Correlation of Molecular Subtypes of Invasive Ductal Carcinoma of Breast with Glucose Metabolism in FDG PET/CT: Based on the Recommendations of the St. Gallen Consensus Meeting 2013

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Abstract

Purpose This study aimed to investigate the relationship between the SUVmax of primary breast cancer lesions and the molecular subtypes based on the recommendations of the St. Gallen consensus meeting 2013.

Methods Clinical records of patients who underwent F-18 FDG PET/CT for initial staging of invasive ductal carcinoma (IDC) of the breast were reviewed. A total of 183 patients were included. SUVmax was correlated with the molecular subtypes defined by the St. Gallen Consensus Meeting 2013, i.e., luminal A-like (LA), luminal B-like HER2 negative (LBHER2-), luminal B-like HER2 positive (LBHER2+), HER2 positive (HER2+), and triple negative (TN), and with the clinicohistopathologic characteristics.

Results The molecular subtype was LA in 38 patients, LBHER2- in 72, LBHER2+ in 21, HER2+ in 30, and TN in 22. The mean SUVmax in the LA, LBHER2-, LBHER2+, HER2+, and TN groups were 4.5 ± 2.3 , 7.2 ± 4.9 , 7.2 ± 4.3 ,

10.2 ± 5.5 , and 8.8 ± 7.1 , respectively. Although SUVmax differed significantly among these subtypes ($p < 0.001$), the values showed a wide overlap. Optimal cut-off SUVmax to differentiate LA from LBHER2-, LBHER2+, HER2+ and TN were 5.9, 5.8, 7.5, and 10.2 respectively, with area under curve (AUC) of 0.648, 0.709, 0.833, and 0.697 respectively. The cut-off value of 5.9 yielded the highest accuracy for differentiation between the LA and non-LA subtypes, with sensitivity, specificity, and AUC of 79.4 %, 57.9 %, and 0.704 respectively.

Conclusion The SUVmax showed a significant correlation with the molecular subtype. Although SUVmax measurements could be used along with immunohistochemical analysis for differentiating between molecular subtypes, its application to individual patients may be limited due to the wide overlaps in SUVmax.

Keywords Breast cancer · F-18 FDG PET/CT · Invasive ductal carcinoma · Molecular subtype · SUVmax

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Introduction

Breast cancer is a heterogeneous tumor with distinct molecular subtypes and characteristics. Histopathologically, breast cancer can be divided into several subtypes. Among them, invasive ductal carcinoma (IDC) is most common. On the basis of gene expression profiling, breast cancer can be divided into five subtypes—luminal A, luminal B, human epidermal growth factor receptor type 2 (HER2)-enriched, basal cell-like, and normal breast like [1]. However, due to complexity, costs, and technical feasibility, application of gene expression profiling to general clinical practice has been limited. Therefore, classification based on immunohistochemistry

is widely used since it is inexpensive, popular, and technically simple.

According to the recommendations of the St. Gallen consensus meeting 2013, breast cancer can be categorized into five subtypes, namely, luminal A-like (LA), luminal B-like HER2 negative (LBHER2-), luminal B-like HER2 positive (LBHER2+), HER2 positive (HER2+), and triple negative (TN) based on the expression status of estrogen receptor (ER), progesterone receptor (PgR), HER2, and Ki-67. Moreover, the method and outcome of treatment in breast cancer is defined by the molecular subtype. For example, unlike other subtypes, LA has good prognosis without chemotherapy [2]. The St. Gallen consensus meeting held in 2013 proposed some changes to the classification of molecular subtypes that were absent in the recommendations of the 2011 consensus meeting, e.g., PgR positivity defined by a cut-off value of 20 % was added to distinguish between LA and LB subtype, the number of patients classified as LA subtype was reduced, and the number for whom cytotoxic therapy is generally recommended was increased [2].

F-18 FDG PET, which evaluates glucose metabolism of tumors, is a widely used technique for diagnosing tumors, assessing treatment response, and patient follow-up. In various tumors including breast cancer, it is well known that maximum standardized uptake value (SUVmax) reflecting glucose metabolism of tumor is an independent prognostic factor [3, 4].

The correlation between SUVmax of the primary tumor and histopathologic factors in breast cancer has been assessed in many studies previously. Most of the previous studies mainly assessed the correlation between each histopathologic factor and SUVmax [5–12]. Garcia et al. [13] reported that semi-quantitative parameters of F-18 FDG PET/CT showed statistically significant differences among the molecular subtypes according to the recommendations of St. Gallen consensus meeting 2011. However, there is no study on the relationship between molecular subtypes and SUVmax based on the recommendations of the St. Gallen consensus meeting 2013. A few studies reported that status of hormonal receptors can be changed after chemotherapy, so they recommended retesting the receptor status of the residual tumor [14]. Ascertainment for the relationship between molecular subtypes and SUVmax might not only give basic data for other clinical studies, but also help to make a diagnostic or therapeutic plan for patients with recurrent breast cancer where a biopsy is difficult to obtain. Therefore, we intended to investigate the relationship between the molecular subtypes proposed by the St. Gallen consensus meeting 2013 and SUVmax of primary breast cancer lesion. Because the pathological and clinical features and FDG avidity of IDC differ from those of invasive lobular carcinoma (ILC) [15], our study specifically enrolled patients with IDC to perform investigations in a homogeneous patients' group.

Material and Methods

Patients

A total of 183 female patients with IDC of breast who underwent F-18 FDG PET/CT for staging between April 2011 to December 2013 were included in the study. The following patients were excluded from the study: patients who received operation or chemotherapy before F-18 FDG PET/CT; patients with tumor size of less than 1 cm in order to avoid the partial volume effect. This retrospective study was approved by the institutional review board of our hospital.

FDG PET/CT Image Acquisition

In all patients enrolled for the study, oral intake and intravenous glucose injection were prohibited for at least 6 h before the PET/CT scan. Before injection of F-18 FDG, blood glucose levels of the patients were checked. PET/CT scans were obtained when the blood glucose level was less than 200 mg/dl (Most of the patients had glucose level lower than 150 mg/dl, only six patients had higher glucose level than 150 mg/dl). A whole-body scan from head to thigh was acquired 60 min following intravenous injection of approximately 370 MBq of F-18 FDG. PET/CT examinations were performed using a PET/CT scanner (Discovery STE; GE Healthcare, Milwaukee, WI, USA). The CT images were acquired using a multidetector CT equipment with the standard protocol that consists of 140 kV, 60–80 mA, a tube rotation time of 0.4 s per rotation, a pitch of 0.984, and a section thickness 3.75 mm. Emission PET data were acquired for 2 min per bed. PET images were reconstructed using an ordered-subset expectation maximization iterative reconstruction algorithm with three iterations, 18 subsets, matrix size of 256x256, 50 cm transaxial field-of-view (FOV). PET images were then fused with CT images.

Image Analysis

Semi-quantitative analysis was performed independently by two experienced nuclear medicine physicians who were aware of the patients' clinical history based on the results of other imaging studies and also by the information provided to them by the referring physician. For semi-quantitative analysis, a three-dimensional volumes of interest (3D VOI) was drawn on the primary tumor by referring to the finding of breast sonography and MRI, and then SUVmax which was defined as the maximum SUV in the pixel within the 3D VOI was calculated. Clinical stages were determined according to the American Joint Committee on Cancer manual, 7th edition [16].

Histopathological Analysis

The histopathological analysis was performed on needle biopsy sections for pathological diagnosis, or on representative sections of surgical specimens from patients who did not receive neo-adjuvant chemotherapy. Histological grade was also classified according to the modified Bloom-Richardson classification: well differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3) [17]. Immunohistochemistry was done using paraffin-embedded tissue sections to examine the expression status of ER, PgR, HER2, and Ki-67.

ER and PgR expression levels were evaluated according to the sum of intensity score (0, weak: 1, moderate: 2, strong: 3) and proportion score (0, <1 %: 1, 1~10 %: 2, 10~33 %: 3, 34~66 %: 4, 67~100 %: 5). Tumors with 1 % or more nuclear expression were considered positive for ER and PgR expression. Expression of PgR in less than 20 % of tumor cells with less than moderate intensity was defined as low PgR expression [18]. According to the guidelines of the American Society of Clinical Oncology (ASCO), tumors were considered HER2 positive only if they were either scored 3+ by IHC or 2+ by IHC and also HER2 amplified (ratio > 2.0) on the basis of fluorescence in situ hybridization (FISH) [19]. The Ki-67 labeling index was recorded as low or high according to the percentage of nuclear expression of Ki67 in 3 high power fields using a cutoff value of 14 % [20].

Molecular Classification

According to the recommendations of St. Gallen Consensus Meeting 2013, molecular subtypes were categorized as follows [2].

1. LA: ER and/or PgR positive, HER2 negative, Ki-67 ‘low’ (<14 %), recurrence risk ‘low’ based on multi-gene-expression assay

2. LBHER2-: ER positive, HER2 negative and at least one of the following: Ki-67 ‘high’, PgR ‘negative or low’ (<20 %), Recurrence risk ‘high’ based on multi-gene-expression assay
3. LBHER2+: ER positive, HER2 over-expressed or amplified, Any Ki-67, Any PgR
4. HER2+: HER2 over-expressed or amplified, ER and PgR absent
5. TN: ER and PgR absent, HER2 negative

Statistical Analysis

Medcalc Statistical Software version 14.12.0 (Medcalc Software bvba, Ostend, Belgium; 2014) was used for all analyses. Pearson correlation was used to evaluate the correlation between tumor size and SUVmax. Kruskal-Wallis test was used to compare the SUVmax among molecular subtypes. Mann–Whitney U test was used to compare the mean SUVmax according to histopathologic factors. Receiver operating characteristic (ROC) curve analysis was performed to examine the diagnostic performance of F-18 FDG PET/CT to differentiate LA subtype from others; $p < 0.05$ was considered statistically significant.

Result

Characteristics of the Study Population

Characteristics of the patients included in the study can be seen in Table 1. The mean age of study population was 54 ± 10.0 years, and the mean size of the primary tumor was 2.1 ± 1.6 cm. The mean SUVmax of the primary tumor was 7.4 ± 5.2 . There was no definite correlation between SUVmax and tumor size ($\rho = 0.09$, $p = 0.224$).

Table 1 Patient’s characteristics and relationship between SUVmax and clinicopathological parameters

	Number (%)	SUVmax (mean $\pm$ SD)	<i>p</i> value
Age (yr) mean $\pm$ SD	54.0 $\pm$ 10.0	7.4 $\pm$ 5.2	
Size (cm)	2.1 $\pm$ 1.6		
Histologic grade			
Well differentiated	42 (23.0)	4.3 $\pm$ 3.1	<0.001
Moderate differentiated	82 (44.8)	7.5 $\pm$ 5.0	
Poorly differentiated	59 (32.2)	9.3 $\pm$ 5.6	
Stage			
I	80 (43.7)	7.4 $\pm$ 5.9	0.527
II	77 (42.1)	7.2 $\pm$ 4.3	
III	20 (10.9)	7.5 $\pm$ 5.0	
IV	6 (3.3)	9.9 $\pm$ 6.2	

SUVmax maximum standardized uptake value

Relationship Between SUVmax and Clinicopathological Parameters

SUVmax was 4.3 ± 3.1 in the well-differentiated group (grade 1), 7.5 ± 4.9 in the moderately differentiated group, and 9.3 ± 5.6 in the poorly differentiated group. There were significant differences in SUVmax among the three grades ($p < 0.001$). Post-hoc analysis using Bonferroni correction revealed significant differences in SUVmax between the well differentiated and moderately differentiated groups ($p < 0.05$), the well differentiated and poorly differentiated groups ($p < 0.05$), and the moderately differentiated and poorly differentiated groups ($p < 0.05$) (Fig. 1). In terms of clinical stage, there was no significant difference in SUVmax among different stages.

Relationship Between SUVmax and Status of ER, PR, HER2, and Ki-67

The ER(−) group showed significantly higher SUVmax than ER(+) group (9.4 vs. 6.3 , $p < 0.001$). In the case of the PgR(−) group, SUVmax of the primary tumor was significantly higher in comparison to that in the PgR(+) group (8.9 vs. 6.1 , $p < 0.001$). The SUVmax of the HER2(+) group was significantly higher than the HER2(−) group (8.9 vs. 6.7 , $p = 0.002$), and the group with a Ki-67 ≥ 14 % showed significantly higher SUVmax than the group with Ki-67 < 14 % (8.7 vs. 4.6 , $p < 0.001$). These results are summarized in Table 2.

Relationship Between SUVmax and Molecular Subtypes

Among the 183 patients included in the study, the molecular subtype was LA in 38 patients, LBHER2- in 72 patients, LBHER2+ in 21 patients, HER2+ in 30 patients, and TN in

Fig. 1 SUVmax according to histologic grade. There was significant differences in SUVmax among histologic grade ($p < 0.001$). Boxplots show interquartile range (box), median (black line within interquartile range), data range (vertical lines), and outliers (open dots). SUVmax maximum standardized uptake value

Table 2 Relationship between SUVmax and status of ER, PgR, HER2, and Ki-67

	Number (%)	SUVmax (mean $\pm$ SD)	<i>p</i> value
ER status			
Negative	62 (33.9)	9.4 ± 6.1	<0.001
Positive	121 (66.1)	6.3 ± 4.2	
PgR status			
Negative	80 (43.7)	8.9 ± 5.8	<0.001
Positive	103 (56.3)	6.1 ± 4.2	
HER2 status			
Negative	132 (72.1)	6.7 ± 5.0	0.002
Positive	51 (27.9)	8.9 ± 5.2	
Ki-67 index			
Low	62 (33.9)	4.6 ± 2.9	<0.001
High	121 (66.1)	8.7 ± 5.5	

ER estrogen receptor, PgR progesterone receptor, HER2 human epidermal growth factor receptor 2, SUVmax maximum standardized uptake value

22 patients. The mean SUVmax of these subtypes was 4.5 ± 2.3 , 7.2 ± 4.9 , 7.2 ± 4.3 , 10.2 ± 5.5 , and 8.8 ± 7.1 respectively (Table 3). There were significant differences in SUVmax among the five molecular subtypes ($p < 0.001$). Post-hoc analysis using Bonferroni correction was performed to identify the subtypes that were different. There were significant differences in SUVmax between the group with LA and the rest of the molecular subtypes ($p < 0.05$), i.e., the SUVmax of LA was significantly lower than that of others. The patient group with the LBHER2 subtype showed significantly lower SUVmax than the patient group with HER2+ tumors ($p < 0.05$) (Fig. 2).

In the ROC curve analysis for differentiation of LA from non-LA subtype, a cut-off SUVmax of 5.9 yielded the highest accuracy (sensitivity of 79.4 %, specificity of 57.9 %, and AUC of 0.704) (Fig. 3).

Discussion

Our study shows significant correlation between status of hormonal receptors and SUVmax of primary lesion of IDC, and difference of FDG uptake according to molecular subtype based on the recommendation of St. Gallen consensus meeting 2013.

The correlation between the expression of hormone receptor and F-18 FDG uptake has been controversial and unclear. While some studies have shown no correlation between the expression of hormone receptor and F-18 FDG uptake [5–7, 21, 22], some recent studies have revealed that the SUVmax of the ER(−) group is significantly higher than that of the ER(+) group [8, 9, 23]. In corroboration to the results of latter groups, we found the ER(−) group to display significantly

Table 3 SUVmax of each molecular subtype according to the recommendations of the St. Gallen consensus meeting 2013

Subtype	Number (%)	SUVmax (mean $\pm$ SD)
LA	38 (20.8)	4.5 $\pm$ 2.3
LBHER2-	72 (39.3)	7.2 $\pm$ 4.9
LBHER2+	21 (11.5)	7.2 $\pm$ 4.3
HER2+	30 (16.4)	10.2 $\pm$ 5.5
TN	22 (12.0)	8.8 $\pm$ 7.1
Total	183	7.4 $\pm$ 5.2

LA luminal A-like, LBHER2- luminal B-like HER2 negative, LBHER2+ luminal B-like HER2 positive, HER2+ HER2 positive, TN triple negative, SUVmax maximum standardized uptake value

higher SUVmax than the ER(+) group (9.4 vs. 6.3, $p < 0.001$). Laudanski et al. [24] have reported a significant correlation between ER- α and glucose transporter-1 (GLUT-1) in breast cancer. According to them, of the total GLUT-1 positive tumors, 45.3 % were also ER- α positive, whereas 81.3 % of ER- α negative tumors were GLUT-1 positive. In view of the fact that GLUT protein and hexokinase are important factors in F-18 FDG uptake by tumor [25], the relationship between expression of ER and GLUT could be a reason for the SUVmax to be higher in the ER(–) group vis-à-vis the ER(+) group.

In our study, the SUVmax of the PgR(–) group was significantly higher than that of the PgR(+) group (8.9 vs. 6.1, $p < 0.001$). Contrary to our result, Mavi et al. [23] reported that PgR status alone had no effect on F-18 FDG uptake. This difference might result from the different criteria for the positivity of hormonal receptor in their study. Mavi et al.

Fig. 2 SUVmax according to molecular subtype. There was significant differences in SUVmax among molecular subtypes ($p < 0.001$). Boxplots show interquartile range (box), median (black line within interquartile range), data range (vertical lines), and outliers (open dots). LA luminal A-like, LBHER2- luminal B-like HER2 negative, LBHER2+ luminal B-like HER2 positive, HER2+ HER2 positive, TN triple negative, SUVmax maximum standardized uptake value

Fig. 3 ROC curve of SUVmax in distinguishing LA from non-LA group. The cut-off value of SUVmax was 5.9 (AUC 0.704). LA luminal A-like, SUVmax maximum standardized uptake value, AUC area under curve

considered tissues with less than 5 % nuclear labeling as negative. Meanwhile, Prat et al. [26] categorized luminal group by PgR positivity using a cutoff value of 20 % and reported that the PgR ≥ 20 % group showed good prognosis as compared to the PgR < 20 % group. Considering that F-18 FDG uptake is associated with prognosis, the relationship between F-18 FDG uptake and Prat et al.'s classification can be worth evaluating. Our study is, however, based on retrospective medical records, so we cannot focus on this question. We think that further study is needed to determine the correlation between PgR positivity categorized by the 20 % cut-off value and glucose metabolism.

Over-expression of the C-erbB2 oncogene is associated with poor response to tamoxifen and other hormonal therapies, and hence, is known as a poor prognostic factor [27]. While our results revealed that the HER2(+) group has significantly higher SUVmax than the HER2(–) group (8.9 vs. 6.7 $p = 0.002$), many studies reported that there was no correlation between SUVmax and HER2 positivity [3, 8–10, 22, 23]. It is not clear why our result is different from those of previous studies, but we cautiously suggest that the histopathology of our study population could be one of the reasons for it. Unlike other studies, all patients in our study had IDC. ILC has a low histological grade, low mitotic index, and is generally hormone receptor positive and HER2, p53, and basal marker negative [28–30].

The expression of Ki-67 represents proliferative activity of a malignant tumor, so the histopathologic grade and the expression of Ki-67 in the breast cancer is an important prognostic factor [31, 32], and the correlation between histopathologic grade and Ki-67 is well known [33]. Akin to others [4, 6, 8, 10, 34], our study revealed that primary malignant lesions with higher histopathologic grade and expression of Ki-67

showed significantly higher SUVmax (4.3 vs. 7.5 vs. 9.3; 4.6 vs. 8.7, respectively $p < 0.001$).

In terms of the difference in FDG uptake among molecular subtypes, our study showed statistical differences between the LA group and every other group. This is in agreement with the observations of Garcia et al. In their study, greatest differences were observed for LA and basal subtype (TNBC). Although our study showed that the LA group had the lowest mean SUVmax among molecular subtypes, the greatest difference was shown for the LA and HER2+ groups. Although Garcia et al. [13] reported discrimination of SUVmax between the LA and TN groups, our results showed substantial overlapping of range of SUVmax among each subtype, even for the LA and HER2+ subtypes. In terms of HER2 expression, this is a predictive marker for treatment with trastuzumab [35], so molecular imaging-aided differentiation between these subtypes can be valuable. But this substantial overlap of SUVmax in each subtype (LA vs. LBHER2+, and LBHER2- vs. LBHER2+) suggests its limited role in clinical application.

In LA group, hormonal therapy is the mainstay of treatment. Unlike non-LA group, cytotoxic therapy is used in only a limited number of patients [2]. Therefore, it is important to distinguish between the LA and non-LA group to decide the treatment plan. Mean SUVmax of LA group was significantly lower than that of non-LA group (4.5 vs. 8.1, $p < 0.001$), and the optimal cut-off value of SUVmax to distinguish between LA and non-LA group was 5.9 (sensitivity: 79.4 %, specificity: 57.9 %, AUC: 0.704). However, there was a wide overlap in SUVmax between the two groups. So, the use of SUVmax to differentiate between LA and non-LA group may also be limited in individual patient.

Our study may suffer from certain limitations. First, because a diagnostic core needle biopsy was done before F-18 FDG PET/CT in all patients, it is likely that the inflammatory reaction in response to the needle biopsy may affect the F-18 FDG uptake. Most patients, however, underwent F-18 FDG PET/CT at least 1 week after the biopsy procedure, and SUVmax for IDC is usually higher than for minor inflammatory reaction following biopsy. So, we think that the SUVmax of breast lesions represents glucose metabolism of malignant lesions. Second, the correlation between F-18 FDG uptake and molecular subtype was evaluated by using only SUVmax. Further investigations with other parameters such as SUVmean, SUVpeak, or tumor heterogeneity measured on F-18 FDG PET/CT are warranted [36, 37].

Conclusion

SUVmax using F-18 FDG PET/CT could be used as an adjunct method to immunohistochemical analysis for differentiating between molecular subtypes based on recommendation of the St. Gallen consensus meeting 2013 in patients with IDC of the breast. However, application to individual patient may be limited due to wide overlap of the SUVmax of each subtype.

Compliance with Ethical Standards

Conflict of Interest Sun Seong Lee, Sang Kyun Bae, Yun Soo Park, Ji SUN Park, Tae Hyun Kim, Hye Kyoung Yoon, Hyo Jung Ahn and Seok Mo Lee declare that they have no conflict of interest.

Ethical statement The study was approved by the Institutional Review Board of Inje University Busan Paik Hospital (IRB No. 15–0050) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Institutional review board waived the need to obtain informed consent for this retrospective study.

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