Original Study

Metabolic Characterization of Inflammatory Breast Cancer With Baseline FDG-PET/CT: Relationship With Pathologic Response After Neoadjuvant Chemotherapy, Receptor Status, and Tumor Grade

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Abstract

The prognostic value of baseline fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was explored in 61 women with inflammatory breast cancer. Higher baseline metabolic activity in primary inflammatory breast cancer tumor did not predict pathologic complete response after neoadjuvant systemic therapy but was likely associated with an increased risk of death. Confirmation and assessment of how this information could affect treatment choices in the neoadjuvant setting is needed in larger studies.

Background: The aim of this study was to determine if, in inflammatory breast cancer (IBC), baseline metabolic activity (maximum standardized uptake value [SUVmax]) of primary tumor and involved regional lymph nodes (IRLN) are prognostic markers of response after neoadjuvant systemic therapy (NAS). **Patients and Methods:** Baseline 2-deoxy-2-[18F]fluoro-D-glucose (FDG) positron emission tomography/computed tomography scans were retrospectively reviewed among 61 women with IBC who received NAS, had mastectomy, and had available pathology reports. Primary tumor and IRLN SUVmax were compared between patients with a pathologic complete response (pCR) versus those with residual disease after NAS. A multivariate Cox model was fit to evaluate the effects of SUVmax on overall survival, adjusting for pCR and stratified by receptor status and disease stage. **Results:** SUVmax in primary IBC tumors tended to increase with tumor grade (trend test $P = .06$) and was lower for stage III, non–triple-negative (TN) versus stage III, TN and stage IV, non-TN disease ($P = .04$). Neither primary tumor nor IRLN SUVmax was significantly different comparing pCR versus residual disease after NAS. Adjusting for pathology response in the overall survival model stratified by stage and receptor status, baseline SUVmax in primary IBC tumor was associated with an estimated hazard ratio of 1.10 (95% confidence interval, 0.97-1.25; $P = .15$) for patients with stage III, TN and stage IV, non-TN disease. This hazard ratio corresponded to a 1.74-fold risk of death with 1 standard deviation (SD = 5.9) increase in baseline SUVmax in primary IBC tumor. **Conclusion:** 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography/computed tomography provides prognostic information for newly

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diagnosed IBC. Larger studies are needed to confirm these findings and assess how such early information could affect treatment choices for IBC in the neoadjuvant setting.

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Introduction

Inflammatory breast cancer (IBC) is an uncommon, clinically aggressive form of invasive breast cancer with approximately 20% to 40% of patients presenting with distant metastases at diagnosis. Five-year survival rates for IBC remain poor (25%-50%) compared with non-IBC.[1,2] IBC is also more frequently triple-negative (TN; estrogen receptor [ER]- and progesterone receptor [PR]-negative, human epidermal growth factor receptor 2 [HER2]-negative) than non-IBC, which is also associated with a poor prognosis.[3,4]

Standard treatment of IBC consists of neoadjuvant systemic therapy (NAS; chemotherapy or chemotherapy and anti-HER2 therapy for HER2-positive disease) because of extensive locoregional disease and skin involvement, followed by modified radical mastectomy and chest wall and regional nodal radiation therapy (post-mastectomy radiation [PMRT]).[2,5] Better clinical outcomes are associated with complete pathologic responses (pCRs) in IBC mastectomy specimens after NAS (ie, no invasive disease in the breast or ipsilateral axillary lymph nodes).[6-9] At present, no clinical or imaging methods accurately predict the degree of pathologic response at mastectomy, which is considered a robust surrogate endpoint for long-term outcomes.[6-9]

Combined 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) is a functional imaging modality evaluating tumor metabolism. Most studies evaluating FDG-PET/CT for patients with breast cancer have focused on non-IBC and its role in identifying distant metastases in patients with locally advanced disease or evaluating indeterminate findings on anatomic imaging.[10,11] Studies in locally advanced non-IBC have found that FDG-PET/CT more accurately stages non-IBC than conventional imaging,[12,13] better predicts tumor response than anatomic imaging, often correlates with clinical outcomes, and may have a role in radiation therapy planning.[12-16] Whether these results apply to IBC is not well-described.

We sought to determine if the baseline metabolic activity (maximum standardized uptake value [SUVmax]) of primary IBC and involved regional lymph nodes (IRLN) can be prognostic markers of response to NAS and/or are associated with tumor subtype, tumor grade, or overall survival (OS). This is clinically significant because achieving a pCR is the goal of NAS for patients with IBC and an early indication of response (or lack of response) could potentially spare patients ineffective therapy and guide optimal therapeutic management.

Patients and Methods

Patients

This retrospective review was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board, and the requirement for written informed consent was waived. Patients were selected from an institutional review board-approved IBC registry of patients seen at Dana-Farber Cancer Institute's dedicated Inflammatory Breast Cancer Program between November 2008 and January 2016. Of 238 patients with confirmed and newly diagnosed IBC, 61 women met the following inclusion criteria and were selected as the study population: (1) underwent NAS for IBC, (2) had baseline FDG-PET/CT for the initial treatment strategy performed at our institution (ie, Dana-Farber Cancer Institute/Brigham and Women's Hospital), and (3) underwent definitive mastectomy with available pathology report of the complete mastectomy and axillary lymph node dissection.

FDG-PET/CT Scans

FDG-PET/CT was performed following standard clinical protocols at our institution. Patients fasted for at least 4 to 6 hours and had blood glucose levels less than 200 mg/dL prior to the intravenous injection of FDG (mean ± SD, 583 ± 116 MBq [15.8 ± 3.1 mCi]). After a planned 60-minute uptake phase time (61 ± 10 minutes), FDG-PET/CT (GE Discovery 16 ST, GE Discovery DSTE/VCT64, GE Discovery DRX/VCT64, and Siemens Biograph 16 Hi-Rez) was obtained from the vertex (n = 6), base of the skull (n = 52), lower face (n = 1), or neck (n = 1, owing to claustrophobia) to the mid-thigh. In 1 patient, the field of view from the base of skull to mid-thigh was extended to the mid-calf owing to a clinical concern for disease in that area. CT was obtained first for attenuation correction without oral or intravenous contrast. PET data were reconstructed using ordered subset expectation maximization iterative reconstruction methods.

Image Interpretation

Baseline FDG-PET/CT scans were reviewed by fellowship-trained nuclear medicine physicians (H.J., H.S., or T.Y.) for the presence of abnormal FDG uptake within the primary IBC and regional lymph nodes. The readers had knowledge of the diagnosis of IBC but no other staging information. Abnormal FDG uptake was defined as increased uptake greater than background not consistent with normal anatomy or physiology and in a pattern definitely or probably due to IBC. The SUVmax of the primary IBC within the breast (now referred to as "primary IBC tumor" and IRLN was determined using Hermes software (Hermes Medical Solutions, Stockholm, Sweden). IBC may or may not present with a discrete mass on imaging. For cases without a discrete mass, but rather diffusely abnormal FDG uptake throughout the breast tissue felt to be due to IBC, SUVmax of the entire area was obtained. The sizes of the primary IBC tumor and IRLN (short axis) were measured on the CT portion of the PET/CT. Regional lymph node

Table 1 Neoadjuvant Systemic Therapy Regimens

	N
AC-T	26
THP	14
DCaH	10
AC-TH	3
DCaH-THP	1
TH-DCaH	1
AC; CMF and eribulin	1
AC-TDM1	1
T; X	1
AC-T; nab-paclitaxel	1
THP; HP; TDM1	1
Clinical trial	1

Regimens distinguished by semi-colon and refer to "followed by".
Abbreviations: A = doxorubicin; C = cyclophosphamide; Ca = carboplatin; D = docetaxel; F = fluorouracil; H = trastuzumab; M = methotrexate; P = pertuzumab; T = paclitaxel; X = capecitabine.

groups were defined as the ipsilateral internal mammary, supraclavicular, axillary, and subpectoral chains. Although not the primary aim of this study, the presence of distant metastases was also recorded.

NAS, Surgery, and Pathology Review

All patients received NAS at the treating oncologist's discretion and proceeded to complete mastectomy and axillary lymph node dissection as per the standard of care for IBC. NAS regimens are listed in Table 1. The majority were anthracycline-based followed by a taxane. Patients with HER2-positive disease also received HER2-directed therapy.

Pathology reports from the 61 mastectomy specimens were reviewed for the presence of pCR or residual disease. A pCR was defined as no residual invasive cancer in the affected breast or ipsilateral axillary lymph nodes. However, in situ cancer may have been present. Pathology reports from the initial tumor biopsy were also reviewed to record hormone receptor status, HER2 status, tumor grade, and histology of the primary IBC tumor.

Statistical Analyses

Patient and primary tumor characteristics, including histology, receptor status, tumor grade, pathologic response, and disease stage at presentation of the entire cohort were summarized by frequency and percentage. The Wilcoxon rank-sum test was used to compare SUVmax and size of the primary IBC tumor for binary variables. The Kruskal-Wallis test and the Cuzick test for trend were used to compare SUVmax and size of the primary IBC tumor between patients with different tumor grades. Analogues analyses were performed on SUVmax of the single hottest IRLN and lymph node length in short axis.

OS was evaluated using the Kaplan-Meier method and log rank test for comparing categorical groups. Cox proportional hazards models were fit to evaluate the effects of metabolic activity on OS, adjusting for pCR and stratified by receptor status and disease stage. All data were analyzed using R i386 3.3.1 statistical software. The level of statistical significance was set at $P < .05$ (2-sided).

Table 2 Patient and Primary Inflammatory Breast Cancer Tumor Characteristics

Histology	Frequency	Percent
Invasive ductal carcinoma	50	82.0
Invasive carcinoma with ductal and lobular features	6	9.8
Invasive lobular carcinoma	4	6.6
Intralymphatic carcinoma[a]	1	1.6
Receptor status		
Triple-negative	9	14.8
ER^+ and/or PR^+, $HER2^-$	21	34.4
$HER2^+$	31	50.8
Tumor grade		
Grade 1	4	6.6
Grade 2	21	34.4
Grade 3	36	59.0
Pathologic response found at mastectomy[b]		
Complete response	21	34.4
Residual disease	40	65.6
Stage		
III	49	80.3
IV	12	19.7
Post-mastectomy radiation therapy		
Yes	58	95.1
No	3	4.9

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.
[a]Carcinoma in the breast was found only within the lymphatic vessels.
[b]Complete pathologic response: absence of invasive carcinoma in the breast and ipsilateral axillary lymph nodes; residual disease: invasive carcinoma in the breast and/or ipsilateral axillary lymph nodes.

Results

All 61 patients had a primary IBC tumor visualized on FDG-PET/CT, and 58 patients had image-identified IRLN, including 1 with an additional FDG-avid lymph node at the lower cervical region. Table 2 shows patient and primary IBC tumor characteristics in our study group. The median age was 53 years (range, 28-78 years). Twelve patients had distant metastases on FDG-PET/CT, including involvement of bone (n = 8), liver (n = 2), bone and lung (n = 1), and a contralateral supraclavicular lymph node (n = 1). Only 3 (4.9%) patients did not have PMRT. Comparisons between those that received or did not receive PMRT are descriptive and are not expected to reach statistical significance. After completing NAS, a pCR was achieved in 21 (34.4%) patients, whereas 40 (65.6%) had residual disease.

For 61 patients, the median SUVmax in primary IBC tumors prior to NAS was 6.7 (range, 1.8-29.3; mean ± SD, 8.2 ± 5.9). Table 3 summarizes comparisons for SUVmax and size of the primary IBC tumors. SUVmax in the primary IBC tumors was not significantly different comparing patients with pCR versus residual disease after NAS ($P = .70$). Although there was overlap of SUVmax based on tumor grade ($P = .18$), SUVmax in primary IBC tumors tended to increase with tumor grade (trend test $P = .06$).

Table 3 Primary Inflammatory Breast Cancer Tumor: Metabolic Activity and Size Comparisons

	N (61)	Median SUVmax (Range)	*P* Value	N[a] (43)	Median Size, mm (Range)	*P* Value
Pathologic response[b]						
pCR	21	6.7 (2.0-29.3)		15	36 (20-81)	
Residual disease	40	6.6 (1.8-20.8)	.70	28	25 (10-107)	.04
Tumor grade						
Grade 1	4	4.2 (2.6-9.2)		2	29.5 (25-34)	
Grade 2	21	5.5 (2.3-20.8)		13	33 (10-81)	
Grade 3	36	7.2 (1.8-29.3)	.18	28	32.5 (13-107)	.87
Receptor status						
TN[c]	9	7.4 (5.2-29.3)		9	22 (14-69)	
Non-TN	52	6.4 (1.8-28.8)	.13	34	33 (10-107)	.33
Stage						
III	49	6.4 (1.8-29.3)		35	32 (10-70)	
IV	12	8.8 (4.1-16.6)	.09	8	46.5 (21-107)	.19
PMRT						
Yes	58	6.6 (1.8-29.3)		40	33 (10-107)	
No	3	14.2 (3.8-16.6)	.28	3	28 (13-60)	.70
Stage, receptor status						
III, non-TN	40	5.2 (1.8-28.8)		26	32.5 (10-70)	
III, TN	9	7.4 (5.2-29.3)		9	22 (14-69)	
IV, non-TN	12	8.8 (4.1-16.6)	.04	8	46.5 (21-107)	.33

Abbreviations: CT = computed tomography; pCR = complete pathologic response; PET = positron emission tomography; PMRT = post-mastectomy radiation therapy; SUVmax = maximum standardized uptake value; TN = triple negative.
[a]n = 43; 18 baseline primary inflammatory breast cancer tumors were nonmeasurable on noncontrast CT performed as part of PET/CT.
[b]pCR: absence of invasive carcinoma in the breast and ipsilateral axillary lymph nodes; residual disease: invasive carcinoma in the breast and/or ipsilateral axillary lymph nodes.
[c]Triple negative: estrogen receptor-, progesterone receptor-, and human epidermal growth factor receptor 2-negative.

SUVmax tended to be higher in the TN versus non-TN primary tumor subtypes ($P = .13$) (Figure 1) and stage IV versus stage III disease at presentation ($P = .09$), but this did not reach statistical significance. No patient with stage IV disease in this cohort had TN tumor. Significant differences were found in SUVmax of primary IBC tumors when comparing stage III, TN or stage IV, non-TN tumors with stage III, non-TN tumors ($P = .04$) (Table 3, Figure 2).

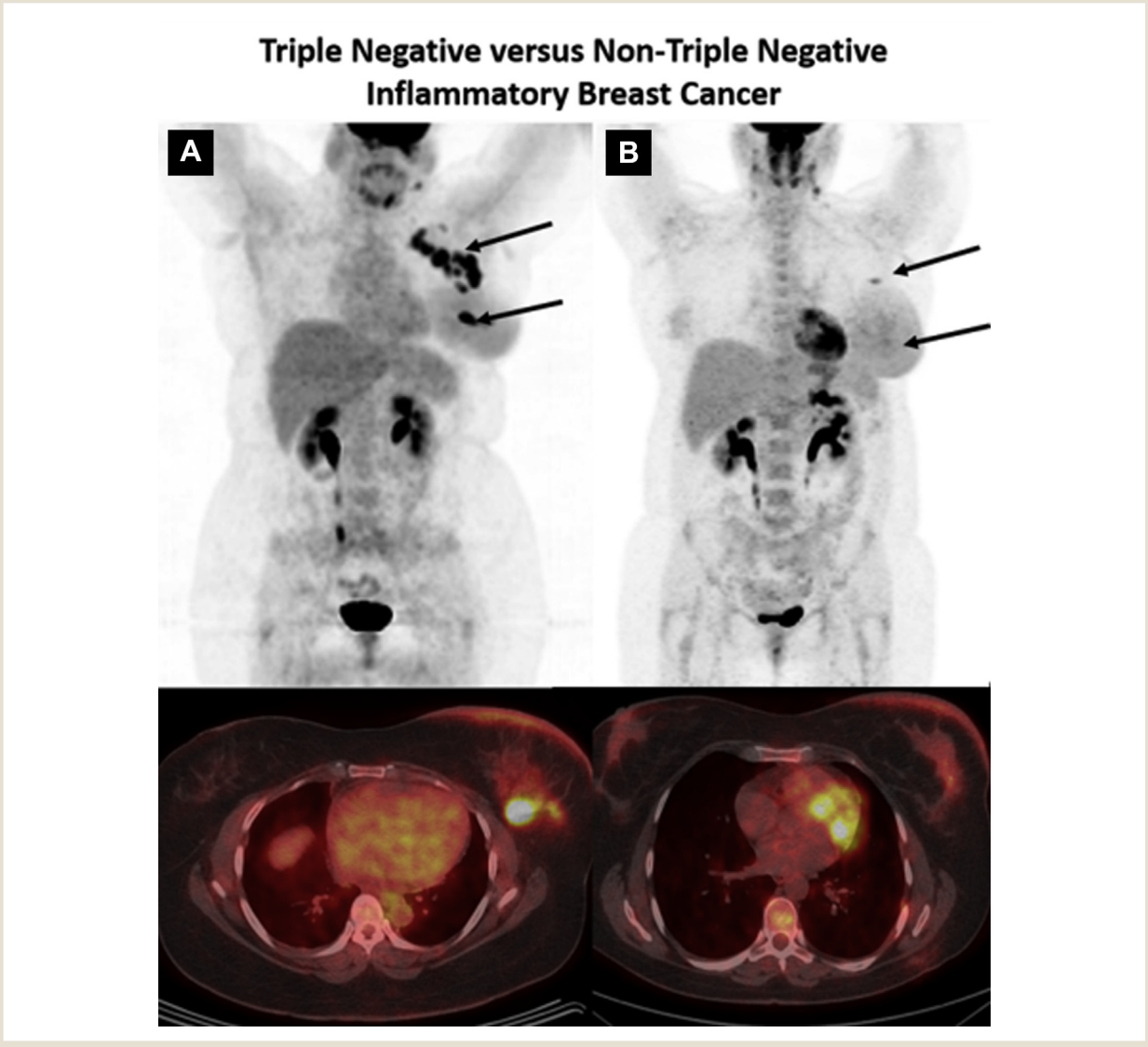
The metabolic activity and short-axis lengths of the IRLN on imaging are summarized in Table 4. Three patients did not have IRLN demonstrated on baseline FDG-PET/CT imaging. The most FDG-avid IRLN was in the ipsilateral axilla for most patients (53 of 58). For 58 patients, the median SUVmax in IRLN was 5.9 (range, 1.1-64.9; mean ± SD, 7.8 ± 9.0). There was no significant difference in IRLN SUVmax by pCR status ($P = .35$). SUVmax of IRLN was higher in grade 2 and grade 3 primary IBC tumors compared with grade 1 primary IBC tumors ($P = .004$) (Figure 3). Similar to SUVmax in primary IBC tumors, SUVmax of IRLN tended to be higher in TN tumors ($P = .09$) and stage IV disease at presentation ($P = .13$). A statistically significant difference was reached when comparing SUVmax of IRLN in patients with stage III, TN and stage IV, non-TN disease to stage III, non-TN disease ($P = .04$).

The local recurrence rate was 11% (7 of 61), and the distant recurrence rate was 31% (19 of 61). Six of the 7 patients with local recurrences also had distant metastases, all within 1 to 4 months of each other. There were no significant differences between baseline SUVmax in primary IBC tumor or IRLN comparing those who had a local or distant recurrence with those who did not.

Overall median OS was not reached, with a median follow-up time of approximately 45 months. Twelve deaths were observed among 61 patients with an estimated 3-year OS rate of 82.5% (95% confidence interval [CI], 72.6%-93.7%). By univariate analysis, decreased OS was significantly associated with TN disease subtype compared with non-TN subtypes ($P = .001$) (Figure 4A); with estimated 3-year OS being 35.6% (95% CI, 12.8%-98.9%) versus 90.8% (95% CI, 82.5%-99.8%), respectively. Similarly, decreased OS was significantly associated with stage IV compared with stage III disease at presentation ($P = .009$) (Figure 4B); 3-year OS: 61.1% (95% CI, 37.4%-100%) versus 87.8% (95% CI, 78.2%-98.5%), respectively. Figure 5A shows comparable OS distributions between patients with stage III, TN and stage IV, non-TN disease, which are significantly worse than those with stage III, non-TN disease ($P < .0001$). OS was not significantly associated with pCR or residual disease after NAS ($P = .21$) (Figure 4C); 3-year OS: pCR, 88.0% (95% CI, 73.5%-100%) versus residual disease, 79.8% (95% CI, 67.4%-94.5%), respectively. OS was not associated with tumor grade or age at baseline ($P > .5$).

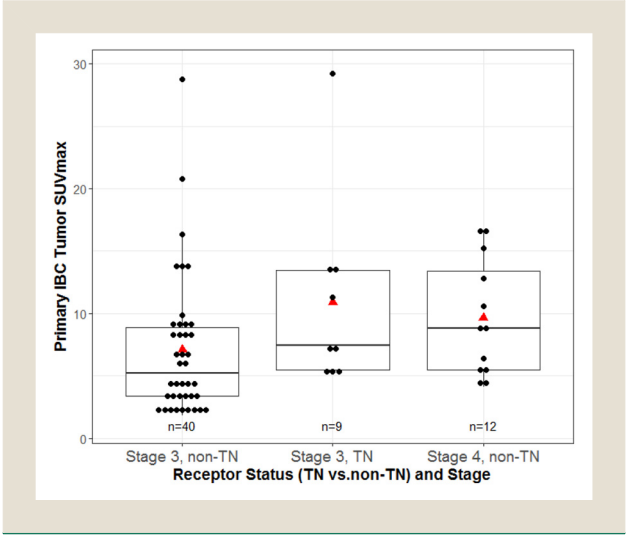
Univariate Cox models suggested baseline SUVmax in primary IBC tumor tended to be associated with OS (hazard ratio [HR], 1.08; 95% CI, 1.00-1.16; $P = .05$), but baseline SUVmax in IRLN

Figure 1 Triple-Negative (TN) Versus Non-TN Inflammatory Breast Cancer. Intense FDG Uptake is Seen in the Primary Tumor of a Patient With TN Inflammatory Breast Cancer Tumor (A, Lower Arrow; Maximum Standardized Uptake Value [SUVmax], 11.3) Compared With a Lower Level of Uptake in a Patient With Non-TN Tumor (B, Lower Arrow; SUVmax, 2.4). The Involved Regional Lymph Nodes of the Patient With TN Disease Also Have Higher 2-deoxy-2-[18F]fluoro-D-glucose Uptake (A, Higher Arrow; SUVmax, 11.2) Compared With the Patient With Non-TN Tumor (B, higher Arrow, SUVmax 3.5). Triple Negative: Estrogen Receptor-, Progesterone Receptor-, and Human Epidermal Growth Factor Receptor 2-Negative



appeared not significantly associated with OS (HR, 1.02; 95% CI, 0.98-1.06; $P = .30$). For multivariate analyses, SUVmax in primary IBC tumor was considered over SUVmax in IRLN mainly because models with the latter were non-robust to missing and extreme values. Figure 5A shows 100% 3-year OS among 40 patients with stage III, non-TN tumors; with 2 observed deaths, their estimated 41-month OS was 92.4% (95% CI, 83%-100%). Given the high survivorship, baseline SUVmax in primary IBC tumor (or any other factor) was not expected to be associated with OS in this group. For the remaining 21 patients, OS distributions were comparable between those with stage III, TN and those with stage IV, non-TN disease (Figure 5A), and they were more likely to have higher baseline SUVmax in the primary IBC tumor compared with those with stage III, non-TN tumors (Figure 2). This could imply that higher baseline SUVmax in the primary IBC tumor tended to be associated with decreased OS as suggested by the univariate analysis. With 10 deaths observed in the 21 patients with stage III, TN or stage IV, non-TN disease, lower OS was observed in higher baseline SUVmax groups even though this did not reach statistical significance ($P = .2$) (Figure 5B). Adjusting for pathology response (HR, 0.39; 95% CI, 0.08-1.80; $P = .23$) in the model on OS stratified by disease stage and receptor status, baseline SUVmax in primary IBC tumor was associated with an estimated HR of 1.10 (95% CI, 0.97-1.25; $P = .15$) for patients with stage III, TN and stage IV,

Figure 2 Primary SUVmax by Receptor Status and Stage. Baseline SUVmax was higher in primary IBC Tumors Comparing Stage III, TN or Stage IV, Non-TN Tumors With Stage III, Non-TN Tumors (P = .04)



Abbreviations: IBC = inflammatory breast cancer; SUVmax = maximum standardized uptake value; TN = triple-negative.

non-TN disease. This HR corresponded to a 1.74-fold risk of death with 1 standard deviation (SD = 5.9) increase in baseline SUVmax in primary IBC tumor.

Discussion

The rarity of IBC has led to challenges gathering data from large cohorts of patients to establish the value of FDG-PET/CT in this specific patient population. Limited data from 3 single institution studies has demonstrated that FDG-PET/CT more accurately stages IBC than anatomic imaging owing to the detection of occult distant metastases in 13% to 20% of cases.[17-23] We aimed to determine if baseline metabolic activity (SUVmax) of primary IBC tumor and IRLN is prognostic of response to NAS, because pCR is the goal of NAS in this population.

The major findings of this study were: (1) baseline SUVmax in primary IBC tumor or IRLN is not significantly associated with a pCR after NAS; (2) higher tumor grade has higher SUVmax in IRLN and tended to have higher SUVmax in primary IBC tumor; (3) higher baseline SUVmax and decreased OS is associated with stage III, TN and stage IV, non-TN disease compared with stage III, non-TN disease.

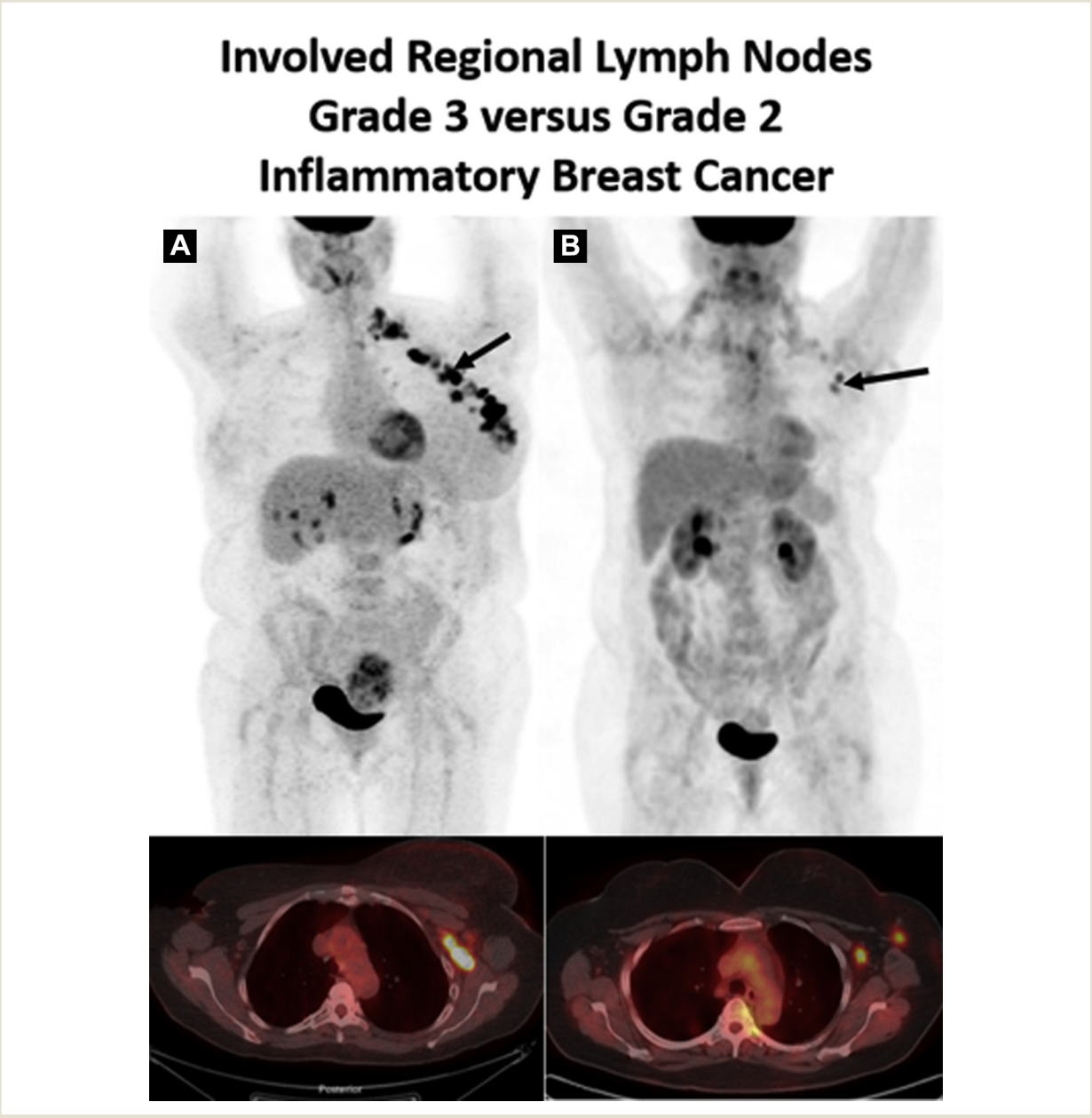
We observed similar levels of increased metabolic activity in primary IBC tumor and IRLN in our population compared with

Table 4 Involved Regional Lymph Nodes: Metabolic Activity and Tumor Length Comparisons[a]

	N (58)	Median SUVmax (Range)	*P* Value	N (58)	Median Short Axis Length, mm (Range)	*P* Value
Pathologic response[b]						
pCR	20	5.8 (1.6-64.9)		20	12 (7-22)	
Residual disease	38	5.9 (1.1-16.2)	.35	38	12 (6-28)	.84
Tumor grade						
1	4	1.7 (1.1-1.9)		4	11 (7-12)	
2	20	6.0 (2.0-13.9)		20	12 (7-20)	
3	34	6.4 (1.5-64.9)	.004	34	12 (6-28)	.43
Receptor status						
TN	9	9.8 (1.6-27.9)		9	14 (9-28)	
Non-TN	49	5.3 (1.1-64.9)	.09	49	12 (6-25)	.02
Stage						
III	46	5.2 (1.1-64.9)		46	12 (6-28)	
IV	12	8.3 (1.6-15.0)	.13	12	16.5 (7-25)	.11
PMRT						
Yes	55	5.8 (1.1-64.9)		55	12 (6-28)	
No	3	9.6 (6.5-13.9)	.15	3	9 (7-20)	.45
Stage, receptor status						
III, non-TN	37	4.8 (1.1-64.9)		37	12 (6-19)	
III, TN	9	9.8 (1.6-27.9)		9	14 (9-28)	
IV, non-TN	12	8.3 (1.6-15.0)	.04	12	16.5 (7-25)	.01

Abbreviations: CT = computed tomography; FDG = fluorine-18 fluorodeoxyglucose; pCR = complete pathologic response; PET = positron emission tomography; PMRT = post-mastectomy radiation therapy; SUVmax = maximum standardized uptake value; TN = triple negative.
[a]n = 58 patients with regional lymph node involvement determined by baseline FDG-PET/CT imaging.
[b]pCR: absence of invasive carcinoma in the breast and ipsilateral axillary lymph nodes; residual disease: invasive carcinoma in the breast and/or ipsilateral axillary lymph nodes.

Figure 3 Involved Regional Lymph Nodes. More Intense 2-deoxy-2-[18F]fluoro-D-glucose Uptake is Seen in the Involved Regional Lymph Nodes of a Patient With Grade 3 Tumor (A, Arrow; Grade 3 Histology; SUVmax, 15.5) Compared With the Uptake in the Involved Regional Lymph Nodes of a Patient With Grade 2 Tumor (B, Black Arrow; Grade 2 Histology; SUVmax, 4.8)

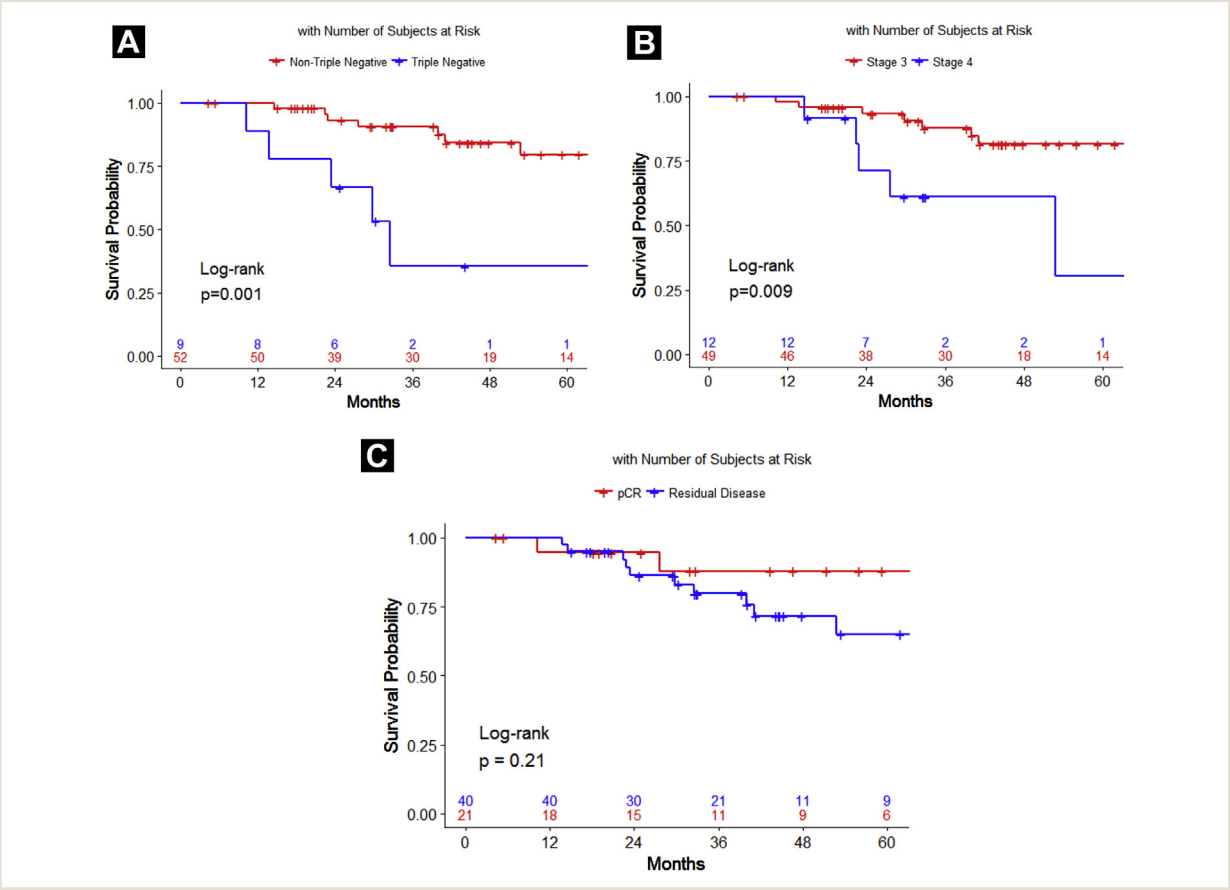


Abbreviation: SUV max = maximum standardized uptake value.

previous reports of patients with IBC.[13,17,20-22] We did not find a statistically significant association with baseline SUVmax in the primary IBC tumor or IRLN and the probability of achieving a pCR after NAS. Our findings support the results of a smaller study including 23 patients with newly diagnosed IBC in which baseline SUVmax was also not significantly associated with pathologic response following NAS.[22] We did not observe the same reported trend of higher mean baseline SUVmax in the pCR versus non-pCR group,[22] but both our study and the smaller analysis are likely constrained by the relatively limited number of patients evaluated.

Although pathologic disease response at mastectomy is considered a robust surrogate endpoint for survival,[6-9] we did not find a statistically significant association of pCR with OS in our study population. This is most likely because only a limited subset of all patients treated for IBC at our institution also had baseline FDG-PET/CT scans at our institution, and thus were available for evaluation in our current study. In our larger experience of 181 patients with newly

Figure 4 Overall Survival (OS) Comparing Triple Negative and Non-triple Negative Disease and Pathologic Complete Response (pCR) Versus Residual Disease at Mastectomy. The Median OS in Our Cohort Was Not Reached, and the Median Follow-up Time Was Approximately 45 Months. A, By Univariate Analysis, Decreased OS Was Significantly Associated With Triple-negative Disease Subtype Compared With Non–triple-negative Subtypes ($P = .001$) With Estimated 3-Year OS Being 35.6% (95% Confidence Interval [CI], 12.8%-98.9%) Versus 90.8% (95% CI, 82.5%-99.8%), Respectively. B, OS Was Significantly Associated With Stage IV Compared With Stage III Disease ($P = .009$). 3-Year OS: Stage IV, 61.1% (95% CI, 37.4%-100%) Versus Stage III, 87.8% (95% CI, 78.2%-98.5%). C, OS Was Not Significantly Associated With pCR or Residual Disease after Neoadjuvant Systemic Therapy ($P = .21$). 3-Year OS: pCR, 88.0% (95% CI, 73.5%-100%) Versus Residual Disease, 79.8% (95% CI, 67.4%-94.5%)



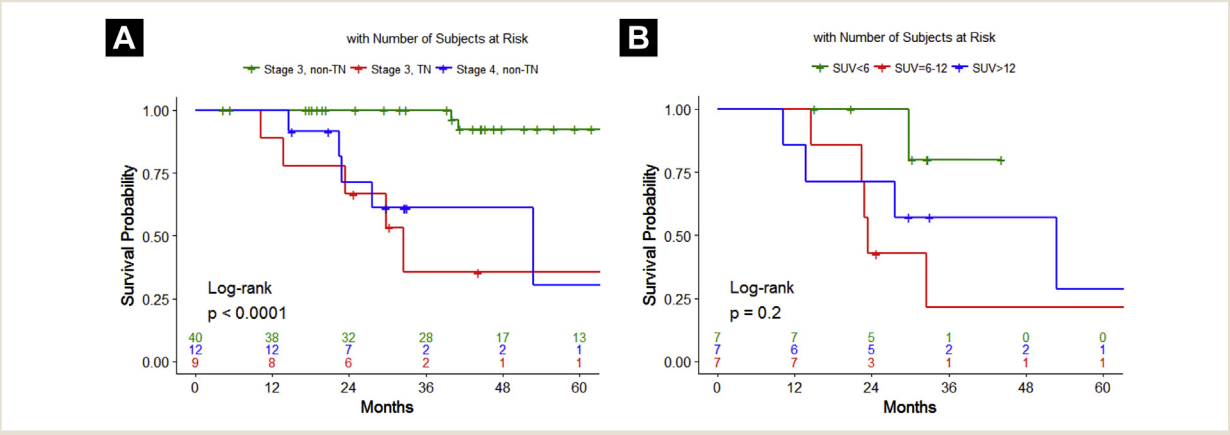
Abbreviation: pCR = complete pathologic response.

diagnosed stage III IBC who underwent NAS, modified radical mastectomy, and PMRT at our institution, Nakhlis et al reported that pCR was associated with improved time to recurrence (HR, 0.20; 95% CI, 0.09-0.46; $P < .01$, univariate; HR, 0.17; 95% CI, 0.087-0.41; $P < .0001$, multivariate) and improved OS (HR, 0.26; 95% CI, 0.11-0.65; $P < .01$, univariate).[9] Furthermore, 12 patients with distant metastases (stage IV) were included in our current analysis, again complicating the association between pCR and OS.

In non-IBC, although some studies have demonstrated an association between higher metabolic activity (ie, higher SUVmax) within the primary breast tumor and histopathologic features of poor prognosis (ie, ER-negative, TN, and higher-grade),[24,25] others have questioned the prognostic value of SUVmax.[26] We also observed higher baseline SUVmax in IRLN and a trend for higher baseline SUVmax in primary IBC tumor in patients with grade 2 and 3 versus grade 1 histology, which is consistent with the more aggressive nature of higher grade malignancy. IBC has a higher association with negative receptor status than non-IBC,[2] and we observed higher, but not significantly different, baseline SUVmax in primary IBC tumor and IRLN in patients with TN versus non-TN IBC. Because the percentage of patients with TN IBC in our population was relatively low (15%) compared with larger cohorts with IBC,[27,28] the lack of significance could be related to sample size.

Furthermore, in multivariate analyses, unbalanced data between TN status and disease stage prompted us to investigate differences in SUVmax between patients with stage III, non-TN, stage III, TN and stage IV, non-TN disease. We found that SUVmax in primary IBC tumor tends to cluster lower in stage III, non-TN disease compared with stage III, TN and stage IV, non-TN IBC. Interestingly, those with stage III, non-TN disease and lower SUVmax also had better OS compared with those with stage III, TN disease. Patients with stage III, TN disease had a prognosis similar to those

Figure 5 SUVmax and OS by Receptor Status and Stage. A, Three-year OS Was 100% for 40 Patients With Stage III, Non–triple-negative (TN) Disease. Comparable OS Distributions Were Seen Between Patients With Stage III, TN and Stage IV, Non-TN Tumors. B, With 10 Deaths Observed in the 21 Patients With Stage III, TN or Stage IV, Non-TN Tumors, Lower OS was Observed in Higher Baseline SUVmax Groups Even Though This Did Not Reach Statistical Significance ($P = .2$)



Abbreviations: OS = overall survival; SUVmax = maximum standardized uptake value; TN = triple-negative.

with stage IV, non-TN disease. Taken together, these data raise the hypothesis of a unique cohort within stage III IBC that prognostically behaves more like stage IV, non-TN disease and that initial discussions regarding prognosis and management strategies could be further refined. More data are needed to further explore interactions between disease stage, receptor status, and SUVmax on OS.

There were too few deaths in the group of patients in our cohort with stage III, non-TN IBC to expect any effect of SUVmax, or any other variable, on OS. In the patients with stage III, TN and stage IV, non-TN disease, we also observed lower OS in the higher baseline SUVmax group even though this did not reach statistical significance. Considering patients with stage III, TN and stage IV, non-TN disease, the risk of death increased 1.74-fold with a 1 standard deviation increase in baseline SUVmax in the primary IBC tumor adjusting for pCR status. This suggests a stronger association between baseline SUVmax and OS in patients with IBC compared with prior data.[17,21]

In a study of 59 patients with IBC who had FDG-PET/CT at initial staging, an SUVmax cutoff of 5 defined primary tumors with high (SUVmax $>$ 5) versus moderate (SUVmax $\leq$ 5) metabolic activity, and no significant difference in OS was seen between these groups (log-rank test, $P = .27$).[17] In a different study of 53 patients with IBC undergoing NAS, the HR for baseline SUVmax predicting OS was 1.01 (95% CI, 0.96-1.06; $P = .59$).[21]

The major limitation of the Alberini et al study is that the SUVmax cutoff point of 5 to define high versus moderate uptake seemed arbitrarily chosen,[17] and an optimal threshold to provide clinically useful information (ie, association of SUVmax with pCR or OS) is not defined for patients with IBC. Furthermore, in the univariate analysis by Carkaci et al, the HR was estimated with an incremental unit increase in baseline SUVmax.[21] In the clinical setting, the variability of SUVmax can be as high as 20% to 30%.[29] Therefore, we chose to report the HR estimate associated with a standard deviation increase in SUVmax (about 6 SUV units) in addition to a unit increase in SUVmax, and as such, an increase could be owing to variability in the measurement and not represent a clinically meaningful change. The association of higher baseline SUVmax in primary IBC tumor with increased risk of death, if confirmed in larger studies, could help inform choices about whether a more aggressive or alternative systemic therapy should be used in the first-line neoadjuvant setting.

Our study had several limitations. This is a small retrospective study and only included patients with IBC who had baseline FDG-PET/CT at our institution and achieved a sufficient clinical response to NAS to undergo surgical mastectomy. We did not include patients with outside baseline FDG-PET/CT owing to the known variability of SUV that can occur because of technical differences, and we do not require all patients with IBC to have imaging performed at our institution. Patients who did not undergo mastectomy most likely did not respond to NAS and/or developed distant metastases on primary treatment, which suggests a more aggressive tumor nature. These tumors may demonstrate higher SUVmax in their primary IBC tumor and IRLN compared with those that respond to NAS and were not captured in our dataset. We also evaluated 1 area in each affected breast and 1 IRLN with the highest metabolism per patient, and our patients did not routinely undergo FDG-PET/CT after neoadjuvant therapy. Appraising both total tumor volume and response to therapy, as has been suggested in early studies,[7,23] may have a stronger association with prognosis. An advantage of a baseline assessment of prognosis versus after completing the entire course of NAS is the avoidance of potentially ineffective therapy.

Despite these limitations, the data showed higher baseline SUVmax and decreased OS were more likely associated with stage III, TN and stage IV, non-TN disease, compared with stage III non-TN disease. In addition, our study suggested that a 1 standard deviation increase in metabolic activity of primary IBC tumor (defined as SUVmax) was associated with a 1.74-fold increased risk

of death for patients with stage III, TN and stage IV, non-TN disease. Larger prospective studies involving FDG-PET/CT imaging of IBC are needed to confirm these findings and assess how such early information could affect choices for treatment in the neoadjuvant setting, thus optimizing therapeutic and clinical outcomes in this patient population.

Clinical Practice Points

- Early studies have demonstrated that FDG-PET/CT more accurately stages IBC than anatomic imaging. However, the data are limited to studies from 3 single institution studies, and the rarity of IBC has led to challenges gathering data from large cohorts of patients to establish the value of FDG-PET/CT in this specific patient population.
- Although the findings of this study did not demonstrate a significant association between baseline SUVmax in primary IBC tumor or regional lymph node metastases and pCR after NAS, it did demonstrate that higher baseline SUVmax and decreased OS were more likely associated with stage III, TN and stage IV, non-TN disease, compared with stage III non-TN disease and that a 1 standard deviation increase in metabolic activity of primary IBC tumor (defined as SUVmax) was estimated to be associated with a 1.74-fold increased risk of death for patients with stage III, TN and stage IV, non-TN disease.
- Larger prospective studies involving FDG-PET/CT imaging of IBC should be aimed at confirming these findings and assessing how such early information could affect choices for treatment in the neoadjuvant setting, thus optimizing therapeutic and clinical outcomes in this patient population.

Disclosure

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