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Role of preoperative 18-FDG- PET/CT in early-stage breast cancer upstaging and modification of treatment

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Original Article

Abstract

Purpose: The aim of this study was to assess the diagnostic and therapeutic impact of preoperative positron emission tomography and computed tomography (PET/CT) in the initial staging of patients with early-stage breast cancer. **Methods:** A total of 72 consecutive patients (age: range 24-78 years, mean 51 years), with newly diagnosed operable breast cancer (Infiltrating Ductal carcinoma: Lobular carcinoma: Others - 49:15:8) with tumor size 10-65 mm were examined preoperatively. All patients underwent conventional assessment imaging modalities like mammography, breast/axillary ultrasound and PET/CT. **Results:** PET/CT identified a primary tumor in all but two patients. PET/CT solely detected unsuspected distant metastases (bones, lung, brain etc) in 9 patients and new primary cancers (endometrium and lung) in another two patients, as well as 11 cases of extra-axillary lymph node involvement. In 6 patients, extra-axillary malignancy was detected by PET/CT only, leading to an upgrade of initial staging in 9% (6/70) and ultimately a modification of planned treatment in 12% (9/70) of patients. PET/CT evaluation led 5 patients of stage II A to stage IV, 3 patients of stage II B to stage IV and 1 patient to Stage IIIB which further modified treatment plan from an adjuvant to a metastatic approach. **Conclusion:** PET/CT is a valuable tool to provide information on extra-axillary lymph node involvement, distant metastases and other occult primary cancers. Preoperative ^{18}F fluorodeoxyglucose PET/CT has a substantial impact on initial staging and on clinical management in patients with early-stage breast cancer.

Keywords: Breast cancer, Initial staging, PET/CT, Upstaging, Treatment modification

1. Introduction

Worldwide, breast cancer accounts for 22.9% of all cancers (excluding non-melanoma skin cancers) in women.[1]In 2008, breast cancer caused 458,503 deaths worldwide (13.7% of cancer deaths in women).[1] Prognosis and survival rates for breast cancer vary greatly depending on the cancer type, stage, treatment, and geographical location of the patient. As per AJCC (American joint committee for cancer) tumors less than 2cm is included in T1; tumor size of 2-5cm is T2 and more than 5 cm is T3 stage. Early breast cancers comprise of T1 and T2 with or without axillary lymph nodal involvement. Breast cancers are notorious for distant metastases. In presence of lymph nodal or extranodal metastases, treatment protocol changes entirely. Therefore, it is necessary to correctly stage the patient for optimization of therapy. For initial assessment of primary breast cancer, mammography is still the most widely utilized modality usually complemented with ultrasound (US) for the evaluation of axillary nodal involvement. Other conventional imaging modalities commonly offered are chest X ray, axillary ultrasound, computed tomography, and positron emission tomography. Combined positron emission tomography and computed tomography (PET/CT) has widely replaced PET as a clinical tool since PET/CT has demonstrated diagnostic superiority compared with PET alone.[2,3]For initial and recurrent breast cancer staging, PET/CT is found to be more accurate than conventional imaging methods in detecting extra-axillary nodal involvement and distant

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metastases.[4-9] In a prospective study of 60 patients with large (>3 cm) primary breast tumors, it was shown that PET/CT changed the initial staging in 42% of patients, but so far other studies published have been retrospective in nature.[5] Therefore, the role of PET/CT in the initial staging of breast cancer remains unclear.

The purpose of the present study was to prospectively assess the clinical impact of preoperative PET/CT in the initial staging of newly diagnosed early breast cancer and to evaluate the potential role of PET/CT in future management of breast cancer patients.

2. Methods and Materials

2.1. Patient Population

From January 2009 to May 2012, 72 consecutive patients (age range 24-78 years, mean 51years, histology infiltrating ductal carcinoma: lobular carcinoma: others - 49:15:8) with newly diagnosed breast cancer scheduled for surgery were included in this prospective study. None of the patients received anticancer therapy or were subjected to curative surgery prior to PET/CT. Patients were subjected to clinical examination and those with operable tumor of more than 2 cm with no clinical suspicion of bilateral cancer, metastases or N3 nodal disease at the time of diagnosis were included. Patients with inflammatory breast cancer, pregnant women as well as patients suffering from uncontrolled diabetes, claustrophobia were excluded. The diagnosis of breast cancer was confirmed by histopathology in all patients and the stage of cancer was assessed by physical examination, mammography, US of the chest wall and axilla and chest X-ray. All study participants provided written informed consent before inclusion.

2.2. PET/CT imaging

All ^{18}F FDG PET/CT scans were carried out using a GE Discovery BGO PET/CT scanner (GE Medical Systems). Patients fasted for at least 6 h before i.v. injection of 370 MBq FDG in the antecubital vein contralateral to the breast cancer. After the FDG injection, patients were encouraged to drink small quantities of oral contrast media (500ml, Ioversol, Optiray-350, Ttco health care Canada,7500, Ponite Claire Quebec).Imaging was carried out 60 min after the administration of FDG in empty bladder. Patients are positioned supine with their arms raised over their heads. Simultaneous contrast enhanced whole body CT images with a breath held CT were obtained from the PET/CT scanner just prior to PET acquisition with the multidetectoreight-slice spiral CT scanner. With a prescan start delay of 40 s, i.v. contrast media was injected with an automatic injection system (Cincinnati, Ohio,9000 ADV,Lieberl-Flarsheim). Whole-body PET scan was acquired from the head to mid-thigh using eight axial fields of view with an acquisition time of 3 min per bed position. The CT data were used for attenuation correction of the PET data. Both image sets were reconstructed in axial, coronal, and sagittal images with a slice thickness of 3 mm. A nuclear medicine physician and a radiologist in collaboration interpreted the PET and the fused PET/CT images. The effective radiation dose for the PET/CT scan was 18 mSv with 8 mSv from the FDG dose and 10 mSv from the CT scan.[10]

2.3. Image interpretation

The PET/CT images were analyzed visually. The maximum standardized uptake value (SUV max) from the primary tumor was used for further analysis. SUV is a semiquantitative analysis of radiotracer uptake and is defined as the ratio of radiotracer activity per milliliter of tissue to the activity in the injected dose corrected for decay and the patient's body weight.[11] Except for the primary tumor site, all foci with pathologic FDG uptake higher than liver activity were reported as positive and suspicious for malignancy if the uptake was focal and related to anatomical structures or pathological findings on the corresponding CT slices. More diffuse pathological sites of uptake with SUV of less than 2.5 was reported as non-malignant inflammatory changes and therefore reported as negative.

2.4. Standard of reference

Distant metastases/new primary cancers were confirmed histologically by biopsy. Where biopsy was not possible or feasible, follow-up PET/CT or other imaging modalities was used as reference.

2.5. Statistical methods

Sensitivity and specificity were calculated using standard methods. Sensitivity and specificity measures the proportion of correctly identified positives and negatives, respectively.

3. Results

A total of 72 consecutive patients with newly diagnosed breast cancer were included in this study. Patient and tumor characteristics in our study group are listed in Table 1.

PET/CT identified the primary tumor in 70/72 patients with a sensitivity of 97%. The two PET-negative tumors were either invasive ductal (n=1, size: 22 mm) or invasive lobular carcinoma (n = 1, size: 15 mm). PET/CT detected 14/72 patients with axillary lymph node metastases. One case proved to be false positive for FDG PET as there were no malignant cells on pathological examination. Extra-axillary lymph node involvement was diagnosed in 6 patients by PET/CT in the internal mammary chain (n= 4) and supraclavicular region (n=2). PET/CT detected 8 sites of distant metastases in nine patients (13%), comprising bone (n=4) (Figure 1), ovary (n=1), lung(n=2) and liver (n=1) metastases (Figure 2). Of these 8 cases, histological examination revealed 2 of them to be new cases of co existing

primary cancers in lung (adenocarcinoma, stage Ib) and in ovary instead of distant metastases.

Nine patients had distant metastases which were confirmed by either biopsy or other imaging methods. Clinical follow up was done in those cases where biopsy site was not feasible or accessible. In total, 15 sites of extra-axillary metastases in 9 patients were detected by PET/CT only (Table 2) leading to upgradation of initial staging in 13% (9/70) of patients and modification of planned treatment in 10% (7/70) of patients (Table 2). PET/CT evaluation led 5 patients of stage II A to stage IV, 3 patients of stage II B to stage IV and 1 patient to Stage IIIB which further modified treatment plan from an adjuvant to a metastatic approach (Table 3). The standard treatment of early stage breast carcinoma is modified radical mastectomy followed by adjuvant chemotherapy. Out of 9 patients, 5 patients PET/CT not only upstaged breast cancer but modified management also. 5 patients were shifted to metastatic approach (chemotherapy is offered first to patients) from adjuvant treatment (Table 3), bisphophonate included and referred for irradiation if required (Table 3 patient number 7).

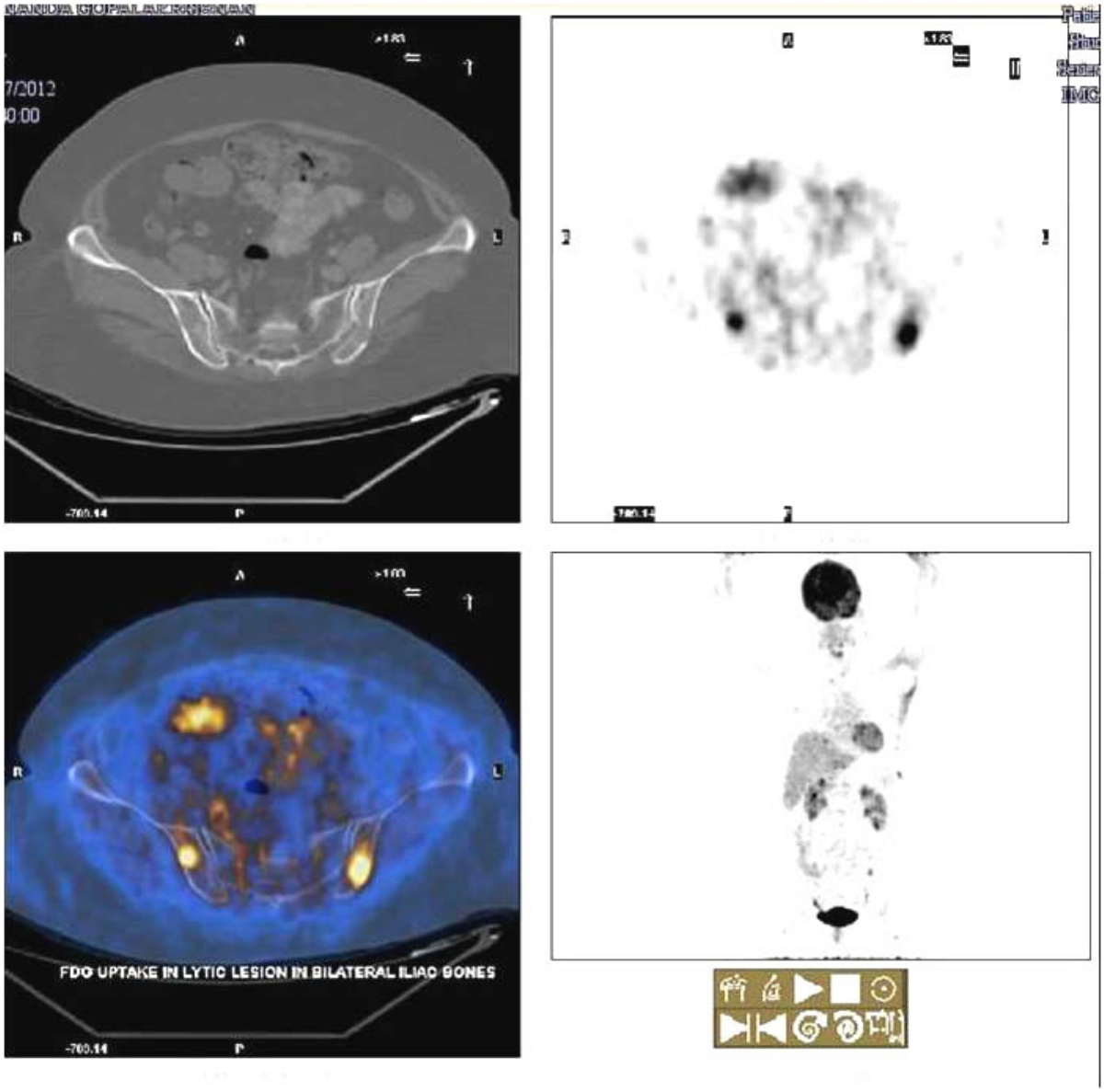

Figure 1: 18-F FDG PET/CT reported focal abnormal FDG uptake in lytic lesions in bilateral iliac bones. (SUV Max 7.4).

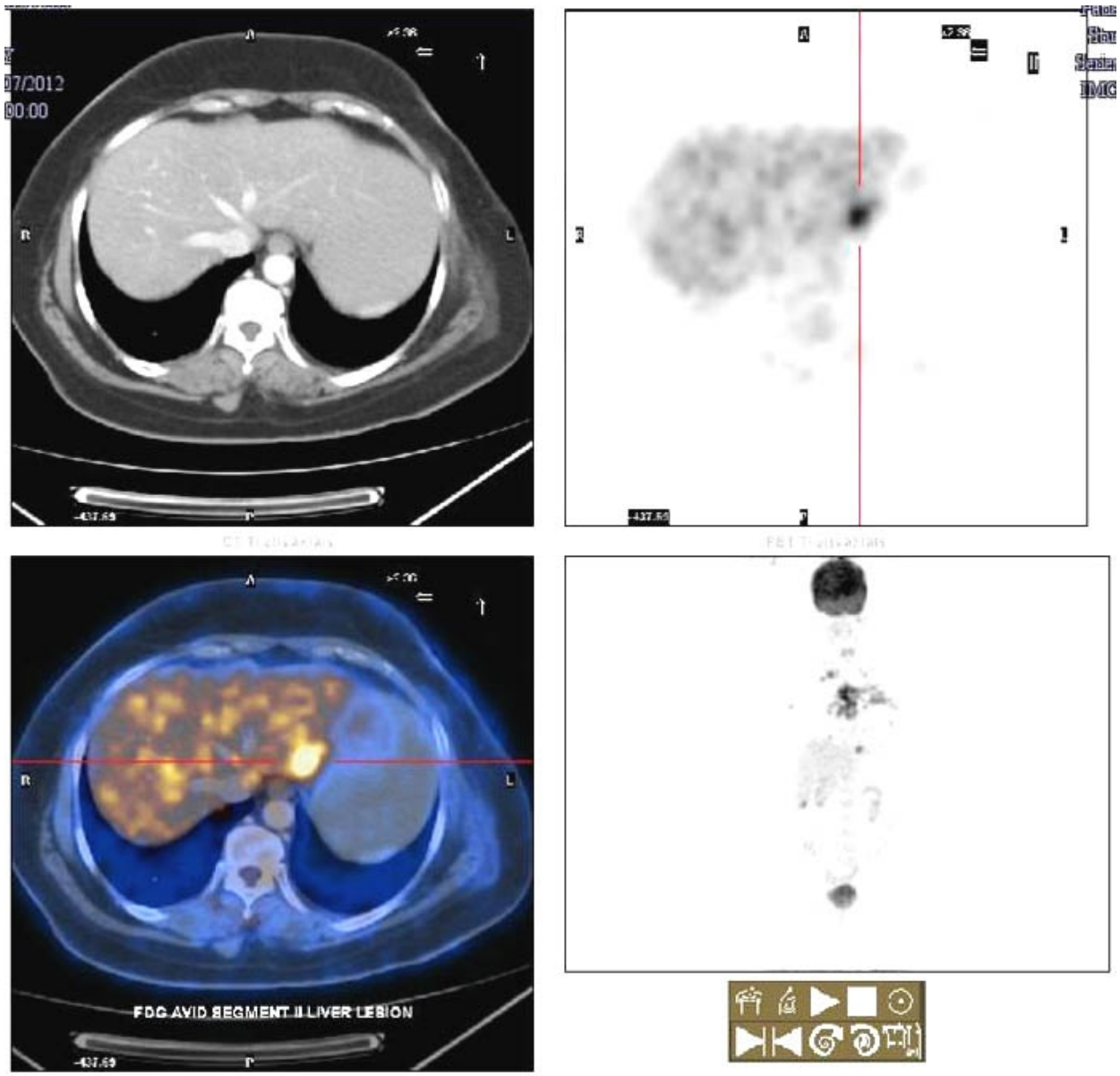

Figure 2: 18-F FDG PET/CT reported focal abnormal FDG uptake in hypodense lesion in segment II of liver (SUV Max 10.9).

Table 1: Various factors in patient and tumor characteristics.

Characteristics	Subdivisions	Initial patient population	Patient population with change in management
Age (years)	Mean	51	40
	Range	24-78	29-51
Histopathology	Infiltrating Ductal carcinoma	49	2
	Lobular carcinoma	15	4
	Others	8	3
Tumor size (mm)	Mean	38	44
	Range	10-65	24-64
ER	+ve	52	5
	-ve	20	4
PR	+ve	40	2
	-ve	30	5
	Unknown	2	2
HER 2	+ve	18	2
	-ve	54	7
SUV max (gm/ml)	Mean	19.3	31.3
	Range	1.2-36.2	13.2-36.2

Table 2: Sites of distant metastases detected by 18 F-FDG PET/CT which further changed initial TNM staging of primary preoperative breast malignancy.

Patient no	PET/CT-positive disease	Initial stage	Final stage
1	Bone metastases	T2N0M0	T2N0M1
2	Internal mammary LN	T2N1M0	T2N3M0
3	Ovaries, bone and internal mammary LN	T2N1M0	T2N3M1
4	Supraclavicular LN	T2N1M0	T2N3M0
5	Internal mammary LN and lung	T2N1M0	T2N3M1
6	Bone metastasis	T2N1M0	T2N1M1
7	Internal mammary LN and bone	T2N1M0	T2N3M1
8	Liver metastases	T2N0M0	T2N0M1
9	Supraclavicular LN	T1N1M0	T1N3M0

Table 3: Upstaging of primary breast malignancy in 9 patients along with modification in management.

Patient no.	Initial stage	Final stage	Treatment Modification
1	Stage IIA	Stage IV	Adjuvant to a metastatic approach. Bisphosphonate was included
2	Stage IIB	Stage III C	Irradiation if axillary LN positive
3	Stage II A	Stage III C	Adjuvant to a metastaticapproach.A bisphosphonate was included
4	Stage II B	Stage III C	None
5	Stage II A	Stage IV	Adjuvant to a metastaticapproach.
6	Stage II A	Stage IV	Adjuvant to a metastatic approach. Bisphosphonate was included
7	Stage II B	Stage IV	Adjuvant to a metastatic approach. Focused irradiation was included
8	Stage IIA	Stage IV	Additional surgery and adjuvant chemotherapy of the tumors.
9	Stage II A	Stage IIIB	None

4. Discussion

Discussions The purpose of this study was to prospectively assess the role of preoperative FDG PET/CT in the initial staging of cT2-3 breast cancer. In patients with breast cancer, correct staging of the disease is mandatory to select the correct treatment protocol. For the tumor localized to extra nodal or distant metastases, patient are treated with adjuvant therapy, surgery followed by chemotherapy, but locally advanced tumors, advanced axillary dissemination with the evidence of distant metastases treatment protocol changes from curative to palliative approach. These patients are commonly treated with neoadjuvant chemotherapy followed by definitive surgery, post operative chemotherapy and external radiation. Henceforth accurate initial staging of patients with breast cancer is essential for precise prognostication and optimal choice of therapy. 18-Fluorodeoxyglucose (18-FDG) PET demonstrates abnormal metabolic features associated with malignancy that often precede morphologic findings demonstrated with anatomic imaging. Positron emission tomography (PET) and PET/computed tomography (CT) are increasingly used for oncologic imaging. Combined PET/CT allows more precise anatomic localization of PET abnormalities and has been shown to improve diagnostic accuracy.[12] In our study, PET/CT solely detected distant metastases (bones, lung, liver etc) in 9 patients and new primary cancers (endometrium and lung) in another two patients. In 6 patients, extra-axillary metastases was detected by PET/CT only, leading to an upgrade of initial staging in 9% (6/70) and ultimately a modification of planned treatment in 12% (9/70) of patients. In present study, PET/CT evaluation led 5 patients of stage II A to stage IV, 3 patients of stage II B to stage IV and 1 patient to Stage IIIB. In previous studies, PET/CT led to a change in stage in up to 42% of cases, resulting in a change of patient management in 13%–32% of cases.[5, 8, 14, 15] In studies with a 42% change of stage, a substantial part of the changes were due to axillary lymph node metastases detected by PET/CT only,[14]which accounts for the large difference in patients with a change of stage detected by PET/CT only as shown in this study. Reasons for the relative variation in frequency of change of treatment in this study could be due to the differences in selection of patients. Several earlier studies included more high-risk and heterogeneous populations.[15]

In present study, PET/CT reported two synchronous co existing primary malignancies; lung adenocarcinoma and other being endometrial carcinoma. The incidental detection of coexisting primary tumors has been reported in previous PET/CT studies [16] and it is well established that cancer patients have a higher risk and higher incidence of co existing dual or new primary tumors. From the two examples in our study, it is plausible that the early detection of the new primary cancer is beneficial to patients. Patient identified with primary lung cancer received curative surgery with no adjuvant treatment and is still recurrence free >25 months after diagnosis whereas other patient diagnosed with endometrial/ovary cancer received both primary surgery (oopho-hysterectomy) and adjuvant chemotherapy and is also recurrence free >27 months after diagnosis.

In our study, a significant proportion of patients were found to have extra-axillary metastases that subsequently led to modification of treatment.[17,18] Whether or not a change in disease stage, the treatment at initial assessment leads to a survival benefit is unknown and also requires further studies.

5. Conclusion

in this study, we found that FDG PET/CT is a valuable tool to provide information on extra axillary lymph node involvement, distant metastases and other occult primary cancers. In the initial stage assessment, preoperative FDG-PET/CT has a substantial impact on staging and on clinical management and we suggest that PET/CTcould be considered in the initial assessment of patients with newly diagnosed node-positive early-stage breast cancer >2 cm.

Conflict of Interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Hayashi M, Murakami K, Oyama T, *et al*. PET/CT supports breast cancer diagnosis and treatment. Breast Cancer. 2008;15(3):224–30.
2. Bar-Shalom R, Yefremov N, Guralnik L, *et al*. Clinical performance of PET/CT in evaluation of cancer: additional value for diagnostic imaging and patient management. J Nucl Med. 2003;44(8):1200–9.
3. Tatsumi M, Cohade C, Mourtzikos KA, *et al*. Initial experience with FDG-PET/CT in the evaluation of breast cancer.Eur J Nucl Med Mol Imaging. 2006;33(3):254–62.
4. Schirrmeister H, Kuhn T, Guhlmann A, *et al*. Fluorine-18 2-deoxy-2-fluoro-D glucose PET in the preoperative staging of breast cancer: comparison with the standard staging procedures. Eur J Nucl Med. 2001;28(3):351–8.
5. Fuster D, Duch J, Paredes P, *et al*. Preoperative staging of large primary breast cancer with [18F] fluorodeoxyglucose positron emission tomography/computed tomography compared

with conventional imaging procedures. J Clin Oncol. 2008;26(29):4746–51.
6. Dose J, Bleckmann C, Bachmann S, *et al*. Comparison of fluorodeoxyglucose positron emission tomography and "conventional diagnostic procedures" for the detection of distant metastases in breast cancer patients. Nucl Med Commun. 2002;23(9):857–64.
7. Klaeser B, Wiederkehr O, Koeberle D, *et al*. Therapeutic impact of 2-[fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography in the pre- and postoperative staging of patients with clinically intermediate or high-risk breast cancer. Ann Oncol. 2007;18(8):1329–34.
8. Landheer ML, Steffens MG, Klinkenbijl JH, *et al*. Value of fluorodeoxyglucose positron emission tomography in women with breast cancer. Br J Surg. 2005;92(11):1363–7.
9. Dirisamer A, Halpern BS, Flory D, *et al.* Integrated contrast-enhanced diagnostic whole-body PET/CT as a first-line restaging modality in patients with suspected metastatic recurrence of breast cancer. Eur J Radiol. 2010;73(2):294–99.
10. Jessen K, Panzer W, Shrimpton P. European Guidelines on Quality Criteria for Computed Tomography. Luxemburg: Office for Official Publications of the European Communities 2000. [EUR 16262].
11. Hubner KF, McDonald TW, Niethammer JG, *et al*. Assessment of primary and metastatic ovarian cancer by positron emission tomography (PET) using 2-[18F]deoxyglucose (2-[18F]FDG). Gynecol Oncol. 1993;51(2):197–204.
12. Eubank WB, Mankoff DA, Schmiedl UP, *et al*. Imaging of oncologic patients: benefit of combined CT and FDG PET in the diagnosis of malignancy. AJR Am J Roentgenol. 1998;171(4):1103–10.
13. Fueger BJ, Weber WA, Quon A, *et al*. Performance of 2-deoxy-2-[F-18]fluoro-D-glucosepositron emission tomography and integrated PET/CT in restaged breast cancer patients. Mol Imaging Biol. 2005;7(5):369–76.
14. Jager JJ, Keymeulen K, Beets-Tan RG, *et al*. FDG-PET-CT for staging of high-risk breast cancer patients reduces the number of further examinations: a pilot study. Acta Oncol. 2010;49(2):185–91.
15. Groheux D, Moretti JL, Baillet G, *et al*. Effect of (18)F-FDG PET/CT imaging in patients with clinical stage II and III breast cancer. Int J Radiat Oncol Biol Phys. 2008;71(3):695–704.
16. Gil-Rendo A, Zornoza G, Garcia-Velloso MJ, *et al*. Fluorodeoxyglucose positron emission tomography with sentinel lymph node biopsy for evaluation of axillary involvement in breast cancer. Br J Surg. 2006;93(6):707–12.
17. Wahl RL, Siegel BA, Coleman RE, *et al*. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. J Clin Oncol. 2004;22(2):277–85.
18. Kim J, Lee J, Chang E, *et al*. Selective sentinel node plus additional non-sentinel node biopsy based on an FDG-PET/CT scan in early breast cancer patients: single institutional experience. World J Surg. 2009;33(5):943–9.