Clinical value of delayed ^{18}F-FDG PET/CT for predicting nipple-areolar complex involvement in breast cancer: A comparison with clinical symptoms and breast MRI

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Abstract

Objective

We aimed to evaluate the predictive value of delayed ^{18}F-FDG PET/CT for identifying malignancies involved in the nipple-areolar complex (NAC) in comparison with clinical symptoms and breast MRI.

Methods

We enrolled 90 patients who underwent preoperative delayed ^{18}F-FDG PET/CT and MRI between October 2015 and May 2017. We calculated the NAC-Standardized uptake value ratio (SUVR) using the following formula: maximum SUV (SUV_{max}) of the NAC in the malignant breast /SUV_{max} of the NAC in the contralateral normal breast on early (NAC-$SUVR_{early}$) and delayed (NAC-$SUVR_{delay}$) phase images. MRI was used to measure the distance between the tumor and NAC and to analyze NAC enhancement patterns. Univariate and multivariate analyses were performed to identify significant predictive factors for NAC involvement.

Results

Seventeen patients were confirmed to have pathologic NAC involvement. NAC symptoms ($p = 0.009$), tumor multiplicity ($p = 0.006$), NAC-$SUVR_{delay}$ (> 1.23, $p = 0.007$), and MRI-based tumor-to-NAC distance (≤ 22.0 mm, $p = 0.003$) were independent predictive factors for NAC involvement. Ten of 76 patients with no clinical NAC symptoms had NAC malignancy. Tumor multiplicity ($p = 0.009$), tumor-to-NAC distance (≤ 20.0 mm, $p = 0.014$)), and NAC-$SUVR_{delay}$ (> 1.23, $p = 0.018$) had independent predictive value for NAC involvement.

Conclusions

Delayed ^{18}F-FDG PET/CT is a useful modality for predicting NAC involvement in breast cancer patients whether or not NAC symptoms are present.

Introduction

Although surgical techniques for breast cancer have developed over the past few years to include less invasive and more cosmetically acceptable approaches, there remains continued interest in improving cosmetic results and oncologic safety [1]. Breast-conserving surgery (BCS) is widely performed, especially in patients with small breast cancer tumors with absence of skin, nipple, or chest involvement [2, 3]. With adjuvant radiotherapy, BCS provides equivalent results in patient survival and local recurrence compared to mastectomy. Although BCS is an attractive alternative surgical procedure to mastectomy, not all patients are eligible. For patients who require mastectomy, breast reconstruction can be performed immediately or delayed until after mastectomy. Conservative mastectomies were introduced in the early 1990s and, combined with breast reconstruction, yield superior cosmetic outcomes for better reconstructed breast contour and preservation of the inframammary fold [4–6]. For breast reconstruction after mastectomy, predicting tumor cell involvement in the nipple-areolar complex (NAC) can be a major issue affecting patient emotional and cosmetic satisfaction and oncologic safety [7, 8]. Recently, there has been significant evolution in nipple-areolar sparing mastectomy (NSM) as a conservative surgical approach, with equivalent local control of disease [9]. NAC involvement is an added challenge in invasive breast cancer cases, particularly in selecting patients who are appropriately indicated for NSM for cosmetic and aesthetic reasons. Several studies have assessed NAC involvement according to clinical and pathological characteristics [10–14]. To the best of our knowledge, however, there have been no investigations into the efficacy of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for detecting NAC involvement.

Standard PET/CT for initial staging work-up is generally performed with the patient in a supine position. However, the prone position PET/CT could provide better visualization of breast lesions than the supine position [15, 16]. Several studies have demonstrated that delayed ^{18}F-FDG PET/CT could be useful for improving diagnostic accuracy for breast cancer since radiopharmaceutical uptake in cancer cells could remain or even become enhanced over time [17, 18].

Since nipple symptoms (e.g., nipple erosion, discharge, retraction) are highly suspicious for NAC invasion, there is a major concern that the possibility of NAC involvement might be greater in patients who suffer from nipple symptoms than in those who are symptom-free. We assumed that it would be more challenging to identify NAC involvement in nipple symptom-free patients than in those with nipple symptoms. In patients with invasive breast cancer, therefore, we aimed to demonstrate the predictive value of preoperative prone position delayed ^{18}F-FDG PET/CT and magnetic resonance imaging (MRI) parameters for determining NAC involvement compared with clinicopathologic factors according to the presence and/or absence of nipple symptoms.

Materials and methods

Patients and clinicopathologic analysis

Between October 2015 and May 2017, 129 female patients with suspected centrally located breast cancer underwent preoperative prone position dual time point (DTP) PET/CT and

dynamic contrast-enhanced breast MRI. A centrally located tumor was defined as a cylinder of breast tissue beneath the NAC from the dermis to the pectoral fascia, based on a previous study [19]. We excluded 21 patients who had received neoadjuvant chemotherapy and 12 patients who did not undergo surgery. Three patients were excluded because they received surgical excisional biopsy before PET/CT, and three patients were excluded for having bilateral breast cancer. Ultimately, 90 patients were enrolled in this study.

We recorded patient ages and clinical NAC symptoms, including nipple pain, nipple discharge, retraction, and erosion, based on our institutional medical database. Pathologic variables of tumor size, axillary lymph node status (ANS), lymphovascular invasion (LVI), combined *in situ* components, and tumor multiplicity were reviewed based on final pathologic reports. Tumor size was defined as the maximum diameter of the surgical specimen. In cases of multifocal/multicentric breast cancer, the diameter of the largest lesion was selected. For examining ANS, either sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) was performed according to the patient's surgical plan and clinical nodal stages. When SLNBs were identified as metastasis, ALND was conducted, including axillary levels I and II. If nodal metastasis was clinically suspected or there were cases for which SLNB was not necessary, surgical removal was performed for determining the pathologic ANS.

Pathologic NAC involvement was determined by the presence of invasive or *in situ* tumor cells in the NAC or nipple ducts or Paget's disease. To evaluate suspicious NAC involvement from a physical examination or imaging work-up, surgical biopsy of subareolar tissue or resection margins of the nipple were done. The subareolar tissue is a thin layer specimen located below the NAC. Intraoperative frozen sections of the subareolar tissue or resection margins were sent to a pathologist. Corresponding specimens were stained with the hematoxylin and eosin method. When specimens showed no evidence of invasive or carcinoma *in situ*, we considered this as negative pathologic finding. Otherwise, in operative specimens involving the NAC by mastectomy, the NAC was evaluated using a single plane dissection in 2–3 mm intervals perpendicular to the skin surface and was submitted perpendicularly for microscopic examination. The identification of cancer cells in these sections was regarded as pathologic NAC involvement. All surgical treatments and pathologic examinations were performed in our hospital, and we considered the final surgical pathology as the standard reference.

This prospective study was approved by the institutional review board of Ewha Womans University Hospital, and written informed consent was obtained from all participants.

Dual time point ¹⁸F-FDG PET/CT and image analysis

All patients were asked to fast for at least six hours, and blood glucose level was required to be less than 140 mg/dL before intravenous ¹⁸F-FDG administration of 5.18 MBq/kg. Patients were also asked to rest for one hour after radioisotope administration, and non-contrast CT was obtained for attenuation correction, followed by a PET scan using a Siemens Biograph mCT with 128-slice CT (Siemens Medical Solutions, Knoxville, TN, USA). Torso images were acquired from the skull base to the proximal thigh with the patient in the supine position. Additional breast images were performed with the patient in the prone position using a mock-up coil for hanging both breasts (Breast Protector™, Body Support Systems, Inc., USA). Two hours after radioisotope injection, delayed phase images were acquired to obtain corresponding images of the breast while the patient remained in the prone position. DTP PET/CT images were interpreted by two nuclear physicians (J.Y and B.S.K with 8 and 14 years of experience, respectively) using a dedicated workstation (syngo.via, Siemens Medical Solutions); the physicians were blinded to all clinicopathologic information and radiologic findings. Qualitative interpretations were performed for the presence of enhanced FDG uptake, and we considered

a PET/CT finding to be positive if there was asymmetric FDG uptake of the nipple that extended into the subareolar and/or periareolar area of the malignant breast.

For quantitative analysis, the maximum standardized uptake value (SUV_{max}) was corrected for each individual patient's body weight and was measured by delineating a three-dimensional volume of interest (VOI) over the NAC. The most representative image was selected, and the VOIs were drawn carefully to not include contiguous lesion areas. SUV_{max} values for the NAC in the malignant breast and the contralateral normal breast were obtained, and we then calculated the NAC-SUV_{ratio} with the following formula: NAC-SUV_{ratio} = SUV_{max} of the NAC in the malignant breast/SUV_{max} of the NAC in the contralateral normal breast. The NAC-SUV_{ratio} was calculated for early (NAC-$SUVR_{early}$) and delayed (NAC-$SUVR_{delay}$) phase images.

MRI protocol and image analysis

Preoperative breast MRI was performed using the 3.0 Tesla (T) Achieva system (Philips Medical System, Best, The Netherlands). A dedicated breast coil (SENSE BREAST 7 Coil) was used with the patient in a prone position. An axial, fat-suppressed, fast-echo T2-weighted image was acquired in advance (TR/TE = 5521/70; flip angle = 90˚; field of view = 320 mm; matrix = 332/261; slice thickness = 3 mm with no gap; bandwidth = 289 Hz; time acquisition = 4 min 23 s). Dynamic MRI using an enhanced T1-weighted high resolution isotropic volume excitation sequence was obtained after continuous intravenous injection of a gadolinium bolus (0.1 mmol/kg of body weight of Gd-DTPA; Gadovist, Bayer Schering Pharma AG, Berlin, Germany) at a rate of 2 ml/s, followed by a 25 ml saline flush using an automatic injector. Six phases of dynamic enhanced images were processed at 55.4 s (axial), 110.8 s (axial), 146 s (sagittal), 221.6 (axial), 292 s (sagittal), and 438 s (axial), respectively. The dynamic axial and sagittal MR variables were as follows: TR/TE = 4.42/2.17; flip angle = 12˚; field of view = 320 mm; matrix = 320/320; receiver bandwidth = 621.4 Hz/pixel; slice thickness = 1 mm and 4.37/2.15; 12˚; 25 cm; 250/250; 704.5 Hz/pixel; 1 mm.

The distance between the tumor and the NAC was measured from the center of the NAC to a representative tumor on both axial and sagittal MRI images; we defined this as the minimum distance between the NAC and the nearest tumor margin. The positive or negative MR finding for NAC involvement was determined according to linear enhancement of the NAC directly from the primary tumor, unilateral NAC enhancement, and asymmetric thickness of the NAC, in accordance with previous studies [20, 21]. Preoperative breast MRIs were interpreted by a radiology specialist (J.C) with 16 years of experience with breast MRI, and consensus was achieved in all patients.

Statistical analysis

Statistical analysis was performed using the Medcalc software package (Version 9.5, Medcalc software). All continuous variables were recorded as mean value ± standard deviation (SD) or median value with interquartile range (IQR), depending on the data distribution. The Kolmogorov-Smirnov test was used to determine if the data were normally distributed. If a normal distribution was suspected, we used an independent t-test to compare continuous variables. If the variables did not appear to be normally distributed, we used the Mann-Whitney test. We also used Pearson's chi-square test to compare categorical variables regarding NAC involvement.

To estimate the optimal cutoff values for continuous variables to predict NAC involvement, we performed receiver operating characteristic (ROC) curve analysis using the Youden index. Multivariate analysis using logistic regression models with a stepwise selection process was

performed to identify independent predictors of NAC involvement. A p-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

Ninety patients (mean age ± SD = 53.4 ± 12.7) were included in this study. The average interval time between PET/CT and MRI was 2.1 days. BCS was performed on 47 patients, modified radical mastectomy was performed on 30, and the remaining 13 patients underwent skin-sparing mastectomy. Seventy-seven patients had invasive ductal carcinoma, 5 had invasive lobular carcinoma, 3 had invasive mucinous carcinoma, 3 had invasive medullary carcinoma, 1 had invasive papillary carcinoma, and 1 had a malignant phyllodes tumor. Five patients had N3 stage, six had N2, and 29 had N1 based on the final pathologic results. Fifty patients had no evidence of axillary lymph node metastasis through SLNB or ALND. Twenty-seven of the 90 patients were evaluated for NAC involvement through the operative specimens involving NAC. The remaining 63 underwent surgical biopsy of subareolar tissue or resection margins of the nipple. Finally, seventeen patients (18.9%) were confirmed to have NAC involvement based on the pathology results.

Table 1 presents the results from univariate analysis of clinicopathologic factors according to NAC involvement. There were 14 patients who complained of NAC symptoms, comprising discharge (n = 1), retraction (n = 8), erosion (n = 3), and pain (n = 2). The presence of NAC symptoms had significant predictive value for NAC involvement (p = 0.004). Tumor multiplicity also revealed predictive significance for NAC invasion (p = 0.037).

Pathologic tumor size was not significantly different between patients with pathologic NAC involvement and those without (p = 0.307). LVI was more common in the NAC-involved group; however, the difference did not reach statistical significance (p = 0.082). There were also no significant differences with respect to patient age (p = 0.144), ANS (p = 0.609) or combined *in situ* components (p = 0.810).

Prediction of NAC involvement by DTP PET/CT and MRI characteristics

The presence of either asymmetric FDG uptake in the nipple or extension to NAC based on visual analysis was not predictive for pathologic NAC involvement (p = 0.167; Table 2). In contrast, our quantitative analysis using SUV_{max} found that both early (p = 0.005) and delayed (p < 0.001) phase NAC-SUV_{ratio} were significantly different between the NAC-involved and non-involved groups. After ROC curve analysis, the optimal cutoff values for NAC-$SUVR_{early}$ and NAC-$SUVR_{delay}$ were 1.32 (area under curve (AUC), 0.721; 95% confidence interval (CI), 0.597–0.796) and 1.23 (AUC, 0.810; 95% CI, 0.700–0.876), respectively.

Positive MRI finding (p = 0.013) including either linear enhancement to NAC, unilateral NAC enhancement and/or asymmetric thickening of NAC was significant predictor of NAC involvement. As shown in Table 2, MRI-based distance from the tumor to the NAC was also significantly different between the two groups (p < 0.001). The optimal cutoff value for the distance from the tumor to the NAC for predicting NAC involvement was ≤ 22.0 mm (AUC, 0.795; 95% CI, 0.687–0.867). There were weak negative correlations between NAC-$SUVR_{early}$ and tumor-to-NAC distance and between NAC-$SUVR_{delay}$ and tumor-to-NAC distance (rho = -0.250, p = 0.018 and rho = -0.259, p = 0.014, respectively).

Our multivariate analysis demonstrated that NAC symptoms, tumor multiplicity, DTP PET/CT parameter of NAC-$SUVR_{delay}$, and MRI-based distance from the tumor to the NAC had independent predictive value for NAC involvement (Table 3). According to these results, patients with NAC symptoms, tumor multiplicity, NAC-$SUVR_{delay}$ higher than 1.23 or a

Table 1. Univariate analysis of clinicopathologic factors according to NAC involvement.

Factor			Pathologic NAC involvement (n = 17)	No pathologic NAC involvement (n = 73)	P-value
Age (year)			49.5 ± 9.9	54.3 ± 13.3	0.144
NAC symptoms	Presence		7	7	0.004*
	Absence		10	66	
Pathologic tumor size (cm)	Median (IQR)		2.35 (1.35–3.90)	2.10 (1.28–3.00)	0.307
ANS	Positive		9	31	0.609
	Negative		8	42	
LVI	Positive		9	20	0.082
	Negative		8	53	
Combined *in situ* component	Positive		14	61	0.810
	Negative		3	12	
Tumor multiplicity	Yes		7	11	0.037*
	No		10	62	

NAC, nipple-areolar complex; ANS, axillary lymph node status; LVI, lymphovascular invasion; IQR, interquartile range;

*, p <0.05

central tumor located equal to or less than MRI-based 22.0 mm from the NAC had a risk of NAC involvement that was 22.08, 32.35, 20.30, and 93.42 times higher than their opposite groups, respectively. Representative cases of pathologic NAC involvement are illustrated in Figs 1 and 2.

Clinical application of imaging parameters for NAC symptom-free patients

There were 76 patients who did not complain of nipple symptoms. Among them, 10 patients (13.2%) had confirmed malignant NAC involvement from final pathologic reports. Table 4 presents predictive variables for NAC involvement in NAC symptom-free patients. Tumor multiplicity, both DTP PET/CT parameters, tumor-to-NAC distance had significant predictive value in univariate analysis.

Table 2. Correlations between NAC involvement and DTP PET/CT and MRI characteristics.

Modality	Factor		Pathologic NAC involvement (n = 17)	No pathologic NAC involvement (n = 73)	p-value
PET/CT	Qualitative analysis	Positive	9	23	0.167
		Negative	8	50	
	NAC-SUVR$_{early}$	Median (IQR)	1.33 (1.12–1.59)	1.06 (0.96–1.27)	0.005*
	NAC-SUVR$_{delay}$	Median (IQR)	1.42 (1.15–2.28)	1.04 (0.95–1.21)	<0.001*
MRI	Tumor-to-NAC distance (mm)	Mean ± SD	13.7 ± 8.7	29.1 ± 16.7	<0.001*
	MR finding	Positive	14	33	0.013*
		Negative	3	40	

NAC, nipple-areolar complex; DTP PET/CT, dual time point positron emission tomography/computed tomography; MRI, magnetic resonance imaging; NAC-SUVR$_{early}$, ratio of early phase maximal standardized uptake value (SUV$_{max}$) of the NAC in the breast with malignancy to that of the NAC in the contralateral normal breast; NAC-SUVR$_{delay}$, ratio of delayed phase SUV$_{max}$ of the NAC in the malignant breast to that of the NAC in the contralateral normal breast; IQR, interquartile range; SD, standard deviation;

*, p <0.05

**Table 3. Multivariate analysis for predicting NAC involvement.**

Variable	Cutoff value	OR	95% CI	p-value
NAC symptoms		22.08	2.148–226.983	0.009*
Tumor multiplicity		32.35	2.707–386.649	0.006*
NAC-SUVR$_{delay}$	> 1.23	20.30	2.317–177.886	0.007*
Tumor-to-NAC distance (mm)	≤ 22.0	93.42	4.647–1877.901	0.003*

NAC, nipple-areolar complex; NAC-SUVR$_{delay}$, ratio of delayed phase SUV$_{max}$ of the affected NAC to that of the unaffected NAC; OR, odds ratio; CI, confidence interval;

*, p < 0.05

After multivariate analysis, tumor multiplicity (p = 0.009), tumor-to-NAC distance (p = 0.014), and NAC-SUVR$_{delay}$ (p = 0.018) were independently predictive (Table 5). Although the DTP PET/CT parameters of NAC-SUVR$_{early}$ (p = 0.018) had predictive significance for NAC involvement in univariate analysis, neither maintained significance after logistic regression analysis. Positive MR finding could not show predictive significance in univariate analysis (p = 0.060).
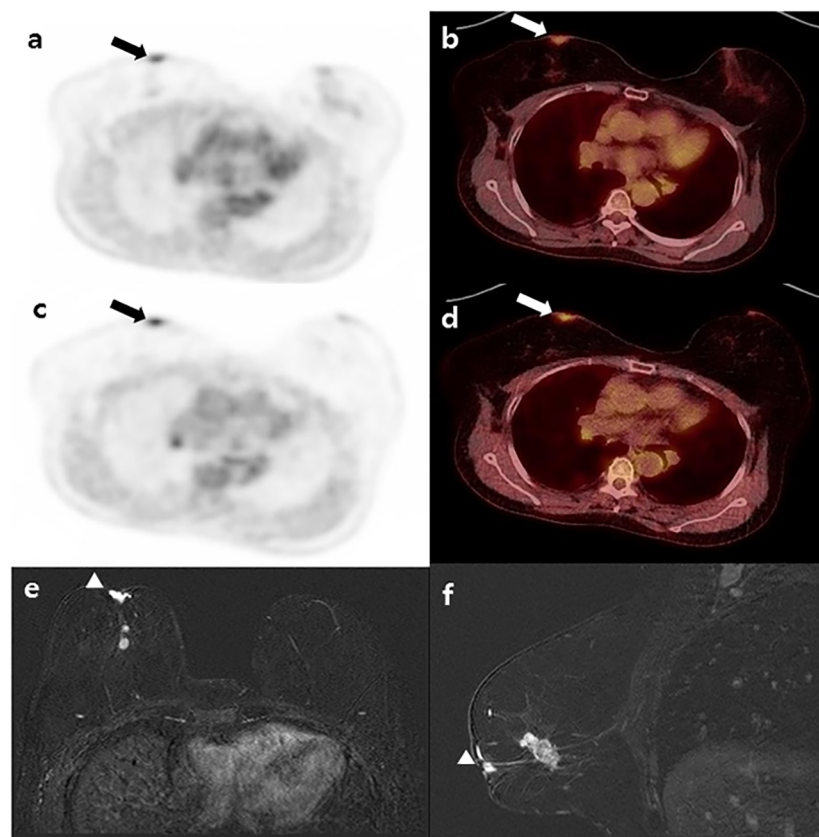
Fig 1. A 51-year-old patient with invasive ductal carcinoma (IDC) in the right breast: (a, b) Early phase ^{18}F-FDG PET and fusion PET/CT; (c, d) Delayed phase PET and fusion PET/CT depict focal FDG uptake in the NAC of the right breast (arrow; ROI of NAC showing green color), NAC-SUVR$_{early}$ = 2.35; NAC-SUVR$_{delay}$ = 2.95; (e) Contrast-enhanced MRI with axial view and (f) MRI with sagittal view; MRI shows unilateral NAC enhancement and asymmetric thickening of the NAC (arrowhead). This patient underwent mastectomy, and NAC involvement was pathologically confirmed.
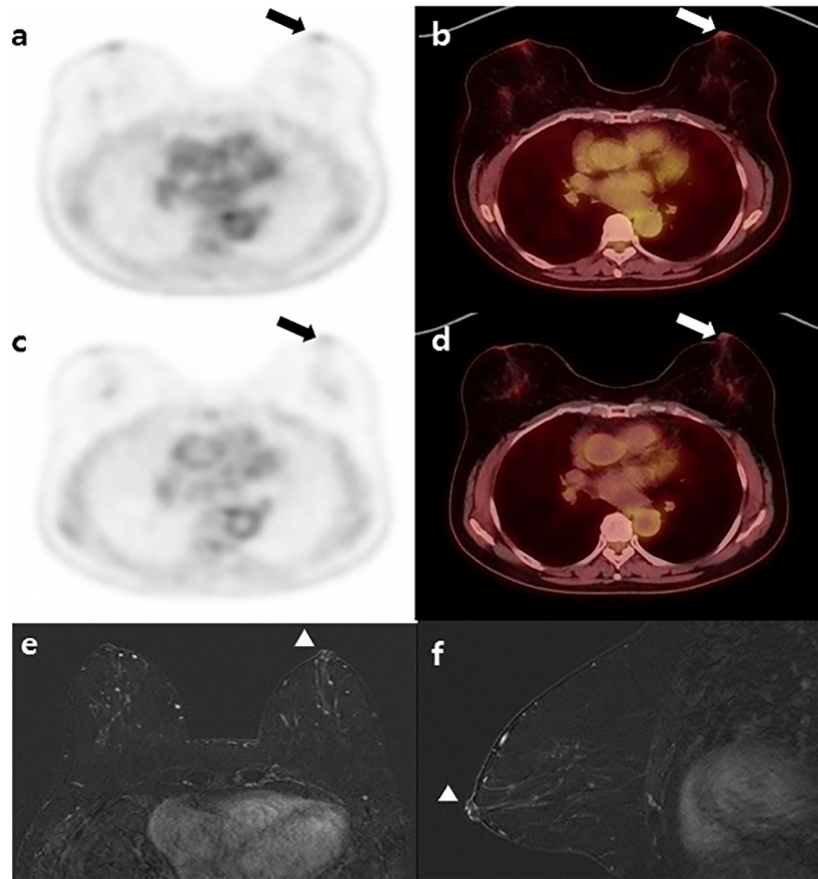
Fig 2. A 48-year-old patient with IDC in the left breast: (a, b) Early phase ^{18}F-FDG PET and fusion PET/CT; (c,d) Delayed phase PET and fusion PET/CT show no significant FDG uptake in the NAC of the left breast (arrow), NAC-SUVR$_{early}$ = 0.95; NAC-SUVR$_{delay}$ = 0.92; (e) Contrast-enhanced MRI with axial view and (f) MRI with sagittal view; MRI reveals no definite evidence of abnormal contrast enhancement of the NAC in the left breast (arrowhead). This patient underwent breast conserving surgery, and pathologic NAC non-involvement was confirmed.

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Discussion

An important finding from our analyses is that quantitative parameters derived from DTP PET/CT, such as both early and delayed phase SUV$_{max}$ ratios of pathologically involved NACs compared to the contralateral normal breast, can offer significant predictive value for determining NAC involvement. However, only the delayed phase parameter appeared to be an independent predictor of NAC involvement in patients with centrally located breast cancer lesions. It is presumed that FDG uptake in cancer cells with an affected NAC would increase and persist on delayed phase images, while the contralateral normal NAC would wash out over time. Several reports have investigated the factors contributing to increased FDG uptake in breast cancer cells on delayed images [22–24].

This study revealed that breast MRI characteristics such as contrast enhancement pattern and distance between the NAC and tumor were correlated with NAC involvement, which is consistent with previous research [11, 20, 25]. Our results are also consistent with results from a previous study that found that clinical symptoms relevant to the NAC and tumor multiplicity were significantly more common in cases with NAC involvement than in those without [10, 14].

Table 4. Univariate analysis for predicting NAC involvement in nipple symptom-free patients.

Factor		Pathologic NAC involvement (n = 10)	No pathologic NAC involvement (n = 66)	P-value
Age (year)		45.5 ± 10.2	51.3 ± 12.5	0.463
Pathologic tumor size (cm)	Median (IQR)	2.45 (0.70–3.30)	2.10 (1.20–3.00)	0.516
ANS	Positive	5	28	0.914
	Negative	5	38	
LVI	Positive	4	18	0.651
	Negative	6	48	
Combined *in situ* component	Positive	9	57	0.853
	Negative	1	9	
Tumor multiplicity	Yes	6	9	0.003*
	No	4	57	
PET/CT				
Qualitative analysis	Positive	5	21	0.440
	Negative	5	45	
NAC-SUVR$_{early}$	Median (IQR)	1.36 (1.12–1.57)	1.06 (0.96–1.27)	0.018*
NAC-SUVR$_{delay}$	Median (IQR)	1.37 (1.15–2.38)	1.06 (0.95–1.22)	0.003*
MRI				
Tumor-to-NAC distance (mm)	Mean ± SD	15.5 ± 10.0	30.1 ± 17.0	0.010*
MR finding	Positive	8	28	0.060
	Negative	2	38	

NAC, nipple-areolar complex; ANS, axillary lymph node status; LVI, lymphovascular invasion; PET/CT, positron emission tomography/computed tomography; NAC-SUVR$_{early}$, ratio of early phase maximal standardized uptake value (SUV$_{max}$) of the NAC in the breast with malignancy to that of the NAC in the contralateral normal breast; NAC-SUVR$_{delay}$, ratio of delayed phase SUV$_{max}$ of the NAC in the malignant breast to that of the NAC in the contralateral normal breast; MRI, magnetic resonance imaging; IQR, interquartile range; SD, standard deviation;

*, p <0.05

In addition, we demonstrated that delayed PET/CT parameter could also be significantly predictive for NAC involvement in breast cancer patients. In the literature of clinically silent NAC involvement, malignancy invasion to the NAC is detected in the range of 8–58% of mastectomy specimens [26–28]. In our study, 13.2% of patients with a clinically normal nipple were determined to have malignancy invasion to the NAC. Based on our findings, tumor multiplicity, tumor-to-NAC distance, and delayed phase of NAC-SUV$_{ratio}$ against the contralateral normal NAC have independently predictive value for NAC involvement in both patient groups with nipple symptom and symptom-free. MR finding according to contrast enhancement patterns was not significantly predictive in the univariate analysis in the symptom-free subgroup, possibly because a considerable number of cases with NAC symptoms were

Table 5. Multivariate analysis for predicting NAC involvement in nipple symptom-free patients.

Variable	Cutoff value	OR	95% CI	p-value
Tumor multiplicity		22.97	2.205–239.211	0.009*
Tumor-to-NAC distance (mm)	≤ 20.0	37.88	2.083–688.586	0.014*
NAC-SUVR$_{delay}$	>1.23	15.45	1.598–149.297	0.018*

NAC, nipple-areolar complex; NAC-SUVR$_{delay}$, ratio of delayed phase SUV$_{max}$ of the affected NAC to that of the unaffected NAC; OR, odds ratio; CI, confidence interval;

*, p <0.05

excluded. To overcome this limitation, further study is needed for a larger group of symptom-free patients.

Our findings depart from those of other studies, since we found that tumor size, ANS, and LVI, which were correlated with NAC involvement in previous reports [12, 20, 25], were not significantly correlated with NAC involvement. We think that these differences are probably due to our relatively small number of research subjects or due to differences in subject populations.

There are several limitations in this study. First, our method for obtaining images with the patient in a prone position for PET/CT is not generally performed in other medical institutions. Supine whole-body image acquisition is still the standard protocol for assessing regional lymph node status and distant metastasis as well as for evaluating primary tumor lesions. Another limiting point may be the methodological problem of quantification. Because two consecutive tests were conducted at regular time intervals, there should be confidence in the high reproducibility of imaging quantification. Since previous studies [29, 30] showed that the mean SUV (SUV$_{mean}$) has higher reproducibility than SUV$_{max}$, it may be necessary to conduct research using SUV$_{mean}$ in the future. DTP PET/CT was performed to acquire images approximately 80 and 120 minutes after administration of radiopharmaceutical agents. The mean ± SD time interval between early and delayed phase prone images was 45 ± 11 minutes. This protocol can lead to less accurate findings in non-avid cancer cells that affect the NAC because these images need to be obtained after longer time delays. However, the consensus for imaging acquisition time periods has not yet been established clinically. Lastly, we considered the pathologic results as the gold standard, including nipple biopsy and frozen sections. These accuracies could depend on variable situations, such as the indication, the location of the lesion, the quality of the pathologic slides, and the expertise of physician, which may cause false-negative findings [31]. This limitation may cause underestimated pathologic NAC involvement in the current study.

Despite these limitations, to the best our knowledge, ours is the first study to evaluate the predictive significance of quantitative parameters for NAC involvement using delayed PET/CT with patients in the prone position and to compare these findings with MRI findings and clinicopathologic factors. In conclusion, quantitative analysis of delay phased PET/CT might aid surgeons in deciding whether nipple saving is possible, as evidenced by NAC involvement, preoperative physical examination, and MRI features. In fact, one patient who had a false negative result according to MRI findings was indicated to be a true positive for NAC involvement according to PET/CT parameters.

Herein, we conclude that quantitative parameters from delayed PET/CT when patients are in a prone position can be used to complement clinicopathologic and MRI factors that are associated with malignant NAC involvement. Regardless of the presence of nipple symptoms on physical examination, delayed PET/CT could be performed for evaluating malignant NAC involvement at the preoperative work-up.

Supporting information

S1 Table. MRI interpretations of study subjects (n = 90).
(DOCX)

Acknowledgments

Author Contributions

Conceptualization: Bom Sahn Kim, Hai-Jeon Yoon.

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Writing – original draft: Jang Yoo.

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References

1. Harness JK, Vetter TS, Salibian AH. Areola and nipple-areola-sparing mastectomy for breast cancer treatment and risk reduction: report of an initial experience in a community hospital setting. Ann Surg Oncol 2011; 18:917–22. https://doi.org/10.1245/s10434-010-1365-9 PMID: 21308484

2. Carty H, McCullough P, Aluwihare N, Matey P. Breast conserving surgery for breast cancer involving the nipple. Breast 2008; 17:107–10. https://doi.org/10.1016/j.breast.2007.07.036 PMID: 17892937

3. Cochrane RA, Valasiadou P, Wilson AR, Al-Ghazal SK, Macmillan RD. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. Br J Surg 2003; 90:1505–9. https://doi.org/10.1002/bjs.4344 PMID: 14648728

4. Carlson GW, Bostwick J 3rd, Styblo TM, Moore B, Bried JT, Murray DR, et al. Skin-sparing mastectomy. Oncologic and reconstructive considerations. Ann Surg 1997; 225:570–5; discussion 575–8. PMID: 9193184

5. Toth BA, Lappert P. Modified skin incisions for mastectomy: the need for plastic surgical input in preoperative planning. Plast Reconstr Surg 1991; 87:1048–53. PMID: 1852020

6. Ueda S, Tamaki Y, Yano K, Okishiro N, Yanagisawa T, Imasato M, et al. Cosmetic outcome and patient satisfaction after skin-sparing mastectomy for breast cancer with immediate reconstruction of the breast. Surgery 2008; 143:414–25. https://doi.org/10.1016/j.surg.2007.10.006 PMID: 18291263

7. Gerber B, Krause A, Reimer T, Muller H, Kuchenmeister I, Makovitzky J, et al. Skin-sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction is an oncologically safe procedure. Ann Surg 2003; 238:120–7. https://doi.org/10.1097/01.SLA.0000077922.38307.cd PMID: 12832974

8. Nahabedian MY, Tsangaris TN. Breast reconstruction following subcutaneous mastectomy for cancer: a critical appraisal of the nipple-areola complex. Plast Reconstr Surg 2006; 117:1083–90. https://doi.org/10.1097/01.prs.0000202103.78284.97 PMID: 16582769

9. Torresan RZ, dos Santos CC, Okamura H, Alvarenga M. Evaluation of residual glandular tissue after skin-sparing mastectomies. Ann Surg Oncol 2005; 12:1037–44. https://doi.org/10.1245/ASO.2005.11.027 PMID: 16244800

10. Billar JA, Dueck AC, Gray RJ, Wasif N, Pockaj BA. Preoperative predictors of nipple-areola complex involvement for patients undergoing mastectomy for breast cancer. Ann Surg Oncol 2011; 18:3123–8. https://doi.org/10.1245/s10434-011-2008-5 PMID: 21861222

11. D'Alonzo M, Martincich L, Biglia N, Pisacane A, Maggiorotto F, Rosa GD, et al. Clinical and radiological predictors of nipple-areola complex involvement in breast cancer patients. Eur J Cancer 2012; 48:2311–8. https://doi.org/10.1016/j.ejca.2012.04.017 PMID: 22647686

12. Gulben K, Yildirim E, Berberoglu U. Prediction of occult nipple-areola complex involvement in breast cancer patients. Neoplasma 2009; 56:72–5. PMID: 19152249

13. Pirozzi PR, Rossetti C, Carelli I, Ruiz CA, Pompei LM, Piato S. Clinical and morphological factors predictive of occult involvement of the nipple-areola complex in mastectomy specimens. Eur J Obstet Gynecol Reprod Biol 2010; 148:177–81. https://doi.org/10.1016/j.ejogrb.2009.10.021 PMID: 19926200

14. Wang J, Xiao X, Wang J, Iqbal N, Baxter L, Skinner KA, et al. Predictors of nipple-areolar complex involvement by breast carcinoma: histopathologic analysis of 787 consecutive therapeutic mastectomy specimens. Ann Surg Oncol 2012; 19:1174–80. https://doi.org/10.1245/s10434-011-2107-3 PMID: 22006374

15. Canevari C, Gallivanone F, Zuber V, Marassi A, Losio C, Gianolli L, et al. Prone 18F-FDG PET/CT changes diagnostic and surgical intervention in a breast cancer patient: some considerations about

PET/CT imaging acquisition protocol. Clin Imaging 2015; 39:506–9. https://doi.org/10.1016/j.clinimag. 2014.11.005 PMID: 25620014

16. Teixeira SC, Koolen BB, Vogel WV, Wesseling J, Stokkel MP, Vrancken Peeters MJ, et al. Additional Prone 18F-FDG PET/CT Acquisition to Improve the Visualization of the Primary Tumor and Regional Lymph Node Metastases in Stage II/III Breast Cancer. Clin Nucl Med 2016; 41:e181–6. https://doi.org/ 10.1097/RLU.0000000000001101 PMID: 26704731

17. Mavi A, Urhan M, Yu JQ, Zhuang H, Houseni M, Cermik TF, et al. Dual time point 18F-FDG PET imaging detects breast cancer with high sensitivity and correlates well with histologic subtypes. J Nucl Med 2006; 47:1440–6. PMID: 16954551

18. Zytoon AA, Murakami K, El-Kholy MR, El-Shorbagy Ebied O. Breast cancer with low FDG uptake: characterization by means of dual-time point FDG-PET/CT. Eur J Radiol 2009; 70:530–8. https://doi.org/10. 1016/j.ejrad.2008.01.045 PMID: 18395387

19. Vlajcic Z, Zic R, Stanec S, Lambasa S, Petrovecki M, Stanec Z. Nipple-areloa complex preservation: Predictive factors of neoplastic nipple-areola complex invasion. Ann Plast Surg 2005; 55:240–244. PMID: 16106159

20. Cho J, Chung J, Cha ES, Lee JE, Kim JH. Can preoperative 3-T MRI predict nipple-areolar complex involvement in patients with breast cancer? Clin Imaging 2016; 40:119–24. https://doi.org/10.1016/j. clinimag.2015.08.002 PMID: 26423158

21. Steen ST, Chung AP, Han SH, Vinstein AL, Yoon JL, Giuliano AE. Predicting nipple-areolar involvement using preoperative breast MRI and primary tumor characteristics. Ann Surg Oncol 2013; 20:633–9. https://doi.org/10.1245/s10434-012-2641-7 PMID: 22965571

22. Caprio MG, Cangiano A, Imbriaco M, Soscia F, Di Martino G, Farina A, et al. Dual-time-point [18F]-FDG PET/CT in the diagnostic evaluation of suspicious breast lesions. Radio Med 2010; 115:215–24.

23. Zytoon AA, Murakami K, El-Kholy MR, El-Shorbagy. Dual time point FDG-PET/CT imaging. . .Potential tool for diagnosis of breast cancer. Clin Radiol 2008; 63:1213–27. https://doi.org/10.1016/j.crad.2008. 03.014 PMID: 18929039

24. Kumar R, Loving VA, Chauhan A, Zhuang H, Mitchell S, Alavi A. Potential of dual-time-point imaging to improve breast cancer diagnosis with (18)F-FDG PET. J Nucl Med 2005; 46:1819–24. PMID: 16269595

25. Ponzone R, Maggiorotto F, Carabalona S, Rivolin A, Pisacane A, Kubatzki F, et al. MRI and intraoperative pathology to predict nipple-areola complex (NAC) involvement in patients undergoing NAC-sparing mastectomy. Eur J Cancer 2015; 51:1882–9. https://doi.org/10.1016/j.ejca.2015.07.001 PMID: 26210374

26. Sarica O, Zeybek E, Ozturk E. Evaluation of nipple-areolar complex with ultrasonography and magnetic resonance imaging. J Comput Assist Tomogr 2010; 34:575–586. https://doi.org/10.1097/RCT. 0b013e3181d74a88 PMID: 20657228

27. Cense HA, Rutgers EJ, Lopes Cardozo M, Van Lanschot JJ. Nipple sparing mastectomy in breast cancer: a vaible option? Eur J Surg Oncol 2001; 27:521–526. https://doi.org/10.1053/ejso.2001.1130 PMID: 11520082

28. Moon JY, Chang YW, Lee EH, Seo DY. Malignant invasion of the nipple-areolar complex of the breast: usefulness of breast MRI. Am J Roentgenol 2013; 201:448–455.

29. Nahmias C, Wahl LM. Reproducibility of standardized uptake value measurements determined by 18F-FDG PET in malignant tumors. J Nucl Med 2008; 49:1804–1808. https://doi.org/10.2967/jnumed.108. 054239 PMID: 18927325

30. Krak N, Boellaard R, Hoekstra OS, Twisk JW, Hoekstra CJ, Lammertsma AA. Effects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial. Eur J Nucl Med Mol Imaging 2005; 32:294–301. https://doi.org/10.1007/s00259-004-1566-1 PMID: 15791438

31. Kneubil MC, Lohsiriwat V, Curigliano G, Brollo J, Botteri E, Rotmensz N, et al. Risk of locoregional recurrence in patients with false-negative frozen section or close margins of retroareolar specimen in nipple-sparing mastectomy. Ann Surg Oncol 2012; 19:4117–4123. Response to Reviewers https://doi. org/10.1245/s10434-012-2514-0 PMID: 22820937