Clinical Research Paper

18F-FDG PET/CT for the detection of primary tumors metastasizing to lymph nodes of the neck

Ying-Ying Hu, Pei-Yan Liang, Xiao-Ping Lin, Xu Zhang, Wei-Guang Zhang and Wei Fan*

State Key Laboratory of Oncology in South China; Guangzhou, Guangdong P.R. China; and Department of Nuclear Medicine; Cancer Center; Sun Yat-sen University; Guangzhou, Guangdong P.R. China

Key words: lymph node metastases, head and neck tumors, 18F-fluorodeoxyglucose, tomography, x-ray computed, tumor, unknown primary

Background and Objective: Cervical metastatic lymph nodes are commonly seen in malignant tumors of the head and neck. Detection of the primary tumors affects the quality of life and survival rates of these patients. This study was to evaluate the application of 18F-FDG PET/CT in detecting primary tumors metastasizing to lymph nodes of the neck, and to assess the positive predictive value of 18F-FDG PET/CT. Methods: In total 93 patients with pathologically confirmed neck lymph node metastases from unknown primary tumors undergoing 18F-FDG PET/CT in Sun Yat-sen University Cancer Center between June 2005 to April 2008 were entered into this study. The primary tumors of patients were initially diagnosed according to different PET/CT standards as definitive diagnosis, suspicious diagnosis and no signs of primary tumors. All diagnosis based on PET/CT images were verified by pathological exams or additional imaging tests. Results: Forty cases receiving definitive diagnosis made by PET/CT were all confirmed by pathological or clinical exams, with a positive predictive value of 100%. Of 28 cases made suspicious diagnosis, 16 were pathologically confirmed, with a positive predictive value of 57.1%. Two patients, who were suggested lymph node metastases in mediastinum without the sign of the primary tumor detected by PET/CT, were clinically verified as primary mediastinal lung cancer. The primary tumors of another two patients were not detected by PET/CT, but were found at endoscopy. The total detection rate of PET/CT for the primary tumors was 60.2% (56/93). Conclusion: PET/CT is of important clinical value in detecting primary tumors metastasizing to lymph nodes of the neck.

Cervical metastatic lymph nodes are the most common malignant neck tumors. The primary tumors can originate from any organs in the head and neck, chest, abdomen and pelvis. Identifying the primary tumors metastasizing to neck lymph nodes has been difficult in clinical practice, which is a labor intensive and time-consuming process. Nevertheless, the primary tumors of some patients still could not be detected after careful and complete examinations. Identification of primary tumors may help prolong the survival and the quality of life of patients. In recent years, some new methods, such as 18F-FDG PET, have been utilized to diagnose the primary tumors metastasizing to neck lymph nodes.1 18F-FDG PET can detect the glycometabolic state in tumor cells. For some small primary tumors which cannot be identified by routine diagnostic imaging methods may be detected by 18F-FDG PET, because the glycometabolism of tumor cells is active. The results of using 18F-FDG PET in identifying primary tumors metastasizing to neck lymph nodes are varied,2-6 which is most probably due to the small sample size and differences in the detection sites. In the past, application of 18F-FDG PET without integration of CT often resulted in low resolution images. So far, there are no standard diagnostic criteria for primary tumors using integrated 18F-FDG PET/CT, especially for those suspicious primary tumors without obvious morphological changes. This study was to evaluate the application of 18F-FDG PET/CT in detecting primary tumors metastasizing to lymph nodes of the neck, and to assess the positive predictive value of 18F-FDG PET/CT.

Patients and Methods

Research subjects. Ninety-three patients undergoing 18F-FDG PET/CT in the Department of Nuclear Medicine, Sun Yat-sen University Cancer Center, from June 2005 to April 2008 were included. These patients were pathologically confirmed to have neck lymph node metastases from unknown primary tumors by biopsy or excision. There were 29 females and 64 males, aged from 14- to 77-years-old (medium, 51 years). The neck lymph node metastases consisted of 38 cases of squamous cell carcinoma, 28 cases of adenocarcinoma, 20 cases of poorly differentiated or undifferentiated
18F-FDG PET/CT for the detection of primary tumors metastasizing to lymph nodes of the neck

Diagnosis by PET/CT imaging and image analysis. The PET/CT images were qualified if the distribution of 18F-FDG in PET images was consistent with the characteristics of physiological glycometabolism and the features of excretion of 18F-FDG; and the fusion images were well matched. The image analysis was accomplished by two qualified doctors, experienced in PET/CT diagnosis in the Department of Nuclear Medicine. The uptake of 18F-FDG was evaluated by macroscopic observation and the SUV was referred to if necessary. The diagnostic criteria for primary tumors were listed below:

1. **Definitive diagnosis**: The uptake of 18F-FDG was higher than that in the mediastinal blood pool, and obvious morphological abnormalities were found in the CT image indicating primary malignant lesions.
2. **Suspicious diagnosis**: The uptake of 18F-FDG was higher than that in the mediastinal blood pool, but no morphological abnormalities were found in the CT images, or minor morphological changes in CT images did not meet the criteria of a definitive diagnosis; clear morphological changes in the CT images indicated possible primary malignant lesions, however, the uptake of 18F-FDG was lower than that in the mediastinal blood pool.
3. **No signs of primary tumors**: The uptake of 18F-FDG and the CT images did not support the indication of primary tumors in any organs.

18F-FDG PET/CT imaging. 18F-FDG was purchased from Guangzhou Branch of Beijing HTA Co., Ltd. Its radiochemical purity was more than 99%.

The patients were fasted for over 6 h. Diabetic patients did not stop using hypoglycemic drugs or insulin before the 18F-FDG PET/CT scan. The blood sugar level of each patient was measured and required to be below 8.1 mmol/L. Insulin was injected subcutaneously if necessary. 18F-FDG (4.4–7.4 MBq/Kg) was injected intravenously. After resting quietly in the dark room for 45 min to 60 min, the patients underwent the PET/CT scan after urination. The PET/CT apparatus (Discovery ST-16) was purchased from GE Company. The patients were scanned from the calva to the middle part of the femur, lying in the supine position. The automatic tracking method was used in the CT scan with a tube tension of 140 KeV. Emission scans were collected in 2-D mode over five to seven bed positions, 2.5 min/bed position. PET images were reconstructed with the slice thickness of 3.75 mm using the OSEM iterative image reconstruction method. The standardized uptake value (SUV) of 18F-FDG was automatically calculated based on the weight, injection dosage and the metabolic rate of patients.

Table 1  
<table>
<thead>
<tr>
<th>Site suspicious for primary tumors</th>
<th>Positivity of PET and CT</th>
<th>Final pathological diagnosis (number of malignancy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharynx</td>
<td>PET+/CT−, 9; PET+/CTza, 5</td>
<td>9</td>
</tr>
<tr>
<td>Lung</td>
<td>PET+/CT+, 2</td>
<td>0</td>
</tr>
<tr>
<td>Tonsil</td>
<td>PET+/CT−, 2</td>
<td>1</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>PET+/CT+, 1; PET−/CT+, 1</td>
<td>0</td>
</tr>
<tr>
<td>Larynx</td>
<td>PET+/CT+, 3</td>
<td>3</td>
</tr>
<tr>
<td>Esophagus</td>
<td>PET+/CT−, 1</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>PET+/CT−, 1</td>
<td>0</td>
</tr>
<tr>
<td>Mammary gland</td>
<td>PET+/CT−, 2</td>
<td>1</td>
</tr>
<tr>
<td>Rectum</td>
<td>PET+/CT−, 1</td>
<td>1</td>
</tr>
</tbody>
</table>

*aNote: one patient gave up therapy and no pathological diagnosis was obtained.*

Figure 1. A definitive diagnosis of the primary tumor made by PET/CT in the right piriform fossa of a 40-year-old man with neck lymph node metastasis. (A) Transverse CT image shows a nodule in the right piriform fossa and an intumescent lymph node in the right neck. (B) Transverse PET image shows pathologic uptake of FDG in the middle and right sides of the neck region. (C) Transverse fused PET/CT image shows intense FDG uptake in the right piriform fossa and the lymph node, confirmed by subsequent biopsy to be the piriform fossa primary tumor.
Figure 2. A suspicious diagnosis of the primary tumor made by PET/CT both in the nasopharynx and esophagus of a 55-year-old woman with neck lymph node metastasis. (A) Transverse CT image is normal in the nasopharynx. (B) Transverse PET image shows moderate uptake of FDG in the middle image. (C) Transverse fused PET/CT image shows moderate FDG uptake in the right lateral pharyngeal fossa and the posterior wall, confirmed by subsequent biopsy to be inflammation. (D) Transverse CT image shows no detectable abnormality in the mediastinum. (E) Transverse PET image shows moderate uptake of FDG in the mediastinum. (F) Transverse fused PET/CT image shows moderate FDG uptake in the esophagus, confirmed by subsequent biopsy to be esophageal primary tumor.

Pathological examination and other examinations. Before or after the PET/CT scan, patients underwent endoscopic examination, pathological examination and other imaging examinations. Biopsy or pathological examination after surgery was conducted for primary tumors under the PET/CT guidance in 23 patients.

Results

Definitive diagnosis of primary tumors by PET/CT. The definitive diagnosis of primary tumors was made in 40 cases by PET/CT, which were verified by pathological or clinical examinations. The positive predictive value was 100%. One of these cases was diagnosed as a malignant lesion in the right piriform fossa (Fig. 1), which was initially diagnosed as inflammatory pseudotumor by biopsy at endoscopy. A second time biopsy after the PET/CT scan found some squamous cell debris, a large amount of necrosis, and severe atypical hyperplasia with early invasion. Among these 40 cases, six were classified as stage II, 15 as stage III, and 19 as stage IV based on the TNM staging system. The sites of the primary tumors were as follows: 17 cases in the lung, seven in the nasopharynx, four in the larynx and hypopharynx, three in the oropharynx (including the lingual root), two in the esophagus, two in the colon (one in the ascending colon and one in the transverse colon), and one in the parotid, liver, gall bladder, ovary and testicle, respectively.

Suspicious diagnosis of primary tumors by PET/CT. Twenty-eight cases were diagnosed as suspicious primary tumors by PET/CT. Among the 23 patients undergoing biopsy or excision, 16 were identified as malignant lesions and seven as benign ones. One patient with suspicious breast carcinoma gave up the therapy and did not receive pathological examination. The other four (three in the lung and one in the thyroid) were identified as benign lesions after careful comparison of the early and late imaging data. The sites of the suspicious primary tumors, the positive findings at PET and CT, and the final pathological diagnosis are shown in Table 1. PET+/CT- was found in both the nasopharynx and esophagus of one patient, whose biopsy reported an inflammatory lesion in nasopharynx and esophageal carcinoma in the esophagus (Fig. 2).

No detection of primary tumors by PET/CT. The primary tumors of 25 cases were not detected by PET/CT. Malignant mediastinal nodes were indicated in two patients by PET/CT, which were assumed to be mediastinal lymph node metastases. After pathological and immunohistochemical examinations, these two patients were diagnosed as primary mediastinal lung cancer. One patient showed lymphadenectomy in the hilum of lung.
PET images. These inconsistency would result in uncertain appearances, such as positive PET images alone, or positive PET plus other imaging modalities; one receiving a suspicious diagnosis made by PET/CT gave up therapy and was not identified by pathological examination; 21 patients showed no primary tumors after PET/CT and other clinical examination. Three months after the PET/CT scan, one patient showed parenchyma lump in maxillary sinus and nasal cavity. The patient was diagnosed as alveolar rhabdomyosarcoma by pathological examination after surgery. Lesions were found in the left lung in one patient one year after the PET/CT scan and the patient was diagnosed as left lung cancer. Seven patients died and were not diagnosed by the pathological examination. Two patients were lost during the follow-up. No primary tumors were found in the other 22 patients when the follow-up ended.

Values of PET/CT in detecting primary tumors metastasizing to neck lymph nodes. Among the 93 patients, 60 were diagnosed as having primary tumors by pathological examination and other clinical examinations (those whose primary tumors were detected in the follow-up visit were excluded). Primary tumors were found in 56 patients by PET/CT (40 were made a definitive diagnosis and 16 were made a suspicious diagnosis). The detection rate for primary tumors by PET/CT was 60.2% (56/93). Two patients showed mediastinal lymph node metastases, but no indications of primary tumors were found in them. They were identified as having primary mediastinal carcinoma. Two patients who did not show indications of primary tumors by PET/CT were detected primary tumors at endoscopy (one nasopharyngeal carcinoma and one lung cancer). The positive predictive value of 40 cases receiving a definitive diagnosis was 100% (40/40), and that of 28 cases made a suspicious diagnosis was 57.1% (16/28).

Discussion

The consistency of anatomy and metabolism is the standpoint for accurate diagnosis of tumors using PET/CT. However, in daily work, the discrepancy between the anatomy and metabolism often appears, such as positive PET images alone, or positive PET plus minor morphological change in CT images, or morphological change in CT images without significant metabolic changes in PET images. These inconsistency would result in uncertain diagnosis of PET/CT. Appropriately 75% primary tumors metastasizing to neck lymph nodes originate from the head and neck, such as the nasopharynx, tonsil, lingual root and so on. These sites tend to show an unspcific increase of glucose uptake detected by $^{18}$F-FDG PET/CT. Primary tumors can not be detected in some other neck lymph node metastases after careful examinations because of insignificant morphological changes in the small primary tumors. The above factors contribute to the difficulties in detecting primary tumors by PET/CT. The false positivity and missed diagnosis limit the application of PET/CT in detecting primary tumors metastasizing to neck lymph nodes.

Rusthoven KE et al. conducted meta-analysis on 16 groups of 302 cases using $^{18}$F-FDG PET or $^{18}$F-FDG PET/CT in diagnosing neck lymph node metastases with unknown primary tumors. They showed that FDG-PET could detect 24.5% primary tumors which could not be identified by routine imaging methods, and that about 27.1% patients were found previously unrecognized metastases by FDG-PET. The results demonstrate that $^{18}$F-FDG PET or $^{18}$F-FDG PET/CT is significant in identifying unknown primary tumors metastasizing to neck lymph nodes. Some researchers compared the detection rate of $^{18}$F-FDG PET with $^{18}$F-FDG PET/CT and believe that the CT image in the integrated PET/CT could accurately detect the sites with abnormal FDG uptake, which would help increase the specificity of $^{18}$F-FDG PET. Regarding to the detection rate of primary tumors, integrated $^{18}$F-FDG PET/CT is superior to PET or CT alone, or non-integrated PET and CT. Different from other studies, we did not emphasize on comparison between $^{18}$F-FDG PET and routine imaging methods, because the integrated CT belongs to routine imaging and is a part of $^{18}$F-FDG PET/CT. We included CT images as the reference for the diagnosis of primary tumors metastasizing to lymph nodes of the neck in addition to considering the uptake of FDG. Different diagnostic standards were set to assess the positive predictive values. The positive predictive value of 40 cases receiving a definitive diagnosis was 100%, and that of 28 cases made a suspicious diagnosis was 57.1%.

Routine imaging methods may also detect primary tumors in the 40 patients with a definitive diagnosis made by PET/CT, because of significant morphological changes observed in the primary tumors. The advantage of PET/CT over routine imaging methods in detecting primary tumors in these patients is that active metabolic lesions in the organs of the head and neck, the chest and the abdomen could be detected by the scan from the calva to the middle part of the femur. In the 40 patients, 15 had primary tumors in the head and neck with an occurrence rate of 37.5%; six had lesions in the abdomen, pelvis and reproductive organs (such as testicle) with an occurrence rate of 15%. Moreover, $^{18}$F-FDG PET/CT could be used to classify the stage of the tumor, which is a more important use. In this study, 47.5% patients (19/40) were classified as stage IV based on the TNM staging system, 13 of which had distant metastases to neck, chest, abdomen, pelvis and skeleton.

The diagnosis of suspicious primary tumors using PET/CT may result in false positive results. However, because most suspicious primary tumors do not show abnormalities or reveal minor morphological changes, routine imaging methods or even

Follow-up of patients who were not found primary tumors. Thirty-three patients whose primary tumors were not detected were followed up with a minimum period of six months and a maximum period of 32 months. Among these 31 patients, 11 who had been identified as having suspicious primary tumors by PET/CT, were diagnosed as benign lesions by pathological examination or other imaging modalities; one receiving a suspicious diagnosis made by PET/CT gave up therapy and was not identified by pathological examination; 21 patients showed no primary tumors after PET/CT and other clinical examination. Three months after the PET/CT scan, one patient showed parenchyma lump in maxillary sinus and nasal cavity. The patient was diagnosed as alveolar rhabdomyosarcoma by pathological examination after surgery. Lesions were found in the left lung in one patient one year after the PET/CT scan and the patient was diagnosed as left lung cancer. Seven patients died and were not diagnosed by the pathological examination. Two patients were lost during the follow-up. No primary tumors were found in the other 22 patients when the follow-up ended.

Values of PET/CT in detecting primary tumors metastasizing to neck lymph nodes. Among the 93 patients, 60 were diagnosed as having primary tumors by pathological examination and other clinical examinations (those whose primary tumors were detected in the follow-up visit were excluded). Primary tumors were found in 56 patients by PET/CT (40 were made a definitive diagnosis and 16 were made a suspicious diagnosis). The detection rate for primary tumors by PET/CT was 60.2% (56/93). Two patients showed mediastinal lymph node metastases, but no indications of primary tumors were found in them. They were identified as having primary mediastinal carcinoma. Two patients who did not show indications of primary tumors by PET/CT were detected primary tumors at endoscopy (one nasopharyngeal carcinoma and one lung cancer). The positive predictive value of 40 cases receiving a definitive diagnosis was 100% (40/40), and that of 28 cases made a suspicious diagnosis was 57.1% (16/28).

Discussion

The consistency of anatomy and metabolism is the standpoint for accurate diagnosis of tumors using PET/CT. However, in daily work, the discrepancy between the anatomy and metabolism often appears, such as positive PET images alone, or positive PET plus other imaging modalities; one receiving a suspicious diagnosis made by PET/CT gave up therapy and was not identified by pathological examination; 21 patients showed no primary tumors after PET/CT and other clinical examination. Three months after the PET/CT scan, one patient showed parenchyma lump in maxillary sinus and nasal cavity. The patient was diagnosed as alveolar rhabdomyosarcoma by pathological examination after surgery. Lesions were found in the left lung in one patient one year after the PET/CT scan and the patient was diagnosed as left lung cancer. Seven patients died and were not diagnosed by the pathological examination. Two patients were lost during the follow-up. No primary tumors were found in the other 22 patients when the follow-up ended.

Values of PET/CT in detecting primary tumors metastasizing to neck lymph nodes. Among the 93 patients, 60 were diagnosed as having primary tumors by pathological examination and other clinical examinations (those whose primary tumors were detected in the follow-up visit were excluded). Primary tumors were found in 56 patients by PET/CT (40 were made a definitive diagnosis and 16 were made a suspicious diagnosis). The detection rate for primary tumors by PET/CT was 60.2% (56/93). Two patients showed mediastinal lymph node metastases, but no indications of primary tumors were found in them. They were identified as having primary mediastinal carcinoma. Two patients who did not show indications of primary tumors by PET/CT were detected primary tumors at endoscopy (one nasopharyngeal carcinoma and one lung cancer). The positive predictive value of 40 cases receiving a definitive diagnosis was 100% (40/40), and that of 28 cases made a suspicious diagnosis was 57.1% (16/28).

Discussion

The consistency of anatomy and metabolism is the standpoint for accurate diagnosis of tumors using PET/CT. However, in daily work, the discrepancy between the anatomy and metabolism often appears, such as positive PET images alone, or positive PET plus other imaging modalities; one receiving a suspicious diagnosis made by PET/CT gave up therapy and was not identified by pathological examination; 21 patients showed no primary tumors after PET/CT and other clinical examination. Three months after the PET/CT scan, one patient showed parenchyma lump in maxillary sinus and nasal cavity. The patient was diagnosed as alveolar rhabdomyosarcoma by pathological examination after surgery. Lesions were found in the left lung in one patient one year after the PET/CT scan and the patient was diagnosed as left lung cancer. Seven patients died and were not diagnosed by the pathological examination. Two patients were lost during the follow-up. No primary tumors were found in the other 22 patients when the follow-up ended.
18F-FDG PET/CT for the detection of primary tumors metastasizing to lymph nodes of the neck

endoscopy cannot identify these abnormalities. Therefore, PET/CT still possesses high clinical values over other diagnosis tools. Among the nine patients who were made suspicious diagnosis and finally diagnosed as nasopharyngeal carcinoma, eight showed no abnormalities at epipharyngoscopy or head MRI before receiving PET/CT. Moreover, five patients who showed abnormalities in the lung or submaxillary gland with PET+/-CT+ or PET-/CT+ were identified as benign lesions. The results suggest that if abnormal glycometabolism does not reach the diagnostic criteria for malignant tumors, the possibility of primary carcinoma is low despite of morphological changes.

Moreover, 35.5% (33/93) patients did not show any manifestations of primary tumors detected by 18F-FDG PET/CT or other clinical examinations, which may be due to the small size of the tumor, the hidden location of the tumor, the damage to the tumor caused by poor angiogenesis and immunity suppression, and anti-tumor therapy resulting in apoptosis and disappearance of tumors. Among the six patients who underwent therapy before PET/CT, the primary tumor was detected in only one patient. The other five patients did not show the signs of primary tumors even during the follow-up. Among the 33 patients in whom no primary tumors were found, the primary tumor was detected in only two patients during the follow-up.

The integrated PET/MR can evaluate the structures, morphology and glycometabolism. The MRI is superior to CT in detecting soft tissues and its multisecuencing capacity could provide much more information, especially in the head and neck. As cervical metastatic lymph nodes mainly originate from the head and neck, we are expecting the clinical application of PET/MR, which will facilitate the identification of primary tumors metastasizing to neck lymph nodes.

In summary, 18F-FDG PET/CT has significant clinical values for identifying primary tumors metastasizing to neck lymph nodes, with a detection rate of 60.2%. It improves the clinical staging of carcinomas and has unique advantages for detecting primary tumors without obvious morphological changes over routine imaging examinations.

References