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ORIGINAL ARTICLE – BREAST ONCOLOGY

Overuse of Preoperative Staging of Patients Undergoing Neoadjuvant Chemotherapy for Breast Cancer

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ABSTRACT

Background. Guidelines of the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO) discourage the use of imaging to stage newly diagnosed early breast cancer (stages 1 and 2). This study aimed to evaluate preoperative staging imaging rates among patients with stage 1 or 2 breast cancer treated with neoadjuvant chemotherapy (NAC).

Methods. From a prospectively maintained database, 303 patients with stage 1 or 2 breast cancer who had NAC from 2008 to 2016 were identified. The main outcome measures were the rate and outcomes of staging imaging performed.

Results. The mean age of the 303 patients with stage 1 or 2 breast cancer was 51 years (range, 26–87 years). Of these 303 patients, 278 (92.4%) had invasive ductal cancer. 90 (30.2%) had estrogen receptor (ER)-positive disease, 79 (26.5%) had triple-negative disease, and 127 (42.6%) had human epidermal growth factor receptor 2 (HER2)-positive disease. Staging positron emission tomography (PET) or computed tomography (CT) scan was performed for 258 patients (85.2%), brain imaging for 94 patients (31%), bone scans for 117 patients (38.6%), and all three for 48 patients (15.8%). As a result, 15 patients (4.9%) with a positive PET/CT scan were upstaged to stage 4 breast cancer. No difference was observed among the ER-positive ($p = 1.000$), HER2-positive ($p = 0.259$), or triple-negative ($p = 0.369$) receptor profiles of the patients upstaged to stage 4 disease. One patient (1.1%) had positive brain imaging. Five patients (4.3%) had a positive bone scan, and three of these patients (60%) had bone metastasis also shown on the PET/CT scan.

Conclusion. Despite guideline recommendations, a high rate of preoperative staging imaging is completed for patients with clinical stage 1 or 2 breast cancer who receive NAC, with few positive results.

Overuse of preoperative imaging to stage patients with invasive breast cancer (BC) contributes to rising health care costs. National and international guidelines discourage the use of imaging to stage newly diagnosed early-stage 1 or 2 BC regardless of nodal status,[1,2] Whereas the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) do not recommend positron emission tomography (PET) or computed tomography (CT) for women with newly diagnosed early BC, the European Society of Medical Oncology (ESMO) recommends its use only if conventional methods of bone or CT scans are inconclusive.[3] Furthermore, whereas ASCO does not recommend use of bone scans for staging, NCCN recommends consideration only if directed by signs or symptoms including localized bone pain or elevated alkaline phosphatase. Brain magnetic resonance imaging (MRI) is recommended only if a patient has signs or symptoms indicating intracranial disease.

Current literature investigating the use of imaging to stage BC rarely analyzes women treated with neoadjuvant chemotherapy (NAC). The objective of this study was to evaluate preoperative staging imaging rates among patients

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with clinical stage 1 or 2 BC undergoing NAC. We aimed to evaluate the overuse of staging imaging because it may lead to increased costs, increased use of resources, and unnecessary exposure to radiation. Specifically, we examined the rates of PET or CT imaging, brain imaging, and bone scans used for preoperative staging.

METHODS

After institutional review board (IRB) approval, all patients with stage 1 or 2 invasive BC who had NAC with a subsequent breast operation were identified from a prospectively maintained database from January 2008 to December 2016. These patients were followed for the duration of their clinic follow-up examinations. In order to calculate the rates of each staging test used, the patients who did not have staging imaging were not excluded from the analysis.

The patient variables collected were age at diagnosis, tumor histology, hormone receptor and human epidermal growth factor receptor 2 (HER2) status, clinical tumor-node-metastasis (TNM) stage, type of body imaging performed, type of brain imaging performed, use of bone scan, number of imaging studies, rates of positive imaging studies, rates of upstaging to stage 4 disease, findings of incidental cancers, and breast and lymph node activity shown on PET/CT.

The primary outcome variable was the use and rate of positive staging imaging. The secondary outcomes were breast and lymph node activity shown on PET or CT and receptor status of breast tumors for patients upstaged to stage 4 disease.

Data are presented as frequency (%) for categorical variables and median (range) for continuous variables. Univariate associations between variables were examined with the Kruskal-Wallis test, the chi-square test, or Fisher's exact test where appropriate. Post hoc pairwise comparisons using the Bonferroni correction adjusted for inflation due to multiple comparisons were further performed where significant associations ($p < 0.05$) were found. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and R version 3.5.1 (R Foundation, Vienna, Austria) with two-sided tests and a significance level of 0.05.

RESULTS

The mean age of the 303 patients with stage 1 or 2 BC was 51 years (range, 26–87 years). Of these 303 patients, 278 (92.4%) had invasive ductal cancer, and 15 (5%) had invasive lobular carcinoma (Table 1). According to the findings, 90 patients (30.2%) had estrogen receptor-positive disease, 79 patients (26.5%) had triple-negative disease, and 127 patients (42.6%) had HER2-positive disease. In terms of clinical staging, 66 patients (21.8%) had T1 disease, 216 patients (71.3%) had T2 disease, and 18 patients (5.9%) had T3 disease. Three patients (1%) had clinical T0, N1 disease and were being treated for node-positive invasive mammary carcinoma without evidence of primary BC. Of the 303 patients, 149 (49.2%) had clinical N0 disease, and 154 (50.8%) had clinical N1 disease (Table 1).

TABLE 1 Demographics and clinical characteristics

Characteristic	Total (n = 303) n (%)
Mean age (years), SD	51.0 ± 13.05
Biopsy pathology	
IDC	278 (92.4)
ILC	15 (5.0)
Mixed invasive carcinoma	7 (2.3)
Estrogen receptor	90 (30.2)
HER2 receptor	127 (42.6)
Triple-negative breast cancer	79 (26.5)
Unknown receptor status	5 (2.3)
Clinical T stage	
0	3 (1.0)
1	66 (21.8)
2	216 (71.3)
3	18 (5.9)
4	0 (0.0)
Clinical N stage	
0	149 (49.2)
1	154 (50.8)

SD, standard deviation; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HER2 human epidermal growth factor receptor 2

A staging PET or CT scan was completed for 258 patients (85.2%). Of these 258 patients, 225 (74.3%) had a PET/CT scan, and 33 (10.9%) had a CT abdomen/pelvis scan. Brain imaging was performed for 94 patients (31%). Of these 94 patients, 84 (27.7%) had an MRI, and 10 (3.3%) had a CT scan. Of the patients who had brain imaging ordered, 55 (58.5%) had HER2-positive BC, and 24 (25.6%) had triple-negative BC. Bone scans were completed for 117 (38.6%) patients.

The majority of imaging was ordered by the medical oncologist (45.7% PET/CT, 73.4% brain imaging, 52.1% bone scan), followed by the surgical oncologist (32.6% PET/CT, 13.8% brain imaging, 35% bone scan), an outside facility (20.5% PET/CT, 12.8% brain imaging, 11.1% bone scan), and an internist (1.2% PET/CT, 1.7% bone scan).

The patients younger than 50 years did not differ from those 50 years of age or older in the frequency of orders for staging imaging using PET/CT ($p = 0.704$), brain imaging ($p = 0.229$), or bone scans ($p = 0.235$) (Table 2). Whereas 48 patients (15.8%) had all three imaging methods completed, only 37 patients (12.2%) had no imaging performed. One imaging study was completed for 111 patients (36.6%), and two imaging studies were performed for 107 patients (35.3%).

Of the 266 patients who underwent staging imaging, 55 (20.7%) were symptomatic. Of these 55 symptomatic patients, 22 (40%) had neurologic symptoms, 18 (32.7%) had musculoskeletal symptoms, 6 (10.9%) had gastrointestinal symptoms, 5 (9.1%) had constitutional symptoms, and 4 (7.3%) had cardiovascular/respiratory symptoms (Table 3).

Overall, 21 patients (8.1%) had a positive PET/CT scan for distant disease. Of these 21 patients with a positive PET/CT scan for distant disease, 15 (71.4%) were upstaged to stage 4 BC, and 4 (19%) were found to have a second primary malignancy (1 patient with a contralateral BC), whereas the remaining patients had biopsy-proven papillary thyroid, ovarian, or neuroendocrine tumors. Two patients (9.5%) underwent resection of a suspicious liver lesion and an anterior mediastinal mass and were found to have benign pathology shown on the surgical excision. Metastatic disease developed in one patient (4.7%), which was diagnosed during NAC.

Of the 228 patients who had a PET or CT, 211 (90.9%) had uptake in the breast tumor. For 139 patients (61%), metastatic nodal disease or suspicious axillary nodal activity was shown on PET/CT. Of these patients, 107 (77%) had clinical N1 disease. Overall, only one patient (1.1%, 1/94) patient had positive brain imaging. Five patients (4.3%) had a positive bone scan, and three of these patients (60%) had a positive bone metastasis also shown on the PET/CT scan.

Our overall rate of 4.9% (15/303) for upstaging to stage 4 BC was low. Of the 15 patients upstaged to stage 4 disease, 2 (13.3%) were symptomatic before staging imaging, with both exhibiting musculoskeletal symptoms (Table 3). Of the 15 patients upstaged to stage 4 disease, 1 (6.7%) patient had clinical T1 disease, 13 (8.7%) patients had clinical T2 disease, and 1 (6.7%) patient had clinical T3 disease. In terms of clinical nodal stage, 1 patient

TABLE 3 Results of preoperative imaging

Characteristic	Total ($n = 303$) n (%)
No. of imaging studies done	
0	37 (12.2)
1	111 (36.6)
2	107 (35.3)
3	48 (15.8)
Positive PET/CT imaging	21/258 (8.1)
Upstaged to stage 4	15 (71.4)
Other incidental cancer	4 (19.0)
PET/CT activity	
Breast activity	211/228 (90.9)
Lymph node activity	139/228 (61.0)
Positive brain imaging	1/94 (1.1)
Positive bone scan	5/117 (4.3)
Correlates to PET/CT	3 (1.2)

PET, positron emission tomography; CT, computed tomography

TABLE 2 Preoperative imaging

Characteristic	Total ($n = 303$) n (%)	Age < 50 years ($n = 154$) n (%)	Age ≥ 50 years ($n = 149$) n (%)	p value
Body imaging				0.704
None	45 (14.9)	22 (14.3)	23 (15.4)	
PET/CT	225 (74.3)	113 (73.4)	112 (75.2)	
CT abdomen/pelvis	33 (10.9)	19 (12.3)	14 (9.4)	
Brain imaging				0.229
None	209 (69.0)	100 (64.9)	109 (73.2)	
MRI	84 (27.7)	47 (30.5)	37 (24.8)	
CT	10 (3.3)	7 (4.6)	3 (2.0)	
Bone scan				0.235
No	186 (61.4)	89 (57.8)	97 (65.1)	
Yes	117 (38.6)	65 (42.2)	52 (34.9)	

PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging

(6.7%) had N0 disease, and 14 patients (93.3%) had clinical N1 disease. Four patients (26.7%) had estrogen receptor-positive disease, whereas nine patients (60%) had HER2 receptor-positive tumors, and two patients (13.3%) had triple-negative BC. The study showed no significant difference among the ER-positive ($p = 1.000$), HER2-positive ($p = 0.259$), and triple-negative ($p = 0.369$) receptor profiles of the patients upstaged to stage 4 disease. Additionally, of the 15 patients upstaged to stage 4 disease, the frequency of orders for staging imaging did not differ significantly between the patients younger than 50 years ($n = 6$, 40%) and the patients 50 years of age or older ($n = 9$, 60%) ($p = 1.000$) (Table 4).

DISCUSSION

The national and international guidelines of the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO) discourage the use of imaging for staging patients with newly diagnosed stage 1 or 2 BC who are asymptomatic, regardless of subtype and nodal involvement.[4,5] This differs for patients with stage 3 disease, for whom routine imaging for staging is recommended. Although these guidelines give clear recommendations based on stage of BC, they do not address the role of staging for patients with high-risk tumor receptor profiles or patients undergoing NAC.

Despite these recommendations, routine use of imaging for staging is commonly used to stage patients with stage 1 or 2 BC before initiation of NAC. Several large-scale database studies have examined the overuse of imaging to stage patients with early BC. Crivello et al.[6] used Surveillance Epidemiology and End Results (SEER) data to examine 67,874 patients with stage 1 or 2 BC from 1992 to 2005 and demonstrated that 12,740 patients (18.8%) had preoperative advanced staging imaging. These authors also showed that the rates of CT/PET and brain MRIs had increased over time, from 1992 to 2005, whereas the rate of bone scans had declined. They reported an increase in brain MRIs, from 0.2% to 1.1%.

Simos et al.[7] used Ontario-Canadian population data to examine 26,547 women with early-stage BC and demonstrated that 22,811 patients (85.9%) had at least one imaging test, with a mean of 3.7 imaging tests performed per patient. These studies did not differentiate patients who had NAC.

Our study showed a similar high rate of women (at least 87.8%) who had at least one staging imaging test performed. Notably, our institution had a much higher rate of brain imaging ordered, for 31% of the patients, only one of whom had positive brain imaging. Although this patient did not have neurologic symptoms, the brain MRI was ordered after symptomatic peritoneal metastasis was detected on a PET/CT scan.

In single-institution studies, Linkugel et al.[8] examined 3291 patients with early BC from 1998 to 2012 and showed that 15% of the stage 1 patients and 46% of the stage 2 patients received a PET/CT or bone scan for staging. They found that younger patients who had hormone receptor-negative or HER2 receptor-positive tumor received more staging imaging. However, they excluded the patients who had NAC from their study. Conversely, our study showed no difference in the rate of PET/CT orders and no difference in the rate of upstaging to stage 4 disease between the patients younger than 50 years and those 50 years of age or older.

When examining the rate of distant metastatic disease detected by staging PET/CT scans, most studies show ranges from 0 to 5.1% for stage 1 BC and ranges from 0% to 5.5% for stage 2 BC.[9–12] Segaert et al.[13] examined 70 patients with stage 2b or stage 3 BC, 56 (80%) of whom had NAC, and demonstrated that 24 patients (34.2%) had metastatic disease detected by PET/CT scan. Our study had a much lower rate (4.9%) of patients with metastatic disease, likely because we excluded patients with stage 3 disease and included patients with stage 1 disease in our analysis.

TABLE 4 Receptor status compared for patients upstaged to stage 4 disease on PET/CT

Characteristic	Total ($n = 298$) n (%)	Upstaged to stage 4 ($n = 15$) n (%)	No upstaging ($n = 283$) n (%)	p value
Estrogen receptor	90 (30.2)	4 (26.7)	86 (30.4)	1.000
HER2 receptor	127 (42.6)	9 (60.0)	118 (41.7)	0.259
Triple-negative breast cancer	79 (26.5)	2 (13.3)	77 (27.2)	0.369
Age (years)				
< 50	–	6 (40.0)	–	1.000
≥ 50	–	9 (60.0)	–	

HER2, human epidermal growth factor receptor 2

Many studies in the literature exclude or do not differentiate patients who had NAC when examining receptor subtypes. Bychkovsky et al.[9] examined 411 patients with stage 2 BC at two different academic centers and showed that of the 237 patients (58%) who had CT imaging, those with HER2-positive or triple-negative BC more often had imaging performed. However the rate for the detection of metastatic disease among these hormone receptor subtypes was not any higher for hormone receptor-positive disease (2.2%) than for HER2-positive disease (1.9%) or triple-negative BC (2.1%).

Whereas most studies focus on PET/CT, some studies examine bone scans for detection of metastasis in patients with early BC. Puglisi et al.[14] examined 516 patients with stage 3 BC and showed that 6.3% of the patients had skeletal metastasis shown on bone scan imaging. Chen et al.[15] examined 5406 patients with BC using bone scans and showed a bone metastasis rate of 0% for the stage 1 patients, 0.6% for the stage 2 patients, and 2.7% for the stage 3 patients. Our rate of positive bone scans was 4.3%, which may be higher than the rates in other reported studies because we examined patients who had NAC.

Finally, similar to our study findings, other studies have found PET/CT to be sensitive and specific in identifying breast activity and moderately accurate in identifying axillary nodal activity.[16,17] Wahl et al.[17] analyzed 360 women with newly diagnosed invasive BC and demonstrated that PET scans were 61% sensitive and 80% specific in detecting axillary nodal metastasis. They concluded that because FDG-PET fails to detect axillae with small and few nodal metastases, it is not routinely recommended for axillary staging. Similarly, our study showed metastatic nodal disease or suspicious axillary nodal activity on PET/CT for 61% of patients, of whom only 77% had clinical N1 disease. Our study showed a high rate for detection of breast activity by PET/CT ($> 90\%$), likely due to the higher clinical T stage seen in this patient population who received NAC.

Our study had some limitations. Because data were extracted from a prospectively maintained database, patients with stage 1 or 2 BC were captured only if they completed NAC with a subsequent breast operation at our institution. Imaging studies completed at an outside facility and not documented or uploaded to the electronic medical record were not captured.

CONCLUSION

Despite guideline recommendations, preoperative staging imaging is completed at a high rate for patients with clinical stage 1 or 2 BC who receive NAC, with few positive results. Our findings suggest that pre-NAC staging is not necessary and may contribute to higher costs for the management of patients with early-stage BC.

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