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Comparison of ^{18}F-FDG positron emission tomography/computed tomography and computed tomography in patients with already-treated breast cancer: diagnostic and prognostic implications

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Aim. **The purpose of the study was to assess the comparison of 18F-FDG PET/CT and CT in patients with breast cancer (BC) already treated with primary therapy, in evaluating the diagnostic and prognostic values.**
Methods. **We retrospectively studied 190 patients (187 women and 3 men, mean age 61±11 years) with previous BC (all stages) after surgery and other primary treatments. They underwent within three months CT and ^{18}F-FDG PET/CT examinations for the evaluation of disease status. Disease relapse was confirmed by clinical evaluation and/or radiological findings. Survival curves of disease-free survival (DFS) and overall survival (OS) were computed using Kaplan-Meier method. Cox analysis regression was used to determine predictive factors of DFS and OS.**
Results. **Of the overall 190 patients, 82 (43%) had evidence of clinical and/or imaging disease relapse, while 108 (57%) did not. Sensitivity, specificity, negative predictive and positive predictive values for disease relapse or progression were of 89% *vs*. 77%, 73% *vs*. 53%, 90% *vs*. 75% and 72% *vs*. 55%, respectively for PET/CT and CT. DFS curves were significantly different in patients with both negative and positive PET/CT and CT (log-rank test 33.6; P<0.0001 and 12.7; P=0.003, respectively). OS curves were similar in patients with positive/negative PET/CT and CT (P=NS). By both univariate and multivariate Cox regression analysis positive PET/CT was found to be related to the disease recurrence (HR 0.18 and 0.20, both P<0.0001, respectively).**
Conclusion. **PET/CT is more accurate than CT in identification of disease relapse in a large population of BC patients. In women at high-risk of recurrence, PET/CT imaging can provide the early detection of BC metastases, tailoring a proper treatment.**

KEY WORDS: Breast neoplasms - Positron-emission tomography and computed tomography - Follow-up studies.

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Breast cancer (BC) is the most common tumour among women in all over the world; its management consisting of diagnosis, staging, treatment and the evaluation of disease evolution with follow-up; all of these steps require the use of imaging techniques, particularly in staging assessment, in evaluation of response to treatment, in restaging and in follow-up. The presence of distant metastasis is a key prognostic factor since women with localized disease have a five-year relative survival rate of ~80% compared with 25% for women with metastatic disease.[1] The American Society of Clinical Oncology (ASCO) proposed the revisited recommendation in 2006 for BC reporting that a careful history taking, physical examination, and regular mammography are recommended for appropriate detection of BC recurrence, whereas Computed Tomography (CT) and ^{18}F-Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET) scanning are not recommended for routine BC surveillance.[2]

The aim of the BC follow-up is an early diagnosis of cancer recurrence, with the goal to treat metastases at the earliest stage of development.[3] Conventional imaging procedures (*i.e.*, chest X-ray, abdominal echography and diagnostic CT) often do

TABLE I.—*Characteristics of study population.*

Characteristics	Value
Age (y)	
— Mean	61
— Range	32-86
Histology (N., %)*	
— DCIS	6 (3)
— IDC	130 (68)
— ILC	24 (14)
— Others	16 (9)
Estrogen Receptor (n, %)**††	
— Negative	25 (16)
— Positive	130 (84)
Progesteron Receptors (n, %)**††	
— Negative	40 (26)
— Positive	115 (74)
HerB2**†	
— Negative	33 (21)
— Positive	122 (79)
Triple negative**	
— No	140 (90)
— Yes	15 (10)
Pathological Stage (n, %)	
— 0	3 (2)
— I	79 (42)
— II	64 (34)
— III	40 (20)
— IV	4 (2)

Values are expressed as mean ± SD or number (%) of patients; *Histological measures were available in 176 patients; * Estrogen Receptors (ER), Progesteron Receptors (PgR) and HerB2 expression were available in 155 patients; †IHC: Immunohistochemistry assay; ††ER and PgR were considered negative when <10% on IHC.

not reliably characterized the extent of disease due to difficult in distinguish abnormalities from benign conditions and thus reducing the ability to anticipate the presence of disease. The lung is a common site for BC metastases; therefore, a chest X-ray is generally ordered during the diagnostic process. Contrast enhanced CT scans of the liver, lung and brain are recommended only if metastases are suspected in these areas. Currently, CT scan represents the state-of-the-art modality for staging and restaging of oncological patients, but it losses in sensitivity for small lesions and sub-centimeter lymph node that do not show obvious morphological changes. PET scans have proved effective in detecting soft tissue metastases;[3] according to Morris *et al.*[4] it is useful also in skeletal localizations. The methodology of PET/CT imaging in BC is based primarily on the ability of PET to detect, visualize and quantify extensive disease by means whole-body FDG studies;[5] moreover, more attention for patient preparation and the choice of imaging protocols, such as dual-time-point, are paramount for an accurate diagnosis.[6] In the past, several studies have suggested a diagnostic advantage of combined 18F-FDG PET/CT over CT and PET as morphological and functional imaging procedures alone.[7, 8] Based on this assumption, the aim of our study was to assess the comparison of diagnostic and prognostic values between 18F-FDG PET/CT and CT in BC patients, already treated with primary therapy, during follow-up.

Materials and methods

Patient population

From November 2006 to July 2009, we selected 190 patients (187 women and 3 men) with a mean age of 61±11 years (range 32-86 years) with BC, already treated with primary surgery and neoadjuvant therapy and/or adjuvant treatment (15 only surgery, 49 surgery plus chemotherapy, 50 surgery plus radiotherapy and 76 surgery plus chemotherapy plus radiotherapy). One hundred thirty-seven patients were administered hormonal therapy; at the time of PET/CT imaging only 56 (41%) continued it. Pathological TNM staging was evaluated according to the criteria of the American Joint Committee on Cancer (AJCC). Characteristics of study population were summarized in Table I.

Inclusion criteria

In this retrospective study we included all patients who performed both CT and PET/CT imaging within three months. The following criteria were used to include patients in the study: 1) suspicion of disease relapse at clinical examination; 2) unclear elevation of tumor markers; and 3) doubtful conventional imaging procedures. The interval between primary surgery and PET/CT was 65±5 months. The availability of follow-up data for a minimum of 10 months after scanning was required.

Some CT examinations were performed at our Institution (36%), whereas in many cases outside (64%); thus, for the interpretation of CT imaging, the final report was used (see interpretation of CT data).

All PET/CT scans were performed at our single Institution and at least two expert nuclear medicine physicians read all images. All patients gave their

informed consent for the PET/CT imaging. The research was carried out according to the Declaration of Helsinki (2000) of the World Medical Association. For the retrospective character of the study, none Institutional Review Board approval was required by the National Institution.

Image interpretation of CT images

Written clinical reports of CT images were reviewed and classified as A) negative, if all imaging test were negative for disease; B) equivocal, when abnormal findings were present on any imaging tests but were not interpreted as suspicious for malignancy; C) suspicious, if any test result was clearly described as suspicious for malignancy; or D) positive, if findings were described as consistent with malignancy. To dichotomize the data, negative and equivocal findings were subclassified as negative, and suspicious and positive findings were categorized as positive. Furthermore, all anatomical localizations with abnormal morphology or size were registered and were interpreted as previously described.

PET/CT imaging

Whole-body 18F-FDG PET/CT was performed using a dedicated PET/CT scanner (Biograph 16, Siemens Medical Solutions, Hoffman Estates, IL, USA). The PET component is a high-resolution scanner with a spatial resolution of 4.7 mm and has no septa, thus allowing three-dimensional only acquisitions. The CT portion of the scanner is the 16-slice Somatom Sensation. Together with the PET system, the CT scanner is used both for attenuation correction of PET data and for localization of 18F-FDG uptake in PET images. All patients were advised to fast for at least 6 h before the integrated PET/CT examination. After injection of about 3 MBq of 18F-FDG per kilogram of body weight, patients rested for a period of about 60 min in a comfortable chair. Emission images ranging from the proximal femur and the base of the skull were acquired for 2-3 min per bed position. Acquired images were reconstructed using the attenuation-weighted ordered subset expectation maximization (OSEM) iterative reconstruction, with 2 iterations and 8 subsets. The Gaussian filter was applied to the image after reconstruction along the axial and transaxial directions. The data were reconstructed over a 128×128 matrix with 5.25-mm pixel size and 2-mm slice thickness. Processed images were displayed in coronal, transverse and sagittal planes. PET data were also displayed on a rotating maximum intensity projection (MIP).

Interpretation and analysis of PET/CT imaging

At visual analysis, increased FDG uptake not corresponding to physiological uptake patterns or with higher FDG uptake than the surrounding or contralateral normal tissue and in any foci of increased uptake corresponding to a CT abnormality (soft tissue or visceral sites and or skeletal abnormalities) were recorded as positive for recurrent lesions. The absence of uptake (out of physiological sites) was used to define a negative PET/CT finding. The diagnosis of metastases was also supported by a maximum standardized uptake value (SUV) greater than 2.5 for malignant lesions, only in some doubtful FDG-sites.

Standard of reference

The diagnosis of disease recurrence was established by invasive and non-invasive (radiological or nuclear medicine) follow-up. The diagnosis was verified by clinical follow-up or histological studies in 54 (28%) patients and through consequent imaging studies (7 chest X-rays, 39 thorax-abdominal diagnostic CT, 25 bone scans, 7 abdominal ultrasounds, two nuclear magnetic resonance, 37 PET/CT and 19 both PET/CT and bone scans) in the remaining population. The diagnosis of metastatic disease was obtained by the combination of positive clinical findings and/or the resolution of the lesions after appropriate therapy and/or increase of number/size/FDG-uptake of preexisting lesions, whereas no disease relapse was defined by combination of negative clinical findings and/or negative findings of other studies. In patients without disease relapse, neither change of on-going treatment nor further treatment was performed and a close follow-up with imaging studies was started. Otherwise in patients with clear and well-determined recurrence of disease, the appropriate treatment was planned. The data obtained from the follow-up were compared with CT and PET/CT findings and comparison/agreement between their results were evaluated.

TABLE II.—*Diagnostic accuracies of PET/CT and CT for detecting breast cancer recurrence.*

	PET/CT	CT
Sensitivity	89%	77%
Specificity	73%	53%
PPV	72%	55%
NPV	90%	75%
Accuracy	80%	63%

Statistical analyses

Continuous variables were expressed as a mean ± SD and categorical data as percentage. The endpoints of the present report were to determine: 1) the diagnostic accuracies of CT and PET/CT for the detection of BC recurrence; 2) the comparison between CT, PET/CT results and disease relapse; 3) the prognostic and independent predictive values of both imaging techniques. Comparisons between continuous and categorical groups were performed by *t*-Student test, analysis of variance, chi-square test, or Fischer exact test, as appropriate. P <0.05 was considered statistically significant. K statistics were use to determine the level of concordance of CT with PET/CT and between both techniques and follow-up results. K value of >0.4, >0.6, and >0.8 indicate fair, good and excellence agreement, respectively. Survival curves were constructed using the Kaplan-Meier method to account for censored survival times and were compared with the log rank test. Disease-free survival (DFS) and overall survival (OS) were defined as the length of time from the date of surgery to any relapse (local or distance recurrence or contra-lateral BC, or second cancer) and to death from any cause, respectively. Effect of PET/CT and CT results on DFS and OS were evaluated by Cox proportional hazards model.[9, 10] A stratified Cox proportional hazards survival model was used and the 95% confidence intervals (CI) were calculated. The incremental value of CT and PET/CT findings were evaluated by calculating the global chi-square of the model before and after adding the imaging results (positive finding) to the other information. The recurrence dynamics were studied using the life-table method to estimate the hazard rate (HR) for recurrence, that is the conditional probability of manifesting recurrence in a time interval. Statistical analysis was performed with SPSS software (SPSS Inc., Advanced Models 15.0, Chicago, IL, USA).

Results

CT yielded negative results in 76 patients (40%) and positive results in 114 patients (60%). PET/CT showed negative findings in 88 patients (43%), whereas 102 patients (57%) had evidence for disease. The presence of relapse was demonstrated in 82 of 190 patients (43%), whereas 108 of 190 patients (57%) were considered disease-free. Furthermore, 12 patients (6%) died.

The identification of disease relapse, obtained by clinical outcome, was more accurate for PET/CT than CT; in Table II are depicted the accuracy values for both techniques. Of all 82 patients with disease relapse, 73 were identified by PET/CT and 63 by CT (sensitivity: 89% vs. 77%), thus true-positive case (PPV) on PET/CT and CT were 72% and 55%, respectively. On the contrary, 108 of the disease-free patients, 79 and 57 patients were true-negative cases, respectively on PET/CT and CT (specificity: 73% *vs.* 53%). PET/CT and CT were concordant in 124 of 190 patients (65%), 75 in which they were both positive and 49 in which they were both negative (K value ± SE: 0.30±0.7; P<0.0001). Whereas, PET/CT and CT were discordant in the remaining 35% of patients, 27 which were positive on PET/CT but negative on CT and 39 which were negative on PET/CT but positive on CT. PET/CT correctly predicted the clinical outcome in 14 of these 27 discordant cases (52%), whereas CT was predictive for recurrence in 4 on 39 cases (10%), all of which were negative on PET/CT. The major number of patients, with discordant results and with final positive PET/CT findings, underwent nuclear examination due to suspicious for loco-regional disease and progressive elevation of tumour markers (mean value of Ca 15.3 =94.3±30.4); these latter subset of patients showed particularly visceral and skeletal metastases. Table III described the positive anatomical and metabolic localizations at CT and PET/CT imaging and their relations with the presence of disease recurrence, established by standard reference. The false positive lesions for PET/CT were loco-regional and distant lymph node (N.=16), lung nodules (N.=8), liver (N.=3) and bone (N.=8); whereas for CT the sites of false-positive findings were lymph node (N.=11), lung (N.=28), liver (N.=17), skin (N.=1), bone (N.=9), adrenal gland (N.=1) and spleen (N.=1).

The false negative patients at PET/CT (N.=9) had evidence of disease recurrence in the brain (N.=1), loco-regional and distant lymph node (N.=3), lung (N.=1), liver (N.=1) and bone (N.=3); whereas among

TABLE III.—*Distribution of recurrence localizations for FDG PET/CT, CT and the relation with presence of disease relapse.*

Organs	No. of sites*			
	PET/CT	CT	Relapse (PET/CT)	Relapse (CT)
Lymph node	47	25	31	14
Lung	29	52	21	24
Liver	20	34	17	17
Skin	5	3	5	2
Uterus or annexes	2	—	2	—
Skeletal	52	34	44	25
Adrenal glands	—	1	—	0
Others	—	2	—	1

*Referred to patients with positive involvement at CT and at FDG-PET in correlation with demonstrated disease relapse.

19 patients with false negative CT scan, 10 had bone lesions, 9 lymph node involvement, 1 brain and 4 liver metastases. Therefore, CT over staged the identification of visceral metastases (lung and liver), whereas PET/CT can better appreciate non visceral sites (skeletal and soft-tissue) of disease.

Kappa index (+ SE) of concordance between CT findings and the recurrence of disease revealed very fair level of agreement (K=0.28±0.07, P<0.0001), whereas the degree of agreement between the PET/CT findings and clinical outcomes (K=0.61±0.06, P<0.0001) was considerably higher.

Prognosis

The median DFS time was 79 months and the median time of OS was 88 months. DFS curves were significantly different in patients with both negative and positive PET/CT and CT (log-rank test 33.61; P<0.001 and 12.76; P=0.003, respectively); but as shown in Figure 1, PET/CT better stratify the risk of BC patients. In fact, after about 20 years of follow-up, the cumulative probability of DFS was 68% in patients with negative and 20% with positive PET/CT, whereas it resulted 48% and 18% respectively for patients with negative and positive CT imaging. OS curves were not statistically different in patients with positive and negative PET/CT and CT (P=NS; Figure 2). By both univariate and stepwise multivariate Cox regression analyses, positive PET/CT findings were found to be related to the recurrence of the disease (HR 0.18 and 0.20, P<0.0001, respectively; Table IV). The glo-

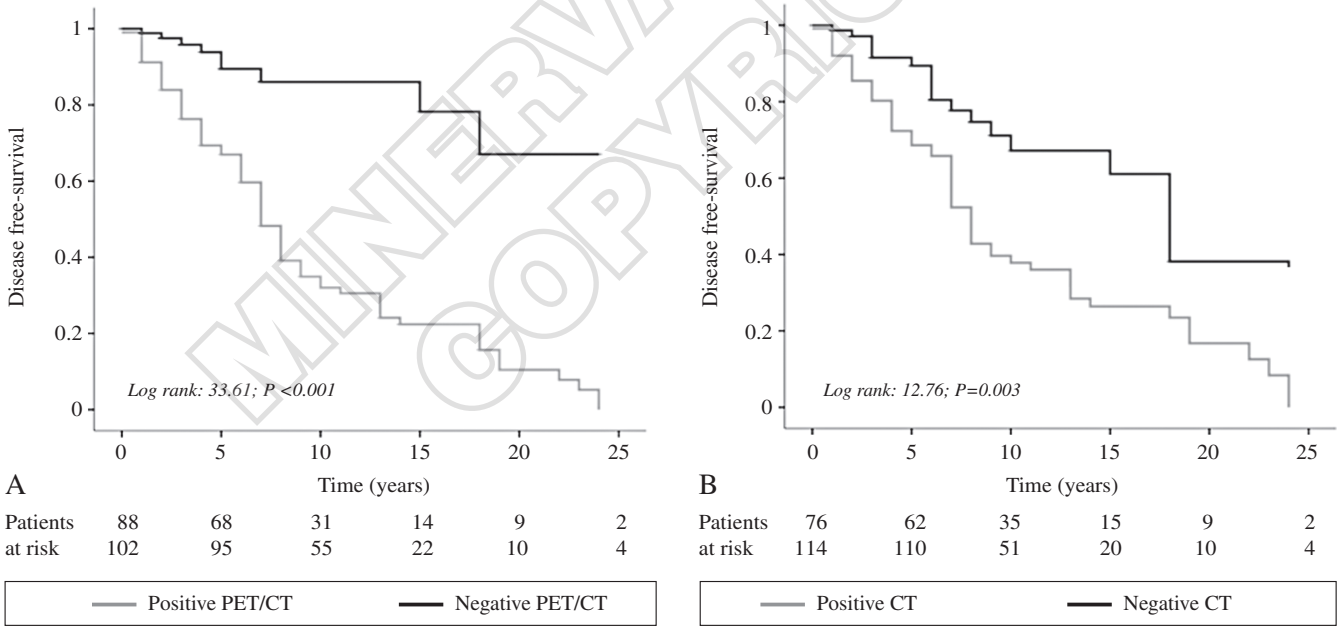

Figure 1.—A) Disease-free survival in 88 patients with positive PET findings compared with 102 patients with negative PET findings (Kaplan-Meier method); B) disease-free survival in 76 patients with negative CT findings compared with 114 patients with positive CT findings (Kaplan-Meier method).

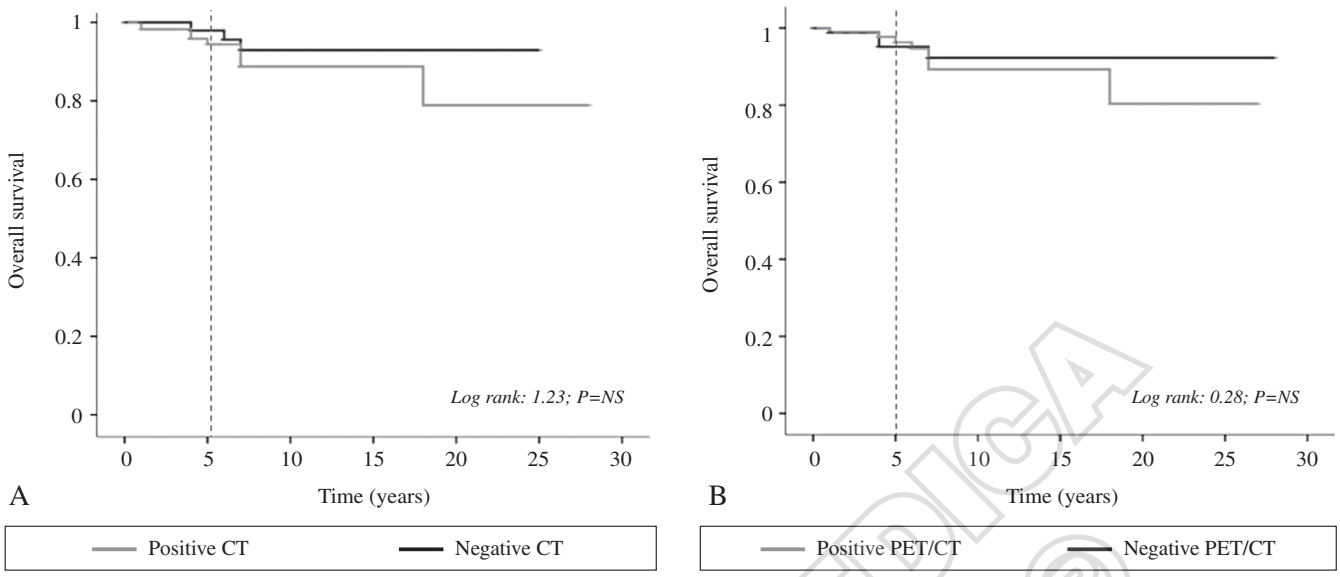

Figure 2.—A) The overall survival curves in patients with negative and positive PET/CT; B) the overall survival curves in patients with negative and positive CT findings (Kaplan-Meier method).

TABLE IV.—*Univariate and multivariate Cox regression analyses.*

	Hazard ratio	Confidence interval 95%	P value
Univariate analysis			
Age category (>55 y)	3.64	0.98-3.40	0.056
IDC	0.77	0.46-1.30	0.332
ILC	1.27	0.63-2.52	0.496
Positive ER	1.41	0.73-2.72	0.303
Positive PgR	0.81	0.52-1.66	0.805
Positive HerB2	0.98	0.52-1.83	0.938
Triple negative	0.80	0.34-1.86	0.607
Stage II-III	0.83	0.53-1.28	0.399
Positive lymph node	0.85	0.55-1.31	0.458
Positive CT	0.42	0.25-0.69	<0.001
Positive PET/CT	0.18	0.09-0.35	<0.0001
Multivariate analysis			
Age category (>55 y)	1.74	0.93-3.25	0.082
Positive CT	0.62	0.36-1.05	0.079
Positive PET/CT	0.20	0.09-0.41	<.0001

IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; ER: estrogen receptors; PgR: progesteron receptors; CT: computed tomography; PET: positron emission tomography.

bal χ^2 of the multivariable Cox proportional hazards model for prediction of disease relapse significantly increased from 3.76 to 38.70 (P<0.0001) after addition of PET/CT to the variables of age >55 years and positive CT imaging (Figure 3). Neither positive PET/CT nor CT were found as independent predictors of OS at both univariate and multivariate analyses (P=NS). The hazard rates for any recurrence (including both local and distant relapses) were analyzed for CT and PET/CT results and were compared with the clinical outcome. As shown in Figure 4, the curves displayed a bimodal pattern with a first surge peaking at about 30 months (estimated risk value=0.09) and a second peak at almost 72 months (estimated risk value=0.16). It is interesting to note that PET/CT had a similar trend as defined recurrence of disease, whereas CT demonstrated a linear course.

Discussion

Diagnostic accuracy

The clinical management and prognosis of BC patients are mainly based on the extent of the loco-regional recurrence and the presence of distant metastases.[11-14] Therefore, an accurate staging is essential for planning treatment of patients with disease relapse. Given that PET/CT provides moderate fidelity anatomical information by virtue of the low-dose, non-contrast CT, in the future could we use PET/CT obviating the need for diagnostic CT in some clini-

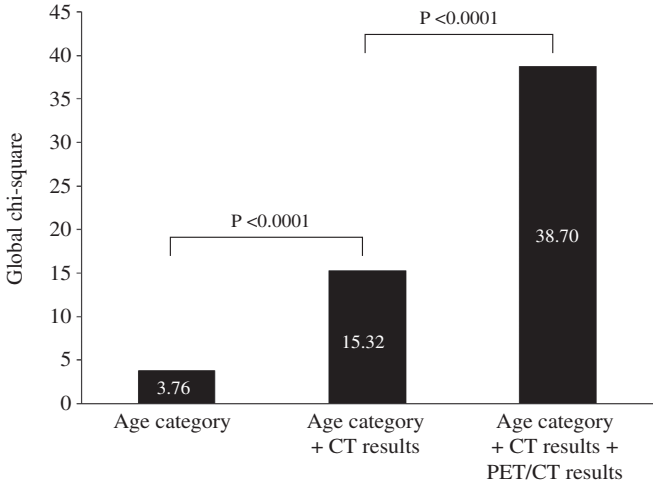

Figure 3.—Incremental prognostic value of addition of PET/CT to clinical variable (age >55 years) and CT findings for detecting disease relapse (global χ^2 from 3.76 to 38.70; P<0.0001).

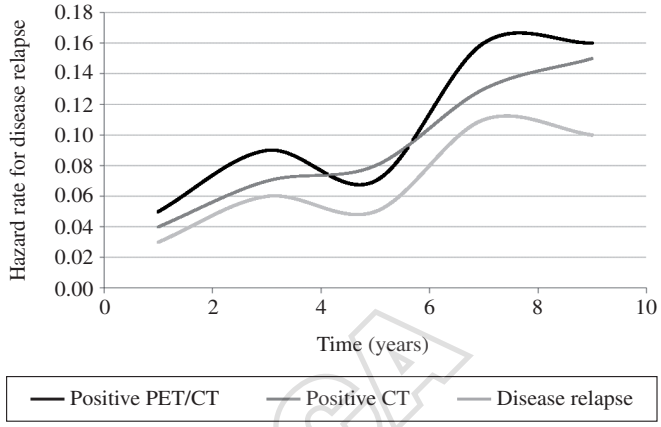

Figure 4.—Hazard rates for selected events in overall study population. The curves displayed a bimodal pattern with a first surge peaking at about 30 months (estimated risk value=0.09) and a second peak at almost 72 months (estimated risk value=0.16).

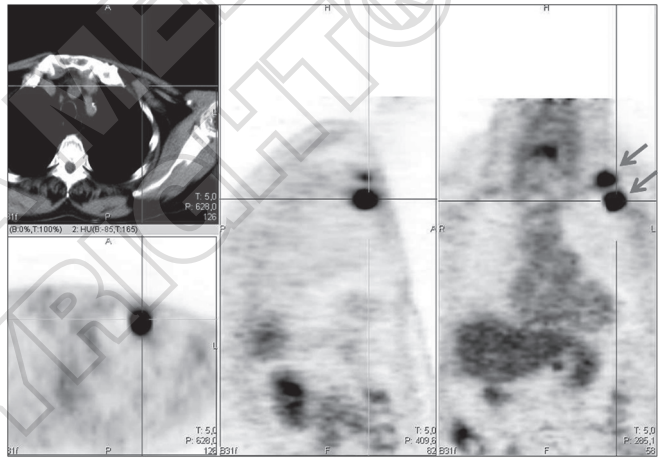

Figure 5.—A 56-year-old woman with left breast cancer, an invasive ductal cancer, treated three years ago with surgery and radiotherapy. Three-planes images of FDG-PET/CT and one of CT (up on left) demonstrate two focal uptakes of radiopharmaceutical, one in supraclavicular left lymph node and another in the proximal homolateral clavicular. Based on PET/CT finding, patient received radiation treatment for the metastatic sites.

cal scenario?.[15] Nowadays, the expert panel does not recommend the use of tumor markers, chest X-ray, routine bone scans, CT scans, MRI scans, PET scans or ultrasound examinations in the asymptomatic BC patients since they did not provide advantage in ability to palliative recurrent disease and in survival.[16, 17] The absence of consensus recommendation in this setting likely reflects the limitations of the imaging modalities themselves. The possibility to perform a combined anatomical and functional imaging during the follow-up of BC patients, could detect osseous and nonosseous metastases, avoiding the need for additional visceral imaging and bone scan. According to Weir et al. FDG PET imaging is indicated in two clinical situations: 1) in the evaluation of patients who are suspected of having a tumor recurrence; and 2) to exclude multifocal or distant sites of malignancy in patients who appears to have an isolated, potentially curable, loco-regional recurrence.[18] Furthermore, PET/CT is considered the appropriate technique for recurrence detection in patients with increase in tumour markers, because it is able to identify the site of metastasis when conventional imaging is inconclusive.[19, 20]

Our results demonstrate that PET/CT is more sensitive than CT in identification of disease relapse in a large population of BC patients (89 *vs.* 77%), giving a map of metastatic spread. The ability of a combined imaging such as PET/CT to recognize earlier the recurrence of cancer, with both high sensitivity and PPV, allows starting the most effective therapy. As known, the detection and the extent of malignant involvement represent the main issues on which oncologic practice today is based, primarily because it can impact on therapy and prognosis. For example, the identification of skeletal and lymph node metastases, located in near structures, could permit to make a radiation therapy (Figure 5).

From our results, PET/CT and CT were concordant in 124 of 190 patients (65%), 75 in which they were both positive and 49 in which they were both negative (K value: 0.30; P<0.0001); in the remaining 35% of patients with discordant findings, PET/CT correctly predicted the clinical outcome in 52%, whereas CT was predictive in only 10% of patients. CT scan showed more false positive than PET/CT for visceral sites of disease due to limitations to distinguish between loco-regional recurrence (size and morphological criteria limitations) and post-surgery inflammation/scar (previous mastectomy or quadrantectomy or lumpectomy), radiation therapy side effects and to increasingly sensitive technology. Moreover, CT alone is already known to be limited for lymph node staging in several body compartments.[21-23] On the contrary, PET/CT has shown the superiority over CT for the detection of mediastinal and internal mammary lymph node metastases;[22-24] moreover, it is more sensitive in the detection of osteolytic metastases or lesion predominantly involving the bone marrow.[25, 26] The specific strengths of PET/CT are the ability to characterize lung involvement when the size of lesions is higher than the limited spatial resolution of the scanner, to determine the presence of osteolytic bone metastases and to evaluate the metabolic behavior of the lesions, of great interesting in monitoring the response to treatment. Previously Keloff *et al.* demonstrated that relative to CT imaging, FDG PET has superior specificity and sensitivity for detecting BC metastases to the liver.[27] The main weak of PET/CT are the false positive results due to non-specific physical and chemical characteristic of FDG and non-avid osteosclerotic lesions. As known, FDG is not a tumor-specific substance, thus its accumulation in some conditions such as inflammations, vertebral collapse and others might reduce the specificity of procedures. However, morphological imaging methods such as CT and magnetic resonance imaging can be particularly impaired by false-positive findings base on surrounding soft tissue changes and contrast enhancement patterns, which can mimic inflammation and/or malignant lesions and vice versa. Furthermore, CT scan due its high resolution tends to overestimate the presence of metastatic lesions particularly in liver and lung.[28] Our results are in accordance with Piperkova *et al.*[29] that studied 49 BC patients for initial and restaging disease with PET/CT and CT. The authors concluded that PET/CT played a more important role than CT scans alone and provided an impact on the BC management. In accordance with Morris *et al.*,[4] it is possible that an efficient single-study strategy with integrated PET/CT is ultimately cost-effective compared with conventional strategies.

Pennant *et al.*[30] reported that some studies have investigated the possibility of using PET/CT as a replacement for, rather than an addition to conventional imaging techniques; considering our findings, we believe that in selected categories of patients (e.g. triple negative, advanced stage at diagnosis, cancer associated with familiar genetic mutations), PET/CT can replace diagnostic CT for the assessment of BC evolution during follow-up.

Imaging and prognosis

The ASCO panel reported that the clinical outcomes include the following: improvements in overall or disease-free survival; improvement in quality of life, as shown by a valid measure of global health outcomes; reduced toxicity and improved cost effectiveness. Based on these criteria, the diagnostic tests are recommended if they demonstrated a positive impact on clinical outcomes.[2] Nowadays, it is not sufficient to assess only sensitivity and specificity of a diagnostic tool, but it is necessary to understand the impact of them on therapeutic choice, that can be translated in an improvement in life quality and global survival. Despite the progression of BC screening, the mortality rate for this disease remains still high, reaching 20-22% of affected women (American Cancer Society). Probably, the increase and the improvement of screening with other approaches in high risk women and more appropriate follow-up methods in the same group could reduce or anticipate the recurrence of disease, favoring a proper treatment.

We found that after about 20 years, the DFS was 68% in patients with negative PET/CT and 20% in patients with positive PET/CT. These results are in accordance with those reported by Vranjesevic *et al.*, who concluded that 18F-FDG PET can be used to improve prediction of the clinical outcome of previously treated BC patients relative to what is achievable through conventional imaging alone.[31] Multivariable modeling revealed that a significant interaction was present between positive PET/CT finding and disease relapse; moreover, PET/CT provides significant incremental prognostic information over CT findings and demographical data (age category) in patients with BC (χ^2 test from 3.76 to 38.70). As demonstrated, the median OS in PET/CT positive findings (10 years) was the same to the median OS time determined for

the CT positive findings (10 years), but the five-year mortality rates were 16% and 19% respectively for PET/CT and CT. Probably, the gain of 3% in this rate indicates that the addition of metabolic data (PET) to anatomical data (CT) could be used to guide in decision making, thus reducing even if at minimum the mortality percentage in BC patients. As demonstrated by Veint-Haibach *et al.*[28] a combined approach of CT and PET for patients with recurrence of BC may be advantageous to tailor patient management, preventing from unnecessary therapy based on more accurate coregistration and localization of metabolic activity. For example, performing PET/CT exams between 24-36 months and 60-72 months from diagnosis might anticipate the recurrence identification and thus permit to start the oncological therapy. Demicheli *et al.*[32] analyzed the recurrence dynamics in series of patients undergoing conservative surgery at the National Cancer Institute of Milan; they studied 1526 BC patients reporting a bimodal pattern for any recurrence (including both local and distant disease relapses) with a first surge peaking at about 24 months and a second peak at almost 60 months. In our analysis we found different peaks estimating the risk level (0.009 *versus* 0.016 for the first peak and 0.016 *versus* 0.009 for the second peak) than in the previous study. These different findings are well explained by the characteristics and the number of the two studied populations (190 *versus* 1526 enrolled patients). Furthermore, based on our results, PET/CT should be able to identify appearance of delayed metastases; therefore, it may be indicated in case of suspected recurrence in advanced stages of follow-up.

Critical approach for the BC surveillance

Based on our results, we can indicate to perform PET/CT during follow-up of BC patients in some clinical scenarios, such as:

1) in the presence of suspected recurrence detecting during physical examination, or doubtful conventional imaging (chest x-ray or abdominal echography), in particular after 2 or 3 yrs and 6 or 7 yrs from the diagnosis;

2) when patient is symptomatic, but previous recommended examinations (clinical visit and conventional imaging procedures) are inconclusive;

3) in the presence of persistent and serial elevation of tumour markers, independently from the presence of symptoms, in patients with high estimated risk value.

Limitations of the study

PET/CT has not routinely been performed in our Institution on all patients with suspected recurrence of disease but has mainly been used instances of diagnostic uncertainty; our cohort is likely enriched for such occurrences. Moreover, only 36% of CT examinations were performed at our Institution, whereas the other outside; thus, for the interpretation of CT imaging, the final report was used and some bias could be introduced.

For the calculation of sensitivity, specificity and other parameters a person-based approach was used instead of one that was lesion-based. This procedure reflects that treatment decisions are generally made based on the presence of recurrent or metastatic disease, rather than the number of lesions involved. Consequently, it is clinically more relevant to consider the patient-based data rather than the lesion-based analysis.

A general problem is also to establish standard criteria for follow-up. In the present report, we used the histological findings only in 28% of patients, while a comparison with other modalities of imaging was used, although sometimes they cannot be completely definitive.

Conclusions

One of the major strength of PET/CT as a cancer staging modality is its ability to identify systemic metastases. At any phase of cancer evaluation, the development of systemic disease can demonstrate profound therapeutic and prognostic implications. The CT scan interpretation is based on changes in density, size and morphology but has limitations of no knowledge about tumour biologic behaviour. According to our findings, metabolic imaging adds important information on decision making and long-term prognosis. In the present study, we found that PET/CT is more accurate than CT in recurrence detection; it can identify more frequently and earlier the presence of BC relapse, engraving on disease free-survival although the overall survival is similar for both techniques. Furthermore, PET/CT can be useful in case of suspected recurrence in advanced stage of follow-up identifying delayed BC metastases.

Further prospective studies for comparison of PET/CT and CT for BC recurrence are warranted; it could necessary provide their potential and discriminator roles in BC follow-up.

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