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Prognostic Value of SUVmax of ^{18}F-FDG PET/CT in Early Stage Breast Cancer with No LN Metastasis

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Abstract

Purpose: To investigate the correlation between SUVmax of FDG-PET/CT and pathological findings including prognostic factors in early-stage T1-T2 breast cancer patients with no LN metastasis. Materials and Methods: This retrospective study investigated 75 patients (mean age 58.9 years; age range 30 - 82 years) with invasive breast cancer who underwent FDG-PET/CT for preoperative staging. All patients underwent subsequent surgery without prior neoadjuvant chemotherapy or endocrine therapy, and those who were confirmed to have T1- or T2-stage by histopathology with no LN metastasis were included. Two patients who had no perceptible FDG accumulation on PET/CT scans were excluded. The correlations between the SUVmax of the tumor and the pathological and immunohistochemical data were evaluated. Results: The mean SUVmax for the total 73 tumors was 5.46 ± 4.05. The mean SUVmax was 3.95 ± 3.28 for the T1 stage group (n = 36) and 7.23 ± 4.10 ($p < 0.001$) for the T2 stage group (n = 37). A high SUVmax was significantly associated with high nuclear grade ($p < 0.001$), negative hormone receptor status ($p < 0.001$), positive HER2 status ($p = 0.008$), and high Ki-67 status ($p < 0.001$), respectively. Conclusion: In T1-T2 breast cancer with no LN metastasis, the SUVmax of FDG-PET/CT had significant positive relationships with several prognostic parameters of pathological status. Even in early-stage breast cancer patients, pretreatment FDG-PET/CT is useful for predicting malignant behavior and prognosis).

Keywords

Breast Cancer, Molecular Subtype, Prognosis, PET/CT, SUVmax

1. Introduction

Breast cancer is a heterogeneous disease. As a result of gene expression analysis, breast cancer is now classified into several different subtypes [1], which is useful for predicting response to treatments [2] [3]. Furthermore, accurate initial staging of patients with breast cancer is essential for providing a precise prognosis and choosing optimal therapies. The primary tumor, lymph node, and metastasis (TNM) staging using a multimodality approach is the most important factor of prognosis and therapeutic planning.

^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has been widely used for initial staging, restaging of recurrence, and monitoring of the therapeutic response in oncology patients and has become the standard imaging tool for several types of cancer. FDG-PET/CT, which demonstrates the high proliferation potential of cancer cells as increased accumulation, has emerged as a useful imaging tool for staging, evaluating the treatment response, and predicting the prognosis of malignant tumors. This diagnostic modality has also been used not only to detect cancer but also to evaluate the proliferative activity and/or malignancy grades of specific types of tumors [4] [5] [6] [7].

As for breast cancer, the practicality of FDG-PET/CT for diagnosis and staging has been established after decades of research and clinical experience, and recent interest has also focused on the prognostic value of FDG-PET/CT. A number of studies have demonstrated a correlation between FDG accumulation on PET/CT and pathological characteristics. The maximum standardized uptake value (SUVmax) can be an independent prognostic factor, and high levels of FDG accumulation indicate more aggressive proliferation potential in breast cancers [8]-[13]. Moreover, several authors have demonstrated that FDG accumulation might be a good predictor for HER2 overexpressing and triple-negative molecular subtypes [12] [13] [14] [15].

Since most studies of PET/CT have used it in cases of large and/or locally advanced breast cancers, its practicality in the early stages, such as small and node-negative breast cancers, remains unknown. Therefore, the prognostic value of SUVmax in these patients has not been fully assessed. The purpose of this study was to assess the correlation between SUVmax on FDG-PET/CT and pathological findings, including prognostic factors, in early-stage breast cancer patients with no lymph node metastasis.

2. Materials and Methods

2.1. Patient Selection

This retrospective study was conducted in accordance with the regulations of the Institutional Review Board, and informed consent was obtained from all patients for access to their histopathological data.

Between January 2012 and December 2015, 698 patients with primary breast cancer underwent curative surgery. Of these, the records of pathologically prov-

en breast cancer patients who underwent FDG-PET/CT for preoperative staging were retrospectively reviewed. Inclusion criteria were 1) curative surgery (breast-conserving surgery or mastectomy) and sentinel lymph node (SLN) sampling, 2) presence of T1-T2 invasive breast cancer with no SLN metastasis in the frozen specimen, 3) no neoadjuvant chemotherapy or endocrine therapy before FDG-PET/CT scans. Finally, 75 patients fulfilling these criteria were included.

2.2. FDG-PET/CT Imaging

All 75 patients in this study underwent FDG-PET/CT. Patients fasted for at least 6 hours before the examination, and 4.0 MBq/kg ^{18}F-FDG was administered intravenously. Acquisition was performed 60 min after the administration of ^{18}F-FDG using a PET/CT combined system (Gemini TF 16; Philips Medical Systems, The Netherlands). No oral or intravenous contrast material was administered. PET/CT images were acquired in time of flight (TOF) mode. TOF kernel: 14.1 cm, energy window: 440 - 590 keV, iteration: 3, subset: 33, matrix size: 144 × 144, voxel size: 4 × 4 × 4 mm, acquisition time: 90s/bed position, slice thickness: 4mm. A low-dose non-contrast CT scan for attenuation correction and anatomical guidance was performed with tube voltage: 140 kVp, tube current time product: 100 mAs, rotation time: 0.5 s, pitch: 0.938, slice thickness: 5 mm, matrix size: 144 × 144. PET data were reconstructed using CT attenuation correction and full list mode TOF 3D-OSEM. Furthermore, the PET and CT data were fused using Syntegra software (Syntegra; Mirada Solutions, Oxford, UK). Co-registered PET/CT scans were displayed using a standard gray scale for the CT images and a colored scale for the PET data, and fused images were available for review in the axial, coronal and sagittal planes, and in maximum-intensity projection 3-dimensional cine mode.

2.3. Imaging Analysis

The image data were stored on an image server (WE View, Hitachi, Japan) and interpreted on an image viewer (Natural VIEW, Hitachi, Japan). PET/CT images were interpreted by two nuclear medicine specialists (with 10 and 12 years of experience in PET) without knowledge of the preexisting radiology results and pathological findings, other than the patients had invasive breast cancer; the diagnoses of the patients were confirmed by mutual agreement. SUVmax was measured in the transaxial PET images for quantitative analysis of FDG accumulation. Regions of interest were drawn on each primary breast tumor in the FDG-PET images and SUVmax was obtained.

2.4. Histological Evaluation

The final diagnosis was histologically confirmed from specimens obtained at surgery. The histological type of the tumor, tumor size, and nuclear grade (1 well differentiated, 2 moderately differentiated, 3 poorly differentiated) were deter-

mined from formalin fixed paraffin-embedded tumor tissue sections cut at a thickness of 5 mm and stained with hematoxylin and eosin. Immunohistochemistry was performed on paraffin-embedded material using primary antibodies against estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), and the proliferation index was determined using Ki-67 antibody. Expression levels of ER, PR, HER2, and Ki-67 were determined immunohistochemically, in terms of the percentages of cancer cells positive for ER, PR and Ki-67 in the nuclei, and membrane staining for HER2. ER and PR were defined as being positive when at least 10% of the tumor cells showed positive immunohistochemical staining for these molecules. The HER2 status was defined as positive when more than 30% of the cells were immunohistochemically positive for this molecule (3+) or, when less than 30% (2+), fluorescence in situ hybridization analysis demonstrated HER2 gene amplification. Ki-67 expression was considered high when at least 14% of the cancer cells exhibited positive staining. The final axillary lymph node status (positive or negative) was established by the clinician performing the pathological confirmation, employing axillary lymph node dissection or sentinel lymph node biopsy.

2.5. Molecular Classification of Groups

According to the different combinations of ER, PR and HER2 status, and in line with the recommendations of the 12th International Breast Conference [16], the patients were categorized into 5 subtypes: luminal A (ER-positive and/or PR-positive, HER2-negative and Ki-67 < 14%), luminal B (ER-positive and/or PR-positive, HER2 negative and Ki-67 ≥ 14%; or ER-positive and/or PR-positive, HER2-positive, irrespective of Ki-67 expression), HER2-positive (ER-negative, PR-negative and HER2-positive), and triple-negative (ER-negative, PR-negative and HER2-negative).

2.6. Statistical Analysis

The correlations between the SUVmax of the breast cancer and the pathological and immunohistological data were evaluated using the Mann-Whitney U test (two variables) and single-factor analysis of variance and a multiple comparison test for parametric data. Receiver operating characteristic (ROC) curve analysis was performed to examine which subgroups could be differentiated from the others on the basis of SUVmax. The diagnostic accuracy of the optimal cut-off value for differentiating one subgroup from the others was also determined by ROC analysis. The data were analyzed using SPSS software (version 20, SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

3. Results

PET/CT depicted T1-T2 breast cancers with no LN metastasis in 73 (97%) of the 75 patients. Finally, a total of 73 breast cancers in 73 patients (mean age, 58.9 years; age range, 30 - 82 years) were analyzed. We excluded two breast cancers

with no focal FDG accumulation on PET/CT (T1b tumor; 9 mm and T1c; 12 mm). Of the total 73 patients, 26 underwent breast-conserving surgery and 47 mastectomy. Surgical resection was performed 7 - 30 days (mean 20.8 days) after FDG-PET/CT. Among these 73 breast cancers, 36 tumors were pathologic stage T1, and 37 were stage T2. The median tumor size was 2.6 ± 1.8 cm (range 0.7 - 4.9 cm). The histologic type included invasive ductal carcinoma (IDC) not otherwise specified (n = 68), invasive lobular carcinoma (n = 1), mucinous carcinoma (n = 1), apocrine carcinoma (n = 1), neuroendocrine carcinoma (n = 1), and medullary carcinoma (n = 1). ER was positive in 56 (76.7%) of the patients, and PR was positive in 42 (57.5%); 10 (13.7%) of the patients were HER2-positive. The intrinsic subtypes of the 73 tumors were luminal A in 37 patients (40.2%), luminal B (HER2-negative) in 27 (29.3%), luminal B (HER2-positive) in 8 (8.7%), HER2-positive in 5 (5.4%), and triple-negative in 15 (16.3%).

The SUVmax values, the pathological findings and the results of univariate regression analysis for the 73 breast cancers are summarized in Table 1. The mean SUVmax of the total 73 tumors was 5.46 ± 4.05. SUVmax for the T1 stage group (n = 36) was 3.95 ± 3.28 and that for the T2 stage group (n = 37) was 7.23 ± 4.10 ($p < 0.001$). ER positivity and PR positivity were significantly associated with lower SUVmax ($p < 0.001$, $p = 0.0134$). The SUVmax was also significantly

Table 1. Correlations between pathological and SUVmax Values.

	Correlations between pathological and SUVmax values		
	Number (%)	SUVmax	P value
Tumor invasive size			
T1	36 (49.3)	3.95 ± 3.28	<0.001
T2	37 (50.7)	7.23 ± 4.10	
ER status			
Positive	56 (76.7)	4.62 ± 3.61	<0.001
Negative	17 (23.3)	8.90 ± 3.73	
PR status			
Positive	42 (57.5)	4.75 ± 3.94	0.0134
Negative	31 (42.5)	6.79 ± 3.95	
HER2 status			
Positive	10 (13.7)	8.66 ± 4.98	0.0176
Negative	63 (86.3)	5.17 ± 3.70	
Ki-67 index (%)			
<14	28 (38.4)	3.24 ± 2.58	<0.001
≥14	45 (61.6)	7.10 ± 4.11	
Nuclear grade			
1	38 (52.1)	3.85 ± 3.15	<0.001
2	17 (23.3)	6.79 ± 3.50	
3	18 (24.6)	7.60 ± 3.73	

influenced by HER2 positivity ($p = 0.0176$). Patients who had more than 14% Ki-67 expression had significantly higher SUVmax ($p < 0.001$). With regard to the tumor nuclear grade, a higher grade was significantly associated with a higher SUVmax ($p < 0.001$). Bonferroni correction revealed significant differences in SUVmax x between nuclear grade 1 and grade 2 ($p = 0.0145$), and grade 1 and grade 3 ($p < 0.001$).

The mean SUVmax values were 3.32 ± 2.60, 4.74 ± 2.69, 10.39 ± 4.95, 3.94 ± 1.64 and 9.86 ± 3.24 for the luminal A, luminal B (HER2-negative), luminal B (HER2-positive), HER2-positive and triple negative subgroups, respectively (Table 2). SUVmax differed significantly among the five subgroups ($p < 0.001$). Moreover, Bonferroni correction revealed significant differences in SUVmax between the luminal A and luminal B (HER2-positive) ($p < 0.001$), the luminal A and triple-negative subgroups ($p < 0.001$), the luminal B (HER2-negative) and luminal B (HER2-positive) ($p < 0.001$), the luminal B (HER2-negative) and triple-negative ($p < 0.001$), the luminal B (HER2-positive) and HER2-positive ($p = 0.0270$), and the luminal B (HER2-positive) and triple negative ($p = 0.0299$).

The mean SUVmax was 4.74 ± 3.69 for luminal tumors and 8.75 ± 3.80 for non-luminal tumors ($p < 0.001$). In the ROC analysis, the optimal area under the ROC curve (AUC) was 0.807. A cut-off SUVmax value of 5.46 yielded a sensitivity of 93.2% (95% confidence interval, CI, 85.5% - 97.5%), a specificity of 44.8% (95% CI 33.2% - 51.4%), and an accuracy of 74.0% (95% CI 64.8% - 79.2%) for differentiation of luminal from non-luminal subtypes. The mean SUVmax was 9.86 ± 3.24 for triple negative tumors and 4.70 ± 3.61 for non-triple-negative tumors ($p < 0.001$). A cut-off SUVmax of 6.33 yielded a sensitivity of 92.3% (95% CI 69.7% - 98.6%), a specificity of 75.0% (95% CI 70.1% - 76.4%), an accuracy of 78.1% (95% CI 70.0% - 80.3%), and an AUC of 0.878 for prediction of triple-negative tumors (Table 3).

PET/CT imaging of representative patients is shown in Figure 1 and Figure 2.

4. Discussion

In this study, we assessed the correlation between SUVmax on FDG-PET/CT

Table 2. SUVmax in relation to intrinsic subgroup.

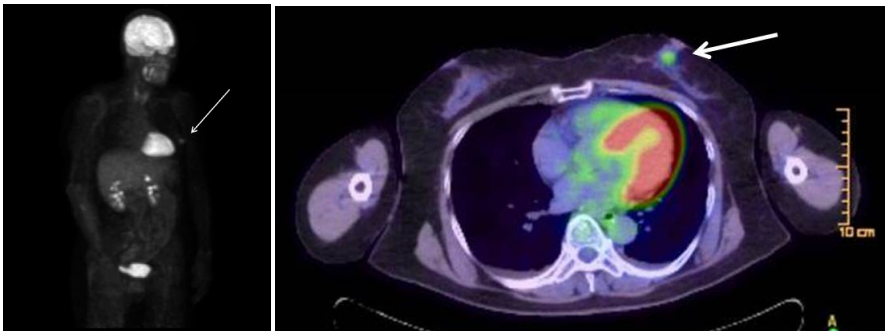
SUVmax in relation to intrinsic subgroup		
Subgroup	Number (%)	SUVmax
Luminal A	28 (38.4)	3.32 ± 2.60
Luminal B (HER2-negative)	22 (30.1)	4.74 ± 2.69
Luminal B (HER2-positive)	7 (9.6)	10.39 ± 4.95
HER2-positive	3 (4.1)	3.94 ± 1.64
Triple-negative	13 (17.8)	9.86 ± 3.24

$P < 0.01$; luminal A vs. luminal B (HER2-positive), the luminal A vs. triple-negative, luminal B (HER2-negative) vs. luminal B (HER2-positive), and luminal B (HER2-negative) vs. triple-negative, $P < 0.05$; triple negative subgroups vs. HER2-positive, and the luminal B (HER2-positive) vs. HER2-positive. Sample of a Table footnote.

Table 3. Results of ROC analysis for prediction of luminal tumors and triple negative tumors.

Results of ROC analysis for prediction of luminal tumors and triple negative tumors			
Luminal tumor (SUVmax)		4.74 ± 3.69	$p < 0.001$
Non-luminal tumors (SUVmax)		8.75 ± 3.80	
	*AUC	0.807	
	Sensitivity	93.2%	
	Specificit	44.8%	
	Accuracy	74.0%	
Triple negative tumors (SUVmax)		9.86 ± 3.24	$p < 0.001$
Non-triple negativetumors (SUVmax)		4.70 ± 3.61	
	**AUC	0.878	
	Sensitivity	92.3%	
	Specificit	75.0%	
	Accuracy	78.1%	

*The optimal cut-off level of SUVmax was 5.46. **The optimal cut-off level of SUVmax was 6.33.

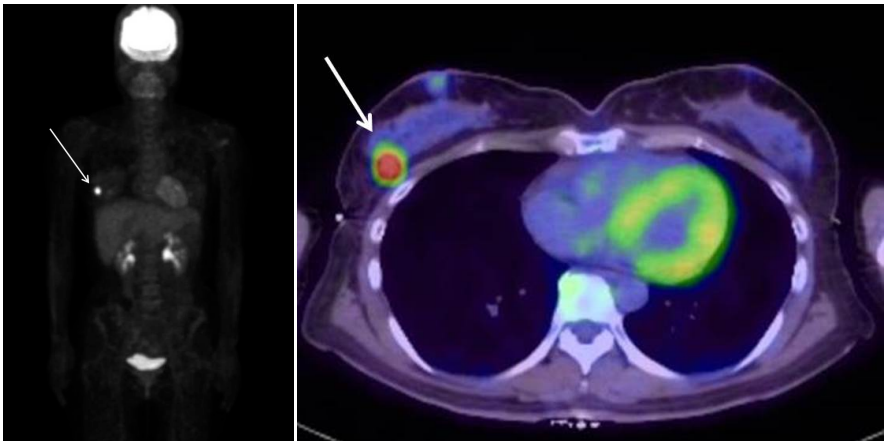


(a) (b)

Figure 1. A 64-year-old woman with luminal A invasive ductal cancer (14 mm; ER 90%, PR 70% HER2 0, Ki-67 1%, nuclear grade 1, T1cN0M0). (a) ^{18}F-FDG PET MIP image. (b) Axial PET/CT image. SUVmax value was 3.2.

and pathological findings, including prognostic factors, in patients with T1N0 or T2N0 stage breast cancer undergoing curative surgery. Our study demonstrates that the SUVmax value on FDG-PET/CT is shown to have significant positive relationships with several parameters of pathological status in patients with T1-T2 breast cancer but no LN metastasis. A higher SUVmax is evident in more biologically aggressive tumors.

In breast cancer patients, the use of PET/CT for assessing both local extent and distant metastatic disease has been investigated. For assessment of local disease, MRI seems to be a better choice due to its higher resolution and ability to detect intra-ductal disease [17]. It should be noted that PET/CT is inferior to



(a) (b)

Figure 2. A 48-year-old woman with triple-negative invasive ductal cancer (17 mm; ER 0%, PR 0% HER2 0, Ki-67 20%, nuclear grade 3, T1cN0M0). (a) ^{18}F-FDG PET MIP image. (b) Axial PET/CT image. SUVmax value was 14.1.

MRI for PET/CT is inferior to MRI for assessing the local extent of the tumor. PET/CT may be helpful for diagnosing axillary disease, but unfortunately its sensitivity is low, *i.e.* less than 70% for axillary involvement. For detection of distant metastasis, however, PET/CT might be superior to conventional imaging methods [17]. PET and PET/CT may lead to upstaging of 9% - 30% of breast cancer patients [18]. However, the value of PET/CT for detecting distant disease in patients with early-stage breast cancers has been questioned. In a recent study including 178 newly diagnosed breast cancer patients with no clinical evidence of LN metastasis, PET/CT resulted in a change of the treatment plan in only 3.9% of the patients, and only 2 patients (1.1%) had extra-axillary metastasis [19]. Garami *et al*. reported a change in treatment plans in 6.3% of stage I patients with the use of PET/CT [20], and Nursal *et al*. reported that detection of distant metastasis was possible in 2.9% of clinical stage I patients [21]. In a small study, Gunalp *et al*. reported a higher rate (26%) of clinical upgrading for even stage I breast cancer with the use of PET/CT [22].

The TNM staging system for breast cancers is internationally accepted and used to determine the disease stage, which in turn guides management and determines prognosis. However, TNM subgroups do not consider the biology of the tumors cells, including tumor behavior. Breast cancer is a heterogeneous disease in terms of histology, dissemination modality, therapeutic response and prognosis. The higher metabolic activity of certain types of breast cancer may be associated with poor prognostic features. Several previous studies have demonstrated relationships between FDG accumulation on PET/CT and pathological characteristics (including tumor size, histological grade, ER, PR, HER2 status, Ki-67 index, axillary lymph node status, and stage) that are known to be important predictors of long-term survival in breast cancer patients [9] [10] [11] [12] [13]. Accounting for the divergent outcomes of FDG-PET/CT for early-stage breast cancer, Gilardi *et al*. have suggested that molecular subtypes and hormon-

al receptor status might be important [23]. The decision to carry out an FDG-PET/CT scan in the initial evaluation of patients with early-stage breast cancer should probably take into account these biological differences. Several more aggressive subtypes of breast cancer have a greater probability of developing systemic dissemination, even in patients with relative small tumors. This could add value to the imaging procedure, further improving its impact on the management of patients.

In this study we excluded two breast cancers (2.7%) with no focal FDG accumulation on PET/CT. These false negative cases were T1b (of 9 mm) and T1c (of 12 mm) IDCs. Among the clinicopathological factors reported to be associated with false negative FDG accumulation in primary breast cancer, only tumor size (≤10 mm) and low tumor grade showed independent associations [13]. A small lesion size with a relatively low tumor glucose metabolic activity and a partial volume effect might explain these results [24]. Use of FDG-PET/CT for detection of the primary tumor is currently not recommended, mainly because of the supposedly low sensitivity for small carcinomas. However, the introduction of TOF technology used in this research has further increased the image quality of PET/CT and dramatically improved cancer detectability [25]. In a recent study, 67% of T1b and 98% of T1c tumors could be visualized with PET/CT. In addition, PET image acquisition can be adapted to the specific situation of the breasts and regional nodes using optimal image reconstruction [26].

Various new imaging technologies have been developed, and the following modalities are predicted to have potential utility for breast cancer diagnosis. Combined PET and MR systems (PET/MR) have emerged as promising imaging modalities. MR is very sensitive and PET may offer specificity. In a feasibility study, multi-parametric FDG-PET/MR improved the differentiation of tumor characteristics, possibly providing additional information for preoperative assessment [27]. In addition to increased spatial resolution, new and more specific markers for breast cancer are being developed in order to improve the value of FDG-PET/CT results. Among these new markers, attention should be drawn to ^{18}F-16-alpha-17-beta-fluoroestradiol and 68 Gatrastuzumab, which can non-invasively depict the tumor expression of estrogen and HER2 receptors, respectively, with potential usefulness for assessment of therapeutic planning and response [28].

Our study had several limitations. First, it had a retrospective design and was conducted at a single institution, which would have unavoidably introduced selection bias. Second, the determination of subtype based on immunohistochemistry might not correspond to the molecular subtype in the gene expression profile. Third, we did not analyze actual survival data and the clinical impact on prognosis because of the short follow-up period. As there may be an association between SUVmax and the prognosis of breast cancer, more thorough investigations of larger cohorts with respect to the association between FDG accumulation and prognosis might yield more precise results.

5. Conclusion

Our study demonstrates that the SUVmax value on FDG-PET/CT is shown to have significant positive relationships with several parameters of pathological status in patients with T1-T2 breast cancer but no LN metastasis. A higher SUVmax is evident in more biologically aggressive tumors. Even in early-stage breast cancer patients, FDG-PET/CT of the pre-treatment is useful for providing additional information and predicting malignant behavior and prognosis.

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