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Semiquantitative analysis of maximum standardized uptake values of regional lymph nodes in inflammatory breast cancer: Is there a reliable threshold for differentiating benign from malignant?

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Abstract

Rationale and Objectives—Our objective is to determine an optimum standardized uptake value (SUV) threshold for identifying regional nodal metastasis on 18 fluoro-deoxy-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) studies of patients with inflammatory breast cancer (IBC).

Materials and Methods—A database search was performed of newly diagnosed IBC patients who had 18F-FDG PET/CT performed at the time of diagnosis in a single institution between January 1, 2001 and September 30, 2009. Three radiologists blinded to the histopathology of the regional lymph nodes retrospectively analyzed all 18F-FDG PET/CT images by measuring the SUVmax in visually abnormal nodes. The accuracy of 18F-FDG PET/CT image interpretation was correlated with histopathology where available. A receiver operating characteristic curve (ROC) analysis was performed to assess the diagnostic performance of PET/CT. Sensitivity, specificity,

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positive predictive value, and negative predictive value were calculated using 3 different SUV cutoff values (2.0, 2.5, 3.0).

Results—A total of 888 regional nodal basins, including bilateral axillary, infraclavicular, internal mammary and supraclavicular lymph nodes were evaluated in 111 patients with a mean age of 56 years. Of the 888 nodal basins, 625 (70%) were negative and 263 (30%) were positive for metastasis. Malignant lymph nodes had significantly higher SUVmax than benign lymph nodes ($p < 0.0001$). An SUVmax of 2.0 showed the highest overall sensitivity (89%) and specificity (99%) for the diagnosis of malignant disease.

Conclusion—SUVmax of regional lymph nodes on 18F-FDG PET/CT may help differentiate benign and malignant lymph nodes in IBC patients. SUV cutoff 2 provided the best accuracy in identifying regional nodal metastasis in this patient population.

INTRODUCTION

Inflammatory breast cancer (IBC) is an aggressive disease and accounts for 1% to 5% of all breast cancers. It is a clinicopathological entity characterized by changes in the breast such as erythema, edema involving more than two-thirds of the breast, peau d'orange, enlargement, warmth, tenderness, and induration on palpation [1]. In general, compared to women with non inflammatory breast cancer, women with IBC present at a younger age, are more likely to have metastatic disease at diagnosis, and have shorter overall survival [2]. The mean 5-year overall survival rate of IBC patients who have undergone current multidisciplinary therapy is between 20% and 40% [2].

The most significant prognostic factor for women with IBC is axillary lymph node involvement. Patients with axillary lymph node metastasis have shorter disease-free and overall survival than patients with node-negative disease [3,4]. Accurate preoperative staging of patients with IBC is vital, as the standard of care for these patients is neoadjuvant therapy prior to mastectomy and surgical removal of the lymph nodes, after which histopathologic information about the number of involved axillary lymph nodes and the actual size of the primary tumor is no longer available.

Detecting disease in nodal basins beyond the axilla also has implications for loco-regional radiotherapy [5] and has prognostic significance. Assessing breast cancer metastasis to regional nodal sites outside the axilla, particularly in the internal mammary, mediastinal, and supraclavicular basins, is more challenging, as these nodal regions are not routinely sampled given their relative inaccessibility. Anatomically based imaging modalities, such as computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI), utilize the size and morphologic features of lymph nodes to determine tumor involvement. These techniques are limited in their ability to detect, metastases in normal-sized lymph nodes.

Studies reported in the literature indicate that 18 fluoro-deoxy-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) has high specificity (84% to 100%) for diagnosing axillary nodal metastasis in breast cancer patients [6-14]. Visual assessment [6, 9, 10, 12] and semiquantitative analysis with standardized uptake value (SUV) cutoffs

that ranged between 1.8 and 2.5 [7-9, 14] were used to differentiate benign from malignant lymph nodes. However, to our knowledge, no data have been published on definitive SUV cutoffs for regional nodal metastasis in patients with IBC. If validated, a reliable SUV cutoff could prove useful for the noninvasive assessment of lymph nodes throughout the body, and SUVmax might have prognostic significance.

In this study, our primary aim was to document the SUVmax of regional lymph nodes (including nodes in the axillary, infraclavicular, supraclavicular, and internal mammary regions) that were identified on the ^{18}F -FDG PET/CT studies of patients with IBC at diagnosis and to determine an optimum SUV threshold for identifying nodal metastasis. The SUVmax of lymph nodes was also correlated with the size of lymph nodes, SUVmax of the breast, and histopathologic and biological features of the tumor.

MATERIALS AND METHODS

Patients

A database search was performed to identify patients at one institution who were either newly diagnosed with IBC between January 1, 2001 and September 30, 2009 or diagnosed with recurrent IBC during the same time period after being in remission for at least one year and had ^{18}F -FDG PET/CT data available for review. Patients who had undergone neoadjuvant chemotherapy or surgery prior to ^{18}F -FDG PET/CT were excluded. A retrospective review of patient records was performed to document patient demographics (age, height, weight, body mass index (BMI)), tumor type and grade; estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) status; and clinical, imaging, and histopathologic findings when available. The Institutional Review Board waived informed consent and approved the retrospective review, which was compliant with the Health Insurance Portability and Accountability Act [15].

Imaging and Review

^{18}F -FDG PET/CT was performed using a Discovery ST camera (GE Healthcare) in combination with the CT component of an 8-slice Light Speed scanner (GE Healthcare). The patients were positioned supine in the PET/CT device, with their arms raised, and had fasted for at least 6 h before the ^{18}F -FDG injection. Normal fasting blood glucose levels of less than 150 mg/dL was a standard requirement for imaging in all patients. An intravenous injection of 555–629 MBq (15–17 mCi) of ^{18}F -FDG was administered in the arm or central venous catheter on the side opposite the cancer, and 2-dimensional emission scans were acquired at 3 min per field of view 70 ± 10 min after the ^{18}F -FDG injection. PET images were reconstructed using standard vendor-provided reconstruction algorithms. Non-contrast-enhanced CT images were acquired in helical mode (speed, 13.5 mm/rotation) from the base of the skull to the mid thigh during suspended mid expiration at a 3.75-mm slice thickness, 120 kVp, 300 mAs, and a 0.5-s rotation.

The CT, PET, and coregistered ^{18}F -FDG PET/CT images were retrospectively reviewed jointly in all standard planes with maximum-intensity whole-body coronal projection images on an AW workstation (GE Healthcare) by 3 radiologists, who had details on the patients'

clinical history but did not know the results of the lymph node biopsies, other imaging studies, and clinical follow-up. Interpretation was based on both semiquantitative and qualitative interpretation (visual comparison of signal intensity between lymph nodes and other physiologic structures such as background soft tissue) and agreement between the 3 readers. The readers visually assessed ipsilateral and contralateral axillary, infraclavicular, supraclavicular, internal mammary basins of each patient and had a region of interest positioned on the lymph nodes with measurement of the SUVmax and the short axis diameter.

Interpretation of ^{18}F -FDG PET/CT Findings

Patients with multiple sites of ipsilateral nodal involvement were subjected to biopsy of a single (the highest) nodal station instead of biopsy of multiple nodal regions to confirm metastases. The accuracy of ^{18}F -FDG PET/CT image interpretation was assessed by histopathological analysis (fine needle aspiration and/or axillary dissection) if available; concurrent or subsequent imaging findings (contrast-enhanced CT, contrast-enhanced MRI, ultrasonography, or follow-up PET/CT); or clinical follow-up. Results were considered true-negative when ^{18}F -FDG PET/CT correctly classified a histologically benign lymph node or when ^{18}F -FDG PET/CT indicated that a lymph node was benign and no evidence of disease was documented during clinical or imaging follow-up (mean 24 months, ranged 6-48 months). Results were considered false-negative when ^{18}F -FDG PET/CT classified a histologically confirmed metastatic lymph node as benign or when ^{18}F -FDG PET/CT classified a lymph node with correlative imaging findings highly suggestive of metastasis (progressive ^{18}F -FDG uptake or increasing size of lesions) as benign. Results were considered false-positive when ^{18}F -FDG PET/CT classified a histologically benign lymph node as malignant or when ^{18}F -FDG PET/CT classified a lymph node with benign findings on correlative imaging as malignant. Results were considered true-positive when ^{18}F -FDG PET/CT classified a histologically malignant lymph node as malignant or when ^{18}F -FDG PET/CT classified a lymph node with correlative imaging findings highly suggestive of metastasis as malignant.

Data Analysis

Statistical analysis was performed on lymph node size and SUVmax, primary tumor size and SUVmax, and ER, PR, and HER2/neu status. The correlation between SUVmax and lymph node size, and the number of metastatic lymph nodes was tested using the Spearman rank correlation coefficient. Frequency tables with counts and percentages were provided for histopathological gold standard and SUV-predicted status of lymph nodes. To overcome the potential effect of varying body size on accuracy of SUVmax measurements, patients were categorized as normal weight ($n=23$), overweight ($n=28$), and obese ($n=60$) according to their body mass indices of 20–25, >25 – <30 , and 30, respectively.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using 3 different SUV cutoffs (2.0, 2.5, 3.0) and a McNemar test was used to compare the accuracy of different SUV cutoffs for each category. A receiver operating characteristic curve analysis was performed to assess the diagnostic performance of

PET/CT. All tests were two-sided, and p values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using SAS, version 9 (SAS Institute).

RESULTS

Clinical Data

A total of 888 nodal basins, including ipsilateral and contralateral axillary, infraclavicular, supraclavicular, and internal mammary lymph nodes, were evaluated in each of the 111 IBC patients with a mean age of 56 years (range, 28-81 years). The predominant histologic type was invasive ductal cancer (89 patients [80%]). The tumor grade was grade 3 in the majority of the patients (68 [61%]) [Table 1].

Of the 888 nodal basins, 625 (70%) were negative and 263 (30%) were positive for metastasis [Table 2]. Biopsy (performed prior to the start of the treatment) confirmed metastasis in 167 nodal basins (19%; 100 axillary, 24 infraclavicular, and 43 supraclavicular); 81 patients (72%) subsequently underwent axillary dissection. Findings in the remaining 721 nodal basins (81%) were confirmed by follow-up (mean 24 months, ranged 6-48 months) and evaluation by other imaging modalities (CT, ultrasonography, and MRI).

FDG Uptake in Regional Lymph Nodes

A total of 249 lymph nodes showed increased FDG uptake on visual assessment. Of these lymph nodes, 5 (2%) were benign, and 244 (98%) were malignant. Malignant lymph nodes had significantly higher SUVmax ($p < 0.0001$) than benign lymph nodes [Table 3].

The mean size of malignant lymph nodes was 1.5 cm (range, 0.3-5.7 cm) [Table 4]. When all nodes were considered together, a direct correlation was noted between lymph node size and SUVmax (Spearman correlation coefficient, $r=0.57$, $p < 0.0001$) [Fig. 1]. The location, SUVmax and size of the 5 false-positive lymph nodes are given in *Table 5*.

There was no correlation between the SUVmax of metastatic lymph nodes and the number of malignant axillary lymph nodes detected at axillary nodal dissection, the histology of the primary breast tumor, breast tumor SUVmax, tumor grade, or ER, PR, Her2/neu status.

Comparison of Different SUV Cutoff Points

The diagnostic performance of ^{18}F -FDG PET/CT SUVmax of 2.0, 2.5, and 3.0 was compared using the entire data set of 888 nodal basins. The SUVmax cutoff 2.0 provided the highest diagnostic accuracy [Table 6], with a sensitivity of 89% and specificity of 99% for predicting true metastatic nodal status and there were no statistical difference between the three BMI categories. With any SUV cutoff point for predicting regional nodal metastasis in patients with IBC, area under the ROC curve was 0.96 (95% CI: 0.94-0.98) [Fig. 2].

DISCUSSION

This study demonstrates that malignant lymph nodes have significantly higher SUVmax than benign lymph nodes ($p < 0.0001$) and an SUV cutoff point of 2.0 showed the highest overall sensitivity (89%) and specificity (99%).

In a study by Ueda et al [6], the accuracy of ^{18}F -FDG PET/CT was compared using various SUV cutoff points ranging from 0.8 to 3.0 in the entire data set of 183 patients. When the SUV cutoff points were increased from 0.8 to 1.8, specificity increased from 95% to 100%, but sensitivity decreased from 51% to 36%. In a study by Wahl et al [16], an SUV-lean cutoff of 2.0 had a sensitivity of 25%, specificity of 99%, PPV of 93%, and NPV of 71%. A slightly lower cutoff value of 1.8 had a sensitivity of 32% and PPV of 90%. Veronesi et al [18] also reported that the sensitivity of ^{18}F -FDG PET for detecting axillary lymph node involvement was 37%, but specificity and PPV were 96% and 88%, respectively, at an SUV threshold of 1.2. In both of these studies [16, 18], the majority of the tumors were T1 (low disease burden), which explains their low sensitivity.

In our study, the sensitivity for the detection of axillary nodal metastasis using SUV cutoff values of 2.0, 2.5 and 3.0 was 94%, 90%, 87% respectively. The specificity for the detection of axillary nodal metastasis using the same cutoff values was 99% [Table 7]. The higher specificity and sensitivity detected in our study compared to previous studies including patients with lower-stage breast cancer [7] can be attributed to the large size of the lymph nodes (mean, 1.5 cm), higher prevalence of lymph node metastasis in this patient population and high metabolic rate of IBC [13,14]. Recent information on IBC suggests that, from both a clinical and a biological perspective, IBC should be considered a separate entity. IBC tumors are high grade, are often ER negative, are more frequently HER-2/neu positive, have over expression of p53, and have characteristics of increased cell motility and migration [19]. Our results are comparable to the recent studies [9,13,14] which evaluated the role of ^{18}F -FDG PET/CT in the initial staging of IBC. The high sensitivity of ^{18}F -FDG PET/CT in the detection of axillary nodal metastases in these studies was also distinct from the findings of prior reports indicating a generally low sensitivity among patients with various tumor stages [7,16, 20-26].

Preclinical studies of several types of tumors demonstrated that FDG uptake was greater in lymph nodes involved by metastatic tumor than in normal lymph nodes [27]. Alberini et al [13] recently observed increased FDG uptake in the metastatic nodes of 53 of 59 patients (90%) with IBC, and the mean SUVmax for the lymph node with the highest FDG uptake in each patient was 6.4 ± 5.7 . They also reported that the SUVmax was lower in the lymph node with false-positive PET results [13]. Similarly, we found that the mean SUVmax in malignant lymph nodes was 7.1 and malignant lymph nodes have significantly higher SUVmax than benign lymph nodes ($p < 0.0001$). We found a direct correlation between the size of the metastatic lymph nodes in each of the nodal basins and the SUVmax.

Factors that determine PET visualization of lymph node metastasis of breast cancer have not yet been precisely determined. Previous reports showed a positive correlation between the sensitivity of PET and the number of histopathologically positive lymph nodes [12, 16, 26,

28, 29]. Others reported that the sensitivity of PET was positively related to the FDG avidity of primary tumors [28,29]. In general, tumors with higher FDG uptake are thought to be more aggressive and to develop and spread faster [17]. The sensitivity of PET was also shown to be associated with the histopathologic grade of primary tumors [28,29] and tends to be higher in lesions with high proliferative rates (Ki67) [30]. Others have suggested that a failure to detect macrometastasis with PET may result from the lower metabolic rate of the tumor, which is an intrinsic tumor characteristic, such as type and grade [9,16, 31,32].

Our findings revealed no statistically significant correlation between the SUVmax of metastatic lymph nodes and the number of malignant axillary lymph nodes detected at axillary dissection or the type, SUVmax, grade, or hormone receptor (ER, PR, Her2/neu) status of the primary tumor. Lobular primary breast cancers have been reported to be less FDG avid than other types of breast cancer [32]. A recent study by Wahl et al suggested that this finding applies to axillary metastases of lobular carcinoma as well [16]. In our study, only a small number (n=3) of the breast cancers were invasive lobular; therefore such a comparison was not available.

An important advantage of ^{18}F -FDG PET/CT for evaluating regional lymph nodes is its greater accuracy for detecting and locating metastases in the internal mammary and supraclavicular lymph nodes [33]. In a study comparing various imaging modalities for IBC, adenopathy in the infraclavicular, supraclavicular, and internal mammary regions was diagnosed by ultrasonography in only half the patients [34]. Knowledge of the status of ipsilateral supraclavicular lymph node disease is important for effective loco-regional treatment of these nodes. Evidence suggests that prognosis improves with definitive therapy in patients with ipsilateral supraclavicular and internal mammary lymph node involvement [35-37]. In a series of 114 patients [38], detection of lymph node metastasis by PET was frequent in the supraclavicular (13%) and internal mammary (16%) basins and significantly affected radiation treatment planning. In another series of 80 patients [39], detection of supraclavicular adenopathy by PET altered the treatment decision in 4 patients (5%).

In our study, the prevalence of internal mammary metastasis was 32/888 (4%) and supraclavicular metastasis was 48/888 (5%). The sensitivity for the detection of internal mammary metastasis (mean size, 1.1 cm; range, 0.4-2.2 cm) using SUV cutoff values of 2.0, 2.5 and 3.0 was 94%, 84%, 75% respectively. The specificity for the detection of internal mammary metastasis using SUV cutoff values of 2.0, 2.5 and 3.0 was 99%, 100%, 100% respectively [Table 7]. This high sensitivity and specificity is concordant with the previous reports of patients with locally advanced breast cancer [27]. However, although the specificity was high (99%), the sensitivity for the detection of supraclavicular nodes was lower (65-79%). The low sensitivity can most likely be attributed to the small size of the lymph nodes (mean 1.1; range, 0.3-2.3 cm) and the pitfall of adjacent brown fat activity in the supraclavicular region. Nevertheless, we concluded that SUVmax of 2 is an effective threshold for differentiating between benign and malignant lymph node disease in patients with IBC, and this threshold may help guide biopsy of suspicious regional nodes that may be occult clinically or on routine imaging.

While SUV is the best method of image quantification, one should be cautious when using SUV alone. Visual assessment by an experienced physician who can consider the clinical context is still critical for the real life practice. However, we maintain that providing a library of lymph node SUVs and cut-offs from a large population of IBC patients may prove useful in evaluation of borderline cases.

It is known that SUV measurements can be influenced by a variety of factors. Important sources of error include: 1) body composition, 2) blood glucose level, 3) dose administered, 4) length of uptake period, 4) partial volume effects (PVE) [40, 41]. Standardized protocols were used with the similar scanners for all patients enrolled in our study. Our data showed that the optimum SUV cutoff for detecting regional nodal metastasis did not differ among IBC patients with different BMI. We did not employ any methods for PVE correction which would likely have resulted in a lower FN rate [40]. Nevertheless, currently there is not a standardized method available for this purpose, therefore our results reflect common practice. Another limitation of this study is that histopathologic findings were not available for all the lymph nodes seen on PET/CT. This limitation is inherent to the retrospective nature of the study and reflects the standard treatment of patients with metastatic cancer. Biopsy of the internal mammary nodes was not routine, as most patients had simultaneous, confirmed metastases in the axillary or the supraclavicular lymph nodes that were sampled by fine-needle aspiration. Although to our knowledge this is one of the largest series to date describing ^{18}F -FDG PET/CT lymph node findings in patients with IBC, the patient population is still relatively small. It should also be noted that the results of this study cannot be generalized to other types breast cancers as from both a clinical and a biological perspective IBC is considered a separate entity.

In the present study, ^{18}F -FDG PET/CT was used as an adjunct diagnostic procedure after routine conventional screening. A prospective study to evaluate the incremental diagnostic value of ^{18}F -FDG PET/CT for diagnosing regional lymph node metastases of patients with IBC would help to validate these initial results ^{18}F -FDG PET/CT for regional nodal staging.

CONCLUSION

Our findings suggest that SUVmax of regional lymph nodes on ^{18}F -FDG PET/CT helps differentiate benign from malignant lymph nodes in IBC patients and may have a role in the evaluation of nodal metastasis and subsequent loco-regional therapy planning in this patient population. Although visual assessment with comparison to the background levels is still relied on primarily in real-life practice, using SUV cut off value of 2 may prove useful in evaluation of borderline cases where positivity of a specific lymph node may be critical to guiding management.

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Figure 1.
Direct correlation between size and SUVmax of 888 lymph nodes.

Figure 2. Receiver operating characteristic curve analysis assessing the diagnostic performance of ^{18}F -FDG PET/CT in differentiating benign from malignant lymph nodes.

Table 1

Histopathological characteristics of breast cancer in 111 patients with IBC.

	N	%
Histology		
IDC	50	45
IDC+DCIS	39	35
ILC	3	3
IM	12	11
IMC+DCIS	7	6
Grade		
Missing	9	8
1	1	1
2	33	30
3	68	61
ER		
Missing	2	3
Negative	56	50
Positive	53	47
PR		
Missing	2	2
Negative	69	62
Positive	40	36
HER2/neu		
Missing	5	4
Negative	65	59
Positive	41	37

DCIS=ductal carcinoma in-situ, ER=estrogen receptor, HER2/neu=human epidermal growth factor receptor 2, IDC=invasive ductal cancer, ILC=invasive lobular cancer, IMC= invasive mammary cancer, PR=progesteron receptor,.

Table 2

Summary of metastatic status of 888 regional lymph nodes by location

Location	Benign	Malignant
AX	107	115
IC	154	68
IM	190	32
SC	174	48
Total	625	263

AX=axillary, IC=infraclavicular, IM=internal mammary, SC=supraclavicular

Table 3

Summary of SUVs of 888 benign and malignant lymph nodes.

	N			SUV > 0				
	Total	No uptake	SUV>0	Mean	SD	Min	Median	Max
Benign	625	620	5	3.6	1.91	1.2	4.3	5.9
Malignant	263	19	244	7.6	5.79	1.2	5.8	42.3

SD=standard deviation, SUV=standardized uptake value

Table 4

Size of 263 malignant lymph nodes by location.

Malignant lymph nodes by location	N	Mean size (cm)	SD	Min size (cm)	Median size (cm)	Max size (cm)
AX	115	2.1	0.86	0.8	1.9	5.7
IC	68	1.1	0.51	0.3	1	3.5
IM	32	1.1	0.44	0.4	1	2.2
SC	48	1.1	0.48	0.3	1	2.3
ALL	263	1.5	0.84	0.3	1.4	5.7

AX=axillary, IC=infraclavicular, IM=internal mammary, SC=supraclavicular, SD=standard deviation

Table 5

SUVmax and size of 5 false positive lymph nodes by location.

Location	SUVmax	Size (cm)
AX	1.2	0.6
AX	5.9	1.7
IC	4.3	0.6
IM	2.1	0.7
SC	4.5	1.4

AX=axillary, IC=infraclavicular, IM=internal mammary, SC=supraclavicular

Table 6

Diagnostic performance with different SUV thresholds in 888 regional lymph nodes.

	SUV 2.0	SUV 2.5	SUV 3.0
TP	235	223	204
TN	621	622	622
FP	4	3	3
FN	28	40	59
PPV	98	99	99
NPV	96	94	91
Specificity	99	100	100
Sensitivity	89	85	78

FN=false negative, FP=false positive, NPV=negative predictive value, PPV=positive predictive value, TN=true negative, TP=true positive

Table 7

Sensitivity and specificity using different SUV thresholds.

	SUV 2.0		SUV 2.5		SUV 3.0	
Location	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
AX	94	99	90	99	87	99
IC	87	99	82	99	72	99
SC	79	99	77	99	65	99
IM	94	99	84	100	75	100

AX=axillary, IC=infraclavicular, IM=internal mammary, SC=supraclavicular