

Breast Cancer Recurrence Diagnosis Suspected on Tumor Marker Rising

Value of Whole-Body 18FDG-PET/CT Imaging and Impact on Patient Management

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BACKGROUND: Breast cancer recurrence is often suspected on tumor marker rising in asymptomatic patients. The value of fluorine-18 fluorodeoxyglucose (18FDG)-positron emission tomography/computed tomography (PET/CT) imaging to detect recurrence and its subsequent impact on patient management were retrospectively assessed. **METHODS:** PET/CT scans were performed on 228 asymptomatic patients (mean, 60.8 years; range, 30-91 years) presenting with rising CA 15-3 and/or CEA serum levels. **RESULTS:** PET/CT scans were positive in 181 patients (79.5%) and normal in 47 patients, whereas 187 true recurrences were diagnosed. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET/CT imaging for detection of breast cancer recurrence were 93.6%, 85.4%, 96.7%, 74.5%, and 92.1%, respectively. When compared with the standard workup available in 67 patients, PET/CT imaging had a higher sensitivity and accuracy (94.5% vs 33% and 94% vs 48%, respectively). Recurrences were confirmed by pathology, conventional imaging techniques, or radiological and clinical follow-up beyond 1 year (mean, 34 months; range, 12-67 years) in 32, 130, and 25 patients, respectively. The diagnosis of recurrence led to a treatment modification in 123 patients (54%). **CONCLUSIONS:** 18FDG-PET/CT imaging is an efficient technique to detect breast cancer recurrence suspected on tumor marker rising in asymptomatic patients. It may thus contribute to improve patient management, providing an earlier diagnosis with complete whole-body staging as a “one-stop shop” procedure. *Cancer* 2011;117:1621-9. © 2010 American Cancer Society.

KEYWORDS: 18FDG-PET/CT, breast cancer, recurrence, patient management, CA 15-3, CEA, tumor marker.

Breast cancer is the most frequent cancer in women from Western countries. Its incidence has progressively increased for the past 30 years, whereas the specific mortality rate is relatively stable.¹ This is a result of both extensive screening and great therapeutic strides.² Nevertheless, around 30% of breast cancer patients are likely to develop recurrence, a bad prognostic event in the course of the disease. Recurrence characteristics (local or metastatic, isolated or multiple localizations, bone or visceral localizations, pathology) are critical for patient management because they have an impact on the decision-making process, helping to select the most adequate treatment: surgery, radiotherapy, chemotherapy, endocrine therapy, or combined modalities.

According to international and scientific guidelines, breast cancer follow-up is based on clinical examination and bilateral mammogram only. Serum tumor markers and conventional imaging techniques (CITs) are used by many physicians, but without clear recommendations. Cancer antigen 15-3 (CA 15-3) and, to a lesser extent, carcinoembryonic antigen (CEA) are the tumor markers most strongly associated with recurrence in asymptomatic breast cancer patients.^{3,4} However, both lack specificity, and the American Society of Clinical Oncology (ASCO) does not recommend their use in routine follow-up of patients treated for breast cancer.⁵ Moreover, tumor marker rising does not predict the number of involved sites or their localization.

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So far, no published study has shown a significant benefit of CIT in screening for recurrence, apart from mammograms focusing on local and contralateral recurrence.⁶ Many studies have suggested that fluorine-18 fluorodeoxyglucose–positron emission tomography (FDG-PET) might improve the rate of detection of breast cancer recurrence.⁷⁻¹⁵ Thus, in a meta-analysis published in 2005,¹⁶ FDG-PET was found to be more sensitive than CIT in the detection of breast cancer recurrence. Such a conclusion supported the hypothesis of earlier detection of metabolic abnormalities deemed prior to morphologic changes. Moreover, FDG–positron emission tomography/computed tomography (PET/CT) yielded information on the functional activity of the recurrence sites and a general picture based on whole-body acquisition, with a high signal-to-noise ratio. Although no breast cancer follow-up recommendation integrating FDG-PET has been published, the ASCO committee has emphasized its potential role in this indication and the need for further validated data.¹⁷ It should be noted that some retrospective studies showed that FDG-PET imaging was more sensitive than serum markers (CA 15-3 and/or the MUC-1 gene–derived glycoprotein CA 27.29) or circulating tumor cells in detecting breast cancer recurrence.^{11,18} The combination of serum markers with imaging techniques was suggested for the follow-up of various tumors to change the treatment at an early stage of recurrence,¹⁹ as in ovarian cancer follow-up.²⁰ For breast cancer, an isolated increase of CA 15.3 in serum is still considered a sensitive indicator of occult recurrence; however, it does not remain sufficient to initiate decision making. Given the high potential value of FDG-PET to diagnose breast cancer recurrence found in several studies,⁷⁻¹⁵ we performed a retrospective analysis of asymptomatic breast cancer patients in whom FDG-PET/CT scan was performed because of rising tumor markers, addressing the issue of its impact on patient management.

MATERIALS AND METHODS

Patient Population

We reviewed the medical files of 378 women followed up in our institution between October 2002 and October 2007 after initial breast cancer treatment who presented with rising CA 15-3 and/or CEA serum levels and who underwent a PET/CT scan. Data regarding associated workup (CIT, pathology) and following treatments were derived from medical files. Our institutional review board does not require the patients' approval or informed con-

sent for the review of patient files and images. An increased serum level of tumor markers was defined as a value greater than 30 UI/mL for CA 15-3 and greater than 5 ng/mL for CEA. We also included patients with serum tumor marker levels that were consistently within normal range but that rose significantly (more than 50%) between 2 subsequent samples ($n = 6$).

Conventional Workup

CIT prescription was heterogeneous because of the lack of consensus for this indication. One hundred and eighty patients had conventional studies within the 4 months preceding the PET/CT scan (mean, 22 days; range, 1-118 days). Sixty-seven patients underwent a complete workup (considered standard in our institution), including chest x-ray, abdominal and pelvic ultrasound, and bone scintigraphy. Another 113 patients underwent either an incomplete standard workup or a CT scan.

PET/CT Imaging

A PET/CT scan was performed 60 minutes after injection of 18F-FDG, using a dedicated PET/CT system (Discovery LS; General Electric Medical System, Milwaukee, WI). Patients were instructed to fast for at least 6 hours before injection, except for glucose-free oral hydration. Blood glucose was measured before injection of the tracer to ensure a level lower than 9 mmol/L. The injected dose of 18F-FDG was 4-5 MBq/kg. After injection, patients were kept in rest conditions under a blanket and without any stimulus. Acquisition was performed in 2-D mode, from skull to midthigh, with 5-7 bed positions of 4-5 minutes each. Patients were allowed to breathe normally (shallow breathing) during the PET and CT acquisitions. Patients were in the supine position. Non-contrast-enhanced CT images were acquired with the following parameters: 40 mAs, 140 kV, 5-mm section thickness, 0.8 seconds per CT rotation, 22.5 mm/s table speed. This acquisition was used for attenuation correction and fusion and also for diagnosis. Immediately after the CT, PET data were collected in a caudocranial direction. The CT data were resized from a 512×512 matrix to a 128×128 one to match the PET data and to fuse the images.

In case of abnormal increased FDG focal uptake (glucose utilization exceeding the surrounding tissue or blood pool level), the FDG-PET/CT scan was considered positive, suggesting malignant lesion, and a complementary workup was performed that focused on the sites of FDG uptake.

To be classified as true positive, a recurrence confirmation was required, based on CIT, pathology, or clinical follow-up. To be classified as true negative or false positive, a minimum of 12 months of follow-up was required, with negative CIT and/or repeated PET/CT imaging and clinical examination.

We considered that the 18F-FDG PET/CT scan had an impact on patient management when it induced intra- and intertherapeutic modality changes.

Data Analysis

The PET/CT scans were analyzed by 2 nuclear medicine physicians, each with more than 5 years' experience (M.W., J.L.A., or L.C.). Exams showing discrepancies with pathology findings, CIT, or follow-up were reviewed for special attention.

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of PET/CT were calculated by patients and by recurrence sites. Subgroup distribution homogeneity (eg, false positive vs true positive, lobular vs ductal histology) was analyzed using the chi-square test. A $P < .05$ was considered statistically significant.

RESULTS

Of 368 patients matching our population definition, 128 were not treated or followed up at our institution and were then excluded from the analysis. Another 2 patients who were followed up for less than 12 months after suspicion of recurrence were also excluded. Ten additional patients were removed because of metastases at the time of diagnosis, leaving 228 cases for the final analysis. Baseline patient characteristics are described in Table 1. The median interval between the initial diagnosis and the workup performed for suspicion of recurrence (including the PET/CT scan) was 9 years (range, 1-31 years).

Among these 228 patients, an increased level of CA 15-3, CEA, or both markers was observed in 199, 5, and 24 patients, respectively. The median interval between the latest CA 15-3 assay and the PET/CT scan was 34 days (range, 1-95 days). For all patients, 2 subsequent measurements of serum marker levels were systematically performed within 1-2 months to confirm the increased value.

The median follow-up from noticing the increase in the tumor marker was 19 months (range, 1-60 months) for the whole study population and 34 months (range, 12-67 months) for patients with a negative PET/CT scan.

Table 1. Characteristics of Patients (n=228) With Suspected Breast Cancer Recurrence Based on Rising Serum Tumor Markers

Characteristic	n (%)	Mean (range)
Age at diagnosis, y		60.8 (30-91)
Primary tumor treatment		
Surgery	225 (98.7%)	
Chemotherapy	143 (62.7%)	
Endocrine treatment	108 (47.4%)	
Histology		
Invasive ductal carcinoma	173 (75.9%)	
Invasive lobular carcinoma	41 (18%)	
Mixed	7 (3%)	
Other	7 (3%)	
pN status		
pN0	89 (39%)	
pN+	127 (55.7%)	
Unknown	12 (5.3%)	
Ellis-Elston grade		
Grade I	36 (15.8%)	
Grade II	132 (57.9%)	
Grade III	49 (21.5%)	
Unknown	11 (4.8%)	
Hormonal receptors status		
HR+	199 (87.3%)	
HR–	26 (11.4%)	
Unknown	3 (1.3%)	
HER2 status		
HER2+ 18 (7.9%)		
HER2–	166 (72.8%)	
Unknown	44 (19.3%)	
Triple negative case (HR–/HER2–)	14 (6%)	
Values of serum markers at time of suspected recurrence		
CA 15-3	199 (87.3%)	137.7 U/mL (28-2800 U/mL)
CEA	5 (2.2%)	73 ng/mL (6-774 ng/mL)
Both CA 15-3 and CEA	24 (12.9%)	178 U/mL and 92 ng/mL

The workup following the detection of rising tumor markers led to the diagnosis of 183 recurrences and 4 second primary cancers.

Value of PET/CT Scan

The distribution of recurrence localizations is displayed in Table 2.

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the PET/CT scan for detection of recurrence were 93.6% (175 of 187),

Table 2. Distribution of Recurrence Localizations

Recurrence Localizations	Percentage of Patients (n)
Bone	49.5% (113)
Extra-axillary lymph node area	34% (78)
Liver	21% (48)
Lung and pleura	13.5% (31)
Local and regional	4% (9)
Adrenal gland	2.5% (6)
Pelvis and peritoneum	7.5% (17)

Table 3. PET/CT Imaging Results for the Diagnosis of Breast Cancer Recurrence (Number of Patients)

	Recurrence	No Recurrence	Total
Positive PET/CT scan	175	6	181
Negative PET/CT scan	12	35	47
Total	187	41	228

85.4% (35 of 41), 96.7% (175 of 181), 74.5% (35 of 47), and 92.1% (210 of 228), respectively (Table 3). Among the 175 true-positive patients, 55 had disseminated disease (corresponding to more than 10 increased FDG uptake foci), including 16 patients with only bone metastases. Eighty-six patients presented with visceral involvement, 47 with only bone recurrence, and 5 with isolated locoregional recurrence. Thirty-seven patients had a single site of recurrence. Thirty-two sites of recurrence were confirmed by histopathology: 15 locoregional (11 ipsilateral and 4 contralateral), 3 supraclavicular lymph nodes, 5 bone (Fig. 1), 1 pleural, 3 ovarian, 4 pelvic (peritoneum or uterus), and 1 liver metastases. Another 4 lesions considered malignant on the PET/CT scan were in fact primary tumors on histology (2 bronchogenic and 2 ovarian), confirmed by surgery.

The other sites of recurrence were confirmed by additional CIT (130 sites) or by radiological and clinical follow-up beyond 1 year (25 sites).

The false-positive lesions were mediastinal lymph nodes (n = 2), bone (n = 1), adrenal gland (n = 1), liver (n = 1), and colon (n = 1). The mediastinal lymph nodes were not found on CT or on repeated PET/CT scan (performed without any therapeutic change). The vertebral lesion was not confirmed by MRI; the patient's tumor markers decreased and returned to normal levels without treatment modification. The adrenal gland focus fitted with a benign lesion on an MIBG scintigraphy. The liver

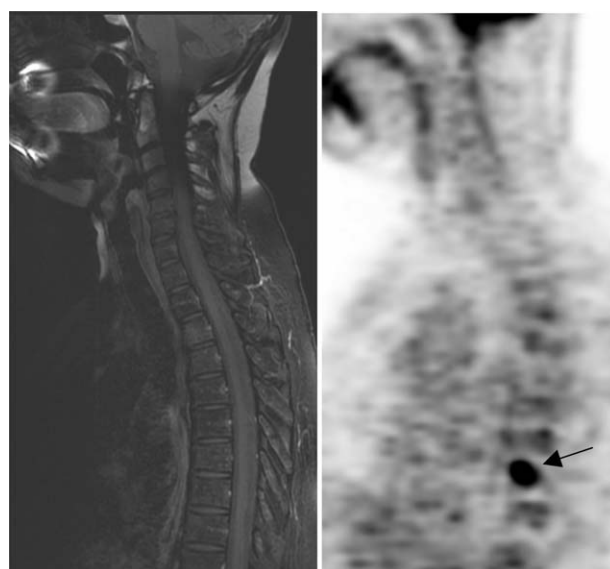


Figure 1. True-positive PET/CT of a vertebral localization (histologically proven) of a 47-year-old woman is shown. On the left is a sagittal view of a negative spine MRI (gadolinium-enhanced T1-weighted images). On the right is a PET/CT scan performed 6 weeks later.

heterogeneity was not confirmed by MRI or by repeated PET/CT scan 6 months later. Both focal increased FDG uptakes in the colon corresponded to benign polyps (villous adenoma) at colonoscopy.

The false-negative patients (n = 12) had recurrence in the breast (n = 1), ipsilateral axillary lymph nodes (n = 5), bone (n = 2), liver (n = 3), lung and pleura (n = 2), distant lymph nodes (n = 2), brain (n = 1), and peritoneum (n = 1). Of these 12 patients, 4 had an initial surgery for invasive lobular carcinoma. Another 2 false-negative cases with proved local recurrence (breast lesion and axillary involvement) might be explained by the small size of the lesions found at surgery (diameter < 1 cm).

Thirty-one sites of recurrence were not shown by PET/CT in false-negative and true-positive patients. These false-negative lesions were detected by CIT in bone (n = 7), liver (n = 6), lung (n = 6), and extra-axillary lymph node areas (n = 5) by histology of the ipsilateral axillary lymph nodes (n = 2), by repeated CT of the adrenal gland (n = 2) and the peritoneum (n = 2), and by MRI of the brain (n = 1). In total, 29 lesions were found by additional CITs and 2 by histopathology.

Specific Entities

Forty-one patients had a lobular cancer. The PET/CT scans was true positive in 32 cases, true negative in 5 cases, and false negative in 4 cases.

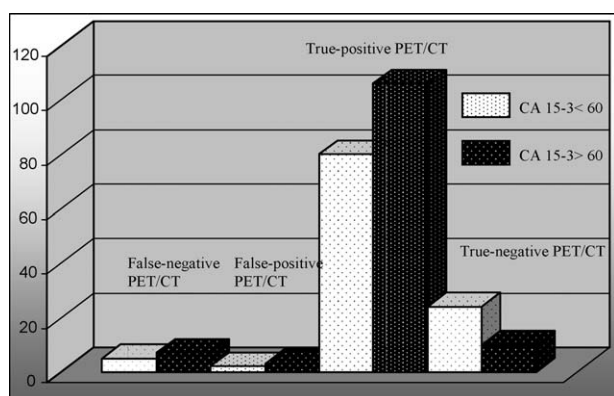


Figure 2. A histogram shows the different groups of PET/CT results expressed as the number of patients against the CA 15-3 blood level (cutoff, 60 UI/mL).

One hundred and seventy-three patients had a ductal carcinoma. Their PET/CT scans were true positive in 131 cases, false positive in 6 cases, true negative in 29 cases, and false negative in 7 cases.

There was no significant difference between lobular and ductal subgroups for the detection of recurrence by PET/CT ($P > .05$), but the groups had very different numbers of patients.

We observed that the rate of patients with HR+ (hormone receptor-positive) primary tumors was higher in our series than the mean rate generally described in breast cancer patients (87.3% versus 70%).

Fourteen patients (6%) had a triple-negative breast cancer (HR and HER2). Their PET/CT scan was true positive in 13 patients and true negative in 1 patient, who did not develop any evidence of recurrence during follow-up. In 3 patients, FDG uptake revealed another primary tumor (ovarian in 2 cases and bronchogenic in 1). In 6 cases, the PET/CT scan was suggestive of disseminated disease, confirmed with CIT and follow-up.

Eighteen patients had prior HER2-overexpressing breast cancer. The PET/CT scan was considered true positive in 14 cases and true negative in 4 patients.

Nine patients with FN results (including 2 patients with lobular carcinoma) were receiving adjuvant endocrine therapy at the time of the restaging PET/CT scan and underwent a second PET/CT scan after treatment withdrawal (median time between second PET/CT and treatment withdrawal, 16 weeks; range, 5-36 weeks). The latter was positive in all patients, showing recurrence in the axilla ($n = 5$), bone ($n = 1$), peritoneum ($n = 1$), pleura ($n = 1$), and multiple sites (brain, bone, and mediastinum: $n = 1$).

Table 4. Comparison of Results of Minimum Workup or CT With Contrast Enhancement and PET/CT Imaging in 114 Patients With Suspected Breast Cancer Recurrence (Number of Patients)

		PET/CT	
		Positive	Negative
CT with contrast enhancement	Positive	20	2
	Negative	18	7
Minimum workup (chest x-ray + abdominal and pelvic ultrasound + bone scintigraphy)	Positive	17	0
	Negative	35	15

The value of a cutoff CA 15-3 serum level was studied using a value of 60 UI/mL, as defined in 2 previous studies.^{9,21} There was no significant difference in the CA 15-3 serum level between false-negative and true-negative PET/CT groups, between true-positive and false-positive groups, and between false-positive and true-negative groups (Fig. 2). But the mean CA 15-3 serum level was significantly higher in the true-positive group than in the false-negative one (166 ± 115 vs 77 ± 52 UI/mL; $P < .001$) and in the true-negative one (166 ± 115 vs 65 ± 56 ; $P < .001$).

PET/CT Compared With Conventional Workup

The conventional workup performed in 180 patients was considered positive in 66 patients and negative in 114 patients. The mean interval between CIT and PET/CT scan was 22 days (range, 1-118 days) for the 180 patients, and 20 days (range, 1-42 days) for the patients with discrepant studies. The standard CIT workup available in 67 patients (Table 4) identified sites of recurrence with sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 33% (17 of 52), 100% (15 of 15), 100% (17 of 17), 30% (15 of 50), and 48% (32 of 67), respectively, versus 94.5% (53 of 56), 91% (10 of 11), 97.5% (53 of 54), 77% (10 of 13), and 94% (63 of 67) for PET/CT.

Whole-body CT with contrast enhancement performed for 47 patients was concordant in 27 patients. Discrepancies between CT and PET/CT were found in 20 patients. Results are detailed in Table 4. Eighteen patients had false-negative CTs and true-positive PET/CT scans. Lesions were localized in bone ($n = 10$), liver ($n = 6$), peritoneum ($n = 6$), mediastinum ($n = 3$), pleura ($n = 2$), and lung and breast ($n = 1$). Two patients had false-negative PET/CT scans and true-positive CT

Table 5. Impact of PET/CT Imaging on Therapy Changes

Therapeutic Modality Induced	Number of Patients (%)
Chemotherapy	48 (21.5%)
Endocrine therapy	21 (9%)
Modification of endocrine therapy	19 (8.5%)
Surgery	18 (8%)
Radiotherapy	17 (7.5%)
Total	123 (54%)

scans; localizations were the axillary lymph node area and the mediastinum, confirmed by follow-up.

PET/CT imaging was more efficient than bone scintigraphy in 12 discordant cases with metastases confirmation by MRI ($n = 8$) or biopsy ($n = 4$). The bone lesions were osteolytic in 3 patients and osteoblastic in 9. The ability of PET/CT to detect osteoblastic lesions was significantly better than that of bone scintigraphy ($P < .01$).

Detection of Recurrence by PET/CT Imaging and Its Impact on Patient Management

Treatment alteration was a direct consequence of detection of recurrence by PET/CT imaging in 123 patients (54% Table 5). Chemotherapy and endocrine therapy were started in 48 and 21 patients, respectively. Endocrine adjuvant treatment was modified in 19 patients. Eighteen patients underwent surgery: mastectomy and axillary lymphadenectomy ($n = 8$), axillary lymphadenectomy ($n = 1$), total hysterectomy with bilateral salpingo-oophorectomy ($n = 5$), resection of lung metastases ($n = 1$), resection of brain metastases ($n = 1$), and resection of bone metastases ($n = 2$). Radiation therapy was delivered to 17 patients.

Only 2 of 35 true-negative patients had their endocrine treatment modified because of rising tumor markers.

DISCUSSION

Detection of Breast Cancer Recurrence

In breast cancer management, locoregional recurrence may benefit from curative treatment based on surgery and/or radiation therapy, whereas distant metastases usually require palliative systemic therapy. A diagnostic modality able to assess the true extent of disease, including the number of sites and their localization, would greatly improve these patients' management. To the best of our knowledge, our series is the first carried out in a large

cohort of patients with suspicion of breast cancer recurrence based only on rising tumor markers. Although our study was also retrospective, it involved a population of women with breast cancer who received homogenous follow-up at a single institution. In our series, PET/CT imaging showed high performance indexes in the detection of recurrence. These results compare favorably with those previously published (Table 6). The combination of PET with CT imaging yields higher performance indexes than does PET or contrast-enhanced CT alone,²² especially in the detection of lymph node metastases.

False-Negative PET/CT Imaging

Of 12 patients with false-negative results, 4 had undergone an initial surgery for invasive lobular carcinoma, which is known to induce false-negative results by FDG-PET.^{23,24}

It is worthwhile to note that 9 patients receiving adjuvant endocrine therapy at the time of their first PET/CT scan had a second exam performed after treatment withdrawal, which then switched to a positive result, while the patients remained asymptomatic. However, they were considered false negatives because only the results of the first PET/CT scan were taken into account. Endocrine therapy reduces cancer metabolism; it could then lead to low FDG uptake by tumor cells.²⁵ Our observations were not numerous enough to recommend endocrine therapy withdrawal before an FDG-PET scan. However, when the first PET scan is negative, it might be useful to interrupt endocrine therapy before performing a second one to look for recurrence.

In 10 true-positive PET/CT scans with false-negative sites, we did not find any particularities in patients or in tumors explaining these discrepant results, except for 1 patient presenting with a lobular carcinoma and lung lesions corresponding to lymphangitic carcinomatosis.

Tumor Biomarkers Cutoff

So far, measurement of CA 15-3 and CEA serum levels are not recommended in the follow-up of breast cancer, given their lack of specificity.²⁶ Before the whole-body PET imaging era, oncologists faced with rising serum markers wondered which investigations should be requested. Nowadays, FDG-PET imaging seems very promising in the management of this critical situation. Two studies^{9,21} showed that the likelihood of discovering recurrence was influenced by the CA 15-3 serum level and its doubling time: it seemed higher when the CA 15-3 serum level was more than 60 UI/mL. In our series, the

Table 6. Review of the Literature: Performance Indexes of PET or PET/CT Imaging in the Detection of Breast Cancer Recurrence

Study	No. of Patients	Indication	Sensitivity	Specificity	Accuracy	Impact of PET/CT Imaging on Patient Management
Veit-Haibach et al, 2007 (PET/CT) Retrospective ¹⁴	44	Suspicion of recurrence	91%			
Radan et al, 2006 (PET/CT) Retrospective ¹³	46	Tumor marker rising	90%	71%	83%	51%
Grahek et al, 2004 (coincidence PET system) Retrospective ¹²	75	Suspicion of recurrence	84%	78%	83%	44%
Gallowitsch et al, 2003 (PET) Retrospective ¹⁰	62	Suspicion of recurrence	97%	82%	90%	
Suarez et al, 2002 (PET) Retrospective ⁹	45	Tumor marker rising	92%	75%	87%	

mean CA 15-3 serum level was significantly higher in the true-positive PET/CT group than in the true-negative and false-negative groups. A low CA 15-3 serum level may decrease PET/CT imaging sensitivity for breast cancer recurrence. Yet this observation was not found by Pecking et al in their study published in 2001.⁸ Because many patients with a CA 15-3 serum level less than 60 UI/mL had true-positive PET/CT scans ($n = 80$), we do not recommend using a cutoff of tumor marker levels as the basis of referring patients for this indication. The doubling time of the CA 15-3 serum level is an important parameter²¹ to take into account, but unfortunately the data available were not usable in our study.

In our study, highly increased CA 15-3 serum level was more frequently observed in cases of multiple lesions or visceral lesions, particularly when there was liver involvement.

Tumoral Phenotype

Triple-negative breast cancer is characterized by a particularly unfavorable outcome.²⁷ In many studies, this subtype has the worst overall survival and the worst disease-free survival. In our series, 14 patients (6%) had a triple-negative breast cancer. Their PET/CT scan was suggestive of liver recurrence and of disseminated disease, both situations that have a poor prognosis. Two patients developed a second primitive ovarian cancer. In the literature, triple-negative breast cancer phenotype is particularly associated with *BRCA1* mutations. However, this mutation was not looked for in either patient.

The high rate of HR+ patients observed in our series is consistent with studies that described a positive correlation between an increase in CA 15-3 serum level and HR status in case of breast cancer recurrence.^{28,29}

Comparison With Conventional Imaging

Several studies have compared FDG-PET with CIT in patients with suspicion of breast cancer recurrence.^{10,13-15} In a series of 37 patients, Radan et al¹³ found congruent results in 19 cases, whereas PET/CT imaging showed recurrence in 4 CT-negative cases and CT was more efficient than PET/CT in 1 case. Two studies^{14,15} have compared PET/CT with contrast-enhanced CT and PET in 44 and 34 patients, respectively, presenting with a suspicion of recurrent breast cancer. The disease stage was more accurately assessed by PET/CT when compared with PET or CT alone.

For those patients with proven breast cancer recurrence, our series confirmed an obvious superiority of PET/CT imaging compared with CIT. Because non-contrast-enhanced CT was used in our study, we were not in the best condition for liver and lymph node assessment. But regarding the skeleton, FDG foci matching osteolytic and/or blastic lesions were an additional argument for bone metastases,¹⁴ although bone scintigraphy and/or MRI remain the gold standard for bone metastasis diagnosis. Bone is the main site of metastatic spread in breast cancer history, as found by PET/CT imaging in our series. In 21 cases, there was no morphologic abnormality found with the low-dose CT. This is known to occur in the case of bone marrow metastases because metabolic changes appear before morphologic ones. PET/CT imaging was more efficient than bone scintigraphy in all cases with discrepancies, with metastasis confirmation by MRI or biopsy, and its ability to detect osteoblastic lesions was significantly better than that of bone scintigraphy, disagreeing with previous studies.³⁰ However, 2 recently published articles found a better specificity for PET/CT than for bone scintigraphy in osteoblastic lesion detection.^{31,32}

In our series, PET/CT imaging identified metastatic deposits in the mediastinum (22%), liver (15%), and lung or pleura (12%). A recent study³³ showed that whole-body MRI was highly sensitive for the detection of bone and liver metastases, but PET/CT imaging seemed to be more sensitive for lymph node involvement; this study finally concluded that the sensitivity and specificity of MRI and PET/CT imaging were very similar. However, it did not clearly yield the criteria and investigations used to confirm malignancy.

Impact on Patient Management

Few studies have evaluated the impact of FDG-PET imaging on the management of patients with breast cancer recurrence. Three series showed that coincidence PET or PET/CT systems led to treatment modifications in about 50% of cases,^{11,12,34} notably by detecting more extensive locoregional disease or distant metastases. Another study¹⁴ showed higher accuracy for PET/CT than for PET or CT alone, although the practical impact on therapeutic management remained moderate. In our observation, restaging performed by PET/CT imaging had an impact on the management of patients in more than 50% of cases. Without solving the debate of the impact of an earlier diagnosis of breast cancer recurrence on survival,³⁵⁻³⁷ our results suggest that this strategy could be more beneficial if used either in some phenotypes or only above a particular CA 15-3 serum level threshold. However, the true impact of this screening strategy should be reassessed prospectively, given the great therapeutic strides accomplished during the past 2 decades, offering new perspectives and contributing to the general improvement in prognosis.

Limits

The current study was a retrospective analysis as were the above-mentioned studies, but we selected patients followed up in a single institution, with a rather standardized therapeutic strategy. However, the lack of a standard CIT workup in our series may have jeopardized the value of the comparison of this workup with PET/CT imaging.

The value of the impact on patient management might be overestimated if we consider that nowadays decision making is mostly oriented by PET imaging.

Systematic pathological confirmation of the malignant character of the detected lesions was not available, but most of the time, the diagnosis of breast cancer recurrence is based on a combination of rising tumor markers

and positive CIT results (probably except for isolated lesions leading to a biopsy/surgical decision).

CONCLUSIONS

In asymptomatic patients with rising tumor markers, FDG-PET/CT imaging is an accurate modality to screen for breast cancer recurrence. It is more sensitive than a conventional imaging workup. Demonstrating the extent of disease, it enables the adjustment of further treatment, providing a general picture in a high-performance “one-stop-shop” procedure. Future directions should prospectively address the potential interference with endocrine treatment and the real impact on patient outcomes.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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