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The Prognostic Impact of Early Change in Standardized Uptake Value of ^{18}F-fluorodeoxy-glucose Positron Emission Tomography after Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer Patients

[*]Hak Woo Lee[1], [*]Hak Min Lee[2], Sung-eun Choi[3], Hanna Yoo[4], Sung Gwe Ahn[1], Min Kyung Lee[5], Joon Jeong[1], Woo-Hee Jung[3]

[*]Hak Woo Lee and Hak Min Lee equally contributed to this work.

1. Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
2. Department of Surgery, MizMedi Women's Hospital, Seoul, Republic of Korea
3. Department of Pathology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
4. Biostatistics Collaboration Lab, Yonsei University College of Medicine, Seoul, Republic of Korea
5. Department of Nuclear Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

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Corresponding author: Prof. Joon Jeong, M.D., Ph.D., Department of Surgery, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul, 135-720, Korea, Tel: 82-2-2019-3379; Fax: 82-2-3462-5994, e-mail: gsjjoon@yuhs.ac

First author: Dr. Hak Woo Lee, Clinical fellow, Department of Surgery, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul , 135-720, Korea, Tel: 82-2-2019-3370; Fax: 82-2-3462-5994, e-mail: lhw82@yuhs.ac; Dr. Hak Min Lee, Department of Surgery, MizMedi Women's Hospital, 295 Gangseo-ro, Gangseo-gu, Seoul, 07693, Korea, Tel: 82-2-2007-1000, Fax: 82-2-3462-5994, e-mail: harumy79@daum.net

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ABSTRACT

Standardized uptake value (SUV), which is an indicator of the degree of glucose uptake in ^{18}F-fluorodeoxy-glucose positron emission tomography (^{18}FDG-PET), can be applied as a prognostic factor in various malignant tumors. We investigated the prognostic impact of early changes in ^{18}FDG-PET uptake in patients with locally advanced breast cancer who received neoadjuvant chemotherapy (NAC).

Methods: We retrospectively identified 87 patients who were treated with NAC followed by surgery for locally advanced breast cancer. All patients underwent ^{18}FDG-PET at baseline and after three cycles of NAC and the maximum SUV (SUV_{max}) of primary tumor mass were assessed in each scan. Pathologic slides were retrospectively reviewed and residual cancer burden (RCB) index was calculated to estimate pathologic response. RCB-0 is referred to no residual disease (RD) and patients with RD is categorized into three classes: RCB-I (minimal RD), RCB-II (moderate RD), and RCB-III (extensive RD).

Results: There was a negative correlation between reduction rate of SUV_{max} (ΔSUV_{max}) and RCB index (correlation coefficient = -0.408; p<0.001). In multivariate analyses, ΔSUV_{max} were significant independent prognostic factor for recurrence-free survival (RFS) and overall survival (OS), and corresponding adjusted hazard ratios were 0.31 (95% CI: 0.12-0.77, p=0.011) and 0.20 (95% CI: 0.26-0.71, p=0.013), respectively. When patients were classified into four groups according to pathologic response (RCB index $\leq$1 vs. $\geq$2) and metabolic response (ΔSUV_{max} $\leq$66.4% vs. >66.4%), metabolic responders presented significantly better RFS and OS than metabolic non-responders within poor pathologic response patients. In contrast, within metabolic responders, there was no survival difference according to pathologic response.

Conclusions: The early change in SUV_{max} of ^{18}FDG-PET after 3rd cycle NAC is an independent and good prognostic marker beyond pathologic response in locally advanced breast cancer patients. We suggest that

ΔSUV_{max} could be considered in predicting post-treatment outcome as well as assessing tumor response for patients receiving NAC.

Keywords: breast cancer, ^{18}FDG-PET, standardized uptake value, neoadjuvant chemotherapy

NAC has been widely accepted as a standard treatment for patients with locally advanced breast cancer as it can improve the surgical options and provide equivalent survival outcomes compared to conventional adjuvant chemotherapy [*1-3*]. Moreover, NAC permits the assessment of sensitivity to chemotherapy that can be helpful to modify subsequent treatment for individual patients according to the response [*4*].

Pathologic complete response (pCR) has been used as a surrogate marker for treatment outcome in some subtypes of breast cancer because patients with pCR showed better survival outcomes than those of women without pCR in these subtypes [*5-8*]. Breast cancer, however, is a heterogeneous disease with different biological characteristics, and pathologic response of NAC is not always matched by prognosis. A recent meta-analysis showed that in subgroups having slowly proliferating tumors, such as luminal type, pCR was not associated with prognosis [*7,8*]. Among the tools evaluating pathologic response, residual cancer burden (RCB) index has been adopted to estimate pathologic response of NAC with an advanced scoring system from dichotomization as pCR or residual disease only [*9*]. It can inform stronger prognostic information which is derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden.

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) is a molecular imaging modality which reflects the biologic characteristics of tumor and can predict tumor behavior and prognosis [*10-12*]. In addition, it has been shown to be a sensitive technique to assess response to therapy and previous studies demonstrated that early changes in ^{18}F-FDG uptake of tumors after one or two courses of NAC can predict pathologic response [*13-16*]. The aim of the present study was to investigate the prognostic impact of early changes in ^{18}F-FDG uptake in breast cancer patients who received NAC, especially compared to the RCB index.

MATERIALS AND METHODS

Patients

Between January 2004 and December 2011, 196 women with clinical stage II or III primary breast cancer received NAC. Of these, 87 patients who underwent ^{18}F-FDG-PET-CT examination before starting NAC and after 3rd cycle of chemotherapy were identified. Patients with distant metastasis or bilateral breast cancer were excluded. This study was approved by the institutional review board of Gangnam Severance Hospital, Yonsei University, Seoul, Republic of Korea in accordance with good clinical practice guidelines and the Declaration of Helsinki and the requirement to obtain informed consent was waived.

The clinical data of each patient was reviewed, and pathological findings were recorded. The modified Scarf-Bloom-Richardson grading system was used for tumor grading. The expression of the estrogen receptor (ER), progesterone receptor, human epidermal growth factor receptor 2 (HER2) and Ki67 were evaluated with formalin-fixed, paraffin-embedded tissue obtained from core biopsy or surgery. IHC staining was performed with appropriate antibodies for ER (6F11: Novocastra, Newcastle upon Tyne, UK), progesterone receptor (16: Novocastra, Newcastle upon Tyne, UK), HER2 (4B5: Ventana Medical Systems, Tucson, AZ, USA), and Ki-67 (MIB-1: Dako, Glostrup, Denmark). ER and progesterone receptor were determined by nuclear staining, which was graded from 0 to 8 using Allred score [*17*]. The results were categorized as positive when the total score, expressed as the sum of the proportion score and intensity score, was 3 or greater. For HER2 evaluation, membranous staining was graded as 0, 1, 2, or 3 [*18*]. Tumor with a score of 3 was considered positive, and equivocal results (in case of score 2) were further tested by fluorescent in situ hybridization to confirm HER2 amplification with the PathVysion HER2 DNA probe Kit (Abbott-Vysis, Des Plaines, IL, USA). Patients were classified as four intrinsic subtypes with use of Ki-67 cut-off of 14%, according to criteria recommended by the St. Gallen panelists [*19*].

Neoadjuvant chemotherapy

All patients in the present study received anthracycline-based NAC except two patients who were treated with CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2 every 4 weeks). Sixty eight women received doxorubicin 50 mg/m^2 and docetaxel 75mg/m^2 every 3 weeks, 19 received cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2, and 5-fluorouracil 600 mg/m^2 every 4 weeks, and 2 received doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks. After completion of NAC, all patients underwent breast-conserving surgery or mastectomy with axillary lymph node dissection. All patients were then treated with anti-HER2 therapy, endocrine therapy, or radiotherapy according to the standard guidelines.

^{18}F-FDG-PET or PET/CT method

All patients fasted for at least 6 hours and had blood glucose levels less than 140 mg/dL before intravenous administration of ^{18}F-FDG (5.5 MBq/kg of body weight). At 60 minutes after intravenous administration of ^{18}F-FDG, whole-body emission scans were obtained using a Philips Allegro PET camera (Philips Medical Systems, Cleveland, Ohio, USA) or PET/CT scans were performed with a hybrid PET/CT scanner (Biograph 40 TruePoint or Biograph mCT 64, Siemens Healthcare Solutions USA, Inc., Knoxville, TN). Whole-body CT images were obtained first for attenuation correction using automatic dose modulation with a reference of 40 mA and 120 kV without contrast enhancement. Then PET data were acquired from the skull base to the proximal thigh for 3 minutes per bed position in a three-dimensional mode. PET images were reconstructed with the ordered subset expectation maximization algorithm. Before 2008, PET scans were performed and from 2008 to 2011 PET or PET/CT scans were performed. Each patient received same method of PET or PET/CT for both of baseline and after 3rd NAC. For semi-quantitative evaluation, the maximum standardized uptake value (SUV_{max}) was calculated by

measuring the absorption of ^{18}F-FDG by tumors in the region of interest as follows: SUV_{max} = [maximal radioactivity concentration in region of interest] / [injected dose / patient's weight (kg)]. The reduction rate of SUV_{max} (ΔSUV_{max}) after 3rd cycle of chemotherapy was calculated as ΔSUV_{max} (%) = 100×(baseline SUV_{max} - 3rd cycle SUV_{max}) / baseline SUV_{max}. All SUV_{max} were measured from primary tumor.

Pathology assessment

All of the H&E-stained slides from the surgical specimen were reviewed and pathologic responses were evaluated. The pCR was defined as no evidence of residual invasive cancer in breast and axillary lymph nodes. Residual ductal carcinoma in situ was also defined as pCR. RCB-index was determined as described by Symmans et al [*9*]. Briefly, RCB-index is derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden. RCB-0 is referred to no residual disease (RD) and patients with RD is categorized into three classes: RCB-I (minimal RD), RCB-II (moderate RD), and RCB-III (extensive RD).

Statistical analysis

We used the method of Contal and O'Quigley to obtain the cutpoint for ΔSUV_{max}. In this method, the optimal cutoff point is determined by an algorithm of maximization of hazard ratio [*20*]. RFS was measured from the date of the first curative surgery to the date of the first tumor recurrence, including loco-regional recurrence or distant metastasis or death. OS was measured from the date of the first curative surgery to the date of the last follow-up, or until death from any reasons during the follow-up period. The Kaplan-Meier method was utilized to estimate RFS or OS. Multivariate Cox regression hazard model was

used to examine risk factors which showed statistically significance in univariate analysis. The C-index which is a scale for a measure of discrimination for model validation was also examined.

All statistical analyses were performed using the SPSS program, 18.0 (SPSS Inc., Chicago, IL) and the R (http://www.r-project.org) software. A *P* value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

Patient's characteristics

The clinicopathologic characteristics of 87 patients are presented in Table 1. There were 17 patients with pCR and 6 patients with minimal RD (RCB-I). Median follow-up period was 61 months (10-107 months), during which 24 (27.6%) patients had recurrence and 15 (17.2%) patients died. All deaths were associated with breast cancer.

Relationship between ΔSUV_{max} and pathologic complete response

Mean ΔSUV_{max} of 87 patients was 69.1% (4.2-100%). Patients with pCR showed higher ΔSUV_{max} than those without pCR (Mean ΔSUV_{max} = 81.6 in patients with pCR versus 66.0 in those without pCR, p=0.016, data not shown). There was a negative correlation between ΔSUV_{max} and RCB-index (correlation coefficient r=-0.408; p<0.001). Mean ΔSUV_{max} in patients classified into RCB-index of 0, 1, 2, and 3 were 81.5% (±21.1), 76.0% (±15.8), 71.4% (±22.9), and 52.9% (±24.5), respectively (Fig. 1).

Prognostic impact of ΔSUV_{max}

In univariate analysis, an increased risk of recurrence was associated with advanced clinical N stage (p<0.001), subtype (p=0.003), and ΔSUV_{max} (p<0.001) (Table 2). In multivariate analysis, clinical N stage,

subtype, and ΔSUV_{max} were significant independent prognostic factors for RFS and c-index of this model was 0.82 (Table 3).

In univariate analysis for OS, clinical T stage (p=0.045), N stage (p=0.005), subtype (p=0.038), and ΔSUV_{max} (p=0.014) were significant (Table 2). Although the Kaplan-Meier OS estimation showed statistically difference according to RCB-index (p=0.034, data not shown), the prognostic value of RCB index was not retained in multivariate analysis because of statistical insignificance in univariate Cox analysis (p=0.120).In multivariate analysis, ΔSUV_{max} and clinical N stage was significant independent prognostic factor for OS (p=0.015 and 0.05, respectively) and c-index of this model was 0.87 (Table 3).

We selected 66.4% for the optimal cutoff value to maximize the difference among the RFS and OS of ΔSUV_{max} by using the method of Contal and O'Quigley. Subsequently, patients with ΔSUV_{max} greater than 66.4% in to metabolic responder and ΔSUV_{max} less than or equal to 66.4% were classified in to metabolic non-responder. There were 55 metabolic responders and 32 non-responders and they showed statistically significant difference in DFS and OS (Fig. 2). In our data, the least reduction rate of SUV_{max} to achieve pathologic response (RCB-0 or I) was 39.3%. When we use this value as a cutoff for ΔSUV_{max}, similar results were observed (data not shown). We further investigated whether there was any survival difference according to metabolic response among molecular subtype of breast cancer. There was a statistically significant difference of RFS and tendency of difference of OS between metabolic responders and non-responders defined by ΔSUV_{max} in luminal subtype of breast cancer (p=0.005 and 0.061, respectively, Supplementary Fig. 1) and only statistically significant difference of RFS in triple-negative and HER2 subtypes (p=0.042).

Comparison of the ΔSUV_{max} and RCB index

More importantly, we investigated whether there were any survival differences according to metabolic response (ΔSUV_{max} >66.4%=metabolic responder, ΔSUV_{max} ≤66.4%=metabolic non-responder) in patients with good pathologic response (RCB-index ≤1) or those with poor pathologic response (RCB-index ≥2). Patients were classified into 4 groups according to RCB-index and ΔSUV_{max}; (1) pathologic responder and metabolic responder, (2) pathologic responder and metabolic non-responder, (3) pathologic non-responder and metabolic responder, (4) pathologic non-responder and metabolic non-responder. Within the groups of pathologic non-responders, the Kaplan-Meier RFS and OS estimates differed significantly according to the ΔSUV_{max} (p=0.007 and p=0.017, respectively, Fig. 3). Conversely, within the groups of metabolic responders, RCB-index did not make difference either in RFS and OS (p=0.185 and 0.523, respectively). When we use pCR and non-pCR to discriminate pathologic response, similar results were observed (Supplementary Fig. 2).

DISCUSSION

A potential advantage of NAC is to monitor the degree of response. The previous randomized phase III study, in which patients were randomly assigned to those maintaining same regimen or to those prolonging or switching regimen according to the early response to NAC, showed that response-guided NAC might improve survival in patients with early breast cancer [*21*]. Thus, it is important to monitor early response in patients receiving NAC, and various imaging and pathologic measurements have been widely used to assess the response so far.

^{18}FDG-PET is an attractive method for assessing the response of NAC as it can reflect the biologic characteristics of tumor [*12*,*13*]. The clinical prospective studies showed that early change in ^{18}F-FDG uptake is a surrogate marker of survival in patients with triple-negative breast cancer and even in those with luminal HER2-negative breast cancer [*22*,*23*]. Results of the present study also support these findings

and we demonstrated that ΔSUV_{max} is significant independent predictive and prognostic factor. Moreover, it is noteworthy that ΔSUV_{max} provided additional prognostic information in patients with pathologic non-response (high RCB-index). While pathologic response in metabolic responders failed to show survival difference, ΔSUV_{max} was able to demonstrate the difference of RFS and OS in pathologic non-responders. Furthermore, we found that the least reduction rate of SUV_{max} to achieve pathologic response was 39.3% indicating that pathologic response becomes relevant only after certain amount of metabolic response occurs. Thus, metabolic response can provide more sensitive information than pathologic response to evaluate patient's response to NAC. Our previous study has shown that the tumor metabolic information provided by ^{18}FDG-PET is more significantly correlated with prognosis than tumor burden in adjuvant setting [*24*]. These findings suggest that tumor biology significantly affects not only prognosis but also response to NAC.

There have been efforts to advance assessment of response to NAC by combining pathologic response and biologic factors. MD Anderson Cancer Center described a new cancer staging for assessing prognosis after NAC on the basis of pretreatment clinical stage, ER status, grade and post-treatment pathologic stage [*25*]. Another group provided proof of principle that the addition of post-treatment Ki67, grade, and ER to RCB improves the prediction of long-term outcome [*26*]. However, all of these modalities essentially need postoperative pathologic findings. ^{18}FDG-PET can provide prognostic information without pathologic findings which entails surgical intervention.

Our study has some limitations, mostly related to its retrospective nature. At this point of time, there is no standard optimal cutoff value to define patients to be classified into metabolic responder and non-responder according to survival outcomes due to different study populations, method of evaluation, treatments and limited number of patients involved in each study. We selected the 66.4% cutoff which differs from that of previous studies [*22*,*23*]. However, the aim of this study was not to define standard

optimal cutoff value from the beginning. Important point is that metabolic response assessed by ^{18}F-FDG uptake can provide additional information to pathologic response and our results support these findings. Further prospective studies to decide optimal cutoff value are required.

CONCLUSION

We highlighted the biologic and prognostic impact of early change in ^{18}F-FDG uptake in locally advanced breast cancer patients who received NAC. The reduction rate of SUV_{max} of ^{18}FDG-PET after 3rd cycle NAC is an independent and good prognostic marker beyond pathologic response. We suggest that ΔSUV_{max} could be considered in predicting post-treatment outcome as well as assessing tumor response for patients receiving NAC.

DISCLOSURE

The authors have declared no conflicts of interest.

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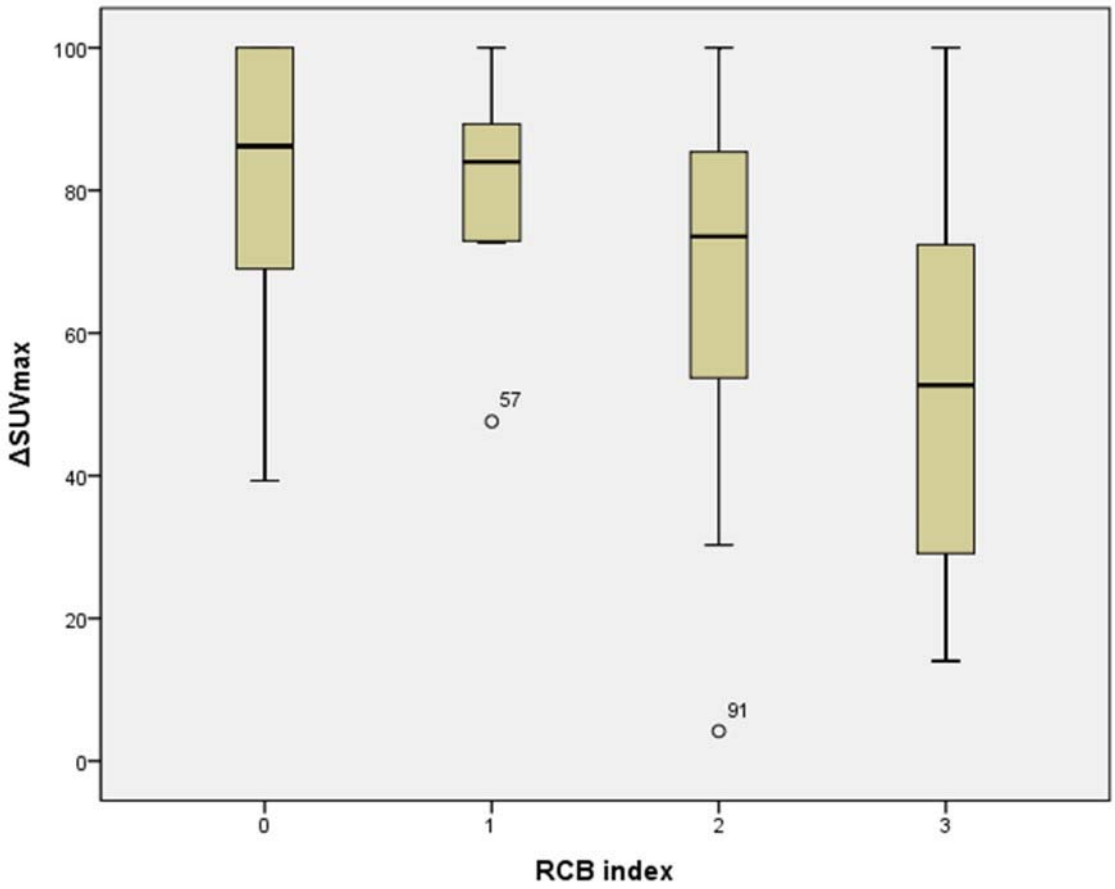

FIGURE 1. Comparison of the ΔSUV_{max} according to RCB-index.

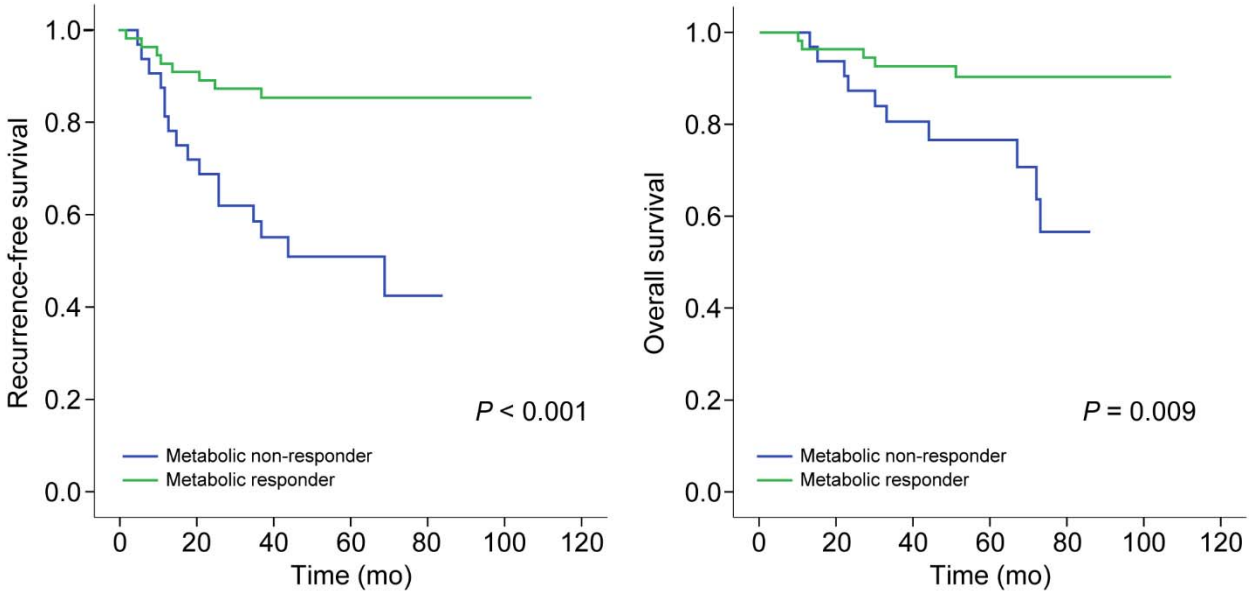

FIGURE 2. Kaplan-Meier survival curve according to a cutoff value of 64.4% of ΔSUV_{max}. (A) Recurrence-free survival, (B) Overall survival.

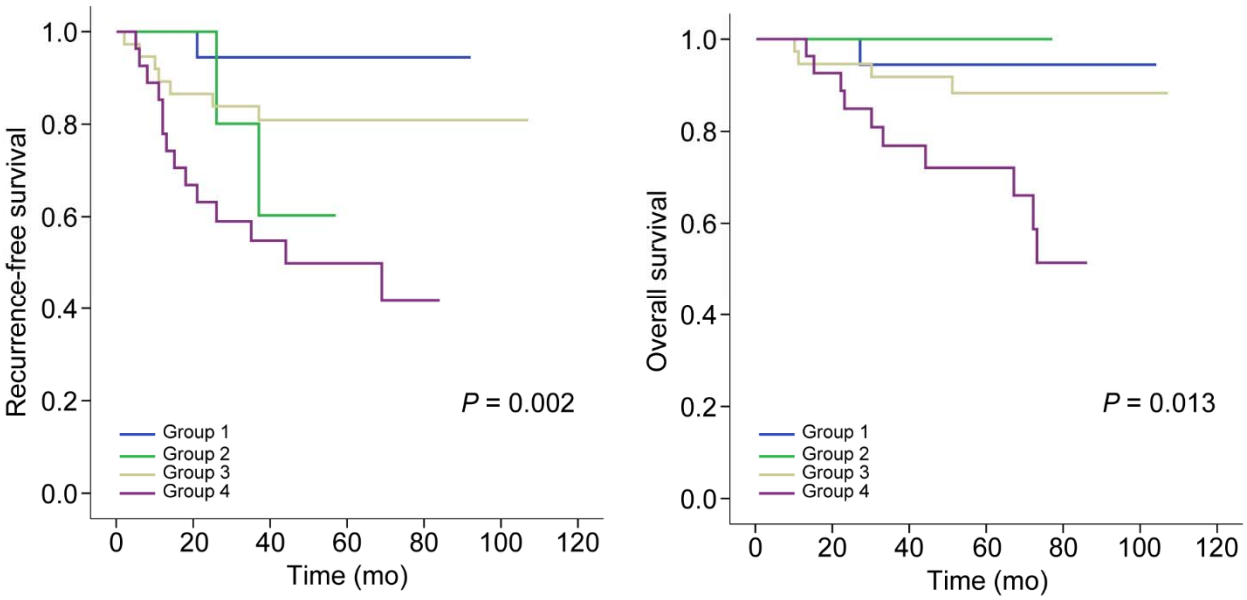

FIGURE 3. Kaplan-Meier estimates of RFS and OS. RFS according to risk group classified by 1: pathologic responder and metabolic responder, 2: pathologic responder and metabolic non-responders, 3: pathologic non-responder and metabolic responder, 4: pathologic non-responder and metabolic non-responder. (A) Recurrence-free survival, log-rank test results: 1) group1 and group2 (p=0.054), 2) group1 and group3 (p=0.185), 3) group2 and group3 (p=0.394), 4) group3 and group4 (p=0.007), (B) Overall survival, log-rank test results: 1) group1 and group2 (p=0.598), 2) group1 and group3 (p=0.523), 3) group2 and group3 (p=0.464), 4) group3 and group4 (p=0.017).

Table 1. Clinical and Pathologic Characteristics of Patients with Invasive Breast Cancer

Characteristics	No. of Patients (n = 87)	Percent (%)
Age, years		
Mean age, years (range)	46.1 (26–73)	
≤50	60	69.0
>50	27	31.0
Clinical T stage		
I	12	13.8
II	61	70.1
III	9	10.3
IV	5	5.7
Clinical N stage		
I	53	60.9
II	12	13.8
III	22	25.3
Modifier Bloom-Richardson Score		
I	10	11.5
II	29	33.3
III	19	21.8
Estrogen receptor		
Positive	36	41.4
Negative	51	58.6
Progesterone receptor		
Positive	29	33.3
Negative	58	67.7
Human epidermal growth factor 2		
Positive	42	48.3
Negative	45	51.7
Ki67		
High	30	34.5
Low	56	64.4
Subtypes		
Luminal A	22	25.3
Luminal B	17	19.5
HER2 type	27	31.0
Triple-negative	21	24.1
Pathologic complete response, positive	17	19.5
RCB-index		
0	17	19.5
I	6	6.9
II	42	48.3
III	22	25.3

Pathologic complete response: no invasive tumor in primary breast and axillary.

Abbreviations: RCB, residual cancer burden

Table 2. Univariate analysis of recurrence-free survival and overall survival

Variable	Recurrence-free survival			Overall survival		
	Hazard Ratio	95% CI	*P*-value	Hazard Ratio	95% CI	*P*-value
Age	1.12	0.48-2.61	0.797	1.09	0.37-3.19	0.877
HG			0.480			0.555
I	Reference			Reference		
II	0.97	0.26-3.67	0.968	0.51	0.11-2.29	0.381
II	1.72	0.46-6.50	0.422	0.99	0.24-4.16	0.993
RCB-index			0.058			0.120
I	Reference			Reference		
II	0.00	0.00	0.982	0.00	0.00	0.987
III	1.47	0.40-5.34	0.560	2.44	0.29-20.28	0.410
IV	4.04	1.12-14.50	0.033	6.96	0.87-55.72	0.067
ΔSUV_{max}*	0.97	0.95-0.98	<0.001	0.98	0.96-0.99	0.014
Clinical T stage			0.113			0.045
I	Reference			Reference		
II	1.71	0.39-7.46	0.478	2.14	0.27-16.90	0.472
III	3.45	0.63-18.90	0.153	4.23	0.38-47.28	0.242
IV	5.97	1.00-35.87	0.051	11.97	1.23-116.06	0.032
Clinical N stage			<0.001			0.005
0 or I	Reference			Reference		
II	1.93	0.51-7.27	0.333	5.02	1.01-24.91	0.049
III	5.97	2.46-14.46	<0.001	8.80	2.38-32.55	0.001
Subtypes			0.003			0.038
Luminal A	Reference			Reference		
Luminal B	1.03	0.23-4.61	0.967	1.48	0.21-10.58	0.695
HER2 type	1.11	0.30-4.12	0.882	1.39	0.24-8.35	0.716
Triple-negative	4.95	1.59-15.44	0.006	5.72	1.21-26.99	0.028

Abbreviations: CI, confidence interval; RCB, residual cancer burden; SUV_{max}, maximum standardized uptake value

* Continuous variable

TABLE 3. Multivariate analysis of recurrence-free survival and overall survival

Variable	Recurrence-free survival			Overall survival		
	Hazard Ratio	95% CI	*P*-value	Hazard Ratio	95% CI	*P*-value
Clinical T stage						0.265
I				Reference		
II				0.56	0.05-6.53	0.645
III				0.62	0.04-9.87	0.735
IV				2.82	0.18-44.20	0.461
Clinical N stage			0.015			0.05
I	Reference			Reference		
II	1.05	0.23-4.66	0.954	5.15	0.91-29.09	0.064
III	3.90	1.35-11.22	0.012	6.35	1.39-29.01	0.017
Subtypes			0.002			0.111
Luminal A	Reference			Reference		
Luminal B	1.54	0.34-7.04	0.579	2.20	0.31-20.46	0.456
HER2 type	1.15	0.30-4.38	0.840	2.18	0.30-15.46	0.436
Triple negative	6.93	2.05-23.35	0.002	6.55	1.15-32.14	0.024
RCB-index			0.924			
0	Reference					
I	0.00	0.00	0.981			
II	1.62	0.41-6.42	0.490			
III	1.49	0.33-6.64	0.605			
ΔSUV_{max}*	0.97	0.95-0.99	<0.001	0.97	0.95-0.99	0.015

Abbreviations: CI, confidence interval; RCB, residual cancer burden; SUV_{max}, maximum standardized uptake value

* Continuous variable

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