The Role of Interim ^{18}F-FDG PET/CT in Predicting Early Response to Neoadjuvant Chemotherapy in Breast Cancer

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Abstract. *Aim: The aim of this study was to prove the diagnostic value of interim ^{18}F-Fluorodeoxyglucose-positron-emission tomography combined with computed tomography (PET/CT) scan for predicting pathological complete response (pCR) compared to other factors in neoadjuvant chemotheraphy. Patients and Methods: Twenty-seven patients with breast cancer were included in this retrospective study. They all underwent scheduled neoadjuvant chemotherapy. Patients underwent PET/CT at baseline, mid-point (interim), and preoperatively (after completion of chemotherapy). The metabolic response was calculated as follows: ΔStandardized uptake value (SUV)(%)=(1st SUV_{max}–2nd SUV_{max})/1st SUV_{max}×100. Results: The change in SUV_{max} between baseline and interim PET/CT scans was significantly larger than between interim and preoperative PET/CT scan. An optimal cut-off ΔSUV value of 78.3% was proposed for discriminating patients with pCR from those without pCR. Metabolic CR, defined as a change of SUV_{max} greater than the cut-off value, can predict pCR according to univariate analysis (p=0.012; Relative risk (RR)=25.3). Furthermore, metabolic CR was the most powerful factor for predicting pCR than other possible factors according to multivariate analysis (p=0.003). Conclusion: It is possible to use interim ^{18}F-FDG PET-CT as an effective method to predict early response in patients with breast cancer treated with neoadjuvant chemotherapy.*

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Neoadjuvant chemotherapy has been regarded as an effective way to treat patients with locally advanced breast cancer to reduce tumor volume and enhance the opportunity for breast-conserving surgery (1, 2). Pathological complete response (pCR) to neoadjuvant chemotherapy has been proven to be a significant prognostic factor for disease-free and overall survival (3-5). That is to say, pCR following neoadjuvant chemotherapy improves the prognosis of patients with breast cancer. Previous studies have shown that 13%-26% of patients show pCR after completion of neoadjuvant chemotherapy (1, 6). The Nottingham histological grading system is the most widely used method to predict prognosis of those patients (7-9). Therefore, it is thought that early prediction of pathological response in neoadjuvant chemotherapy may provide an early opportunity to change the treatment plan in case of ineffectiveness. It is also possible to avoid unnecessary side-effects from ineffective chemotherapy, such as nausea, alopecia, hematological toxicity, cardiotoxicity, or neurotoxicity (10).

Positron-emission tomography combined with computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (FDG) is widely used in patients with malignant cancer. It can be used in detection of the malignant lesion, finding the metastatic lesion, staging the tumor, and monitoring the response to therapeutic approaches. In addition, ^{18}F-FDG PET/CT has been playing a major role for the early prediction of response to neoadjuvant chemotherapy in many types of malignant cancers such as esophageal, rectal and lung cancer and some types of aggressive lymphomas (11-14).

Table I. *Study population*.

Patient no.	Age staging (years)	Initial	Histology	ER	PR	HER2 expression	Ki-67	Grade	Response	Chemotherapy regimen
1	38	IIIC	Ductal	Positive	Positive	Negative	Low	2	Non-pCR	ED
2	45	IIIA	Ductal	Negative	Negative	Negative	High	3	Non-pCR	ED
3	48	IIIA	Ductal	Negative	Negative	Negative	High	2	Non-pCR	ED
4	40	IIIA	Lobular	Positive	Positive	Negative	Low	2	Non-pCR	ED
5	67	IIIA	Ductal	Negative	Negative	Negative	Low	3	Non-pCR	AC-D
6	52	IIIA	Ductal	Negative	Negative	Positive	Low	2	pCR	AC-D
7	40	IIIA	Ductal	Negative	Negative	Negative	Low	1	Non-pCR	AC-D
8	53	IIIA	Ductal	Negative	Negative	Positive	Low	2	Non-pCR	ED
9	66	IIIA	Ductal	Negative	Negative	Negative	Low	3	Non-pCR	ED
10	68	IIIA	Ductal	Negative	Negative	Negative	High	3	Non-pCR	ED
11	54	IIA	Ductal	Negative	Negative	Negative	Low	2	Non-pCR	ED
12	45	IIIA	Ductal	Negative	Negative	Positive	High	2	pCR	ED
13	40	IIA	Ductal	Positive	Positive	Negative	Low	2	Non-pCR	ED
14	48	IIA	Ductal	Negative	Negative	Positive	High	3	Non-pCR	ED
15	57	IIIA	Ductal	Negative	Negative	Negative	Low	3	Non-pCR	ED
16	62	IIIA	Ductal	Negative	Negative	Positive	High	3	pCR	AC-D
17	54	IIA	Ductal	Negative	Negative	Negative	High	2	Non-pCR	AC-D
18	42	IIIA	Ductal	Negative	Negative	Negative	High	2	Non-pCR	AC-D
19	46	IIIA	Ductal	Negative	Negative	Negative	High	3	pCR	AC
20	50	IIIA	Ductal	Negative	Negative	Positive	Low	3	Non-pCR	ED
21	35	IIIA	Ductal	Negative	Negative	Negative	High	3	Non-pCR	ED
22	55	IIIC	Ductal	Negative	Negative	Positive	Low	2	Non-pCR	ED
23	39	IIIA	Ductal	Positive	Positive	Positive	High	3	Non-pCR	ED
24	51	IIIA	Ductal	Positive	Positive	Positive	Low	2	Non-pCR	ED
25	47	IIIA	Ductal	Positive	Positive	Negative	High	3	Non-pCR	ED
26	47	IIIA	Ductal	Negative	Negative	Negative	Low	2	Non-pCR	ED
27	54	IIIA	Ductal	Positive	Positive	Negative	High	3	pCR	ED

ER: Estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor-2. ED: Epirubicin, docetaxel; AC-D: doxorubicin, cyclophosphamide, docetaxel; AC: doxorubicin, cyclophosphamide. pCR: pathological complete response. Low expression of Ki-67 was defined as ≤20%.

^{18}F-FDG PET/CT is regarded as one of the essential imaging modalities for evaluation of breast cancer in patients (15, 16). Several studies have reported a correlation between early changes in 18F-FDG uptake after one or two cycles of neoadjuvant chemotherapy with the pathological response in patients with breast cancer (10, 17-18).

The aim of this study was i) to assess the feasibility of interim ^{18}F-FDG PET/CT scan for early response evaluation, ii) to propose an optimal cut-off value of ΔSUV(%) for predicting pCR, and iii) to justify the effectiveness of an optimal cut-off value for predicting pCR compared to other possible factors.

Patients and Methods

Patients. Twenty-seven patients [mean (±SD) age=50±9 years] with newly diagnosed, non-inflammatory, large or locally advanced breast cancer, were included in this study, retrospectively (four patients with stage IIA, 21 patients with stage IIIA and two patients with IIIC). The study population and the characteristics of the 27 patients are shown in Tables I and II. Initial core needle biopsy was performed in all patients. One patient had invasive lobular carcinoma and the others had invasive ductal carcinoma subtype. They then underwent 4, 6 or 8 cycles of neoadjuvant chemotherapy. PET/CT scan was taken at baseline (before initiating neoadjuvant chemotherapy), and after the 2nd, 3rd or 4th cycle of chemotherapy (interim). Additionally, among the 27 patients, 19 patients also underwent preoperative PET/CT scan after completion of neoadjuvant chemotherapy. Breast surgery was performed for all patients and final pathological reports were also presented. This study was approved by the Hospital Institutional Review Board (AN 13022-002).

Neoadjuvant chemotherapy. Three different regimens were used for chemotherapy in this patient series. Twenty patients (74%) received six cycles of docetaxel/epirubicin (75/75 mg/m^2 of body surface area). Six patients (22%) received an initial four cycles of doxorubicin/cyclophosphamide (60/600 mg/ m^2 of body surface area) and followed by four cycles of docetaxel (75 mg/m^2 of body surface area). One patient (4%) received four cycles of doxorubicin/cyclophsphamide (60/600 mg/m^2 of body surface area). Chemotherapy was repeated every three weeks.

Table II. *Overall characteristics of patients*.

Characteristic	No. of patients (n=27) (%)
Tumor classification	
T1	3 (11)
T2	18 (67)
T3	6 (22)
T4	0
Lymph node classification	
N0	4 (15)
N1	0
N2	21 (78)
N3	2 (7)
AJCC clinical stage	
IIA	4 (15)
IIB	0
IIIA	21 (78)
IIIB	0
IIIC	2 (7)
Tumor type	
Invasive ductal, no special type	26 (96)
Metaplastic	0
Lobular	1 (4)
Grade	
1	1 (4)
2	13 (48)
3	13 (48)
Hormonal status	
Luminal A	5 (19)
Luminal B	2 (7)
HER2	7 (26)
Triple-negative	13 (48)
Ki-67 expression	
High	13 (48)
Low	14 (52)
Chemotherapy	
ED	20 (74)
AC-D	6 (22)
AC	1 (4)
Pathologic response	
pCR	5 (19)
Non-pCR	22 (81)

AJCC: American Joint Committee on Cancer; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; ED: epirubicin, docetaxel; AC-D: doxorubicin, cyclophosphamide, docetaxel; AC: doxorubicin, cyclophosphamide. pCR: pathological complete response. Low expression of Ki-67 was defined as ≤20%.

Response to chemotherapy. All specimens were confirmed by histopathological analysis after breast surgery. Pathological response was classified into two groups: pCR and non-pCR. pCR was defined as no invasive and no in situ residuals in breast and regional lymph nodes. Pathological grades were assessed as grade 1 to 3 according to the Nottingham histological grade (11-13). In addition, biological subgroups were defined as using hormonal receptor and Ki-67 status (luminal A type: Estrogen receptor positive (ER^+)/Human epidermal growth factor receptor 2-negative ($HER2^-$) and Ki-67 expression <20%; luminal B type: ER^+HER2^- and Ki-67 expression ≥20%, HER2 type: ER^-PR^- and $HER2^+$; triple-negative type: ER^-PR^- and $HER2^-$).

PET/CT imaging. Images were obtained with PET-CT scanner (Gemini TF, Philips Medical Systems, Cleveland, OH, USA). All patients fasted for at least six hours and serum glucose level was less than 180 mg/dl before scanning. Forty-five to sixty minutes after intravenous injection of 370 to 480 MBq (10 to13 mCi) ^{18}F-FDG, CT scans were obtained followed by PET emission scans for one minute per bed. The PET unit had an axial field of view of 18 cm and a spatial resolution of 4.4 mm. A low-dose CT scan was obtained for attenuation correction and for localization, with a 16-slice multidetector helical CT unit, using the following parameters: 120 kVp; 50 mA; 0.75-s rotation time; 0.75-mm slice collimation; 4-mm scan reconstruction, with a reconstruction index of 4 mm; 60-cm field of view; and 512×512 matrix. PET data were reconstructed iteratively using a 3-dimensional row action maximum likelihood algorithmwith low-dose CT datasets for attenuation correction. Maximum intensity projection and cross sectional views and fusion images were generated and reviewed.

PET/CT image analysis. Two experienced nuclear physicians evaluated the PET/CT images. Malignant breast lesions were classified as positive if there was focally increased ^{18}F-FDG uptake, compared with the uptake in surrounding normal soft-tissue. A region of interest (ROI) was targeted on each malignant breast lesion by manual adjustment. The maximum standardized uptake value (SUV) was calculated as follows:

SUV=Mean activity (ROI) (MBq/ml)/injected dose (MBq)/total body weight (g)

From these SUVs from targeted ROIs, the maximum standardized uptake values (SUV_{max}) were acquired for analysis. The metabolic response after the interim PET/CT was calculated as follows:

$\Delta SUV(\%) = (baseline\ SUV_{max} - interim\ SUV_{max}) / baseline\ SUV_{max} \times 100\ (\%)$

Statistical analysis. The Mann-Whitney *U*-test, receiver-operating characteristic (ROC), logistic regression analysis, and multivariate regression anlysis were used as statistical methods. A value of $p<0.05$ was defined as being statisticaIly significant. SPSS 17.0 (SPSS inc, Chicago, IL, USA) and Medcalc software (Medcalc Software, Mariakerke, Belgium) were used for data analysis.

Results

A total of 27 lesions were identified on baseline PET/CT scan in 27 patients. SUV_{max} of the lesion in baseline and interim PET/CT scan was 8.6±3.8 (mean±SD) and 2.7±1.9, respectively ($p<0.001$) (Figure 1). ΔSUV(%) was 66.9±14.9%.

Interim and preoperative PET/CT scans. In the 19 patients that underwent baseline, interim, and preoperative PET/CT scans, SUV_{max} of the lesion in baseline, interim, and preoperative PET/CT scan was 8.7±4.1, 2.6±2.0, and 1.9±1.2 respectively. The SUV_{max} of the baseline was significantly higher than interim and preoperative PET/CT scan ($p<0.001$). There was no significant statistical difference between the SUV_{max} of the interim and preoperative PET/CT scan ($p=0.07$) (Figure 2a).

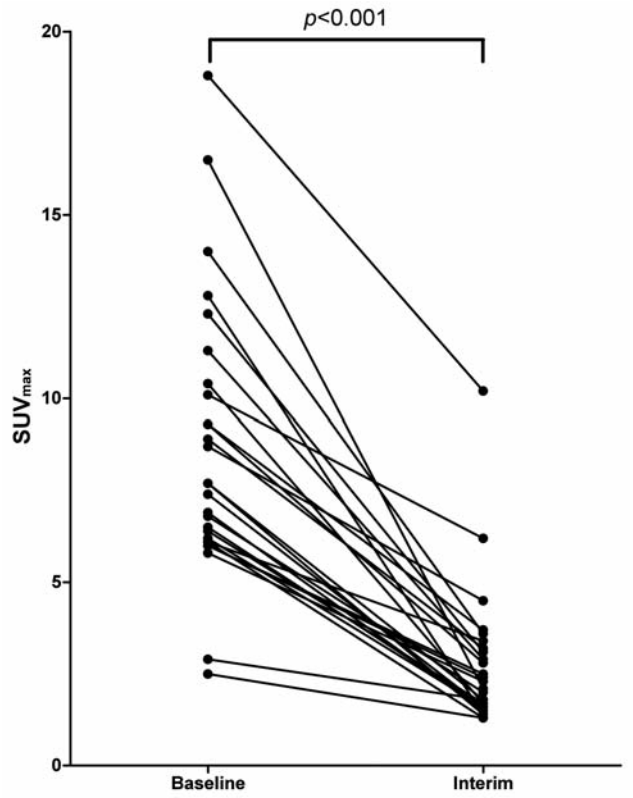

Figure 1. *Comparison of glucose metabolism between baseline and interim group in a total of 27 patients.*

ΔSUV(%) between baseline and interim and between interim and preoperative PET/CT scan was 67.8±15.0% and 22.6±14.4%, respectively (p<0.001) (Figure 2b).

pCR group vs. non-pCR group. Among the 27 patients, five were confirmed as having pCR, but 22 patients had residual invasive cancer (non-pCR). SUV_{max} of pCR and non-pCR groups in the baseline PET/CT scan were 8.9±5.1 and 8.6±3.5, respectively (p=0.74) (Figure 3a). SUV_{max} of pCR and non-pCR groups in the interim PET/CT scan were 1.6±0.3 and 3.0±2.0, respectively (p=0.03) (Figure 3b). ΔSUV(%) between baseline and interim PET/CT scan of pCR and non-pCR groups were 75.8±15.9% and 64.9±14.3%, respectively (p=0.04) (Figure 3c).

Determination of ΔSUV cut-off value to discriminate the pCR group from non-pCR group. ROC analyses were performed to determine the optimal cut-off value of ΔSUV(%) to differentiate pCR from non-pCR patients. The ROC curve is presented in Figure 4. A cut-off ΔSUV(%) of 78.3% was found to identify those patients with pCR. The area under the ROC curve (AUC) was 0.8 [standard error=0.1; 95% confidence interval (CI)=0.6-0.9]. The sensitivity and specificity were 80.0% and 90.9%, respectively

Metabolic CR and pCR. We defined metabolic CR (complete response) as a change of SUV_{max} greater than the cut-off value. Univariate analysis was performed on the pCR-related factors. As shown in Table III, metabolic CR significantly predicted the pCR through univariate analysis (p=0.012; relative risk (*RR*)=25.3; 95% CI=2.1-310.8). Furthermore, according to multivariate analysis, metabolic CR showed superior predictability of the pCR to other known parameters such as HER2 type and Ki-67 status (p=0.003 vs. p=0.171 and 0.131, respectively).

Possible variables and metabolic CR. Possible variables that may have an effect on the metabolic CR were assessed by univariate analysis through separate logistic regression analysis. The variables included age, clinical stage, tumor grade, receptor status of ER, PR, HER2, Ki-67 expression status, and biological subgroups mentioned above. According to the logistic regression analysis, luminal B type group had a significant possibility of presenting metabolic CR (p=0.049; *RR*=5.427; 95% CI=1.007-29.255) (Table IV). As shown in Table IV, those in the triple-negative type group might also have a possibility of presenting metabolic CR. The p-value was of marginal significance (p=0.061; *RR*=0.111; 95% CI=0.011-1.106).

Discussion

Systemic neoadjuvant chemotherapy is increasingly being used nowadays and has been proven useful in patients with locally advanced breast cancer (19, 20). The main purpose of the study was to evaluate early changes caused by neoadjuvant chemotherapy in malignant tumor FDG uptake that have highly predictive value for the pathological response in patients with breast cancer.

Therefore, firstly, we assessed the feasibility of interim PET/CT scan for early response evaluation. Secondly, we attempted to propose an optimal cut-off value for predicting pCR. Thirdly, we tried to justify the effectiveness of the optimal cut-off value for predicting pCR compared to other possible factors.

As shown in Figure 2, the change in the SUV_{max} was greater between baseline and interim PET/CT than between interim and preoperative PET/CT scan (p<0.001). There was no significant statistical difference between the SUV_{max} of the interim and preoperative PET/CT scan (p=0.07). From these observations, we could expect that the therapeutic effect of neoadjuvant chemotherapy was early with interim PET/CT and the metabolic change was maintained until preoperative PET/CT scans. Therefore, if the chemotherapy regimen was not effective, it is possible to give an early insight using interim PET/CT to enable the treatment plan to be modified and to avoid adverse side-effects. It is feasible to

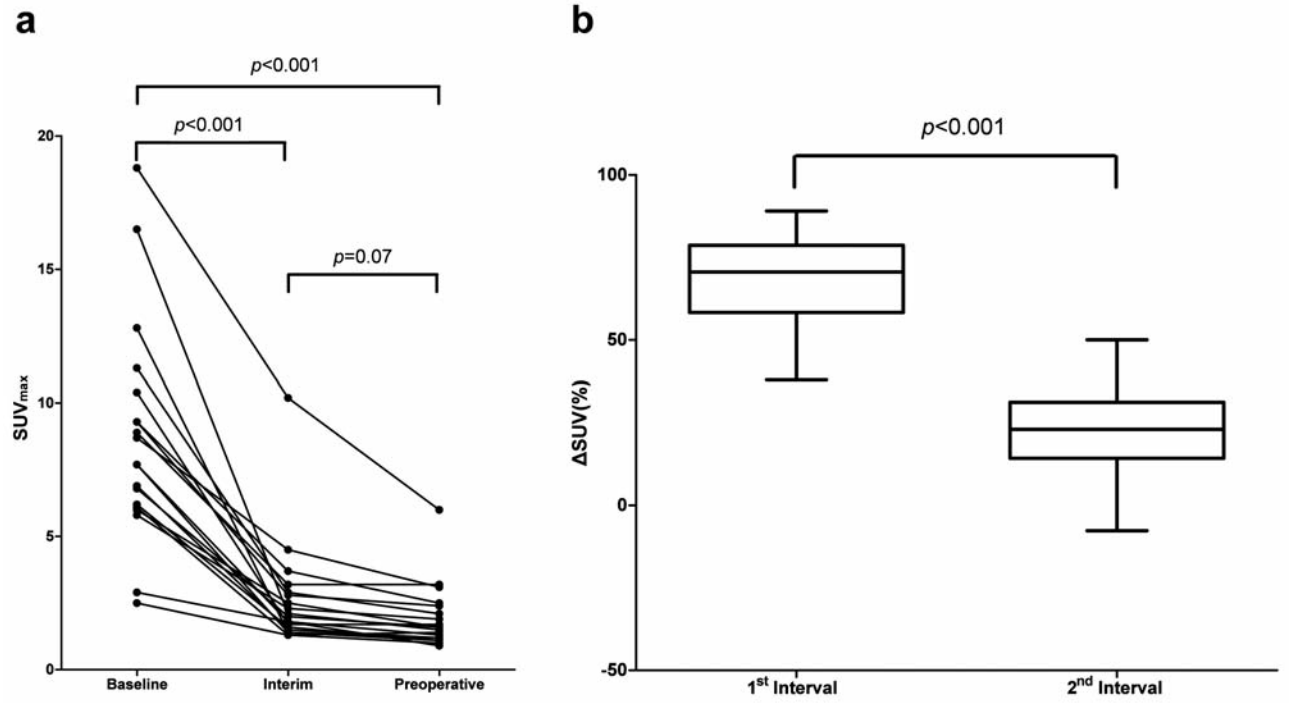

Figure 2. *a: Comparison of glucose metabolism between three positron-emission tomography combined with computed tomography (PET/CT) scans in 19 patients (baseline, interim, and preoperative PET/CT scan), b: Comparison of changes in glucose metabolism between three PET/CT scans in 19 patients. 1st Interval: between baseline and interim, 2nd interval: between interim and preoperative PET/CT scan.*

use interim PET/CT scan for early assessment of response to neoadjuvant chemotherapy.

This retrospective study demonstrated that patients with pCR can be distinguished by interim ^{18}F-FDG PET/CT during the interim neoadjuvant chemotherapy. The pCR and non-pCR goups had similar mean SUV_{max} in baseline PET/CT scan. However, the pCR group presented significantly lower mean SUV_{max} than the non-pCR group on the interim PET/CT scan (p=0.03). Furthermore, the pCR group had a significantly larger change in SUV_{max} than did the non-pCR group (p=0.04). An optimal cut-off ΔSUV value of 78.3% was proposed for discriminating pCR patients (change of SUV_{max} greater than cut-off value) from non-pCR patients in ROC analysis.

Similar to our results, several studies have suggested a cut-off value of ΔSUV in neoadjuvant chemotherapy for discriminating pCR from non-pCR patients, acquiring values ranging from 40 to 88% (17, 18, 21-23). Thus, differentiation of the pCR from non-pCR group using interim PET/CT scan may be possible. However, the wide range of cut-off values limits application in clinical practice. Several factors can contribute to the wide range of cut-off values (24). Firstly, the timing of PET/CT evaluation is very variable. Many groups performed PET/CT after one or two cycles of neoadjuvant chemotherapy (21, 22). McDermott *et al*. took PET/CT at midpoint and end of neoadjuvant chemotherapy (23). Secondly, breast carcinomas consist of different subtypes depending on hormonal receptors, such as ER^+ tumors, HER2 overexpression, and triple-negative tumors. Thus, heterogenous characteristics of tumor biology can cause differences in response to neoadjuvant chemotherapy.

Using a cut-off ΔSUV(%) of 78.3%, patients were classified according to metabolic CR (change of SUV_{max} greater than the cut-off value). According to univariate analysis, metabolic CR significantly predicted the pCR. As shown in Table III, in predicting pCR, relative risks of Ki-67 status and HER2 type were quite high but the p-values were not significant. These factors are well-known for predicting pCR on receiving neoadjuvant treatment (25-28). Considering these factors, the present study demonstrated that metabolic CR was a strong or predictor for pCR than other variables.

Regarding metabolic CR, as shown in Table IV, luminal B type was significantly associated with metabolic CR than in patients non-luminal B type. Luminal B type had been known to be more responsive to chemotherapy than luminal A type (28). Luminal B type was also regarded as more

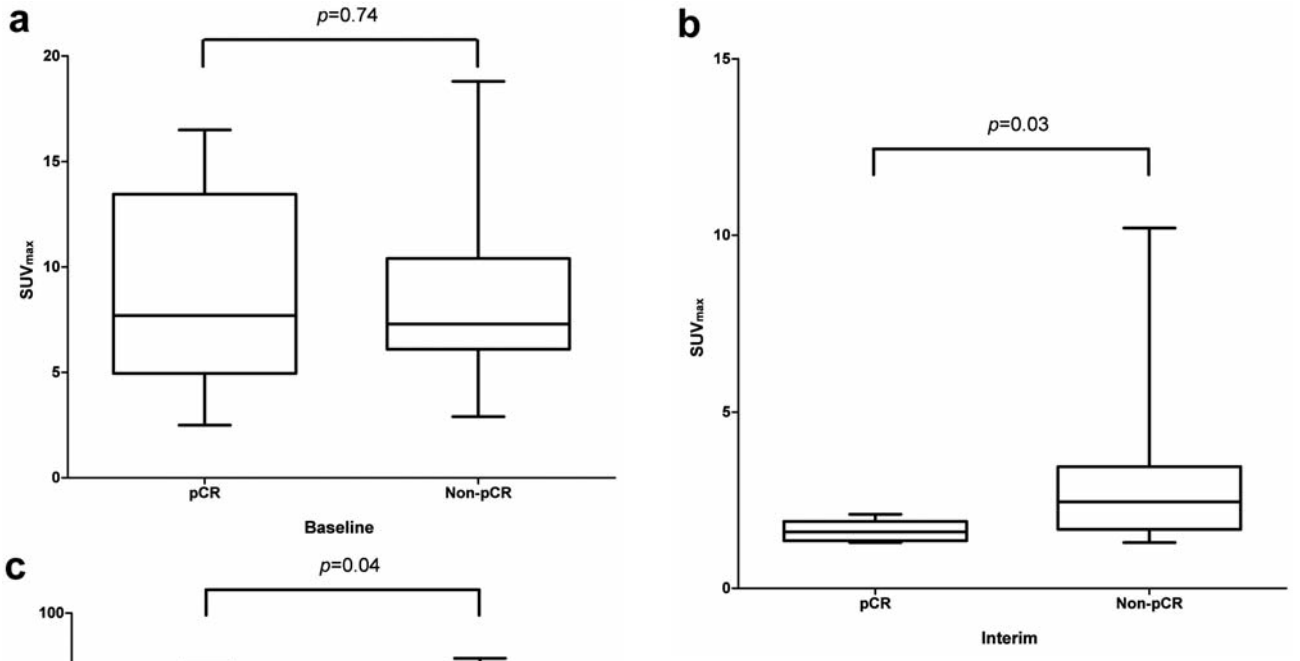

Figure 3. *a: Comparison of glucose metabolism between pathologic complete response (pCR) and non-pCR groups in baseline positron-emission tomography combined with computed tomography (PET/CT) scan, b: Comparison of glucose metabolism between pCR and non-pCR groups in interim PET/CT scan. c: Comparison of changes in glucose metabolism (ΔSUV) between pCR and non-pCR groups.*

proliferative than luminal A type (29). Therefore, these factors might explain the association of metabolic CR and luminal B type.

Another impressive finding was the triple-negative type group might also have a greater possibility of achieving metabolic CR (p=0.061) than the non triple-negative type. Patients with triple-negative breast cancer are known to have better responsiveness to neoadjuvant chemotherapy than those with ER^+ tumor (30). In other words, metabolic CR could be interpreted as a good response to neoadjuvant chemotherapy.

Although a limitation of this study is the small number of patients, it clearly identifies the feasibility of interim PET/CT scan for early response evaluation and presents an optimal cut-off ΔSUV value to predict pCR. Metabolic CR is proven to be a powerful predictor of pCR.

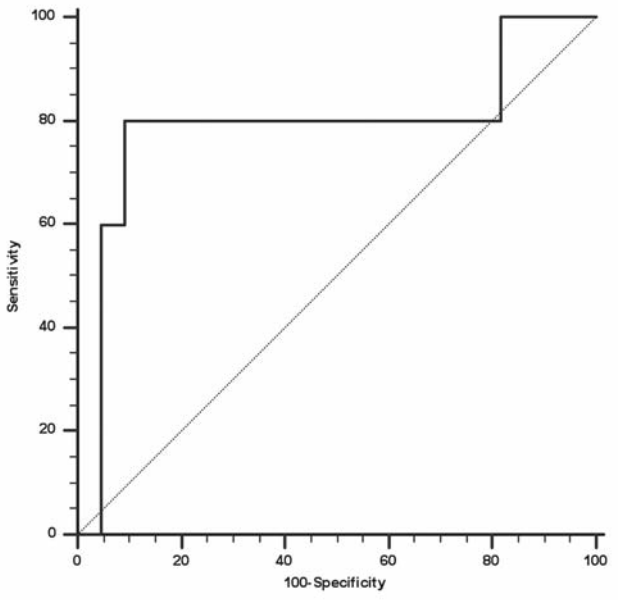

Figure 4. *Receiver-operating characteristic (ROC) analysis to differentiate patients with pCR from those without pCR. Cut-off Δstandardized uptake value (SUV) (%): 78.3%, area under the curve: 0.8, Standard error=0.1, 95%, confidence interval=0.6-0.9, sensitivity=80.0%, specificity=90.9%.*

Table III. *Uni- and multivariate analysis of factors for pathological complete response (pCR)*

Variable	Univariate analysis			Multivariate
	RR	95% CI	*p*-Value	*p*-Value
Age (continuous)	1.032	0.926-1.150	0.565	
Clinical stage (II *vs*. III)	1.535	0.181-12.997	0.694	
Tumor grade (1 and 2 *vs*. 3)	1.126	0.194-6.354	0.895	
Hormonal receptor type (ER+ and PR+ *vs*. The others)	0.667	0.061-7.230	0.739	
HER2 type (HER2 type *vs*. Non-HER2 type)	5.1	0.658-39.548	0.119	0.171
Ki-67 status (High *vs*. Low)	5.778	0.551-60.605	0.144	0.131
Luminal A type (Luminal A type *vs*. Non-luminal A type)	1.125	0.098-12.965	0.925	
Luminal B type (Luminal B type *vs*. Non-luminal B type)	1.551	0.359-6.705	0.557	
Triple-negative type (Triple negative type *vs*. Non-triple negative type)	0.208	0.020-2.177	0.208	
Metabolic CR (Metabolic CR *vs*. Non-metabolic CR)	25.333	2.065-310.757	0.012*	0.003*

RR: Relative risk, CI: confidence interval. *$p<0.05$ is considered significant. Hormonal receptor type=Estrogen receptor positive (ER^+) and progesterone receptor positive (PR^+) type. Luminal A type: ER+/HER2- and Ki-67 expression <20%, Luminal B type: $ER^+/HER2^-$ and Ki-67 expression ≥20%, HER2 type: ER^-/PR^- and $HER2^+$, Triple-negative type: ER^-/PR^- and $HER2^-$. Metabolic complete response (CR): A change of maximum standardized uptake value (SUV_{max}) superior to cut-off value.

Table IV. *Univariate analysis of factors for metabolic complete response (CR).*

Variable	Univariate analysis		
	RR	95% CI	*p*-Value
Age (continuous)	0.514	0.871-1.072	0.514
Clinical stage (II *vs*. III)	4.915	0.475-50.822	0.182
Tumor grade (1 and 2 *vs*. 3)	0.35	0.065-1.901	0.224
Hormonal receptor type (ER^+ and PR^+ *vs*. The others)	3	0.469-19.177	0.246
HER2 type (HER2 type *vs*. Non-HER2 type)	2.25	0.369-13.707	0.379
Ki-67 status (High *vs*. Low)	1.63	0.297-9.256	0.582
Luminal A type (Luminal A type *vs*. Non-luminal A type)	1.5	0.115-19.640	0.757
Luminal B type (Luminal B type *vs*. Non-luminal B type)	5.427	1.007-29.255	0.049*
Triple-negative type (Triple negative type *vs*. Non-triple negative type)	0.111	0.011-1.106	0.061

RR: Relative risk, CI: confidence interval. *$p<0.05$ is considered significant. Hormonal receptor type=Estrogen receptor positive (ER^+) and progesterone receptor positive (PR^+) type. Luminal A type: $ER^+/HER2^-$ and Ki-67 expression <20%, Luminal B type: $ER^+/HER2^-$ and Ki-67 expression ≥20%, HER2 type: ER^-/PR^- and $HER2^+$, Triple-negative type: ER^-/PR^- and $HER2^-$.

Conclusion

In patients with breast cancer treated with neoadjuvant chemotherapy, the change in ^{18}F-FDG uptake at midpoint (interim) of chemotherapy provides valuable information of therapeutic response in early time. An optimal cut-off ΔSUV value of 78.3% was proposed for discriminating patients with pCR from those non-pCR. Using this cut-off value, metabolic CR in interim PET-CT showed better predictability for pCR than other possible factors. It is possible to use interim ^{18}F-FDG PET/CT as a valuable method for predicting early response of neoadjuvant chemotherapy. This may be helpful for establishing individual treatment strategies for patients with breast cancer.

Conflicts of Interest

The Authors have no conflicts of interests.

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