ONCOLOGY, Original Article

Role of Positron Emission Tomography in Detecting Primary Site in Patients with Metastatic Cancer of Unknown Primary

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Abstract
The management of patients presenting with metastases of unknown primary origin remains a clinical challenge despite a large variety of imaging modalities. **The aim of this study** was to evaluate FDG PET in detecting the sites of primary cancer in these patients. **Methods:** A total of 39 patients who had known or suspected primary malignant lesions and who had undergone whole-body 18F-FDG PET in international medical center during the period of September 2004 till March 2009 were retrospectively included for analysis. All patients had undergone prior investigations with a minimum of clinical examination, biopsy and CT. Clinical, surgical, and histopathologic findings and complete correlative imaging were used to assess the results. **Results:** PET-positive lesions suggestive of primary malignant tumors were found in 28 (71.8%) of 39 patients. These lesions were pathologically proven to be malignant (TP) in 25 (64.1%), In 3 of 39 patients, PET was proven falsely positive after pathologic assessment. In 11 of 39 (28.2%) patients, no site of a primary could be detected by PET. 8 of them (20.5%) were subsequently proven True-Negative (TN), and the other 3 cases were false negative. The FDG PET sensitivity was 89.3%, with a specificity of 72.7% and accuracy in the search for the presence of a malignancy was 84.6%. Positive predictive value % (PPV) was (89.3%) and the Negative predictive Value % (NPV) was (72.72%). **Conclusion:** FDG PET is a valuable additional diagnostic tool in patients with cancer of unknown primary because it can image unknown primary tumor sites in about two third of all patients investigated. In addition, FDG PET assists in both guiding biopsies for histologic evaluation and selecting the appropriate treatment protocol for these patients.
Key words: FDG-PET; cancer of unknown primary; metastases; oncology.

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Introduction

Carcinoma of unknown primary (CUP) syndrome comprises numerous different malignancies with two common features: failure to identify the primary site by full physical and laboratory examination and conventional imaging, and a generally poor outcome.[1]

The most frequent sites for metastatic primary are the lymph nodes of the supraclavicular and cervical regions. While histopathologic analysis frequently provides hints as to the location of the primary site, not all primary tumors are identified despite a comprehensive diagnostic work-up. The inability to do so prevents the optimization of therapeutic strategies, which is dependant on tumor differentiation, tumor location, and tumor stage as determined according to the TNM system.[2]

The site of origin of a histologically documented carcinoma is not identified clinically in approximately 3% to 5 % of the patients; this situation is often referred to as carcinoma of unknown primary origin or occult primary malignancy (CUP syndrome).[3] CUP syndrome is the fourth cause of cancer death in both men and women, with a median age of 60 years at presentation.[4]

A complete disease staging and the detection of the primary tumor could significantly change the prognosis by allowing a more rational and efficient treatment. Previous reports described that in CUP syndrome only 10-35 % of the primary sites are detected by conventional imaging modalities. [3, 5]

Positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) is an attractive tool for this indication since most malignancies are FDG avid. Its bio-distribution is favorable and the whole body is scanned in a single session with minimal patient discomfort .[6]

Materials and Methods

A total of 39 patients (28men and 11 women; mean age ±SD, 56.46± 14.345 y) who had known or suspected primary malignant lesions and who had undergone whole-body 18F-FDG PET in international medical center during the period of September 2004 till March 2009 were retrospectively included for analysis.

All patients had undergone prior investigations with a minimum of clinical examination, biopsy and CT.

Accounting for the largest subgroup of patients with CUP syndrome, 13/39 patients had skeletal metastases, and 1 patient showed axillary lymph node metastases but had normal physical examination of the breast and normal mammograms. Two patients had liver metastases, and 5 had cerebral metastases. Two patients had malignant pleural effusions, but a radiograph of the chest showed no primary lung cancer.

Also, 4 patients had lung nodules, 2 patients had bone and lung lesions, 2 patients had lung and liver metastases, 1 patient had lung, liver and bone metastases, 2 patient had mediastinal mass, and 1 patient had abdominal lymph node. The remaining 4 patients had clinical suspicion of the presence of a malignancy (CSM). The medical history and laboratory examinations suggested a potential malignancy (i.e. on the basis of an increase in tumor marker levels, a paraneoplastic syndrome, weight loss, fatigue, progressive weakness or other factors). So, these patients presented the same challenges as the CUP patients with histologically proven malignancy (HPM).

Before PET a complete history and an accurate physical examination were performed in all patients. Additionally, all patients underwent Conventional diagnostic work-up. Finally, patients were presumed to have CUP syndrome because all diagnostic studies did not detect the primary tumor.

PET Imaging

Patients fasted for at least 6 hrs before PET scanning to minimize blood insulin levels and glucose utilization of normal tissue. Whole-body images were acquired 60 minutes after intravenous injection of an average dose of 10 mCi, 370 MBq F18-FDG using Philips,

ADAC-CPET plus scanner or the body torso. Reconstruction is done in transversal, coronal and sagittal slices in two sets with and without attenuation correction via RAMLA software.

Whole-body images were interpreted by 2 nuclear medicine physicians. Qualitative assessment for presence of hypermetabolic lesions was evaluated on both corrected and uncorrected PET images in the invert grey scale.

Data Analysis

All reports from clinical whole-body 18F-FDG PET scans were reviewed, and the patients who had reports indicating the presence of unexpected increased 18F-FDG uptake suggestive of a primary malignant lesion were identified. A suspected primary lesion was defined as a lesion that was discovered on PET, and had not previously been detected by other imaging modalities.

All primary malignancies were hypermetabolic on PET, for all such cases, the final diagnosis was obtained from the medical records, including pathologic reports by biopsy or operation. A diagnosis of the primary site of a malignancy was classified as true positive (TP) only when it was confirmed histologically during the follow up. If the finding with active hypermetabolic lesion on PET was confirmed as benign, or if the patient was without any signs of malignancy during the follow-up for 6 months, the diagnosis was classified as false positive (FP). An evaluation was classified as true negative (TN) if neither FDG-PET nor histological findings or clinical follow-up for at least 6 months period (including subsequent imaging tests) determined the site of the primary. When the site of the primary was not identified by FDG-PET, but was proven histologically, the finding was classified as false negative (FN).

Statistical analysis

The accuracy of FDG-PET was expressed in terms of sensitivity and specificity.

The difference in accuracy was tested using the chí-square test.

Results

PET-positive lesions suggestive of primary malignant tumors were found in 28 of 39 patients (71.8%). Fig (1) representing a case with metastatic liver lesion and PET revealed primary site in lung. These lesions were pathologically proven to be malignant (TP) in 25 patients (64.1%), The proven sites of the malignant primary lesion were lung 12 of 39 (30.8%), liver 2/39 (5.1%), breast 1/39 (2.6%), colon 1 of 39 (2.6%), rectum 1/39 (2.6%), thyroid 1/39 (2.6%), and head and neck other than thyroid (3 lesions), esophagus 1/39 (2.6%), stomach 1/39 (2.6%), cholangiocarcinoma 1/39 (2.6%), and bone 1/39 (2.6%) (Table 1). In 3 of 39 patients, PET was proven falsely positive after pathologic assessment. False-positive sites included right parahilar lymph node (sarcoidosis), right supraclavicular lymph node (patient with reactive lymph node or lymphoid hyperplasia), and a lower neck lesion which was proven to be benign after clinical follow-up with regression after medical therapy (6-12 mo; median, 9 mo).

Table 1: site of primary tumors. As detected by FDG PET

Site of primary	Number	%
Lung	12/39	30.8%
Head and neck other than thyroid	3/39	7.7%
Liver	2/39	5.1%
Breast	1/39	2.6%
Colon	1/39	2.6%
Rectum	1/39	2.6%
Thyroid	1/39	2.6%
Esophagus	1/39	2.6%
Stomach	1/39	2.6%
Cholangiocarcinoma	1/39	2.6%
Bone	1/39	2.6%

* 3 patients had false positive results.

In 11 of 39 (28.2%) patients, no site of a primary could be detected by PET (figure 2). However, 8 out of 39 (20.5%) were subsequently proven True-Negative (TN). The remaining three negative patients, no FDG-PET avid lesions were detected, but during the follow up with other modalities and pathological assessment colonic, breast, urinary bladder cancers were found. Thus, they were considered false negative (FN) cases. The presence of any malignancy was correctly diagnosed in 25 patients and correctly excluded in 8 patients. In 3 patients PET was FP and FN results were met in 3 patients. Hence, the FDG PET sensitivity was 89.3%, with a specificity of 72.7% and accuracy in the search for the presence of a malignancy was 84.6%. Positive predictive value % (PPV) was (89.3%) and the Negative predictive Value % (NPV) was (72.72%). (Table 2)

Table 2: sensitivity, specificity and accuracy of FDG PET in diagnosis of primary tumor sites in MUO:

Sensitivity	89.3 %
Specificity	72.7 %
Accuracy	84.6 %

Discussion

Cancer of unknown origin is a very aggressive disease that encompasses a variety of different pathologic entities, with an overall dismal 5-year survival.

Therefore The earlier detection of primary tumors in patients with CUP may be important for several reasons, including the discovery of a potentially treatable tumor, allowing therapy to be targeted as appropriately as possible, and significantly improving the prognosis.[7] However, the detection of CUP is often time consuming and still 20-27% of the cases are undetected by a conventional workup.[8]

In this study, FDG-PET was able to identify the primary site in 28/39 cases (64.1% true positives, TP). In 11 patients where FDG-PET did not identify a primary site, 3 eventually became clinically evident (7.7% False Negatives, FN). PET suggested

primary sites in another 3 patients but none of these were confirmed by biopsy or during follow up (False Positives, FP).

In Seve et al (2007) study[9], 59.3% of all primary tumors in patients with CUP was found in the lung, likewise with the current study, a high incidence of primary tumors of the lung (30.8%) , with a high rate of single metastatic site has been found.

In the same study, FDG-PET exhibited its highest accuracy for tumors of the lung, breast, and pancreas. The high sensitivity and low false-positive rates that were observed indicate that FDG-PET is a valuable supplement to conventional imaging at these locations. FDG-PET had a low false-positive rate for tumors located in the lungs, breast, and pancreas. The low false-positive rate that was observed corresponds to a high specificity and positive predictive value for FDG-PET detection of tumors at these sites. The lower gastrointestinal tract was the most common site of false-positive FDG uptake. In the present study there was only one false-negative case of: colonic cancer.

PET does not play a role in the routine detection of primary colorectal cancer. The primary colorectal tumor may be detected when PET is obtained because of strong clinical suspicion of tumor spread and when conventional diagnostic technique yield equivocal results. PET cannot detect microscopic foci of tumor, but in general, metabolically active tumors are detected before morphologic change is present.[14, 15]

The other sites of false- negative FDG-PET findings in the current analysis were in the breast and urinary bladder. These false negative cases could be related to low FDG uptake in some cancers as highly differentiated tumors or normal FDG uptake in organ as urinary bladder which limits the utility of FDG PET.[12, 13] Also, false negative results are found with small lesions below the resolution of FDG-PET (< 1 cm), especially in breast as the ability of PET to detect breast cancer greatly depends on tumor size. Regarding sensitivity for breast tumors less than 1 cm (pT1a & b) was 25 % compared to 84.3 % for tumors between 1 and 2 cm in diameter (pT1c). Another important finding in breast cancers was that invasive ductal carcinoma has more often false negative results than invasive lobular carcinoma (65.2 versus 23.7 %).[16]

Although the role of routine FDG-PET early in the workup of patients with CUP remains unproven, it may have several practical advantages. Alberini et al, in 2003[10], retrospectively assessed the value FDG-PET prior to conventional imaging in 41 patients with CUP: PET diagnosis was superior to conventional diagnosis in 11 patients and prompted 11 treatment modifications. The sensitivity of PET was markedly superior to CT in detecting lung cancers and abdominal primary tumors. The present study also shows the value of added PET imaging in diagnosis of primary site in 28 patients (71.8%).

Delgado-Bolton and his colleagues in 2003[11], performed a meta analysis of the literature to evaluate the accuracy of FDG PET in detecting primary tumors in patients with CUP. In this meta-analysis, the sensitivity and specificity of FDG-PET were found to be 87 % and 71 % respectively, which is comparable to our results (89.3 % and 72.7 % respectively).

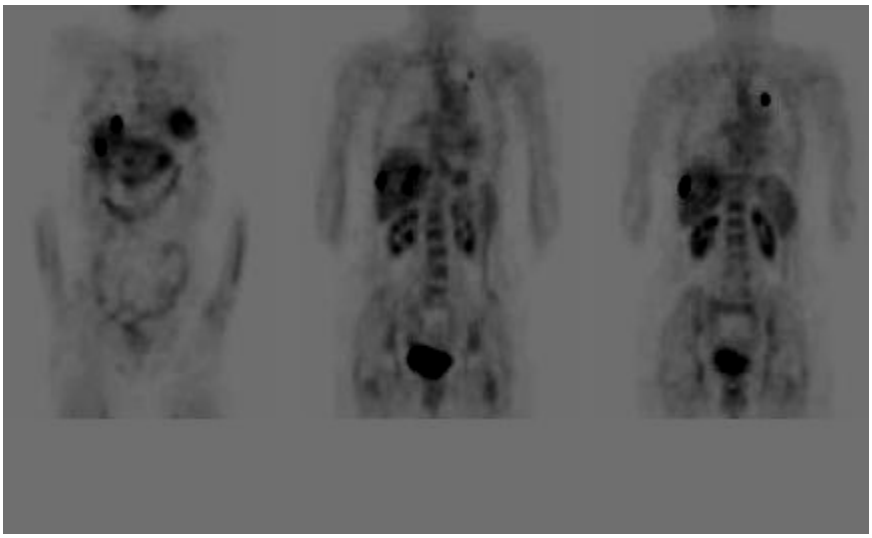
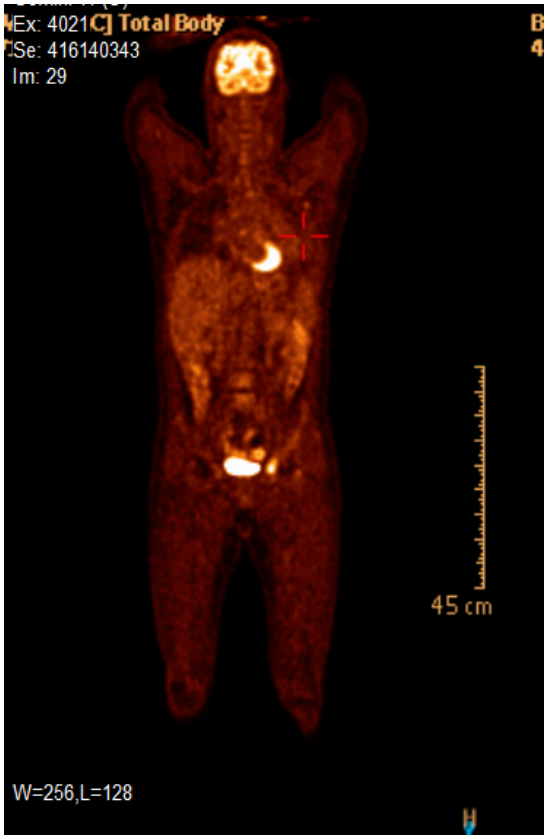


Fig (1): A case of metastatic liver lesion and PET/FDG revealed primary site in the lung.



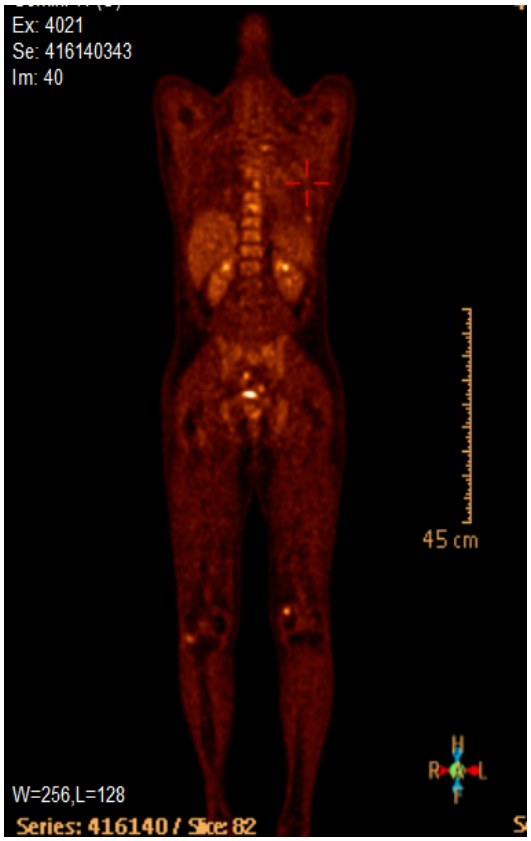


Fig (2) FDG PET imaging revealed multiple bone metastases with no suspicious primary site detected (false negative study).

Conclusion

- FDG-PET information improves the accuracy of diagnostic imaging in patients with CUP syndrome. The sensitivity of 89.3% and the specificity of 72.2% in the search for presence of a malignancy indicate that FDGPET is an effective test.
- FDG-PET was sensitive for the detection of primary tumors, in approximately 64.1% of patients, that were undetected by other modalities

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