Original Article

The value of F-18 FDG PET/CT for detecting primary foci in the metastatic cancer of unknown primary origin

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Abstract. Cancers of unknown primary origin (CUP) have poor prognosis and the median survival for patients with CUP is approximately 1 year. This survival can be extended by the identification of the primary origin and treating with specific therapy.

F-18 FDG PET/CT scans of 75 patients (39 female, 36 male, mean age 60 ±12) with CUP referred to our clinic between January 2009 and January 2011 were evaluated retrospectively. Whole body images were obtained 60 minutes after the injection of approximately 370 MBq (10 mCi) F-18 FDG by PET/CT (Gemini-TOF-Philips). Emission scans were obtained for 1.5 min per bed position and transmission scans were obtained with low dose CT using 50 mA and 120 kvp.

The tumor was identified histopathologically in 58 of 75 patients. 4 of 58 patients were treated as CUP. 17 of 75 patients could not be followed, so final diagnosis could not be made. In 54 patients, the primary was identified as 17 lung, 8 colorectal, 7 breast, 3 stomach, 3 pancreas, 2 endometrial, 2 nasopharynx, 2 gallbladder cancers, 2 lymphoma, 2 peritoneum, 1 maxillary sinus, 1 salivary gland carcinoma, 1 brain tumor, 1 leiomyosarcoma, 1 ovary cancer and 1 multiple myeloma. If reports are considered, F-18 FDG PET/CT helped to detect primary origin in 65% of these 58 patients, 38 of 54 primary sites were true positive (70%). There were 6 false positive sites (10.3%), 16 false negative (27.5%) results in F-18 FDG PET/CT. After the retrospective evaluation of the false negative patients, we have realized that primary sites were ignored in 5 of 14 patients, so actually F-18 FDG PET/CT helped in 74% of the patients showing 43 of 54 primary sites (80%). In first evaluation, F-18 FDG PET/CT missed 2 breast cancers, 1 lymphoma, 1 colon cancer and 1 intra maxillary sinus cancer.

F-18 FDG PET/CT is an important imaging tool for detecting primary origin in the patients with CUP. F-18 FDG PET/CT helped in 74% of the patients showing the primary sites. In the patients with CUP, lung, breast, colon and the physiologic uptake areas should be scrutinized carefully for any tumor location.

Key words: F-18 FDG, unknown primary origin, metastatic cancer

1. Introduction

Carcinoma of unknown primary tumors (CUP) composes 3–5% of the patients with solid tumors (1–3). CUP includes heterogeneous group of metastatic tumors that no primary foci can be detected with the patient history, physical examination, laboratory testing and wide radiological tools (4). Because growth rate may be slower in the primary focus of CUP, the primary site becomes less obvious and the detection of primary focus is difficult (5, 6). Only 20–27% of primary sites can be detected before the patients' death (7). It was reported that survival of the patients with CUP is less than one year and this survival can be increased when the primary focus is determined and treated with specific therapy (8, 9). F-18 fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) is widely used for the detection of primary site of the patients with CUP (10). It has been reported that PET detects 24.5- 41% (11, 12) and FDG PET/CT detects 22-73% (13) of the patients with CUP. These variable results can be due to the different patient inclusion criteria and the extent

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Received: 12.03.2013
Accepted: 10.07.2013

of the diagnostic workup in different studies (14). We investigated additional benefits of F-18 FDG PET/CT to the conventional diagnostic tools in the patient with CUP.

2. Materials and Methods

75 patients (39 female; 36 male, mean age 60 ±12) who were diagnosed with CUP were referred to our clinic to find the primary origin between January 2009-2011. The patients were evaluated retrospectively, the file records were reexamined and 58 of 75 patients were followed up to one year. 17 of 75 patients did not have any records in their hospital file after the PET/CT scan and we could not reach the final diagnosis of these patients.

Whole body images were obtained 60 minutes following the administration of approximately 370 MBq (10 mCi) F-18 FDG using PET/CT (Gemini-TOF-Philips) with 3D mode. After at least 6 h of fasting and blood glucose levels lower than 200 mg/dl, patients underwent PET/CT scan. No IV contrast material was used for the CT scans. Emission scans were obtained for 1.5 min per bed position and transmission scans were obtained with low dose CT using 50 mA and 120 kvp.

Two evaluations were performed by two experts in nuclear medicine. First evaluation was done according to the PET/CT reports. In the first evaluation, experts did not know what the final diagnosis was while writing the reports. Second evaluation was done retrospectively, after reaching the final diagnosis. Experts knew the final diagnosis during the second PET/CT evaluation. We checked if PET/CT scan missed any primary tumors in the first evaluation. During this evaluation, we realized that the first evaluation missed some foci and guided to wrong foci in some patients. The results of both evaluations were examined separately. The average SUVmax of primary tumors and the average SUVmax in metastatic lesions are also calculated. SPSS for Windows 11.0 program (SPSS 11, Chicago, IL, USA) was used for descriptive analysis. The sensitivity and positive predictive value (PPV) of PET-CT is calculated with the standard diagnostic tests.

3. Results

In 58 patients (32 female, 26 male, mean age 58.4±11.8), the tumor was identified histopathologically as shown in Table 1. Four of 58 patients were treated as CUP. 17 of 58 patients were lost to follow up, so final diagnosis could not be reached. The average SUVmax of primary lesions were 6.2±6.3 and the average SUVmax of metastatic lesions were 10.0±7.4.

Table 1. Histopathology of the tumors identified in 58 patients

	Number of patients with tumor proven histopathologically (%)
Lung	17 (29.3)
Breast	7 (12)
Colon-Rectum	8 (13.7)
Uterus	2 (3.4)
Stomach	3 (5.1)
Pancreas	3 (5.1)
Gallbladder	2 (3.4)
Lymphoma	2 (3.4)
Nazofarenx	2 (3.4)
Other	8 (13.7)
Peritoneum	2
Maxillary sinus	1
Salivary gland carcinoma	1
Brain tumor	1
Leiomyosarcoma	1
Ovary cancer	1
Multiple myeloma	1
Total	54
CUP	4 (6.8)
Total	58

If reports are considered, F-18 FDG PET/CT helped to detect primary origin in 65% of these 58 patients, 38 of 54 primary sites were true positive (70%). There were 6 false positive sites (10.3%) and 16 false negative sites (27.5%) in F-18 FDG PET/CT. There were 16 false negative sites: Lung (3), Breast (3), Colon-Rectum (2), Stomach (1), Gallbladder (1), Lymphoma (2) and others (4). PET/CT gave wrong foci in 6 of 16 patients (false positive foci). After the retrospective evaluation of the false negative patients, we have seen that primary sites were ignored in 5 of 14 patients, so actually F-18 FDG PET/CT helped in 74% of the patients showing 43 of 54 primary sites (80%). 5 patients with 2 breast cancers, 1 lymphoma, 1 colon cancer and 1 intra maxillary sinus cancer (Figure 1) were ignored during the first evaluation (Table 2). One true positive patient with breast cancer is presented in Figure 2.

4. Discussion

Since the prognosis of patients with CUP is poor and survival of these patients is between 4

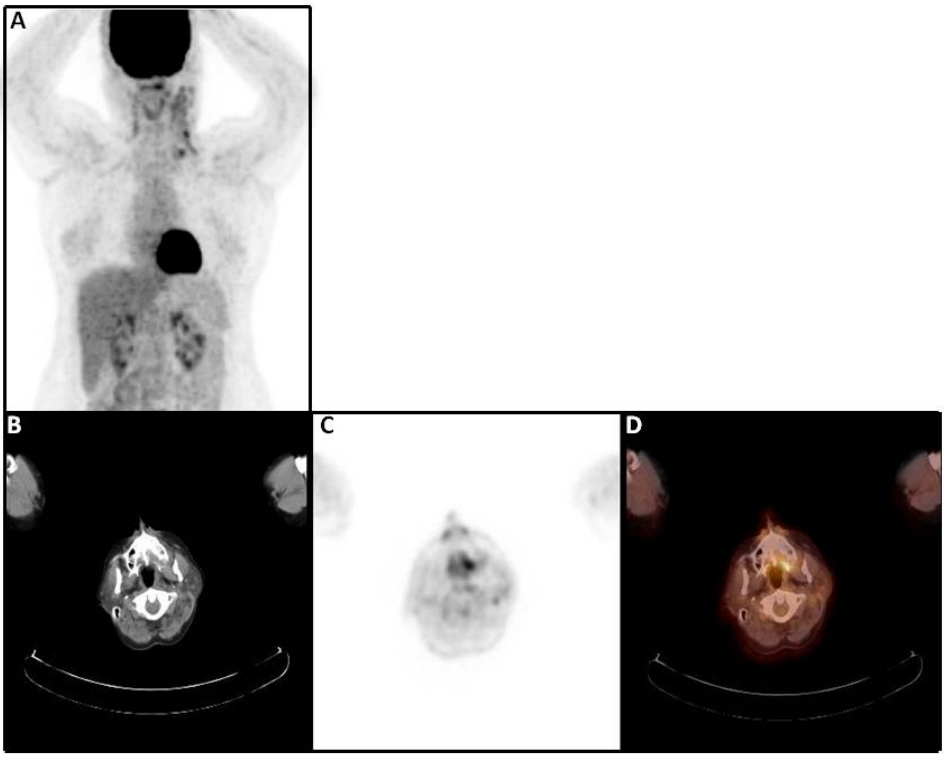

Fig. 1. 55 year-old female patient with multiple metastatic cervical lymph nodes is presented in MIP (A) and transaxial (B,C,D) PET/CT images. In the first evaluation, F-18 FDG uptake was thought as a physiological uptake in left maxillary sinus. In the second evaluation, the asymetrical accumulation was considered as the primary tumor. Maxillary sinus cancer was proven with biopsy (False negative according to the first evaluation, true positive according to the second evaluation).

Table 2. The results of primary site evaluations in F-18 FDG PET-CT

	True positive results according to the report results(Before histopathological diagnosis)	True positive results according to the images (After histopathological diagnosis)
Lung (17)	14	14
Breast (7)	4	6
Colon-Rectum (8)	6	7
Uterus (2)	2	2
Stomach (3)	2	2
Pancreas (3)	3	3
Gallbladder (2)	1	1
Lymphoma (2)	0	1
Nazofarenx (2)	2	2
Other (8)	4	5
Total (54)	38 (%70)	43 (%80)
CUP (4)	Primary not shown	Primary not shown
Total (58)		

and 12 months (8, 15), identifying the primary focus of the patients with CUP is so important. Unfortunately, the size of the primary lesion and the resolution of conventional imaging procedures make it difficult (4). It was also reported that the primary tumor might disappear after metastasis because of its angiogenetic characteristic (16). In our study, the average SUVmax of metastatic lesions was higher than the average SUVmax of primary lesions. Lower angiogenetic characteristics in primary lesions or higher angiogenetic characteristics in metastatic lesions might cause this result.

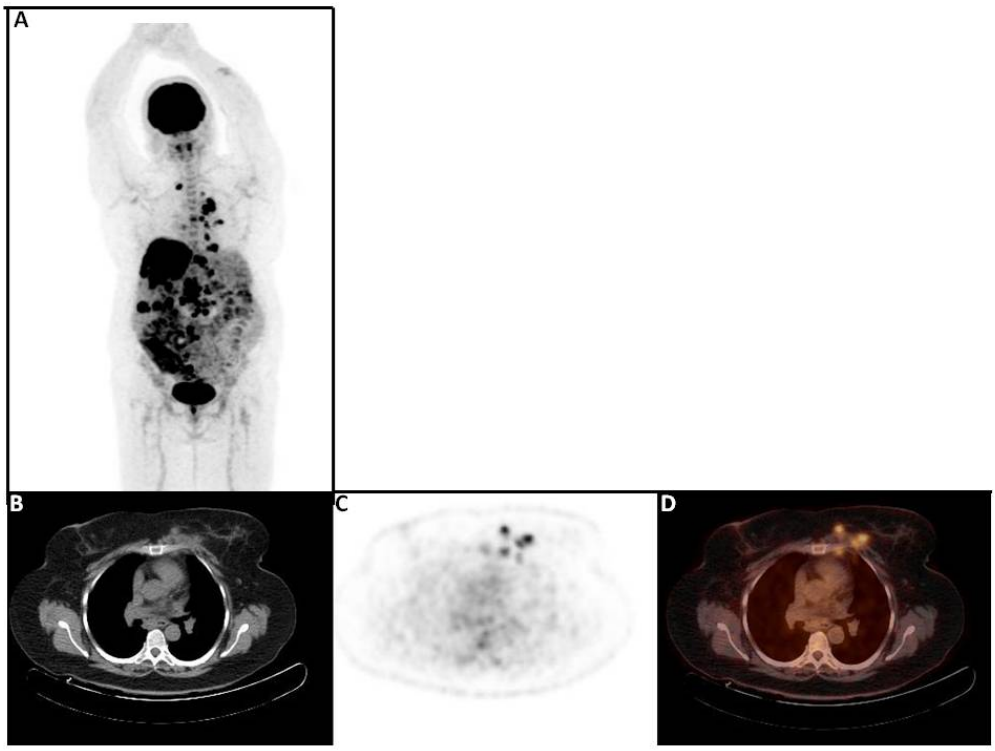

Fig. 2. 47 year old female patient with multiple liver metastasis and abominal lymph nodes is presented. MIP (A) and transaxial (B,C,D) images are shown. PET/CT revealed small nodules in the left breast with high F-18 FDG uptake (SUVmax: 6,7). Invasive ductal carcinoma was proven histopathologically in these small nodules.

The rate of detection of the primary tumor origin by F-18 FDG PET/CT in our study (70-80%) is higher than the studies in literature (17-19). The sensitivity of PET scan for the detection of the primary tumor origin is divergent in the literature (24, 59 and 37.8 % with 29, 44 and 53 patients, respectively) (20-22). The detection rate of the primary tumor origin may be expected to be higher in PET/CT due to anatomic location; however the rates are similar to PET. The sensitivity of PET/CT was 33, 57 and 35.3 % in the literature with 45, 21 and 68 patients, respectively (18,23,17). In our study, If reports are considered (Before histopathological diagnosis), the sensitivity of PET-CT is 70%, PPV is %86. After the retrospective evaluation of the patients (After histopathological diagnosis), sensitivity and PPV is found as 80% and 88% respectively. Furthermore, it was reported that PET/CT is a good alternative modality to separate the morphologic and functional data during the evaluation of the images (18).

In our study, there were 6 false positive sites (10.3%) and 16 false negative sites (27.5%) in F-18 FDG PET/CT. The false positive sites might be due to infection and inflammation. On the other hand, tumors with low glycolytic activity such as adenomas, bronchioloalveolar carcinomas, carcinoid tumors, low grade lymphomas and small sized tumors might cause false negative findings on PET scan. Furthermore, FDG PET might miss the foci located near the physiologic uptake sites (heart, bladder, kidney, and liver). So, FDG-PET should be complemented with other imaging modalities to minimize false negative findings (24).

On the other hand, the visual evaluation of the PET/CT effects the detection of primary tumor localization. In our patients, the primary origin was mostly detected in the lung, breast and colon (55%). Thus, these areas should be evaluated firstly. Lung cancers were proven in 59% of the patients with CUP syndrome (12). Additionally, breast can be missed out for tumor location, so it should be examined carefully. Physiologic uptake areas should be also scrutinized carefully for any tumor location. Physiologic F-18 FDG uptake hampered the detection of the primary tumors at the localizations such as colon and maxillary sinus.

F-18 FDG PET/CT is an important imaging tool for detecting primary origin in the patients with CUP. Besides, F-18 FDG PET/CT can help to determine the extent of the disease and help to evaluate the therapy response.

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