^{18}F-FDG PET-CT in Unknown-Source of Elevated Serum Carcinoembryonic Antigen (CEA) Level

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ABSTRACT

Objective: To investigate the clinical value of ^{18}F-FDG PET-CT in the diagnosis of malignant tumor when serum carcinoembryonic antigen (CEA) level is elevated for unknown primary lesion.

Study Design: A descriptive study.

Place and Duration of Study: Department of Nuclear Medicine, Luoyang Central Hospital Affiliated to Zhengzhou University, Henan, China, from March 2015 to March 2017.

Methodology: A total of 120 cases of parallel ^{18}F-FDG PET-CT examination with serum CEA level of patients with unexplained source examined were chosen. Those with a known disease or with incomplete record of clinical and/or relevant laboratory examinations were excluded. Pathological examination, results of clinical follow-up and other imaging tests constituted the clinical value of ^{18}F-FDG PET-CT in the diagnosis of tumor. For patients who had underwent the determination of serum CEA more than twice, CEA doubling time (DT) was also calculated. The serum CEA level and CEA DT of benign *versus* malignant ^{18}F-FDG PET-CT imaging results were compared.

Results: Thirty (25.00%) cases were finally diagnosed as malignant tumors, and 90 (75.00%) cases were excluded labelled benign condition. There was one false positive case and one false negative case each with ^{18}F-FDG PET-CT diagnosis. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value were 96.7%, 98.9%, 98.3%, 96.7% and 98.9%, respectively. The serum CEA level of patients with positive ^{18}F-FDG PET-CT imaging was higher than that of ^{18}F-FDG PET-CT negative patients ($p<0.001$). The serum CEA DT of patients with positive ^{18}F-FDG PET-CT imaging was shorter than that of ^{18}F-FDG PET-CT negative patients ($p<0.001$). The receiver operating characteristic (ROC) curve analysis showed that the diagnostic efficacy of ^{18}F-FDG PET-CT was best at serum CEA of 14.31 μg/L.

Conclusion: ^{18}F-FDG PET-CT imaging has high diagnostic value for patients with elevated serum CEA. For patients with serum CEA over 14.31 μg/L, the diagnostic value of ^{18}F-FDG PET-CT for malignant tumors is more reliable.

Key Words: *Positron emission tomography, Fluorodeoxyglucose 18 fluorodeoxyglucose, Carcinoembryonic antigen, Malignant tumor.*

INTRODUCTION

Carcinoembryonic antigen (CEA) is a substance produced by tumor cells and secreted in body fluid. It is an embryonic carcinogenic antigen and a representative tumor marker.[1] Some patients with symptoms are found to have serum CEA level increased without a known primary lesion. An abnormal or progressive increase of serum CEA level often indicates a malignant tumor.[2] At present, pathological examination is the gold standard for diagnosis of tumor. However, this invasive examination can only reflect local conditions and lacks comprehensiveness.[3] ^{18}F-FDG PET-CT as a new and non-invasive functional imaging technique, it is possible to evaluate the degree of progression of the tumor in a comprehensive way with some anatomic localisation of the site of tumor.[4]

At present, there are several researches where ^{18}F-FDG PET-CT is used in patients with elevated serum CEA after operation of various malignant tumors to monitor recurrence and metastasis,[5] but there are few reports on the studies on the unknown primary lesion.

The purpose of this study was to evaluate the clinical value of ^{18}F-FDG PET-CT imaging in patients with the elevation of serum CEA for unknown primary lesion, and to analyse the relationship between serum CEA level and its doubling time (DT) and ^{18}F-FDG PET-CT.

METHODOLOGY

This study was conducted at the Department of Nuclear Medicine, Luoyang Central Hospital Affiliated with Zhengzhou University, China, from March 2015 to March 2017. A total of 120 cases, who were found with the elevation of serum CEA for unknown primary lesion, were examined with ^{18}F-FDG PET-CT and enrolled in this study. Inclusive criteria were no previous history of malignant tumor, no obvious recent symptoms, serum

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CEA level over 5 μg/L, conventional ultrasonography, chest radiography and MRI being negative for a definite diagnosis. Exclusion criteria were patients who had cancer, with other serious diseases or with incomplete record of clinical and/or relevant examinations and those with elevated CAE with known primary sources. The study was conducted after approval from the Hospital Ethical and Research Committee. All the patients signed Informed Consent before examination.

All patients who had been fasting for more than 6 hours, and the fasting blood glucose less than 8.0 mmol/L, were intravenously injected with ^{18}F-FDG according to the body mass of 5.55 MBq/kg, rested for about one hour, then scanned with PET-CT scanner from skull base to the middle of the thigh. CT data were used for attenuation correction, and the image was reconstructed by iterative method. The images were read by two senior nuclear medicine doctors on the SIEMENS MMWP workstation by semi-quantitative method.

Serum CEA level was detected by automatic electro-chemiluminescence immunoanalyser and its matching reagent. The upper limit of the reference value of serum CEA level was 5 μg/L. For patients who had serum CEA determination more than two times, DT was calculated by the most recent two CEA measurements in closest time to ^{18}F-FDG PET-CT imaging. The calculation formula is: DT=0.693 x (Day1-Day2)/ (lgCEA1-lgCEA2). The CEA1 and CEA2 were the CEA of first time and second time respectively. Day1 and Day2 were the detected time for two times respectively. The first time of serum CEA was measured within two weeks before ^{18}F-FDG PET-CT examination.

The diagnostic effect was evaluated keeping histop-athological results as the gold standard, combined with clinical follow-up and imaging examination to make the final diagnosis. The sensitivity, specificity and accuracy of ^{18}F-FDG PET-CT in the diagnosis of malignant tumors were calculated. Combined with the diagnostic results of pathology and ^{18}F-FDG PET-CT, the operating characteristics of subjects (ROC) was drawn according to the level of CEA, the area under the curve was calculated and the critical value for diagnosis of CEA was established.

SPSS version 21.0 was used to analyse, independent sample t-test for the comparison of CEA level and CEA DT, and p <0.05 the difference was statistically significant.

RESULTS

Among the 120 cases, 68 (56.67%) were males and 52 (43.33%) were females, aged 43-78 years, with mean age of 62.63 ±2.52 years. By ^{18}F-FDG PET-CT, 30 (25.00%) cases were diagnosed as malignant tumor (positive result), including 15 (12.50%) cases of lung cancer, 10 (8.33%) cases of colorectal cancer, three (2.50%) cases of gastric cancer, and two (1.67%) cases of thyroid carcinoma. There were 30 (25.00%) positive results, 90 (75.00%) negative results. One (0.83%) case each was false-positive and false-negative. PET scan of all primary tumors showed increased metabolism of FDG in varying degrees. The corresponding CT findings were soft tissue nodule or mass shadow. PET finding in patients with metastatic lesions were similar to those of primary tumors, *i.e.* increased metabolism of FDG. The sensitivity, specificity, accuracy, positive predictive value and negative predictive value of ^{18}F-FDG PET-CT in diagnosis of malignant tumors were 96.7%, 98.9%, 98.3%, 96.7% and 98.9%, respectively.

The serum CEA level of patients with positive ^{18}F-FDG PET-CT result was higher than that of patients with negative imaging ($p < 0.001$, Table I). Among the 86 (71.67%) patients who had determination of serum CEA more than two times, 25 (20.83%) patients had malignant tumor. Of them, 5 (4.17%) patients had a

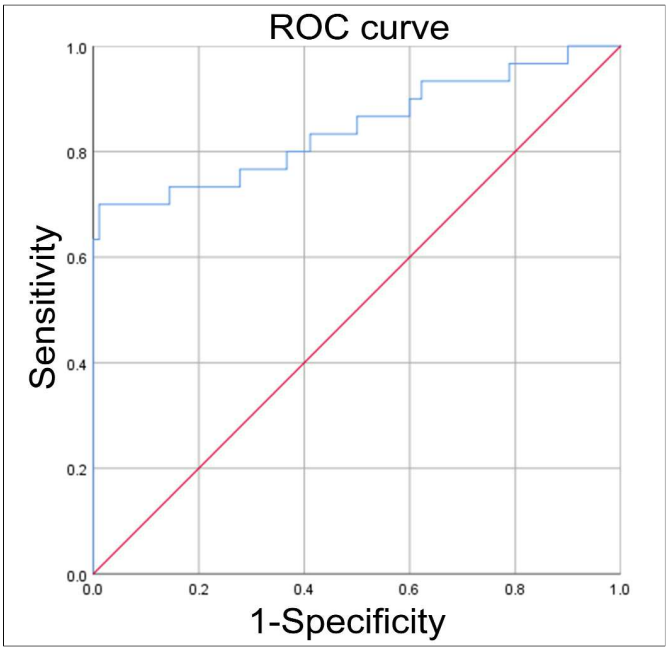

Figure 1: ROC curve of serum CEA in predicting malignant tumor.

Table I: The comparison of CEA levels and CEA DT in patients with different ^{18}F-FDG PET-CT imaging results.

Imaging results of ^{18}F-FDGPET/C	Number of cases of CEA	CEA (ug/L)	Number of cases of CEA DT	CEA DT (d)
Positive	30	43.56 ±7.05	25	97.81 ±4.52
Negative	90	8.63 ±1.34	61	984.42 ±8.16
p		<0.001		<0.001

slight decrease and 7 (5.83%) patients remained stable, 13 (10.83%) patients showed progressive elevation. Of the 61 (50.83%) patients without malignant tumor, 28 (23.33%) cases showed persistent or fluctuating decline, 29 (24.17%) patients remained stable, and four (3.33%) patients showed progressive elevation. The serum CEA DT of patients with ^{18}F-FDG PET-CT positive patients was shorter than that of ^{18}F-FDG PET-CT negative patients ($p < 0.001$, Table I).

The AUC that serum CEA predicted malignant tumor was 0.846 (95%CI: 0.748-0.943). The diagnostic threshold was 14.31 μg/L, and when the sensitivity and specificity were 85.6% and 87.9%, respectively, the diagnostic efficiency was the best, as shown in Figure 1.

DISCUSSION

CEA is one of the commonly used tumor markers of embryonic antigens in clinical practice at present.[6] The molecular weight of CEA is about 150 ~ 300 kD and the proportion of sugar is up to 45%~55%. It belongs to the cell surface glycoprotein family. The molecular structure of CEA is similar with the γ heavy chain of immunoglobulin G. So that some scholars define it as a member of the immunoglobulin superfamily.[7] Elevated serum CEA level may be seen in many benign or malignant diseases, such as pancreas, stomach, lung and mammary glands.[8] The distribution of lesions in the whole body can be fully understandable by ^{18}F-FDG PET-CT scanning, which has the advantage of unparalleled conventional imaging and higher accuracy.[9] A study found that the sensitivity and specificity of ^{18}F-FDG PET-CT in diagnosing malignant tumors in patients with elevated CEA were above 85%.[10] The results showed that 30 cases of 120 patients with elevated serum CEA were diagnosed with malignant tumors. The sensitivity and specificity of ^{18}F-FDG PET-CT was 96.7% and 98.9%, which was consistent with the report of Li *et al*.[11] The results showed that digestive tract tumor and lung tumor accounted for the majority of 30 cases of malignant tumors. In general, if gastroenteroscopy did not find the primary focus, the low-dose chest CT should be the first choice. In this study, 15 cases of lung cancer were examined by ^{18}F-FDG PET-CT, 3 cases were examined by chest radiography, 10 cases had chest CT, none of them was diagnosed. It was speculated that most of the lesions were located at the apex of the lung, the hilar lung and the medial field aorta of the lung are easily missed, and the malignant signs of the lesions are difficult to diagnose by CT.[12-14] ^{18}F-FDG PET-CT can provide information on both functional metabolism and anatomic structure, taking advantage of the high glucose metabolism in malignant tumors, metabolism has been significantly increased before typical morphologic changes and was demonstrated by PET. In this study, 30 patients were detected by ^{18}F-FDG PET-CT, which can better guide clinical treatment, including chest and abdominal tumors, and thyroid carcinoma should be considered. In this study, neck ultrasound and ^{18}F-FDG PET-CT did not clearly diagnose medullary thyroid carcinoma in one patient, which was confirmed by surgery and histopathology.

Serum CEA level and FDG uptake are correlated with tumor load.[15-17] The results of this study showed that the level of serum CEA in patients with positive ^{18}F-FDG PET-CT imaging was higher than that in patients with negative ^{18}F-FDG PET-CT imaging ($p <0.001$). Studies on dynamic changes of serum CEA and ^{18}F-FDG PET-CT imaging for diagnosis of malignant tumors were rare. The results showed that the serum CEA DT of the patients with positive ^{18}F-FDG PET-CT imaging was shorter than that of the patients with negative ^{18}F-FDG PET-CT imaging ($p <0.001$), which was consistent with the report of Giovanella *et al*.[18] It suggested that the shorter the serum CEA DT was, the faster the tumor growth and the easier it was to be detected by ^{18}F-FDG PET-CT. Relevant data showed that preoperative serum CEA over 10 μg/L in patients with non-small cell lung cancer was more likely to predict postoperative recurrence.[19] Some researchers thought that serum CEA over 15 μg/L was a high risk factor for brain metastasis in patients with advanced non-small cell lung cancer before initial treatment.[20] It was found that the best diagnostic effect could be obtained when the diagnostic threshold of serum CEA was 14.31 μg/L.

CONCLUSION

^{18}F-FDG PET-CT imaging has high diagnostic value for differentiating patients with elevated serum CEA from unknown primary source. For patients with serum CEA over 14.31 μg/L, the diagnostic value of ^{18}F-FDG PET-CT for malignant tumors is more reliable.

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