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Value of volume-based metabolic parameters for predicting survival in breast cancer patients treated with neoadjuvant chemotherapy

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Abstract

We evaluated the role of metabolic parameters in the prediction of disease recurrence in operable invasive ductal breast cancer patients treated with neoadjuvant chemotherapy (NAC).

We retrospectively evaluated 139 female patients (mean age, 46.5 years; range: 27–72 years) with invasive ductal breast cancer, treated with NAC followed by surgery. All patients underwent ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and magnetic resonance imaging at baseline and after completion of NAC before surgery. The prognostic significance of clinicopathological and imaging parameters for disease-free survival (DFS) was evaluated.

Recurrence of cancer was detected in 31 of 139 patients (22.3%; follow-up period: 6–82 months). Baseline maximum standardized uptake value, metabolic tumor volume (MTV), and reduction rate (RR) of MTV after NAC were significant independent prognostic factors for DFS in a multivariate analysis (all $P < 0.05$). The survival functions differed significantly between low and high histological grades ($P < 0.001$). DFS of the patients with high baseline MTV ($\geq 5.23\,cm^3$) was significantly poorer than that of low MTV patients ($P = 0.019$). The survival function of the group with low RR of MTV after NAC ($\leq 90.72\%$) was poorer than the higher RR of the MTV group ($P = 0.008$).

Our findings suggest that breast cancer patients who have a high histological grade, large baseline MTV, or a small RR of MTV after NAC should receive great attention to check for possible recurrence.

Abbreviations: AC-T = adriamycin and cyclophosphamide followed by paclitaxel, AD = adriamycin and docetaxel, AJCC = American Joint Committee on Cancer, DFS = disease-free survival, ER = estrogen receptor, FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, HER2 = human epidermal growth factor receptor 2, MRI = magnetic resonance imaging, MTV = metabolic tumor volume, NAC = neoadjuvant chemotherapy, pCR = pathological complete response, PR = progesterone receptor, RR = reduction rate, SUV_{max} = maximum standardized uptake value, SUV_{mean} = mean standardized uptake value, TLG = total lesion glycolysis.

Keywords: breast cancer, disease-free survival, F-18 FDG PET/CT, invasive ductal carcinoma, neoadjuvant chemotherapy

1. Introduction

Recently, neoadjuvant chemotherapy (NAC) has emerged as a primary therapeutic strategy in breast cancer patients. The main goals of NAC in breast cancer are to avoid an extensive mastectomy, to increase the chances of performing breast-conserving surgery through reduction of tumor size, and finally to improve clinical outcomes, providing prognostic information through the response to treatment.[1–3]

Various breast imaging modalities are used to monitor the response of NAC in breast cancer patients in clinical practice. The conventional modalities, including mammography, breast ultrasound, and magnetic resonance imaging (MRI), have weaknesses in assessing NAC responses in that it is hard to distinguish fibrosis from viable residual tumor, and there is a delay in discovering tumor size shrinkage after NAC.[4,5] To compensate for these weaknesses, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has become widely used to assess changes in tumor viability for monitoring the response to NAC.[5,6] Metabolic reduction within a tumor can occur much earlier than an anatomical response to NAC.

There are several previous studies reporting the utility of FDG PET for response assessment in breast cancer patients treated with NAC, and most studies have largely focused on the association between metabolic parameters and postoperative histopathological outcomes.[7–10] Although a pathological complete response (pCR) is well known as a powerful prognostic factor in breast cancer with NAC,[11,12] 13% to 25% of patients achieving pCR after NAC still show disease recurrence during

Editor: Kavindra Nath.

This work was supported by a National Research Foundation of Korea (NRF) grant, funded by the Korean government (MEST) (NRF-2015R1C1A2A01052005).

The authors report no conflicts of interest.

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Medicine (2016) 95:41(e4605)

Received: 5 April 2016 / Received in final form: 8 July 2016 / Accepted: 19 July 2016

http://dx.doi.org/10.1097/MD.0000000000004605

follow-up.[2,13–15] The ability of FDG PET to identify factors predicting clinical survival outcome might have more important clinical implications than those predicted by pCR. However, there are only a few reports dealing with FDG PET and survival in breast cancer patients treated with NAC; moreover, the results were inconsistent.[16–18]

Given this background, we assessed operable invasive ductal breast cancer patients who underwent FDG PET/CT before and after NAC to determine metabolic parameters for predicting patient clinical outcomes.

2. Methods

2.1. Patients

This study involved 139 females aged 46.5 ± 9.0 years (range: 27–72 years) with histologically confirmed stage II or III invasive ductal breast cancer treated with NAC followed by surgery between March 2009 and July 2015 at a single institution (Ajou University Hospital, Suwon, Korea). All patients underwent both MRI and FDG PET/CT at baseline and after completion of NAC before surgery. Details of patient characteristics, including age, histology, stage, and treatment modalities, were obtained from chart review by an independent reviewer blinded to the MRI and PET results. Clinical stage was determined according to the American Joint Committee on Cancer (AJCC), 6th edition.[19] The original tumor size was assessed by MRI before NAC. After cancer staging, all patients underwent NAC. The patients received adriamycin and docetaxel (AD) for 6 cycles or adriamycin and cyclophosphamide followed by paclitaxel (AC-T) for 8 cycles. All patients subsequently underwent a mastectomy or breast-conserving surgery with sentinel node biopsy and/or axillary dissection within 5 weeks after the last cycle of chemotherapy. Adjuvant chemotherapy and/or radiation therapy followed the surgery. Clinical follow-up was done every 6 months and the mean follow-up duration was 26.2 ± 16.1 months (range: 6–82 months). Patient characteristics are shown in Table 1.

The clinical design of this retrospective study was approved by the Institutional Review Board of Ajou University (MED-MDB-15-071). The need for informed consent was waived.

Table 1

Patient characteristics.

Characteristics	Number
Age, y	
Mean (range)	46.5 (27–72)
Histopathology, %	
Invasive ductal carcinoma	139 (100)
Tumor size, cm	
Median (range)	3.1 (1.2–11.0)
Clinical T stage before NAC, %	
T1/T2/T3/T4	15 (11)/107 (77)/17 (12)/0 (0)
Clinical N stage before NAC, %	
N0/N1/N2/N3	29 (21)/88 (64)/2 (1)/20 (14)
AJCC stage before NAC, %	
Stage II/stage III	111 (80)/28 (20)
Type of surgery, %	
Mastectomy/breast-conserving surgery	41 (29)/98 (71)
Sentinel lymph node biopsy/axillary lymph node dissection	27 (19)/112 (81)
NAC regimens, %	
Adriamycin and docetaxel	19 (14)
Adriamycin and cyclophosphamide followed by paclitaxel	120 (86)
Nuclear grade, %	
Grade 1/grade 2/grade 3	66 (47)/62 (45)/11 (8)
Histological grade, %	
Grade 1/grade 2/grade 3	29 (21)/61 (44)/49 (35)
Tumor subtype	
HER2-positive, %	38 (27)
ER- and/or PR-positive, HER2-negative, %	76 (55)
Triple negative, %	25 (18)
Adjuvant treatment after surgery, %	
Adjuvant chemotherapy with radiation therapy	119 (86)
Adjuvant chemotherapy without radiation therapy	20 (14)
pCR after NAC, %	
pCR/non-pCR	22 (16)/117 (84)

AJCC = American Joint Committee on Cancer, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, NAC = neoadjuvant chemotherapy, pCR = pathological complete remission, PR = progesterone receptor.

2.2. FDG PET/CT protocol

After fasting for at least 6 hours, patients were administered 5 MBq/kg of FDG intravenously. The blood glucose level at the time of injection of FDG was <150 mg/dL in all patients. Patients were instructed to rest comfortably for 60 minutes and to urinate before scanning. Whole-body PET/CT images were obtained with a Discovery ST scanner (GE Healthcare, Milwaukee, WI). Seven or 8 frames (3 minutes/frame) of emission PET data were acquired in 3-dimensional (3D) mode after a noncontrast CT scan from the base of the skull to the upper thigh (120 kV, 30–100 mA in the AutomA mode; section width = 3.75 mm). Emission PET images were reconstructed using an iterative method (ordered-subsets expectation maximization with 2 iterations and 20 subsets, field of view = 600 mm, slice thickness = 3.27 mm) and attenuation corrected with noncontrast CT.

2.3. MRI protocol

MR images were acquired on a 1.5-T scanner (Signa; GE Healthcare) or 3-T system (Achieva; Philips Healthcare, Best, The Netherlands) using a dedicated breast coil. Patients underwent imaging in the prone position with the breasts immobilized. Contrast material was injected into an antecubital vein with an automatic injector (0.1 mmol/kg gadopentetate dimeglumine; Magnevist; Bayer Schering Pharma AG, Berlin, Germany) and followed by a 20 mL saline flush at a rate of 2 mL/s.

The imaging protocol with the 1.5-T scanner consisted of fat-suppressed axial fast spin-echo T2-weighted images (TR/TE, 4000/74; slice thickness, 3 mm) and dynamic unenhanced and contrast-enhanced fat-saturated 3D gradient-echo T1-weighted imaging (TR/TE, 5.1/2.4; flip angle, 10°; image matrix, 300 × 300; field of view, 300 × 300 mm; section thickness, 1.5 mm; and section gap, 0 mm).

The imaging protocol for the 3-T scanner consisted of fat-suppressed axial fast spin-echo T2-weighted images (TR/TE, 7562/70; slice thickness, 3 mm) and dynamic unenhanced and contrast-enhanced fat-saturated 3D gradient-echo T1-weighted imaging (TR/TE, 7.6/3.9; flip angle, 10°; slice thickness, 3 mm). Sagittal and coronal reformatted images were obtained using raw data. Standard subtraction images were obtained by subtracting the precontrast images from the early peak postcontrast image (obtained at 80 seconds after contrast injection) on a pixel-by-pixel basis. In addition, maximum intensity projection (MIP) reconstructions were applied to the subtraction images.

2.4. Image analysis

A specialist in nuclear medicine with 11 years of PET experience reviewed the FDG PET/CT images on a MIMvista workstation (ver. 6.5; MIM Software Inc, Cleveland, OH). All metabolic parameters were measured from the tumor volume segmented by a gradient-based method, as previously described.[20,21] A gradient segmentation method is available in the MIMvista software with an operator-defined starting point near the center of the breast tumor lesion. Once the primary target lesion was segmented, maximum standardized uptake value (SUV_{max}), mean standardized uptake value (SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated automatically by the MIMvista software. All SUVs were estimated based on injected dose and body weight.

All MR images were reviewed by a radiologist with 9 years of experience in interpreting breast imaging data. The lesion size was measured as the longest diameter of the lesion on the MIP image using a picture archiving and communication system workstation with electronic calipers. For multiple lesions, the longest diameter of each lesion was recorded separately and the sum of the lesions was calculated.

The response to NAC was assessed by calculating the percentage of change in each metabolic and MRI value (SUV_{max}, MTV, TLG, and diameter of main breast lesion) of post-NAC images relative to those of baseline images: % reduction rate (RR) = [(baseline value) − (post-NAC value)/(baseline value)] × 100.

2.5. Histopathological evaluation

Surgical specimens from the areas of the macroscopic tumor were sliced serially at 5-mm intervals, prepared as paraffin wax-embedded sections, and stained with hematoxylin and eosin. The specimens were evaluated according to the following histopathological features: histological type of carcinoma, Black nuclear grade (nuclear grade 1, poorly differentiated; grade 2, moderately differentiated; and grade 3, well differentiated), and modified Bloom–Richardson histological grade (histological grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated). Expression levels of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) were evaluated in the surgically removed specimens using standard avidin-biotin complex immunohistochemical staining methods. All primary antibodies were monoclonal antibodies: ER (1:50; Dako Corp., Carpinteria, CA), PR (1:50; Dako Corp.), and c-erbB2 (1:200; Novocastra Laboratories Ltd, Newcastle-Upon-Tyne, UK). ER and PR positivity was defined as the presence of 1% or more positively stained nuclei at ×10 magnification. The intensity of c-erbB2 staining was scored as 0, 1+, 2+, or 3+. Tumors with a 3+ score were classified as HER2-positive, and tumors with a 0 or 1+ score were classified as negative. In tumors with a 2+ score, gene amplification using fluorescence in situ hybridization was used to determine HER2 status. A pCR was defined as no evidence of residual invasive cancer in either breast tissue or axillary lymph nodes.[22] All specimens were reviewed by a pathologist with 17 years of experience.

2.6. Statistical analysis

A sample size calculation was performed using MedCalc (ver. 14.8.1; MedCalc Software bvba, Ostend, Belgium). A significance (α) level of 5% and a statistical power ($1-\beta$) level of 80% were used and considered acceptable for study purpose. A sample size of 108 was required to achieve confidence range, so the sample size of our study (n = 139) was sufficient to perform statistical analysis.

A Kolmogorov–Smirnov test was used to assess whether parameter distributions differed significantly from a normal distribution. All data were normally distributed; thus, parametric analyses were used and all data are presented as means with standard deviations.

Disease-free survival (DFS) was used to measure patient clinical outcomes and was defined as the period from initial diagnosis to recurrence. Ipsilateral/contralateral invasive breast tumor recurrence, local/regional recurrence, distant recurrence, second primary nonbreast invasive cancer, and death from any cause were considered events.[23] To assess the prognostic significance of clinicopathological and imaging parameters, univariate and multivariate analyses using a Cox proportional hazards regression model were performed. Covariates that achieved a significance level of <0.2 in the univariate model were included in the multivariate model. Survival functions of parameters were estimated using the Kaplan–Meier method and compared using the log-rank test. We selected the cutoff value maximizing the profile partial likelihood in the Cox regression model with a binary explanatory variable. The MedCalc software package was used for all statistical analyses. P values <0.05 were considered to indicate statistical significance.

3. Results

3.1. Assessment values of imaging parameters at baseline and after NAC

The mean value of baseline SUV_{max} was 8.93 ± 4.64 in all patients. The SUV_{max} decreased after NAC, with a mean value of 2.00 ± 3.40. The mean %RR of SUV_{max} after NAC was 76.23 ± 39.85. The baseline MTV of 13.84 ± 26.32 declined after NAC to 3.95 ± 13.13. The mean value of %RR MTV was 62.10 ± 71.76. The pre-NAC TLG also decreased after NAC, from 67.9 ± 136.52 to 14.70 ± 72.28. The mean %RR of TLG was 77.00 ± 83.23. The mean tumor diameter at baseline was 3.55 ± 1.73, and it decreased after NAC to 1.82 ± 1.83. The mean %RR of tumor diameter was 54.04 ± 43.05 after NAC.

3.2. Assessment of prognostic parameters for DFS

In total, 31 patients (31/139, 22.3%) showed recurrence during follow-up. Local/regional recurrence was seen in 17 patients and distant recurrence in 14. On univariate analysis, AJCC stage, nuclear grade, histological grade, baseline MTV, baseline tumor diameter, post-NAC PET parameters (SUV_{max}, MTV, TLG, tumor diameter), and %RR of metabolic parameters (SUV_{max}, MTV, TLG) were significant prognostic factors for DFS (all $P < 0.05$). Baseline SUV_{max}, baseline TLG, and %RR of tumor diameter after NAC did not show statistical significance as prognostic factors. The results of the univariate analysis of the Cox regression model are shown in Table 2. Multivariate analyses showed that histological grade, baseline MTV, and % RR of MTV were independent prognostic parameters for DFS (Table 3).

The Kaplan–Meier estimates for histological grade, baseline MTV, and %RR of MTV are shown in Figure 1. The survival functions differed significantly between low and high histological grades (Fig. 1A). The survival function of the high baseline MTV group (baseline MTV $\geq 5.23\,cm^3$) was poorer than that of the low

Table 2

Univariate analysis for recurrence-free survival using Cox proportional hazards regression model.

Covariate	*P*	HR	95% CI
Age (<40 vs ≥40)	0.319	1.82	0.86–3.88
AJCC stage (II vs III)	0.001*	3.42	1.62–7.23
NAC regimens (AD vs AC-T)	0.330	2.54	0.76–8.45
Type of surgery (mastectomy vs breast-conserving surgery)	0.466	0.62	0.17–2.26
Adjuvant treatment (CTx with RTx vs CTx without RTx)	0.424	1.63	0.49–5.35
Nuclear grade (grade 1 vs 2, 3)	0.004*	3.76	1.52–9.36
Histological grade (grade 1, 2 vs 3)	<0.001*	5.92	2.50–14.06
Tumor subtype			
HER2-positive vs ER- and/or PR-positive, HER2-negative	0.810	1.12	0.44–2.87
HER2-positive vs triple negative	0.295	1.15	0.12–2.88
pCR after NAC (pCR vs non-pCR)	0.839	0.92	0.42–2.02
Baseline SUV_{max}	0.098	1.06	0.99–1.14
Baseline MTV	0.003*	1.01	1.00–1.02
Baseline TLG	0.149	1.00	0.99–1.00
Baseline diameter	0.009*	1.24	1.10–1.46
Post-NAC SUV_{max}	<0.001*	1.20	1.12–1.28
Post-NAC MTV	<0.001*	1.02	1.01–1.03
Post-NAC TLG	<0.001*	1.00	0.99–1.00
Post-NAC diameter	0.007*	1.22	1.05–1.40
%RR of SUV_{max}	<0.001*	0.99	0.98–0.99
%RR of MTV	0.007*	1.00	0.99–1.00
%RR of TLG	<0.001*	0.99	0.99–1.00
%RR of diameter	0.147	1.00	0.99–1.00

AC-T = adriamycin and cyclophosphamide followed by paclitaxel, AD = adriamycin and docetaxel, AJCC = American Joint Committee on Cancer, CI = confidence interval, CTx = chemotherapy, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, MTV = metabolic tumor volume, NAC = neoadjuvant chemotherapy, pCR = pathological complete remission, PR = progesterone receptor, RR = reduction rate, RTx = radiation therapy, SUV_{max} = maximum standardized uptake value, TLG = total lesion glycolysis.
* $P < 0.05$.

baseline MTV group (Fig. 1B). Also, the group with a low RR of MTV after NAC (%RR ≤90.72%) showed poorer prognosis than the high RR of MTV group (Fig. 1C).

4. Discussion

Many previous studies have reported that FDG PET could provide useful information to predict the pathological response to NAC in breast cancer patients.[5,7,9,14] A meta-analysis by Wang et al[5] reported on the predictive value of FDG PET for pCR after NAC, with a sensitivity of 84% and specificity of 66%. However, pCR does not guarantee freedom from recurrence,[15] so we sought to assess whether metabolic parameters using FDG PET could predict the clinical outcome in breast cancer patients treated with NAC.

There are a few previous studies reporting the value of metabolic parameters using FDG PET for predicting survival outcome. A small study by Emmering et al[17] showed that visually positive FDG uptake of the primary tumor after NAC was inversely associated with DFS. The next study to include quantitative metabolic parameters by Jung et al[18] revealed that high RR of SUV_{max} (≥84.8%) was a good prognostic factor for DFS. The most recent study by Hyun et al[16] reported that post-NAC SUV_{max}, MTV, relative decreases of SUV_{max}, and MTV after NAC were significantly associated with DFS. According to the present study, baseline MTV and RR of MTV after NAC were independent and valuable metabolic parameters for predicting DFS via a multivariate analysis. There were some differences between our results and those of previous studies. First, in our study, post-NAC SUV_{max} and %RR of SUV_{max} were found to be significant factors in univariate analyses, but they failed to predict DFS in a multivariate analysis. A possible explanation for this result could be that SUV_{max} only reflects a single part of the tumor with a highly variable degree of noise[24] and is thus less reliable for detecting subtle metabolic response to therapy.[25] Second, Hyun et al[16] emphasized MTV after NAC as a prognostic factor for DFS, but MTV before NAC was revealed as an independent prognostic parameter, rather than post-NAC MTV. Although post-NAC MTV was a valuable parameter for predicting DFS in our univariate analysis, it failed to predict patient outcome according to the multivariate result. It is hard to explain the reason for the difference in results between our study and that of Hyun et al,[16] but our results are consistent with other studies showing that the MTV of an initial primary tumor was a prognostic indicator for patient outcome in various types of cancer including breast malignancies.[26–28] The present results suggest that patients with large MTV on pre-NAC status (MTV ≥5.23 cm^3) should receive more attention during follow-up because of the higher risk of disease recurrence than those with smaller MTV. Also, patients with a low RR of MTV after NAC (%RR ≤90.72%) must be followed closely because of their high risk of recurrence. The RR of MTV after NAC was a common independent prognostic factor in our study and in that of Hyun

Table 3

Multivariate analysis for recurrence-free survival using Cox proportional hazards regression model.

Covariate	*P*	HR	95% CI
Histological grade (grade 1, 2 vs 3)	<0.001*	7.00	2.44–20.1
Baseline MTV	0.002*	1.01	1.00–1.02
%RR of MTV	<0.001*	0.99	0.98–1.00

CI = confidence interval, HR = hazard ratio, MTV = metabolic tumor volume, RR = reduction rate.
* $P < 0.05$.

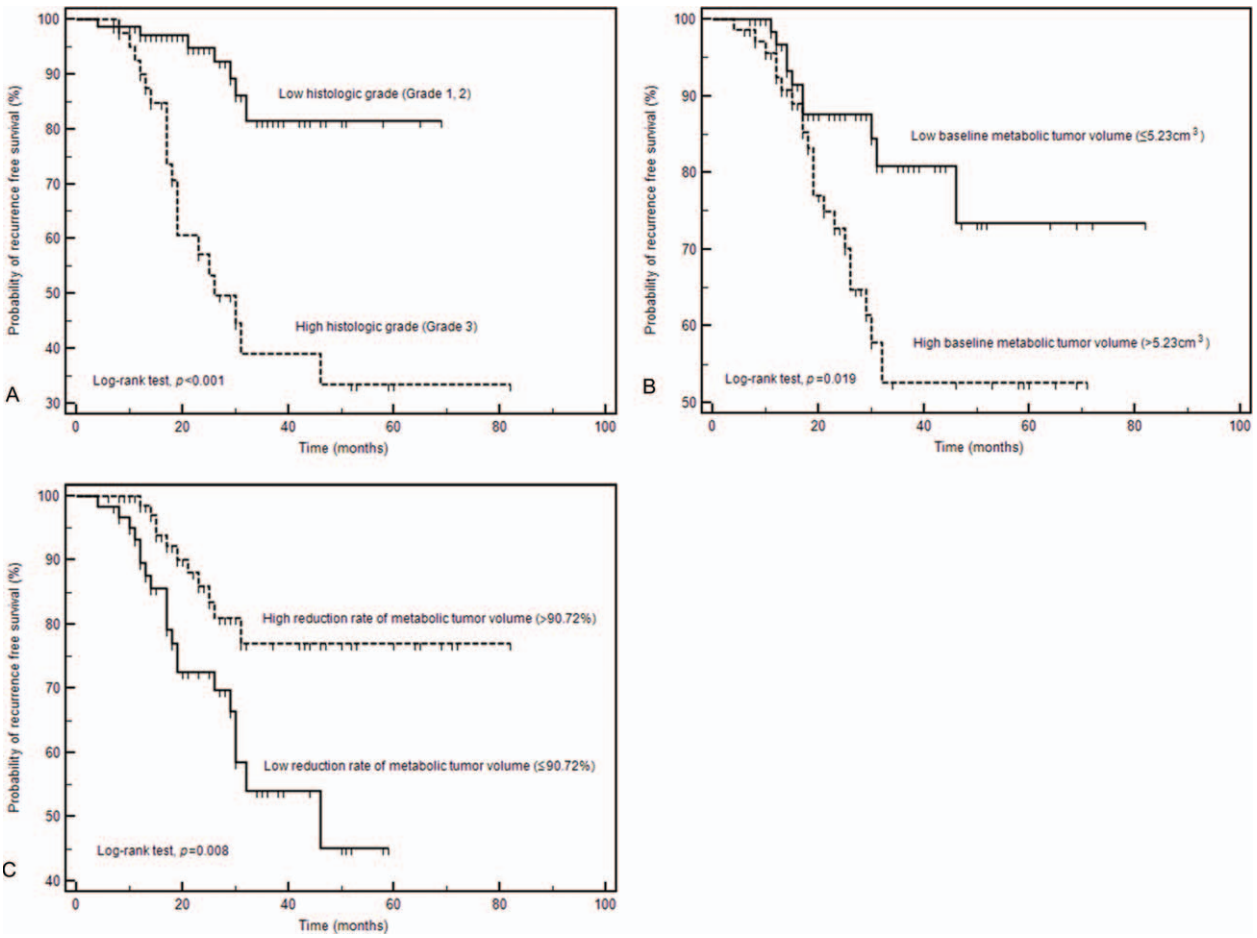

Figure 1. Kaplan–Meier estimates of survival functions for disease-free survival (DFS) by histological grade, baseline metabolic tumor volume (MTV), and reduction rate (%RR) of MTV. (A) The group with high histological grade showed significant poorer prognosis than the low histological grade group ($P < 0.001$, HR = 5.81, 95% CI = 2.61–12.97). (B) The prognosis of patients with high MTV tumors at baseline (baseline MTV $\geq 5.23\,cm^3$) was poorer than those with low baseline MTV tumors ($P = 0.019$, HR = 2.38, 95% CI = 1.18–4.82). (C) Patients with a low RR of MTV after NAC (%RR $\leq 90.72\%$) showed poorer prognoses than those with a high RR ($P = 0.008$, HR = 2.57, 95% CI = 1.26–5.25).

et al.[16] One unexpected result in our study was that TLG was not an independent prognostic factor; in contrast, MTV parameters showed useful prognostic power for DFS. A similar result was reported by Kim et al[27] in pancreatic tumors. The reason for this is unclear, but one possible explanation might be that the large TLG may represent not only large MTV tumors but also small MTVs with a high SUV,[29] so a small MTV with intense FDG uptake tumor might affect the prognostic value of TLG. On the basis of our results, we suggest that a large MTV may be a better predictor of DFS than large TLG. Further studies are needed to validate this suggestion.

A notable point of the present study is that we acquired volume-based metabolic parameters by a gradient-based method. The most popular method for achieving volume-based PET parameters is the fixed-threshold method at SUV 2.5 or a fixed % (25%–70%) of SUV_{max}. The gradient-based method has emerged as being more accurate than threshold methods, and it showed excellent reproducibility for volume contouring in PET images.[20] Thus, its potential role for tumor delineation in clinical studies has already been confirmed in various types of cancer.[30,31] The principle of gradient-based segmentation is to associate the tumor boundaries with the gradient-intensity crests observed in the image.[21] In this study, we could measure gradient-based volumetric parameters within a few minutes using a commercially available tool, which could be readily applied in clinical practice. As the operator drags the cursor from the center of the tumor lesion, 6 axes extend outward and spatial gradients are calculated along each axis interactively. The 6 axes define an ellipsoid that is then used as an initial boundary region for gradient-based volume detection.[20]

Previous studies reported that the pathological response after NAC showed a significant correlation with patient survival outcome.[11,12] However, in this study, the achievement of pCR after NAC was not associated with DFS. Indeed, in our study, 15.8% of patients (22/139) achieved pCR after the completion of NAC and recurrence was seen in 22.7% (5/22) of patients during follow-up, which was similar to the recurrence rate of 22.2% (26/117 patients) in the non-pCR group. The similar clinical outcome observed between pCR and non-pCR patients in our study might be explained by a previous report, which demonstrated that residual isolated tumor cells of pathological tissues, in patients with complete surgical removal of cancers after NAC, do not adversely affect patient outcome.[32]

The notion that breast cancer subtype affects metabolic changes during NAC has been previously reported.[33,34] Despite emerging evidence that tumor subtype may play a role in

monitoring the response to NAC, stratification into subgroups by tumor subtype did not provide sufficient statistical power to predict DFS in breast cancer patients. Our result is consistent with that of Hyun et al[16]; they reported that volume-based metabolic tumor responses could be used as a predictor for patient recurrence regardless of tumor subtype.

Changes in tumor size have been widely accepted for assessing responses after NAC using conventional imaging methods.[35] We evaluated not only the metabolic parameters by FDG PET, but also the size of the tumor on MRI. According to our study, change in tumor size after NAC (%RR of tumor diameter) did was not a significant predictor of DFS in either the univariate or multivariate analysis. However, all data on changes in metabolic parameters (%RR of SUV_{max}, TLG, and MTV) were significant prognostic factors for DFS in univariate analyses, and moreover the change in MTV was an independent prognostic factor for DFS in a multivariate analysis. To the best of our knowledge, no previously reported study used a design comparable with that of the current study. We suggest that changes in metabolic parameters (on PET) should receive more attention for predicting patient recurrence rather than changes in tumor size.

Previous studies mostly reported early metabolic responses to NAC, performing FDG PET after the first or second course of NAC.[7,36] However, we evaluated the final endpoint FDG PET after the completion of NAC instead of an interim PET. Although previous studies demonstrated that nonresponders in interim PET had poorer prognoses than early metabolic responders,[37,38] it is hard to change the treatment plan according to the results of interim PETs, and most patients complete their NAC cycles even though they are nonresponder patients during NAC in current clinical practice. Moreover, there is no consensus with regard to the precise time point(s) for performing PET during NAC. Thus, we evaluated the baseline and endpoint FDG PET parameters and sought to determine significant factors to predict DFS in breast cancer patients with NAC.

The histological grade of the tumor had been reported as a strong predictor of NAC response and DFS in operable breast cancer.[34] Thus, it is not surprising that histological grade was found to be an independent prognostic factor for DFS in this study. We suggest that patients with high histological grades (grade 2, 3) must be followed carefully because of the higher chance of recurrence than those with low histological grade (grade 1).

The present study had some limitations: first, tumor diameter data were from MRI images only. Information on tumor blood flow and microvascular permeability can be acquired with dynamic contrast-enhanced MRI (DCE-MRI), but our patients were analyzed retrospectively and DCE-MRI is not routinely performed in clinical practice. Also, tumor volume measured by MRI might have the potential to provide additional information for evaluating response to NAC in breast cancer, but we could not measure the tumor volume on MRI due to a lack of appropriate software. Further studies including various MRI parameters, for comparison with metabolic parameters in terms of predicting survival after NAC in breast cancer patients, may be useful. Another limitation of the current study is that we only evaluated imaging parameters of the primary tumor lesion. The response of axillary lymph nodes to NAC also can be monitored by FDG PET,[39] so we plan to examine whether metabolic parameters in axillary lymph nodes could be valuable for predicting survival in breast cancer patients with NAC in future studies.

In conclusion, histological grade, baseline MTV, and the RR of MTV after NAC were significantly associated with disease recurrence in operable breast cancer patients treated with NAC. Patients with tumors of high histological grade, large baseline MTV, or a small RR of MTV after NAC must continue to receive intensive clinical follow-up because of their high risk of recurrence.

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