

Clinical implication of ^{18}F -FDG PET/CT in carcinoma of unknown primary

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The value of ^{18}F -Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in the detection of carcinoma of unknown primary (CUP) differs among the studies. This study aimed to evaluate the role of ^{18}F -FDG PET/CT in CUP.

Fifty-one patients (19 women, 32 men) with metastasis confirmed by histopathology from an unknown primary tumor were included in this study. Patients received 370 MBq of ^{18}F -FDG intravenously, and PET/CT was performed at 60 minutes after injection.

Primary tumor sites were detected in 5 of 51 patients (9.6%): in 2 patients with carcinoma of the lung, in 1 patient with carcinoma of the gallbladder, in 1 patient with carcinoma of the esophagus, and in 1 patient with carcinoma of the stomach. No primary tumor was discovered in the remaining 46 patients (90.4%) during the follow-up. The sensitivity, specificity, and accuracy of ^{18}F -FDG PET/CT were 100%, 80.4%, and 82.4%. The positive and negative predictive values were 35.7 and 100%, respectively.

Based on the data presented, ^{18}F -FDG PET/CT has a clinical implicative value in detecting the primary tumor of CUP. PET/CT can be useful to rule out the possibility of detecting the primary tumor during the follow-up.

Key words: Fluorodeoxyglucose F18, positron-emission tomography, neoplasms, unknown primary

Carcinoma of unknown primary (CUP) is a biopsy-proven malignancy which is failed to identify the primary site by full physical and laboratory examination and conventional imaging [1, 2]. CUP is one of the 10 most frequently occurring cancers worldwide, accounting for 3-5% of all malignancies [3, 4]. Its prognosis is poor with a median survival time of only 4 months [5]. If we succeed in detecting the primary tumor, thus converting the unknown primary tumor into a defined tumor disease with a primary tumor and metastases, it may lead to more specific treatment planning and improving the outcome [6, 7]. Less than 20% of patients with CUP have a primary site of their cancer identified even antemortem. Autopsy studies have reported that 70% of cases remained undiagnosed [1].

Studies have shown that positron emission tomography/computed tomography (PET/CT) utilizing ^{18}F -Fluorodeoxyglucose (FDG) is a valuable tool in patients with CUP, but with large difference between studies from 24 to 80 percent of detection rates [8-12].

In this study, we retrospectively evaluate the clinical implication of ^{18}F -FDG PET/CT in the localization of primary tumors in patients of CUP.

Patients and methods

Patients. We retrospectively analyzed the consecutive records of ^{18}F -FDG PET/CT performed between January 2005 and April 2010 and collected 51 patients (19 women, 32 men; mean age, 58.7 years) with metastases from unknown primary tumor. Inclusion criteria were biopsy proven malignancy prior to ^{18}F -FDG PET/CT, no past history of malignancy and unknown primary tumor after conventional diagnostic workup. For all patients, routine workup consisted of a complete medical history, physical examination, routine laboratory evaluation, serum tumor markers and chest X-ray. Further workup before ^{18}F -FDG PET/CT consisted of chest CT in 31, abdomen and pelvis CT in 33, neck CT in 18, brain CT in 3, spine magnetic resonance imaging (MRI) in 2, brain MRI in 4, abdomen and pelvis MRI in 6, neck MRI in 3, gastroscopy in 35, colonoscopy in 23, bronchoscopy in 2, bone scintigraphy in 12, mammography in 11, gallium scan in 1, abdominal ultrasonography (US) in 6, breast US in 5 and neck US in 2. Additionally, in patients with head and neck metastases, laryngoscopy and nasopharyngoscopy were performed prior to ^{18}F -FDG PET/CT. This study was approved by our

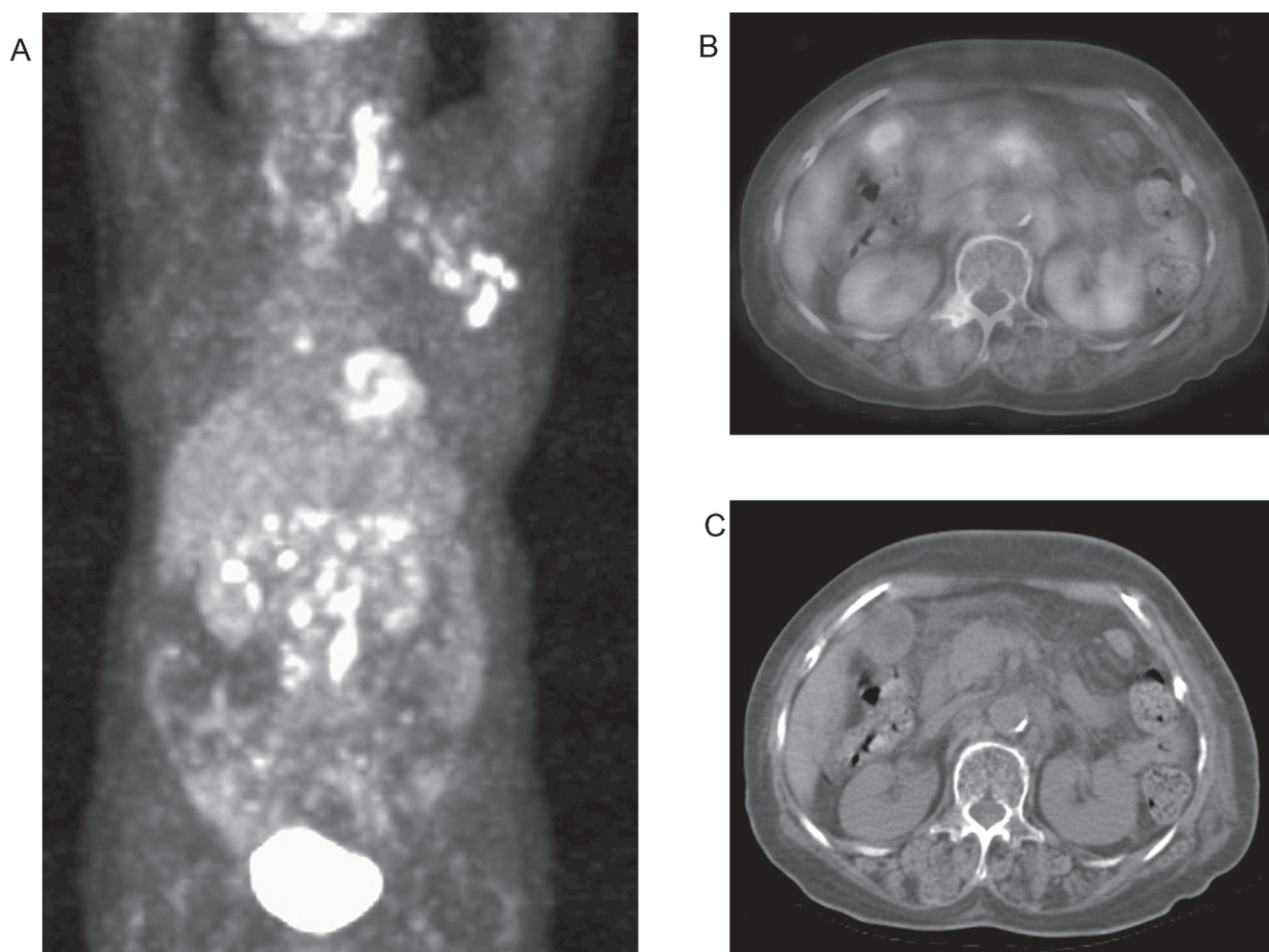


Figure 1. ^{18}F -FDG PET/CT images of a 81-year-old female presenting with cervical lymphadenopathy. Maximum intensity projection image (A), axial PET (B) and CT (C) show focally increased FDG uptake of the gallbladder, abdominal lymph nodes and L1 spine on the right.

institutional review board and written informed consent was obtained from each patient.

^{18}F -FDG PET/CT. Standard patient preparation included at least 8 h fasting and a serum glucose level of less than 120 mg/dL before ^{18}F -FDG administration. ^{18}F -FDG PET/CT imaging was performed 60 min after injection of 370Mbq of ^{18}F -FDG. Patients were hydrated with 500ml of water per oral before the PET/CT imaging. At 60 min after administration of ^{18}F -FDG, low-dose area from the base of the skull to the proximal thighs was performed for the purpose of attenuation correction and precise anatomical localization.

Forty seven patients were examined on a PET/CT scanner (Gemini, Philips, Milpitas, CA, USA), consisting of a germanium oxyorthosilicate full-ring PET scanner and a dual slice helical CT scanner. Thereafter, emission scan was conducted in the 3-dimensional mode. Emission scan time per bed position was 3 min; 9 bed positions were acquired. PET data were obtained using a high resolution whole body

scanner with an axial field of view of 18 cm. The average axial resolution varied between 4.2 mm full width at half maximum (FWHM) in the center and 5.6 mm at 10 cm. The average total PET/CT examination time was 30 minutes. After scatter and decay correction, PET data were reconstructed iteratively with attenuation correction and reoriented in axial, sagittal, and coronal slices. The row action maximum-likelihood algorithm was used for 3-dimensional reconstruction.

Four patients were examined on a PET/CT scanner (Biograph40, SIEMENS, Knoxville, TN, USA). Emission scan time per bed position was 3 min; 6 bed positions were acquired. PET data were obtained using a high resolution whole body scanner with an axial field of view of 21.6 cm. The average axial resolution varied between 2.0 mm full width at half maximum (FWHM) in the center and 2.4 mm at 28 cm. The average total PET/CT examination time was 20 minutes. Attenuation correction was performed for all patients with iterative reconstruction. PET/CT images were analyzed in three different

planes (transverse, coronal and sagittal). PET/CT images were interpreted visually by two nuclear physicians. In the event of disagreement, a consensus was established.

Results

Fifty-one patients with CUP were included in this study. Twenty-one patients showed cervical metastatic adenopathy on conventional diagnostic workup. Thirty patients had extracervically located metastases. The characteristics of the patients are shown in Table 1. If a suspected PET/CT abnormality was confirmed as the primary tumor, either histologically or during the follow-up, PET/CT result was defined as true positive. A true negative was a negative PET scan if the primary remained unknown during the follow-up. If a primary tumor was suspected by PET/CT without confirmation during the follow-up, the result was considered as false positive. A false negative was considered with negative PET/CT if the primary tumor was identified later. The sensitivity, specificity, positive predictive value, and negative predictive value of ^{18}F -FDG PET/CT to detect a primary tumor were calculated. The patients were followed up for a median 11.8 months (range, 1-58months). During the follow-up, no additional primary tumors was detected. Table 2 summarizes the diagnostic values of ^{18}F -FDG PET/CT in CUP.

True positive results. PET/CT was able to detect a biopsy-proven primary tumor in 5 (9.6%) patients: the lung (n=2), the esophagus (n=1), the stomach (n=1), and the gallbladder (n=1). Four of 5 patients showed cervical lymphadenopathy. Primary tumors of the esophagus and the stomach were confirmed histologically by the gastroscopy. In 2 patients, primary tumors of the gallbladder (Figure) and the lung detected by PET/CT identified the presence of the malignancy in abdomen and chest by CT. The other primary tumor of the lung showed axillary lymphadenopathy which was evaluated with chest CT, gastroscopy, mammography and breast US. Chest CT scan was reported as 'not conclusive'. PET/CT detected primary tumor of the lung which was later confirmed with immunohistochemistry.

True negative results. Primary tumor was not detected during the follow-up in 37 (73.1%) patients with negative PET/CT.

False positive results. PET/CT identified focal FDG uptake indicative of a primary tumor in 14 patients. Of these, 9 (17.3%) were false-positives; 2 patients were suspected of having a malignancy in the tonsil, 1 in the soft palate, 1 in the vocal cord, 1 in the nasopharynx, 1 in the common bile duct, 1 in the uterus, 1 in the ovary and 1 in the kidney. However, no results of positive PET/CT were confirmed histologically or identified during the follow-up.

False negative results. No primary tumor was detected during the follow-up of patients with negative PET/CT

Based on these numbers, the sensitivity, specificity, and accuracy of ^{18}F -FDG PET/CT were 100%, 80.4%, and 82.4%. The positive and negative predictive values were 35.7 and 100%, respectively.

Table 1. Patient characteristics

Patients (n = 51)	Number (%)
Age (mean±SD, years)	58.73±12.55
Gender	
Male	32 (62.7)
Female	19 (37.3)
Follow-up (months)	11.82.
Histology	
Undifferentiated carcinoma	17 (33.3)
Adenocarcinoma	23 (45.1)
Squamous cell carcinoma	9 (17.7)
Neuroendocrine	2 (3.9)

Table 2. Diagnostic values of PET/CT in CUP

Diagnostic values	%
Sensitivity	100
Specificity	80.4
Positive predictive value	35.7
Negative predictive value	100
Diagnostic accuracy	82.4

Discussion

The use of ^{18}F -FDG, a glucose analogue is based on the fact that cancer cells generally have a higher level of metabolic activity than normal tissues resulting in it's increasing uptake [13]. ^{18}F -FDG PET/CT has been recommended for the diagnosis of head and neck, lung, and pancreatic cancer and also for staging of breast, colon, head and neck, esophageal and lung cancer [14]. Studies of PET/CT in CUP could be divided in 2 groups: whole body metastases and cervical metastases. Most of the studies in evaluating PET/CT in CUP of whole body metastases have reported that ^{18}F -FDG PET/CT is a valuable diagnostic tool in patients with CUP [15-17]. But the usefulness of ^{18}F -FDG PET/CT in CUP of cervical metastases is a subject of controversy. Roh J et al have reported PET CT can be a valuable tool in identifying primary occult tumors with cervical metastases [18]. Fogarty G.B. et al have reported that PET did not add significantly to the detection of an occult primary tumor in patients of cervical metastases [19]. The inability to detect a primary tumor by PET/CT has several reasons. The limit of resolution for detecting typical cancers by ^{18}F -FDG PET/CT generally ranges between a 0.4 and 1.0cm diameter, which translates into a tumor size roughly of 0.1-0.5 to 1.0g or 10^8 - 10^9 cells [20]. This explains a small and superficial lesion can be missed due to the limited resolution of ^{18}F FDG PET. Because of the partial volume effect, the smaller tumors also yield images with underestimated uptake values [21]. The reduced signal-to-noise ratio may be a reason. The detection of tumors with PET/CT depends on the difference between the intensity of the signal from the tumor and that of the background [10]. Another explanation is that the primary lesion has involuted and is not detectable when the metastasis becomes evident [22, 23].

According to the studies of ^{18}F -FDG PET/CT in CUP, the detection rates of PET/CT were from 24 to 80 percent with large differences between studies [8-12]. Results of this study show the detection rate of 9.6% which is much lower than the results of previous studies. The definition of CUP has varied over time, because development of diagnostic tests has led to better detection of a primary tumor than before. Up to the 1970s, CUP constituted 10-15% of patients with solid tumors in general medical oncology practice [24]. The extent of the pre-PET workup has an impact on the detection rate of the PET/CT. Some studies were evaluated with minimal pre-PET, which makes the diagnostic performance of PET/CT overestimated. The chance of a tumor still being undetected after the thorough pre-PET workup will then have less chance of finding a primary tumor missed by the previous investigations and PET/CT may seem less efficient [19]. Primary tumors may be found in 4 (the lung, the esophagus, the stomach and the gallbladder) of 5 true positive results of this study if chest CT (the lung and the esophagus) or abdomen CT (the stomach and the gallbladder) was performed before ^{18}F -FDG PET/CT. They might be no longer CUP and would be classified according to its origin. Results of this study show the similarity to those of the previous study which reported that there were no significant differences between the diagnostic accuracies of PET/CT and the other imaging modalities [26].

The histology of the primary tumor may influence FDG uptake and the visibility of a lesion on PET/CT. Also tumor differentiation may be a limiting factor. Differences in pathology and differentiation among the studies may influence the identification of primary tumor by PET/CT. Another reason that may make differences of detection rate is publication bias. Studies with significant results were more likely to lead to a great number of publications and presentations [27]. Though PET/CT has the limitation in detecting the primary tumor of CUP, it can be beneficial from a different point of view. PET/CT can rule out the possibility of detecting the primary tumor or additional metastatic sites during the follow-up. In this study, there was no false negative finding, which means if PET/CT fails to locate the primary tumor, there will be little chance of detecting it later.

As PET/CT can explore the whole body at once, it should be tested as the initial workup in CUP before the conventional investigations. That may reduce the cost, save the time of the investigations and guide the other examinations and biopsies.

In conclusion, based on the data presented, ^{18}F -FDG PET/CT has a clinical implicative value in detecting the primary tumor of CUP. PET/CT can be useful to rule out the possibility of detecting the primary tumor during the follow-up.

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