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Original Article

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Prognostic Value of Neutrophil-to-Lymphocyte Ratio and Early Standardized Uptake Value Reduction in Patients With Breast Cancer Receiving Neoadjuvant Chemotherapy

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ABSTRACT

Purpose: We investigated the treatment response and prognosis using the neutrophil-to-lymphocyte ratio (NLR) and standardized uptake value (SUV) of ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) in neoadjuvant settings.
Methods: Baseline NLR and maximum SUV (SUV_{max}) were retrospectively analyzed in 273 females with breast cancer who received neoadjuvant chemotherapy followed by surgery. Of these, 101 patients underwent ^{18}F-FDG PET after 3–4 neoadjuvant chemotherapy cycles, which allowed the measurement of ΔSUV_{max}, an early reduction in SUV_{max}. NLR and early SUV_{max} reduction (ΔSUV_{max}) were classified as low and high, respectively, relative to the median values.
Results: The mean NLR was lower, and the mean ΔSUV_{max} was higher in patients with pathologic complete response (pCR) than in those with residual tumors. The ΔSUV_{max} was an independent variable associated with pCR. Furthermore, the high NLR group had poor recurrence-free survival (RFS) and overall survival. Among patients with ΔSUV_{max} data, high NLR (adjusted hazard ratio, 2.82; 95% confidence intervals [CI], 1.26–6.28; $P = 0.016$) and low ΔSUV_{max} (adjusted hazard ratio, 2.39; 95% CI, 1.07–5.34; $P = 0.037$) were independent prognostic factors for poor RFS. The categorization of the patients into four groups according to the combination of NLR and ΔSUV_{max} showed that patients with high NLR and low ΔSUV_{max} had significantly poorer RFS.
Conclusion: Baseline NLR and ΔSUV_{max} were significantly associated with the prognosis of patients with breast cancer who received neoadjuvant chemotherapy. These results suggest that metabolic non-responders with defective immune systems have worse survival outcomes.

Keywords: Breast Neoplasms; Lymphocytes; Neoadjuvant Therapy; Neutrophils; Positron Emission Tomography Computed Tomography

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Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
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INTRODUCTION

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is a useful tool for diagnosing breast cancer because it reflects glucose metabolism, which is generally higher in tumors than in normal tissues [1]. Preclinical data have shown the contribution of aggressive tumor biology to increased FDG uptake in breast cancer [2,3]. Active ^{18}F-FDG uptake, as assessed by the maximum standardized uptake value (SUV), was found to be associated with poor clinicopathological factors such as larger tumor size, axillary lymph node metastasis, higher histologic grade (HG), triple-negative breast cancer (TNBC), and worse survival in patients with breast cancer [4,5]. Furthermore, the response to neoadjuvant chemotherapy has been accurately predicted with ^{18}F-FDG PET in several studies [6]. We previously showed that the prognostic impact of maximum SUV (SUV_{max}) on ^{18}F-FDG PET was greater than that of the traditional anatomical stage in an adjuvant setting [7]. Furthermore, we found that early reduction in SUV_{max} after neoadjuvant chemotherapy is a prognostic factor in patients with locally advanced breast cancer [8].

The host immune system has been the subject of attention for various carcinomas, including breast cancer. Studies have been conducted to identify immunological parameters, such as tumor-infiltrating lymphocytes that are related to therapeutic benefits and prognosis in breast cancer [9]. In particular, a high neutrophil-to-lymphocyte ratio (NLR), which reflects the nature of the host immune system and proinflammatory conditions, can induce neutrophilia and/or lymphopenia linked to the inflammatory response and depletion of antitumor immune function, consequently leading to tumor progression [10,11]. Preclinical data have shown that neutrophils can inhibit the cytolytic activity of lymphocytes or natural killer cells, cancer cell apoptosis, and adhesion to the extracellular matrix [12,13], while lymphocytes are known to upregulate anticancer effects [14]. Neutrophils in the blood can secrete soluble factors that enhance the interaction between circulating tumor cells and the endothelium, thus facilitating metastasis [12]. Several studies have shown that peripheral blood cell counts, such as neutrophils, lymphocytes, and monocytes, are related to tumor-infiltrating lymphocytes (TILs), which means that NLR may reflect localized immune activity in the tumor microenvironment [15,16]. Furthermore, tumor factors may influence systemic inflammation represented by NLR status, and the prognostic effect of NLR may originate from proinflammatory conditions such as tumor necrosis or the absence of TILs [17,18]. Most studies that investigate NLR in breast cancer have highlighted the association between a high NLR and poor response to chemotherapy and worse clinical outcomes [10].

The molecular biology of the tumor itself, as well as the host immune factor, is important in response to treatment or prognosis. We hypothesized that SUV_{max} can reflect tumor biology with respect to glucose metabolism and that NLR can represent the host immune system. However, there are limited data on the predictive and prognostic value of NLR and SUV_{max} in terms of response to treatment and survival in patients with breast cancer who received neoadjuvant chemotherapy. Here, we assessed whether the response to neoadjuvant chemotherapy and clinical outcomes differed depending on the baseline NLR, SUV_{max}, and early SUV_{max} reduction.

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METHODS

Patients

We retrospectively identified 391 patients with non-metastatic breast cancer who received neoadjuvant chemotherapy followed by breast surgery at Gangnam Severance Hospital between January 2004 and June 2018. Of these, 279 patients underwent ^{18}F-FDG PET and complete blood cell count (CBC) analysis before neoadjuvant chemotherapy. Patients with a history of cancer (n = 2), bilateral breast cancer (n = 3), or inflammatory breast cancer (n = 1) were also excluded. As a result, 273 females with breast cancer were included and evaluated for baseline values of NLR and SUV_{max}. Of these, 101 patients underwent ^{18}F-FDG PET before initiation and after 3–4 cycles of neoadjuvant chemotherapy. Data for ΔSUV_{max}, that is, the reduction percentage in SUV_{max}, were obtained. Most patients received anthracycline- or taxane-based neoadjuvant chemotherapy (**Supplementary Table 1**). Medical records including medical history, age, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor 2 (HER2) status, HG, Ki-67 levels, clinical T stage, clinical N stage, pathologic complete response (pCR), and laboratory data were reviewed.

Baseline NLR

The baseline NLR was calculated as the neutrophil count divided by the lymphocyte count obtained from the CBC analysis performed within 2 weeks before neoadjuvant chemotherapy initiation. It was analyzed as a continuous value and divided into two predefined categories (low and high) according to a median value of 2.04 (range, 0.84–10.59).

^{18}F-FDG PET

^{18}F-FDG (5.5 MBq/kg body weight) was administered intravenously after the patient had fasted for at least 6 h and achieved a blood glucose level < 140 mg/dL. After 6 min, whole-body emission scans were obtained using an Allegro PET camera (Philips Medical Systems, Cleveland, OH, USA) for patient imaging before 2008, while PET/computed tomography (CT) scans were performed using a hybrid scanner (Biograph 40 TruePoint or Biograph mCT 64; Siemens Healthcare Solutions USA, Inc., Winston-Salem, NC, USA) for patients imaged since 2008. For attenuation correction, whole-body computed tomographic scans were obtained using automatic dose modulation with a reference of 40 mA and 120 kV without contrast enhancement. PET data were obtained from the base of the skull to the proximal thigh for 3 minutes per bed position in the three-dimensional mode.

The baseline SUV_{max} was calculated by measuring ^{18}F-FDG uptake by the primary breast tumor in the region of interest as follows:

$$\frac{\text{Maximal Concentration of Radioactivity in the Region of Interest}}{\text{Injected Dose/Patient Weight (kg)}}$$

ΔSUV_{max}, the percentage SUV_{max} reduction between baseline and after 3–4 neoadjuvant chemotherapy cycles, was calculated as follows:

$$\frac{100 \times (\text{Baseline } SUV_{max} - SUV_{max} \text{ after 3–4 Neoadjuvant Chemotherapy Cycles})}{\text{Baseline } SUV_{max}}$$

Baseline SUV_{max} and early SUV_{max} reduction (ΔSUV_{max}) were grouped into low and high values according to the median values (baseline SUV_{max}, 7.88; ΔSUV_{max}, 73.3).

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Pathological evaluation

In our immunohistochemical study, formalin-fixed, paraffin-embedded tissue sections obtained from surgical specimens were stained using appropriate antibodies specific for the following four markers: ER (1:100 dilution, clone 6F11; Novocastra, Newcastle upon Tyne, UK), PR (clone 16; Novocastra), HER2 (4B5 rabbit monoclonal antibody; Ventana Medical Systems, Tucson, AZ, USA), and Ki-67 (MIB-1; Dako, Glostrup, Denmark). ER and PR positivity were defined using the modified Allred system as follows: positive, Allred scores 3–8; negative, Allred scores 0 and 2. HER2 status was defined as positive with a score of 3+ and negative with a score of 0 or 1+. Tumors with a score of 2+ were subjected to a silver-enhanced in situ hybridization analysis according to the manufacturer's protocol (PathVysion kit; Vysis, Downers Grove, IL, USA or HER2 inform; Ventana Medical Systems). The Ki-67 level was considered high when the Ki-67 proliferation index was ≥ 14%. pCR was defined as no evidence of invasive cancer residues in the breast parenchyma and all axillary lymph nodes (ypT0/is, ypN0) based on the pathological evaluation of surgical specimens after neoadjuvant chemotherapy.

Statistical analysis

We evaluated clinicopathological factors, including pCR, according to the baseline NLR, baseline SUV_{max}, and ΔSUV_{max}, using the χ^2 test and Student's *t*-test. Multivariate analysis of clinicopathological factors associated with pCR was performed using a binary logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) with two-sided *p*-values are presented. Recurrence-free survival (RFS) was measured from the date of breast cancer diagnosis to the date of the first breast tumor recurrence, including locoregional and distant recurrences. Overall survival (OS) was measured from the date of breast cancer diagnosis to the date of death from any cause. The Kaplan–Meier method was used to estimate RFS and OS, while the estimated survival curves were compared using the log-rank test. Multivariate analysis of survival outcomes was performed using the Cox proportional hazards model. Hazard ratios and 95% CIs with two-sided *p*-values are presented. Multivariable binary logistic regression and Cox proportional hazard regression models were used to investigate risk factors that showed a value of $p < 0.10$ in the univariate analysis. All analyses were performed with SPSS version 23 (SPSS, Chicago, IL, USA), and the statistical significance was set at $p < 0.05$.

Ethics statement

Our study was carried out following the Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the Institutional Review Board of the Severance Hospital, Yonsei University, Seoul, Republic of Korea (number 3-2017-0350). The requirement for written informed consent was waived due to the retrospective nature of the study.

RESULTS

Baseline characteristics

From January 2007 to June 2018, 273 patients with clinical stage II–III breast cancer who underwent neoadjuvant chemotherapy followed by surgery at Gangnam Severance Hospital were investigated. The baseline characteristics of the patients are summarized in **Table 1**. A comparison between all patients and the 101 patients evaluated for ΔSUV_{max} revealed similarities in clinicopathological factors, except for the proportion of those who received radiotherapy (**Table 1**). Among all patients, the high NLR group (≥ 2.04) was younger than

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Table 1. Baseline patient characteristics

Baseline characteristics	Patients with ΔSUV_{max} (n = 101)	All patients (n = 273)	*p*-value
Age (yr)	45 (24–73)	47 (20–75)	0.403
Baseline NLR	2.48 (0.89–10.59)	2.39 (0.84–10.59)	0.618
Baseline SUV_{max}	7.71 (1.40–24.70)	8.60 (1.40–40.00)	0.095
cT			0.690
1	10 (9.9)	20 (7.3)	
2	66 (65.3)	188 (68.9)	
3	25 (24.8)	65 (23.8)	
cN			0.711
Positive	9 (6.9)	23 (8.4)	
Negative	94 (93.1)	250 (91.6)	
Histologic grade*			0.689
1 or 2	56 (73.7)	164 (71.3)	
3	20 (26.3)	66 (28.7)	
ER			0.765
Positive	48 (47.5)	135 (49.5)	
Negative	53 (52.5)	138 (50.5)	
PR			0.860
Positive	40 (39.6)	106 (38.8)	
Negative	61 (60.4)	167 (61.2)	
HER2			0.411
Positive	52 (51.5)	153 (56.0)	
Negative	49 (48.5)	120 (44.0)	
Ki-67*			0.269
< 14	53 (53.5)	117 (47.2)	
≥ 14	46 (46.5)	131 (52.85)	
Subtype			0.819
HR+HER2−	27 (26.7)	82 (30.0)	
HR+HER2+	22 (21.8)	56 (20.5)	
HR−HER2+	28 (27.7)	65 (23.8)	
TNBC	24 (23.8)	70 (25.6)	
pCR			0.209
Yes	19 (18.8)	68 (25.0)	
No	82 (81.2)	204 (75.0)	
Adjuvant hormone therapy			0.675
Yes	46 (45.5)	131 (48.0)	
No	55 (54.5)	142 (52.0)	
Adjuvant trastuzumab			0.296
Yes	29 (28.7)	94 (34.4)	
No	72 (71.3)	179 (65.6)	
Adjuvant radiotherapy			0.029
Yes	72 (71.3)	223 (81.3)	
No	29 (28.7)	50 (18.3)	

Values are presented as mean (range) number of patients (%).
ΔSUV_{max} = early maximum standardized uptake value reduction; NLR = neutrophil-to-lymphocyte ratio; cT = clinical T stage; cN = clinical N stage; ER = estrogen receptor; PR = progesterone receptor; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; pCR = pathologic complete response.
*Missing values.

the low NLR group (< 2.04) (**Supplementary Table 2**). Furthermore, patients with a high baseline SUV_{max} (≥ 7.88) had poorer prognostic factors, such as negative ER, high HG, high Ki-67 levels, and TNBC, than those with a low baseline SUV_{max} (< 7.88) (**Supplementary Table 3**). In the 101 patients evaluated for ΔSUV_{max}, no significant differences were observed in clinicopathological factors according to the baseline NLR (**Supplementary Table 4**). In contrast, those with high ΔSUV_{max} had significantly higher HG than those with low ΔSUV_{max} (**Supplementary Table 5**). There was no difference in baseline SUV_{max} and ΔSUV_{max} according to the baseline NLR. Furthermore, the proportion of patients with high baseline SUV_{max} stratified by ΔSUV_{max} was not different (**Supplementary Table 5**).

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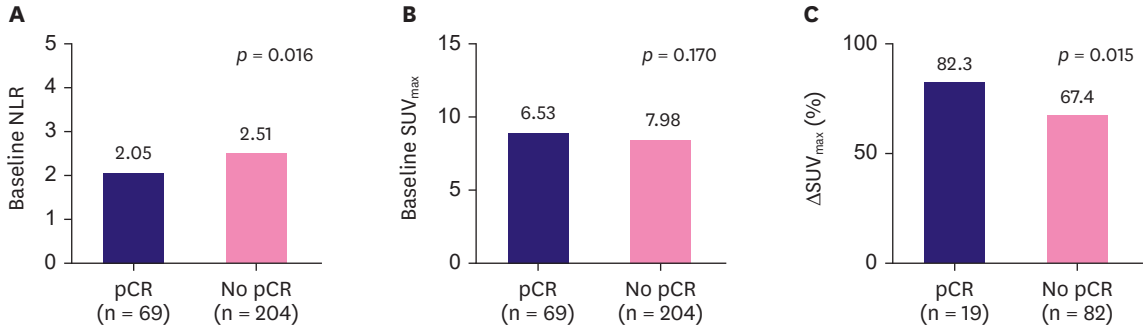

Figure 1. Comparison between patients with pCR and those with residual tumors. (A) Baseline NLR, (B) baseline SUV_{max}, and (C) ΔSUV_{max}.
pCR = pathologic complete response; NLR = neutrophil-to-lymphocyte ratio; SUV_{max} = maximum standardized uptake value; ΔSUV_{max} = early maximum standardized uptake value reduction.

Treatment response according to the baseline NLR, baseline SUV_{max}, and ΔSUV_{max}

We assessed the data of 68 (25.0%) patients with pCR and 204 (75.0%) with residual tumors after neoadjuvant chemotherapy. Patients with residual tumors had a higher mean baseline NLR than those with pCR (2.51 vs. 2.05, $p = 0.016$; **Figure 1A**); however, no association was observed between baseline SUV_{max} and pCR (**Figure 1B**). Multivariable analysis revealed that the breast cancer subtype was the only independent factor for pCR (**Supplementary Table 6**). Of the 101 patients with ΔSUV_{max} data, 19 (18.8%) showed pCR and 82 (81.2%) had residual tumors. The mean ΔSUV_{max} was significantly higher in patients with pCR than in those with residual tumors (82.3% vs. 67.4%, $p = 0.015$; **Figure 1C**). Furthermore, a high ΔSUV_{max} (≥ 73.3) was significantly associated with pCR compared to a low ΔSUV_{max} (< 73.3) (OR, 3.41; 95% CI, 1.12–10.33; $p = 0.030$; **Table 2**). ΔSUV_{max} was determined to be an independent factor for pCR in the multivariable analysis (OR, 3.77; 95% CI, 1.19–12.01; $p = 0.025$; **Table 2**). When stratified breast cancer subtypes were analyzed, the trend was similar to the results for the entire cohort, although they did not show statistical significance (**Supplementary Table 7**).

Prognostic impact of baseline NLR, baseline SUV, and ΔSUV_{max}

The median follow-up period was 52.0 (interquartile range [IQR], 43.0–61.0) months for all patients. The high NLR group had significantly poorer RFS (log-rank $p = 0.001$) and OS (log-rank $p = 0.026$) than the low NLR group (**Figure 2A and B**). Furthermore, low NLR was significantly associated with poor RFS and OS in TNBC (**Supplementary Figure 1**). However, no differences in RFS and OS were observed according to the baseline SUV_{max} (**Figure 2C and D**). In the multivariable analysis, after adjustment for other clinicopathological factors, the baseline NLR was an independent prognostic factor for RFS (hazard ratio, 2.32; 95% CI, 1.17–4.60; $p = 0.016$) and OS (hazard ratio, 5.52; 95% CI, 1.18–25.87; $p = 0.030$) (**Table 3**).

Among patients with ΔSUV_{max} data, the median follow-up period was 105.0 (IQR, 87.0–123.2) months. Consistent with the results obtained for all patients, the high NLR group had significantly poorer RFS (log-rank $p = 0.016$) and OS (log-rank $p = 0.038$) than the low NLR group (**Figure 3A and B**). Low NLR was significantly associated with poor RFS and OS in TNBC (**Supplementary Figure 2**). Furthermore, the low ΔSUV_{max} group had significantly poorer RFS (log-rank $p = 0.037$) and OS (log-rank $p = 0.218$) than the high ΔSUV_{max} group (**Figure 3C and D**). Low ΔSUV_{max} was significantly associated with poor RFS in HER2+ breast cancer (**Supplementary Figure 2**). Multivariable analysis showed that baseline NLR (hazard ratio, 3.20; 95% CI, 1.29–7.92; $p = 0.012$) and Î SUV_{max} (hazard ratio, 0.40; 95% CI, 0.17–0.94; $p = 0.035$) were independent prognostic factors for RFS (**Table 4**). Univariate analysis showed

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Table 2. ORs and 95% CIs for pathologic complete response in the 101 patients with data for ΔSUV_{max}

Characteristics	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0.99 (0.94–1.05)	0.710		
NLR (continuous value)	0.94 (0.66–1.34)	0.743		
NLR				
Low (< 2.04)	Ref.			
High (≥ 2.04)	1.52 (0.55–4.16)	0.419		
ΔSUV_{max} (continuous value)	1.03 (1.01–1.06)	0.020		
ΔSUV_{max}				
Low (< 7.88)	Ref.		Ref.	
High (≥ 7.88)	3.41 (1.12–10.33)	0.030	3.77 (1.19–12.01)	0.025
cT		0.918		
1	Ref.			
2	0.98 (0.19–5.18)	0.982		
3	0.76 (0.17–5.01)	0.777		
cN				
Positive	Ref.			
Negative	1.42 (0.16–12.55)	0.752		
Histologic grade				
1 or 2	Ref.			
3	0.44 (0.05–3.89)	0.459		
Ki-67				
< 14	Ref.			
≥ 14	1.03 (0.36–2.93)	0.957		
Subtype		0.227		0.208
HR+HER2−	Ref.		Ref.	
HR+HER2+	9.75 (1.07–88.59)	0.043	9.16 (0.99–85.21)	0.052
HR−HER2+	8.67 (0.99–76.12)	0.051	10.61 (1.16–96.74)	0.036
TNBC	6.84 (0.74–63.44)	0.091	7.89 (0.82–75.53)	0.073

OR = odds ratio; CI = confidence interval; ΔSUV_{max} = early maximum standardized uptake value reduction; NLR = neutrophil-to-lymphocyte ratio; cT = clinical T stage; cN = clinical N stage; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer.

that the baseline NLR was the only significant factor for OS (hazard ratio, 6.82; 95% CI, 1.55–30.15; $p = 0.035$; **Supplementary Table 8**).

We assessed the treatment response and survival outcomes according to the baseline NLR and ΔSUV_{max} in 101 patients. The patients were classified into four groups as follows: group 1, low baseline NLR and high ΔSUV_{max} (n = 27); group 2, high baseline NLR and high ΔSUV_{max} (n = 24); group 3, low baseline NLR and low ΔSUV_{max} (n = 24); and group 4, high baseline NLR and low ΔSUV_{max} (n = 26). The pCR rate was 18.5%, 37.5%, 12.5%, and 7.7% in groups 1, 2, 3, and 4, respectively, in which group 4 had the lowest pCR rate ($p = 0.055$). A significant difference was observed in RFS ($p = 0.012$) but not in OS ($p = 0.113$), according to the baseline NLR and ΔSUV_{max} (**Figure 4A and B**). When stratified breast cancer subtypes were analyzed, the trend was similar to the results for the entire cohort, although they did not show statistical significance (**Supplementary Figure 3**). Furthermore, we found a significant difference in RFS in patients who had a residual tumor ($p = 0.045$) but not in those who achieved pCR (**Supplementary Figure 4**). Multivariable analysis showed that patients with a high baseline NLR and low ΔSUV_{max} had poorer RFS than those with a low baseline NLR and high ΔSUV_{max} (hazard ratio, 8.71; 95% CI, 1.87–40.64; $p = 0.006$; **Table 4**).

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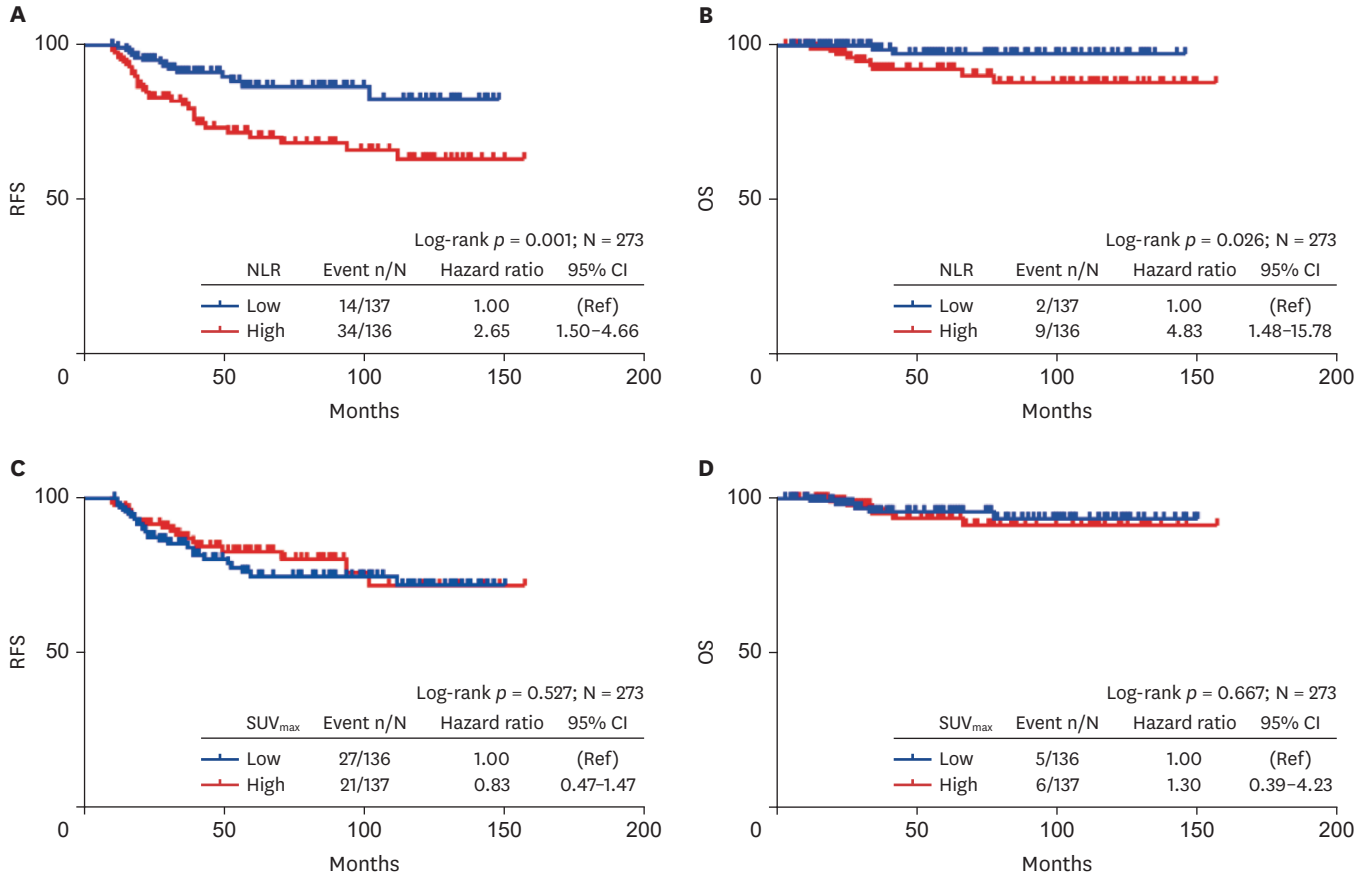

Figure 2. Kaplan–Meier curves of RFS and OS in all patients. (A) RFS and (B) OS according to the baseline NLR; (C) RFS, and (D) OS according to the baseline SUV_{max}. RFS = recurrence-free survival; OS = overall survival; NLR = neutrophil-to-lymphocyte ratio; SUV_{max} = maximum standardized uptake value; CI = confidence interval.

DISCUSSION

In this study, we investigated the response to neoadjuvant chemotherapy and survival outcomes according to the baseline NLR, baseline SUV_{max}, and ΔSUV_{max} in patients with breast cancer who underwent neoadjuvant chemotherapy. The percentage of change in ΔSUV_{max} alone was a significant independent factor associated with pCR. The results showed the applicability of the percentage changes in SUV_{max} between baseline and the second ^{18}F-FDG PET scan to predict the response to treatment. Furthermore, the baseline NLR and ΔSUV_{max} showed prognostic significance for tumor relapse. In particular, patients with high NLR and low ΔSUV_{max} had adverse survival outcomes compared to those with low NLR and high ΔSUV_{max} after assigning them to four subgroups according to NLR and ΔSUV_{max}.

Because the ΔSUV_{max} derived from serial ^{18}F-FDG PET can trace changes in the glucose metabolism of tumors after treatment, it is a useful method to predict the therapeutic response. Moreover, we previously showed that ΔSUV_{max} could demonstrate differences in survival in pathological non-responders [8]. Although the cut-off ΔSUV_{max} and timing of interim ^{18}F-FDG PET were slightly different in various studies [19-22], accumulating evidence, including our findings, commonly suggests the applicability of monitoring SUV on ^{18}F-FDG PET to predict response to chemotherapy and prognosis in patients with breast cancer. Therefore, the strategy of escalating or de-escalating treatment during the neoadjuvant period based on early response may be feasible in breast cancer patients who received

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Table 3. Hazard and odds ratios with 95% CIs for RFS and OS in all patients

Characteristics	RFS				OS			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0.96 (0.94–0.99)	0.028	0.98 (0.95–1.01)	0.192	0.97 (0.91–1.03)	0.342		
NLR								
Low (< 2.04)	Ref.		Ref.		Ref.		Ref.	
High (≥ 2.04)	2.65 (1.42–4.94)	0.002	2.32 (1.17–4.60)	0.016	4.84 (1.05–22.41)	0.044	5.52 (1.18–25.87)	0.030
SUV_{max} (continuous value)	0.98 (0.92–1.04)	0.525			1.05 (0.96–1.15)	0.253		
SUV_{max}								
Low (< 7.88)	Ref.				Ref.			
High (≥ 7.88)	0.83 (0.47–1.47)	0.529			1.30 (0.40–4.26)	0.668		
cT		0.449				0.772		
1	Ref.				No event			
2	2.49 (0.60–10.39)	0.209			Ref.	–		
3	2.25 (0.50–10.17)	0.292			1.57 (0.46–5.36)	0.474		
cN								
Positive	Ref.				Ref.			
Negative	1.81 (0.44–7.48)	0.410			0.67 (0.09–5.26)	0.706		
Histologic grade								
1 or 2	Ref.		Ref.		Ref.			
3	2.10 (1.13–3.90)	0.018	1.91 (0.94–3.89)	0.076	2.46 (0.66–9.18)	0.181		
Ki-67								
< 14	Ref.				Ref.			
≥ 14	1.59 (0.88–2.89)	0.126			1.76 (0.51–6.03)	0.371		
Subtype		0.016		0.078		0.180		0.161
HR+HER2–	Ref.		Ref.		Ref.		Ref.	
HR+HER2+	0.40 (0.15–1.08)	0.071	0.28 (0.06–1.21)	0.088	3.125 (0.28–34.50)	0.352	4.63 (0.41–51.71)	0.214
HR–HER2+	0.56 (0.32–3.86)	0.195	0.51 (0.18–1.51)	0.227	3.27 (0.30–36.03)	0.334	3.68 (0.33–40.61)	0.288
TNBC	1.56 (0.81–3.00)	0.185	1.33 (0.63–2.79)	0.458	8.29 (1.00–68.86)	0.050	9.72 (1.16–81.09)	0.036
pCR								
No pCR	Ref.				Ref.			
pCR	0.59 (0.26–1.32)	0.197			0.42 (0.05–3.28)	0.408		

CI = confidence interval; RFS = recurrence-free survival; OS = overall survival; OR = odds ratio; NLR = neutrophil-to-lymphocyte ratio; SUV_{max} = maximum standardized uptake value; cT = clinical T stage; cN = clinical N stage; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; pCR = pathologic complete response.

neoadjuvant chemotherapy. It is expected that the results of the PHERGain trial on survival outcomes will be able to answer this question [23].

In this study, baseline NLR was a significant prognostic factor, especially in TNBC. This is because TNBC is more immunogenic than other subtypes of breast cancer [24]. A previous report showed consistent findings that differences in pCR and survival according to the baseline NLR were more pronounced in TNBC [10]. Furthermore, the baseline NLR provided additional prognostic information on survival outcomes according to the ΔSUV_{max}. Our findings suggest that patients with an impaired immune system and poor metabolic response after neoadjuvant chemotherapy should be considered a high-risk group for relapse. Similar results were observed in patients with residual tumors, but not in those who achieved pCR. In this study, patients with residual tumors did not receive additional adjuvant treatment. Considering the poor prognosis in patients with high NLR and low ΔSUV_{max} who have a residual tumor after neoadjuvant chemotherapy, additional adjuvant treatment such as capecitabine or trastuzumab emtansine (TDM-1) should be administered in this subpopulation. Moreover, future work to verify whether the combined analysis of NLR and ΔSUV_{max} can identify patients who do not need additional treatment or those who need additional treatment beyond capecitabine or TDM-1 in cases of residual tumor after neoadjuvant chemotherapy is needed to develop a new therapeutic strategy.

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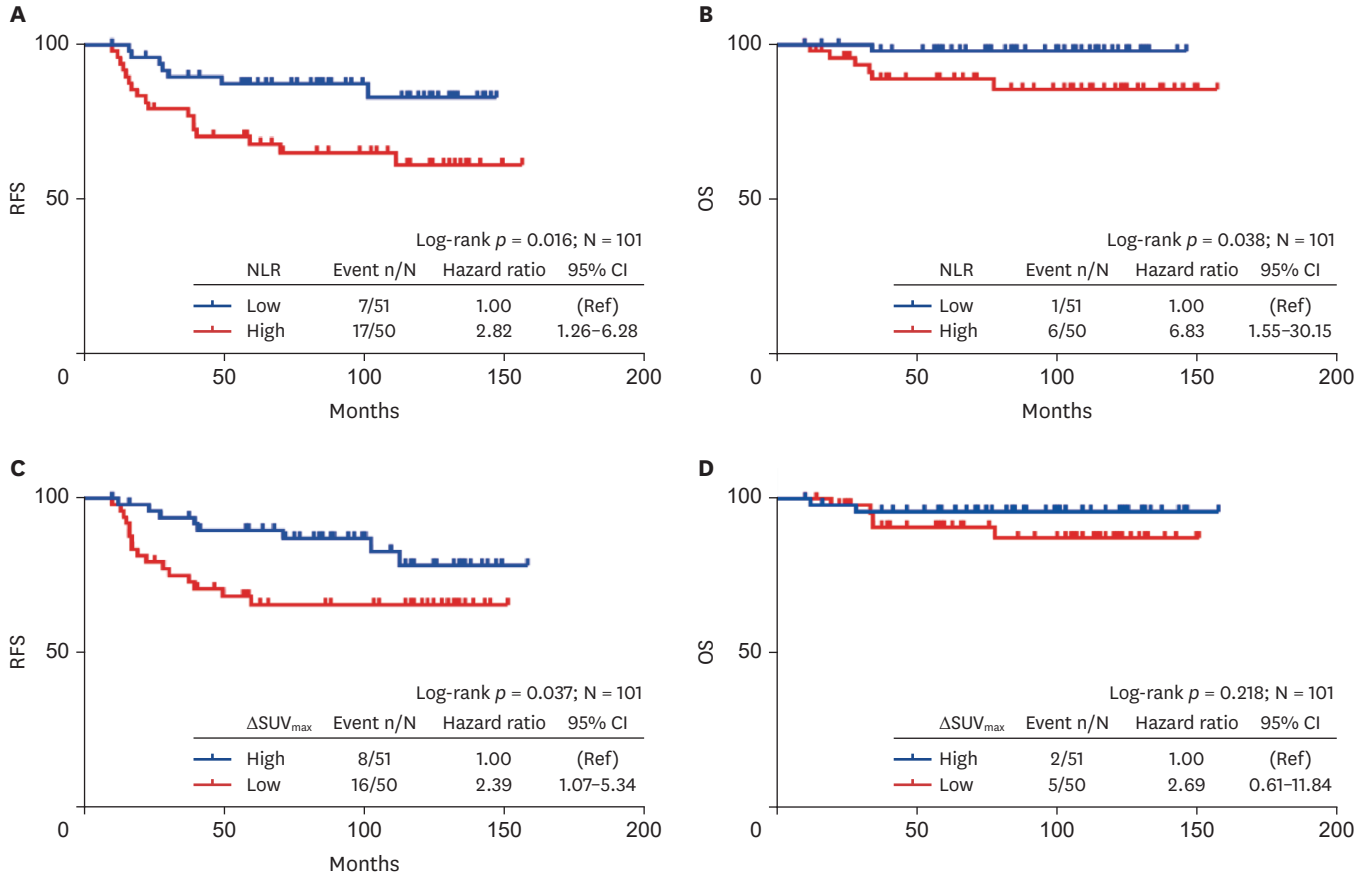

Figure 3. Kaplan–Meier curves of RFS and OS in 101 patients with ΔSUV_{max} data. (A) RFS and (B) OS according to the baseline NLR. (C) RFS and (D) OS according to the ΔSUV_{max}.
RFS = recurrence-free survival; OS = overall survival; ΔSUV_{max} = early maximum standardized uptake value reduction; NLR = neutrophil-to-lymphocyte ratio; CI = confidence interval.

In contrast, in our study, neither discrete nor continuous baseline SUV_{max} values were associated with chemotherapy response or survival. Previous studies that reported the prognostic value of the baseline SUV_{max} in breast cancer included most patients with stage I–II breast cancer and showed an average SUV_{max} of 2.61–5.76 [7,25,26]. In contrast, we included patients with clinical stages II–III, and the average SUV_{max} was relatively high (8.6). The inclusion of fewer patients with low SUV_{max} may have affected the results. As other PET-derived values, such as total lesion glycolysis, metabolic tumor volume, and metabolically active tumor volume, have recently been suggested as predictive or prognostic factors, more studies are needed to determine whether these values are more useful in patients with an overall high SUV_{max} [5,27,28]. Furthermore, the baseline SUV_{max} did not correlate with ΔSUV_{max}. Given that ΔSUV_{max} was related to pCR and survival in this study, we assumed that metabolic reduction after treatment is more important than the initial metabolic status of cancer before treatment in patients with a relatively high SUV_{max}, due to clinical tumor burden.

The limitations of this study include a selection bias due to its retrospective nature. In particular, ΔSUV_{max} was obtained only for 101 patients; therefore, the subanalysis of breast cancer subtypes was restricted. The treatment responses and survival outcomes according to the NLR and ΔSUV_{max} differed from those according to breast cancer subtype [29,30]. In addition, treatment regimens for breast cancer subtypes also vary. Most patients received

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Table 4. Hazard ratios and 95% CIs for recurrence-free survival in the 101 patients with data for ΔSUV_{max}

Characteristics	Univariable analysis		Multivariable model 1*		Multivariable model 2†	
	Hazard ratio (95% CI)	*p*-value	Hazard ratios (95% CI)	*p*-value	Hazard ratios (95% CI)	*p*-value
Age	0.99 (0.95–1.04)	0.895				
NLR						
Low (< 2.04)	Ref.		Ref.			
High (≥ 2.04)	2.82 (1.17–6.80)	0.021	3.20 (1.29–7.92)	0.012		
ΔSUV_{max}						
Low (< 73.3)	Ref.		Ref.			
High (≥ 73.3)	0.42 (0.18–0.98)	0.044	0.40 (0.17–0.94)	0.035		
ΔSUV_{max} & NLR						0.019
High ΔSUV_{max} & low NLR	Ref.				Ref.	
High ΔSUV_{max} & high NLR	3.45 (0.70–17.12)	0.129			3.65 (0.72–18.53)	0.119
Low ΔSUV_{max} & low NLR	2.97 (0.58–15.35)	0.193			2.89 (0.55–15.10)	0.208
Low ΔSUV_{max} & high NLR	7.71 (1.71–34.88)	0.008			8.71 (1.87–40.64)	0.006
cT		0.445				
1	Ref.					
2	2.85 (0.38–21.49)	0.310				
3	3.79 (0.47–30.83)	0.213				
cN						
Positive	Ref.					
Negative	22.50 (0.03–20,364.36)	0.370				
Histologic grade						
1 or 2	Ref.					
3	0.77 (0.36–1.62)	0.483				
Ki-67						
< 14	Ref.					
≥ 14	1.59 (0.88–2.89)	0.126				
Subtype		0.099		0.056		0.056
HR+HER2−	Ref.		Ref.		Ref.	
HR+HER2+	0.97 (0.26–3.62)	0.966	1.63 (0.42–6.28)	0.479	1.64 (0.43–6.30)	0.473
HR−HER2+	1.12 (0.32–3.86)	0.860	1.30 (0.37–4.59)	0.683	1.29 (0.37–4.50)	0.688
TNBC	3.06 (1.04–8.97)	0.042	3.86 (1.29–11.59)	0.016	3.84 (1.29–11.45)	0.016
pCR						
No pCR	Ref.					
pCR	0.73 (0.25–2.12)	0.560				

CI = confidence interval; ΔSUV_{max} = early maximum standardized uptake value reduction; NLR = neutrophil-to-lymphocyte ratio; cT = clinical T stage; cN = clinical N stage; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; pCR = pathologic complete response.
*Covariates for multivariable models were NLR, ΔSUV_{max}, and subtype; †Covariates for multivariable models were ΔSUV_{max} & NLR and subtype.

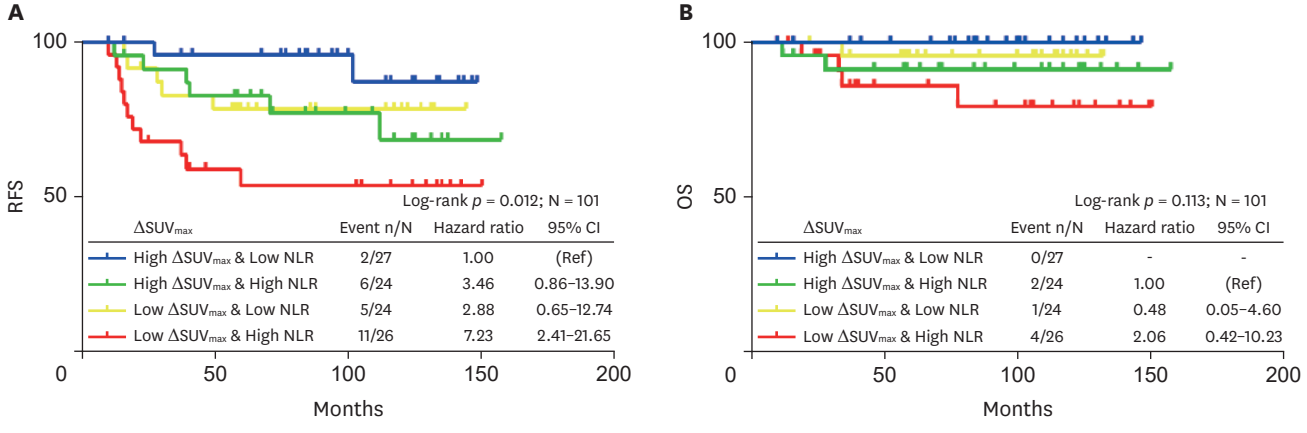

Figure 4. Prognostic ability of the combination of baseline NLR and ΔSUV_{max}. (A) RFS and (B) OS in 101 patients with ΔSUV_{max} data according to the baseline NLR and ΔSUV_{max}.
NLR = neutrophil-to-lymphocyte ratio; ΔSUV_{max} = early maximum standardized uptake value reduction; RFS = recurrence-free survival; OS = overall survival; CI = confidence interval.

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anthracycline/taxane-based chemotherapy; however, approximately 45% of patients with HER2-positive breast cancer received HER2-targeted therapy. This may have affected pCR and survival outcomes. More studies with larger populations receiving homogeneous therapy are warranted. Another limitation is that our study did not determine the optimal cut-off values for the baseline NLR, SUV_{max}, and ΔSUV_{max}. Currently, there is no definite consensus on the optimal cut-off values for these factors. Because our study aimed to evaluate whether the host's immune system and metabolic response could provide information on treatment response and prognosis, not to define the cut-off values, we used the median value of each parameter as the cut-off point.

Baseline NLR, which reflects the host immune system status, is a potential biomarker to predict the prognosis of breast cancer. Furthermore, the early reduction in ΔSUV_{max} on ^{18}F-FDG PET served as an independent factor for treatment response and survival in patients with breast cancer who received neoadjuvant chemotherapy. We found that metabolic non-responders with defective immune systems had the worst survival outcomes. Therefore, a novel treatment model is necessary for these patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Chemotherapy regimen

Click here to view

Supplementary Table 2
Characteristics according to the baseline NLR in all patients

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Supplementary Table 3
Characteristics according to the baseline SUV_{max} in all patients

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Supplementary Table 4
Characteristics according to the baseline NLR in the 101 patients with data for ΔSUV_{max}

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Supplementary Table 5
Characteristics according to ΔSUV_{max} in the 101 patients with data for ΔSUV_{max}

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Supplementary Table 6
ORs and 95% CIs for pCR in all patients

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Supplementary Table 7

NLR, SUV_{max}, and ΔSUV_{max} according to pCR stratified by breast cancer subtypes

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Supplementary Table 8

Hazard ratios and 95% CIs for overall survival in the 101 patients with data for ΔSUV_{max}

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Supplementary Figure 1

Kaplan–Meier curves of RFS and OS in all patients stratified according to breast cancer subtypes. (A) RFS and (B) OS according to the baseline NLR. (C) RFS and (D) OS according to the baseline SUV_{max}.

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Supplementary Figure 2

Kaplan–Meier curves of RFS and OS in 101 patients with ΔSUV_{max} data stratified according to breast cancer subtypes. (A) RFS and (B) OS according to the baseline NLR. (C) RFS and (D) OS according to the ΔSUV_{max}.

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Supplementary Figure 3

Prognostic ability of the combination of baseline NLR and ΔSUV_{max} stratified according to breast cancer subtypes. (A) RFS and (B) OS in 101 patients with ΔSUV_{max} data according to the baseline NLR and ΔSUV_{max}.

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Supplementary Figure 4

Kaplan–Meier curves of RFS and OS in 101 patients with ΔSUV_{max} data stratified according to pathological treatment response. (A) RFS and OS according to the baseline NLR and ΔSUV_{max} in 19 patients who achieved pCR and (B) RFS and OS according to the baseline NLR and ΔSUV_{max} in 82 patients with residual tumor.

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