted therapy, gene mutation status of lung cancer's epidermal growth factor receptor (EGFR) is one of the most important predictors to evaluate lung cancer targeted therapy clinical curative effect. EGFR is a transmembrane receptor tyrosine kinase involved in the signaling pathways that regulate cell proliferation, apoptosis, angiogenesis, and invasion [2,3]. Ninety-five percent of EGFR mutations are found in adeno carcinomas, which are the most common histologic type of Peripheral Non-Small Cell Lung Cancer (PNSCLC) [4]. Approximately 90% of EGFR mutations are exon 19 short in frame deletion (exon 19) and exon 21 L858R point (exon 21) mutations [5]. CT examination, with its effortless scanning program, precise positioning and economic advantages, has become the main imaging examination method for lung cancer. Recently, we have studied on clinical data for our hospital Peripheral Non-Small Cell Lung Cancer (PNSCLC) from January 2009 to December 2015, to explore the CT features and the relationship between *EGFR* gene mutation and strengthen the sign by CT scan and enhancement features provide theoretical basis for gene mutation probability assessment. The report is as follows.

Methods

Objective

60 PNSCLC cases in our hospital, including 30 males and 30 females, age 31-83, average 57.8 y old. Maximum diameter of tumor is 3.63 ± 1.56 cm and 24 cases of smoking. Histopathological types: 58 cases of adenocarcinoma, 2 cases of squamous carcinoma. Biopsy: 5 cases of operation, 51 cases of puncture, 4 cases of fiberoptic bronchoscope. All patients had complete clinical, pathological and imaging data and had not received chemotherapeutic treatment before admission. All patients had complete clinical, pathological and imaging data and had not received chemotherapeutic treatment before admission.

Equipment and scanning methods

Using the American general motors Light Speed 64 row helical CT scanner, the scanning conditions and parameters: 120 kV,

100~400 mA (automatic), 5 mm collimator, pitch of 0.984:1, reconstruction of 5 mm, with a thick layer of scanning range from the thoracic inlet to diaphragmatic surface. Enhanced scanning was used to inject a high pressure syringe with a concentration of 350 mg/ml of non-ionized iodine, 1.5 ml/kg injections, 2.3 ml/s injection rates, and 45 s delay. All of the patients were screened before the scan, and the scan was completed in the calm breathing.

Image evaluation

The image information of each patient was extracted from the image archiving and communication system (PACS) of the hospital. The evaluation includes the following aspects:

(1) **The selection of interest area (ROI):** ROI area ≥ 1 cm^2, which should avoid empty, calcified and blood vessels in measurement, and not be measured at the upper and lower edges in order to avoid the influence of partial volume effect.

(2) **CT enhancement amplitude:** To browse enhance the image and choose the most obvious parts, measure and record lesions on CT value. At the same level scan images of the same parts with the same ROI, measure and record the size of CT values, both by subtracting it is concluded that the lesion of CT enhancement amplitude.

(3) **Deep sub-division:** The ratio of the arc chord distance to the arc distance was greater than or equal to 4/10.

(4) **Short burrs:** Fine short burrs, which refer to the radiated and un-branched extension of the edge of the tumor to the surrounding lung, and the width<2 mm, length<5 mm.

(5) **Collection of blood vessels:** The collection of blood vessels is the aggregation of peripheral blood vessels to the tumor, which breaks or runs through the blood vessels at the edge of the tumor.

(6) **Sign of pleural sag:** The pleural depression sign is also called the pleural traction sign, which was the linear or triangular image between the tumor and the pleura.

Measurement of gene mutation

All the histological or cytological specimens of the group of cases were tested and analyzed by using the amplification block mutation system (ARMS) or gene sequencing method to detect the mutation status of EGFR.

Statistic treatment

SPSS 22.0 was used for statistical processing, and the counting data were tested by χ^2. The measurement data were tested by t, with P<0.05 as significant difference.

Results

Among the 60 cases of PNSCLC, there were 29 cases of *EGFR* gene mutation, of which women accounted for 53.3%, and the non-smokers accounted for 55.6%. The CT enhancement of the lesion of *EGFR* gene mutation was 49.07 ± 12.57 Hu, *non-EGFR* gene mutation 38.43 ± 13.93 Hu. The difference is very significant (P<0.01). In the PNSCLC, with CT angiography, pleural depression and bone metastasis, the mutation rate of *EGFR* gene and *non-EGFR* gene mutation was 33.3%, 66.7% and 38.5%, 61.5% and 70.6%, 29.4%, respectively. The difference was significant (P<0.05). There was no significant difference between *EGFR* gene mutation rate and *non-EGFR* gene mutation rate (PBBB 0.05) in the PNSCLC with CT deep lobulated, fine short burrs, pleural effusion and other metastatic signs (Table 1).

Table 1. *With or without different CT features of PNSCLC had an EGFR gene mutation comparison example (%).*

CT feature	*EGFR* gene mutation	Non-EGFR gene mutation	P
Gender Male	14 (50.0)	16 (50.0)	0.7961
Female	15 (50.0)	15 (50.0)	
Deep lobulated (+)	28 (50.9)	27 (49.1)	0.392
(-)	1 (20.0)	4 (80.0)	
Fine short burrs (+)	14 (46.7)	16 (53.3)	0.796
(-)	15 (50.0)	15 (50.0)	
Vessel convergence (+)	9 (33.3)	18 (66.7)	0.035
(-)	20 (60.6)	13 (39.4)	
Pleura indentation (+)	15 (38.5)	24 (61.5)	0.037
(-)	14 (66.7)	7 (33.3)	
Pleural effusion (+)	14 (53.8)	12 (46.2)	0.455
(-)	15 (44.1)	19 (55.9)	

Swollen lymph node (+)	24 (52.2)	22 (47.8)	0.281
(-)	5 (35.7)	9 (64.3)	
Bone metastasis (+)	12 (70.6)	5 (29.4)	0.03
(-)	17 (39.5)	26 (60.5)	
Liver metastasis (+)	5 (62.5)	3 (37.5)	0.63
(-)	24 (46.2)	28 (53.8	

Discussion

EGFR is a manifestation product of the original oncogene eRB B-1. It is a type of tyrosine kinase receptor, and only a small number of expression of normal lung tissues play an important role in tumor progression [6]. EGFR is mainly involved in cell signal transduction, after its extracellular domain and the corresponding ligand binding are activated, by extracellular signaling kinases in response to inside cells lead to excessive cell proliferation, apoptosis, inhibiting, eventually undergo malignant transformation. At present, for PNSCLC and *EGFR* gene mutation patients, the use of EGFR tyrosine kinase inhibitor has good clinical efficacy and safety, and it can significantly improve progression-free lifetime of patients compared with a line chemotherapeutic drug [7]. Therefore, the detection of *EGFR* gene mutation is of great significance for the clinical guidance of Non-Small Cell Lung Cancer (NSCLC) targeting therapy. Relevant literature reported that *EGFR* gene mutation rate was higher in women and non-smoking history in NSCLC [8-10]. 60 cases of PNSCLC, including 29 cases of EGFR mutations, women accounted for 53.3%, no smoking accounted for 55.6%, consistent with the result, we did not find *EGFR* mutator gene with *EGFR* mutator gene exist significant differences in sex, and smoking history.

Studies demonstrated that *EGFR* gene mutation can cause excessive gene expression, and promote the expression of vascular endothelial growth factor, stimulate the pulmonary vascular endothelial cell differentiation, migration and increased vascular permeability to change of extracellular matrix, thereby inducing new angiogenesis [6,11-14]. The more new blood vessels, the higher the CT enhancement of the tumor [15,16]. The results showed that patients with PNSCLC with *EGFR* gene mutation were significantly higher than PNSCLC patients with non-EGFR mutation, which was consistent with the above report. The reason may be related to the abundance of blood supply in the tumor with EGFR mutation. On the one hand, the new blood vessels provide the oxygen and nutrients needed for the tumor to grow rapidly. On the other hand, new blood vessels, for the abnormal blood vessels, which growth is not mature, lack of muscular layer, endothelial cell interval is big, tumor cells easily through the blood vessels into the blood stream, thus form transfer throughout the body tissues and organs. Youcai et al. believed that lung cancer *EGFR* gene expression enhancer, tumor invasion and metastasis are higher and easy to occur distant metastasis [17]. In this study, the incidence of bone metastasis of *EGFR* gene mutation was 41.4% (12/29), which significantly higher than 16.1% (5/31) of *non-EGFR* gene mutation. It is suggested that PNSCLC with *EGFR* gene mutation is more prone to bone metastasis.

It is generally accepted that the pathologic basis of pleural indentation is the formation of tumor fibrosis, namely the contracture of the fibrous scar will bring the visceral pleura into the tumor [18]. Pleural indentation is a common sign of lung cancer invasion of the visceral pleura, and the prognosis is worse [19]. The formation of the vascular convergence is the tumor's infiltration of the bronchial sheath or lobular septum, or the formation of fibrous scarring in the tumor, and the surrounding blood vessels [20]. Both of these signs are closely related to the formation of fibrosis in tumors, but there are still differences in the relationship between genes and mutations. Rizzo et al. reported that the mutation rate of NSCLC and *EGFR* gene was 27.5%, which higher than the 15.2% of the nodular depression [10]. Yano et al. thought that there was no correlation between the blood vessel cluster sign and the *EGFR* gene mutation [21]. The results showed that the mutation rate of *EGFR* gene was significantly lower than *non-EGFR* gene mutation rate in PNSCLC accompanied by these two CT signs. The formation of fibrosis in tumor tissues requires two foundations. One is the material basis, which is the raw material of fibrinogen. The second is the biological basis, which is the participation of fibroblasts. Lung cancer growth, depends on the generation of tumor angiogenesis, due to the new blood vessels wall structure is not complete, big endothelial cell gap, fibrinogen large molecules such as clearance easily penetrate into the organization lead to fibrin deposition. There are also reports thought that fibroblasts have been found in tumor cells during the formation of angiogenesis [22]. The condition that the basic condition of fibrosis is formed, it is easier to form fibrosis in tumor tissues. Generally, fibrous production of tumor tissue is the result of relative hypoxia. Compared with the mutated lesion of *EGFR* gene, tumor angiogenesis in the lesion without gene mutation was less, and ischemic hypoxia relatively. Because of the close correlation between the intra-pleural depression and vascular cluster, *EGFR* gene mutation may decrease the fibrosis formation in PNSCLC. This result was different with Rizzo et al. reported the results, pleural indentation sign and blood vessels of the cluster may be related to gender, tumor size, is apart from the chest wall distance and other factors [8,21,23]. In addition, the differences in the inclusion criteria, imaging evaluation criteria and sample size of the cases are also the reasons for the difference.

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