Clinical Utility of ^{18}F -FDG PET/CT in Staging Localized Breast Cancer Before Initiating Preoperative Systemic Therapy

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ABSTRACT

Background: ^{18}F -fluorodeoxyglucose PET/CT is recommended as an optional study in the current NCCN Clinical Practice Guidelines in Oncology for Breast Cancer after CT of the chest, abdomen, and pelvis with contrast and bone scan (CTBS) in stage IIA–IIIC breast cancer. We evaluated our experience with the use of PET/CT in this setting before beginning primary systemic therapy (PST) prior to planned surgery. **Methods:** We performed medical record abstractions of all adult female patients with clinical stage IIA–IIIC breast cancer diagnosed at Montefiore Medical Center from January 1, 2014, through January 1, 2019, who underwent PET/CT before PST. We calculated the proportion of patients upstaged after PET/CT and examined the cost and radiation exposure associated with PET/CT compared with CTBS. **Results:** A total of 195 patients with 196 breast cancers (bilateral disease in 1 patient) met the study inclusion criteria and had PET/CT as the first imaging study before PST. The overall upstaging rate for regional nodal metastasis and/or distant metastasis was 37% (73/196), including 24% for stage IIA (9/38), 39% for stage IIB (31/79), 54% for stage IIIA (22/41), 27% for stage IIIB (8/30), and 37% for stage IIIC (3/8). The overall upstaging rate for distant metastasis was 14% (27/196), including 0% for stage IIA, 13% for stage IIB (10/79), 22% for stage IIIA (9/41), 17% for stage IIIB (5/30), and 37% for stage IIIC (3/8). Medicare reimbursement rates were \$1,604.37 for PET/CT and \$1,679.94 for CTBS. The radiation dose for PET/CT was 14 mSv versus 21 mSv for CTBS. **Conclusions:** Approximately 37% of patients with clinical stage IIA–IIIC breast cancer who underwent PET/CT before PST showed more extensive disease, including 23% with more extensive nodal metastasis and 14% with distant metastasis. Given its high detection rate, comparable cost, lower radiation dose, and greater convenience, PET/CT should be considered as an alternative to CTBS rather than “optional” after CTBS, especially in patients who require an efficient and expeditious workup before initiating PST.

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Background

Breast cancer is the most common cancer and the second leading cause of cancer mortality in women in the United States and globally, with approximately 270,000 women diagnosed in 2019 and >40,000 breast cancer-related deaths in the United States. The disease is localized to the breast in 62% of patients and to the breast and regional nodes in 30%.¹ Primary preoperative systemic therapy (PST) is commonly used in patients with localized disease with a larger primary tumor or regionally advanced disease; it results in the downstaging of breast and regional nodal disease burden and facilitates breast conservation and/or less extensive axillary surgery.² Upstaging to a higher regional stage or detection of metastatic disease may impact prognosis and management. Therefore, accurate staging of breast cancer is critical in prognostication and guiding local and systemic treatments and their optimal sequencing.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer recommend CT of the chest, abdomen, and pelvis with contrast and bone scan (CTBS) for staging of patients with clinically staged localized breast cancer (cT0–4N1–3 or T2–4N0) who are candidates for PST and who display clinical symptoms based on category 2B evidence.³ ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT is considered optional in circumstances in which CTBS is equivocal or suspicious. Prior studies reported greater sensitivity of PET/CT versus CT of the body for the detection of regional nodal metastases and distant metastases, and greater accuracy versus bone scan in the detection of bone metastases.^{4–6} One retrospective study by Niikura et al⁷ reported 97.4% sensitivity and 91.2% specificity for PET/CT imaging compared with 85.9% sensitivity and 67.3% specificity for conventional techniques, including CT, ultrasonography, radiograph, and bone scan, in detecting distant metastases. In regard to upstaging rates, studies have reported that approximately 15% of patients with initial clinical stage $\geq$ IIB breast cancer were upstaged to stage IV breast cancer after systemic staging with PET/CT.^{8,9} Similarly, Riedl et al¹⁰ showed that PET/CT revealed unsuspected distant metastases in 17% of patients aged <40 years

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with clinical stage IIB breast cancer. A recent retrospective study by Yazarbas et al¹¹ showed that overall upstaging rates based on identification of extra-axillary regional lymph nodes and distant metastases were 18.6% of patients with initial stage IIA, 30% of those with stage IIB, and 46.3% of those with stage IIIA breast cancer after PET/CT.

Compared with CTBS, PET/CT has several potential advantages for staging that need to be considered, especially in patients who have locally advanced breast cancer and are candidates for PST before surgery who require an efficient and expeditious workup. These include greater patient convenience, reduced procedure time, and imaging with only 1 rather than 2 contrast/tracer injections. In addition, a PET/CT base-of-skull-to-thigh scan has a lower radiation dose than a combination of CTBS, 14 mSv, and 21 mSv, respectively.^{12,13} We report the results of a retrospective study evaluating upstaging rates after PET/CT as initial and/or only imaging study in patients with newly diagnosed clinical stage IIA–IIIC breast cancer who received PST before planned surgery, and our institution's total Medicare reimbursement rates for PET/CT and CTBS.

Methods

Study Cohort

This retrospective study was conducted at Montefiore Medical Center, the University Hospital of Albert Einstein College of Medicine and Albert Einstein Cancer Center, an NCI-designated cancer center, after approval of the Institutional Review Board and the Cancer Center Protocol Review and Monitoring Committee. We accessed Montefiore Medical Center “Clinical Looking Glass” software to identify all adult female patients with newly diagnosed breast cancer from January 1, 2014, through January 1, 2019, who underwent PET/CT within 4 months of their disease diagnosis. Electronic medical records were reviewed and the following exclusion criteria were applied: patients with stage IV disease, ductal carcinoma in situ, lobular carcinoma in situ, or stage I disease before PET/CT; treatments before PET/CT; and no adequate clinical follow-up of at least 1 year. Subsequently, patients with initial clinical stage IIA–IIIC breast cancer who underwent PET/CT before receiving PST were identified. Initial clinical stage was determined from physical examination, mammography, breast sonography, and in many cases MRI according to the *AJCC Cancer Staging Manual*, seventh edition.¹⁴ It was the policy of the breast medical oncology service at Montefiore Medical Center during this time period to recommend FDG PET/CT as the preferred imaging modality, unless CTBS was required by a patient's health insurance carrier. Our analysis focused only on those who received a

PET/CT scan within 4 months of diagnosis, and did not include patients who underwent CTBS scan without a PET/CT.

Patient age at diagnosis, tumor histology and receptor status (estrogen receptor, progesterone receptor, HER2 expression), initial clinical stage (cTcN), and type of preoperative systemic therapy (chemotherapy, endocrine therapy, and anti-HER2 therapy) were recorded for each patient. PET/CT reports were then evaluated to identify unsuspected regional nodal and distant metastases.

Imaging Modalities

¹⁸F-FDG PET/CT images were obtained in 1 day after an intravenous administration of a weight-adjusted dose of 5.18 MBq/kg (0.14 mCi/kg) of ¹⁸F-FDG. Approximately 60 minutes after administration of the radiopharmaceutical, PET images from the base of the skull to midthigh were acquired using the Philips Gemini TF PET/CT scanner (Philips Medical Systems) in 3D acquisition mode. A low-dose CT scan was used for nonuniform attenuation correction.

Image Interpretation

As a normal protocol at our institution, a board-certified nuclear medicine physician with 18.3 ± 4 years of experience interprets the PET/CT studies. PET/CT was read in context with all other available imaging studies in accordance with best practices. We analyzed the data based on nuclear medicine physicians' interpretations. According to standard FDG PET/CT reporting, abnormal uptake is defined as nonphysiologic, noninflammatory, and focal signal that has intensity greater than the local background. An imaging finding was considered positive for radiographic evidence of unsuspected regional nodal metastases when the radiologist reported a malignancy found outside of the N1 axillary region, such as subpectoral, internal mammary, or supraclavicular; imaging was considered positive for distant metastases when the radiologist reported disease in other organs besides the breasts. Histology was our preferred method of confirmation for malignancy in those positive PET/CT findings. However, in patients with unavailable histology, follow-up imaging study (MRI or CT) was used to confirm the distant metastases before patients received systemic therapy.

Upstaging Frequencies

The overall upstaging frequencies and proportions, stratified by initial disease stage, were estimated and reported as percentages with 95% CIs. Data were expressed as medians (interquartile ranges [IQR]) for continuous variables and proportions for categorical variables.

Association Between Clinical Characteristics and Upstaging Frequencies

Associations between clinical characteristics and upstaging frequencies were assessed using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables; those with P values $<.05$ were considered statistically significant. All statistical analyses were performed using JMP software (SAS Institute Inc).

Results

Patient Characteristics and Treatments

As shown in Figure 1, a total of 415 adult female patients with newly diagnosed breast cancer who underwent PET/CT within 4 months of their diagnosis from January 2014 to January 2019 were identified. After applying study exclusion criteria, 283 patients with clinical stage IIA–IIIC breast cancer (280 with unilateral and 3 with bilateral disease) were evaluated. Stratified by treatments received after PET/CT, there were 227 patients with 230 breast cancers (3 with bilateral disease) who received PST

including endocrine therapy or chemotherapy alone or plus anti-HER2 therapy, of whom the final study cohort consisted of 195 patients (196 cancers) with PET/CT as the initial imaging study.

Characteristics of the study cohort are shown in Table 1. Median age at diagnosis was 60 years (IQR, 50–69 years) and the most common tumor histology was invasive ductal carcinoma (172 patients; 88%). In all 195 patients who received PST, the plan was surgery after PST. A total of 140 patients received preoperative chemotherapy (plus

Table 1. Baseline Patient and Tumor Characteristics

Characteristic	n (%)
Patients, N	195
Median age, y (IQR)	60 (50–69)
Race/Ethnicity	
Hispanic	73 (37)
Non-Hispanic	99 (51)
Unknown	23 (12)
Clinical stage before PET/CT ^{a,b}	
IIA	38 (19)
IIB	79 (40)
IIIA	41 (21)
IIIB	30 (15)
IIIC	8 (4)
Tumor histology ^b	
Invasive ductal carcinoma	172 (88)
Invasive lobular carcinoma	14 (7)
Mixed	2 (1)
Others	8 (4)
Tumor receptor phenotype ^b	
ER+/HER2+	29 (15)
ER+/HER2–	76 (39)
ER–/HER2+	22 (11)
ER–/HER2–	69 (35)
Treatment choices	
Preoperative chemotherapy followed by surgery	140 (72)
Preoperative chemotherapy followed by surgery + anti-HER2	45 (32)
Preoperative endocrine therapy followed by surgery	12 (6)
Preoperative endocrine therapy followed by surgery + anti-HER2	4 (33)
Systemic therapy only because of metastatic disease found	27 (14)
Declined surgery	16 (8)

Abbreviations: ER, estrogen receptor; IQR, interquartile range.

^aClinical classification according to the seventh edition of the *AJCC Cancer Staging Manual*.¹⁴

^bA total of 195 patients with 196 breast cancers (bilateral disease in 1 patient).

Figure 1. Study design and flowchart.

Abbreviations: BS, bone scan; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; PST, primary systemic therapy.

combination anti-HER2 therapy in 45 patients) followed by surgery and 12 patients received preoperative endocrine therapy (plus combination anti-HER2 therapy in 4 patients) followed by surgery. However, 43 of 195 patients did not undergo surgery after systemic therapy, including 27 who were found to have metastatic disease on PET/CT and 16 who declined surgery.

Upstaging Rates

Overall Upstaging Rates and Sensitivity/Specificity of FDG PET/CT

Upstaging rates are summarized in Table 2. The overall upstaging rate for regional nodal metastases and/or distant metastases was 37% (73/196), including 24% for stage IIA (9/38), 39% for stage IIB (31/79), 54% for stage IIIA (22/41), 27% for stage IIIB (8/30), and 37% for stage IIIC (3/8).

The sensitivity and specificity of PET/CT in detecting distant metastases were 100% (95% CI, 87%–100%) and 94% (95% CI, 89%–97%), respectively. The positive predictive value of PET/CT in detecting distant metastases was 73%. PET/CT showed metastatic disease in the bone in 23 patients, lung/mediastinal lesions in 7, liver lesions in 4, and adrenal lesions in 3. Of these 37 patients, 10 had subsequent biopsies (6 bone, 2 lung, and 2 liver biopsies) and 27 had follow-up imaging such as MRI, CT, or bone scan (17 MRIs or bone scans for bone disease, 5 CTs for lung lesions, 2 MRIs for liver lesions, and 3 MRIs for adrenal lesions). Pathology confirmed metastatic disease found on PET/CT in 9 patients with 1 false-positive in the bone, and follow-up imaging confirmed metastatic disease in 18 patients with 9 false-positives, including 4 false-positives in the bone, 2 false-positives in the lung, and 3 false-positives in the adrenal glands. A total of 27 patients had confirmed metastatic disease, including 18 in the bone, 5 in the lung/mediastinum, and 4 in the liver. Figure 2 shows examples of images from 2 patients with invasive ductal carcinoma who received ¹⁸F FDG PET/CT.

Upstaging Rates for Regional Nodal Metastases

The overall upstaging rate to a higher regional stage based on unsuspected nodal metastases was 23% (46/196), including 24% for stage IIA (9/38), 27% for stage IIB (21/79), 32% for stage IIIA (13/41), and 10% for stage IIIB (3/30).

The overall upstaging to rate infraclavicular or supraclavicular nodal (N3) disease was 24% (48/196), including 8% for stage IIA (3/38), 19% for stage IIB (15/79), 44% for stage IIIA (18/41), and 23% for stage IIIB (7/30). Downstaging from N3 to N1 disease occurred in 25% of initial stage IIIC (2/8).

Upstaging Rates for Distant Metastases

The overall upstaging rate to stage IV based on unsuspected distant metastases was 14% (27/196), including 0% for stage IIA, 13% for stage IIB (10/79), 22% for stage IIIA (9/41), 17% for stage IIIB (5/30), and 37% for stage IIIC (3/8). In this group of patients who were upstaged to stage IV, 56% (15/27) showed more extensive regional nodal metastases than suspected based on initial clinical examination and nonfunctional imaging studies.

Associations Between Clinical Parameters and Upstaging to Stage IV

There were no associations found between patients who were upstaged to stage IV and those who were not in terms of age (median age, 65 years [IQR, 53–69] vs 60 years [IQR, 49–69]; $P=.4$), race (Hispanic, 43% [10/23] vs 43% [64/150]; $P=1.0$), tumor histology (invasive ductal carcinoma, 89% [24/27] vs 89% [150/169]; $P=1.0$), and triple-negative receptor status (37% [10/27] vs 35% [59/169]; $P=.83$).

Cost Estimates

Medicare reimbursement rates for PET/CT and CTBS were obtained from the Montefiore Medical Center Department of Radiology billing office. The total Medicare reimbursement rates of PET/CT and CTBS were \$1,604.37 and \$1,679.94, respectively.

Table 2. Summary of Patients Upstaged by PET/CT Categorized by Initial Clinical Stage

Initial Clinical Stage	n	Post-PET/CT Stage, n (% Upstaged; 95% CI)						Overall Upstaging
		IIA	IIB	IIIA	IIIB	IIIC	IV	
IIA	38	29 (76; 61%–87%)	6 (16; 7%–30%)	0	0	3 (8; 3%–21%)	0	9 (24; 13%–39%)
IIB	79	1 (1; 0.02%–7%)	47 (59; 48%–70%)	12 (15; 9%–25%)	0	9 (11; 6%–20%)	10 (13; 7%–22%)	31 (39; 29%–50%)
IIIA	41	1 (2; 1%–12%)	0	18 (44; 30%–59%)	0	13 (32; 20%–47%)	9 (22; 12%–37%)	22 (54; 39%–68%)
IIIB	30	0	0	0	22 (73; 56%–86%)	3 (10; 3%–26%)	5 (17; 7%–34%)	8 (27; 14%–44%)
IIIC	8	1 (12; 2%–47%)	0	1 (12; 2%–47%)	0	3 (37; 14%–69%)	3 (37; 14%–69%)	3 (37; 14%–69%)
Total ^a	196	35	61	37	23	43	27 (14; 10%–19%)	73 (37; 31%–44%)

^aA total of 195 patients with 196 breast cancers (bilateral disease in 1 patient).

Figure 2. (A) A female patient aged 67 years with clinical stage IIIB triple-negative IDC of the right breast was found to have hypermetabolic left iliac bone focus (SUV max, 5.6) with no correlate on the low-dose CT for the PET/CT study. This lesion was biopsied and returned positive for osseous metastasis. Patient was upstaged to stage IV. (B) A female patient aged 49 years with clinical stage IIB ER+/PR-/HER2- IDC of the left breast with nodal metastases was found to have focal activity in the right side of T11 (SUV, 2.9) with no low-dose CT correlate. MRI for further evaluation (not shown) showed only degenerative changes in T11 and no evidence of tumor invasion. Abbreviations: ER, estrogen receptor; IDC, invasive ductal carcinoma; PR, progesterone receptor; SUV, standardized uptake value; T11, 11th thoracic vertebra.

Discussion

We have found that approximately 37% of patients with clinical stage IIA–IIIC breast cancer who underwent ^{18}F -FDG PET/CT before receiving primary PST before planned surgery showed more extensive disease, including 23% with more extensive regional nodal metastases and 14% with distant metastases. These rates are similar to upstaging rates that were previously reported in patients with localized breast cancer who underwent systemic staging with PET/CT.⁴ We also observed that the costs between CTs of the chest, abdomen, and pelvis with CTBS and PET/CT were comparable. Although the sensitivity of PET/CT in this setting seemed ideal, this result should be interpreted with caution because our study was not designed to examine the sensitivity of PET/CT relative to other imaging modalities. Nevertheless, the positive predictive value of 73% for detecting distant metastases supports the clinical utility of PET/CT as a screening tool for distant metastases in this setting, so long as distant recurrence is confirmed by histologic confirmation.

Regional extra-axillary lymph nodes, such as internal mammary, infraclavicular, and supraclavicular nodes (N2 and N3), can be clinically occult. Studies have shown that PET/CT can detect regional nodes with higher sensitivity than conventional imaging procedures such as contrast enhanced CT, ultrasound, or radiograph.^{4,5,15} Identification of regional nodal involvement can guide local treatment decisions and their optimal sequencing. Two prospective studies have shown that detection of

extra-axillary regional nodal metastases on PET/CT resulted in modification of surgery or extension of radiation treatment fields.^{15,16} In the first study, Cochet et al¹⁵ found that the overall upstaging rate from N1 to N3 disease was approximately 20%, which was similar to the rate of 24% found in our study. Krammer et al¹⁶ also showed that a substantial number of patients (57%) with changes in local management had been upstaging from N1 to N3 disease.

In this study, we also found that some patients were downstaged by PET/CT. The highest downstaging frequency occurred in those with initial clinical stage IIIC breast cancer, wherein regional lymph node with N3 disease, identified on breast MRI and axillary ultrasound, was modified to N1 disease. This downstaging effect could result from the low specificity of nonfunctional imaging studies in detecting regional extra-axillary nodes.⁵

Our evaluation of unsuspected distant metastases showed that PET/CT resulted in a detection rate of 13% for those with initial clinical stage IIB disease, and at greater rates of 17% to 37% for those with stage III disease. A prospective study by Groheux et al¹⁷ in 2012 showed that disease-specific survival was significantly shorter for patients found to have unsuspected distant metastases on PET/CT (88% without metastases vs 57% for those with metastases; $P < .001$). In our study, we observed that patients found to have unsuspected distant metastases on PET/CT received palliative systemic therapy instead of curative PST followed by planned

surgery. Therefore, identification of unsuspected distant metastases during clinical staging is essential in prognostication, because it can convert management from curative to palliative intent.

Historically, the triple-negative breast cancer subtype is known for its aggressive behavior and high rates of node positivity, metastatic disease, and early peak of recurrence. It is found more commonly in younger Hispanic women and non-Hispanic black women who carry a mutation in the *BRCA1* gene.^{18,19} We found no associations between upstaging to stage IV disease and clinical characteristics, including race, tumor histology, and triple-negative receptor phenotype. This finding is also consistent with another study of 232 patients with early triple-negative breast cancer that found no associations between upstaging to stage IV disease and clinical characteristics, including age, race (white vs nonwhite), tumor histology, and tumor grade.⁸

The strengths of this study are the large number of patients evaluated who received PST and the report of Medicare reimbursement cost differences between CT chest, abdomen, and pelvis with CTBS versus PET/CT. Systemic staging scans can be costly; the NCCN Guidelines³ recommend performing them only when indicated based on clinical symptoms in early-stage breast cancer. Although downstream costs were not included in our analysis, Merrill et al²⁰ reported additional downstream costs, including follow-up scan and biopsy of \$1,506 per patient, for patients who underwent systemic staging with PET/CT or CTBS when they were not clinically indicated.²⁰

Our study has several limitations. Data were obtained from a single institution retrospectively with potential for inherent selection and interpretation biases, and we did not directly compare PET/CT with CTBS.

In addition, histologic confirmation was not available for most patients with metastatic disease found on PET/CT. We also detected 10 false-positives for distant metastases, resulting in PET/CT specificity and a positive predictive value of 94% and 73%, respectively. Therefore, findings of distant metastases on PET/CT required additional histologic biopsy or corroboration with other imaging modalities. Finally, most cases in this study were ductal carcinoma in histology; therefore, the clinical utility of PET/CT in other histologies such as lobular carcinoma cannot be interpreted from this study.

Conclusions

Given the high detection rate, comparable cost, lower radiation dose, and greater patient convenience, PET/CT should be considered as an alternative to CTBS rather than considered as optional when systemic staging is clinically indicated in patients with stage IIA–IIIC breast cancer who require an efficient and expeditious workup before initiating PST prior to planned surgery.

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