Rate of Distant Metastases on ^{18}F-FDG PET/CT at Initial Staging of Breast Cancer: Comparison of Women Younger and Older Than 40 Years

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Women who have breast cancer and are younger than 40 y have a poorer outcome than older women. A higher rate of undetected metastases at the time of diagnosis in younger women has been proposed to account for this difference. Our main objective was to test this hypothesis by comparing the distant metastasis rate (DMR) on initial ^{18}F-FDG PET/CT in a group of breast cancer patients younger than 40 y (<40 y group) with that in a group of breast cancer patients older than 40 y (≥40 y group). An assessment of associations between distant metastases and tumor characteristics was a second objective of the present study. **Methods:** A retrospective single-institution study was performed on women who had breast cancer and no prior malignancy, who were asymptomatic for metastatic lesions on initial clinical examination, and who had initial ^{18}F-FDG PET/CT within 3 mo after pathologic breast cancer diagnosis and before initial treatment. On the basis of these criteria, data for 2 groups of women differing only in age (<40 y and ≥40 y) were extracted from the hospital information system of Curie Institute–Paris. ^{18}F-FDG PET/CT examinations were reviewed, and the DMR was recorded for each clinical stage subgroup (stages I–III). **Results:** For each group (<40 y and ≥40 y), 107 patients were included, with the same number of patients in each clinical stage subgroup (12 stage I patients, 32 stage IIA patients, 30 stage IIB patients, and 33 stage III patients). The ages of the patients (mean ± SD) were 34.5 ± 4.0 y (<40 y group) and 56.0 ± 10.7 y (≥40 y group). No significant difference in DMRs was observed between the <40 y group and the ≥40 y group (DMRs, 21% and 22%, respectively; $P = 1$). The DMRs in patients not selected for age were 8% for stage I, 11% for stage IIA, 15% for stage IIB, and 44% for stage III. **Conclusion:** The DMR was not significantly higher in younger breast cancer patients (<40 y) than in older breast cancer patients (≥40 y), ruling out the assumption that undetected metastases at diagnosis explain the poorer outcome of younger women. However, our results highlight the high yield of ^{18}F-FDG PET/CT for initial breast cancer staging, even in stage II patients, whatever their age.

Key Words: breast cancer; PET; ^{18}F-FDG; age; metastases

Breast cancers affect women younger than 40 y at rates of 5%–7% (*1*). Women in this age category have lower breast cancer–specific survival than older women (*2*). In a large epidemiological study, Gnerlich et al. showed that specific mortality was higher in women younger than 40 y and diagnosed with stage I or II disease than in older women diagnosed with stage I or II disease (*3*).

One possible hypothesis for this higher specific mortality is that initial staging could underestimate distant metastases in low stages more often in women younger than 40 y than in older women. In a recent study, Riedl et al. took advantage of the superiority of ^{18}F-FDG PET/CT over conventional imaging for the detection of breast cancer metastases (*4–8*) to examine this hypothesis; they reported relatively high distant metastasis rates (DMRs) in patients younger than 40 y (from 17% at stage IIB to 50% at stage IIIB) (*9*). These DMRs appeared to be higher than the range of 11%–36.5% previously reported for stage IIB–IIIB patients (*10*). However, comparisons of studies with different designs have a limited impact (*11*), emphasizing the need for studies comparing the yield from ^{18}F-FDG PET/CT staging in patients younger than 40 y with that in patients older than 40 y.

The question as to whether initial staging in women younger than 40 y underestimates distant metastases in stages I and II is of great importance for staging recommendations. Indeed, current international guidelines recommend the use of ^{18}F-FDG PET/CT only for clinical stages III and IV, regardless of age (*12*); U.S. guidelines do not recommend the systematic use of ^{18}F-FDG PET/CT for breast cancer staging but state that "^{18}F-FDG PET/CT may be helpful in identifying unsuspected regional nodal disease or distant metastases in locally advanced breast cancer when used in addition to standard imaging studies" (*13*).

In this context, our objectives were to compare the DMRs on initial ^{18}F-FDG PET/CT in a group of breast cancer patients younger than 40 y (<40 y group) with that in a group of breast cancer patients older than 40 y (≥40 y group) and to search for associations between DMRs and tumor characteristics.

MATERIALS AND METHODS

Study Design

This retrospective single-institution study was approved by the local ethics committee of Curie Institute–Paris, and the requirement to obtain informed consent was waived. The hospital information system was screened to extract data for women treated for breast cancer at Curie Institute, Paris, France, between 2006 and 2015.

For the <40 y group, data for patients were automatically extracted from the PACS on the basis of the following selection criteria: ^{18}F-FDG PET/CT scans performed for breast pathology and an age of less than 40 y. The electronic medical records were reviewed to exclude patients with any of the following exclusion criteria: male patients, patients with disease other than breast cancer, patients with prior malignancy, patients symptomatic for metastatic lesions on initial clinical examination, and patients who underwent initial ^{18}F-FDG PET/CT more than 3 mo after pathologic diagnosis or after initial chemotherapy/endocrine therapy/radiation therapy.

The following parameters were extracted from the electronic medical records: age at the time of initial PET/CT, clinical stage (based on clinical examination, mammography, breast MRI, and ultrasonography; according to the *AJCC Cancer Staging Manual* (*14*)), tumor grade (according to the modified Scarff–Bloom–Richardson system), histology, original ^{18}F-FDG PET/CT report, and molecular phenotype. Hormone receptor status was assessed with immunohistochemistry tests. Tumors were considered estrogen-positive in cases of moderate or high positivity in at least 10% of cells. The same criteria were used for the progesterone receptor. Tumors were considered HER2-positive if more than 30% of cells showed definite membrane staining. Fluorescence in situ hybridization was used in cases of ambiguity.

For the ≥40 y group, the PACS was screened for ^{18}F-FDG PET/CT scans performed for breast pathology and an age of greater than or equal to 40 y. Data were extracted in alphabetical order of patients' names. The electronic medical records were reviewed to exclude patients with any of the exclusion criteria applied to the <40 y group (described earlier). The clinical stage was checked for each patient. When the number of patients with a given stage subgroup reached that in the corresponding <40 y group, the corresponding clinical stage became an exclusion criterion, so that the number of patients older than 40 y was matched with the number of patients younger than 40 y for each clinical stage (I, IIA, IIB, and III).

^{18}F-FDG PET/CT Acquisition and Interpretation

Unless otherwise specified, acquisitions were performed on a hybrid PET/CT scanner (Philips Gemini GXLi 16). Patients fasted for at least 4 h before ^{18}F-FDG administration. Only drinking of water was allowed and encouraged for good hydration. Patients were injected intravenously with ^{18}F-FDG at 5 MBq/kg when the plasma glucose concentration was less than 2.0 g/L. After ^{18}F-FDG administration and during the 60-min uptake phase, patients avoided exercising, talking, or chewing. A standard protocol was used to acquire scans from the midthigh to the vertex, with 2 min per bed position. Low-dose CT scans were used for attenuation correction.

All PET/CT scans were reinterpreted by an interpreter who was unaware of the original PET/CT report and any other imaging that could have been ordered in parallel (morphologic imaging or bone scanning). The interpreter had 20 y of PET/CT experience. In case of disagreement with the original PET/CT report, a second interpreter was consulted to determine a consensus.

The interpretation of malignant lesions was based on the combined anatomic information and metabolic information from PET/CT images. For distant lymph nodes, CT features (such as round shape, dense center, and necrosis) and the topography of node distribution were considered. Symmetric hypermetabolic mediastinohilar nodes were not considered positive for metastasis without histologic confirmation, which was performed in one patient. Asymmetric hypermetabolic mediastinohilar nodes were rated positive only in the absence of a homolateral active infectious process. For liver lesions, ^{18}F-FDG uptake was considered to indicate malignancy when it exhibited a focal increase that was significantly higher than the surrounding background (*15,16*). The lungs were considered to have metastatic disease when several hypermetabolic nodular lesions were detected in different lung

segments. For bone lesions, high uptake in a classic area of metastasis was considered malignant even when the results on coregistered CT images were normal (*17*). Bone ^{18}F-FDG uptake associated with typical degenerative findings on CT was not considered to be metastatic. A multidisciplinary committee considered malignant lesions after the initial workup before making a therapeutic decision. Finally, lesions revealed by ^{18}F-FDG PET/CT were considered to be malignant on the basis of follow-up imaging and response to treatment.

For each patient, the anatomic location of a metastatic lesion was based on the *AJCC Cancer Staging Manual* classification (*14*): axillary, internal mammary, supraclavicular, or distant lymph node, lung, liver, or bone. Evidence of a malignant visceral lesion (distant lymph node, liver, or lung) or bone lesion on ^{18}F-FDG PET/CT was considered to indicate distant metastases.

Statistical Analysis

Fisher exact tests were used to assess statistical differences between the <40 y group and the ≥40 y group for tumor type, tumor grade, receptor phenotype, and DMR.

Tumor grades were grouped as grade 1, 2, or 3. Receptor profiles were grouped as hormone receptor–positive/HER2-negative (HR+/HER2−), HER2-positive (HER2+), and triple-negative breast cancer (TNBC). Associations between pathologic characteristics (grade and receptor profile) and DMRs were assessed with logistic regression. The odds ratio and the 95% confidence interval were provided for each comparison. P values of less than 0.05 were considered statistically significant. All analyses were performed with R software (*18*).

RESULTS

Characteristics of Patients Younger Than 40 Years

Data for 281 patients younger than 40 y and undergoing ^{18}F-FDG PET/CT for breast pathology were extracted from the PACS. On the basis of the aforementioned exclusion criteria, 174 patients were excluded, so that 107 patients were included in the <40 y group. About 93% of these patients underwent ^{18}F-FDG PET/CT examinations with the same PET/CT system (Philips Gemini GXLi 16) at Curie Institute–Paris. Data acquired with other systems were transferred to our PACS. Clinical stages for patients were classified as follows: 12 with stage I, 32 with stage IIA, 30 with stage IIB, and 33 with stage III. The patients were 34.5 ± 4.0 y old (mean ± SD). Pathology revealed that most tumors were invasive ductal (89%) and grade 3 (73%) tumors. Receptor phenotypes were almost equally distributed among the 3 phenotype groups: HR+/HER2− (34%), HER2+ (33%), and TNBC (33%).

Characteristics of Patients 40 Years Old or Older

The same number of patients (107) was included in the ≥40 y group, with the distribution of clinical stages matching that in the <40 y group, that is, 12 stage I, 32 stage IIA, 30 stage IIB, and 33 stage III patients. About 88% of these patients underwent ^{18}F-FDG PET/CT examinations with the Philips Gemini GXLi 16 at our institution. Data acquired elsewhere were transferred to our PACS. The patients were 56.0 ± 10.7 y old. Pathology revealed that most tumors were invasive ductal (80%) and grade 3 (51%) tumors. Receptor phenotypes were HR+/HER2− (50%), HER2+ (24%), and TNBC (26%).

The main characteristics of the patients in the 2 age groups are shown in Table 1.

Detection of Distant Metastases by ^{18}F-FDG PET/CT

Table 2 shows the numbers of patients in the <40 y group and the ≥40 y group for whom ^{18}F-FDG PET/CT revealed distant

TABLE 1
Characteristics of Patients and Tumors at Diagnosis

	Group		
Characteristic	<40 y old	≥40 y old	P
No. of patients	107	107	
Age (y)*	34.5 ± 4.0	56.0 ± 10.7	
AJCC stage before PET/CT			
I	12 (11)	12 (11)	
IIA	32 (30)	32 (30)	
IIB	30 (28)	30 (28)	
III	33 (31)	33 (31)	
Tumor type			
Invasive ductal	95 (89)	86 (80)	0.13
Invasive lobular	1 (1)	9 (8)	0.02
Other	11 (10)	12 (11)	
Tumor grade			
1	3 (3)	10 (9)	0.08
2	26 (24)	42 (39)	0.03
3	78 (73)	55 (51)	0.002
Receptor phenotype			
HR$^+$/HER2$^-$	36 (34)	53 (50)	0.03
HER2$^+$	35 (33)	26 (24)	0.23
TNBC	35 (33)	28 (26)	0.37
Unspecified	1 (1)		

*Reported as mean ± SD.

AJCC = American Joint Committee on Cancer.

Data are reported as number (percentage) of patients unless otherwise indicated.

metastases. In the <40 y group, distant metastases were present in 21% of the patients (23/107). The DMRs were 8% for stage I (1/12), 9% for stage IIA (3/32), 17% for stage IIB (5/30), and 42% for stage III (14/33). Bone-only metastases were detected in 11 patients, viscus-only metastases were detected in 6 patients (distant lymph nodes in 6 patients and lung in 2 patients), and bone and visceral metastases were detected in 6 patients (distant lymph nodes in 5 patients, lung in 1 patient, and liver in 2 patients). Figure 1 shows typical ^{18}F-FDG PET/CT images for a younger patient (<40 y) with metastases.

In the ≥40 y group, distant metastases were present in 22% of the patients (24/107). The DMRs were 8% for stage I (1/12), 13% for stage IIA (4/32), 13% for stage IIB (4/30), and 45% for stage III (15/33). Bone-only metastases were detected in 7 patients, viscus-only metastases were detected in 9 patients (distant lymph nodes in 5 patients, lung in 1 patient, and liver in 3 patients), and bone and visceral metastases were detected in 8 patients (distant lymph nodes in 3 patients, lung in 1 patient, liver in 5 patients, and adrenal gland in 1 patient). Figure 2 shows typical ^{18}F-FDG PET/CT images for an older patient (≥40 y) with metastases.

Fisher exact tests revealed no significant difference in DMRs between the <40 y group (DMR, 21%) and the ≥40 y group (DMR, 22%) (P = 1). Subgroup analysis for each clinical stage (I–III) also showed no significant difference in DMRs.

Association of Tumor Characteristics and Distant Metastases

No statistically significant relationship between DMR and tumor grade was found (P = 0.53 for the <40 y group and P = 0.23 for the ≥40 y group). A significant negative relationship between DMR and TNBC phenotype was found for both patient groups (for the <40 y group: P = 0.04; odds ratio, 0.24; 95% confidence interval, 0.05–0.77; for the ≥40 y group: P = 0.01; odds ratio, 0.09; 95% confidence interval, 0.01–0.46).

DISCUSSION

The primary objective of this study was to compare the DMRs at the time of diagnosis between younger women (<40 y old) and older women (≥40 y old) with breast cancer. The representativeness of our 2 age groups was compared with the general population for tumor characteristics. As shown in Table 1, several tumor characteristics differed between the 2 age groups. Regarding tumor type, patients in the <40 y group had significantly fewer invasive lobular tumors than patients in the ≥40 y group (1/107 vs. 9/107; P = 0.02). This difference is in agreement with a previous study reporting a strong dependence between age and tumor type in breast cancer (19). The rate of lobular tumors was approximately 5-fold lower in premenopausal patients than in postmenopausal patients (19). In the present study, the mean age of the 10 patients with lobular tumors was 57.8 y and the mean age of the 204 patients with nonlobular tumors was 44.1 y, confirming the age-related difference in tumor type.

In terms of tumor grade, our results showed more grade 3 tumors in the <40 y group than in the ≥40 y group (~45% higher rate in the <40 y group; P = 0.002). This difference was also reported by Gnerlich et al. in a large cohort study, in which the rate of grade 3 tumors in women younger than 40 y was approximately 60% higher than that in older women (3). The 2 age groups in our study exhibited a similar, although less pronounced, difference. The rate of grade 2 tumors also differed between the 2 age groups in our study. Here again, our data (~40% lower rate of grade 2 tumors in the <40 y group than in the ≥40 y group; P = 0.03) agreed with those of Gnerlich et al. (3).

The phenotypic characteristics of breast cancer have been proposed to account for mortality differences between younger patients and older patients (20), so that the representativeness of our

TABLE 2
Numbers of Patients with Distant Metastases on ^{18}F-FDG PET/CT

	Group		
AJCC stage before PET/CT (no. of patients)	<40 y old	≥40 y old	P
I (12)	1 (8)	1 (8)	1
IIA (32)	3 (9)	4 (13)	1
IIB (30)	5 (17)	4 (13)	1
III (33)	14 (42)	15 (45)	1
All (107)	23 (21)	24 (22)	1

AJCC = American Joint Committee on Cancer.
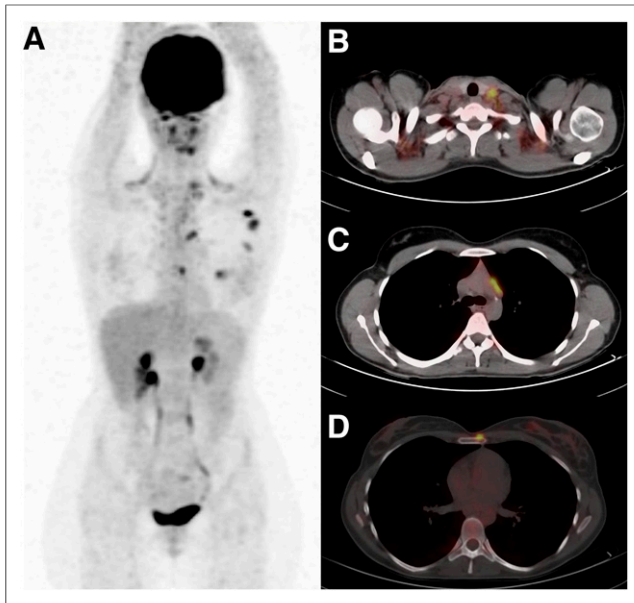Data are reported as number (percentage) of patients.

FIGURE 1. ^{18}F-FDG PET/CT at initial staging in 35-y-old patient with invasive ductal carcinoma of left breast, classified as clinical stage IIA disease. (A) Maximum-intensity projection. (B–D) Axial PET/CT fusion images showing cervical (B) and mediastinal (C) lymph node and bone (D) metastases.

patient groups for receptor phenotypes is a crucial point. The ≥40 y group had receptor profiles very similar to those reported for breast cancer patients not selected for age: 50% HR$^+$/HER2$^-$ (range reported in the literature: 51%–58% (*10,21,22*)), 24% HER2$^+$ (vs. 20%–23%), and 26% TNBC (vs. 19%–23%). The phenotype profiles of the <40 y group exhibited significantly less HR$^+$/HER2$^-$ than those of the ≥40 y group (34% vs. 50%; $P = 0.03$) and slightly more HER2$^+$ (33% vs. 24%; $P = 0.23$) and TNBC (33% vs. 26%; $P = 0.37$). These age-related differences are in agreement with previous studies reporting significantly lower HR$^+$/HER2$^-$ rates in younger patients than in older patients (*23*), unchanged or increased HER2$^+$ rates (*23–25*), and increased TNBC rates (*23,26,27*). Altogether, the tumor characteristics of our 2 patient groups seemed to be representative of those of breast cancer patients in the general population.

To our knowledge, until now, only one study reported DMRs determined by PET/CT at initial staging of breast cancer in women younger than 40 y (*9*). The DMRs in our <40 y group compared well with those in the study of Riedl et al. (*9*): 8% (vs. 5% (*9*)) for stage I, 9% (vs. 5%) for stage IIA, 17% (vs. 17%) for stage IIB, and 42% (vs. 39%) for stage III. In our ≥40 y group, the DMRs were 8% for stage I, 13% for stage IIA, 13% for stage IIB, and 45% for stage III. These rates are in good agreement with previously reported metastasis rates of 11%–15% for stage IIB breast cancer and 18%–47% for stage III breast cancer, whatever the age (*5,10,28*). However, the DMR for the IIA subgroup in the present study was higher than previously published data for the general population (13% vs. 2%–6%). This difference can be partially explained by the lack of systematic histologic proof in the present study, possibly resulting in DMR overestimation. Another explanation can be found in our inclusion criteria; as opposed to Groheux et al. (*10,28*), we did not exclude patients staged node-positive after sentinel node biopsy. Indeed, our objective was to compare 2 age groups rather than to establish the yield of PET/CT at

different stages. Therefore, our data do not argue against those of Groheux et al., who reported a significantly higher yield of PET/CT for stage IIB than for stage IIA in sentinel node–negative patients (*10,28*).

To our knowledge, the present study is the first comparative study of metastatic status between 2 age groups of women with breast cancer. A statistical comparison of the <40 y group and the ≥40 y group did not reveal a significant difference in DMRs determined by PET/CT for any stage subgroup (Table 1). The lack of a difference between age groups was recently suggested on the basis of a comparison of studies performed by different teams (*11*).

The large epidemiology study on breast cancer by Gnerlich et al. (*3*) showed that only women who had clinical stages I and II and were younger than 40 y had a poorer outcome than older women, as opposed to stage III patients. The finding of similar DMRs in the 2 age groups for stages I, II, and III does not support the hypothesis of undetected metastases at diagnosis as an explanation for the poorer outcome of younger women with breast cancer (*9*). However, our results highlight the high yield of ^{18}F-FDG PET/CT for initial breast cancer staging in stages II and III (*9,10*).

We found a significant association between the TNBC phenotype and the DMR for the 2 age groups. Surprisingly, the relationship was negative; that is, the TNBC phenotype was associated with a lower DMR. A literature review revealed higher rates of recurrence and reduced breast cancer–specific survival with TNBC (*29–32*) but no significant difference in terms of stage or lymph node positivity with other breast cancers at diagnosis (*31*). Regarding the rate of distant metastases at diagnosis, the literature data showed either higher or lower rates with TNBC than with breast cancers that were not TNBC (*10,33–35*), but no study reported statistically significant lower rates. Further studies are needed to confirm the statistical significance of this relationship.
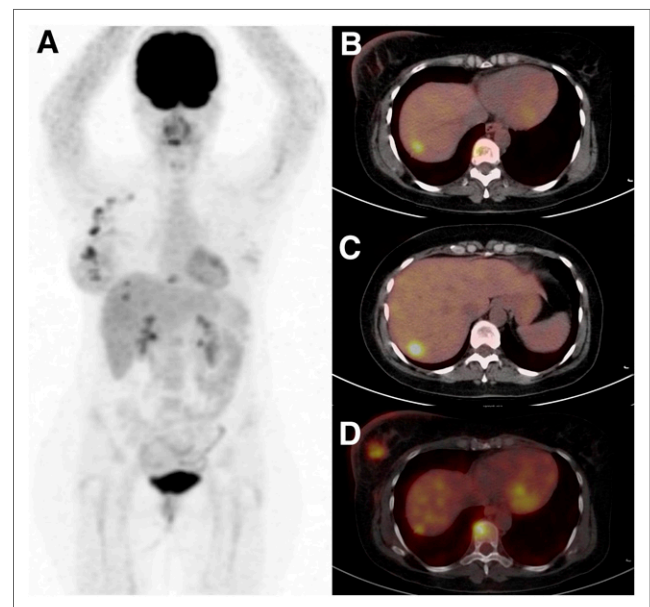

FIGURE 2. ^{18}F-FDG PET/CT at initial staging in 46-y-old patient with invasive ductal carcinoma of right breast, classified as clinical stage IIIA disease. (A) Maximum-intensity projection. (B–D) Axial PET/CT fusion images showing liver (B and C) and bone (D) metastases.

One limitation of the present study is the single-institution retrospective design, which could lead to certain selection biases. For this reason, we carefully checked the representativeness of the 2 age groups in terms of tumor characteristics. On the other hand, an advantage of the single-institution design is that patients in the 2 age groups were monitored in the same oncology department, and their PET/CT scans were interpreted by the same physician. In addition, for most of the 214 patients (90%), PET/CT scans were done on the same system. Therefore, possible biases are likely to have affected both age groups in the same way, limiting the impact on group comparisons.

In the present study, we did not assess the correspondence of ^{18}F-FDG PET/CT findings for metastases with histology or morphologic imaging as proof of malignancy because that was not the goal of the study. Furthermore, only a small percentage of patients had pathologic verification of ^{18}F-FDG PET/CT findings for distant metastases.

The small number of patients is another limitation, mainly due to the low incidence of breast cancer in women younger than 40 y (1). The number of patients was particularly small for stage I, with only 12 patients in each age group, whereas 62 stage II patients and 33 stage III patients were included in each age group. The small number of stage I patients was due to current guidelines recommending against the routine use of imaging to detect asymptomatic distant metastases at the time of diagnosis for stage I patients. Given that the higher specific mortality of women younger than 40 y (compared with older women) only holds for stages I and II (3) and given the limited number of stage I patients, our results should be interpreted as ruling out higher DMRs in women younger than 40 y with stage II than in older women with stage II.

CONCLUSION

We observed no significant difference in DMRs between women younger than 40 y and older women for any clinical stage. The DMRs ranged from 8% (stage I) to 42% (stage III) in women younger than 40 y and from 8% (stage I) to 45% (stage III) in older women. Therefore, our data do not support the hypothesis that undetected metastases at diagnosis explain the poorer outcome of younger women with breast cancer. In the 2 age groups (<40 y and ≥40 y), the DMR for TNBC was lower than that for other phenotypes. Further studies are needed to confirm this observation. Our results highlight the high yield of ^{18}F-FDG PET/CT for the initial staging of breast cancer, even in stage II patients, whatever their age. These data add to previous observations in stage IIB and III patients suggesting that women with breast cancer might benefit from ^{18}F-FDG PET/CT staging, even at stage IIB.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

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