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PET/CT imaging in diagnosing lymph node metastasis of esophageal carcinoma and its comparison with pathological findings

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Abstract. – OBJECTIVE: To investigate the usefulness of ^{18}F-FDG PET/CT imaging in the diagnosis of lymph node metastasis of esophageal carcinoma and to compare its results with pathological findings.

PATIENTS AND METHODS: This study examined 43 cases of patients (32 males and 11 females, aged 54 ± 13 years old) being diagnosed with lymph node metastasis of esophageal carcinoma in our hospital between 2005 and 2014. All of these patients accepted ^{18}F-FDG PET/CT imaging 10 days before the operation. Before reconstruction, each patient went through the body scan. PET/CT images were subject to comprehensive diagnostic analyses, by three experienced radiologists and/or professional nuclear physicians, on the number of metastatic lymph nodes and the maximum standardized uptake value (SUV_{max}). A control study was also performed on the pathological findings according to the latest esophageal cancer lymph node partition.

RESULTS: A total of 846 lymph nodes were taken out from the patients, among which 154 were confirmed with metastasis. When the SUV_{max} cutoff values were set at 2.5 and 5, 201 and 173 metastatic lymph nodes were found by ^{18}F-FDG PET/CT imaging, respectively. Additionally, under such condition, ^{18}F-FDG PET/CT imaging had the esophageal sensitivity of 69.48% *vs* 87.66%, specificity of 92.71% *vs* 94.51%, accuracy of 83.33% *vs* 93.26%, positive predictive value of 53.23% *vs* 78.03%, and negative predictive value of 92.71% *vs* 97.18%.

CONCLUSIONS: ^{18}F-FDG PET/CT had high accuracy in imaging lymph node metastasis of esophageal cancer. SUV_{max} cutoff value of 5 had a higher diagnostic accuracy and should be recommended in clinical practice

Key Words:

Rectal adenocarcinoma, Differentially expressed genes, Gene coexpression network, Small molecule drugs, Transcription factors, microRNAs.

Introduction

Esophagus cancer is a common gastrointestinal tumor. China is one of the high-incidence regions of esophagus cancer, seeing a yearly death of one hundred and fifteen thousand, which accounts for more than one-third of the total death worldwide[1]. While the rates of incidence and mortality are geographically different in China, males have a higher risk of esophagus cancer than females, and the most vulnerable populations are those over 40 years old[2].

Lymphatic metastasis is a common transfer method of esophageal cancer metastasis. The metastasis condition of lymph nodes is, thus, an important factor in the prognostic evaluation of esophageal cancer, and evaluating lymph node metastasis is of great clinical significance in esophageal cancer management [3].

In this retrospective study, we analyzed the PET/CT imaging results of 43 patients who had confirmed lymph node metastasis of esophageal cancer. Results from PET/CT imaging and post-operative pathology were compared. The sensitivity, specificity, accuracy of ^{18}F-FDG PET/CT imaging in the diagnosis of lymph node metastasis was evaluated, and selection of SUV_{max} cutoff value was also assessed.

Patients and Methods

Patients

A total of 43 patients (aged 54.3 ± 13.4 years old) who had been diagnosed with lymph node metastasis in our hospital were included in our study. Among them, 32 were males and 11 were females. None of the patients had accepted any radiotherapy or chemotherapy before PET/CT

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examination. All of the lymph node metastasis results under PET/CT examination were diagnosed according to the revised standard (2009) of AJCC-UICC. In order to make correlation with the pathological results after operation, the mediastinal lymph nodes were divided into 8 different groups according to the location from where the lymph node was removed: the para esophageal part, the aortic-pulmonary window, the lower trachea, the left and right recurrent laryngeal nerve, the subcarinal part, the hilus pulmonis, the cardia section and the left gastric area.

The protocol of this study was approved by our hospital Ethical Committee. Written informed consent was obtained from all patients before participating.

Instrument and Examination Methods

The Gemini GXL 16 Power PET/CT scanner was obtained from Philips Corporation, (Amsterdam, The Netherlands) and the ^{18}F-FDG reagent was provided by Nanjing JYAMS, Ltd. Before the examination, patients were asked to keep fasting for at least 6 hours prior to taking the blood sugar test. After the blood sugar level < 6.60 mmol/L was confirmed, ^{18}F-FDG was injected intravenously at the standard dose of 4.44 MBq·kg^{-1}. The patients were asked to lie in bed calmly for 60-90 minutes, and they were also required to void their bladders before the examination. To conduct early imaging, 2.0-3.0 min/bed was collected. The number of collected beds was 8-10 and the scanning started from the top area of the head to the upper femora. The images were reconstructed after attenuation correction to obtain three-dimensional CT, PET images, including cross-sectional planes, coronal planes, and vertical planes of 5 mm, as well as the PET/CT blending images.

Image Analysis

All collected PET/CT images were examined jointly by three experienced radiologists and professional nuclear physicians. First of all, the region of interest (ROI) was delineated on all images of the metastatic lymph nodes at early and delayed scans. SUV_{max} was then computed, with cut-off values set at 2.5 and 5 according to the diagnostic standard for lymphatic metastasis[4]. Cut-off value of 0.7 cm was taken. All three evaluators confirmed the results jointly and compared the number and size of lymph nodes that were taken out from the mediastinal lymph node partition with the number of metastatic lymph nodes under postoperative pathological confirmation.

Statistical Analysis

Statistical analysis was performed using SPSS20.0 software (SPSS Inc., Chicago, IL, USA). Differences in the number of metastatic lymph nodes of esophageal cancer, acquired by PET/CT imaging, as well as its sensitivity, specificity and accuracy for diagnosis of esophageal cancer lymph node metastasis, were compared by the χ^2 test, with SUV_{max} cutoff values set at 2.5 versus 5. p-values < 0.05 were considered statistically significant.

Table I. Comparison of the number of metastatic lymph nodes acquired by PET/CT imaging, with SUVmax cutoff values set at 2.5 and 5, to those by pathological diagnosis.

	Metastatic Lymph Nodes Number			
	By PET/CT Imaging		By Pathological Diagnosis	
Group[a]	2.5[b]	5[b]	Diagnosed[c]	Taken out[d]
1	42	35	32	185
2	7	4	5	43
3	22	19	17	158
4	69	65	58	169
5	12	9	7	64
6	18	11	12	95
7	12	14	9	76
8	19	16	14	56

[a]Group assignment was made according to the locations from where the lymph node was removed. Group 1: from the paraesophageal part; Group 2: from the aortic-pulmonary window; Group 3: from the lower trachea; Group 4: from the left and right recurrent laryngeal nerve; Group 5: from the subcarinal part; Group 6: from the inferior pulmonary vein; Group 7: from the hilus pulmonis; Group 8: from the cardia section. [b]Values of SUV_{max} cut-off. [c]Number of lymphonodus diagnosed by pathology. [d]Number of lymphonodus taken out from pathology.

Results

A total of 846 lymph nodes were taken out from the 43 patients with lymph node metastasis of esophageal cancer, among which, 154 cases had been confirmed. Table I compares the results from PET/CT imaging in terms of number of metastatic lymph nodes under confirmation to postoperative pathological diagnosis. Results from χ^2 test showed that the sensitivity, positive predictive value and accuracy were significantly higher when SUVmax cutoff value was set at 5 vs 2.5 (χ^2 = 7.45, χ^2= 19.31, and χ^2 = 12.36, respectively, all with p <0.05). In contrast, the differences in the specificity (χ^2= 14.72) and in the negative predictive value (χ^2= 21.56) were not statistically significant whether SUVmax cutoff value was set at 5 or 2.5 (both with p> 0.05). These results suggested that setting the SUVmax cut-off value at 5 was more reliable and practical for diagnosis of esophageal cancer lymph node metastasis.

Discussion

Esophagus cancer is one of the most common malignant tumors in the digestive system, and the staging of lymph nodes metastasis has become an important factor in treatment selection, prognosis prediction, and outcome evaluation[5].

Lymph node metastasis of esophageal cancer is closely related to N stage and M stage, which makes it possible to use different imaging methods in estimating lymph node metastasis of esophageal cancer[6]. Nowadays, the commonly used methods in estimating lymph node metastasis include computer tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), and photon emission tomography/computed tomography (PET/CT), all with distinct features and indications[7].

In clinical practice, CT is most commonly used in estimating lymph node metastasis. Many literature reports have shown a sensibility of CT in diagnosing esophagus cancer at about 11.0%-84.0%, specificity at 67%-100%, accuracy at 62.5%-78%[8]. In CT, the shortest diameter of mediastinal lymph node, 1.0 cm, was usually considered as the diagnostic resolution of lymphatic metastasis.

MRI was quite similar to CT in that it also takes the diameter of lymph nodes as the diagnostic standard of lymphatic metastasis. But MRI imaging was slow and could be influenced by heart fluctuation artifacts, so it was not the first choice in diagnosing lymph node metastasis of esophageal cancer in the past. With the development of new MRI sequence and new contrast agents, MRI's sensibility and specificity have been greatly improved. According to Alper et al[9], the sensibility, specificity, positive predictive value and negative predictive value of MRI short time inversion recovery (STIR) were 81.3%, 98.3%, 92.9%, 95.2%, respectively. Besides, MRI was believed to have great advantages in estimating the benign and malignant lymph nodes[10]. But some other scholars argued that no big difference was seen on the accuracy of MRI and CT in diagnosing lymph node metastasis[11].

EUS was an esophagus endoscopic ultrasonography technology. Its working mechanism lied in the combination of morphological changes and substantive echo. Since its ultrasonic probe was located inside the esophagus, which was closer to the lesion lymph nodes, it could improve the relevance ratio of minimal lesion. Diagnostic standard of EUS includes hypoechoic nodules, which have clear-cut margin and quasi-circular profile, with a diameter over 1.0 cm. According to the literature, its sensibility was 42%-91%, specificity was 67%-91%[12]. Compared with CT, its sensibility was higher and specificity was relatively lower. Its false negative rate was low. So it was of great value in excluding regional lymph node metastasis of esophageal cancer.

In recent years, a new EUS-based method, the so-called fine needle aspiration (FNA) has developed for diagnosing lymph node metastasis. FNA could help improve the sensibility, specificity, and accuracy in the diagnosis of lymph node metastasis of esophageal carcinoma. But its examination was invasive. It may get through the esophageal wall, leading to false positive. Moreover, it could not be used in esophagus cancer with serious esophageal stenosis and with abundant fibrous connective tissues[13].

PET/CT is different from CT, MR and EUS in that it could not only diagnose lymph node metastasis of esophageal carcinoma from morphology, but also detect the metabolism state of the diseased lesion and evaluate the distant metastasis conditions of lymph node metastasis. The most commonly used eikonogen of PET/CT was ^{18}F-FDG (glucose), which could monitor the glucose metabolism state of histiocytes. PET/CT combines CT with PET, and evaluation on lymph node metastasis is made by combining the morphological characteristics with the biological me-

tabolism of esophageal carcinoma lymph nodes. In diagnosing lymph node metastasis of esophageal carcinoma, ^{18}F-FDG PET/CT would also take lymph node grouping metabolism into account, and use SUV_{max} for analysis. Diagnosis of lymph node metastasis by this method may be more acutely and objectively.

Relevant literature reported that the sensibility, specificity, and accuracy of PET/CT was 46.0%-93.8%, 81.0%-94.4%, 78.0%-95.1%, respectively[14]. Our results, sensibility, specificity, and accuracy of 69.46%/87.66%, 92.71/94.51%, 83.33%/93.26%, respectively, were in coincidence with literature reports[15]. Okada et al[16] also shown that ^{18}F-FDG PET/CT image fusion technology was superior to CT in that it could improve the positive predictive value to a greater extent, better diagnose the metastasis of lymph nodes and confirm clinical stages.

In recent years, scholars have made further studies on other kinds of PET/CT imaging besides FDG. 3-deoxy-3-fluorothymidine (FLT) was a kind of thymine, also an imaging agent for tumor proliferation. High uptake of FLT reflected dense deployment of tumor cells in Stage G and Stage S. So it had an advantage in identifying the tumor, inflammation and granuloma. Hans et al[17] reported that ^{18}F-FLT had a higher sensibility and specificity than ^{18}F-FDG, thus of greater value in diagnosing lymph node metastasis of esophageal carcinoma. L-3-18 F-α-methyl tyrosine (^{18}F-FMT) was an amino acid imaging agent. Its mechanism was that malignant tumor cells had a high expression of amino acid transport protein and thus expressed high intake in PET/CT, so it could also be applied in cancer diagnosis. Sohad et al[18] found that the false positive rate of ^{18}F-FMT-PET was 0, so it could diagnose the lymph node metastasis of esophageal carcinoma more accurately.

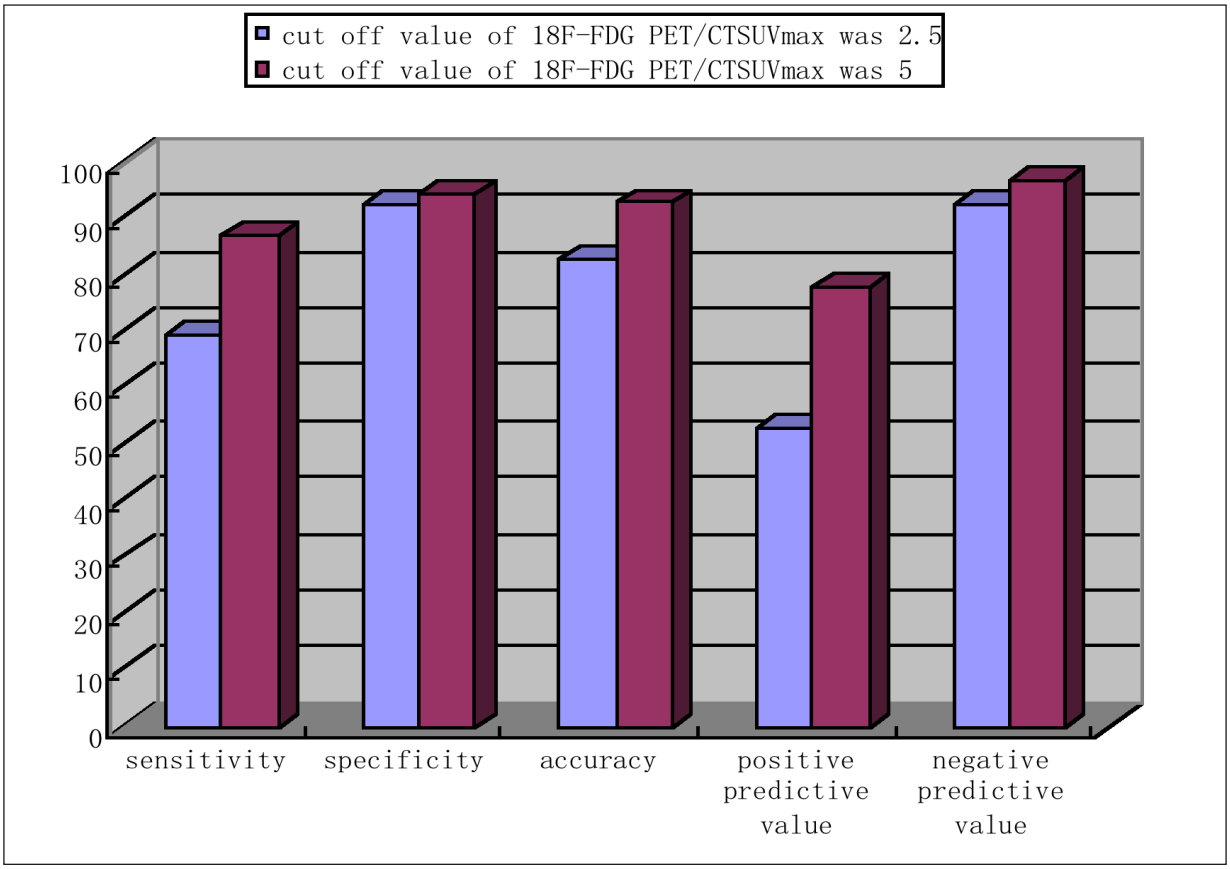

Figure 3. Comparison of diagnostic features in cases of positive and negative lymphatic metastasis under different conditions when the cut off value of 18F-FDG PET/CTSUVmax was 2.5 and 5. Results from the contrast analysis showed that by ^{18}F-FDG PET/CT imaging, the sensitivity, positive predictive value and accuracy in diagnosing esophageal cancer lymph node metastasis was significantly higher when the SUVmax cut-off value was set at 5 versus 2.5 ($p < 0.05$); however, no significant difference was seen in the specificity and in the negative predictive value (both with $p > 0.05$). SUV_{max} cut-off value at 5 was more applicable for diagnosis of esophageal cancer lymph node metastasis.

False positive rate and negative rate were important factors that would influence the diagnostic efficacy of ^{18}F-FDG PET/CT. The major reason for false positive rate of lymphatic metastasis was that esophageal carcinoma was accompanied with inflammatory changes of peripheral lymph nodes, whose imaging performance in PET/CT included enlargement of lymph nodes and augmentation of SUV_{max}. The performance of false high metabolism in PET/CT imaging may lead to misdiagnosis of metastatic lymph nodes. In our study, we didn't take lymph nodes diameter >1.0 cm as the standard for metastatic diagnose of lymph nodes. Considering the spatial resolution of FDG and PET/CT, we took lymph nodes diameter >0.7 cm as the standard for metastatic diagnose of lymph nodes, and combined with FDG SUV_{max} to determine the metastasis state of lymph nodes. False negative mainly came from certain metastatic lymph nodes with a diameter less than 0.5 cm, showing low intake or non-intake in PET/CT imaging. Due to the limited spatial resolution of PET/CT, the number of little lymph nodes was relatively small and their ability to intake glucose was relatively weak. Despite this, results from our study still suggested that ^{18}F-FDG-PET/CT could be a valuable method for diagnosing lymph node metastasis of esophageal carcinoma.

There are some limitations in our study. For instance, the comparison between PET/CT imaging and pathological results was made according to unpaired sections, which reduced the power of this comparison. Another limitation of our study lies in patient selection, since cases that could not take operation or could not be confirmed by pathology were excluded from this study. Nevertheless, two different SUV_{max} cut-off values were explored for diagnosis of lymph node metastasis in this study. The metastasis status on all enrolled 43 cases was observed under the condition that SUV_{max} cut-off value was set at 2.5 and 5, and the obtained imaging data were compared with their pathological results.

Conclusions

Our results showed that the sensibility, specificity and accuracy of lymph node metastasis diagnosis were higher when PET/CT imaging SUV_{max} cut-off value was set at 5. However, further studies with larger sample size are required to confirm this finding.

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Conflict of Interests

The Authors declare that they have no conflict of interests

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