Value of $^{18}$F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Breast Cancer (ILC) as Compared with Invasive Ductal Breast Cancer (IDC)

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Running title: FDG PET/CT for staging ILC
ABSTRACT

Although guidelines, such as those of the National Comprehensive Cancer Network, consider $^{18}$F-FDG PET/CT for systemic staging of newly diagnosed stage III breast cancer patients, factors in addition to stage may influence PET/CT utility. As invasive lobular carcinoma (ILC) demonstrates lower conspicuity on $^{18}$F-FDG PET than invasive ductal carcinoma (IDC), we hypothesized that tumor histology may be one such factor. We evaluated PET/CT systemic staging of newly diagnosed patients with ILC compared to IDC.

Methods: In this Institutional Review Board approved retrospective study, our Hospital Information System was screened for ILC patients who underwent PET/CT in 2006-2013 prior to systemic or radiation therapy. Initial stage was determined from exam, mammography, ultrasound, magnetic resonance and/or surgery. PET/CT was performed to identify unsuspected distant metastases. A sequential cohort of stage III IDC patients was evaluated for comparison. Upstaging rates were compared using Pearson chi square test.

Results: 146 ILC patients fulfilled criteria. PET/CT revealed unsuspected distant metastases in 12 (8%): 0/8 initial stage I, 2/50 (4%) stage II, and 10/88 (11%) stage III. All patients upstaged to IV by PET/CT were confirmed by biopsy. 3/12 upstaged patients were upstaged only by the CT component of the PET/CT, as metastases were non-$^{18}$F-FDG -avid. In the comparison stage III IDC cohort, 22% (20/89) of patients were upstaged to IV by PET/CT. All 20 demonstrated $^{18}$F-FDG -avid metastases. The relative risk of PET/CT revealing unsuspected distant metastases in stage III IDC patients was 1.98 times (95% CI 0.98-3.98) that of stage III ILC patients (p=.049). For $^{18}$F-FDG -avid metastases, the relative risk of PET/CT revealing unsuspected $^{18}$F-FDG -avid distant metastases in stage III IDC patients was 2.82 times (95% CI 1.26-6.34) that of stage III ILC patients (p=.007)
Conclusion: $^{18}$F-FDG PET/CT was more likely to reveal unsuspected distant metastases in stage III IDC patients than in stage III ILC patients. In addition, some ILC patients were upstaged by non-$^{18}$F-FDG -avid lesions visible only by the CT component. Overall, PET/CT may have lower impact on systemic staging of ILC patients than IDC patients.

Keywords: Lobular, ductal, breast cancer, $^{18}$F-FDG, PET/CT, staging
INTRODUCTION

The 2014 National Comprehensive Cancer Network guidelines consider using of 2-deoxy-2-((18)F)fluoro-D-glucose (18F-FDG) positron emission tomography / computed tomography (PET/CT) for systemic staging of patients with newly diagnosed stage III breast cancer, as the detection of distant metastases in these patients would alter treatment and prognosis (1). However, additional factors besides initial clinical stage may be important when determining whether a staging PET/CT is clinically indicated. For example, patient age has been advanced as a potentially important clinical factor, as younger patients with breast cancer may have more aggressive breast cancers that are more easily detected by 18F-FDG PET/CT at earlier stages (2).

Another potential factor for determining whether staging PET/CT may be of value is the histologic subtype of the primary breast malignancy. The two most common histologies of breast cancer are infiltrating ductal carcinoma (IDC), which accounts for ~75-80% of primary breast malignancies, and infiltrating lobular carcinoma (ILC), which accounts for ~10-15% of primary breast malignancies (3,4). While both are primary breast malignancies, IDC and ILC have distinct epidemiologic, molecular, pathologic, and imaging features (5-17). ILC is more difficult to detect on imaging than IDC, including mammography, ultrasound, and magnetic resonance imaging (MRI) (7,8). Primary ILC is less appreciable on 18F-FDG PET and demonstrates lower SUV values than comparable IDC tumors (9-12). Metastases from ILC may also be less appreciable on 18F-FDG PET than comparable IDC tumors (17). In addition, ILC differs in its patterns of metastatic spread when compared with IDC (13-16). While both IDC and ILC commonly metastasize to lymph nodes, bone and liver, ILC demonstrates a predilection for metastases to the peritoneum, retroperitoneum, hollow viscera (including the gastrointestinal
and genitourinary tracts), and leptomeninges (13-16). Not only do these sites of metastatic
disease often remain clinically silent until extensive, they may also be more difficult to assess on
PET/CT. Lung metastases, which may be easier to assess on the CT component of PET/CT, are
more common in IDC. Given the differences in $^{18}$F-FDG -avidity and patterns of metastatic
spread of ILC, $^{18}$F-FDG PET/CT may be less suited for evaluation of ILC than IDC. We
therefore evaluate the utility of $^{18}$F-FDG PET/CT for the systemic staging of patients with newly
diagnosed stage I-III ILC.

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 (MSKCC) Hospital Information System (HIS) was screened for patients
with stage I to IIIC ILC who underwent $^{18}$F-FDG -PET/CT between January 2006 and December
2013 prior to beginning treatment with chemotherapy, hormonal therapy, or radiation. Electronic
medical records (EMR) were reviewed and patients with the following characteristics were
excluded: Known stage IV disease for the current malignancy prior to PET/CT; prior or
concurrent malignancies (except non-melanoma skin cancer); systemic therapy or radiation prior
to PET/CT; and/or male gender. Surgical management of the primary breast lesion and axillary
nodes was allowed. Age at diagnosis and race were recorded for each patient.
To compare staging PET/CT results from ILC patients to patients with the more common diagnosis of IDC, a comparison cohort of IDC patients was selected sequentially during the same time period. IDC patients also underwent $^{18}$F-FDG-PET/CT prior to beginning treatment with systemic therapy or radiation. Exclusion criteria remained the same, including known stage IV disease for the current malignancy prior to PET/CT; prior or concurrent malignancies (except non-melanoma skin cancer); and chemotherapy, hormonal therapy, or radiation prior to PET/CT. To provide an appropriate comparison with the stage III ILC patients, the IDC cohort included only patients with initial stage III disease. In addition, to allow comparison of $^{18}$F-FDG PET and $^{99m}$Tc-methylene diphosphonate (MDP) bone scan findings in the IDC cohort, only patients with both $^{18}$F-FDG PET/CT and bone scan before treatment were included. As IDC is much more common than ILC, the additional criteria of pre-treatment bone scan did not prevent identification of an appropriately sized comparison cohort.

**Determination of Initial Stage**

Initial stages were determined according to the American Joint Committee on Cancer (AJCC) Staging Manual (18). Initial clinical stage was determined from physical exam, mammography, breast ultrasound, and, if available, breast MRI and/or surgical findings.

**PET/CT Imaging and Interpretation**

All patients in this retrospective study had a staging $^{18}$F-FDG PET/CT. Prior to $^{18}$F-FDG injection for PET/CT, patients fasted for at least 6 hours. Each patient was injected
intravenously with 444-555 MBq (12-15mCi) 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. PET/CT scans were acquired supine from the base of the skull to the mid-thigh. In most cases low-dose CT scans with oral contrast were obtained. Occasionally, intravenous contrast was administered. In all cases, attenuation-corrected 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, not considered physiologic or inflammatory, and with intensity greater than the local background. Suspicion for malignancy was based on the integration of metabolic information from the PET images, the anatomic information on CT images, and the fused PET/CT images. PET/CT studies were reinterpreted by a radiologist (G.U.) dually boarded in diagnostic radiology and nuclear medicine with nine years of PET/CT experience, blinded to the original PET/CT report and the results of other imaging modalities. Unsuspected local extra-axillary nodal metastases (internal mammary and supraclavicular) and distant metastases were recorded. If unsuspected local extra-axillary nodal metastases and/or distant metastases were noted on imaging, a new stage was assigned.

Bone Scan Imaging and Interpretation

All patients in the IDC comparison cohort had a pre-treatment bone scan. MDP bone scans were reinterpreted and presence of osseous metastases recorded. Each patient had been injected intravenously with 740-925 MBq (20-25mCi) of MDP, followed by a three hour uptake
period and image acquisition. Bone scans were acquired supine from the skull apex to the toes. Images were reviewed on a picture-archiving and communication system workstation, displaying anterior and posterior whole body images, as well as spot images of the skull, chest, and pelvis. SPECT images of a body region were obtained as part of 2 bone scans. Uptake was considered abnormal when it was focal, not considered physiologic or inflammatory, and with intensity greater than that of the local background. Bone scans were reinterpreted by the same radiologist, but at a separate time from the PET/CT image interpretation, and blinded to the original bone scan report and the results of other imaging modalities. The presence of osseous metastases was recorded. If osseous metastases were noted, a post imaging stage (stage IV) was assigned.

Verification of Metastases

For distant metastases, all patients with newly discovered distant metastases had pathologic verification. For local extra-axillary nodal metastases, pathologic verification was preferred, however if histology was not available, follow-up imaging was used. Local extra-axillary nodes had to be suspicious on initial imaging and then demonstrate treatment response or progression on follow-up imaging.

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 to stage III or IV. Race was grouped into African American, Asian, Caucasian, and other. Receptor profiles were grouped as estrogen receptor positive/human epidermal growth factor 2 negative (ER+/HER2-), HER2+, triple negative, and other/unspecified. The associations between histologic subtypes with clinical parameters and rates of upstaging were evaluated using Pearson chi square test for categorical variables and Wilcoxon Rank Sum for continuous variables. Proportion of upstaging in ILC versus IDC patients were compared using Pearson chi square test and calculated the relative risk along with the 95% confidence interval. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

ILC Cohort

Our search revealed 146 patients with stage I to III ILC breast cancer who underwent $^{18}$F-FDG PET/CT prior to systemic therapy or radiation between 2006 and 2013 and met all eligibility criteria. The median age of the ILC cohort was 57 years (range 34-92). Before PET/CT imaging, 8 patients (6%) were stage I, 50 (34%) were stage II, and 88 (60%) were stage III. Details on patient and tumor characteristics are summarized in Table 1.

Comparison IDC Cohort

To compare staging PET/CT results from stage III ILC patients to patients with the more common diagnosis of IDC, we selected a comparison cohort of IDC patients with initial stage III
disease. To allow further comparison of systemic staging of stage III IDC patients with $^{18}$F-FDG PET/CT versus staging with CT and bone scan, only patients with both pre-treatment $^{18}$F-FDG PET/CT and MDP bone scan were included. Our search revealed 89 patients with stage III IDC breast cancer patients for this comparison cohort. The median age of the IDC cohort was 59 years (range 33-90). All patients in the IDC cohort were stage III by inclusion criteria. Details on patient and tumor characteristics are summarized in Table 1.

**Associations Between Clinical Parameters and Histologic Subtype**

Receptor status was found to differ between the cohorts (p<0.0001). Nearly all the ILC patients were ER+/HER2- (90.4%), compared to only about half (51.7%) of the IDC patients. Additionally, 21.3% of IDC patients were HER2+ compared to 5.5% of ILC, and 25.8% of IDC were triple negative compared to 3.4% of ILC. The differences in receptor status were expected, given multi-institutional historic data demonstrating differences in receptor status between IDC and ILC (19). Race was found to approach significance between ILC and IDC patients (p=0.06). The majority in both cohorts were white (88.4% vs 77.5% respectively); however, 14.6% (13/89) of the IDC patients were African American compared to 6.2% (9/146) of ILC patients. Additionally, 6.7% (6/89) of IDC patients identified as Asian and only 5.5% (8/146) did for the ILC cohort. The differences in race may also have been expected, given multi-institutional data demonstrating lower rates of ILC in African American patients (19).

**Upstaging by PET/CT in the ILC Cohort**

PET/CT did not reveal unsuspected local extra-axillary nodes in any of the 146 ILC patients. Thirteen of 146 (9%) patients demonstrated abnormalities suspicious for distant
metastases on PET/CT. In 12 of 13 patients, histology confirmed metastatic disease, including 10 patients with osseous metastases (Figures 1 and 2), 2 with distal nodal metastases (Figure 3), and 1 with hepatic metastases. One patient had both osseous and nodal distant metastases. In one patient, an $^{18}$F-FDG avid (SUV 2.9) 2.1 cm adrenal nodule with average Hounsfield units of 29 led to a biopsy demonstrating an adrenal adenoma. This lesion was stable on follow-up imaging and classified as benign, and was thus deemed a false positive for malignancy (Figure 4). After excluding this false positive, 12 of 146 (8%) ILC patients had distant metastases demonstrated by $^{18}$F-FDG PET/CT. Classified by initial stage, PET/CT revealed unsuspected distant metastases in 0 of 8 (0%) initial stage I, 2 out of 50 (4%) initial stage II, and 10 of 88 (11%) initial stage III ILC patients.

Of the 12 ILC patients for whom PET/CT led to the discovery of stage IV disease, 9 (75%) demonstrated $^{18}$F-FDG -avid metastases. The remaining 3 (25%) patients were upstaged only by the CT component of the PET/CT, as they had sclerotic osseous lesions that demonstrated only background $^{18}$F-FDG -avidity (Figure 2). All 3 with non-$^{18}$F-FDG-avid metastases upstaged by the CT component of the PET/CT were initially stage III ILC patients.

In one patient in the ILC cohort an unsuspected synchronous malignancy was discovered, a non-small cell lung cancer, which was proven on biopsy.

**Upstaging by PET/CT in the IDC Cohort**

In the stage III IDC cohort, PET/CT demonstrated unsuspected local extra-axillary nodes in 7 of 89 (8%) patients, including internal mammary and supraclavicular nodal lesions. A total of 22 of 89 (25%) patients demonstrated abnormalities suspicious for distant metastases. In 20 of 22 of these patients, histology confirmed metastatic disease, including 17 patients with
osseous metastases (Figure 5), 3 with distant nodal metastases, 2 with hepatic metastases, 2 with lung metastases, and 1 with pleural metastases. Five patients had more than one site of distant metastases. In 1 patient, an $^{18}$F-FDG avid hepatic focus without CT correlate led to an MR of the liver demonstrating out-of-phase signal loss and a diagnosis of probable hepatic adenoma. This lesion was stable on follow-up imaging, never biopsied, and presumed to be benign. In 1 other patient, a non-$^{18}$F-FDG -avid T1 vertebral osseous sclerotic lesion was biopsied with benign histology. The osseous lesion remained stable on followup imaging and was classified as benign, and was thus deemed a false positive for malignancy (Figure 6).

Of the 20 stage III IDC patients in which PET/CT led to the discovery of stage IV disease, all 20 (100%) demonstrated $^{18}$F-FDG -avid metastases. No IDC patients were upstaged only by the CT component of the PET/CT. In addition to the identification of distant metastases in 20 patients based on $^{18}$F-FDG avidity on PET, 11 of 20 (55%) had findings suspicious for malignancy on both the CT component of the PET/CT as well as on the bone scan, 2 (10%) had suspicious findings on the CT component of the PET/CT but not the bone scan, and 1 (5%) had suspicious findings on the bone scan but not the CT component of the PET/CT. Thus, of 20 stage III IDC patients that were upstaged due to the detection of $^{18}$F-FDG -avid metastases on PET, 6 (30%) had no evidence of metastases on either the CT component of the PET/CT or the bone scan. Of these 6, 4 had $^{18}$F-FDG -avid osseous metastases without a corresponding lesion on either CT or bone scan (Figure 5), and 2 had $^{18}$F-FDG -avid subcentimeter distant nodal metastases.

**Comparison of Upstaging by PET/CT in the ILC and IDC Cohorts**
The relative risk of PET/CT revealing unsuspected distant metastases in stage III IDC patients (20 of 89) was 1.98 times (95% CI 0.98-3.98) that of stage III ILC patients (10 of 88, p=.049). When limiting to \(^{18}\)F-FDG -avid metastases, the relative risk of PET/CT revealing unsuspected \(^{18}\)F-FDG -avid distant metastases in stage III IDC patients (20 of 89) was 2.82 times (95% CI 1.26-6.34) that of stage III ILC patients (7 of 88, p=.007).

With respect to clinical characteristics, no differences were found between the upstaged and non-upstaged patients cohort in terms of race (p=1.00), age (p=0.35), or receptor status (p=0.60) in the ILC cohort, or the IDC cohort (race (p=0.85), age (p=0.08), or receptor status (p=0.94)).

DISCUSSION

The systemic staging of locally advanced breast cancer is important, as the detection of distant metastases will generally alter patient management from neoadjuvant therapy and surgery for stage II or III disease to palliative systemic therapy regimens for stage IV disease. While \(^{18}\)F-FDG PET/CT has proven to be valuable for systemic staging in patients with breast cancer, it is important to define patient and tumor characteristics that affect \(^{18}\)F-FDG PET/CT performance. Tumor histology may be one such important tumor characteristic, since ILC has distinct epidemiologic and imaging features compared to the more common IDC (5-17).

Our data suggest that \(^{18}\)F-FDG PET/CT has a lower utility for systemic staging of patients with stage III ILC than for stage III IDC. PET/CT revealed stage IV, distant metastatic, disease in 20 of 89 (22%) patients with stage III IDC prior to PET/CT, a percentage that
correlates well with prior published studies (2,20,21). In comparison, PET/CT revealed stage IV disease in only 10 of 88 (11%) patients with stage III ILC prior to PET/CT, a histologic subtype on which there is little published data. Furthermore, all 20 stage III IDC patients upstaged to IV by PET/CT demonstrated $^{18}$F-FDG-avid distant metastases, while only 7 of 10 stage III ILC patients upstaged to IV by PET/CT demonstrated $^{18}$F-FDG-avid distant metastases, with the remaining 3 upstaged by non-$^{18}$F-FDG-avid CT findings. Overall, the rate of detecting unsuspected $^{18}$F-FDG-avid distant metastases, and thus stage IV disease, in patients with initial stage III ILC was lower than in patients with initial stage III IDC ($p=.007$).

Our data confirms that $^{18}$F-FDG PET has utility for the detection of unsuspected $^{18}$F-FDG-avid distant metastases in stage III IDC patients. In addition to PET/CT detecting unsuspected distant metastases in 20 of 89 (22%) patients with stage III IDC, 6 of the 20 (30%) were upstaged by the $^{18}$F-FDG PET component of the PET/CT, without corresponding suspicious findings on CT or bone scan. Our data supports prior work suggesting that $^{18}$F-FDG PET/CT may replace CT and bone scan for some forms of breast cancer (22,23), and extends prior work by suggesting that this replacement may be favorable in patients with IDC, but not necessarily ILC.

The majority of instances where $^{18}$F-FDG PET/CT suspected metastases in initial stage III IDC patients, but the bone scan or CT alone did not, were due to the detection of unsuspected osseous metastases. MDP is a radiotracer that accumulates at sites of osteoblastic remodeling, thus MDP detects the osseous response to tumor, rather than the tumor itself (24). Osteolytic tumors or marrow tumors that do not elicit a sufficient osteoblastic response may result in false negatives on MDP bone scan, so the sensitivity of bone scan is variable (62-100%) (24). $^{18}$F-FDG PET offers more direct information about the tumor by measuring tumor metabolism.
Hybrid PET/CT, which allows the integration of both metabolic and anatomic information, may provide enhanced detection of osseous metastases compared to $^{18}$F-FDG PET alone (20,24). The lower $^{18}$F-FDG -avidity of ILC tumors and the tendency for ILC osseous metastases to be more sclerotic may both help explain why $^{18}$F-FDG PET/CT detected more unsuspected metastases than CT and bone scan alone in IDC, but not ILC.

While the detection of unsuspected local extra-axillary nodal disease does not have the same impact on patient care as the detection of distant metastases, detection of such nodal disease may still increase the patient’s stage, impact prognosis, and lead to changes in a patient’s treatment plan, such as additional surgery or radiotherapy. Several studies have demonstrated the value of $^{18}$F-FDG PET/CT over other imaging modalities for the detection of local extra-axillary nodal disease (2,20,25). As with distant metastases, $^{18}$F-FDG PET/CT in this study had a greater yield for the detection of local extra-axillary nodal disease in IDC patients than for ILC patients. There was no additional local extra-axillary local nodal disease identified in 88 patients with stage III ILC, while additional local extra-axillary nodal disease was detected in 7 of 89 (8%) patients with stage III IDC.

Our study has several limitations. The retrospective single institution study design lends itself to selection biases that are difficult to control. For instance, we attempted to provide a cohort of patients with stage III IDC to compare against stage III ILC patients. In order to allow assessment of $^{18}$F-FDG PET/CT versus CT/bone scan, an inclusion criterion for our comparison IDC cohort was to have both PET/CT and bone scan at baseline. However, the selection of patients that underwent both $^{18}$F-FDG PET/CT and MDP bone scan may have caused a patient selection bias. In this retrospective study, the reasons for a patient having undergone both studies were not identified. We can state that the rate of detection of local extra-axillary and
distant metastases for IDC patients in this study is comparable to that of prior breast cancer studies, but this does not negate the intrinsic selection biases. Likewise, the reasons that certain ILC patients were selected to have $^{18}$F-FDG PET/CT were not identified in this study. The potential selection biases, which are innate to this retrospective study, make prospective evaluation of these findings important for confirmation.

While all distant metastases were histologically proven for all patients in both the ILC and IDC cohorts, suspected local extra-axillary nodal metastases were often not histologically confirmed. When local extra-axillary nodal lesions were found in patients with distant metastases, confirmation of the nodal disease was usually not clinically relevant. Likewise, internal mammary nodes suspected of metastases are not always confirmed histologically. The lack of histologic verification of nodal disease limits the utility of the local extra-axillary nodal $^{18}$F-FDG PET/CT findings.

Fewer breast cancer patients undergo $^{18}$F-Sodium Fluoride (NaF) PET/CT bone scans relative to MDP bone scan, although the frequency of utilization of NaF PET/CT may be increasing. Due to the limited number of patients undergoing NaF PET/CT at our institution during the time period of our study, our study did not evaluate NaF PET/CT as a method of systemic staging. There is still relatively little known about the added value of SPECT/CT to compliment MDP bone scan for the detection of bone metastases in patients with breast cancer (26).

**CONCLUSION**
This retrospective study suggests $^{18}$F-FDG PET/CT is more likely to reveal unsuspected distant metastases in stage III IDC patients than in stage III ILC patients. In addition, some ILC patients were upstaged only by the CT component of PET/CT, as metastases detected on CT were non-$^{18}$F-FDG -avid. As PET/CT may have lower impact on systemic staging of ILC patients than IDC patients, we recommend that ILC patients should be analyzed independently from IDC patients in future studies exploring the utility of $^{18}$F-FDG PET/CT. Prospective evaluation of the impact tumor histology has on the utility of $^{18}$F-FDG PET/CT for systemic staging of patients with breast cancer is warranted.

ACKNOWLEDGMENTS

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REFERENCES


FIGURE 1. 62-year-old woman with initial stage III ILC upstaged to stage IV by $^{18}$F-FDG PET and CT. (A) Axial fused $^{18}$F-FDG PET/CT image demonstrates the previously unknown right humeral head metastases as an $^{18}$F-FDG -avid osseous lesion (solid arrow). (B) The metastatic lesion is apparent as a sclerotic osseous lesion on CT (dashed arrow). Biopsy confirmed an osseous metastasis.
FIGURE 2. 56-year-old woman with initial stage III ILC upstaged to stage IV on the CT component of an $^{18}$F-FDG PET/CT. (A) Axial $^{18}$F-FDG PET does not demonstrate suspicious foci. (B) The axial CT component of the PET/CT demonstrates multiple osseous sclerotic lesions, suspicious for metastases (solid arrow). (C) Axial fused $^{18}$F-FDG PET/CT image confirms that the osseous sclerotic lesions demonstrate background $^{18}$F-FDG avidity. Biopsy confirmed an osseous metastasis.
FIGURE 3. 52-year-old woman with initial stage III left breast ILC upstaged to stage IV by 18F-FDG PET and CT. (A) Axial fused 18F-FDG PET/CT image demonstrates the previously known ipsilateral left axillary nodal metastasis as an 18F-FDG-avid lesion (solid arrow), as well as a previously unknown contralateral right axillary node (dashed arrow). (B) Both ipsilateral and contralateral axillary nodal lesions are apparent as enlarged and rounded nodes on CT. Biopsy of the contralateral right axillary node demonstrated a nodal metastasis. Contralateral axillary nodal metastases are distant metastases (M1 disease) as classified by the AJCC (18).
FIGURE 4. 64-year-old woman with initial stage III ILC with a false positive for distant metastasis on $^{18}$F-FDG PET/CT.  (A) Axial $^{18}$F-FDG PET demonstrates an $^{18}$F-FDG avid (SUV 2.9) focus in the left abdomen (black solid arrow).  (B) The axial CT component of the PET/CT demonstrates a 2.1 cm adrenal nodule with average Hounsfield units of 29 (white solid arrow). Biopsy resulted in a diagnosis of benign adrenal adenoma.
FIGURE 5. 42-year-old woman with initial stage III IDC upstaged to stage IV by $^{18}$F-FDG PET. (A) Axial fused $^{18}$F-FDG PET/CT image demonstrates the previously unknown right ilium metastases as an $^{18}$F-FDG-avid osseous lesion (black solid arrow). (B) No definite corresponding lesion is seen on the axial CT component of the PET/CT. (C) Axial fused $^{18}$F-FDG PET/CT image confirms the osseous localization of the $^{18}$F-FDG-avid focus. (D) No corresponding focus is seen on MDP bone scan (anterior and posterior spot views of pelvis shown). Biopsy confirmed an osseous metastasis.
FIGURE 6. 46-year-old woman with initial stage III IDC with a false positive for distant metastasis on the CT component of $^{18}$F-FDG PET/CT. (A) Axial $^{18}$F-FDG PET does not demonstrate suspicious foci. (B) The axial CT component of the PET/CT demonstrates an osseous sclerotic lesion in the T1 vertebra. (C) Axial fused $^{18}$F-FDG PET/CT image confirms that the osseous sclerotic lesion demonstrates background $^{18}$F-FDG -avidity. Biopsy of the sclerotic lesion yielded dense cortical bone without evidence of malignancy, consistent with a bone island.
### TABLE 1. Characteristics of patients and tumors

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</tbody>
</table>

AJCC = American Joint Committee on Cancer; IDC = invasive ductal cancer; ILC = invasive lobular cancer; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2.

* Clinical classification according to the seventh edition of the AJCC Staging Manual (18).

Inclusion criteria for the IDC cohort specified initial stage III disease, to allow comparison to stage III ILC patients.
Value of $^{18}$F-FDG PET/CT for Systemic Staging of Newly Diagnosed Invasive Lobular Breast Cancer (ILC) as Compared with Invasive Ductal Breast Cancer (IDC)

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