The clinical value of serum tumor markers combined PET / CT diagnosis on non-small cell lung cancer

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Abstract: Objective To investigate the clinical value of serum tumor markers combined positron emission tomography and computed tomography (PET / CT) diagnosis on non-small cell lung cancer (NSCLC). **Methods** 65 cases of patients with suspected lung cancer of X-ray examination were considered as NSCLC group, in which 39 cases were males, 26 cases were females, the age was from 38 to 75 years old and the mean one was (56.4±6.5) years old. 30 patients with benign lung disease patients were selected as benign lung disease group, in which 18 cases were males, 12 cases were females, the age was from 34 to 67 years old and the mean one was (55.2±6.0) years old; 30 healthy subjects were as the healthy control group, in which 17 cases were males, 13 cases were females, the age was from 36 to 74 years old and the mean one was (55.3±5.7) years old. The NSCLC patients hospitalized line 18F-FDG PET / CT and serum tumor markers in check, and cells or pathological results. Healthy control group and benign lung disease group, only test serum tumor markers. The detection of serum tumor markers: serum carcinoembryonic antigen (CEA), cytokeratin fragment antigen (Cyfra21-1), neuron-specific enolase enzyme (NSE), the squamous cell antigens (SCCAg), tissue polypeptide specific antigen (TPS), gastrin-releasing peptide precursor (Pro-GRP). **Result** Benign lung disease serum TPS, NSE level was significantly higher than the healthy control group (P<0.01), TPS positive rate was significantly higher than the healthy control group (P<0.05). NSCLC group, serum TPS CYFRA21-1, NSE, Pro-GRP, CEA, SCCAg levels and the positive rate was significantly higher than the healthy control group and lung benign disease group (P <0.01). The sensitivity, specificity, positive predictive value and negative predictive value of PET / CT combined with tumor markers were higher than simple tumor markers. **Conclusion** Serum tumor markers joint 18F-FDG PET / CT imaging has a higher diagnostic value, could better guide clinical treatment of NSCLC.

Key words: serum tumor markers; non-small cell lung cancer; positron emission tomography; computed tomography

Lung cancer has higher morbidity and mortality of malignant tumors, rather than small-cell lung cancer (NSCLC) accounts for about 80% of lung cancer. Early symptoms of lung cancer, early diagnosis and treatment and prognosis of clinical stage of its great significance. Detection of serum tumor markers for cancer screening, early detection and early diagnosis are of great reference value [1-2]. It has been found in the serum carcinoembryonic antigen (CEA), cytokeratin fragment antigen (Cyfra21-1), neuron-specific enolase (NSE), squamous cell antigen (SCCAg), tissue polypeptide specific antigen (TPS), gastrin-releasing peptide (Pro-GRP) associated with lung cancer and other tumor markers [3-4]. Positron emission tomography and computed tomography (PET / CT) is used in clinical diagnosis of this century, early tumor latest medical imaging method, from the molecular level observed in vivo metabolic changes [5]. In this study, serum tumor markers combined PET / CT diagnosis of NSCLC, are to investigate its diagnostic value in NSCLC.

1 Materials and Methods
1.1 General Information

April 2009 - September 2011 our hospital by chest X-ray examination of 65 patients with suspected lung cancer (NSCLC group), including 39 males and 26 females, aged 38-75 years, mean (56.4 ± 6.5) years old; 26 cases of squamous cell carcinoma, adenocarcinoma in 23 cases, 9 cases of adenosquamous carcinoma, large cell carcinoma, 7 cases; well-differentiated carcinoma in 19 cases, 25 cases of anaplastic carcinoma, poorly differentiated carcinoma 21 cases; Ⅰ of 17 cases, Ⅱ of 32 cases, Ⅲ 16 cases; 29 cases with lymph node metastasis, distant lymph node metastasis in 36 cases. Also selected were treated the same period, 30 patients with benign lung disease patients with benign lung disease group, including 18 males and 12 females, aged 34-67 years, mean (55.2 ± 6.0) years, 26 cases of

chronic pneumonia, pulmonary hemorrhage, inflammation pseudotumor, pulmonary interstitial fibrosis and hamartoma in 1 case; 30 cases of healthy people healthy control group, including 17 males and 13 females, aged 36-74 years, mean (55.3 ± 5.7) years of age. Three groups of patients by age, sex and other general information was no significant difference between comparable (P> 0.05).

1.2 Methods

NSCLC patients hospitalized underwent F-2-deoxy-O-glucose (18F-FDG) PET / CT examination and serum tumor markers, and cells or pathological findings, patients signed informed consent. Healthy control group and benign lung disease group, only its examination of serum tumor markers.

1.2.1 cells or pathological examination: The patient first sputum cytology, if found in cancer cells, are no longer for pathological examination; finding out if the cancer cells, the central lesions usually bronchoscopy for peripheral Lesions can be CT localization biopsy or thoracoscopy invasive examination.

1.2.2 tumor marker tests: All patients were in the early morning fasting blood samples, the application of electrochemiluminescence analyzer, enzyme-linked immunosorbent assay: CEA, CYFRA21-1, NSE, SCCAg, TPS, Pro-GRP levels, thresholds were of ≥ 5.9 ng / mL, ≥ 4.3 ng / mL, ≥ 18.2 ng / mL, ≥ 1.5 μg / L, ≥ 15 u / L, ≥ 50 pg / mL.

1.2.3 18F-FDG PET / CT examination: imaging using the U.S. company GE Discovery STE PET / CT scanner, 18F-FDG from the domestic professional manufacturers supply (radiochemical purity ≥ 95%). Patients fasted keep quiet more than 6 hours before the test routine fasting blood glucose levels, controlled at 7.0 mmol / L or less, cubital vein injection of 18F-FDG 3.7-7.4 MBq / Kg, calm rest 50 minutes underwent CT and PET were systemic faults image. Chest examination on the move when placed in both upper sides of the head, supine position, in order to reduce chest artifacts. Scanning parameters 120KV, automatic current 90-235mA. After positioning CT scanning and imaging scope clear, calm breathing status and image reconstruction CT scan, PET image acquisition range with CT, 2 min / bed, thickness 3.75 mm, FOV 50 cm, an average of six beds in 12-14 min to complete systemic examination, PET data with CT attenuation correction after XELERIS iterative reconstruction workstation line, multi-level, multiple imaging with CT image fusion, reconstruction method using ordered subsets iterative algorithm (expectation maximization, OSEM). In the whole body imaging analysis, based on the location selected region of interest lung lesions (ROI) and measured standard uptake value (SUV), the maximum SUV (SUVmax) ≥ 2.5 diagnosed as malignant (positive).

1.3 Statistical analysis

By pathology or cytology results as the gold standard, were calculated 18F-FDG PET / CT and tumor marker sensitivity, specificity, positive predictive value, negative predictive value, and use the McNemar test to analyze the statistical difference. Differences between groups using ANOVA, LSD pairwise comparison method applied to P <0.05 was considered statistically significant. All data are SPSSl3.0 statistical software package for statistical processing.

2 Results

2.1 The levels of serum tumor marker levels and positive rates

Benign lung disease serum TPS, NSE levels were significantly higher than the healthy control group (P <0.01), TPS was significantly higher than the healthy control group (P <0.05). NSCLC patients serum TPS, CYFRA21-1, NSE, CEA, SCCAg, Pro-GRP levels and the positive rate was significantly higher than that in healthy controls and lung benign disease group (P <0.01). Table 1.

2.2 Tumor markers and PET / CT detection of NSCLC group evaluation results

This study compared the two, three, six tumor markers and PET / CT combined tumor markers detection sensitivity, specificity, positive predictive value and negative predictive value. Tumor markers showed: NSE + CEA combination, CEA + SCCAg + Pro-GRP portfolio specificity; TPS + CYFRA21-1 + NSE combination, TPS + CYFRA21-1 + NSE + CEA + SCCAg + Pro-GRP portfolio highest sensitivity; NSE + CEA combination, SCCAg + Pro-GRP portfolio positive predictive value; TPS + CYFRA21-1 + NSE + CEA + SCCAg + Pro-GRP portfolio, CEA + SCCAg + Pro-GRP portfolio highest negative predictive value . PET / CT combined tumor markers detection sensitivity, specificity, positive predictive value and negative predictive values were higher than that of tumor markers, but the difference was not statistically significant. Table 2. The detection index ROC curve shown in Figure 1-7.

Table 1. 3 levels of serum tumor marker levels and positive rates

Measures of outcome	Control(n=30)	Benign lung disease(n=30)	NSCLCgroup(n=65)
TPS			
Serum levels (u/L)	41.0±4.5	57.1±5.2**	350.5±36.7**[##]
Positive rate (%)	6.7	26.7*	64.6** [##]
CYFRA21-1			
Serum levels (ng/mL)	2.4±0.3	2.5±0.3	8.5±0.9**[##]
Positive rate (%)	6.7	16.7	69.2**[##]
NSE			
Serum levels(ng/mL)	9.2±1.1	11.2±1.2**	20.5±2.1**[##]
Positive rate (%)	3.3	10.0	60.0**[##]
CEA			
Serum levels (ng/mL)	2.4±0.3	2.7±0.3	6.1±0.6**[##]
Positive rate (%)	6.7	6.7	46.2**[##]
SCCAg			
Serum levels (μg/L)	1.4±0.2	1.5±0.4	4.4±0.4**[##]
Positive rate (%)	3.3	6.7	60.0**[##]
Pro-GRP			
Serum levels (pg/mL)	51.2±5.5	55.1±5.9	69.4±7.1**[##]
Positive rate (%)	3.3	3.3	64.6** [##]

Compared with the healthy control group, * P <0.05, ** P <0.01; compared with benign lung disease group, # # P <0.01.

Table 2. tumor markers and PET / CT detection of NSCLC evaluation results (%)

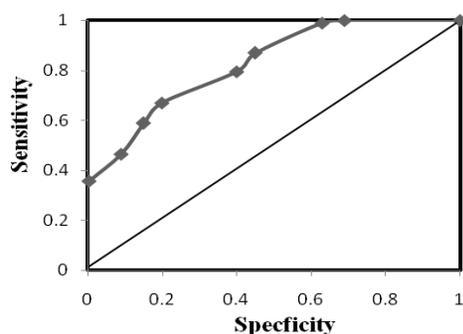| Detection index	specificity	sensitivity	Positive predictive value	Negative predictive value
TPS+CYFRA21-1	63.5	61.9	71.2	80.5
NSE+CEA	87.01	73.2	84.3	86.2
SCCAg + Pro-GRP	66.5	80.4	79.6	88.7
TPS+CYFRA21-1+NSE	62.3	93.8	72.4	91.6
CEA+SCCAg+Pro-GRP	79.2	88.4	75.3	89.3
TPS+CYFRA21-1+NSE+CEA+SCCAg+Pro-GRP	64.3	100	72.0	100
PET/CT+ TPS+CYFRA21-1+NSE+CEA+SCCAg+Pro-GRP	89.4	100	88.6	100

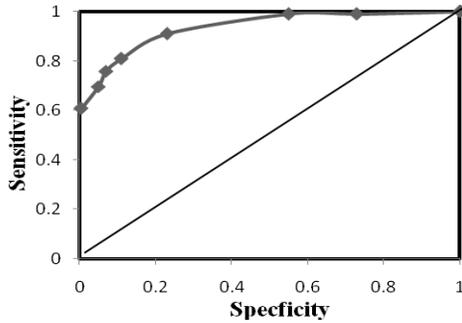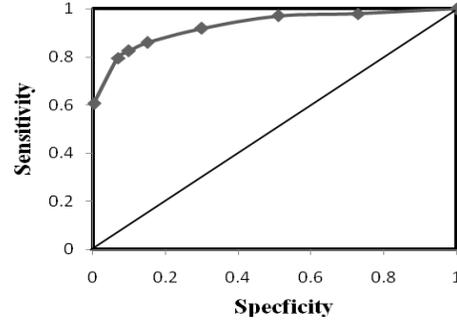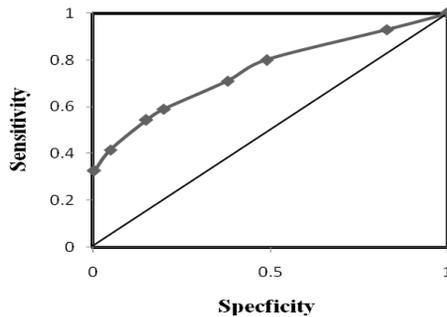**Figure 1** TPS+CYFRA21-1 ROC Curve
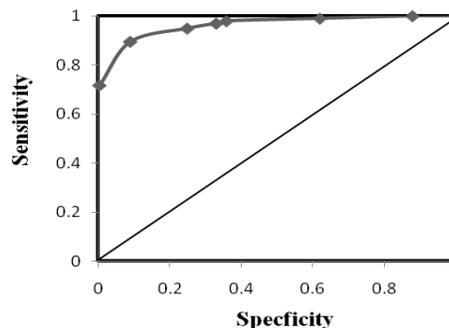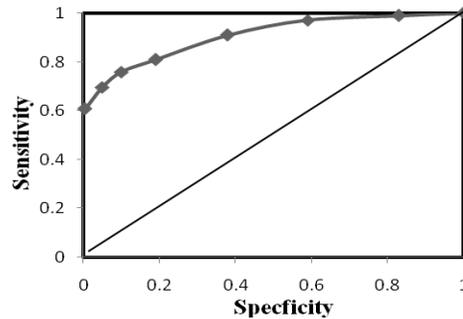

Figure 2 NSE+CEA ROC curve
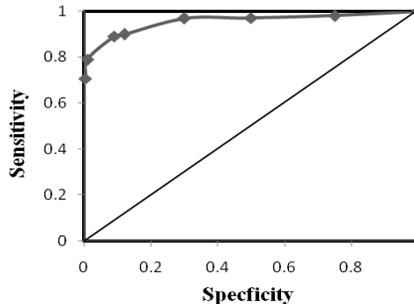
Figure 3 SCCAg + Pro-GRP ROC curve

Figure 4 TPS+CYFRA21-1+NSE ROC curve

Figure 5 CEA+SCCAg+Pro-GRP ROC curve

Figure 6 TPS+CYFRA21-1+NSE+CEA+SCCAg+Pro-GRP ROC curve

Figure 7 PET/CT+TPS+CYFRA21-1+NSE+CEA+SCCAg+Pro-GRP ROC curve

3 Discussion

In recent years, the incidence of lung cancer increased year by year, according to the American Cancer Society (ACS) statistics, in 2007 there are 213,380 new cases of lung cancer, accounting for 15% of all malignant tumors, the incidence rate under section 2, the mortality rate for all malignant tumors in the first place. Diagnosis of lung cancer diagnostic imaging methods include, clinical examination, cytology and histology. After both the tumor biomarkers for the detection of targets, tumor diagnosis is considered the "gold standard." Medical technology in recent years with the development of tumor markers and PET, etc. in the early diagnosis of lung cancer, prognostic monitoring showed a greater clinical value [6]. Tumor markers is defined by serum biochemical and immunological detection methods, and can distinguish between tumor and normal tissue of the

material. Ideal tumor marker should have a high sensitivity of the tumor, tumor-specific, organ-specific. But so far has not found full compliance with the above criteria tumor markers.

Currently, for the diagnosis of lung cancer serum tumor markers including CEA, Cyfra21-1, NSE, SCCAg, TPS, Pro-GRP, etc., because of its detection method is simple, rapid, and the feasibility of the operation and other aspects of the advantages in the clinical widely used [7-9]. CEA 1965 from colorectal cancer tissue antigens extracted substances, abnormal expression in a variety of malignant diseases, cancer diagnosis is the most widely used markers. CEA can be used clinically to monitor the recurrence of lung cancer. Cyfra21-1 is currently more mature study of lung cancer biomarkers, non-small cell lung cancer patients with the most valuable serum tumor markers, all lung Cyfra21-1 positive rate higher, at around 50% to 60%.

NSE is now widely used in detection of small cell lung cancer tumor markers. In neuroblastoma and other neurogenic tumor, neuroendocrine tumors and other diseases, visible NSE increased. Small cell lung cancer can also produce high degree of NSE, which helps to identify small-cell lung cancer and non-small cell lung cancer. SCC-Ag is squamous cell carcinoma antigen for early diagnosis of lung squamous cell carcinoma has a certain significance. TPS is cytokeratin 18 fragment M3 epitopes, can better reflect the activity of tumor cell proliferation. Pro-GRP non-small cell lung cancer more sensitive diagnostic indicators. In this study, benign lung disease serum TPS, NSE levels were significantly higher than the control group; NSCLC patients serum TPS, CYFRA21-1, NSE, CEA, SCCAg, Pro-GRP levels and the positive rate was significantly higher than the control group benign lung disease group. Visible tumor markers has become an important basis for the early diagnosis of cancer.

PET / CT is used in clinical diagnosis of this century, early tumor latest medical imaging method, from the molecular level by observing the changes in metabolism [10]. 18F-FDG is the most commonly used clinical tracer [11]. Compared with CT, PET / CT to early functional and metabolic changes suggesting that tumor [12]. Compared with the conventional PET, PET / CT in CT applications can improve the positioning accuracy lesions [13-14]. PET / CT image fusion will anatomy and function, can significantly improve the accuracy of diagnosis and staging of the tumor. 18F-FDG-PET imaging for cancer, you can display the biological characteristics of the tumor tissue for other purely structural imaging studies incomparable. This study compared the observed serum tumor markers with 18F-FDG PET / CT imaging and combined application of NSCLC diagnostic sensitivity, specificity and positive predictive value, negative predictive value. The results show that, PET / CT combined tumor markers detection sensitivity, specificity, positive predictive value and negative predictive values were higher than that of tumor markers. Visible, serum tumor markers combined 18F-FDG PET / CT imaging for NSCLC has a high diagnostic value, to better guide clinical treatment.

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