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Breast Cancer

Initial Staging Impact of Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Locally Advanced Breast Cancer

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ABSTRACT

Purpose. **Fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) may reveal distant metastases more accurately than conventional imaging (CT, skeletal scintigraphy, chest radiography). We hypothesized that patients diagnosed with stage III noninflammatory breast cancer (non-IBC) and IBC by conventional imaging with PET/CT have a better prognosis than patients diagnosed without PET/CT.**

Patients and Methods. **We retrospectively identified 935 patients with stage III breast cancer in 2000–2009. We compared the relapse-free survival (RFS) and overall survival (OS) times of patients diagnosed by conventional imaging with those of patients diagnosed by conventional imaging plus PET/CT. Univariate and multivariate Cox proportional hazards regression models were used to assess associations between survival and PET/CT.**

Results. **RFS and OS times were not significantly different between patients imaged with PET/CT and those imaged without PET/CT. However, the RFS time in IBC patients was significantly different between patients imaged with PET/CT and those imaged without PET/CT on both univariate (hazard ratio [HR], 0.43; $p = .014$) and multivariate (HR, 0.33; $p = .004$) analysis. There was a trend for a longer OS duration in IBC patients imaged with PET/CT.**

Conclusion. **Among IBC patients, adding PET/CT to staging based on conventional imaging might detect patients with metastases that were not detected by conventional imaging. The use of conventional imaging with PET/CT for staging in non-IBC patients is not justified on the basis of these retrospective data. The use of conventional imaging plus PET/CT in staging IBC needs to be studied prospectively to determine whether it will improve prognosis.** *The Oncologist* 2011;16:772–782

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Introduction

Locally advanced breast cancer (LABC) has very high rates of relapse and eventual disease-related death. The 5-year relative survival rate for women with stage III breast cancer is 55%, with a median survival duration of 6.4 years, according to the National Cancer Institute's Surveillance, Epidemiology, and End Results program. Women with inflammatory breast cancer (IBC) have much worse prognosis, with a median survival time of just 2.9 years [1]. These poor long-term outcomes despite initial staging investigations that did not identify distant spread call into question the accuracy of current staging modalities. These investigations may underestimate the true incidence of metastases, which has led to speculation about whether or not other investigational modalities would be more accurate for detecting systemic spread [2]. Conventional imaging modalities (i.e., computed tomography [CT], ultrasonography, chest radiography, whole-body skeletal scintigraphy [SS]) have limitations for precisely detecting distant metastases of breast cancer [3].

In women presenting with LABC, staging evaluations, which can include chest radiography, SS, CT, and magnetic resonance imaging (MRI), are conducted to exclude the possibility of distant metastasis before therapy is initiated. The National Comprehensive Cancer Network (NCCN) guidelines recommend bilateral mammography, ultrasonography as necessary, chest imaging, and, as optional studies directed by symptoms, breast MRI, SS, and/or abdominal CT, ultrasonography, MRI, or PET/CT [4].

Many studies have evaluated the sensitivity and specificity of various imaging modalities for detecting distant metastases and lymph node metastases in primary breast cancer patients, but there is yet to be a study proving that the use of a specific imaging modality in the staging of breast cancer patients can affect relapse-free survival (RFS) and overall survival (OS) times among patients with the same stage of disease.

In addition to conventional imaging techniques, fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) may be useful in the detection of distant metastases from breast cancer. Previous studies have shown that PET/CT is more sensitive than conventional imaging in detecting distant metastases [5–9]; however, in those studies, the numbers of patients ($n = 40–62$) and the numbers of patients diagnosed with distant metastases ($n = 4–20$) were too small to prove that PET/CT was more sensitive than conventional imaging. In a study of 60 patients with primary breast cancer, Fuster et al. [5] reported that PET/CT was able to reveal previously unsuspected metastatic lesions caused by infiltration of axillary lymph nodes in 10 patients, infiltration of extra-axillary lymph nodes in three patients, and distant metastases in five patients, all of which led to a change in the initial staging in 42% of patients included in this study. The results of two studies of patients with IBC led the investigators to recommend the use of PET/CT in the initial staging of IBC [6, 7]. However, the role of PET/CT in primary breast cancer staging is not yet well defined. Because there is limited evidence to support its use, PET/CT is thus far not indicated in the staging of breast cancer.

We recently showed that the sensitivity and specificity in the detection of distant metastases were significantly higher for PET/CT (97.4% and 91.2%, respectively) than for conventional imaging (85.9% and 67.3%, respectively; $p = .009$ and $p < .001$). In that study of 225 patients, 11 patients had distant metastases revealed by PET/CT that were clinically occult and not evident on conventional imaging [10].

The results of our previous study led us to hypothesize that PET/CT is superior to conventional imaging for accurately detecting metastases in regional lymph nodes and distant sites. Therefore, patients diagnosed with stage III disease by conventional imaging plus PET/CT would have a better prognosis than patients diagnosed with stage III disease by conventional imaging only. The aim of this retrospective study of the role of PET/CT in staging LABC was to compare the RFS and OS times of primary breast cancer patients with stage III disease in whom the absence of distant metastasis was determined by conventional imaging with those of patients diagnosed by conventional imaging plus PET/CT. We also compared RFS and OS times between patients with IBC and patients with noninflammatory forms of breast cancer (non-IBC).

Patients and Methods

Patients

We retrospectively identified patients with breast cancer who were newly diagnosed with stage III disease at The University of Texas MD Anderson Cancer Center from January 1, 2000 to September 30, 2009. To identify these patients, we used a prospectively maintained database of the Department of Breast Medical Oncology at MD Anderson Cancer Center. Patients who had undergone systemic therapy, such as chemotherapy or endocrine therapy, before undergoing PET/CT were excluded. Patients who had undergone local therapy, such as surgery, before undergoing PET/CT were included in the study.

The following characteristics were recorded for each patient: age at diagnosis, tumor size, clinical tumor–node–metastasis (TNM) stage, pathologic TNM stage, time to disease relapse, site(s) of initial relapse, and his-

topathologic findings, when available. The MD Anderson Cancer Center Institutional Review Board approved this study. We defined conventional imaging as chest radiography, SS, and/or CT of the chest and abdomen. CT studies of the chest and abdomen were performed with an i.v. contrast agent. In total, 99% of patients underwent chest radiography, 84% of patients underwent SS, 39% of patients underwent chest CT, and 85% of patients underwent abdominal CT.

Staging and Pathology Review

Primary breast cancer was staged according to the sixth edition of the American Joint Committee on Cancer's *AJCC Cancer Staging Manual* [11]. All patients included in the study had histologic confirmation of breast cancer.

Tumors were graded according to the modified Black's nuclear grading system [12] and histologically classified according to the World Health Organization criteria [13]. A patient was considered to have human epidermal growth factor receptor (HER)-2^+ disease if the primary tumor or a metastatic tumor had a score of 3+ on HER-2 immunohistochemical analysis or if amplification of the *HER-2* gene was found on fluorescence in situ hybridization.

PET/CT Imaging and Image Interpretation

FDG-PET/CT was performed using one of the following: Siemens ECAT HR with dedicated CT (Siemens/CTI, Knoxville, TN), GE Discovery ST 8-slice PET/CT, GE Discovery STE 16-slice PET/CT, GE Discovery RX 16-slice PET/CT, or GE VCT 64-slice PET/CT scanner (General Electric Medical Systems, Milwaukee, WI). Normal fasting blood glucose levels $<$150 mg/dL were a standard requirement for imaging in all patients. Patients fasted for at least 6 hours before the ^{18}F-FDG injections. An i.v. injection of 555–740 MBq (15–20 mCi) of ^{18}F-FDG was administered, and 60–90 minutes later, two- or three-dimensional emission scans were acquired at 3–5 minutes per bed station. PET images were reconstructed using standard vendor-provided reconstruction algorithms. Noncontrast-enhanced CT was used for attenuation correction and diagnosis and acquired in helical mode with tube current modulation (120 kV, 300 mA, 0.5-second rotation) from the vertex or base of the skull to the midthigh, calf, or toes during quiet respiration at a 3.75-mm slice thickness. Images were viewed on GE Advantage 4.2–4.4 workstations (General Electric Medical Systems, Milwaukee, WI). The maximum standardized uptake value, a semiquantitative measure of FDG uptake, was most commonly reported on focal abnormalities.

Statistical Methods

Means and standard deviations are used to summarize the patients' age at diagnosis. Frequencies and proportions are used to present categorical clinical characteristics. Pearson χ^2 tests and Fisher's exact tests were used to test associations between imaging methods (conventional imaging with PET/CT versus conventional imaging without PET/CT) and categorical clinical characteristics. Two independent-sample *t*-tests were used to determine differences in the mean age. The RFS duration was defined as the time interval from diagnosis to first distant metastasis, death, or last follow-up date, whichever occurred first. Patients who had been alive without relapse at the last follow-up were censored in the RFS analyses. The OS time was defined as the length of time from diagnosis to death or last follow-up date if patients were alive at the last follow-up. Patients who were alive at the last follow-up were censored in the OS analyses. RFS and OS were estimated by the Kaplan–Meier product-limit method. Univariate and multivariate Cox proportional hazards (PH) regression models were used to assess the effect of PET/CT and other predictive factors on RFS and OS times. In the multivariate Cox models, adjustments were made for lymph node involvement (N0, N1, and N2 versus N3), menopausal status, age ($<$50 years versus $\geq$50 years), nuclear grade (I and II versus III), whether or not the patient had undergone radiation therapy, estrogen receptor status, HER-2 status, and tumor size (T1, T2, and T3 versus T4). The analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC).

RESULTS

Characteristics of Patients Diagnosed by Conventional Imaging Plus PET/CT and Conventional Imaging Only

Of 8,510 patients diagnosed with primary breast cancer during the study period, 935 patients were newly diagnosed with stage III breast cancer. Eight hundred fifty-three were diagnosed as stage III by conventional imaging. Eighty-two of these 935 patients were diagnosed with stage III disease by conventional imaging plus PET/CT. Of the 935 patients with stage III disease, 811 received neoadjuvant chemotherapy and 124 did not receive neoadjuvant chemotherapy. Of the latter 124 patients, 93 received adjuvant chemotherapy and 31 did not receive adjuvant chemotherapy. Among the 555 patients with hormone receptor–positive primary tumors, 469 (85%) received adjuvant endocrine therapy. There was no significant difference between patients who underwent conventional imaging with PET/CT and without

Table 1. Characteristics of IBC and non-IBC patients with stage III disease by imaging method

	All patients with stage III disease			Non-IBC			IBC		
Characteristic	**Conventional imaging (*n* = 853) *n* (%)**	**Conventional imaging plus PET/CT (*n* = 82) *n* (%)**	***p***	**Conventional imaging (*n* = 734) *n* (%)**	**Conventional imaging plus PET/CT (*n* = 31) *n* (%)**	***p***	**Conventional imaging (*n* = 119) *n* (%)**	**Conventional imaging plus PET/CT (*n* = 51) *n* (%)**	***p***
Age, yrs, at primary diagnosis, mean (SD)	50.6 (11.7)	51.6 (11.8)	.447	50.5 (11.7)	50.7 (12.5)	.897	51.5 (11.7)	52.2 (11.6)	.722
Primary tumor size									
T0, Tis	12 (2%)	2 (2%)	<.001						
T1	63 (7%)	3 (4%)							
T2	208 (24%)	6 (7%)							
T3	221 (26%)	7 (9%)							
T4 (non-IBC)	230 (27%)	12 (15%)							
T4 (IBC)	119 (14%)	52 (63%)							
Regional lymph node status									
N0	55 (7%)	7 (9%)	.023	49 (7%)	4 (13%)	.131	6 (5%)	3 (6%)	.003
N1	298 (35%)	20 (24%)		252 (34%)	6 (19%)		46 (39%)	14 (27%)	
N2	122 (14%)	6 (7%)		112 (15%)	3 (10%)		10 (8%)	3 (6%)	
N3	378 (44%)	49 (60%)		321 (44%)	18 (58%)		57 (48%)	31 (61%)	
Stage									
IIIA	243 (29%)	6 (7%)	<.001	243 (33%)	6 (19%)	.211			
IIIB	232 (27%)	27 (33%)		170 (23%)	7 (23%)		62 (52%)	20 (39%)	.123
IIIC	378 (44%)	49 (60%)		321 (44%)	18 (58%)		57 (48%)	31 (61%)	
Estrogen receptor status									
Positive	551 (60%)	43 (53%)		461 (63%)	19 (61%)	.774	50 (42%)	24 (47%)	.573
Negative	340 (40%)	37 (45%)	.272	272 (37%)	10 (32%)		68 (57%)	27 (53%)	
Unknown	2 (0.2%)	2 (2%)		1 (0.1%)	2 (7%)		1 (1%)	0 (0%)	
Progesterone receptor status									
Positive	380 (44%)	28 (34%)	.076	342 (46%)	13 (42%)	.705	38 (32%)	15 (29%)	.719
Negative	468 (55%)	53 (65%)		388 (53%)	17 (55%)		80 (67%)	36 (71%)	
Unknown	5 (1%)	1 (1%)		4 (1%)	1 (3%)		1 (1%)	0 (0%)	
HER-2 status									
Positive	235 (28%)	32 (39%)	.031	193 (26%)	9 (29%)	.346	42 (35%)	23 (45%)	.518
Negative	445 (52%)	35 (43%)		392 (54%)	12 (39%)		53 (45%)	23 (45%)	
Unknown	173 (20%)	15 (18%)		149 (20%)	10 (32%)		24 (20%)	5 (10%)	
Nuclear grade									
I	28 (3%)	1 (1%)	.634	25 (3%)	1 (3%)	.879	3 (3%)	0 (0%)	.521
II	215 (25%)	19 (23%)		194 (26%)	7 (23%)		21 (18%)	12 (24%)	
III	586 (69)	60 (73%)		496 (68%)	23 (74%)		90 (75%)	37 (72%)	
Unknown	24 (3%)	2 (2%)		19 (3%)	0 (0%)		5 (4%)	2 (4%)	
Radiation therapy									
Yes	740 (87%)	63 (77%)	.019	643 (88%)	25 (80%)	.266	97 (82%)	38 (75%)	.308
No	113 (13%)	19 (23%)		91 (12%)	6 (20%)		22 (18%)	13 (25%)	

Abbreviations: HER-2, human epidermal growth factor receptor 2; IBC, inflammatory breast cancer; PET/CT, positron emission tomography/computed tomography; SD, standard deviation.

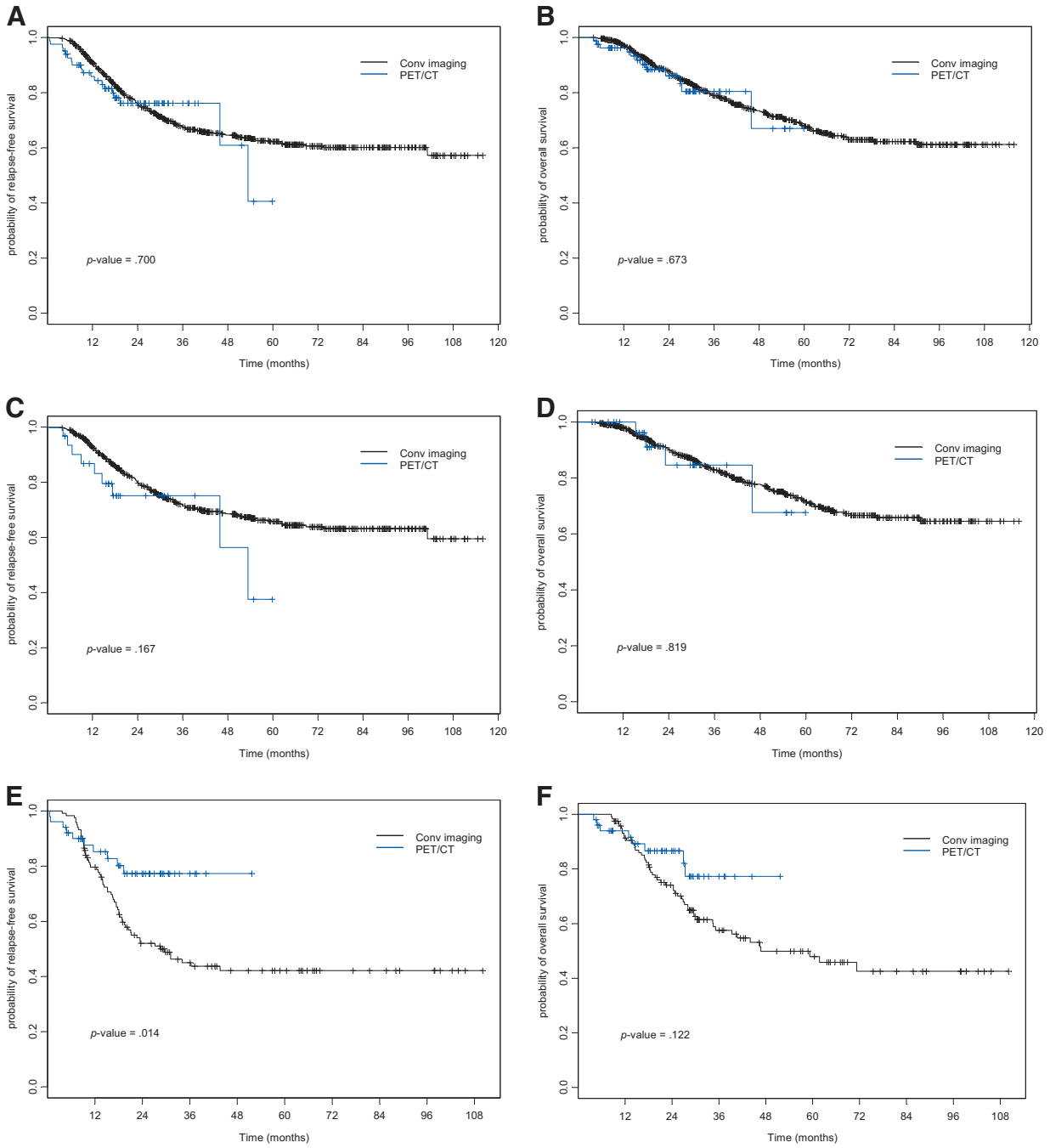

Figure 1. Kaplan–Meier curves for breast cancer patients diagnosed by conventional imaging only and by conventional imaging plus PET/CT. **(A):** RFS by imaging method in all patients with stage III disease. **(B):** OS by imaging method in all patients with stage III disease. **(C):** RFS by imaging method in non-IBC patients. **(D):** OS by imaging method in non-IBC patients. **(E):** RFS by imaging method in IBC patients. **(F):** OS by imaging method in IBC patients.

Abbreviations: IBC, inflammatory breast cancer; OS, overall survival; PET/CT, positron emission tomography/computed tomography; RFS, relapse-free survival.

PET/CT in whether or not they had received endocrine therapy. Among the 268 patients with HER-2$^+$ primary tumors, patients who underwent conventional imaging with PET/CT had a trend to receive trastuzumab ($p = .001$); among the 235 patients who did not undergo PET/CT, 157 (67%) received trastuzumab, and among the 33 patients who underwent PET/CT, 31 (94%) received trastuzumab. Table 1 shows the characteristics of all patients with stage III disease and compares the characteristics of non-IBC patients with those of IBC patients. Patients who underwent

Table 2. Multivariate Cox proportional hazards model of relapse-free survival in all patients with stage III disease

Variable	Relapsed or died, *n* (%)	HR	95% CI	*p*
Imaging method				
Conventional imaging	253/853 (29%)	Referent	–	–
Conventional imaging plus PET/CT	19/82 (23%)	0.70	0.40–1.23	.213
Local lymph node status				
N3	138/427 (32%)	Referent	–	–
N0/N1/N2	134/508 (26%)	0.52	0.39–0.69	<.001
Menopausal status				
Postmenopausal	154/498 (31%)	Referent	–	–
Premenopausal	118/436 (27%)	0.99	0.67–1.47	.971
Age, yrs				
<50	148/494 (30%)	Referent	–	–
≥50	124/441 (28%)	1.10	0.74–1.65	.639
Nuclear grade				
III	210/646 (33%)	Referent	–	–
I/II	55/263 (21%)	0.74	0.52–1.06	.102
Radiation therapy				
No	67/132 (51%)	Referent	–	–
Yes	205/803 (25%)	0.24	0.19–0.41	<.001
Estrogen receptor status				
Negative	153/377 (41%)	Referent	–	–
Positive	118/554 (21%)	0.54	0.40–0.72	<.001
HER-2 status				
Negative	148/480 (31%)	Referent	–	–
Positive	71/267 (27%)	0.77	0.57–1.03	.078
Primary tumor size				
T4	159/413 (39%)	Referent	–	–
T0/Tis/T1/T2/T3	113/522 (22%)	0.46	0.35–0.62	<.001

Abbreviations: CI, confidence interval; HER-2, human epidermal growth factor receptor 2; HR, hazard ratio; PET/CT, positron emission tomography/computed tomography.

conventional imaging with PET/CT had breast cancer with a higher T stage, N stage, and HER-2 status than those who underwent conventional imaging only.

Characteristics of Non-IBC and IBC Patients Diagnosed by Conventional Imaging with PET/CT and by Conventional Imaging Alone

Of the 935 patients with stage III disease, 170 had IBC and 765 had non-IBC. Among non-IBC patients, 734 were diagnosed by conventional imaging without PET/CT and 31 had PET/CT data available for review. Primary tumor size, local lymph node status, clinical stage, estrogen receptor status, and HER-2 status were not significantly associated with imaging method in non-IBC patients.

Among IBC patients, 119 were diagnosed with stage III disease by conventional imaging without PET/CT and 51 had PET/CT data available for review. Regional lymph node status was significantly associated with imaging method in IBC patients ($p = .003$).

RFS and OS in Patients with Stage III Disease

RFS was not significantly different between patients with stage III disease diagnosed by conventional imaging with PET/CT and those diagnosed by conventional imaging only in the univariate Cox PH model of RFS (hazard ratio [HR], 1.10; 95% confidence interval [CI], 0.69–1.75; $p = .7$). Figure 1A shows the Kaplan–Meier RFS curves by imaging method for all patients with stage III disease.

Table 2 shows the multivariate Cox PH model of RFS for all patients with stage III disease. Imaging method was not significantly associated with RFS (HR, 0.70; 95% CI, 0.40–1.23; $p = .213$). Moreover, we estimated the univar-

Table 3. Multivariate Cox proportional hazards model of overall survival in all patients with stage III disease

Variable	Died/*n* (%)	HR	95% CI	*p*
Imaging method				
Conventional imaging	198/853 (23%)	Referent	–	–
Conventional imaging plus PET/CT	12/82 (15%)	0.75	0.38–1.51	.428
Primary lymph node status				
N3	106/427 (25%)	Referent	–	–
N0/N1/N2	104/508 (20%)	0.47	0.34–0.66	<.001
Menopausal status				
Postmenopausal	122/498 (25%)	Referent	–	–
Premenopausal	88/436 (20%)	0.94	0.59–1.50	.808
Age, yrs				
<50	117/494 (24%)	Referent	–	–
≥50	93/441 (21%)	0.98	0.61–1.56	.938
Nuclear grade				
III	168/646 (26%)	Referent	–	–
I/II	39/263 (15%)	0.68	0.45–1.04	.075
Radiation therapy				
No	54/132 (41%)	Referent	–	–
Yes	156/803 (19%)	0.22	0.16–0.33	<.001
Estrogen receptor status				
Negative	127/377 (34%)	Referent	–	–
Positive	82/554 (15%)	0.48	0.34–0.67	<.001
HER-2 status				
Negative	116/480 (24%)	Referent	–	–
Positive	51/267 (19%)	0.66	0.47–0.93	.016
Primary tumor size				
T4	128/413 (31%)	Referent	–	–
T0/Tis/T1/T2/T3	82/522 (16%)	0.44	0.31–0.61	<.001

Abbreviations: CI, confidence interval; HER-2, human epidermal growth factor receptor 2; HR, hazard ratio; PET/CT, positron emission tomography/computed tomography.

iate Cox PH models of RFS in patients with stage IIIB (HR, 0.92; 95% CI, 0.40–2.11; $p = .934$) and stage IIIC (HR, 0.94; 95% CI, 0.52–1.72; $p = .86$) disease and found no significant differences between patients imaged with and without PET/CT. In the univariate Cox PH model of OS in all patients with stage III disease, there was no significant difference between patients imaged with and without PET/CT (HR, 1.14; 95% CI, 0.62–2.04; $p = 0.673$). Figure 1B shows the Kaplan–Meier OS curves for all patients with stage III disease by imaging method. Table 3 shows the multivariate Cox PH model of OS in all patients with stage III disease, and there was no association between OS and imaging method (HR, 0.75; 95% CI, 0.38–1.51; $p = .428$). Moreover, there were no significant differences in OS between patients diagnosed by conventional imaging and those diagnosed by conventional imaging plus PET/CT in patients with stage IIIB disease (HR, 1.30; 95% CI, 0.51–3.28; $p = .58$) and in patients with stage IIIC disease (HR, 0.86; 95% CI, 0.15–0.69; $p = .706$). In a subgroup analysis with hormone receptor–positive, HER-2^+ and triple-negative patients, RFS and OS were not significantly different between patients with stage III disease diagnosed by conventional imaging plus PET/CT and those diagnosed by conventional imaging alone.

RFS and OS in Non-IBC Patients

In the univariate Cox PH model of RFS in stage III patients, there was no significant difference between non-IBC patients with stage III disease diagnosed by conventional imaging alone and those diagnosed by conventional imaging plus PET/CT (HR, 1.60; 95% CI, 0.82–3.14; $p = .167$). Figure 1C shows the Kaplan–Meier RFS curves for non-IBC

Table 4. Multivariate Cox proportional hazards model of relapse-free survival in inflammatory breast cancer patients

Variable	Relapsed or died, *n* (%)	HR	95% CI	*p*
Imaging method				
Conventional imaging	62/119 (52%)	Referent	–	–
Conventional imaging plus PET/CT	10/51 (20%)	0.33	0.15–0.69	.004
Primary lymph node status				
N3	44/88 (50%)	Referent	–	–
N0/N1/N2	28/82 (34%)	0.42	0.24–0.75	.004
Menopausal status				
Postmenopausal	39/93 (42%)	Referent	–	–
Premenopausal	33/76 (43%)	1.47	0.63–3.40	.368
Age, yrs				
<50	40/97 (41%)	Referent	–	–
≥50	32/73 (44%)	1.47	0.64–3.37	.365
Nuclear grade				
III	60/127 (47%)	Referent	–	–
I/II	10/36 (28%)	0.84	0.38–1.88	.669
Radiation therapy				
No	24/35 (69%)	Referent	–	–
Yes	48/135 (36%)	0.14	0.07–0.27	<.001
Estrogen receptor status				
Negative	49/95 (52%)	Referent	–	–
Positive	22/74 (30%)	0.59	0.30–1.14	.113
HER-2 status				
Negative	32/76 (42%)	Referent	–	–
Positive	28/65 (43%)	1.07	0.62–1.86	.805

Abbreviations: CI, confidence interval; HER-2, human epidermal growth factor receptor 2; HR, hazard ratio; PET/CT, positron emission tomography/computed tomography.

patients by imaging method. In the multivariate Cox PH model of RFS in non-IBC patients, imaging method was not significantly associated with RFS (HR, 1.81; 95% CI, 0.80–4.10; $p = .158$). In the univariate Cox PH model of OS in non-IBC patients, there was no significant difference between patients diagnosed by conventional imaging and those diagnosed by conventional imaging plus PET/CT (HR, 1.12; 95% CI, 0.42–3.04; $p = .819$). Figure 1D shows the Kaplan–Meier OS curves for non-IBC patients by imaging method. In the multivariate Cox PH model of OS in non-IBC patients, imaging method was not significantly associated with OS (HR, 0.86; 95% CI, 0.21–3.49; $p = .827$).

RFS and OS in IBC Patients

In the univariate Cox PH model of RFS, IBC patients diagnosed with stage III disease by conventional imaging plus PET/CT had a longer RFS interval than did patients diagnosed by conventional imaging alone (HR, 0.43; 95% CI, 0.22–0.84; $p = .014$). Figure 1E shows the Kaplan–Meier RFS curves for IBC patients by imaging method. In the multivariate Cox PH model of RFS in IBC patients, imaging with PET/CT was significantly associated with a longer RFS interval (HR, 0.33; 95% CI, 0.15–0.69; $p = .004$) (Table 4). The univariate Cox PH model of OS in IBC patients showed no significant difference between patients diagnosed by conventional imaging and those diagnosed by conventional imaging plus PET/CT (HR, 0.51; 95% CI, 0.26–1.17; $p = .122$). Figure 1F shows the Kaplan–Meier OS curves for IBC patients by imaging method. Table 5 shows the multivariate Cox PH model of OS for IBC patients. Again, imaging method was not associated with OS (HR, 0.57; 95% CI, 0.25–1.33; $p = .192$).

Discussion

In this study, we showed that there is no major role for PET/CT in defining stage III disease for non-IBC patients. In contrast, it is possible that accurate diagnosis by conventional imaging with PET/CT in IBC patients may affect the

Table 5. Multivariate Cox proportional hazards model of overall survival in inflammatory breast cancer patients

Variable	Died, *n* (%)	HR	95% CI	*p*
Imaging method				
Conventional imaging	52/119 (44%)	Referent	–	–
Conventional imaging plus PET/CT	8/51 (16%)	0.57	0.25–1.33	.192
Primary lymph node status				
N3	37/88 (42%)	Referent	–	–
N0/N1/N2	23/82 (28%)	0.50	0.27–0.93	.029
Menopausal status				
Postmenopausal	34/93 (37%)	Referent	–	–
Premenopausal	26/76 (34%)	1.03	0.40–2.67	.949
Age, yrs				
<50	34/97 (35%)	Referent	–	–
≥50	26/73 (36%)	1.10	0.43–2.78	.846
Nuclear grade				
III	51/127 (40%)	Referent	–	–
I/II	7/36 (19%)	0.59	0.25–1.39	.228
Radiation therapy				
No	20/35 (57%)	Referent	–	–
Yes	40/135 (30%)	0.21	0.10–0.42	<.001
Estrogen receptor status				
Negative	43/95 (45%)	Referent	–	–
Positive	16/74 (22%)	0.57	0.27–1.17	.123
HER-2 status				
Negative	30/76 (39%)	Referent	–	–
Positive	21/65 (32%)	0.62	0.34–1.11	.109

Abbreviations: CI, confidence interval; HER-2, human epidermal growth factor receptor 2; HR, hazard ratio; PET/CT, positron emission tomography/computed tomography.

long-term prognosis for these patients. To our knowledge, this is the first study to show that imaging techniques can affect RFS and OS in patients with primary breast cancer.

The most important prognostic factor for primary breast cancer is stage of disease at initial diagnosis [14]. Risk is stratified according to the TNM classification system, because many patients who are diagnosed at an early stage will experience a relapse [14]. There is currently no definitive evidence supporting the use of combined imaging procedures to carry out baseline staging in breast cancer patients. Indeed, several studies have reported a limited value of breast cancer baseline staging, suggesting that a complete diagnostic workup should be limited to patients with a higher pretest probability of distant metastases [3, 15–20]. However, among 144 patients with LABC studied by Al-Husaini et al. [2], initial staging evaluations identified 15 patients (10.4%) with overt metastatic disease, and additional imaging investigations revealed another four patients with metastatic disease, resulting in a 13.2% prevalence of metastasis. Because accurate staging in LABC patients is crucial, Al-Husaini et al. [2] recommended that further research be done to define the role and sequence of newer imaging techniques such as MRI and PET [2]. But our survival data suggest that PET/CT at baseline staging should be limited to IBC patients and not be recommended in all LABC patients.

Our study has some limitations. First, this study is a retrospective evaluation. Retrospective studies are affected by selection bias on the basis of factors such as insurance status and socioeconomic status. Second, this study was done in a single institution. Third, patient and tumor characteristics were not well balanced between the groups imaged without PET/CT and those imaged with PET/CT. For example, the group of patients imaged with PET/CT included higher percentages of patients with N3 lymph node status and with IBC than did the group diagnosed by conventional imaging only. Another limitation was that the number of patients diagnosed using PET/CT was small in our study. Moreover,

the median follow-up was short (3.2 years), and the median follow-up for IBC patients was only 2.7 years. Longer follow-up times could potentially lead to a significant statistical difference in OS. Finally, not all patients underwent full conventional imaging (SS, chest CT, and radiography). However, for patients who have no symptoms, the NCCN guidelines recommend only bilateral mammogram, ultrasonography as necessary, and chest imaging.

There has been little evidence, from our study or others, that a long survival duration of patients is closely linked to accurate staging, but the ability to accurately stage patients may still have clinical benefits. First, accurate staging could allow patients to avoid unnecessary surgery. Conversely, the anatomic information contained in a PET/CT scan can help clinicians provide appropriate interventions to prevent complications such as pathologic fracture. Second, clinicians would be better able to advise patients on their prognosis. In the current NCCN guidelines, PET/CT is not used in the primary staging of LABC except in those clinical situations in which other staging studies are equivocal or suggestive of distant metastasis [4]. Our study showed that conventional imaging plus PET/CT was associated with a longer RFS interval and a trend toward a longer OS time in IBC patients. The reason for these longer survival times may be that IBC patients have a higher rate of systemic relapse than patients with other types of breast cancer. In patients who have a high risk for distant metastases or relapse, such as those with symptoms, abnormal liver function, and abnormal alkaline phosphatase levels, conventional imaging plus PET/CT could definitively detect metastases and improve quality of life.

In summary, among patients with non-IBC stage III disease, the use of PET/CT in staging does not result in a better prognosis. However, in patients with IBC, the addition of PET/CT to the workup to rule out metastases prolongs survival. On the basis of previous studies, as well as our study, we do not recommend conventional imaging plus PET/CT for non-IBC patients, although PET/CT might be able to replace conventional imaging for detecting distant metastases in primary breast cancer staging. Our results indicate a need for a prospective study for screening distant metastases during breast cancer staging in IBC patients.

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References

1 Hance KW, Anderson WF, Devesa SS et al. Trends in inflammatory breast carcinoma incidence and survival: The Surveillance, Epidemiology, and End Results program at the National Cancer Institute. J Natl Cancer Inst 2005;97:966–975.

2 Al-Husaini H, Amir E, Fitzgerald B et al. Prevalence of overt metastases in locally advanced breast cancer. Clin Oncol (R Coll Radiol) 2008;20:340–344.

3 Puglisi F, Follador A, Minisini AM et al. Baseline staging tests after a new diagnosis of breast cancer: Further evidence of their limited indications. Ann Oncol 2005;16:263–266.

4 Carlson RW, McCormick B. Update: NCCN breast cancer clinical practice guidelines. J Natl Compr Canc Netw 2005;3(suppl 1):S7–S11.

5 Fuster D, Duch J, Paredes P et al. Preoperative staging of large primary breast cancer with [18F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. J Clin Oncol 2008;26:4746–4751.

6 Carkaci S, Macapinlac HA, Cristofanilli M et al. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: Preliminary data. J Nucl Med 2009;50:231–238.

7 Alberini JL, Lerebours F, Wartski M et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. Cancer 2009;115:5038–5047.

8 Heusner TA, Kuemmel S, Umutlu L et al. Breast cancer staging in a single session: Whole-body PET/CT mammography. J Nucl Med 2008;49:1215–1222.

9 Groheux D, Moretti JL, Baillet G et al. Effect of (18)F-FDG PET/CT imaging in patients with clinical stage II and III breast cancer. Int J Radiat Oncol Biol Phys 2008;71:695–704.

10 Niikura N, Costelloe C, Madewell J et al. Role of FDG-PET/CT in metastatic staging of newly diagnosed primary breast cancer [abstract P5-01-02]. Presented at San Antonio Breast Cancer Symposium, San Antonio, TX, December 8–12, 2010.

11 Singletary SE, Allred C, Ashley P et al. Staging system for breast cancer: Revisions for the 6th edition of the AJCC Cancer Staging Manual. Surg Clin North Am 2003;83:803–819.

12 Black MM, Speer FD. Nuclear structure in cancer tissues. Surg Gynecol Obstet 1957;105:97–102.

13 The World Health Organization. Histological typing of breast tumors. Neoplasma 1983;30:113–123.

14 Buck AK, Herrmann K, Stargardt T et al. Economic evaluation of PET and

PET/CT in oncology: Evidence and methodologic approaches. J Nucl Med 2010;51:401–412.

15 Ravaioli A, Pasini G, Polselli A et al. Staging of breast cancer: New recommended standard procedure. Breast Cancer Res Treat 2002;72: 53–60.

16 Myers RE, Johnston M, Pritchard K et al. Baseline staging tests in primary breast cancer: A practice guideline. CMAJ 2001;164:1439–1444.

17 Dillman RO, Chico S. Radiologic tests after a new diagnosis of breast cancer. Eff Clin Pract 2000;3:1–6.

18 Samant R, Ganguly P. Staging investigations in patients with breast cancer: The role of bone scans and liver imaging. Arch Surg 1999;134:551–553; discussion 554.

19 Gerber B, Seitz E, MÏller H et al. Perioperative screening for metastatic disease is not indicated in patients with primary breast cancer and no clinical signs of tumor spread. Breast Cancer Res Treat 2003;82: 29–37.

20 Schneider C, Fehr MK, Steiner RA et al. Frequency and distribution pattern of distant metastases in breast cancer patients at the time of primary presentation. Arch Gynecol Obstet 2003;269:9–12.