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

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Running title: PET staging of male breast cancer

ABSTRACT

^{18}F-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 benefit similarly. This study assesses ^{18}F-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 Healthcare Information System was screened for stage I-III male patients with breast cancer who underwent ^{18}F-FDG PET/CT prior to systemic or radiation therapy from 2004 to 2017. Initial stage was determined by mammography, ultrasound, and/or surgery. ^{18}F-FDG PET/CT was evaluated to identify unsuspected extra-axillary 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-year period, 10,124 unique patients underwent ^{18}F-FDG PET/CT for breast cancer at our institution. Of these, 106 patients were male, and 39 of these patients were imaged at initial staging and met the inclusion criteria. Median age was 62 years (range: 31-90), most had ductal carcinoma (95%), and most were ER+ (97%). In 7 of 39 patients (18%), ^{18}F-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. ^{18}F-FDG PET/CT also detected an unsuspected synchronous lymphoma in one patient.

Conclusion: ^{18}F-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. ^{18}F-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.

Keywords: Male breast cancer; ^{18}F-FDG PET/CT; staging

INTRODUCTION

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has proven clinical value in appropriately selected women with breast cancer, including for the detection of unsuspected extra-axillary regional nodal metastases and distant metastases in patients with newly diagnosed breast malignancy (*1-6*). This is reflected in National Comprehensive Cancer Network (NCCN) guidelines, which considers systemic staging with ^{18}F-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 ^{18}F-FDG PET/CT for male breast cancer (*8-10*) and no sex-specific recommendations or guidelines have been issued for the use of ^{18}F-FDG PET/CT for initial staging of breast cancer (*7,11*).

While 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, while in women about 15% are lobular in histology (*15,16*). This is significant, as lobular breast malignancies and their metastases are less FDG-avid than ductal malignancies (*17-22*), and ^{18}F-FDG PET/CT may have less impact on the systemic staging of lobular breast cancers (*22*). Male breast cancers are almost always estrogen receptor-positive; in women, about 80% are estrogen

receptor-positive. This is significant, as estrogen receptor-positive tumors have been shown to demonstrate lower FDG avidity (*23-25*). These epidemiologic and biologic differences may affect the value of ^{18}F-FDG PET/CT in male breast cancer as compared to female breast cancer.

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

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, categorize the rate of distant metastasis detection by pre-PET stage, and demonstrate histologic proof for lesions suspicious for 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 (HIPAA) and with Institutional Review Board (IRB) approval. The requirement to obtain informed consent was waived. The Memorial Sloan Kettering Cancer Center Healthcare Information System was screened for patients with male breast cancer who underwent ^{18}F-FDG PET/CT between January 2004 and December 2017, prior to beginning treatment with chemotherapy, hormonal therapy, or radiation therapy. Electronic medical records (EMR) were reviewed and patients with the following characteristics were excluded: Known stage IV disease for the current malignancy prior to ^{18}F-FDG PET/CT, symptoms suspicious for metastatic disease, prior or concurrent malignancies (except non-melanoma skin cancer), and/or systemic therapy or radiation prior to ^{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 estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) receptor status were recorded for each primary tumor. Criteria for ER+ and 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 estrogen receptor and/or progesterone receptor, as well as negative for HER2, were defined as ER+/HER2- tumors. Tumors with positive immunochemistry and/or in situ hybridization for HER2, regardless of status of estrogen or progesterone receptor, were defined as HER2+. Tumors negative for all three receptors were classified as triple-negative. The presence or

absence of a BRCA1 or BRCA2 mutation was recorded, if known. Survival data was recorded from all patients using the Memorial Sloan Kettering Cancer Center Healthcare 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 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual (*28*). Initial clinical stage was determined from physical exam, mammography, breast ultrasound, and/or surgical findings.

PET/CT Imaging and Interpretation

All patients in this retrospective study underwent ^{18}F-FDG PET/CT prior to systemic or radiation therapy. Prior to ^{18}F-FDG injection for PET/CT, patients fasted for at least four to six hours. 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-minute uptake period followed by image acquisition on one of several GE Healthcare Discovery PET/CT systems. PET/CT scans were acquired supine from the mid-skull 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 picture-archiving and communication system workstation (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 (G.U.) dually boarded in diagnostic radiology and nuclear medicine with 13 years of PET/CT experience. Evidence of unsuspected regional extra-axillary 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 Fisher's 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, Cary, NC).

RESULTS

Characteristics of Patients and Primary Breast Malignancies

Our search of the Memorial Sloan Kettering Cancer Center Healthcare Information System from 2004 to 2017 identified 10,124 unique patients who had undergone ^{18}F-FDG PET/CT for breast cancer, 106 of whom were male. Of these 106 patients, 67 were excluded for systemic or radiation therapy prior to ^{18}F-FDG PET/CT, known stage IV disease prior to ^{18}F-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 Fig 1.

The median age of the final cohort of 39 patients with male breast cancer was 62 years (range 31-90 years). 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, while the 33 ER+ tumors that were

negative for HER2 receptor 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 ^{18}F-FDG PET/CT

^{18}F-FDG PET/CT demonstrated findings suspicious for unsuspected distant metastases in 7 of 39 (18%, 95% CI: 8-34%) patients with male breast cancer (Figs. 2 and 3). Suspected metastatic sites included bone in six, lung in three, and distant nodal metastases in three patients. Four patients had metastatic disease involving more than one organ site. For five of seven patients with ^{18}F-FDG PET/CT findings suspicious for unsuspected distant metastases, metastases were confirmed by pathology. The time intervals between suspicious ^{18}F-FDG PET/CT findings and pathologic confirmation in these five patients were 2, 7, 21,27, and 64 days (median 26 days). In the remaining two patients, metastatic disease was confirmed by follow-up imaging demonstrating resolution of 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 ^{18}F-FDG PET/CT findings and follow-up imaging confirmation in these two patients was 94 and 123 days).

Stratified by pre-PET/CT clinical stage, ^{18}F-FDG PET/CT demonstrated metastases in 0/8 (0%) patients with pre-PET/CT stage I or IIA, 3/19 (16%) patients with pre-PET stage IIB, and 4/12 (33%) patients with pre-PET/CT stage III male breast cancer (Table 2). 95% 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 extra-axillary 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 to those who were not for age [median: 56 years (range: 44-70) vs. 66 years, range: 31-90, p=0.14], race (Caucasian 86% (6/7) vs. 78% (25/32), p=0.30), or receptor status (ER+/HER2- 100% (7/7) vs. 81% (26/32), p=0.64). As only two patients had non-ductal 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.

Overall Survival

By the end of follow-up, 7 patients had died, with a one-year OS of 97.1% (95% CI: 80.9-99.6%) and a five-year OS of 72.6% (95% CI: 50.2-86.1%). Median follow-up in survivors was 47.3 months (range: 0.4-102.3). 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 one patient, which was proven by pathology. It was a clinically significant lymphoma for which the patient was subsequently treated.

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 exam, 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, prior to any therapy. ^{18}F-FDG PET/CT revealed unsuspected 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 following mastectomy but prior to further systemic or radiation therapy. ^{18}F-FDG PET/CT reveled unsuspected distant metastases, and thus stage IV disease. If the ^{18}F-FDG PET/CT had been performed prior to 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. While 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 two patients with ^{18}F-FDG PET/CT findings suspicious for distant metastases were not pathologically proven, and these had confirmation from follow-up imaging demonstrating resolution of FDG avidity following therapy and new osseous sclerosis representing healing of metastases (Fig. 2).

Unsuspected synchronous additional malignancies have been detected on ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET/CT. The potential for selection biases, including the possibility of unappreciated data that raises the risk of distant metastases is inherent it retrospective studies. The number of patients in the cohort was small, limiting statistical analyses. However, male breast cancer is an uncommon malignancy and compared to prior available data, the number of male patients with breast cancer

who had ^{18}F-FDG PET/CT performed at initial staging was high and pathologic proof of PET/CT findings was available in the majority of 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

^{18}F-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 ^{18}F-FDG PET/CT for systemic staging at initial diagnosis of male breast cancer, particularly for patients with stage IIB and III disease.

FIGURE LEGENDS

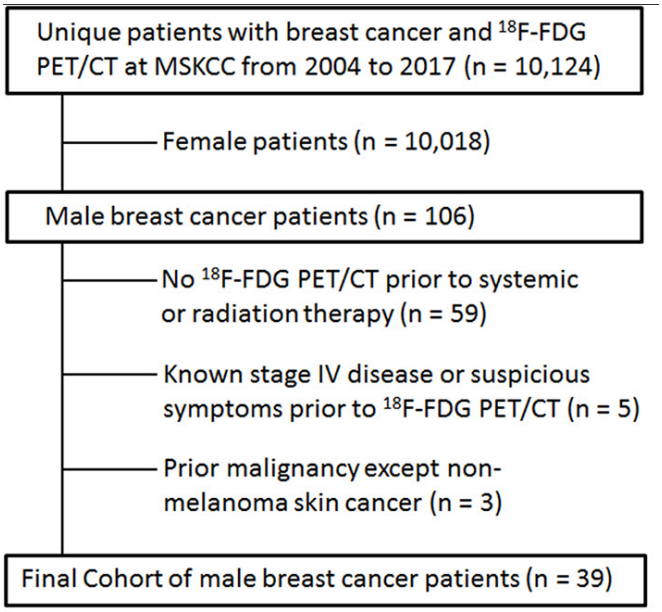

FIGURE 1. Standards for Reporting of Diagnostic Accuracy Diagram (STARD) for patients in this study

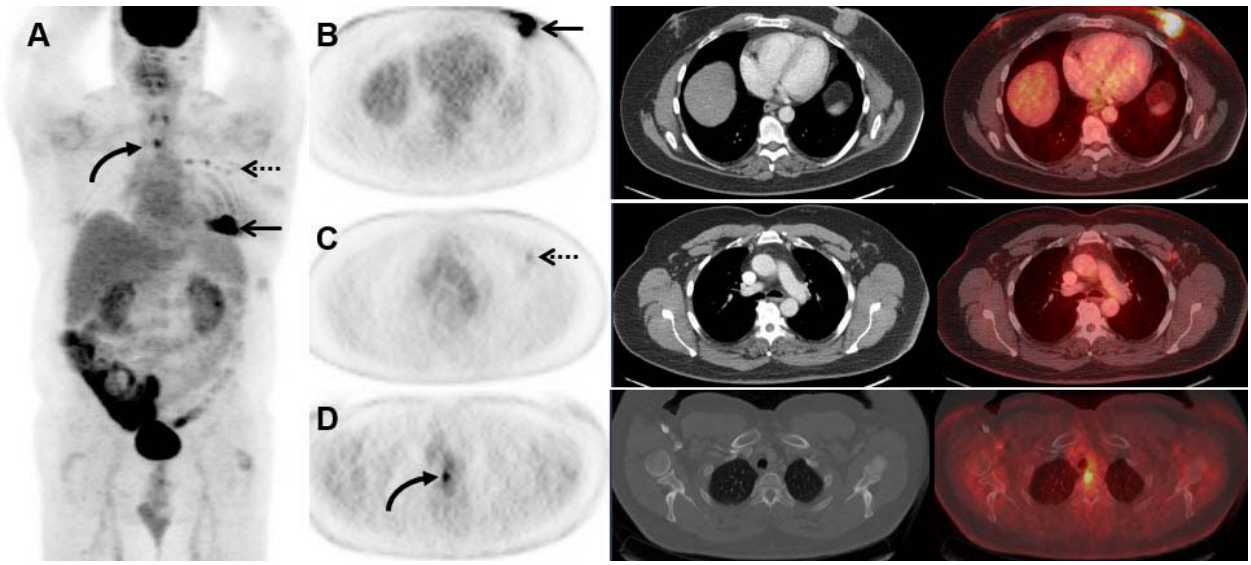

FIGURE 2. 53-year-old man with a pre-PET/CT stage IIB breast cancer, which was upstaged to stage IV by ^{18}F-FDG PET/CT. (A) ^{18}F-FDG MIP image demonstrates FDG avidity in the left breast (arrow), left axilla (dashed arrow), as well as overlying the midline chest (curved arrow). (B) Axial FDG PET,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

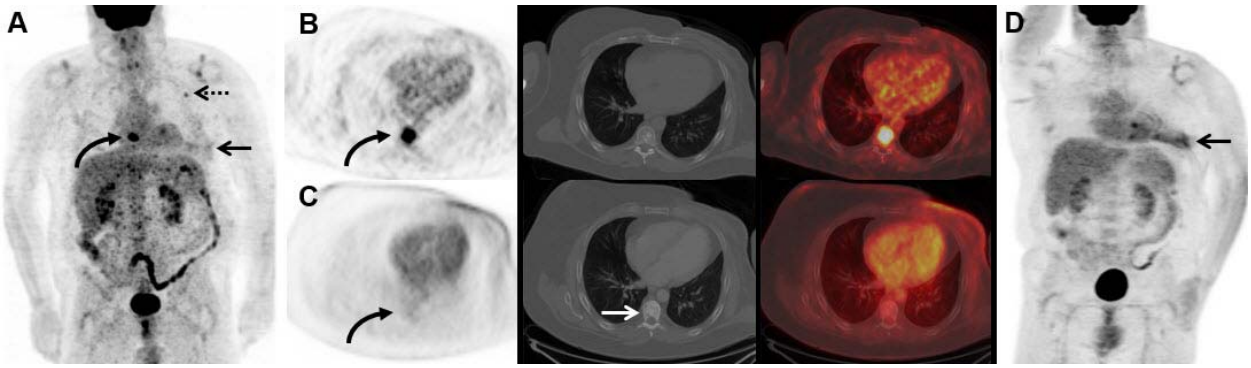

FIGURE 3. 58-year-old man with a pre-PET/CT stage IIB breast cancer, which was upstaged to stage IV on ^{18}F-FDG PET/CT. (A) ^{18}F-FDG MIP image demonstrates mild FDG avidity in a left mastectomy bed (arrow) and left axillary node (dashed arrow), as well as overlying the midline chest (curved arrow).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

TABLE 1. Characteristics of patients with male breast cancer and their primary tumors

		N (%)
# Patients		39
Age, years	Median (range)	62 (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)

TABLE 2. Summary of patients with male breast cancer upstaged by ^{18}F-FDG PET/CT stratified by pre-PET/CT stage

		Post-PET/CT Stage						
Pre-PET/CT stage	**Total**	**I**	**IIA**	**IIB**	**IIIA**	**IIIB**	**IIIC**	**IV (%)**
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)

DISCLOSURE

The authors have no conflicts of interest to disclose. This research was funded in part through the Susan G. Komen for the Cure Research Grant KG110441 (GAU) and the NIH/NCI Cancer Center Support Grant P30 CA008748 (Biostatistics Core).

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