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2-[18f]-Fluoro–2-deoxy-d-glucose positron emission tomography in the evaluation of breast lesions and axillary involvement: a comparison with mammography and histopathological diagnosis

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Aim: The objective of this prospective study was to evaluate the potential role of 2-[18f]-fluoro–2-deoxy-d-glucose (FDG) positron emission tomography (PET) in the differentiation of malignant and benign breast masses and the evaluation of axillary lymph node involvement. The secondary objective of this study was to assess the value of FDG PET in the initial staging of patients with breast cancer.

Materials and methods: We evaluated 82 lesions in 79 consecutive patients (mean age of 54.4 ± 13.0; age range: 25–82 years) with FDG PET. While ultrasounds were performed in all cases, of the 79 patients, 72 had mammography and 58 had whole-body bone scintigraphy. All patients had a histopathological diagnosis made by 2 experienced pathologists.

Results: The sensitivity and positive predictive value of FDG PET in the differentiation of breast masses was found as 78% and 98%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of FDG PET in the detection of metastatic axillary invasion was 50%, 76%, 53%, and 64%, respectively. FDG PET changed the stage of 41 patients (52%) by either downstaging [33 (41%) patients] or upstaging [8 (11%) patients], respectively.

Conclusion: Our results suggest that FDG PET has limited value in differentiating between malignant and benign breast lesions and in the detection of metastatic axillary lymph nodes. However, FDG PET appears to have great impact in the initial staging of patients with breast cancer and could be very helpful in the management of selected cases.

Key words: Breast cancer, FDG PET, axillary lymph node metastases, staging

Introduction

Breast cancer is the most common malignant tumor among women all over the world and accounts for about 30% of all cancers in women (1). It accounts for 18% of cancer deaths in women, second only to lung cancer for cancer-related deaths (2,3). Although periodic physical examination and screening mammography (MG) are very important diagnostic methods for the early detection of breast cancer, the specificity of these conventional methods is still limited. Mammographic accuracy rate is low in dense, fibrocystic, or postoperative breast tissue and in patients who receive hormonal therapy (3). As many as 15% of cancers are not visible on screening MG, and only 1 out of 5 to 6 patients who underwent biopsy for suspicious mammographic findings is found to have breast cancer upon histopathologic examination.

One of the most recent noninvasive methods to overcome these problems in the diagnosis of

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breast cancer and to demonstrate axillary lymph node metastases could be 2-[18f]-fluoro–2-deoxy-d-glucose (FDG) positron emission tomography (PET). FDG PET is not only used for imaging the primary breast tumor, but it can be utilized in staging patients by demonstrating regional lymph node infiltration and distant metastasis. In this prospective study, we aimed to evaluate the role of FDG PET in differentiating between malignant and benign breast masses and in the detection of axillary lymph node metastasis.

Materials and methods

Patients

We evaluated FDG PET results of 82 lesions in 79 patients. Of 79 patients, 58 had palpable masses, and 21 patients had nonpalpable lesions with suspicious mammographic and/or ultrasonographic findings. Three patients had bilateral breast carcinoma. The mean age of the patients was 54.4 ± 13.0 (range: 25–82) years. Of 79 patients, only 1 patient was male. Of 79 patients, 40 were premenopausal, 10 were perimenopausal, and 28 were in the postmenopausal period. According to ultrasonography (US) and physical examination findings, lesions greater than 1 cm were defined as palpable whereas lesions smaller than 1 cm were defined as nonpalpable breast masses.

Of 79 patients, 73 were diagnosed with breast cancer upon histopathological examination. Despite benign findings upon histopathological examination, 6 patients were included in the study due to highly suspicious findings upon US and physical examination. Final histopathological diagnosis was made by excisional biopsy (13 patients), incisional biopsy (5 patients), or fine-needle aspiration biopsy (FNAB) (61 patients). Histopathological examinations were performed by 2 pathologists experienced in this field. MG could not be performed in 7 patients for technical reasons (4 patients), male sex (1 patient), or young age (2 patients). Whole-body bone scintigraphy was performed in 58 of 79 patients.

Patients with a palpable mass upon physical examination within the last 4 weeks or patients with highly suspicious mammographic and/or ultrasonographic findings such as a solid mass or calcification were included in the study. Each patient had a comprehensive physical breast examination done by an experienced breast surgeon. Local ethics committee approval and informed consent forms from all patients were obtained.

Mammography and ultrasonography

Craniocaudal and mediolateral oblique mammographic examinations (MAMMOMAT 3 Stereo, Siemens) were performed for all patients. US was performed using either the Acuson 128 XP/10 system + L7384 or the Philips HD I 500 system equipped with a 50 MHz, 5–12 mm linear array transducer. Patients were classified in 3 categories according to mammographic and ultrasonographic findings: suspicious, positive, and negative for malignancy. US-guided FNAB was performed for all suspicious lesions.

FDG PET

FDG PET images were obtained with an ECAT EXACT PET scanner (Siemens/CTI). Following 8 h of fasting and 45 min after intravenous injection of 10 mCi (370 MBq) 18F-FDG, sequential transmission and emission images of the region from the base of the scalp to the proximal femoral head were obtained in the supine position. All FDG PET images were interpreted by 2 experienced nuclear medicine physicians who were aware of the clinical information. The standardized uptake values (SUVs) of abnormal metabolic foci were calculated.

Results

In this prospective study, we evaluated a total of 82 lesions (58 palpable and 21 nonpalpable) in 79 consecutive patients. Based on the final histopathological results, 77 cases were diagnosed as malignant and 2 cases were diagnosed as benign. Three patients had bilateral breast carcinoma. Focal pathologic FDG uptake was observed in 61 (77.2%) of 79 patients. No pathologic FDG uptake was observed in 18 (22.8%) patients. A total of 60 of 61 lesions that showed FDG uptake were malignant, and 1 lesion was benign based on histopathological examination. On the other hand, 1 of 18 lesions that did not show FDG uptake was a true negative, and 17 lesions were shown to be false negatives upon histopathological examination. FDG PET results

in overall palpable and nonpalpable lesions as well as sensitivity, specificity, and positive and negative predictive values are presented in Table 1. On the other hand, comparison of FDG PET with US and MG in the evaluation of primary breast tumor is summarized in Table 2.

The masses evaluated ranged in size from 0.8 to 11 cm in diameter. The benign patient group consisted of ductal epithelial hyperplasia and granulomatous tuberculosis mastitis. Distribution of patients by histopathological findings is presented in Table 3.

True-positive results

Compared with histopathological results, 60 of 61 lesions that showed FDG uptake were true positives. PET demonstrated focal areas of increased FDG uptake corresponding to breast carcinoma in all patients in this group (Figure 1). SUVs were 4.14 ± 2.84 for the malignant lesions. FDG PET showed multifocal breast cancer in 9 patients.

False-negative results

One out of 18 lesions that did not show FDG uptake was a true negative, and 17 of 18 lesions were false

Table 1. Comparison of the histopathological results with FDG PET findings for overall, palpable, and nonpalpable lesions.

Histopathologic results	FDG PET results						
	Positive	Negative	Sv	Spc	PPV	NPV	Total
Overall lesions							
Malignant	60	17					77
Benign	1	1					2
Total	61	18	77%	50%	77%	22%	79
Palpable lesions							
Malignant	44	13					57
Benign	1	0					1
Total	45	13	77%	N/A	77%	22%	58
Nonpalpable lesions							
Malignant	16	4					20
Benign	0	1					1
Total	16	5	80%	100%	76%	23%	21

Sv: sensitivity, Spc: specificity, PPV: positive predictive value, NPV: negative predictive value, N/A: not applicable.

Table 2. Comparison of FDG PET, US, and MG in the diagnosis of breast cancer.

	FDG PET	US	MG
Sensitivity	78%	83%	87%
Specificity	50%	N/A	50%
PPV	98%	97%	98%
NPV	55%	N/A	10%

PPV: positive predictive value, NPV: negative predictive value, N/A: not applicable.

Table 3. Histopathological distribution and FDG PET results in 79 patients.

FDG PET results	Histopathological diagnosis	#
True negative (1/18)	Ductal epithelial hyperplasia	1
False negative (17/18)	DCIS	3
	IDC	7
	ILC	1
	Tubular carcinoma	1
	DCIS + IDC	4
	DCIS + tubular carcinoma	1
True positive (60/61)	IDC	33
	ILC	2
	DCIS	1
	IDC + DCIS	12
	IDC + ILC	2
	Mucinous carcinoma	1
	DCIS + mucinous carcinoma	2
	DCIS + ILC + IDC	2
	DCIS + ILC	1
	IDC + micropapillary carcinoma	4
False positive (1/61)	Granulomatous mastitis (tuberculosis)	1
Total		79

#: number of patients, DCIS: ductal carcinoma in situ, IDC: infiltrating ductal carcinoma, ILC: infiltrating lobular carcinoma.

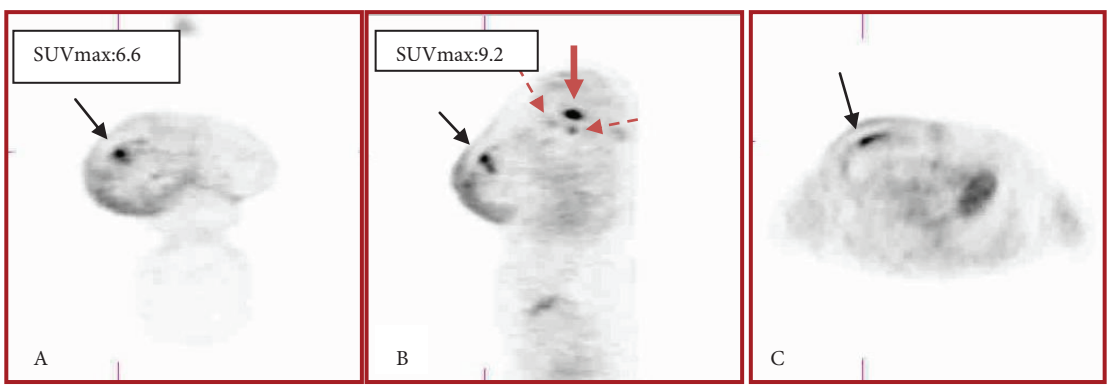

Figure 1. A) Coronal, B) sagittal, and C) axial FDG PET images of a 42-year-old patient diagnosed with infiltrating ductal carcinoma on fine needle aspiration biopsy. Black arrow shows focal FDG uptake corresponding to a mass in the right breast, whereas red arrows show multiple metastatic axillary lymph nodes.

negatives. Of the false negative lesions, 13 (76.4%) were palpable and 4 (23.6%) were nonpalpable tumors. Of 17 lesions, the largest pathologic tumor reported was 4 cm in size, while the smallest tumor was 0.2 cm in size.

True-negative results

All patients with benign breast masses were true negative on FDG PET. Although there was high suspicion of malignancy on US and MG in one patient, there was no pathological FDG uptake. The final histopathological diagnosis was ductal epithelial hyperplasia.

False-positive results

One patient with high suspicion of malignancy on US and MG showed focal increased FDG uptake (SUV= 5.3) on FDG PET. We observed multiple focally increased FDG uptakes in right paratracheal, right infraclavicular, right interpectoral, and right deep axillary lymph nodes. Two foci of right superficial axillary lymph nodes were also detected, which were thought to be metastatic. The patient underwent axillary lymph node dissection and was histopathologically diagnosed with granulomatous (tuberculosis) mastitis.

Metastatic axillary involvement

Histopathological examination revealed lymph node metastases in 28 patients. All patients were assessed in terms of axillary lymph node involvement with US, FDG PET, and MG. FDG PET was found consistent with axillary invasion in 25 of 28 patients. One patient with positive axillary uptake on FDG PET was diagnosed with granulomatous mastitis on histopathological examination. Most of the metastatic lymph nodes missed on FDG PET were less than 1 cm in size. Two metastatic lymph nodes with infiltrating ductal carcinomas (IDC), the first of which was 0.7 cm in size and the second of which was 2 cm in size, were missed on FDG PET. Of all patients, 53% (n = 42) underwent modified radical mastectomy, 34.2% (n = 27) underwent breast-conserving surgery, and neoadjuvant chemotherapy was given to 2.7% (n = 10). Comparison of FDG PET, MG, and US in the detection of metastatic axillary lymph node involvement is presented in Table 4. FDG PET changed the stage of 41 patients (52%), by downstaging for 33 patients (41%) and upstaging for 8 patients (11%).

Discussion

Breast cancer is the second leading cause of cancer-related deaths among women. As early detection of breast cancer results in an obvious improvement in survival, clinical imaging focuses on detecting asymptomatic woman with small lesions. To date, many types of imaging methods have been tested for primary diagnosis, as well as for disease staging and the evaluation of response to therapy for breast cancer. MG has clearly been shown to be quite sensitive for the detection of breast cancer (4). The positive predictive value of MG has ranged from approximately 15% to 75% (4,5). Dense breast pattern, hormonal therapy, prior surgery or radiotherapy, implants, and fibrocystic disease of the breast may decrease mammographic sensitivity (6–8). US is also known to have a low sensitivity, with a rate of false negativity of up to 47% (4,7,9). Moreover, breast tumors may mimic a variety of benign parenchymal disorders, resulting in false positive or negative screening results. Although

Table 4. Comparison of FDG PET, US, and MG in the assessment of metastatic axillary involvement.

	FDG PET	US	MG
Sensitivity	50%	64%	42%
Specificity	76%	75%	81%
PPV	53%	58%	53%
NPV	64%	79%	74%

PPV: positive predictive value, NPV: negative predictive value.

left-sided lateralization of breast cancer and axillary involvement were reported in previous studies, we did not investigate these data (10). Another method is scintimammography with Tc-99m sestamibi, which mainly accumulates in cancerous tissue as a result of multiple factors, including mitochondrial and plasma membrane potentials and tissue vascularization (11). It was proven that metabolic changes in tumor tissue generally occur before changes in anatomical structure (12–14). Increased rate of aerobic glycolysis can be used to detect areas of malignancy and tumor growth with 18F-FDG molecules. Therefore, FDG PET may have a role complementary to other imaging modalities (12–14).

In this study, we tried to evaluate the role of FDG PET in diagnosing primary tumor and axillary involvement, as well as initial staging in recently diagnosed breast cancer patients, by comparing it with US and MG. According to our results, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in primary breast cancer diagnosis are 77%, 50%, 77%, and 22%, respectively. The sensitivity, specificity, and PPV rates that we found were similar to those reported by Avril et al. in their study of 144 patients (80.3%, 75.5%, and 96.6%, respectively) (14). Sensitivity rates for palpable and nonpalpable lesions in our study were 77% and 80%, respectively. In a study of 170 patients, sensitivity rates for tumors smaller than and greater than 1 cm were 57% and 91%, respectively (14). The sensitivity value obtained for the palpable lesions in this study was higher than the value obtained for nonpalpable lesions and/or lesions smaller than 1 cm in size, which was consistent with previous literature data.

FDG PET's specificity for discriminating between benign and malignant lesions is approximately 50%, whereas infections, inflammation, fibroadenomas, ductal adenomas, and some granular cell tumors may show FDG uptake and cause false positive results. In some previous reports, the false positivity rate has been reported as 5%–10%; this rate was only 2% in our patient group. The cause of this may be the fact that all patients in our group who underwent FDG PET scanning had either breast cancer diagnosis or a lesion highly suspicious for breast cancer.

The mean SUV for malignant lesions was 4.14 ± 2.84 in our study. It was reported in previous studies that a SUV higher than 2.5 for tumors larger than 1 cm would indicate a 90% probability of malignancy. Dehdashti et al. reported that the SUV for malignant breast lesion was 4.5 ± 2.8, while the SUV was 1.05 ± 0.41 for benign ones (15). Avril et al. reported that the SUV of malignant tumors was 2.5-fold that of benign lesions. On the other hand, Adler et al. reported that FDG accumulation is correlated with the pathologic grade of the tumor (16). Slowly growing or well-differentiated subtypes such as tubular or lobular carcinoma and carcinoma in situ show low FDG uptake (14,17). Lesions smaller than 1 cm, which have lower tumor burden, may show lower FDG uptake or may be missed as a result of limited system resolution (17).

Previous studies conducted by Avril et al., Adler et al., and Neiweg et al. reported false negativity rates of 19.7%, 4%, and 9%, respectively (14,18,19). Specifically, Adler et al. reported FDG accumulation was correlated with the pathologic grade of the tumor (18). In our study, the false negativity rate for FDG PET was 21.5%; this was not statistically different from that obtained by MG or US. FDG PET has difficulty in detecting small-sized tumors. In addition, FDG PET has limited use as a screening method because of increased whole-body radiation exposure dose, low sensitivity in some kinds of breast tumors, and high expense (14,20).

Staging of axillary lymph nodes is known as one of the most important prognostic factors in breast cancer, where physical examination has sensitivity as low as 50% (4). Computed tomography (CT), US, and magnetic resonance imaging (MRI) do not have enough sensitivity to demonstrate every axillary metastasis. The sensitivity of FDG PET in demonstrating axillary lymph nodes (50%) was greater in comparison to that of MG (40%) in our study group, although it has been shown to have high false negative results in lymph nodes smaller than 1 cm (13,21,22). FDG PET has 85% sensitivity in detecting mediastinal and internal mammary lymph node involvement, while the sensitivity of CT is around 54% (23). Today, sentinel lymph node biopsy (SLNB) is the most advanced technique for detecting axillary lymph node metastases in primary

breast cancer. Although FDG PET cannot replace SLNB due to its low sensitivity (31%), it may have a complementary role in this subset of patients (24).

FDG PET has a sensitivity of 80%–97% in determining distant metastases, while specificity is 75%–94% (25,26). As the majority of our cases consisted of early-stage disease, 11 patients (19%) had distant metastases proven by FDG PET, which is responsible for this relatively low rate.

FDG PET results also have significant effects on treatment planning. In previous studies, it was found that FDG PET imaging identified involved lymph nodes or distant metastases not known before in 20% of patients, which changed clinical management in 58% (27). Similarly, in our study, FDG PET altered clinical management and staging, which were determined by other methods, in 41 patients (52%). Of those 41 patients, 33 patients (41%) were downstaged and 8 patients (11%) were upstaged. The results of our study are consistent with previous studies on this issue.

FDG PET's sensitivity is equal to that of bone scanning, but it has a higher specificity (28). Although Cook et al. reported that they had identified more bone metastases using FDG PET than with scans, there was no statistically significant difference between either test (29). FDG PET imaging is thus not an alternative to bone scanning, but it has a complementary role for detecting bone metastases as recently supported by several articles (30,31).

Although high primary tumor sensitivity rates were reported in previous studies, it is known that the results can be influenced by histological grade, tumor type, tumor size, and image reconstruction. The functional characteristics of breast tissue may be helpful when MG and US have discrepant or inconclusive results. Precise correlation of PET images with those from other conventional techniques and the introduction of new agents may give rise to reduced biopsies of benign growths (32,33). More sophisticated and organ-targeted newly developed imaging systems like positron emission mammography may help reduce the discrepancy between radiologic and molecular imaging.

FDG PET/CT imaging may help early diagnosis of malignant breast lesions in inconclusive MG/US findings and may change the treatment protocols by revealing multicentric or multifocal disease, contributing to noninvasive staging of breast cancer. As FDG PET has a low resolution in well-differentiated tumors and low sensitivity both in detecting in situ cancers and axillary lymph node involvement, it cannot be used as a screening test.

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