
¹⁸F-FDG PET/CT for Systemic Staging of Newly Diagnosed Breast Cancer in Men

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¹⁸F-FDG PET/CT has demonstrated substantial value in systemic staging of newly diagnosed breast cancer in women. However, it is not known whether breast cancer in male patients benefits similarly. This study assesses ¹⁸F-FDG PET/CT systemic staging in patients with newly diagnosed male breast cancer and determines detection rates for unsuspected distant metastases stratified by pre-PET/CT stage. **Methods:** In this Institutional Review Board–approved retrospective study, our Health Care Information System was screened for stage I–III male patients with breast cancer who underwent ¹⁸F-FDG PET/CT before systemic or radiation therapy from 2004 to 2017. Initial stage was determined by mammography, ultrasound, or surgery. ¹⁸F-FDG PET/CT was evaluated to identify unsuspected extraaxillary regional nodal and distant metastases, and a post-PET/CT stage was determined. Rates of upstaging to stage IV were determined for each initial stage. **Results:** During the 14-y period, 10,124 unique patients underwent ¹⁸F-FDG PET/CT for breast cancer at our institution. Of these, 106 patients were men, and 39 of these patients were imaged at initial staging and met the inclusion criteria. Median age was 62 y (range, 31–90 y), most had ductal carcinoma (95%), and most were estrogen receptor–positive (97%). In 7 of 39 patients (18%), ¹⁸F-FDG PET/CT identified previously unsuspected distant metastases, which increased patient stage to IV. This included 3 of 19 (16%) initial stage IIB patients and 4 of 12 (33%) initial stage III patients. ¹⁸F-FDG PET/CT also detected an unsuspected synchronous lymphoma in 1 patient. **Conclusion:** ¹⁸F-FDG PET/CT revealed previously unsuspected distant metastases in 16% of male patients with pre-PET/CT stage IIB breast cancer and 33% of those with stage III breast cancer. These rates are comparable to previously published upstaging rates in female patients. ¹⁸F-FDG PET/CT demonstrates value for systemic staging of male patients with breast cancer and should be considered for use in newly diagnosed patients, particularly those with stage IIB and III disease.

Key Words: male breast cancer; ¹⁸F-FDG PET/CT; staging

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PET/CT with ¹⁸F FDG has proven clinical value in appropriately selected women with breast cancer, including for the

detection of unsuspected extraaxillary regional nodal metastases and distant metastases in patients with newly diagnosed breast malignancy (1–6). This is reflected in National Comprehensive Cancer Network guidelines, which consider systemic staging with ¹⁸F-FDG PET/CT for patients with newly diagnosed stage III breast cancer (7). However, these guidelines are predominantly based on cohorts of female patients, as breast cancer is far more common among women. There is still limited information regarding the value of ¹⁸F-FDG PET/CT for male breast cancer (8–10), and no sex-specific recommendations or guidelines have been issued for the use of ¹⁸F-FDG PET/CT for initial staging of breast cancer (7,11).

Although there are many similarities between breast cancer in women and men, there are also several notable differences. Breast cancer is uncommon in men, accounting for only 1% of all breast cancers (11,12). As there are no screening guidelines for the detection of breast cancer in men, male breast cancer is often detected at more advanced stages than in women (13). At initial detection, male breast cancers are larger than those in women and nodal involvement is more common (13). Male breast cancers are also more commonly higher grade than breast cancers in women (14). Male breast cancers are almost always ductal in histology, whereas in women about 15% are lobular in histology (15,16). This is significant, as lobular breast malignancies and their metastases are less ¹⁸F-FDG–avid than ductal malignancies (17–22), and ¹⁸F-FDG PET/CT may have less impact on the systemic staging of lobular breast cancers (22). Male breast cancers are almost always estrogen receptor (ER)–positive; in women, about 80% are ER–positive. This is significant, as ER–positive tumors have been shown to demonstrate lower ¹⁸F-FDG avidity (23–25). These epidemiologic and biologic differences may affect the value of ¹⁸F-FDG PET/CT in male breast cancer as compared with female breast cancer.

Given the rarity of male breast cancer, it is not surprising that data on the use of ¹⁸F-FDG PET/CT are limited (8–10). Groheux et al. reported on ¹⁸F-FDG PET/CT in 15 men with breast cancer (9). Seven of these patients were evaluated at initial diagnosis, and among these, 2 demonstrated lesions suggestive of distant metastases. Evangelista et al. evaluated 25 men with breast cancer who underwent ¹⁸F-FDG PET/CT. Five of these patients were scanned at initial diagnosis. By report, osseous lesions were seen in 2 patients. Vatankulu et al. discussed 15 male breast cancer patients, all of whom underwent ¹⁸F-FDG PET/CT for initial staging. Again, 2 patients had lesions suggestive of distant metastases. In none of these cohorts was pre-PET/CT stage reported or histologic proof provided for the suspected distant metastases.

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Given the lack of data and the absence of guidelines for ^{18}F -FDG PET/CT in the initial staging of male breast cancer, an analysis of the value of ^{18}F -FDG PET/CT for systemic staging of male breast cancer is warranted. In this manuscript, we retrospectively reviewed the database of a large cancer center to evaluate the value of ^{18}F -FDG PET/CT in patients with male breast cancer, categorized the rate of distant metastasis detection by pre-PET stage, and demonstrated histologic proof for lesions suggestive of distant metastases.

MATERIALS AND METHODS

Study Design and Patients

This retrospective single-institution study was performed in compliance with the Health Insurance Portability and Accountability Act and with Institutional Review Board approval. The requirement to obtain informed consent was waived. The Memorial Sloan Kettering Cancer Center Health Care Information System was screened for patients with male breast cancer who underwent ^{18}F -FDG PET/CT between January 2004 and December 2017, before beginning treatment with chemotherapy, hormonal therapy, or radiation therapy. Electronic medical records were reviewed, and patients with the following characteristics were excluded: known stage IV disease for the current malignancy before ^{18}F -FDG PET/CT, symptoms suggestive of metastatic disease, prior or concurrent malignancies (except non-melanoma skin cancer), or systemic therapy or radiation before ^{18}F -FDG PET/CT. Surgical management of the primary breast lesion and axillary nodes was allowed. Age at diagnosis and race were recorded for each patient. Histology and grade, as well as ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) receptor status were recorded for each primary tumor. Criteria for ER-positive (ER+) and HER2-positive (HER2+) immunohistochemistry and in situ hybridization were based on the recommendations of the American Society of Clinical Oncology (26,27). Tumors with positive immunochemistry for ER or PR, as well as negative for HER2, were defined as ER+/HER2-negative (HER2-) tumors. Tumors with positive immunochemistry or in situ hybridization for HER2, regardless of status of estrogen or PR, were defined as HER2+. Tumors negative for all 3 receptors were classified as triple-negative. The presence or absence of a BRCA1 or BRCA2 mutation was recorded, if known. Survival data were recorded from all patients using the Memorial Sloan Kettering Cancer Center Health Care Information System to document whether the patient was alive at each follow-up appointment and if there was a date of death.

Determination of Initial Pre-PET/CT Stage

Initial stages were determined according to the seventh edition of the American Joint Committee on Cancer Staging Manual (28). Initial clinical stage was determined from physical examination, mammography, breast ultrasound, or surgical findings.

PET/CT Imaging and Interpretation

All patients in this retrospective study underwent ^{18}F -FDG PET/CT before systemic or radiation therapy. Before ^{18}F -FDG injection for PET/CT, patients fasted for at least 4–6 h. Each patient was injected intravenously with 444–555 MBq of ^{18}F -FDG when plasma glucose was less than 200 mg/dL. After ^{18}F -FDG injection, patients rested for a scheduled 60-min uptake period followed by image acquisition on one of several GE Healthcare Discovery PET/CT systems. PET/CT scans were acquired with the patient supine, from the midskull to the mid thigh. In most cases, low-dose CT scans with oral contrast were obtained. Occasionally, intravenous contrast was administered. Images were reviewed on a PACS (GE Healthcare), displaying a maximum-intensity-projection image and multiplanar PET, CT, and PET/CT fusion images. According to standard ^{18}F -FDG PET/CT reporting,

uptake was considered abnormal when it was focal, was not considered physiologic or inflammatory, and had intensity greater than the local background. Suspicion for malignancy was based on the integration of metabolic information from the PET images and anatomic information from the CT images and fused PET/CT images. PET/CT studies were reinterpreted by a radiologist dually boarded in diagnostic radiology and nuclear medicine with 13 y of PET/CT experience. Evidence of unsuspected regional extraaxillary nodal metastases and distant metastases were recorded, and if they were noted on imaging, then a new post-PET/CT stage was assigned.

Verification of Metastases

Histology was the preferred method to verify malignancy for ^{18}F -FDG PET/CT findings. When histology was not available, follow-up imaging was used. Lesions had to show typical features of metastatic disease on initial imaging and show progression or response to treatment on follow-up imaging. Time interval between ^{18}F -FDG PET/CT and reference standard test (biopsy or follow-up imaging) was determined.

Statistical Analysis

Medians and ranges were used to summarize continuous variables and frequencies, and percentages were used to summarize categorical variables, including distant metastases and upstaging. Race was grouped into African American, Asian, Caucasian, and other. Upstaging rates were provided by pre-PET stage along with binomial confidence intervals. The associations between clinical characteristics and upstaged to stage 4 status were assessed with the Fisher exact test and the Wilcoxon rank-sum test, where appropriate. Overall survival (OS) was calculated from time of PET scan until death. Patients alive at last follow-up were censored. OS was estimated with Kaplan–Meier methods. Two sided *P* values less than 0.05 were considered statistically significant, and all analyses were performed using SAS 9.4 (The SAS Institute).

RESULTS

Characteristics of Patients and Primary Breast Malignancies

Our search of the Memorial Sloan Kettering Cancer Center Health Care Information System from 2004 to 2017 identified

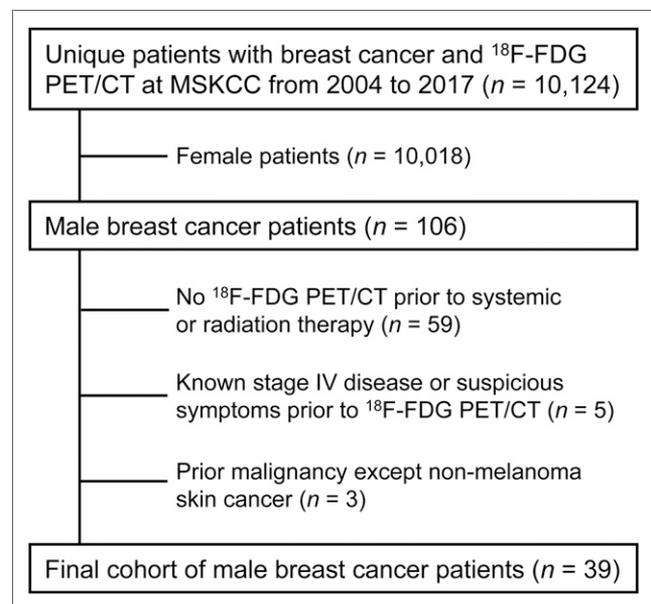


FIGURE 1. Standards for Reporting of Diagnostic Accuracy Diagram (STARD) for patients in this study. MSKCC = Memorial Sloan Kettering Cancer Center.

TABLE 1
Characteristics of Patients with Male Breast Cancer and Their Primary Tumors

Characteristic	n (%)
No. of patients	39
Median age (y)	62 (range, 31–90)
Race	
African American	4 (10)
Asian	3 (8)
Caucasian	31 (79)
Other	1 (3)
Histology	
Ductal	37 (95)
Adenoid cystic	1 (3)
Papillary	1 (3)
Tumor grade	
High	28 (72)
Intermediate	9 (23)
Unknown	2 (5)
Receptor status	
ER+/HER2-	33 (84)
HER2+	5 (13)
Triple-negative	1 (3)
BRCA1 or 2 mutation	
Yes	4 (10)
No	16 (41)
Unknown	19 (49)
Initial staging	
Pre-PET/CT stage	
I	2 (5)
IIA	6 (15)
IIB	19 (49)
IIIA	5 (13)
IIIB	4 (10)
IIIC	3 (8)
T stage	
T1	5 (13)
T2	29 (74)
T3	1 (3)
T4	4 (10)
N stage	
N0	10 (26)
N1	22 (56)
N2	4 (10)
N3	3 (8)
M stage, M0	39 (100)

Data in parentheses are percentages, unless otherwise indicated.

10,124 unique patients who had undergone ¹⁸F-FDG PET/CT for breast cancer, 106 of whom were men. Of these 106 patients, 67 were excluded for systemic or radiation therapy before ¹⁸F-FDG PET/CT, known stage IV disease before ¹⁸F-FDG PET/CT, or history of a prior malignancy. This left a cohort of 39 patients who met all inclusion and exclusion criteria. A Standards for Reporting of Diagnostic Accuracy Diagram for patients in this study is provided in Figure 1.

The median age of the final cohort of 39 patients with male breast cancer was 62 y (range, 31–90 y). Of these 39, 37 primary breast malignancies (95%) were ductal in histology and 38 of 39 (97%) of primary breast malignancies were ER+. As 5 of these malignancies were also HER2+, they were categorized as HER2+ tumors, whereas the 33 ER+ tumors that were negative for HER2 were categorized as ER+/HER2-. One tumor was triple-negative for ER, PR, and HER2. Patient and tumor demographics, including age, race, histology, tumor grade, receptor classification, and initial pre-PET/CT clinical stage, are summarized in Table 1.

Detection of Unsuspected Metastases by ¹⁸F-FDG PET/CT

¹⁸F-FDG PET/CT demonstrated findings suggestive of unsuspected distant metastases in 7 of 39 (18%, 95% confidence interval: 8%–34%) patients with male breast cancer (Figs. 2 and 3). Suspected metastatic sites included bone in 6, lung in 3, and distant nodal metastases in 3 patients. Four patients had metastatic disease involving more than one organ site. For 5 of 7 patients with ¹⁸F-FDG PET/CT findings suggestive of unsuspected distant metastases, metastases were confirmed by pathology. The time intervals between suspicious ¹⁸F-FDG PET/CT findings and pathologic confirmation in these 5 patients were 2, 7, 21, 27, and 64 d (median, 26 d). In the remaining 2 patients, metastatic disease was confirmed by follow-up imaging demonstrating resolution of ¹⁸F-FDG avidity in osseous lesions and new osseous sclerosis, consistent with treatment response to therapy and osseous healing (Fig. 3). The time interval between suspicious ¹⁸F-FDG PET/CT findings and follow-up imaging confirmation in these 2 patients was 94 and 123 d.

Stratified by pre-PET/CT clinical stage, ¹⁸F-FDG PET/CT demonstrated metastases in 0 of 8 (0%) patients with pre-PET/CT stage I or IIA, 3 of 19 (16%) patients with pre-PET stage IIB, and 4 of 12 (33%) patients with pre-PET/CT stage III male breast cancer (Table 2). Ninety-five percent confidence intervals for upstaging to distant metastatic disease were 4%–40% for patients with pre-PET stage IIB and 10%–65% patients with pre-PET stage III disease.

In no patients were unsuspected extraaxillary nodal metastases identified that resulted in a new post-PET/CT stage. No false-positives were noted for distant metastases among the patients with male breast cancer. Patients in this study were not down-staged by PET/CT results.

Associations Between Clinical Parameters and Upstaging

No significant differences were found between patients who were upstaged compared with those who were not for age (median, 56 y; range, 44–70 vs. median, 66 y; range, 31–90; *P* = 0.14), race (Caucasian, 86% (6/7) vs. 78% (25/32); *P* = 0.30), or receptor status (ER+/HER, 2%–100% (7/7) vs. 81% (26/32); *P* = 0.64). As only 2 patients had nonductal histologies, we did not examine the association between histology and upstaging rate. Additionally, almost half the patients (49%, 19/39) were missing BRCA status, so this was not examined further.

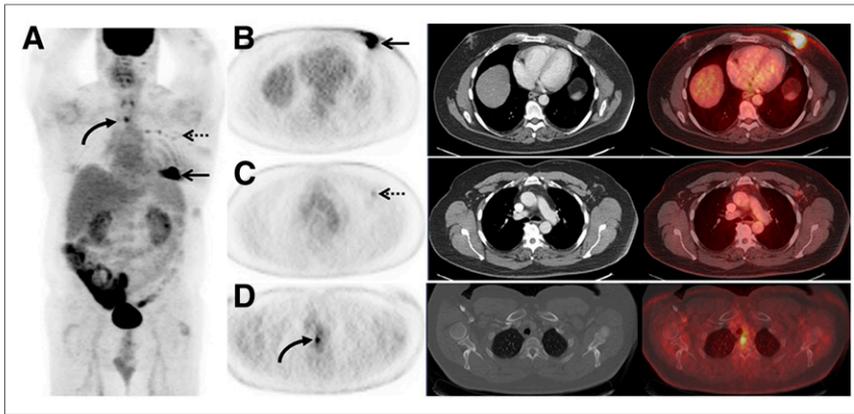


FIGURE 2. A 53-y-old man with a pre-PET/CT stage IIB breast cancer, which was upstaged to stage IV by ^{18}F -FDG PET/CT. (A) ^{18}F -FDG maximum-intensity-projection image demonstrates ^{18}F -FDG avidity in left breast (arrow), left axilla (dashed arrow), as well as overlying midline chest (curved arrow). (B) Axial ^{18}F -FDG PET, CT on soft-tissue window, and fused ^{18}F -FDG PET/CT demonstrate the ^{18}F -FDG-avid known primary left breast malignancy (arrow). (C) Axial ^{18}F -FDG PET, CT on soft-tissue window, and fused ^{18}F -FDG PET/CT demonstrate ^{18}F -FDG-avid known left axillary nodal metastases (dashed arrow). (D) Axial ^{18}F -FDG PET, CT on bone window, and fused ^{18}F -FDG PET/CT demonstrate ^{18}F -FDG avidity in midline chest on the maximum-intensity-projection image corresponding to a thoracic vertebra without CT correlate. This lesion was biopsied and proven to be a previously unsuspected osseous metastasis, increasing patient's stage to IV. This altered patient's management from surgical management to systemic therapy without surgical management.

OS

By the end of follow-up, 7 patients had died, with a 1-y OS of 97.1% (95% confidence interval, 80.9%–99.6%) and a 5-y OS of 72.6% (95% confidence interval, 50.2%–86.1%). Median follow-up in survivors was 47.3 mo (range, 0.4–102.3 mo). As only 7 patients died, we could not formally examine the association between OS and upstaging rates on ^{18}F -FDG PET/CT.

Synchronous Malignancies

^{18}F -FDG PET/CT resulted in the detection of an unsuspected synchronous lymphoma in 1 patient, which was proven by pathology. It was a clinically significant lymphoma for which the patient was subsequently treated.

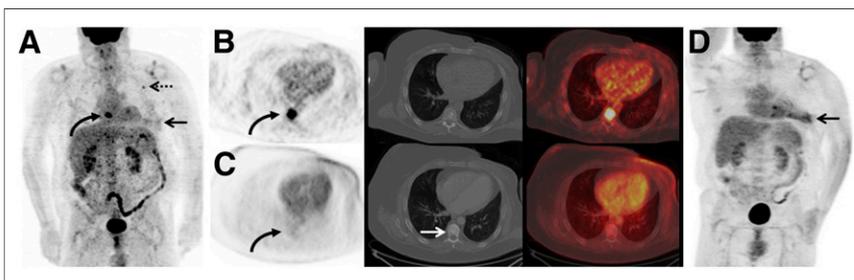


FIGURE 3. A 58-y-old man with a pre-PET/CT stage IIB breast cancer, which was upstaged to stage IV on ^{18}F -FDG PET/CT. (A) ^{18}F -FDG maximum-intensity-projection image demonstrates mild ^{18}F -FDG avidity in left mastectomy bed (arrow) and left axillary node (dashed arrow), as well as overlying midline chest (curved arrow). (B) Axial ^{18}F -FDG PET, CT on bone window, and fused ^{18}F -FDG PET/CT demonstrate an ^{18}F -FDG-avid thoracic vertebra (curved arrow) corresponding only with small, benign-appearing sclerotic focus on CT. This patient was subsequently treated with systemic therapy. (C) Axial ^{18}F -FDG PET, CT on bone tissue window, and fused ^{18}F -FDG PET/CT after systemic therapy demonstrate resolution of ^{18}F -FDG avidity (curved arrow) and increased sclerosis of the vertebra (white arrow), consistent with therapy response in an osseous metastasis and osseous healing. (D) ^{18}F -FDG maximum-intensity-projection image after systemic therapy demonstrates persistence of ^{18}F -FDG-avid postmastectomy inflammation (arrow) but resolution of avidity in the node and osseous metastasis.

DISCUSSION

Our retrospective review of patients with male breast cancer demonstrates that ^{18}F -FDG PET/CT detects unsuspected distant metastases at a rate of 16% for initial pre-PET/CT stage IIB disease and 33% for initial pre-PET/CT stage III disease. These rates are comparable to upstaging rates seen in female patients with breast cancer (1–6) and suggest a role for ^{18}F -FDG PET/CT in the initial staging of male patients with breast cancer, particularly for those with stage IIB–III disease based on physical examination, mammography, and ultrasound. The detection of unsuspected distant metastatic disease by ^{18}F -FDG PET/CT in these patients will increase the correct characterization of initial stage IV disease, which will result in substantial altering of treatment strategy and prognosis.

The probable impact of systemic staging with ^{18}F -FDG PET/CT can be seen in Figures 2 and 3. The patient in Figure 1 was initially stage IIB and underwent ^{18}F -FDG PET/CT at initial staging, before any therapy. ^{18}F -FDG PET/CT revealed unsus-

pected distant metastases, and thus stage IV disease. The treatment plan for this patient was changed from surgical management to systemic therapy without surgical management. The patient in Figure 2 was also initially stage IIB and underwent ^{18}F -FDG PET/CT after mastectomy but before further systemic or radiation therapy. ^{18}F -FDG PET/CT revealed unsuspected distant metastases, and thus stage IV disease. If the ^{18}F -FDG PET/CT had been performed before mastectomy, surgical management may have been foregone in lieu of systemic therapy.

No patients with stage I–IIA disease were found to have unsuspected distant metastases. Although the numbers of stage I–IIA patients were small, this is consistent with the low levels of upstaging in female patients with stage I–IIA breast malignancies (1–6). Avoiding ^{18}F -FDG PET/CT in these early-stage patients may help maximize the clinical utility of ^{18}F -FDG PET/CT. Even if the patient is presumed to be only stage I or IIA, signs or clinical symptoms that suggest metastatic disease may still warrant systemic staging, and the role of ^{18}F -FDG PET/CT in this situation has not been evaluated.

In this study, there were no false-positive findings for distant metastases on ^{18}F -FDG PET/CT. Low rates of false-positives for distant metastases have been reported in prior studies of ^{18}F -FDG PET/CT for female patients with breast cancer (29). The low rate of false-positive findings is supported by the high proportion of pathologic proof of distant metastases in our cohort. Only 2 patients with ^{18}F -FDG PET/CT findings suggestive of distant metastases were not pathologically proven, and these had confirmation from follow-up imaging demonstrating resolution of

TABLE 2
Summary of Patients with Male Breast Cancer Upstaged by ¹⁸F-FDG PET/CT Stratified by Pre-PET/CT Stage

Pre-PET/CT stage	Total	Post-PET/CT stage						IV (%)
		I	IIA	IIB	IIIA	IIIB	IIIC	
I	2	2						0 (0)
IIA	6		6					0 (0)
IIB	19			16				3 (16)
IIIA	5				4			1 (20)
IIIB	4					1	0	3 (75)
IIIC	3						3	0 (0)
Total	39	2	6	16	4	1	3	7 (18)

¹⁸F-FDG avidity after therapy and new osseous sclerosis representing healing of metastases (Fig. 2).

Unsuspected synchronous additional malignancies have been detected on ¹⁸F-FDG PET/CT studies at rates of 1%–2% (30,31). One of the 39 patients in this study had an unsuspected synchronous malignancy on the ¹⁸F-FDG PET/CT study performed for systemic staging of primary breast cancer, and this case was pathologically proven.

The study has several limitations. The retrospective single-institution study design lends itself to biases, for example, why these patients were initially selected to undergo ¹⁸F-FDG PET/CT. The potential for selection biases, including the possibility of unappreciated data that raises the risk of distant metastases, is inherent in retrospective studies. The number of patients in the cohort was small, limiting statistical analyses. However, male breast cancer is an uncommon malignancy and compared with prior available data, the number of male patients with breast cancer who underwent ¹⁸F-FDG PET/CT at initial staging was high and pathologic proof of PET/CT findings was available in most cases. This allowed for an evaluation of upstaging rates based on pre-PET/CT stage, which was previously unavailable. An evaluation of survival was planned for patients with male breast cancer; however, there were too few deaths in the cohort to conduct formal survival comparisons.

CONCLUSION

¹⁸F-FDG PET/CT revealed previously unsuspected distant metastases in 16% of male patients with stage IIB breast cancer and in 33% of male patients with stage III breast cancer. This demonstrates the potential value of ¹⁸F-FDG PET/CT for systemic staging at initial diagnosis of male breast cancer, particularly for patients with stage IIB and III disease.

DISCLOSURE

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