Impact of ^{18}F-FDG PET/CT for Detecting Primary Tumor Focus in Patients with Histopathologically Proven Metastasis

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Abstract: *Purpose:* To describe the impact of fluorine (^{18}F) - fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in detecting primary tumor focus in our patient population who had histopathologically proven metastasis.

Methods: 37 patients who underwent ^{18}F-FDG PET/CT to detect primary tumor focus in our department were included in the study. The results of PET/CT and clinical follow-up data were reviewed retrospectively. PET/CT results were compared with histological analysis and/or clinical follow-up data.

Results: Primary site of malignancy was correctly identified by PET/CT in 16 patients (16/37, 43%). Lung was the most common detected site (7/16). The mean SUV of metastatic tumor was higher than that of primary tumor. False positive and false negative results were obtained in 2 patients, respectively. In the remaining patients (17/37; 46%) the primary tumor was not localized by PET/CT. According to these results, the sensitivity and specificity of PET/CT were calculated as 89% and 90%, respectively. However, PET/CT scan determined additional metastatic focus and therapy management was changed (9/37, 24%). The primary focus was established in 4 of 8 (50%) patients with metastatic cervical adenopathy and in 12 of 29 (41%) patients with extra cervical metastases.

Conclusions: ^{18}F-FDG PET/CT can detect the primary tumor focus in about half of all patients with histopathologically proven metastases. In the remaining patients, it may contribute to therapy management by identifying additional foci.

Keywords: Cancer of unknown primary, ^{18}F-FDG, Positron emission tomography, Therapy management, Metastases.

INTRODUCTION

Cancer of unknown primary (CUP) is responsible for 2-5% of all new diagnosed cancer cases in the world [1]. CUP is described as a disorder whose primary tumor can not be established in patients with tumor metastases detected histopathologically. Usually the detection of primary tumor is quite difficult and this situation makes it difficult for clinicians to choose a suitable approach to patients.

Histopathological examinations of metastatic lesions frequently do not provide sufficient information about primary tumorsite [2]. Conventional diagnostic techniques (thoraco-abdomino-pelvic computed tomography (CT) and/or magnetic resonance imaging (MRI) and mammography in women) have also limited accuracy in detecting primary site of malignancy in CUP. In the literature, the success of conventional imaging modalities for the determination of primary site of malignancy is about 10-35%. Together with improvement of imaging techniques, the detection rate of primary tumoris increasing [3-5]. However, the problem on detection of primary tumor still continues in most of cases because of microscopic primary tumor foci or angiogenetic incompetence of primary tumor which leads to marked apoptosis [4, 6]. Nowadays, Fluorine (^{18}F) - fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is a common used imaging tool in oncologic patients [7]. In the literature, ^{18}F-FDG PET/CT imaging has been recommended for searching primary focus in CUP [8-11].

The goal of this study is to describe the impact of ^{18}F-FDG PET/CT in detecting primary tumor focus in our patient population who had histopathologically proven metastasis.

MATERIALS AND METHODS

Patients

A total of 37 patients who had histopathologically proven metastases (20 female, 17 male; mean age: 58.4 ± 10.6; age range: 34 - 80 years) were included in this retrospective study. All patients had undergone ^{18}F-FDG PET/CT in our department. ^{18}F-FDG PET/CT results are compared with histological analysis and/or clinical follow-up data. Patients have been followed-up 44.6±3.8 months. ^{18}F-FDG PET/CT imaging was

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E-ISSN: 2408-9788/16

performed either before or after conventional imaging methods.

^{18}F-FDG PET/CT

Informed consent was taken from patients before imaging. PET/CT images were acquired with Discovery ST PET/CT scanner (General Electric, Milwaukee, Wisconsin, USA). Patients were fasted at least 6 hours before scanning and blood glucose levels were checked before ^{18}F-FDG injection. A nonionic, water-soluble radiographic contrast medium was given to only patients with suspicion of abdominal malignancy. Intravenous contrast agent was not used. Patients were rested in a quiet room without administrating muscle relaxant during waiting period. Whole body PET/CT imaging was performed while patients were in supine position, from skull base to mid thighs. Images were obtained approximately 1 hour after an intravenous injection of 555 MBq of ^{18}F-FDG. CT image was obtained from the integrated PET/CT scanner with the use of a standardized protocol involving 140 kV, 70 mA, a tube rotation time of 0.5 s per rotation, a pitch of 6 and a section thickness of 5 mm. Immediately after the CT part, PET images were acquired for 4 minutes per bed position. PET images were reconstructed using non-contrast CT data for attenuation correction.

Image Analysis

Whole body PET/CT images were interpreted by two experienced nuclear medicine physicians by consensus. Comparison was made between focus showing increased uptake and background/blood pool activity. Their anatomic confirmation was made with CT images. The criteria for malignancy were accepted as ^{18}F-FDG hypermetabolism at the site of pathological changes on CT or marked focal hypermetabolism at the physiological uptake sites. Maximum standardized uptake value (SUV) was calculated for all pathologic lesions

Data Analysis

When the detected primary site on ^{18}F-FDG PET/CT confirmed histopathologically, these lesions were accepted true positive (TP). If findings were not confirmed histopathologically, they would be accepted false positive (FP). When primary site was not detected on ^{18}F-FDG PET/CT and conventional diagnostic techniques, this was accepted true negative (TN). ^{18}F-

Table 1: Histological Types and Localizations of Metastases of 37 Patients with Histopathologically Proven Metastasis

Histological Types				
Localizations	**Epithelial**	**Adenocarcinoma**	**Undefined**	**Total**
Lymph Nodes	8	5	2	15 (41%)
Cervical LN	6		2	8
Axillary LN	1	2		3
Supraclavicular LN		1		1
Mediastinal LN	1			1
Abdominal LN		2		2
Bone	1	1	6	8 (22%)
Liver	3	2		5
Intraabdominal Mass			2	2
Fluid				
Peritoneal	1	1		2
Pleural	1			1
Brain	2			2
Thyroid		1		1
Ovary	1			1
TOTAL	17 (46%)	10 (27%)	10 (27%)	100 (100%)

LN: lymph node, Undefined metastases could not be described as epithelial or adenocarcinoma origin.

FDG PET/CT didn't show any focus, but some foci were established histopathologically and the classification was accepted false negative (FN). If there was pathologic uptake in more than one region, it was defined as generalized disease.

Statistical Analysis

TP/FP and TN/FN results were described according to criterion mentioned above. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (NPV) and accuracy were computed by use of above mentioned data. SPSS 19.0(SPSS Inc; Chicago, Illinois, USA) was used for describing statistics.

RESULTS

Thirty seven patients with histopathologically proven metastasis were evaluated. The localizations of metastasis were demonstrated on Table **1**. Lymph nodes were the most common metastatic area (41%), especially in the cervical region. The second site of metastasis was bone. Although the histologic subtype could not be described in 10 cases, the most common detected histological subtype was epithelial tumor metastasis in 17 cases.

^{18}F-FDG PET/CT Findings

The comparison of ^{18}F-FDG PET/CT positive and negative findings and histopathological examination and/or clinical follow-up results were represented on Tables **2** and **3**.

Primary tumor was correctly identified by ^{18}F-FDG PET/CT in 16patients (16/37, 43%). The primary sites of malignancy were lung in 7 patients, nasopharynx in 3 patients, colon, thyroid, tongue, breast, GEP NET (gastroenteropancretic neuroendocrine tumor) and leukemia in each patient. The mean SUV of metastatic tumor was higher than that of primary tumor

Table 2: The Comparison of ^{18}F-FDG PET/CT Positive Results and Histopathological Analysis/Clinical Follow-Up Data

Gender	Age/Gender	Metastatic Localizations (SUV max)	Metastatic Histology	18F-FDG PET/CT Results (SUV max)	Gold Standard	Accuracy
1	45/M	Bone (4.1)	Malign tumor	Bone marrow (4.4)	T-cell leukemia	TP
2	59/M	Servical LN (14.1)	Malign epithelial tumor	Nasopharynx (12.1)	Nasopharyngeal Carcinoma	TP
3	45/F	Brain (operated)	Malign epithelial tumor	Thyroid (4.7)	Papillary Thyroid Carcinoma	TP
4	57/F	Supraclaviculary LN (7.7)	Adenocarcinoma metastasis	Lung (5.4)	Lung carcinoma	TP
5	55/F	Axillary LN (11.5)	Malign epithelial tumor	Lung (15.5)	Lung carcinoma	TP
6	64/F	Mediastinal LN (9.1)	Malign epithelial tumor	Lung (8.1)	Lung carcinoma	TP
7	69/M	Bone (21.3)	Metastatic cancer	Lung (21.0)	Lung carcinoma	TP
8	49/F	Servical LN (15.0)	Undifferantiated tumor met.	Nasopharynx (7.1)	Nasopharyngeal Carcinoma	TP
9	56/F	Liver (10.1)	Adenocarcinoma metastasis	Lung (5.1)	Lung carcinoma	TP
10	61/M	Servical LN (10.8)	Undifferantiated tumor met.	Tongue (9.5)	Tongue cancer	TP
11	61/M	Bone (15.6)	Malign epithelial tumor	Lung (4.7)	Lung carcinoma	TP
12	57/M	Brain (operated)	Malign epithelial tumor	Lung (16.1)	Lung carcinoma	TP
13	73/F	Peritoneal fluid (12.6)	Adenocarcinoma metastasis	Colon (19.8)	Colon carcinoma	TP
14	42/M	Intraabdominal mass	Malign tumor	Tongue (12.3)	-	FP
15	55/F	Liver (16.8)	Adenocarcinoma metastasis	Colon (5.0)	-	FP
16	61/M	Servical LN (13.9)	Malign epithelial tumor	Nasopharynx (8.6)	Nasopharyngeal Carcinoma	TP
17	72/F	Axillary LN (4.4)	Adenocarcinoma metastasis	Breast (2.5)	Breast carcinoma	TP
18	34/F	Liver (10.5)	Malign epithelial tumor	Jejenum (7.9)	GEP NET	TP

^{18}F-FDG PET/CT: ^{18}Fluorine-fluorodeoxyglucose positron emission tomography/ computed tomography; LN: lymph node; TP: true positive; FP: false positive; GEP NET: gastroenteropancreatric neuroendocrine tumor.

Table 3: The Comparison of [18]F-FDG PET/CT Negative Results and Clinical/Gold Standard Findings

Gender	Age/Gender	Metastatic Localizations	Metastatic Histology	[18]F-FDG PET/CT Results	Gold Standard	Accuracy
1	40/F	Bone	Metastatic cancer	Bone metastases	-	TN
2	68/F	Liver	Malign epithelial tumor	Generalized disease	-	TN
3	50/F	Bone	Metastatic cancer	Generalized disease	-	TN
4	59/M	Intraabdominal mass	Metastatic cancer	Normal	-	TN
5	35/M	Thyroid	Adenocarcinoma metastasis	Thyroid metastasis	-	TN
6	37/F	Ovary	Malign epithelial tumor	Normal	-	TN
7	63/F	Intraabdominal LN	Adenocarcinoma metastasis	Generalized disease	-	TN
8	66/F	Pleural fluid	Malign epithelial tumor	Pleural metastasis	-	TN
9	58/M	Bone	Adenocarcinoma metastasis	Generalized disease	-	TN
10	66/M	Servical LN	Malign epithelial tumor	Generalized disease	-	TN
11	69/F	Servical LN	Malign epithelial tumor	Lymphatic metastasis	-	TN
12	59/F	Bone	Metastatic cancer	Bone metastasis	-	TN
13	63/M	Intraabdominal LN	Adenocarcinoma metastasis	Lymphatic metastasis	Pancreatic carcinoma	FN
14	58/M	Servical LN	Epithelial tumor metastasis	Lymphatic metastasis	-	TN
15	75/F	Peritoneal fluid	Epithelial tumor metastasis	Peritoneal metastasis	-	TN
16	80/M	Liver	Malign epithelial tumor	Generalized disease	-	TN
17	78/F	Axillary LN	Adenocarcinoma metastasis	Generalized disease	Breast carcinoma	FN
18	63/M	Bone	Metastatic cancer	Generalized disease	-	TN
19	60/M	Servical LN	Epithelial tumor metastasis	Generalized disease	-	TN

[18]F-FDG PET/CT: [18]Fluorine- fluorodeoxyglucose positron emission tomography/computed tomography; LN: lymph node; FN: false negative; TN: true negative.

(11.5 vs 8.6). Lung was the most common detected site for primary tumor. The mean SUV for primary lung carcinoma was 10.8. However the mean SUV of metastatic foci of primary lung carcinoma was 12.6. In the detailed analysis of histopathologic groups, the mean SUV of metastases was higher than that of primary tumor in both groups. Undefining histologic subtype group could not be evaluated. Due to the small number of histologic subtype, statistical analysis could not be performed.

The findings of [18]F-FDG PET/CT were concordant with histopathologic examination and/or clinical follow-up results on 33/37 (89%) patients. The findings were TP in 16 (49%) and TN in 17 (51%) of them. While the stage was not changed in 8 of 19 cases in whom primary focus hasn't been established, generalized disease was detected in 9 patients. [18]F-FDG PET/CT results were normal in 2 patients also. According to this, [18]F-FDG PET/CT had changed the therapy management in 9 of 32 patients. In 4 (11%) patients, [18]F-FDG PET/CT findings were discordant with histopathologic examination and/or clinical follow-up results. Two of them were FN and the others were FP findings. In one patient who had intraabdominal metastatic lymph nodes, [18]F-FDGPET/CT could not localized primary site, but this patient was accepted as pancreatic cancer in the follow-up (FN). In other patient who had axillary metastatic lymph nodes, generalized disease was detected by [18]F-FDG PET/CT. Breast carcinoma was accepted as primary site in the follow-up (FN). In detailed analysis of FP findings, FDG uptakes in tongue (SUV:12.3) and colon (SUV:5.0) were seen in two patients. Focal increased uptake on tongue was accepted as physiologic in the follow-up. The histopathologic examination result of colon was polyp.

When the findings were evaluated for the localization of metastatic foci, in 8 of 37 cases were metastatic cervicaladenopathy, and the rest was extracervical metastases. The primary focus was established by [18]F-FDG PET/CT in 4 of 8(50%) patients with metastatic cervical adenopathy and in 12 of 29(41%) patients with extracervical metastases.

The sensitivity and specificity of ^{18}F-FDG PET/CT for detecting primary site were calculated 89% and 90%, respectively.

DISCUSSION

CUP is a clinical process which makes up 2-5% of all new diagnosed cancers, including heterogeneous tumor groups, and which makes it difficult to establish the way to approach the patient. Detection of the primary focus in early period may help clinician by providing the use of a more specific and effective therapy method. For this reason, early detection of the primary focus and/or correct staging is an important point in approaching patients with CUP.

The usefulness of conventional imaging methods establishing the primary focus is limited. In studies that have been done, the rate of success is between 10-35% [3-5]. On the other hand, the studies with ^{18}F-FDG PET/CT, it is emphasized that ^{18}F-FDG PET/CT is a useful method in establishing in tumors with both metastatic cervical adenopathyand extracervical metastases [12-14]. According to our study, it has been found that primary focus could be establish in 50% of cases with metastatic cervical adenopathy and 41% of cases with extracervical metastases.

The accuracy of ^{18}F-FDG PET/CT on the detection of primary tumor site was reported between 24-63% in different studies [2, 5, 8-11, 15-16]. Many causes can lead to different results. Firstly, the patient populations of different studies are very heterogeneous. In addition, clinical examination and imaging tools may vary according to the centers. Clinic presentation of disease is very important especially patients with disseminated focus. The prediction of primary site is easier in patients with typical clinical presentation. In our study, ^{18}F-FDG PET/CT showed primary tumor focus in 16 patients of total 37patients (43%). This rate is similar with literature. Generalized disease was established in 9 of the cases after ^{18}F-FDG PET/CT and PET/CT also added to change the therapy management in 9 of 37 patients (24%). In the current literature, the sensitivity and specificity of ^{18}F-FDG PET/CT in the search for the primary was reported as 62% and 82% respectively [10]. The sensitivity and specificity was calculated 89% and 90% in our study, respectively.

During follow-up period, primary site could not be detected histopathologically in any patients without primary site on PET/CT. Only in two patients, primary tumor sites were accepted as clinically. It does not mean that primary site does not exist. In some cases ^{18}F-FDG PET/CT could not show the primary site because of physiological uptake sites or resolution limitation (such as microscopic primary tumor focus or low metabolic activity). The detection of primary tumor foci is get harder in tumors with high metabolic metastasis. The histologic grade of tumor varies the visibility of tumor on ^{18}F-FDG PET/CT. In addition to, the cause of the problem on detection of primary tumor could be still continues in most of cases because of microscopic primary tumor foci or angiogenetic incompetence of primary tumor which leads to marked apoptosis. Because none of patients have died or suffered any serious complication related with malignancy in ^{18}F-FDG PET/CT negative group during the follow-up period, the primary malignancies of these patients probably were well differentiated or low grade. This could be a reason for decreasing the success of ^{18}F-FDG PET/CT in this group. Nowadays, it seems that there is not more sensitive imaging tool in ^{18}F-FDG PET/CT negative patient groups.

Seve *et al.* [16] reported that the most common detected primary site was lung in patients with CUP. The most common detected primary site was lung also in our study in 7 patients (44%). When compare with the sites which have intense physiologic activity distribution such as gastrointestinal and genitourinary system, especially the detection of lung lesions larger than 1 cm is easier. In our study, ^{18}F-FDG PET/CT imaging had been performed before conventional imaging methods in patients who had lung carcinoma. CT also could help to define the lung carcinoma in these patients. However, in clinical practice, whole body imaging with ^{18}F-FDG PET/CT appears to be an easier but not excellent method to define primary site. The mean SUV of metastatic tumor was higher than that of primary tumor. That SUV was lower in primary tumor may be explained with necrosis of tumor in primary focus and poor differentiation of metastatic focus.

Recently, anatomic and functional information has been obtained simultaneously by use of conventional systems that get PET and CT together. This shows that integrated PET/CT systems are more correct than P *Et al*one in evaluation of presents of tumor focus and localization. Despite of all these, physiological distribution areas (gastrointestinal uptake, urinary uptake, ovarian uptake, brain uptake vs) of ^{18}F-FDG and processes of inflammation may cause false positive and negative results. In this study, there were

two false negative results. However, there were false positive findings (in tongue and colon), which has mimicking primary tumor focus in 2 cases. Focal increased uptake on tongue was accepted as physiologic in the follow-up. The histopathologic examination result of colon was polyp.

Yaganawa *et al.* [17] reported that the difference between sensitivity of ^{18}F-FDG PET and conventional imaging methods was not significant in patients with CUP. However, in that study most of patients had been evaluated by ^{18}F-FDG PET instead of ^{18}F-FDG PET/CT. In this patient group, PET/CT via to give both anatomic and metabolic information is more sensitive than PET. Garin *et al.* [18] published an article about the usefulness of ^{18}F-FDG PET in CUP. They showed the accuracy for identification primary tumor by immunohistochemical profile of metastasis has much information about the primary as ^{18}F-FDG PET. In our study, the immunohistochemical examination has not been performed routinely, so we did not compare the immunohistochemical examination and ^{18}F-FDG PET/CT.

CONCLUSION

In this retrospective analysis we concluded that ^{18}F-FDG PET/CT can detect the primary tumor focus in about half of all patients with histopathologically proven metastases. In the remaining patients, it may contribute to therapy management by identifying additional foci. Despite the relatively low number of patients, the sensitivity of ^{18}F-FDG PET/CT seems to be unaffected by the presence of cervical or extracervical metastases in clinical presentation.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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Received on 23-09-2016 Accepted on 04-10-2016 Published on 14-10-2016

http://dx.doi.org/10.15379/2408-9788.2016.03.02.03