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Role of F-18 FDG PET/CT in Patients with Suspected Recurrent Breast Cancer: Additional Value over Conventional Imaging Modalities

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ABSTRACT

Background: The aim of the present study was to investigate the added value of F-18 fludeoxyglucose (FDG) positron-emission tomography (PET)/computed tomography (CT) compared with conventional imaging modalities for the evaluation of locoregional and distant sites of recurrence in breast cancer patients.

Methods: From May 2013 to September 2016, 109 patients with suspected recurrent breast cancer who underwent conventional imaging and F-18 FDG PET/CT with an interval of 6 weeks were consecutively enrolled (mean age: 52.66 years; range: 29-79). Histopathologic results and clinical follow up based on the gold-standard imaging modality or serial imaging were considered as the reference for verification of F-18 FDG PET/CT findings.

Results: Of 109 patients, 81 were found to have at least one site of recurrence (74.31%). Local recurrence was correctly identified in 32/32 patients following PET/CT, which was higher than that on conventional imaging (20/32, 62.5%). PET/CT detected 27 additional nodal metastases compared with conventional imaging (59 vs. 32, 45.76%), most frequently in the hilar/mediastinal region (n=27), followed by the supraclavicular lymph nodes (n=20, 62.5%), internal mammary lymph nodes (n=6, 18.77%), and axillary basin (n=6, 18.77%). Additional sites of distant metastasis were identified in 41 patients (37.61%) following F-18 FDG PET/CT imaging, 48.78% of which were localized in the skeletal system (n=20), 21.95% in the liver (n=9), 12.19% in the lungs (n=5), 12.19% in the brain (n=5), and 4.87% in the adrenal glands (n=2).

Conclusion: F-18 FDG PET/CT serves as a useful supplement to conventional imaging techniques by identifying additional sites of disease recurrence in patients with breast cancer, which may change the preferred treatment strategy, particularly in regions that are not routinely evaluated by conventional imaging.

Introduction

Breast cancer recurrence occurs in 10-75% of patients depending on the extent of disease at the time of initial diagnosis.[1] Treatment approaches can be stratified based on the location of disease recurrence (locoregional vs. distant) and extension (oligofocal vs. multifocal metastasis). Locoregional recurrence in the primary site, chest wall, axillary basin, internal mammary lymph nodes, and supraclavicular lymph nodes comprises up to 20% of all recurrences [2] and may be treated with curative therapy.[3] The vast majority of disease relapse, however, occurs more frequently at distant sites such as in the skeletal

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system (20-60%), lungs (15-20%), liver (5-15%), and brain (5-10%).[4] Patients with disease relapse have a poor prognosis and generally undergo palliative treatment.[3]

According to current guidelines, patients suspected for breast cancer recurrence should undergo clinical examination and multimodality imaging, including X-ray mammography, breast and axillary ultrasound, liver ultrasound, chest X-ray, and bone scintigraphy.[5, 6] However, there are some major limitations regarding their diagnostic accuracy; post-surgical structural changes, limited field of view and interobserver variability may negatively influence the diagnostic accuracy of X-ray mammography and breast ultrasound for the early detection of local recurrences.[5, 7] Small malignant supraclavicular and mediastinal lymph nodes may be missed by ultrasound or computed tomography (CT), based only on morphologic criteria. Bone scintigraphy has limited sensitivity for the detection of osteolytic metastasis and may potentially underestimate the extent of skeletal disease.[8, 9] In addition, unifocal or oligofocal lesions suspected as bone metastases detected by bone scan must be verified by correlative imaging due to limited specificity.[9,10]

F-18 fludeoxyglucose (FDG) positron-emission tomography (PET)/CT has recently gained widespread acceptance in oncologic imaging as a highly-sensitive, whole body imaging modality. PET/CT can detect malignant lesions before any morphological changes develop by identifying accelerated metabolism in cancerous cells; however, due to high cost and limited resolution in small lesions, the benefits over conventional imaging must be verified in individual clinical settings.

On the basis of current recommendations, PET/CT imaging has limited application in patients with suspected recurrent breast cancer.[11] However, a growing body of evidence suggests a complementary role for F-18 FDG PET/CT in such patients as well as the potential for F-18 FDG PET/CT to replace conventional imaging modalities based on its high sensitivity and large field of view.[12-15] Thus, the aim of the present study was to investigate the potential added value of F-18 FDG PET/CT over conventional imaging modalities in detecting breast cancer recurrence.

Methods

The Review Board of Shahid Beheshti University of Medical Sciences approved this retrospective study and waived the need for informed consent.

Patients

This retrospective study included 443 patients with suspected recurrent breast cancer who were referred to the PET/CT division of Masih Daneshvari Hospital between May 2013 and September 2016. Results were available for 109 patients upon final verification. Breast cancer recurrence was suspected for the following reasons: increased tumor markers (n=41, 37.61%); equivocal findings on conventional imaging (n=15, 13.76%); biopsy-proven local recurrence (n=20, 18.35%); disease extension in known cases of distant metastasis (n=33, 30.27%).

Conventional imaging

Conventional diagnostic work up was performed as follows: chest CT, abdominopelvic CT, bone scintigraphy, and liver ultrasound (n=32); chest CT, liver ultrasound, and bone scintigraphy (n=21); bone scintigraphy, chest X-ray, and liver ultrasound (n=43); bone scintigraphy and chest CT scan (n=13). Breast and axillary ultrasound investigations were performed in all 109 patients.

F-18 FDG PET/CT acquisition protocol

An integrated PET/CT device (GE 690 Discovery, 64 Slice, Time of Flight) was used. The fasting period was maintained for at least 8 hours. The level of blood glucose at the time of radiotracer injection was <150 mg/dL. Sixty minutes (±10%) after the intravenous (IV) administration of 4.6 MBq/kg F-18 FDG (0.12 mCi/kg), craniocaudal CT acquisition was initiated from the vertex to the mid-thigh (or to the toe as indicated) in the supine position. A multidetector CT scanner was used at 50-120 auto mAs with a tube current of 120 kV, a noise factor of 19, and 2.5 mm thickness under tidal breathing. Thirty minutes before imaging acquisition, 40 cc of 76% meglumine (containing 370 mg iodine/cc) in 1500 cc water was administered as an oral contrast solution. The PET data were collected in the reverse direction for 3 minutes per bed position immediately after CT acquisition. Corrections were made to the raw data in terms of attenuation, dead time, random and scatter coincidence. Images were subsequently reconstructed using an iterative method and high-definition (HD) technique.

Diagnostic criteria

The PET (attenuation corrected [AC] and non-AC), CT and fused PET/CT images of the eligible cohort were retrieved and reviewed using a workstation (Advantage Window, 4.5, Volumeshare software, GE 690) by a team consisting of an experienced radiologist and a nuclear physician, who reached a consensus regarding disease status.

Metabolic criteria

The criteria for malignancy were defined as follows: 1) foci of abnormal increased F-18 FDG uptake markedly greater than liver activity for local recurrence in the chest wall, lymph nodes, adrenal and skeletal system, and more than the surrounding background activity in the lungs and brain, with or without corresponding CT abnormalities; 2) multiple foci of increased F-18 FDG uptake randomly

Table 1. Patients' demographic and cancer-related characteristics.

Variables		
Age		
	Mean	52.6
	range	29-79
Gender		
	Male	3
	Female	106
Histopathologic subtype		
	Invasive Ductal Carcinoma	98 (89.9%)
	Invasive Lobular Carcinoma	11 patients (10.09%)
Reason for recurrence		
	Tumor marker rise	(n=41, 37.61%);
	equivocal findings on conventional imaging	(n=15, 13.76%);
	biopsy-proven local recurrence	(n=20, 18.35%);
	disease extension in known cases of distant metastasis	(n=33, 30.27%).
Baseline Conventional Imaging Work up		
	Breast and axillary ultrasound	N= 109 patients
	Chest/abdominopelvic CT plus bone scintigraphy plus liver ultrasound	(n=32);
	chest CT plus liver ultrasound plus bone scintigraphy	(n=21);
	bone scintigraphy plus chest X-ray plus liver ultrasound	(n=43);
	bone scintigraphy plus chest CT scan	(n=13).

distributed in distant organs with or without corresponding CT abnormalities; 3) highly suspicious morphological abnormalities with or without discernible associated metabolic activity.

Standard of reference

All of the included lesions were verified as benign or malignant according to their histopathology (n=32, 29.36%) or clinical follow up, using the gold-standard imaging modality or serial imaging (n=77, 70.64%).

Results

Patients' Characteristics

Of 109 cases, 106 were women and 3 were men. The mean age of the study cohort was 52.66 years (range: 29-79). In total, 98 patients (89.9%) had invasive ductal carcinoma and 11 patients (10.09%) had invasive lobular carcinoma (Table 1).

Lesion detection

Local recurrences confirmed by biopsy were identified in 20 patients, located within the region of the previous surgery (n=8), axillary basin (n=3) or both (n=9) (Table 2).

Conventional imaging

Conventional imaging correctly identified 12 nodal metastases in the supraclavicular lymph nodes, 3 in the internal mammary lymph nodes, and 17 in the hilar/mediastinal stations. Distant metastasis was detected in 40 patients with the following distribution pattern: skeletal system only (n=15); lung and bone (n=12); lung only (n=5); bone and liver (n=6); bone, liver and lung (n=2). The most common site of distant metastasis was the skeletal system (n=35), followed by the lungs (n=28) and liver (n=11).

F-18 FDG PET/CT

F-18 FDG PET/CT correctly identified 12 additional sites of local recurrence within the region of the previous surgery, which were verified as malignant (n=32). Additional locoregional nodal metastasis was detected in the supraclavicular lymph nodes (n=20), axillary basin (n=6), internal mammary lymph nodes (n=6) and hilar/mediastinal lymph nodes (n=27) with an overall additional detection rate of 45.76% (n=59).

Distant metastasis was detected in 81 patients with the following distribution pattern: skeletal system (n=26); lung, liver and bone (n=11); lung only (n= 10); lung and bone (n=9); abdominal cavity (including liver, adrenal glands, lymph nodes, and peritoneum) (n=8). Additional sites of distant metastasis (n=41) were identified mostly in bone

Table 2. Local Recurrence: Comparison between Conventional work up and PET/CT

Local Recurrence		Conventional Imaging	PET/CT
Detection Rate		32	20
Location			
	Site of previous surgery	12	8
	Axillary Basin	6	3
	Both	14	9

Table 3. Distant Metastasis: Comparison between Conventional work up and PET/CT

Distant Metastasis Location			Conventional Imaging	PET/CT
Lymph node			32	53
		Supraclavicular	12	20
		Internal mammary	3	6
		Hilar/mediastinal	17	27
Organ			40	
	Distribution	Bone (only)	15	26
		Lung+ bone	12	9
		Lung (only)	5	10
		Bone + liver	6	18
		Bone + liver + lung	2	11
		Brain		5
		Adrenal		1
		Peritoneum		1

(n=20, 48.78%), liver (n=9, 21.95%), lungs (n=5, 12.19%), brain (n=5, 12.19%), adrenal glands (n=1, 2.43%), and the peritoneum (n=1, 2.43%).

Previously unidentified brain metastases were detected in 5 patients; brain and lung metastases (n=2); brain and bone metastases (n=2); brain and liver metastases (n=1) (Table 3).

Discussion

The present study revealed that F-18 FDG PET/CT is superior to conventional imaging techniques for the detection of locoregional and distant metastases in patients with suspected breast cancer recurrence and may play a major complementary role in the accurate assessment of disease extension, which is considered the main prerequisite for treatment decision making.

Locally advanced breast cancer may be treated with curative therapy. One study showed that PET/CT successfully detected 21 additional intrathoracic and 5 additional cervical lymph node metastases in patients suspected to have breast cancer recurrence.[12] Another study revealed that the mediastinal, supraclavicular, axillary and internal mammary lymph nodes were frequent sites for tumor recurrence, as detected by PET. [13] In line with the literature, the present study revealed that F-18 FDG PET/CT correctly identified 45.76% additional sites of regional nodal involvement, mainly in the extra-axillary basin. F-18 FDG PET/CT imaging can identify accelerated metabolic changes in small lymph nodes before the development of morphological changes, and thus may play an important role in the early detection of malignant lymph nodes.

Several studies have compared the diagnostic accuracy of PET/CT imaging with bone scintigraphy, as the imaging modality of choice for the detection of skeletal metastases. PET/CT demonstrated a significantly higher accuracy for the detection of both osteolytic and osteoblastic skeletal metastases.[14,15] The results of our study demonstrated that the most frequent site of additional distant metastasis detected by PET/CT was the skeletal system with a high level of diagnostic confidence and no subsequent need for further verification.

Most hepatic metastases, from different sites of primary origin, have been shown to be highly amenable to F-18 FDG detection. Several studies have shown that F-18 FDG PET/CT may serve as the most sensitive imaging modality for the identification of liver metastases and may have a significant impact on stratification for surgical resection.[16-18] The results of the current study revealed that in patients with suspected breast cancer recurrence, F-18 FDG PET/CT identified 6 additional hepatic metastases, 50% of which were not identified by conventional imaging.

Brain metastasis occurs in 10-16% of patients with breast cancer.[19] The incidence of brain metastasis in patients with breast cancer is increasing due to higher detection rates and improved survival. Brain metastases have a significant negative impact on patients' quality of life and prognosis. Brain magnetic resonance imaging (MRI) is considered the imaging modality of choice to detect brain metastases; however, routine screening of brain metastases is not recommended in asymptomatic patients. Due to a high level of F-18 FDG uptake in normal cerebral parenchyma, F-18 PET/CT has limited sensitivity for the detection of brain metastases.[20] Consequently, most PET/CT centers define the standard field of view for PET/CT acquisition from the skull base to the mid-thigh. One study demonstrated that F-18 FDG PET/CT imaging of the brain may help to stratify lung cancer patients prior to further evaluation of cerebral metastases by MRI.[21] The present study revealed that in patients with suspected breast cancer recurrence, PET/CT correctly identified previously unidentified cerebral metastases in 12% of patients.

There are some major limitations to the present study. The clinical impact of the detection of additional lesions on the optimal treatment strategy and subsequent survival is an important issue that was not evaluated in this study and should be addressed in the future. In addition, the significance of F-18 FDG PET/CT in terms of decreased cost and time intervals from the beginning of diagnostic work up until the initiation of treatment was not evaluated. Furthermore, clinical follow up was not performed in most patients; therefore, a considerable number of potentially eligible patients who underwent neither biopsy nor gold-standard imaging did not undergo further investigation.

In conclusion, F-18 FDG PET/CT serves as a useful supplementary technique to conventional imaging that can detect additional sites of disease recurrence in the supraclavicular lymph nodes and axillary basin in addition to the skeletal system, liver, and brain, which may have a significant impact on the treatment strategy. Large-scale prospective studies are required to investigate the influence of these additional lesions on the optimal treatment strategy and overall survival.

Conflict of Interest

None.

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