Original Article

Diagnostic Performance of F-18 FDG PET/CT in Patients with Cancer of Unknown Primary: Additional Benefit over CT-Based Conventional Work up

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Abstract

Background: In the era of well-developed site-specific treatment strategies in cancer, identification of occult primary is of paramount importance in CUP patients. Furthermore, exact determination of the extent of the disease may help in optimizing treatment planning. The aim of the present study was to investigate additional value of F-18 FDG PET/CT in patients with cancer of unknown primary (CUP) as an appropriate imaging tool in early phase of initial standard work up.

Materials and Methods: Sixty-two newly diagnosed CUP patients with inconclusive diagnostic CT scan of chest, abdomen and pelvis referring for F-18 FDG PET/CT were enrolled in this study. Standard of reference was defined as histopathology, other diagnostic procedures and a 3-month formal clinical follow up. The results of PET/CT were categorized as suggestion for primary site and additional metastasis and classified as true positive, false positive, false negative and true negative. The impact of additional metastasis revealed by F-18 FDG PET/CT on treatment planning and the time contribution of F-18 FDG PET/CT in diagnostic pathway was investigated.

Results: Sixty-two patients with mean age of 62 (30 men, 32 women), PET/CT correctly identified primary origin in 32% with false positive rate of 14.8%. No primary lesion was detected after negative PET/CT according to standard of reference. Sensitivity, Specificity and accuracy were 100%, 78% and 85%, respectively. Additional metastatic site was found in 56% with 22% impact on treatment planning. Time contribution for PET/CT was 10% of total diagnostic pathway.

Conclusion: Providing higher detection rate of primary origin with excellent diagnostic performance, shortening the diagnostic pathway and improving treatment planning, F-18 FDG PET/CT may play a major role in diagnostic work up of CUP patients and may be recommended as an alternative imaging tool in early phase of investigation.

Keywords: F-18 FDG PET/CT, Cancer of Unknown Primary, Diagnostic Performance

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Introduction

Cancer of unknown primary (CUP), which is defined as histopathologically-proven metastatic disease for which no primary site is detected despite through investigation, account for 3-5% of all diagnosed cancer cases[1,2]. Occult primary site may remain unidentified in up to 35-70% even at autopsy[2,3]. Diagnostic pathway of the CUP is quite variable[4] and mostly time consuming with a yield of a slow as 30-40%[3,5]. Therefore, early application of a highly sensitive and noninvasive diagnostic procedure early in initial standard work up of patient with CUP is of paramount importance. In addition to reveal the primary site, determining the best location for biopsy as well as the extent of the disease are other main issues should be addressed in CUP patients' work up[6].

Indeed, recognition a small subset of patients (20%) with a more favorable outcome who benefit from site-specific treatment strategies is the major role of imaging in CUP patients[7,8]. F-18 FDG PET/CT, as a whole body highly sensitive cross sectional imaging modality has gained a wide acceptance in oncology. Regarding the presumed hypothesis in biology of CUP, primary site may follow the parallel progression model which result in small sized primary lesion in the presence of metastasis development[9].

The advantage of PET/CT over the anatomical imaging is to reveal pathologic metabolic activity in normal sized structures. In patients with CUP, primary site may be located anywhere through the body, furthermore, CUP often tends to follow unpredictable metastatic pattern[10] and so whole body imaging modalities seem be the most useful diagnostic tools to achieve the highest diagnostic yield. In comparison with other whole body imaging, PET/CT has a less sophisticated interpretation.

According to a large postmortem cohort studies[11,12], the most common site of primary lesion include lung (27%), pancreas (24%), liver and bile duct (8%), kidney or adrenal glands (7%), colorectal (7%), genital system (7%) and stomach (6%). Recent professional guidelines in radiology, nuclear medicine as well as oncology highly recommend the use of F-18 FDG PET/CT in staging, restaging, treatment planning and response to treatment in most of the above-mentioned cancers[13,14]. Indeed, there is strong evidence indicating that patients with lung, hepato-pancreatic, genitourinary and colorectal cancer will benefit from the advanced diagnostic evaluation by F-18 FDG PET/CT, which results in improved management and outcome[13,14]. Therefore, it can be inferred that by any modality the occult primary lesion is detected, like the putative primary tumor, CUP patients may benefit from PET/CT assessment as a part of routine work up for staging, restaging and treatment planning as well as response to treatment.

There is still debate in application of F-18 FDG PET/CT in CUP patients. No large-scale prospective study has yet validates the use of FDG PET/ in CUP. A recent meta-analysis including small retrospective studies demonstrates 37% increase in lesion detection rate by application of F-18 FDG PET/CT in comparison with conventional standard work up with a good sensitivity and specificity of as high as 84%[15]. Except for some particular scenario, the routine use of F-18 FDG PET/CT is not advocated in initial standard wok up of patent with CUP, especially early in diagnostic pathway.

The present study evaluated retrospectively the diagnostic performance of F-18 FDG PET/CT in CUP patients in whom chest, abdominal and pelvic CT scan, as the cornerstone of imaging procedure in initial standard work up, fail to reveal the occult primary site, regardless the extent of the additional diagnostic work up. Furthermore, the contributory role of F-18 FDG PET/CT in shortening the diagnostic pathway is investigated. The aim of this study is to purpose the use of F-18 FDG PET/CT early in diagnostic evaluation of patient with CUP.

Methods

Patients: Seventy tow newly diagnosed CUP patients who were referred to PET/CT division of Masih Daneshvari Hospital (NRITLD) in Tehran, Iran, for advanced investigation by whole body PET/CT between May 2013 and May 2015 were enrolled in the study. All the patients with primary presentation of either biopsy-verified metastasis or related clinical

symptomsin whom standard initial work up including complete history and physical exam, full blood count, biochemistry as well as diagnostic contrast-enhanced chest, abdominal and pelvic CT scan failed to identify the occult primary lesion or suggest the most appropriate site for biopsy were considered to be eligible. Regardless of the extend of baseline diagnostic work up, the main inclusion criterion considered necessary for eligibility was a negative full dose contrast-enhanced CT scan of chest, abdomen and pelvis.

Exclusion criteria were met in 10 patients as the following: previous history of known malignancy (1), previous history of chemotherapy or radiation therapy (2), patients with lymphoma (2), incomplete medical records or follow-up (5) and diabetes mellitus (0). Finally, 62 patients registered as the cohort analyzed in current study. A stepwise approach was carried out for immunohistochemisry (IHC) assay of metastatic tissue diagnosis as the following: defining cell lineage by basic panel and then indentifying subtypes and predicting the site of origin, if possible.

PET/CT acquisition protocol: Whole body F-18 FDG PET/CT was performed by using an integrated PET/CT scanner (GE 690 Discovery, 64 Slice, Time Of Flight). Patients were fasted for at least 8 hours before injection. Blood glucose level was below 150 mg/dl at the time of radiotracer injection. Sixty minutes after IV administration of 4.6MBq/Kg (0.13 mCi/Kg) ^{18} F FDG image acquisition commenced craniocuadally with the CT component performing by a multidetector CT scanner and the following parameters: auto mAs (50-120), 120 kV, noise factor 19, 2.5 mm thickness. Thirty minutes before imaging acquisition, 40cc meglumine 76% (containing 370mg Iodine /cc) in 1500 water was administered as oral contrast. The PET data were then collected in the reverse direction immediately after CT acquisition with time of 3 minutes per bed position. The PET raw data were corrected for attenuation, dead time, random and scatter coincidence, and subsequently reconstructed by iterative method and HD (high definition) technique. No premedication was administrated before injection.

Interpretation criteria: A team comprised of experience radiologist and a nuclear medicine physician reviewed AC and NAC PET, CT and fused PET/CT images on advantage window 4.5, side-by side and reached in consensus for suggesting primary lesion and additional metastatic site. In current study positive case was considered as abnormal focal increased metabolic activity on PET images with inconclusive correspondence on CT images.

Time contribution of F-18 FDG PET/CT

The diagnostic pathway is defined as the time interval from the date of clinical manifestation or histological confirmation of metastasis to the end of the diagnostic pathway (whole course), i.e., the date of either biopsy verification of occult primary or the end of the 3-month formal clinical follow-up. The time interval from F-18 FDG PET/CT study to the end of diagnostic course is subsequently extracted from the whole course (PET/CT course). The time contribution of F-18 FDG PET/CT was represented as the following: (PET/CT course/whole course)×100.

Standard of Reference: The vast majority of occult primary site remain unidentified even in postmortem study, hence a multidisciplinary approach was considered as the standard of reference. The suggestion for primary site was further correlated with the following standard of reference: (1) histopathology, (2) other imaging modalities with or without tissue diagnosis and (3) at least 3 months formal clinical follow up, including repeated physical examination and conventional diagnostic procedure (CT, US, mammography, endoscopy and MRI wherever indicated). Finally a conclusion was drawn by the oncologist based on all clinicoradipathologic evidences and classified the F-18 FDG PET/CT results as true positive, false positive, false negative and true negative.

Data Analyses: By correlating the F-18 FDG PET/CT findings with standard of reference, the diagnostic performance of F-18 FDG PET/CT including sensitivity, specificity, and accuracy were calculated based on the standard formula as the following:

Sensitivity: TP/(TP+FN), Specificity: TN/(TN+FP), and Accuracy: TP+TN/(TP+TN+FP+FN).

Statistical analyses were conducted using SPSS version 18. Impact of additional metastatic sites revealed by PET/CT on treatment planning was evaluated as change the therapeutic strategy from local to systemic.

Results

Demographic characteristics: Sixty-two patients (30 men: 48.4%, 32 women: 51.6%), with mean age of 62 years (range: 31-82 years) were enrolled in the study. In addition to a negative contrast-enhanced diagnostic chest, abdominal and pelvic CT scan, all the patients had inconclusive conventional diagnostic work up,

Table 1: Baseline Examination other than Diagnostic CT scan of chest, abdomen and pelvis.

Baseline Examination	No. of patient	% of Total
Ultrasound Exam	21	33.8%
Bone Scan	10	16.1%
Colonoscopy	6	9.7%
Endoscopy	5	8.1%
MR mammography	4	6.5%
Chest X-ray	1	1.6%
Mammography	2	3.2%
Larygoscopy	1	1.6%
Ultrasound Exam + Bone Scan	7	11.3%
Ultrasound Exam + Endoscopy	5	8.1%
Ultrasound Exam + Endoscopy + Bone Scan	2	3.2%
Ultrasound Exam + Endoscopy + Mammography	1	1.6%
Exclusively Bone Scan	1	1.6%
Exclusively MRM	1	1.6%

including ultrasound examination, endoscopic procedure, MRI/MRM and bone scan. The detailed base line examinations are summarized in Table 1.

Except for 8 patients presented with relevant clinical symptom (13.1%), at least one biopsy-proven metastatic site was indentified in 54 patients (68.9%). The distribution of the most common sites of metastasis was in order as the following: bone (11/54, 20.4%), extra-cervical adenopathies (10/54, 18.6%), liver and lung (8/54: 14.8%). The most frequent histopathologic findings in metastatic location was adenocarcinoma (29/54; 53.8%) followed by poorly differentiated adenocarcinoma (9/54; 16.6%), squamous cell carcinoma and small cell undifferentiated cancer (5/54; 9.3%). An overview of location and histopathology of metastatic site are provided in Table 2.

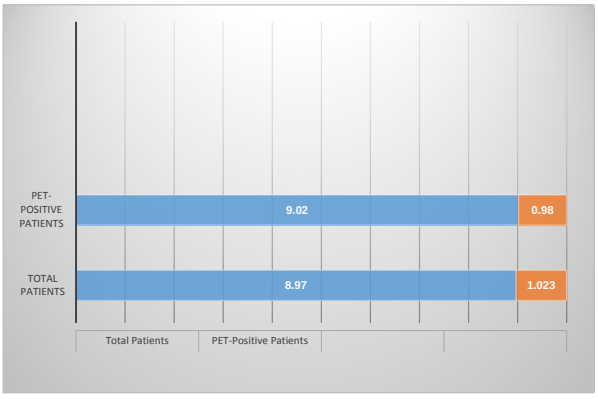

Figure 1. Time contribution ofF-18 FDG PET/CT in diagnostic pathway.

Table 2: Distribution and histopathology of metastasis.

	No. of patient	% of Total
Location of Metastasis		
Bone	11	20.4
Extracervical lymphadenopathy	10	18.6
Lung	8	14.8
Liver	8	14.8
Brain	5	9.3
Peritoneum	2	3.7
Others	4	7.4
Histopathology		
Adenocarcinoma	29	53.8
Poorly differentiated Adenocarcinoma	9	16.6
Squamous Cell Carcinoma	5	9.3
Small cell undifferentiated carcinoma	5	9.3
Neuroendocrine	2	3.7
others	3	5.6

PET/CT suggestion for primary origin: 62 patients, PET/CT suggested primary site in 29 cases (48.8%), 20 of which were subsequently proved to be correct by histopathologic confirmative examination as the standard of reference (true positive rate; 32.3%), mainly in the following locations: lung (13/20, 65%), pancrease and hepatobiliary (2/20, 10%) and colorecatal and nasopharynx (1/20, 5%). True positive findings mostly occurred in patients presented with liver (6/20, 30%), extracervical lymph node (5/20, 25%) and bone (4/20, 20%) metastasis. Findings for other 9 cases were categorized as false positive since no evidence of cancer tissue was identified in histopathologic study (false positive rate: 14.5%). False positive findings were recognized in lung (5/9, 55.5%), breast and colorectal (2/9. 22.2%). An overview of PET/CT findings are provided in Table 3.

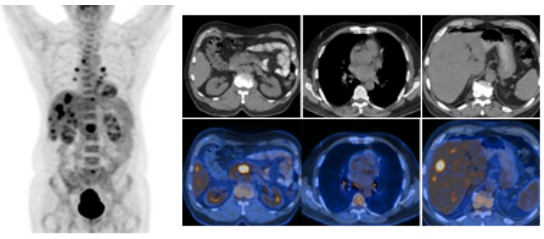

Figure 2. A 58-year old man with metastatic adenocarcima of liver. Chest, abdominal and pelvic CT scan failed to identify the site of origin. The occult primary in pancreas was suggested only on PET and fused PET/CT images which were subsequently proven by histopathologic confirmative study.

Table 3: Overview of PET/CT primary suggestion.

	Location															
	Lung		**Pancreas**		**Hepatobiliary**		**Colorectal**		**Nasopharynx**		**Muscle**		**Breast**		**Total**	
	no	**%**	**no**	**%**	**no**	**%**	**no**	**%**	**no**	**%**	**no**	**%**	**no**	**%**	**no**	**%**
True Positive	13	65	2	10	2	10	1	5	1	5	1	5			20	32.3
False Positive	5	55.5					2	22.2					2	22.2	9	14.5

Of 33 PET/CT-negative patients, no primary lesion were identified by other diagnostic procedures and formal clinical follow up, results in false negative rate of 0 and true negative rate of 53.2%. Sensitivity, specificity and accuracy were calculated as 100%, 78% and 85%, respectively. In patients presented with clinical symptoms, PET/CT failed to identify any primary lesion correctly, however, false positive rate was 4 out of 8 (6.4% of total patients).

PET/CT detection rate for additional metastasis: PET/CT revealed additional metastasis in 56.4% (35/62) which results in change in treatment planning in 22% (13/62). The most frequent sites of additional metastasis detected by PET/CT were mediastinal, hilar, retroperitoneal lymph nodes and adrenal gland.

PET/CT revealed additional metastatic sites in 11 out of 33 patients in whom PET/CT failed to suggest primary origin (33.3%). These findings resulted in change in treatment planning in 7 cases (13.5% of total patients).

Time contribution of PET/CT in diagnostic pathway: The mean total diagnostic pathway and time interval between PET/CT to end of the study were demonstrated as 264 days (range of 88-585 days) and 27 days (range 15-80 days), respectively. PET/CT contributed only the terminal10% of the total diagnostic course (Figure 1). This ratio was calculated as 9.8% in patient with true positive suggestion of primary origin on PET images (Figure 2).

Discussion

Debates still present on the role of F-18 FDG PET/CT in CUP patients. According to the last updated practical guidelines of NCCN in April 2013, the application of F-18 FDG PET/CT in CUP patients is confined to the detection of primary tumor in patients presenting with cervical metastatic adenopathies of squamous cell origin with a higher detection rate of 25-50% in comparison with contrast-enhanced CT or CT/MRI[16, 17] as well as performing additional information about the extent of disease which may help in optimizing treatment planning, particularly field of radiotherapy[18].

Except for some clinical scenario, the routine use of F-18 FDG PET/CT is not yet advocated in CUP patients. It seems that the lack of homogenous cohort large-scale prospective studies validating the use of F-18 FDG PET/CT in CUP patients has been impeded the wide application of this imaging modality as a part of standard work in CUP. Demonstrating 37% more detection rate of primary origin with an acceptable sensitivity and specificity (84%), the results of a recent meta-analysis and systematic reviews are promising for F-18 FDG PET/CT application in CUP[16] which is compatible with the results of present study; however, some other investigations considered no superiority for F-18 FDG PET/CT over conventional diagnostic work up in either detection of primary lesion or impact on patient's management in CUP[19,20].

Moderate-quality methodologies such as small sample size[19] as well as methodological differences including various interpretation criteria and standard of reference may have great influence on the results. Furthermore, the wide variety of patients' characteristics such as various sites of metastatic presentation and the extent of baseline examinations may negatively influence the validity of results.

A recent study which prospectively compared the diagnostic performance of F-18 FDG PET/CT with full dose contrast-enhanced CT have demonstrated no statically significant difference in detection rate of

primary lesion (28.1% vs.31.9%) as well as sensitivity (57.6 vs. 65.2), specificity (71 vs. 60.9) and accuracy (64.4 vs. 63) between these two modalities[21]. In the mentioned study, hyper-metabolic lesion on PET images with no apparent correspondence on CT images was considered as negative, however, there are strong evidences indicating that malignant metabolic changes, which can be easily identified by F-18 FDG PET/CT, frequently occur in very small sized or even normal sized structures in CUP[22,23] resulting in missing the small sized primary lesions in the presence of such interpretation criteria. Hence, the diagnostic performance of F-18 FDG PET/CT may be underestimated in the mentioned study. Considering interpretation criteria on the basis of abnormal metabolic activities corresponding with in determinate CT findings, the current study attributed 32.3% more detection ratetoF-18 FDG PET/CT. This may represent the diagnostic power of F-18 FDG PET/CT more accurately.

Some reports have claimed that in the presence of complete diagnostic work up, PET/CT may not show any significant additional benefits in either detection of occult primary or in the patient's management and hence, the additional value of FDG PE/CT in CUP patients may be overestimated[24]. However, identification of primary origin is not the only issue should be addressed in CUP patients. Determination of the extent of the disease not only is helpful in recognition of the small population of CUP patients with favorable outcome[6,25] but also may help in optimizing treatment planning including field of radiation therapy and also evaluation of response to treatment[25]. In the current study, PET/CT detected additional metastatic site in56.4% which results in 22% change in treatment planning. This result is in line with some other reports demonstrating 27% additional metastasis revealed by PET/CT[22].

No standard and harmonized diagnostic algorithm is currently accepted for initial work up of CUP patients. According to the literatures, CUPs do not behave exactly the same as putative known primary tumor including the pattern of metastatic spread[10]. Hence, the focused stepwise diagnostic approach, as the most advocated diagnostic work up in CUP, may encounter a great challenge. On the other hand, despite extensive diagnostic work up, primary tumor detection yield is generally low, even on postmortem studies. In addition, nonselective exhaustive tests are usually time consuming and rarely result in improved diagnostic yield[2,3].False negative rate is greatly influenced by the various interpretation criteria and standard of reference; however, recent studies demonstrated that after a negative PET study, the probability of developing a primary tumor in CUP with a cervical metastatic presentation is extremely low(5/60, 5.3% with a mean follow-up period of 31.1 months and 1/17, 5.8% with a mean follow-up period of 31.1 months)[22,26]. Though not conclusive because of short follow-up period, this is in line with the results of current study which demonstrated that no primary origin was detected after a negative PET/CT during a 3-month clinical follow- up. Accordingly, application of PET/CT as a highly sensitive whole body imaging modality may be advisable in early phase of diagnostic pathway.

There are growing evidences indicating that F-18 FDG PET/CT has a major role in management of patients with lung, pancreas, hepatobiliary and colorectal cancer[13, 14] which are demonstrated as the most common primary sites in CUP[11]. The most frequently sites of primary lesion detected by PET/CT are lung (33%), oropharynx (16%), pancreas (4.8%) and breast (4.3%)[15] which are in line with the results of the present study. Currently, it is believed that occult primary site may still retain some characteristics of putative known primary tumors[26], so by any diagnostic modality the primary origin is picked up, CUP patients may benefit from complementary evaluation by PET/CT scan for staging, treatment planning and evaluation of treatment response[8].

It is of paramount importance to note that CUP is inherently a heterogeneous group of metastatic cancer and no common biologic behavior could be attributable to this entity[26]. Furthermore, it has been shown that CUPs do not confirm the similar behavior as the putative known tumor even in the pattern of metastatic spread[10]. Therefore, researches on CUP should be carried out on homogenous cohorts. Recent studies have indicated that F-18 FDG PET/CT diagnostic performance may vary depending on the location of the firs metastatic presentation. One study demonstrated that detection rate of primary tumor in

patients who present with lung and peripheral lymph node metastasis is considerably higher than those who present with liver, brain and other sites of metastasis. Detection rate for the patients who present with bone metastasis do not show statically significant difference between CT and FDG PET in this study[27]. Conversely, another study has been shown that PET/CT is more helpful in CUP patients with primary presentation of bone metastasis[28]. In the present study, primary lesion detection mostly occurred in patients presented with liver, extracervical lymph node and bone metastasis, however the results may greatly influenced by the distribution pattern of metastatic locations in this study which occurred mainly in bone, extracevical lymph nodes and liver. Though not conclusive, the highest rate of false positivity occurred in patients who were referred for PET/CT evaluation based on relevant clinical symptom. Regarding the fact that sample size of CUP subclasses in considerably low, validation of the results requires more large-scaled studies.

In the present study, the time contribution of F-18 FDG PET/CT was the terminal 10.23% of total time of diagnostic pathway. It can be inferred that application of F-18 FDG PET/CT in early phase of initial work up may be considered as a time-saving approach results in reaching at the endpoint of the investigation earlier. However, the impact on prognostic outcome is not investigated in current study.

Some limitations are encountered in the present study. Unavailability of postmortem investigation as well as short follow-up period may negatively effect on the accuracy of true-negative rate and hence the sensitivity. Furthermore, not all the additional metastatic sites were confirmed histopathologically. The definite value of PET/CT application in early phase of diagnostic pathway require a prospective randomized clinical trial with 2 arms evaluatingthe impact of early versus late PET/CT investigation in CUP patients. Small sample size restricted the validation of the result in different subclasses of CUP patient. Other potential drawback can be summarized as below: retrospective nature of the study, relatively small sample size as well as heterogeneity of patients' population.

Conclusion

Providing higher detection rate of primary origin with excellent diagnostic performance and improving treatment planning as well as shortening the diagnostic pathway, F-18 FDG PET/CT may play a major role in diagnostic work up of patients with CUP and may be recommended as an alternative imaging tool in early phase of investigation.

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