ORIGINAL ARTICLE

The Relationship Between Estrogen Receptor, Progesterone Receptor and Human Epidermal Growth Factor Receptor 2 Expression of Breast Cancer and the Retention Index in Dual Phase ^{18}F-FDG PET/CT

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Abstract

Purpose This study investigates the correlation of retention index (RI) using the dual phase FDG PET/CT scan with the breast cancer biomarkers.

Methods A total of 55 patients with breast cancer underwent dual phase FDG PET/CT scans (60 and 120 min after FDG injection) before treatment. SUVmax and SUVmean of the primary breast tumors were measured, then the percent change of SUVmax and SUVmean between the two scans were calculated, and denoted as RImax and RImean, respectively. After the surgical resection of the breast tumor, the status of biomarkers (ER, PR, and HER-2) was evaluated in the post-surgical specimen.

Results RImean was significantly higher in ER (−) (median, 16.2; IQR, 10.8–21.0) or HER-2 (+) (median, 16.1; IQR, 10.7–21.6) tumors than in ER (+) tumors (median, 9.9; IQR, 5.5–15.3) or HER-2 (−) tumors (median, 10.5; IQR, 5.5–16.1). However, there were no significant differences of SUVmax or RImax according to the ER or HER-2 status. There were no significant differences of any PET parameters between PR (+) and PR (−) tumors. Based off ROC curve analyses, RImean predicted the ER (+) tumors (AUC, 0.699; $p = 0.006$), and HER-2 (+) tumors (AUC, 0.674; $p = 0.022$), but not the PR (+) tumors. However, neither SUVmax nor RImax predicted ER (+), PR (+), or HER-2 (+) tumors.

Conclusions Retention index of SUVmean can reflect the ER and HER-2 status of breast cancers. Higher retention index of SUVmean might associate with lower ER expression and higher HER-2 expression.

Keywords Breast cancer · Dual phase · Estrogen receptor · Human epidermal growth factor receptor 2 · Positron emission tomography · Retention index

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Introduction

Breast cancer is the second most common cancer of women in Korea [1], and its incidence of rates are rising rapidly [2]. There are a variety of factors associated with breast cancer including environmental, hormonal, and genetic factors [3, 4]. Among these factors, molecular biomarkers, such as the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) have been reported to be associated with the patients' prognosis and influence the treatment planning [5].

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET/CT) has been important in the management of breast cancer patients [6]. It is used for screening for the extra-axillary lymph node metastasis [7] and distant metastasis [8, 9], assessing for the treatment responses [10, 11], and predicting prognosis [12], but the benefit of FDG PET/CT scanning for staging remains a matter of debate [13]. Several studies have suggested that the characteristics of FDG uptake in breast cancer are relevant to biological or histological attributes of primary tumor, including its biomarker status [14–19]. Among these previous studies using diverse PET parameters, such as the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), or total lesion glycolysis (TLG), the correlations between the biomarker status and PET parameters were weak or modest in many studies [17, 20, 21].

The dual phase PET/CT scan is an evolving diagnostic tool in breast cancer [22, 23], but is not regarded as the standard tool. The retention index (RI) is as an alternative PET parameter which is useful not only for distinguishing malignancy from benignancy of FDG-avid lesions [24], but also for predicting survival of the patients with several malignancies such as lung [25, 26], pancreatic [27, 28], and head and neck cancer [29, 30]. Recently, the association between the RI using SUVmax and biomarker status of breast cancer was reported [21]. However, there is no data on the role of the RI using the mean standardized uptake value (SUVmean) with the biomarker status of breast cancer. Therefore, the aim of this study is to evaluate whether the calculation of the RI using both the SUVmax and the SUVmean of FDG PET/CT would be useful to predict the biomarker status of breast cancer.

Materials and Methods

Patient Population

A total of 59 consecutive patients with histologically proven breast cancer who underwent dual phase FDG PET/CT scans before treatment between September 2009 and May 2011 were retrospectively analyzed. All patients had newly diagnosed AJCC stage II or III breast cancer. To avoid the partial volume effects, patients whose tumors were less than 1.5 cm based on the MRI were excluded from the study. Other eligibility requirements included no evidence of distant metastasis confirmed by other methods previous to the PET/CT scan, no history of other malignancies except the breast cancer, and primary breast tumor showing higher FDG uptake (SUVmax of the tumor > 2.0). The Institutional Review Board of the institute approved the current study, and informed consent was waived due to its retrospective design.

FDG PET/CT Imaging

PET/CT data were acquired using a Biograph6 PET/CT scanner (Siemens Medical Solutions; Knoxville, TN, USA). All patients fasted for at least 6 h before the intravenous administration of FDG (7.4 MBq per kg of body weight), and all patients' blood glucose levels were less than 7.2 mmol/L before the FDG injection. PET/CT imaging from the skull base to the upper thigh (5 to 6 bed positions) was performed beginning 60 min after FDG injection (first PET image). During the PET/CT scans, CT images without intravenous iodinated contrast were obtained using a 6-slice helical CT scanner, and the imaging parameters used for CT scanning were as follows: 130 kVp, 30 mA, 0.6-s/CT rotation, and a pitch of 6. Then, PET emission data were acquired over the corresponding area with a 16.2-cm axial field of view at 3.5 min per bed position. The CT data were used for attenuation correction, and the images were reconstructed using a conventional iterative algorithm (ordered-subsets expectation-maximization, two iterations, and eight subsets). The second PET imaging from the T1 to T12 level was performed beginning 120 min after FDG injection, and CT images without intravenous iodinated contrast were also obtained. The same protocols were used for the first and second PET imaging procedures.

Imaging Analysis

All PET/CT images were reviewed on e-soft workstations (Siemens Medical Systems, Iselin, NJ). An ellipsoid volume of interest (VOI) was drawn to include the entire primary tumor of the breast, the SUVmax corrected for body weight and the dose of FDG injected was measured for each PET/CT dataset.

We chose 2.0 as cut-off SUV for determining the tumor VOI. From the VOI at the cut-off SUV of 2.0, SUVmean was measured. Then the percent change of SUVmax and SUVmean between the first and second PET images, denoted as RImax and RImean, were calculated as follows:

Retention index of SUVmax (RImax) (%)
$$= \frac{(\text{SUVmax of second PET}) - (\text{SUVmax of first PET})}{(\text{SUVmax of first PET})} \times 100$$

Retention index of SUVmean (RImean) (%)
$$= \frac{(\text{SUVmean of second PET}) - (\text{SUVmean of first PET})}{(\text{SUVmean of first PET})} \times 100$$

MTV was measured by using a semi-automated contouring program with VOI at the cut-off SUV of 2.0.

Biomarker-Based Subgroup

According to the criteria suggested by Cheang et al. [31], the cases were classified into four biologically distinct subgroups based on the expression of ER, PR, HER-2, and the Ki-67 index. This classification system has been reported to be useful for both treatment planning and prediction of prognosis. Because the Ki-67 index was not evaluated, all subtypes were determined only by biomarker status as follows: a) hormone receptor-positive and HER-2-negative, b) hormone receptor-positive and HER-2-positive; c) hormone receptor-negative and HER-2-positive; and d) hormone receptor- and HER-2-negative.

Statistical Analysis

All parameters were expressed as mean ± standard deviation (SD) or median and interquartilie range (IQR). Differences of PET parameters (SUVmax, RImax, RImean, and MTV) according to the biomarker status were assessed by using a Mann–Whitney U test. The receiver-operating-characteristic (ROC) curve was analyzed to determine the ability of each PET parameter to predict the biomarker status. Area under the ROC curve (AUC), 95 % confidence interval (95 % CI), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for predicting biomarker status were reported. A Pearson correlation coefficient test was used to check for association between MTV and other PET parameters. All tests were 2-sided, and p values of 0.05 or less were considered significant. All statistical tests were performed using MedCalc (MedCalc Software 12.5.0.0, MedCalc Software bvba).

Result

Patient Characteristics

Three of 59 patients were excluded because the SUVmax of their respective tumors was less than 2.0. One patient was excluded because of the small size of tumor. Therefore, a total of 55 patients were retrospectively analyzed in the current study. The median age of the 55 patients was 46 y (IQR, 42–51), and all patients were women. On the postsurgical specimen, ER (+), PR (+), and HER-2 (+) tumors were identified in 30 (55 %), 43 (78 %), and 21 patients (38 %), respectively. About half of patients (53 %) had T3 or T4 tumors, and most patients (95 %) had regional lymph node metastasis (N1–N3). Pathologic subtypes of the primary tumor were intraductal carcinoma in 51 patients (93 %), and other in four patients (7 %) (Table 1).

PET Parameters According to the Biomarker Status

Comparisons of PET parameters according to the biomarker status are detailed in Fig. 1 and Table 2. RImean was significantly higher in ER (−) tumors (median, 16.2; IQR, 10.8–21.0; Range, 0.4–42.6) than in ER (+) tumors (median, 9.9; IQR, 5.5–15.3; range, −3.2–27.9). SUVmax (median, 9.0; IQR, 6.5–12.3; range, 3.2–17.6) and RImax (median 16.2; IQR, 8.7–21.7; range, −15.1–35.6) of ER (−) tumors were also higher than those of ER (+) tumors (median 7.2; IQR, 3.5–11.1; range, 2.3–17.0 for SUVmax, and median, 15.5; IQR,

Table 1 Patient characteristics ($n = 55$)

| Characteristics	Number of patients (%)
Age	
< 35 y	6 (10.9 %)
≥ 35 y	49 (89.1 %)
Gender	
Male	0 (0 %)
Female	55 (100 %)
Estrogen receptor status	
Positive	30 (54.5 %)
Negative	25 (46.5 %)
Progesterone receptor status	
Positive	43 (78.2 %)
Negative	12 (21.8 %)
HER-2/neu status	
Positive	21 (38.2 %)
Negative	34 (61.8 %)
Menopausal	
Premenopausal	21 (38.2 %)
Menopausal	34 (61.8 %)
T stage	
T1	4 (7.2 %)
T2	22 (40.0 %)
T3	18 (32.7 %)
T4	11 (20.0 %)
N stage	
N0	3 (5.5 %)
N1	14 (25.5 %)
N2	33 (60.0 %)
N3	5 (9.1 %)
M stage	
M0	55 (100 %)
M1	0 (0 %)
Pathologic subtypes	
Invasive ductal carcinoma	51 (92.7 %)
Invasive lobular carcinoma	2 (3.6 %)
Mucinous carcinoma	1 (1.8 %)
Signet ring cell carcinoma	1 (1.8 %)
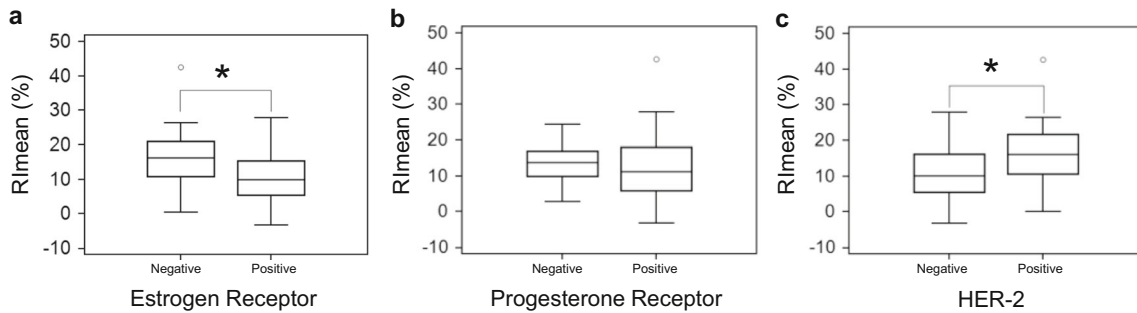
Fig. 1 RImean according to the biomarker status. Data are presented as box plots indicating median and interquartile range; whiskers extend to most extreme data points up to 1.5 times the interquartile range. Asterisk indicates $p < 0.05$

8.0–25.4; range, −10.3–47.3 for RImax). However, there were no significant differences of SUVmax ($p = 0.089$) or RImax ($p = 0.839$) between ER (+) tumors and ER (−) tumors.

With respect to the HER-2 status of the tumors, RImean was higher in HER-2 (+) tumors (median, 16.1; IQR, 10.7–21.6; range, 0–42.6) than in HER-2 (−) tumors (median, 10.5; IQR, 5.5–16.1; range, −32.–27.9). SUVmax (median, 9.5; IQR, 6.4–11.9; range, 2.3–16.3) and RImax (median, 16.3; IQR, 11.1–20.8; range, 1.9–30.9) of HER-2 (+) tumors were also higher than those of HER-2 (−) tumors (median, 7.2; IQR, 5.1–11.1; range, 2.5–17.6 for SUVmax, and median, 15.5; IQR 4.3–25.0; range, −15.1–47.3 for RImax), but there were no significant differences of SUVmax ($p = 0.279$) or RImax ($p = 0.456$) between HER-2 (+) and HER-2 (−) tumors.

The SUVmax of PR (+) tumors (median, 7.9; IQR, 5.3–12.8; range, 2.3–17.6) was similar to the SUVmax of PR (−) tumors (median, 8.2; IQR, 6.4–9.4; range, 3.5–11.6). RImax (median, 16.4; IQR, 14.5–20.8; range, 8.8–30.9) and RImean

(median, 14.5; IQR, 10.6–17.5; range, 2.8–24.3) of PR (−) tumors were slightly higher than those of PR (+) tumors (median, 15.5; IQR, 4.8–25.3; range, −15.1–47.3 for RImax, and median, 11.3; IQR, 5.9–18.0; range, −3.2–42.6 for RImean). However, there were no significant differences of any PET parameters between PR (+) and PR (−) tumors.

MTV showed statistically significant correlation with SUVmax ($p < 0.001$), RImean ($p = 0.015$), and the ER status ($p = 0.031$), but did not with the PR status ($p = 0.501$), HER-2 status ($p = 0.795$), or RImax ($p = 0.139$). SUVmean did not show correlation with any biomarker status.

PET Parameters to Predict the Biomarker Status

Based on ROC curve analyses, RImean predicted the ER (+) tumors (AUC, 0.699; 95 % CI, 0.560–0.815; $p = 0.006$), and HER-2 (+) tumors (AUC, 0.674; 95 % CI, 0.535–0.795; $p = 0.022$), but not the PR (+) tumors (AUC, 0.590; 95 %

Table 2 Comparisons of PET parameters according to the biomarker status

	Number of patients	SUVmax	SUVmean	PET parameters*		
				RImax (%)	RImean (%)	MTV (mL)
All patients	55	7.9 (5.7–11.5)	3.4 (2.8–4.7)	16.0 (8.3–24.1)	11.7 (7.0–18.0)	20.1 (9.2–44.0)
ER						
Positive	30	7.2 (3.5–11.1)	3.1 (2.5–4.5)	15.5 (8.0–25.4)	9.9 (5.5–15.3)	17.4 (6.3–36.3)
Negative	25	9.0 (6.5–12.3)	3.6 (3.1–4.8)	16.2 (8.7–21.7)	16.2 (10.8–21.0)	33.8 (16.3–51.8)
p value		0.090	0.099	0.839	0.012	0.031
PR						
Positive	43	7.9 (5.3–12.8)	3.4 (2.6–5.2)	15.5 (4.8–25.3)	11.3 (5.9–18.0)	20.2 (10.9–47.7)
Negative	12	8.2 (6.4–9.4)	3.7 (3.2–4.4)	16.4 (14.5–20.8)	14.5 (10.6–17.5)	19.0 (8.8–35.9)
p value		0.744	0.863	0.313	0.343	0.501
HER-2						
Positive	21	9.5 (6.4–11.9)	4.1 (3.1–4.7)	16.3 (11.1–20.8)	16.1 (10.7–21.6)	24.9 (8.8–47.9)
Negative	34	7.2 (5.1–11.1)	3.3 (2.6–4.7)	15.5 (4.3–25.0)	10.5 (5.5–16.1)	19.0 (10.6–40.9)
p value		0.279	0.396	0.456	0.031	0.795

*PET parameters are presented as median values (interquartile range)

CI, 0.449–0.721; $p = 0.276$). However, neither SUVmax nor RImax predicted ER (+) tumors (AUC, 0.634; 95 % CI, 0.493–0.760; $p = 0.076$ for SUVmax, and AUC, 0.516; 95 % CI, 0.377–0.653; $p = 0.841$ for RImax, respectively), PR (+) tumors (AUC, 0.531; 95 % CI, 0.392–0.667; $p = 0.691$ for SUVmax, and AUC, 0.596; 95 % CI, 0.455–0.726; $p = 0.215$ for RImax, respectively), and HER-2 (+) tumors (AUC, 0.588; 95 % CI, 0.447–0.719; $p = 0.268$ for SUVmax, and AUC, 0.560; 95 % CI, 0.420–0.694; $p = 0.437$ for RImax, respectively) (Fig. 2). The AUC of RImean was significantly higher than that of RImax for predicting the ER status ($p = 0.002$). However, there were no significant differences between the AUC of SUVmax and RImean for predicting the ER status ($p = 0.299$) and HER-2 status ($p = 0.160$). There was also no significant difference between the AUC of RImax and RImean for predicting the HER-2 status ($p = 0.076$) (Fig. 3).

The optimal criteria, sensitivity, specificity, PPV, NPV, and accuracy of RImean were < 16.0 %, 76.7 %, 56.0 %, 67.7 %, 66.7 %, and 67.2 % for predicting ER(+) tumors, and > 12.1 %, 66.7 %, 67.7 %, 56.0 %, 76.7 %, and 67.2 %, for HER-2(+) tumors, respectively (Table 3).

PET Parameters Among Biomarker-Based Subgroups

The median values of RImean of subgroup a ($n = 33$), b ($n = 15$), c ($n = 6$), and d ($n = 1$) were 10.2 % (IQR, 5.2–16.0; range, −3.2–27.9), 15.3 % (IQR, 10.1–21.7; range, 0–42.6), 16.3 % (IQR, 13.7–19.6; range, 2.8–24.3), and 18.5 %, respectively. However, there were no significant differences between PET parameters among these subgroups ($p = 0.107$ for RImean; $p = 0.444$ for SUVmax; $p = 0.559$ for RImax) (Fig. 4).

Discussion

There are two major findings in the current study: First, among SUVmax, RImax and RImean, only RImean correlated with the biomarker status of breast cancer. Second,

pretreatment RImean was useful for predicting biomarker status of breast cancer.

In the current study, SUVmax tended to be higher in ER (−) and HER-2 (+) tumors than ER (+) and HER-2 (−) tumors; however, the trend did not reach statistical significance. Other previous studies are consistent with our result [14, 16, 21, 32]. It has been reported that SUVmax of breast cancer shows a linear relationship in T1–T3 tumors and correlates with tumor size. Due to the small population in the present study, we could not evaluate the correlation between SUVmax and biomarker status in the controlled T-stage groups. Further large-scale study may be warranted.

Like SUVmax, SUVmean also failed to show the correlation with any biomarker status. It was a predictable consequence, because SUVmax would be more expected to reflect the metabolic status of the tumor than SUVmean [33].

Unlike SUVmax, RImean was significantly higher in ER (−) and HER-2 (+) tumors. It is reported that patients with ER (−) and HER-2 (+) breast cancer have poorer prognoses than patients with ER (+) and HER-2 (−) breast cancer [5, 34, 35]. Higashi et al. [36] reported that RI can predict the hexokinase-II expression and suggested possible prognostic values of RI. Because hexokinase-II is attributed with maintaining the malignant state of a tumor due to the closing of voltage-dependent anion channels [37] and prevention of mitochondria-mediated apoptosis [38], a higher RI might be relevant to the poor prognosis and negative prognostic factors such as ER (−) and HER-2 (+).

In this study, SUVmax, RImax, or RImean did not correlate with the PR status of breast cancer. Conflicting results have been reported as the correlation between FDG uptake and PR status. Some studies have claimed higher SUVmax in the PR (−) breast cancer [39, 40], but other reports showed no association between PR status and FDG uptake [41, 42]. Ekmekcioglu et al. [42] suggested that the cut-off level of the PR limit of positivity might be relevant to the result.

Although SUVmax has been widely used as a practical method, there is a limit to the complete analysis of tumor characteristics. Because SUVmax is determined by a single pixel with the highest SUV [43], it could also be effected by its

Fig. 2 ROC curves of RImean for predicting the status of ER (a), PR (b), and HER-2 (c). RImean predicted the status of ER and HER-2, but not that of PR
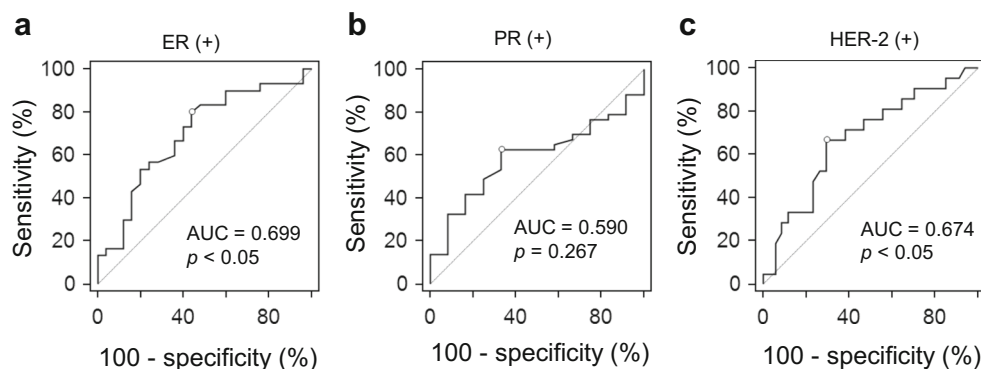
a ER (+)
AUC = 0.699
$p < 0.05$

b PR (+)
AUC = 0.590
$p = 0.267$

c HER-2 (+)
AUC = 0.674
$p < 0.05$

Fig. 3 Comparisons of ROC curves between RImean and other PET parameters for predicting the status of ER and HER-2. Although there are no significant differences between SUVmax and RImean for predicting the status of ER (**a**) or HER-2 (**b**), there are significant differences between RImax and RImean for predicting the status of ER (**c**) or HER-2 (**d**)
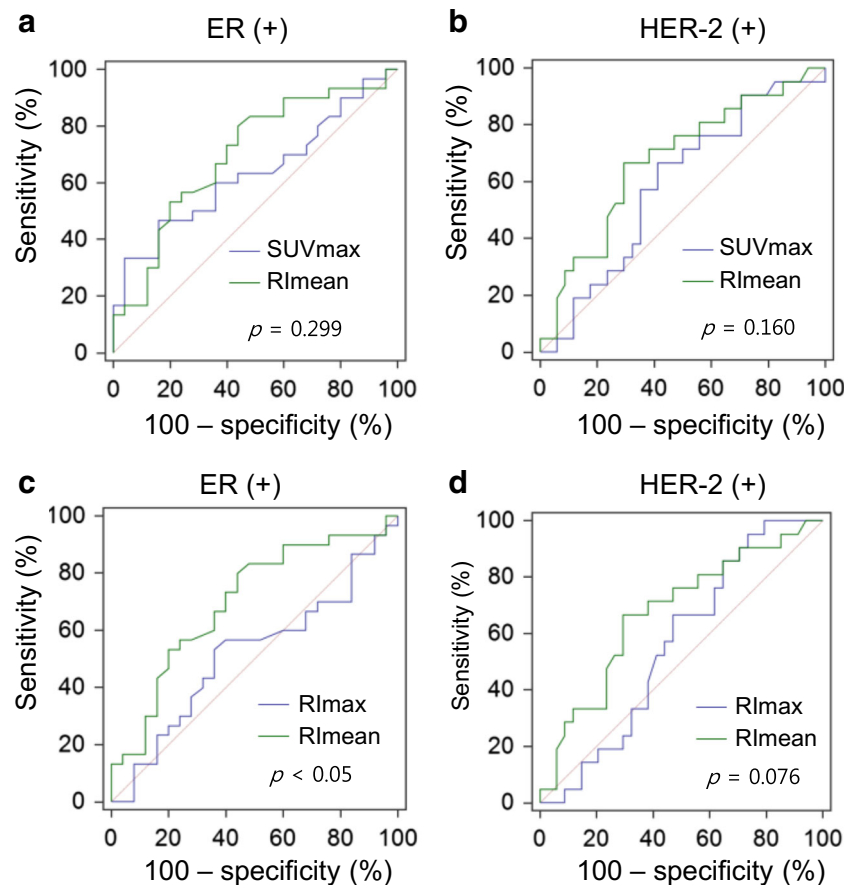
vulnerability to statistical noise. Lodge et al. [33] reported that SUVmax was much more biased by noise properties than multi-pixel summarized SUV. In the current study, the PET images were acquired for 3.5 min for each bed, and therefore, the average positive biases of SUVmax and SUVmean are expected to be about 10 and 5 %, respectively. Based on this previous study, RImean would be less influenced by the SUV bias. Nonetheless, there is a limitation in the use of RImean, especially for determining the VOI of PET. Because SUVmean is strongly dependent on the region of interest [44], further studies are warranted to determine the VOI of PET from enhanced MRI of recently introduced PET-MRI [45].

We performed the dual phase PET/CT scan at 60 and 120 min after FDG injection. The dual phase PET/CT scan appears to improve the diagnostic value of PET/CT in breast

cancer [22, 46]. Previous studies using dual phase PET/CT scans were also performed at 60 and 120 min after FDG injection [47–49], the delayed time of 120 min after FDG injection was decided as the scan time of the second PET in the present study. Boerner et al. [50] reported that tumor contrast in breast cancer is stronger in images 3 h after FDG injection than 1.5 h. Another study of Hamberg et al. [51] indicated that the tumor concentration of FDG in lung cancer did not reach the peak point of uptake even 120 min after FDG injection, a finding probably related to the low glucose-6-phosphatase activity and increased cellular glucose uptake [52]. These studies suggested the delayed PET/CT scan at the time of more than 120 min after FDG injection could improve the diagnostic value more than the conventional protocol of the scan at the time of 60 min after FDG injection or 120 min. In this study,

Table 3 RImean to predict the biomarker status of the breast cancer

	Optimal criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
For prediction of ER (+)	<16.0 %	77.7	56.0	67.7	66.7	67.2
For prediction of HER-2 (+)	> 12.1 %	66.7	67.7	56.0	76.7	67.2

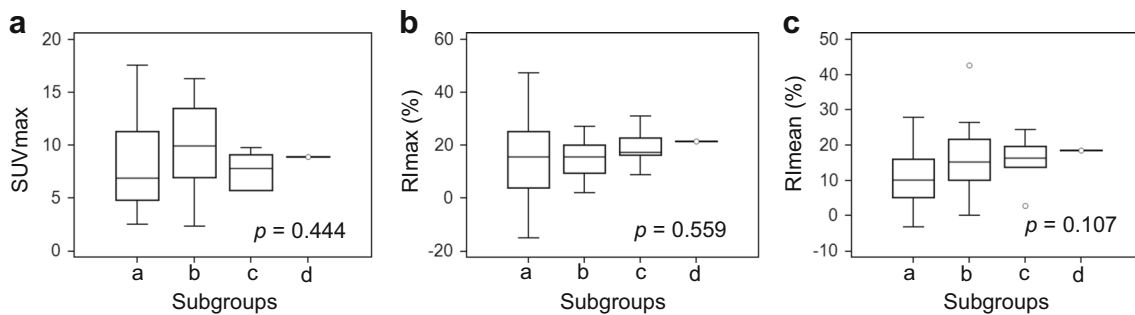*PPV* positive predictive value, *NPV* negative predictive value

a

b

c

we did not acquire the delayed PET/CT scan at the time of more than 120 min after FDG injection. Further studies are needed to evaluate the optimal scan time for dual phase PET/CT in breast cancer.

In this study, 2.0 was chosen as the cut-off SUV for analyzing the malignant tissue. By using this cut-off SUV, three of 59 patients were excluded because these patients had tumors showing a SUVmax < 2.0. Although a SUV of 2.5 has usually been considered as the threshold for distinguishing malignant from benign lesion [24, 53], it may not be applicable as the optimal threshold for diagnosing breast cancer [49] because phosphorylation of FDG in the breast cancer cells might be less complete, consequently it is expected that SUV of the breast cancer would be lower. In this study, five of the 59 patients had tumors showing SUVmax < 2.5. These five patients had relatively small-sized tumors or low-grade tumors. RImean using by cut-off SUV of 2.5 failed to show the correlation with the ER ($p = 0.052$), PR ($p = 0.214$), or HER-2 status ($p = 0.065$) in our study. On the contrary, breast tumors were not easily distinguished from surrounding breast tissue by using a cut-off SUV of 1.5. Therefore, adopted 2.0 was determined as the optimal cut-off SUV in the current study.

Biological subtypes of breast cancer determined by ER, PR, HER-2, and Ki-67 are the most common prognostic and therapeutic markers [54], and are widely used for disease stratification. These subtypes are relevant to the expression of genes to specify the tumor characteristics [55–58], and strongly supported by The 12th St Gallen International Breast Cancer Conference (2011) as the definition of therapy indication, as the subtypes incorporate many of the risk and predictive factors of breast cancer [59]. In our study, SUVmax, RImax, or RImean did not show correlation with the biological subtypes of breast cancer. The small population of the present study seemed to be not enough to show a significant difference among the subtypes. Further large-scale study may be warranted.

The present study has several limitations. First, a small number of patients were included. Second, Ki-67, which is considered to be the marker of proliferation, was not available. Finally,

because of the short follow-up duration, the relationship between the PET parameters and prognosis was not evaluated.

Conclusions

Retention index of SUVmean can reflect the ER and HER-2 status of breast cancers. Higher retention index of SUVmean might associate with lower ER expression and higher HER-2 expression.

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