FDG Avidity at PET/CT During Adjuvant Hormonal Therapy in Patients With Breast Cancer

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Background: We aim to retrospectively evaluate the impact of hormone therapy (HT) on FDG avidity of metastatic lesions in patients with breast cancer (BC) undergoing PET/CT.

Patients and Methods: Three hundred eight patients with BC were scanned with PET/CT at 2 Italian institutions (mean time from diagnosis 4 yrs, range: 1–24 yrs). Main indications for PET/CT were elevation of tumor markers (34.4%) and clinical or radiological suspicion of relapse (65.6%). The diagnostic accuracy of FDG PET/CT was computed according to the standard method. Student *t* test was used to assess the mean differences between the study groups, whereas categorical data were compared with chi-square test. Significance was set at $P < 0.05$.

Results: Two hundred sixty-four patients with positive estrogen receptor and who had received adjuvant HT were included in the analysis. At the time of PET/CT scan, HT was ongoing in 176 patients (66.7%) and 88 (33.3%) had completed adjuvant HT. Ninety-eight (55.7%) patients on HT and 59 (67%) off HT had a positive PET/CT; therefore, the scan resulted negative in the remaining 107 patients, 78 and 29 on and off HT, 44.3% and 33%, respectively ($P < 0.001$). At a median follow-up of 7 months (range 1–48 mos), disease recurrence was confirmed in either clinical or radiological examinations in 126 (47.7%) patients; 72 (40.9%) versus 54 (61.4%) patients on and off HT, respectively ($P < 0.005$). True-positive PET/CT results were found in 82% and 91% of patients on and off HT, respectively, whereas it failed to identify disease relapse in 13 (18%) and 5 (9%) patients on and off HT, respectively.

Conclusions: In our series, FDG PET/CT shows a similar diagnostic accuracy in detecting disease relapse between patients with BC on adjuvant HT versus those who have completed therapy. These preliminary results suggest that the glucose metabolism is not altered by hormonal suppression at the time of the scan.

Key Words: FDG PET/CT, breast cancer, hormone therapy, recurrence, diagnostic accuracy

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Approximately two thirds of breast cancers (BCs) express the estrogen receptor (ER) gene and synthesize ER protein. Half of these ER-positive tumors express both ER and progesterone receptor (PR) genes and are thus ER positive/PR positive.[1] Estrogens promote proliferation of breast cells by accelerating their G1/S phase transition. Endocrine therapy has led to a significant improvement in outcomes for women with BC that expresses ER (ER-positive), while in women with negative ER cancer only systemic chemotherapy has provided a substantial reduction in the risk of disease recurrence and death.[2,3]

Hormone medications determine their effects in different ways: primarily blocking the effect of specific enzyme; secondly, suppressing the hormone production; and thirdly, inactivating the target receptors, preventing estrogen from binding to receptors and eliminating them. Tamoxifen acts as anti-estrogen against BC cells through a competitive inhibition of estrogen binding to the ER and inhibition of the expression of estrogen-modulated genes. The result is a slowing of cell proliferation and arrest in G1 phase of proliferative process. Patients with ER-positive tumors who received tamoxifen for 5 years experienced significantly reduced rates of recurrence and death.[4] Aromatase inhibitors (AI) (third generation: anastrazole, letrozole, and exemestane) act by inhibition of the cytochrome P-450 enzyme that promotes the conversion of androstenedione and testosterone to estrone and estradiol, respectively, with a resulting fall in circulating estrogens to very low levels. The final effect is an effective strategy for inhibiting growth and survival of cancer cells. The "metabolic transformation" that is the ability to obtain nutrients (such as glucose) in a cell-autonomous fashion confers to cancer cells a selective growth advantage and/or resistance to apoptosis. This high metabolic potential can be imaged by functional imaging modalities, ie, ^{18}F-FDG PET. The effect of hormonal therapy (HT) on FDG PET is an interesting issue that has not yet been explored. Different formulations of HT are widely employed in BC as adjuvant treatment (AI, tamoxifen, and fulvestrant), but to date no guidelines addressing the question as to whether HT should be withdrawn in restaging PET/CT studies. Reduced FDG avidity in metastasis of patients with BC receiving HT may suggest a lower sensitivity of PET/CT in the detection of disease recurrence in these patients; furthermore, if a significant inhibitory effect of HT on FDG uptake is exerted, the diagnostic accuracy of technique to detect the recurrence of disease might be limited. We aim to evaluate the impact of HT on glucose metabolism of metastatic lesions with FDG PET/CT imaging in patients with BC.

PATIENTS AND METHODS

Study Design and Data Acquisition

For this bicentric institutional study, between January 2007 and January 2012, 308 patients undergoing PET/CT for restaging of BC were consecutively and retrospectively included. All clinical and histopathological information was extracted from the patient's charts in agreement with referring clinicians. This included the TNM classification and localization of the primary tumor, the receptor status, the type of treatment, the interval time from diagnosis until the first PET/CT, and the current reason for FDG PET/CT referral and consecutive therapy after PET/CT imaging.

Patient Population

Records for 308 BC patients (306 females; median age: 60 yrs, range: 27–86 yrs) who underwent ^{18}F-FDG PET/CT for the assessment of disease relapse were reviewed. Main indications were (1) increase of tumor markers (Ca15.3 and CEA) in 106 (34.4%)

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TABLE 1. Clinical and Histopathological Characteristics of Study Population (n = 264)

Characteristics	HT (n = 176)	HT-off (n = 88)	*P*
Age, yrs			
<55	61 (34.7%)	32 (36.4%)	0.785
>55	115 (65.3%)	56 (63.6%)	
Primary histology			
DCIS	3 (17%)	6 (6.8%)	0.038
IDC	115 (65.3%)	57 (64.8%)	
ILC	34 (19.3%)	10 (11.4%)	
Mixed	13 (7.4%)	3 (3.4%)	
Others	4 (2.3%)	3 (3.4%)	
Unknown	1 (0.6%)	3 (3.4%)	
Tumor invasion size, cm			
≤2	109 (61.9%)	50 (56.7%)	0.784
>2	67 (38.1%)	33 (37.5%)	
Unknown	0	5 (5.8%)	
Estrogen receptors*			
Positive	172 (97.7%)	81 (92%)	0.002
Negative	4 (2.3%)	1 (1.2%)	
Unknown	0	6 (6.6%)	
Progesterone receptors*			
Positive	163 (92.6%)	77 (87.5%)	0.002
Negative	12 (6.8%)	5 (5.7%)	
Unknown	1 (0.6%)	6 (6.8%)	
Her2 receptor†			
Positive	22 (12.5%)	9 (10.2%)	0.016
Negative	147 (83.5%)	67 (76.1%)	
Unknown	7 (4%)	12 (13.7%)	
Staging according to 7th ASCO classification			
Stage 0	0	2 (2.3%)	0.142
Stage I	67 (38.1%)	39 (44.3%)	
Stage II	71 (40.3%)	29 (32.9%)	
Stage III	38 (21.6%)	18 (20.4%)	
Grading			
I	26 (14.8%)	15 (17%)	0.623
II	74 (42%)	30 (34%)	
III	59 (33.5%)	24 (27.3%)	
Unknown	17 (9.7%)	19 (21.7%)	
Lymph node involvement			
Yes	96 (54.5%)	36 (40.9%)	0.051
No	72 (40.9%)	43 (48.9%)	
Unknown	8 (4.6%)	9 (10.2%)	
Surgery			
Conservative	96 (54.5%)	44 (50%)	0.485
Mastectomy	80 (45.5%)	44 (50%)	
Chemotherapy			
None	61 (34.7%)	27 (30.6%)	0.585
Neoadjuvant	9 (5.1%)	7 (7.9%)	
Adjuvant	106 (60.2%)	54 (61.5%)	
Radiotherapy			
No	56 (31.8%)	32 (36.3%)	0.460
Yes	120 (68.2%)	56 (63.7%)	
Hormonal therapy			
Tamoxifen (±LH-RH analogue)	71 (40.2%)	56 (63.6%)	0.004
Aromatase inhibitors (±LH-RH analogue)	95 (54%)	30 (34.1%)	
Fulvestrant	2 (1.1%)	0	
TAM switch AI	8 (4.5%)	2 (2.3%)	

*Hormone receptor status was defined as positive when the expression of both estrogen receptor and progesterone receptor was ≥10% by immunohistochemistry (IHC).

†HER-2 was considered positive when scored 3+ in IHC or positive for fluorescence in situ hybridization.

DCIS indicates ductal cancer in situ; IDC, invasive ductal cancer; ILC, invasive lobular cancer; TAM, tamoxifen; AI, aromatase inhibitors.

patients, (2) suspicious for disease relapse in 52 (16.9%) patients, (3) suspected conventional imaging for disease recurrence in 123 (39.9%) patients, and (4) oncologist's decision in 27 (8.8%) patients. The mean time between primary diagnosis of BC and PET/CT was 48 months (range 7–288 mos). Primary surgery was conducted in all patients [breast-preserving surgery n = 164 (53.2%); mastectomy n = 144 (46.8%)]. All patients had received additional chemotherapy (neoadjuvant n = 18; adjuvant n = 189), radiotherapy (n = 206), and a combination of both (n = 139) after the first diagnosis of BC. The mean time interval between the last therapy cycle (chemotherapy or radiotherapy) and the restaging PET/CT was 30 months (range 1–156 mos). Two hundred sixty-four (85.7%) out of 308 patients received HT as adjuvant treatment and thus were eligible for the analysis. At the time of PET/CT scan, 176 (66.7%) were ongoing HT (called as HT) and 88 (33.3%) were off HT (called as HT-off). All patients gave their informed written consent to the work in accordance with the Declaration of Helsinki, and the study was conducted taking into consideration the regulation of the local Institutional Review Board for retrospective analysis. Characteristics of 264 patients with and without ongoing HT are described in Table 1.

PET/CT and Image Analysis

Whole-body ^{18}F-FDG PET/CT was performed using a dedicated PET/CT scanner (Biograph 16 HR; Siemens Medical Solutions, IL, USA) and a Gemini TF PET/CT scanner (Philips Medical Systems). Together with the PET system, the CT scanner was used both for attenuation correction of PET data and for localization of ^{18}F-FDG uptake in PET images. All patients were advised to fast for at least 6 hours before the integrated PET/CT examination. Each patient's blood glucose levels were obtained prior to tracer injection (median glycemia value: 97 mg/dL; range: 57–177 mg/dL). The threshold of blood glucose level for FDG injection was below 180 mg/dL.[11] After injection of about 3 MBq of ^{18}F-FDG per kilogram of body weight (median: 243 MBq, range 144–463 MBq), the patients rested for a period of about 60 minutes in a comfortable chair. Emission images ranging from the proximal femur and the base of the skull were acquired for 2–3 minutes per bed position. Acquired images were reconstructed using the attenuation-weighted ordered subset expectation maximization 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/CT images were also assessed quantitatively using the maximum standardized uptake value (SUV_{max}) that was computed according the following formula: K (SUV) = K (Bq/mL) × [weight (kg)/dose (Bq)] ×

1000 mL/kg, where K (Bq/mL) = calibrated and scaled pixel volume, and dose (Bq) = injected dose in becquerels at injection time decay corrected. All the images were completely re-reviewed by 2 nuclear medicine physicians in both Institutions (by LE-GS and by MR-TV, respectively). At visual analysis, increased FDG uptake on the basis of either highly suspicious or definite CT morphologic changes and not corresponding to physiological uptake patterns was recorded as positive for metastases. In contrast, the absence of uptake, out of normal physiological sites, was used to define a negative PET/CT finding. The support of metastases was given by a SUV_{max} greater than 2.5 in some doubtful lesions outside liver and greater than 3.5 for hepatic lesions.[5]

Standard of Reference

A conclusive diagnosis of recurrence was obtained from the results of histopathological examinations after biopsy (available in 88 patients) or clinical/imaging follow-up median time 8 months (1–26 mos). Biopsy was omitted if metastases were multiple or bone relevant. Clinical and radiological recurrences were defined as detection of recurrent disease by abnormal clinical visit, continuously rising CA 15.3 levels, or appearance of new lesions or size increase of old lesions (previously described as not clinically significant) on imaging examinations (PET/CT, CT, and bone scan) after PET/CT. Based on presence/absence of disease relapse, therapeutic management was planned.

Statistical Analysis

Continuous data were described as mean or median and categories as percentage. Comparisons of continuous variables between 2 groups were performed using Student t test, while chi-square test was used for categorical variables. ANOVA test was used in case of comparison among more than 2 groups. True positive (TP), true negative (TN), false positive (FP), and false negative (FN) were defined as follows: TP is concordance of a positive FDG PET/CT result with conventional imaging and/or biopsy, TN is concordance of a negative FDG PET/CT result with conventional imaging and/or biopsy, FP is discordance of a positive FDG PET/CT with a negative result of conventional imaging and/or biopsy, and FN is discordance of a negative FDG PET/CT result with a positive result of conventional imaging and/or biopsy. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were defined as follows: sensitivity = TP/(TP + FN), specificity = TN/(TN + FP), PPV = TP/(TP + FP), NPV = TN/(TN + FN), and overall accuracy = (TP + TN)/(TP + TN + FP + FN). The FN rate was calculated as the proportion of FN studies among all patients with disease (FN/TP + FN). The difference in FN rates between patients with and without HT was assessed for statistical significance using the chi-square test for homogeneity of proportions. A P value ≤ 0.05 was considered to be significant. All statistical analyses were performed using SPSS version 15.0 statistical software package (SPSS Inc., Chicago, IL, USA).

RESULTS

As illustrated in Table 1, the 2 populations were substantially similar, except for a higher prevalence in the use of AI in patients ongoing HT than HT-off ones. In 88 patients who had already finished the adjuvant HT, the time between the last HT administration and PET/CT scan was 43 ± 47 months (range: 1–209 mos). No difference between the 2 institutions was found for the glycemic levels (96.28 ± 13.77 mg/dL vs. 94.80 ± 19.30 mg/dL; $P = 0.482$, respectively).

PET/CT was positive in 157 patients, 98 (55.7%) on HT and 59 (67%) HT-off ($P < 0.001$). After a median follow-up of 7 months (range 1–48 mos), disease relapse was clinically and radiologically confirmed in 126/264 (47.7%) patients; 72/176 vs. 54/88 patients on and off HT, respectively (40.9% vs. 61.4%, $P < 0.005$). At the time of analysis, 20 (7.6%) patients died, in particular 12 patients of HT subset and 8 patients of HT-off groups (6.8 vs. 9.1%, $P = 0.511$). In Figure 1 are depicted 2 examples of positive FDG PET/CT in HT and HT-off patients.

PET/CT was positive in 98 (55.7%) and in 59 (67%) patients, respectively of HT and of HT-off groups ($P < 0.001$). Sensitivity was slightly higher in HT-off than HT subset (90.7% vs. 81.9%) while the contrary was found for the specificity (70.6% vs. 81.7%). Finally, the diagnostic accuracy resulted similar, being 81.8% and 83% in HT and HT-off, respectively. The results were not different between the 2 institutions in terms of sensitivity and specificity in both groups (76% vs. 79.4% and 80.6% vs. 82.1% in HT-on, and 91.6% vs. 89.1% and 68.6% vs. 73.9% in HT-off, respectively). No significantly different results for the diagnostic accuracy in dependence of time period between systemic therapy and PET/CT were reported for all study populations (sensitivity between 1 and 12 mos, 12–24 mos, and >24 mos: 76.9% vs. 80% and 81.2%, respectively). In Table 2 are reported the diagnostic accuracies for PET/CT in both groups of patients. Moreover, no statistically significant difference in the FN rates was observed between the 2 groups (13/72, 18% vs. 5/54, 9.3%, respectively, for HT and HT-off; $P = 0.162$). In HT-off patients, a high FP rate was demonstrated (29.4%).

There were 59 TP studies in HT subset and 49 ones in HT-off patients; therefore, PET/CT yielded true-positive results in 81.9% and 90.7% of patients with and without HT, respectively; on the other site, it failed to identify disease relapse in 13/72 and 5/54 patients (18% and 9.3% HT and HT-off, respectively).

The FP studies included 29 patients with significant uptake in lymph node (n = 15), in soft tissue (n = 6), bone (n = 2), liver (n = 1), and lung (n = 5). Moreover, the main reasons for 18 false-negative findings were small-size lesion in lung or in mediastinum and lesion with low glucose activity (eg, lobular cancer). The rates of PET/CT positivity based on the type of HT were depicted in Table 3. As shown, the majority of patients with a positive scan were in the aromatase group, both for HT and HT-off patients (46.3% and 73.3%, respectively). Furthermore, among 176 patients who underwent HT, the administration of tamoxifen was correlated with a better diagnostic accuracy of PET/CT than of AIs (84.5% vs. 78.9%, respectively).

Bone lesions were found in 76 (28.8%) patients: 41 (53.9%) were under HT and 35 (46.1%) did not, thus no difference for bone involvement between patients on and off-HT was reported, being the same in both categories of patients. On lesion-based analysis, 273 bone lesions were identified: 179 (66%) lytic, 38 (14%) blastic, 27 (10%) mixed, and 29 (11%) bone marrow (no evidence of CT abnormalities) ones. Nine out of 29 (31%) blastic lesions did not show a FDG uptake, while 178/179 (99%) lytic lesions had a significant FDG avidity. The SUV_{max} value was significantly higher for lytic lesion than the other ones (ANOVA test $P = 0.025$). The prevalence of lytic and blastic lesions was similar in HT and HT-off group ($P = 0.119$; Fig. 2). Furthermore, no differences in SUV_{max} between HT and HT-off group were demonstrated both for lytic and blastic bone lesions (7.55 ± 3.55 vs. 7.24 ± 3.84 and 5.87 ± 2.73 vs. 5.98 ± 2.64, respectively; both P = NS). Furthermore, no differences for mean value of the SUV_{max} for visceral (liver and lung) and nonvisceral (lymph node, skeletal, and soft tissue) metastatic sites between patients with and without HT were reported, as shown in Table 4.

The value of Ca15.3 before PET/CT was available in 133 patients. The mean values were 29.44 ± 38.79 and 80.84 ± 191.93, respectively, in HT and HT-off patients ($P = 0.014$). Moreover, PET/CT was able to change the therapy in 55 (31.3%) and 42 (47.7%),

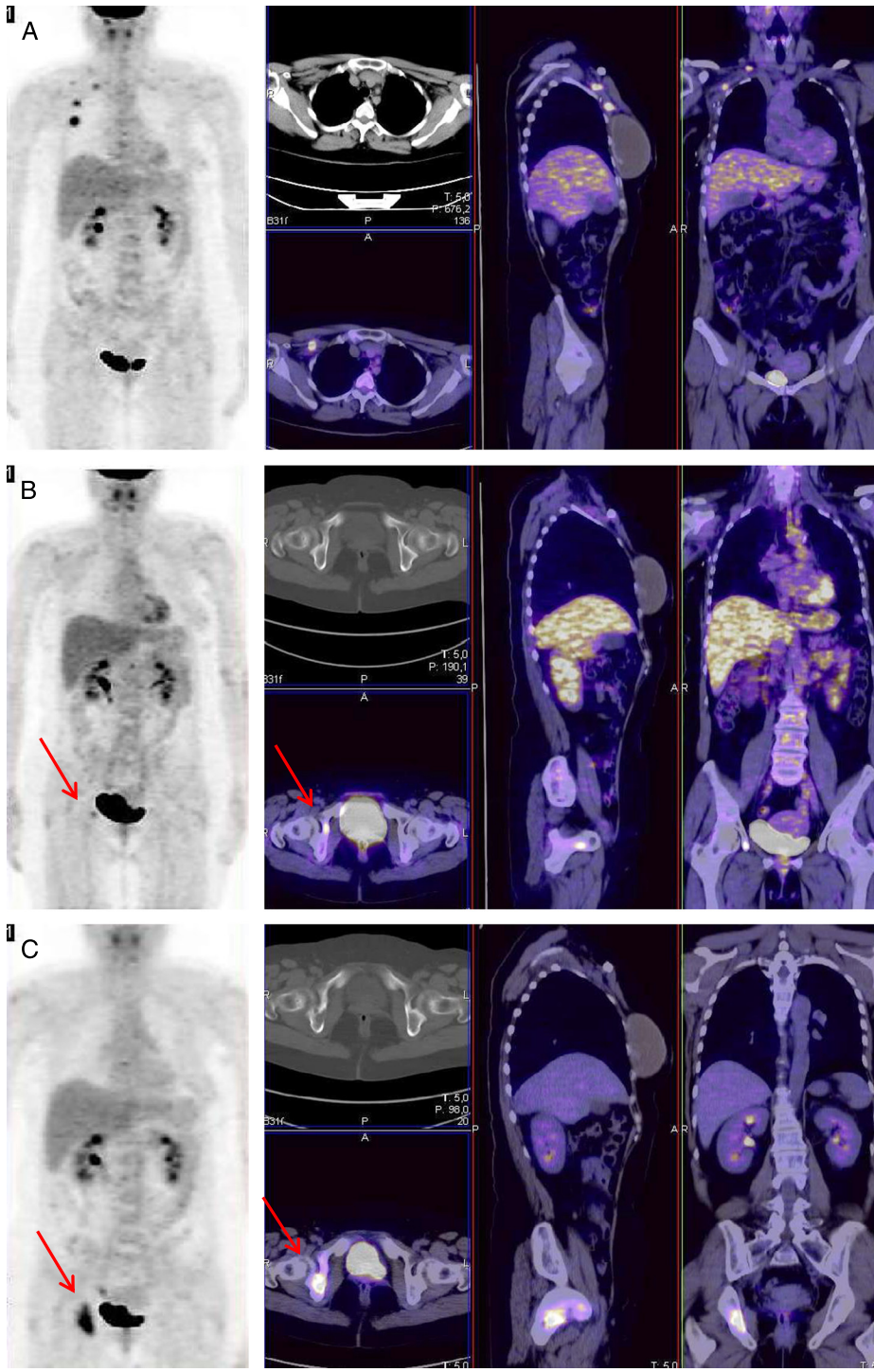

FIGURE 1. Serial PET/CT scans in a 57-year-old female patient with invasive ductal breast cancer who underwent right radical mastectomy and axillary dissection in 2003 followed by chemotherapy (FEC and CMF combination) and tamoxifen for 5 years (from 2004 to 2009). In 2010, for a suspicion of locoregional recurrence of disease, she underwent PET/CT showing a focal FDG uptake in the right supraclavicular lymph nodes and behind the right great pectoralis muscle (**A**). Therefore, radiotherapy was performed with a curative target therapy and a hormonal therapy with aromasin inhibitor was started. In 2011, for the appearance of skeletal pain, a second PET/CT scan was performed demonstrating a slight uptake of FDG in the right ischium (arrow) without evidence of anatomical abnormalities (**B**). The patient was clinically followed and for the persistence of pain nonetheless during the hormonal therapy, she underwent a third PET/CT scan. In these latter images, an intense FDG uptake was reported in the right ischium (arrow) associated with a lytic lesion (**C**).

TABLE 2. Accuracies of PET/CT Based on Ongoing Hormone Therapy (HT)

	HT	HT-off
Sensitivity (95% CI)	81.9 (73–91)	90.7 (83–98)
Specificity (95% CI)	81.7 (74–89)	70.6 (55–86)
PPV (95% CI)	75.6 (66–86)	83.1 (73–93)
NPV (95% CI)	86.7 (80–93)	82.7 (70–95)
Accuracy (95% CI)	81.8 (76–88)	83 (75.91)

PPV indicates positive predictive value; NPV, negative predictive value.

respectively, for patients without and with ongoing HT ($P < 0.01$), thus changing the management in 36.7% of all populations.

DISCUSSION

Few studies have shown that the metabolic flare reaction depicted as an increase of tumor FDG uptake 7–10 days after introducing therapy appeared to be predictive of response to endocrine therapy,[6,7] but data are lacking on the delayed effect of endocrine therapy on the tumor metabolism. Reducing recurrence risk is a primary goal of adjuvant HT. There is an early peak of recurrence 2 years after surgery; most are distant metastases rather than local or regional events. Therefore, treatment strategies such as initial therapy with AIs, which reduce early distant recurrence events, can be expected to improve long-term survival outcomes.[8] Prompt and appropriate use of hormonal or cytotoxic drugs can reduce or delay tumor-related syndromes.

In the present report, we have evaluated the effect of HT on the detection recurrence rate of PET/CT studies. For this end point, we selected 264 patients who have undergone HT (n = 176) or have already completed the hormonal therapeutic scheme (n = 88). In the first patient subset, the mean time between the beginning of HT and PET/CT scan was 30 ± 18 months (range: 1–71 mos). As known, tamoxifen is a selective estrogen receptor modulator with a slow onset of action; it has estrogen agonist effects that peak 1–2 weeks after beginning therapy and may contribute to the development of the "flare reaction" or "metabolic phenomenon" particularly in bone.[6,7] Our study population was composed of patients who underwent PET/CT after at least 1 month from the start of HT. As illustrated, we found a similar diagnostic accuracy in both subset of patients (81.8% and 83% in HT and HT-off, respectively), further reporting a high sensitivity and specificity of PET/CT for BC recurrence detection, in accordance with previous studies.[9,10] The small differences between sensitivities and specificities of PET/CT in HT-on and HT-off subset (81.9% vs. 90.7% and 81.7% vs. 70.6%, respectively) could be due to the heterogeneity of study population (age, type of HT performed, and previous systemic treatments) and to the retrospective nature of the report.

Endocrine therapy plays a major role for the control of bone-dominant disease. Veit-Haibach et al[11] compared the value of combined PET/CT, PET plus CT, PET alone, and CT alone concerning the restaging TNM stage and the influence on therapy in patients with recurrent BC. By a single institutional evaluation, they selected 44 patients with a history of BC, who already underwent surgery, chemotherapy, or radiotherapy and who underwent FDG PET/CT for restaging evaluation. Thirty patients (68%) received prophylactic antihormonal medication at the time of PET/CT procedure. PET/CT resulted to be more accurate than PET and CT alone in disease relapse detection. As already discussed in literature,[12–14] the authors found that the most common reason for false-negative results on PET imaging was PET-negative sclerotic bone lesions. On the contrary, PET showed high sensitivity when staging lytic or mixed lytic/blastic osseous metastases, and the addition of CT may be able to add substantial information, especially in sclerotic, non–FDG-avid lesions, as reported by Morris et al.[15] Veit-Haibach et al[11] concluded that the intake of prophylactic antihormonal medication may be a reason for the nonavidity of those lesions. Therefore, they request for dedicated studies on this important topic to describe the long-term effect of antihormonal treatment on bone metastases, with prophylactic antihormonal medication being the standard method of care in BC patients. In the present report, we found true-positive bone lesions in 76 patients; in particular, 41 were under HT and 35 were not (53.9% and 46.1%, respectively), hence the similar incidence in both groups. Furthermore, no difference in FDG uptake was found in blastic lesions both in HT and HT-off groups (47.5% vs. 40%, P = NS).

GLUT4 represents the most expressed transporter of glucose into muscle, and other insulin-dependent tissues, and also the most important regulator of glucose intake. Estradiol regulates GLUT4 in muscle and at high concentration reduces GLUT4 expression, decreasing insulin sensitivity; in fact, hyperestrogenism is involved in insulin resistance and/or gestational diabetes.

Tamoxifen treatment increased GLUT4, GLUT3, and IGF1 expression in the brain showing a similar role of estradiol[16]; thus, considering its physical characteristics of partial estrogen agonist, it should be correlated with a normal or increased FDG uptake.

Rogers et al[17] have recently demonstrated that estradiol stimulates Akt (a kinase that plays a key role in mediating signals for cell growth, cell survival, cell-cycle progression, differentiation, transcription, translation, and glucose metabolism) in intact skeletal muscle, promoting GLUT4 transport to membrane but not stimulating muscle glucose uptake. Moreno et al[18] reported that during aging, 17β-estradiol treatment improves glucose homeostasis in the absence of the sexual steroid mainly at level of GLUT4. Ko et al[19] have shed a new light on the biofactors that influence cancer cell glucose metabolism. The authors showed that 17β-estradiol is able to increase

TABLE 3. Type of Hormone Therapy (HT) and PET/CT Results in Patients Without and With Recurrence of Disease

HT-off (n = 88)				
PET Result	**TAM (±analogue LH-RH) (n = 56)**	**AI (±analogue LH-RH) (n = 30)**	**Fulvestrant**	**TAM switch AI (n = 2)**
Negative	21 (37.5%)	8 (26.7%)	—	0
Positive	35 (62.5%)	22 (73.3%)	—	2 (100%)
HT (n = 176)				
	TAM (±analogue LH-RH) (n = 71)	**AI (±analogue LH-RH) (n = 95)**	**Fulvestrant (n = 2)**	**TAM switch AI (n = 8)**
Negative	45 (63.4%)	51 (53.7%)	1 (50%)	1 (12.5%)
Positive	26 (36.6%)	44 (46.3%)	1 (50%)	7 (97.5%)

TAM indicates tamoxifen; AI, aromatase inhibitor.

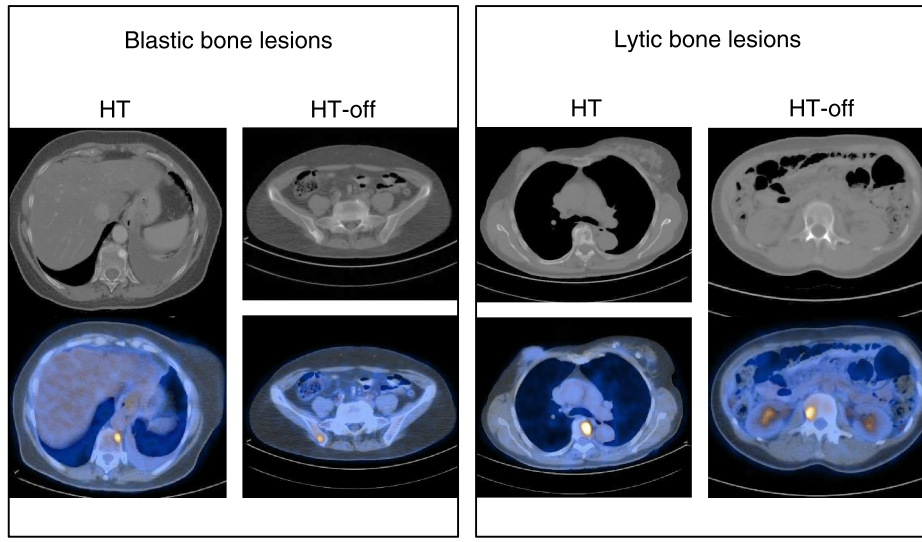

FIGURE 2. Examples of positive PET/CT for different bone lesions (blastic and lytic) in patients ongoing HT and off HT.

^{18}F-FDG uptake by stimulating glycolysis and hexokinase in estrogen-responsive BC cells, but this action is not mediated by nuclear ER but via membrane-initiated rapid PI3K-Akt activation pathway. This observation might illustrate why non-nuclear ER could constitute a target for estrogen action, with consequences on glucose metabolism.

Aliaga et al[20] performed a study on 2 lines of cells derived from mouse mammary tumors and from standard epithelial picture (MC7-L1 and MC4-L2, respectively). Both lines gave rise to metastases and express estrogen and progesterone receptors. The MC4-L2 cell line expresses very high levels of the c-erbB2 protein which has been associated with resistance to HT,[21] but nevertheless after 1 day from start of treatment with letrozole, they observed an overall decrease in cellular metabolic activity as measured by FDG-PET imaging. Furthermore, in both cell lines, the treated (letrozole) tumors presented a relative decrease in metabolic activity compared to baseline, while the control tumor FDG uptake increased. A sharp decrease was observed 1 day after therapy, with increased in uptake or return to baseline at day 7, and then a decrease on day 14. The metabolic measurements showed more variability as compared to volume measurements. In terms of absolute FDG uptake rather than relative values, the difference between the control and the treated tumor was only statistically significant for doxorubicin single-dose regimen, but not for letrozole regimen (time 0: 9.56 vs. 11.44; time 1 day: 11.1 vs. 10.10; time 7 days: 10.90 vs. 10.31; time 14 days: 10.01 vs. 10.55; control vs. letrozole administration, respectively). Time 0 represents the time of administration, and a high level of FDG for letrozole group is typical for flare response to HT. Obviously, the presence of hormone receptors does not indicate that the receptors will be functional nor that agents affecting estrogen levels will result in tumor cell death.[22,23] According to their results, endocrine therapy had reduced cancer metabolism; it could then lead to low FDG uptake by tumor cells.[20] Nevertheless, they concluded that their observations were not enough to recommend endocrine therapy withdrawal before an FDG-PET scan.

As reported in literature, androgen depletion markedly suppressed the uptake of radiolabeled choline, FDG, and FLT.[24,25] In fact, in prostate cancer the decrease of androgens due to anti-androgenic therapy, such as bicalutamide, is associated with a reduction in FDG uptake.[26] Can we suppose that the administration of AIs in BC patients increases FDG uptake because of the increase of androgens? Could it be considered the reason of intermediate rate of FP findings? Or is the loss of specificity related to osteo-articular disease that is a typical side effect of AIs? Currently, AIs have largely replaced tamoxifen as first-line therapy for advanced disease because they produce a higher response rate and a longer duration of response than tamoxifen, and it is mainly employed in postmenopausal women reducing the response rate of estrogen due to the inhibition of aromatase enzyme which converts androgen-like hormones to estrogen-like hormones.[27] Therefore, many questions are still unclear and require prompt answers.

Champion et al[28] studied 368 patients with BC who underwent PET/CT for suspicion of disease recurrence. The authors noted that 9 patients receiving adjuvant endocrine therapy at the time of their first PET/CT scan had a second examination performed after treatment withdrawal, which then switched to a positive result, while the patients remained asymptomatic. This question should be better addressed by a prospective randomized multicenter trial which can clearly evaluate the effect of HT on FDG uptake, but the withdrawal of HT could alter the effect of therapy on the control of disease. In the present report, 67% of patients who had already finished HT had a recurrence of disease versus 55.7% who had ongoing endocrine therapy ($P < 0.001$), thus the percentage of recurrence was significantly higher in HT-off subset. As reported in the literature, the recurrence rate after surgery shows a nonlinear time trend, with a first peak of relapse after 2–3 years and a second peak after 5–6 years from the diagnosis, independent of the expression of hormone receptors in the primary tumor.[29] Moreover, the risk of early relapse is higher in patients with no receptor expression, while late relapse is more frequent in patients with a positive receptor tumor.[30,31] Therefore, the withdrawal of HT in this unsteady period could be hazardous to the patient's health.

TABLE 4. Values of SUV_{max} for Visceral or Nonvisceral Site of Disease in HT and HT-off Group

	n	HT	n	HT-off	*P*
SUV_{max} (visceral)	57	7.52 ± 4.13	45	7.92 ± 4.28	0.640
SUV_{max} (no visceral)	28	7.09 ± 5.16	21	7.64 ± 6.39	0.742
SUV_{max} (visceral + no visceral)	13	8.89 ± 3.76	12	9.54 ± 4.26	0.692

HT indicates hormone therapy.

LIMITATIONS AND CONCLUSION

A "metabolic flare" phenomenon (increase in SUV under antihormonal therapy) has been described by Dehdashti and coworkers[6] in patients with metastatic BC undergoing antihormonal therapy. As this phenomenon was noted in a shorter follow-up time than that evaluated here and imaging and clinical data were used in conjunction for follow-up assessment in our study, we did not note any difficulties concerning this phenomenon in our patient population, but nevertheless it can represent the main limitation. Furthermore, most of the references mentioned in the discussion were about cell study, and the number of patients in some reports[11,28] was too small. Moreover, there is a limitation in the study population. No one can be sure that either the 2 groups (HT-on and HT-off) are independent in terms of HT or HT-off can represent those without a HT, but for obviating this limit a prospective clinical trial should be drawn comparing ER-positive breast cancer patients undergoing HT with those without it. Moreover, the PET images obtained by the time-of-flight unit (second-generation scan) are considered superior in quality to the first generation of PET scanner; therefore, a type of "bias" could be introduced by the type of device. However, in the present study a similar diagnostic performance was found for both institutions. No crossover revisions of PET images were performed between the 2 institutions; this can be considered a further limitation.

In conclusion, in our series, FDG PET/CT shows a similar diagnostic accuracy in detecting disease relapse between BC patients on adjuvant HT versus those who have completed therapy. HT does not alter FDG uptake, but probably the start of HT few days before PET/CT (for example within 0–14 days) could change the metabolism of lesion determining a high false-positive rate.

From the present report, it emerges that a prospective study is necessary; in particular, a comparison between patients with a positive-ER BC and undergoing HT versus HT-off should be planned. Furthermore, the employment of ^{18}F-fluoroestradiol or other new highly specific tracers for ER or PR could help the clinicians to better understand the effect of HT on the metabolism of cancer cells.

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