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The role of PET and MRI in evaluating the feasibility of skin-sparing mastectomy following neoadjuvant therapy

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Abstract

Objective: To investigate the role of positron emission tomography (PET) and magnetic resonance imaging (MRI) in evaluating the feasibility of skin-sparing mastectomy in patients with locally-advanced breast cancer (LABC) who will undergo neoadjuvant chemotherapy (NAC) by evaluating the sensitivity and specificity of PET and MRI compared with skin biopsy results before and after NAC treatment.

Methods: Patients with LABC who were treated with NAC between November 2013 and November 2015 were included in this study. Demographic, clinical, radiological and histopathological features of the patients were recorded.

Results: A total of 30 patients were included in the study with a mean age of 52.6 years (range, 35–70 years). Sensitivity and specificity for detecting skin involvement in LABC was 100%/10% (62%/85%) with MRI and 60%/80% (12%/92%) with PET before (after) NAC, respectively. When radiological skin involvement was assessed in relation to the final histopathological results, the preNAC PET results and histopathological skin involvement were not significantly different; and there was no difference between postNAC MRI and histopathological skin involvement.

Conclusions: As preNAC PET and postNAC MRI more accurately determined skin involvement, it might be possible to use these two radiological evaluation methods together to assess patient suitability for skin-sparing mastectomy in selected patients.

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Keywords
Locally-advanced breast cancer, skin-sparing mastectomy, PET, MRI

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Introduction

Breast cancer is the most common cancer among women.[1] Although the frequency of breast cancer is increasing, the rates of mortality are decreasing in developed countries but are increasing in low-to-middle income countries.[2] The most important reasons for this increase in frequency are the widespread use of screening mammography combined with increased life span, changes in reproductive functions, environmental factors, lack of exercise, stress, and increased consumption of products containing additives.[2] Locally-advanced breast cancer (LABC) accounts for 5–15% of newly diagnosed breast cancers in developed countries.[2] In the low-to-middle income countries, the LABC rate is over 50%.[3] LABC is a heterogeneous group of patients in terms of staging and the risk of local/regional and systemic recurrence is high.[4] LABC includes clinical stage IIB (T3N0M0) and stages IIIA, IIIB, and IIIC.[5] The high rate of systemic metastases in LABC patients results in treatment being initiated with chemotherapy.[5] In the last 20 years, neoadjuvant chemotherapy (NAC) has begun to be applied as a standard treatment in patients with LABC.[5,6] With the new generation of chemotherapeutic agents, the complete pathological response rate has reached 30%.[7] The application of chemotherapy prior to surgical treatment has the advantage of determining the sensitivity of the tumour to chemotherapy and allows the tumour to shrink and facilitates breast-conserving surgery in selected cases.[5,8] The most important disadvantages of NAC are tumour progression and the difficulty of surgical treatment in chemotherapy-insensitive patients.[8] In previous studies, NAC showed partial responses in 70–80% and complete clinical responses in 15–20% of patients with stage IIIA and IIIB disease.[9–14] Factors such as complete resolution of skin swelling as a result of chemotherapy, residual mass < 5 cm (appropriate breast/tumour ratio), no skin or thorax wall invasion, no suspected widespread microcalcification and multicentricity on mammography, tumour being unifocal or multifocal, having no contraindications for radiotherapy and the patient requesting breast-conserving surgery were considered for breast-conserving surgery.[15] In patients with skin involvement in LABC, it has been found that the involvement regressed and completely resolved following chemotherapy.[16] If this regression, which can be confirmed by histopathological examination, could be predicted before NAC, then skin-sparing mastectomy and/or prosthesis may be applied to patients in whom mastectomy was planned after NAC therapy. In cases where breast-conserving surgery is not performed due to multifocal and multicentric disease, oncoplastic surgeries performed via this method had positive findings and reliable oncological results were reported.[16]

Radiological imaging methods are able to successfully assess skin involvement.[17] In particular, dynamic contrast-enhanced magnetic resonance imaging (MRI) and oncological positron emission tomography (PET) are widely used to evaluate treatment response and to help plan surgery in patients with LABC treated with NAC.[18–21]

This study investigated the role of PET and MRI in evaluating the feasibility of skin-sparing mastectomy in patients with LABC who will undergo NAC by evaluating the sensitivity and specificity of PET and

MRI compared with skin biopsy results before and after NAC treatment.

Patients and methods

Study population

This prospective observational study enrolled consecutive patients with LABC who were due to be treated with NAC in the Department of General Surgery, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey between November 2013 and November 2015. Demographic, clinical, radiological and histopathological features of the patients were recorded. The exclusion criteria were as follows: (i) patients who did not accept skin-sparing mastectomy; (ii) patients who did not agree to participate in the study; (iii) patients who definitely had skin involvement or those who were suspected of having skin involvement after NAC; (iv) patients who had preNAC satellite skin lesions.

Ethics committee approval for this study was obtained from the local Ethics Committee of the Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey (no. 71306642/050-01-04/262). Patients who agreed to participate in the study provided written informed consent. All study procedures were carried out in accordance with the Declaration of Helsinki.

Pretreatment evaluation

Patients with LABC who had stage IIB–IIIC disease underwent a full physical examination and radiological investigations (mammography, ultrasonography, MRI). A pathological diagnosis was made using a routine core biopsy. PET/computed tomography (PET/CT) was undertaken to investigate the presence of systemic metastases. All fluorodeoxyglucose (FDG)-PET/CT examinations were performed using a PET/CT scanner combined with 16-multi-detector computed tomography (Biograph 16 PET/CT system; Siemens Medical Solutions, Knoxville, USA). Patients were instructed to fast for 5h before the scan, and blood glucose was measured immediately before an intraven-ous injection of 4.0 MBq/kg body weight FDG. No patients showed a blood glucose level >160 mg/dl. Static emission images were obtained approximately 60 min after the FDG injection. For attenuation correc-tion and anatomical localization, helical CT scans from the top of the head to the bottom of the feet were obtained. Immediately after completion of the CT, PET images of the region from the head to the mid-thigh were acquired for 3 min per bed position. Attenuation-corrected PET images were reconstructed with an ordered-subset expectation maximization iterative reconstruction algorithm (18 subsets, 2 iterations).[22] SUVmax values were calculated as described previously.[23] In patients with suspected clinical or radiological skin involvement, an additional skin biopsy was performed and the presence of tumour was recorded. Two dimensional regions of interest were placed in areas of tracer uptake and measures of ^{18}F-fluorodeoxyglucose accumulation were recorded, including SUVmax, SUVmean. A background SUVmax was also measured for each examination.[24] A SUVmax cut-off value for skin involvement of 5 has been previously suggested.[25] However, this cut-off value has not been proven to be applicable to all patients. When an elevated FDG uptake was demonstrated on the PET scan, this suggested skin involvement, so it was better to compare scans before and after NAC.

Systemic treatment and response

Neoadjuvant chemotherapy was administered using regimens containing taxane and anthracycline every 3 weeks as described as follows. Six cycles of the TAC regimen (75 mg/m^2 docetaxel; 50 mg/m^2 doxorubicin;

500 mg/m^2 cyclophosphamide; all administered intravenously every 3 weeks) or four cycles of the AC regimen (60 mg/m^2 doxorubicin; 600 mg m^2 cyclophosphamide; all administered intravenously every 3 weeks) and four courses of docetaxel (100 mg/m^2 administered intravenously every 3 weeks) were applied. Trastuzumab was added to the regimens for the treatment of patients with tumours that were positive for human epidermal growth factor receptor 2 receptor (HER2). Patients received 6 mg/kg trastuzumab intravenously every 3 weeks concomitantly with all chemotherapy cycles, starting with a loading dose of 8 mg/kg trastuzumab intravenously on day 1 of the first AC regimen. If chemotherapy was discontinued early, the missed trastuzumab cycles were given postoperatively. Total pre- and postoperative duration of trastuzumab treatment was 1 year.

Pathological complete response to chemotherapy (pCR) was defined as complete resolution of the tumour both in the breast and axilla. Partial response (pPR) was defined as $\geq 30\%$ shrinkage of the largest diameter of the tumour. Minimal regression or stabilization of the tumour was defined as unresponsiveness to chemotherapy. Routine radiotherapy and hormone therapy in hormone receptor-positive patients were applied following surgery.

Receptor immunohistochemistry

Routine immunohistochemistry was performed on formalin-fixed, paraffin-embedded breast cancer tissues. Oestrogen receptor (ER) (Clone SP1; Thermo Fisher Scientific Inc., Rockford, IL, USA) and progesterone receptor (PR) (Clone SP2; Thermo Fisher Scientific Inc.) status was considered as positive if $> 10\%$ of tumour cells showed staining.

An immunohistochemical score of 3 + or fluorescence *in situ* hybridization (FISH) (INFORM HER2 Dual ISH DNA Probe Cocktail Assay; Ventana Medical Systems, Tuscon, Arizona, USA) for HER2 was accepted as HER2 positivity.

A mindbomb E3 ubiquitin protein ligase 1 (MIB-1) clone (Dako, Glostrup, Denmark) was used for the immunohistochemical analysis of Ki-67. Immunohistochemical staining was quantitatively evaluated by light microscopy, in which the entire tissue section was scanned at low-power magnification ($\times 10$) to determine areas with the highest number of positive nuclei (hot-spots) within the invasive component. Ki-67 was expressed as the percentage of cells positive for MIB-1 among a total of at least 1000 malignant cells at high-power magnification ($\times 40$). Nuclear staining of the tumour cells was considered negative if $\leq 14\%$ were stained for Ki-67 and as positive if $> 14\%$ were stained for KI-67.

The final pathological response was assessed using the Miller–Payne grading system, in which pathological response is divided into five grades based on a comparison of tumour cellularity between the preNAC core biopsy and a definitive surgical specimen. The Miller–Payne grading system is as follows: grade 1: no change or some minor alteration in individual malignant cells, but no reduction in overall cellularity; grade 2: a minor loss of tumour cells, but overall cellularity remains high with up to 30% reduction of cellularity; grade 3: between an estimated 30% and 90% reduction in tumour cellularity; grade 4: a marked disappearance of $> 90\%$ of tumour cells such that only small clusters or widely dispersed individual cells remain (almost pCR); and grade 5: no invasive malignant cells identifiable in sections from the site of the tumour (pCR).

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Descriptive statistical methods (mean, number, percentage, median) were

used to evaluate the data. For survival analyses, the time between the first pathological diagnosis of the tumour and the local/regional first recurrence of the disease was calculated as local recurrence-free survival and time to local/regional recurrence of the disease or distant organ metastasis was calculated as disease-free survival. Follow-up time was defined as the time between first pathological diagnosis date and the last appointment date for the patient. Survival calculations were undertaken using the Kaplan–Meier method. The log-rank univariate analysis test was used to investigate tumour and patient characteristics; and the effects of skin involvement on local and systemic recurrence. The effects of multiple factors on skin involvement were investigated by Cox regression test in multivariate analyses and the proportional differences between the groups were calculated using χ^2-test (Continuity Correction, Fisher's Exact Test). The relationship between skin involvement in PET and MRI findings with histopathological skin involvement was assessed using McNemar's test. A P-value ≤ 0.05 was considered statistically significant.

Results

A total of 30 patients with LABC were enrolled in the study (mean age, 52.6 years; range, 35–70 years). The detailed characteristics of the tumours are presented in Table 1. Complete response rates following NAC were five (16.7%), two (6.7%) and three (10.0%) patients when using PET, MRI and histopathology, respectively. According to the presence of tumour receptors, 10 (33.3%) patients were evaluated as luminal A, nine (30.0%) were evaluated as luminal B, six (20.0%) were evaluated as HER2-enriched and five (16.7%) were evaluated as triple-negative. Eighteen (60.0%) patients were surgically treated with classical mastectomy, 10 (33.3%) with breast-conserving surgery and two (6.7%) with skin-sparing mastectomy.

The presence of skin involvement before and after NAC was assessed by PET and MRI (Table 2). Patients with clinical and radiological evidence of skin involvement were confirmed using a skin biopsy before NAC was undertaken. After NAC, skin involvement was recorded in surgical specimens using a histopathological examination. There was skin involvement in 14 (46.7%) patients on PET scans before NAC and in three (10.0%) patients on PET scans after NAC. Skin involvement was recorded in 29 (96.7%) patients on MRI scans before NAC and in 12 (40.0%) on MRI scans after NAC. The final histopathological examinations found skin involvement in 16 (53.3%) patients.

When radiological skin involvement was assessed in relation to the final histopathological results, the preNAC PET results and histopathological skin involvement were not significantly different (Table 3). PostNAC PET and histopathological skin involvement were significantly different ($P = 0.001$). PreNAC MRI and histopathological skin involvement were also significantly different ($P = 0.001$), but there was no significant difference between postNAC MRI and histopathological skin involvement. These results suggest that preNAC PET and postNAC MRI more accurately identified skin involvement than postNAC PET and preNAC MRI. Table 4 presents the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of preNAC PET, postNAC PET, preNAC MRI and postNAC MRI for predicting skin involvement.

There was no significant relationship between preNAC multifocality and skin involvement (data not shown). Regression of skin involvement was observed with the increase of radiological and pathological response given to neoadjuvant therapy (data not shown). Seven of 18 patients who

Table 1. Tumour features of patients ($n = 30$) with locally-advanced breast cancer who underwent neoadjuvant chemotherapy (NAC) and who participated in this study to investigate the role of positron emission tomography (PET) and magnetic resonance imaging (MRI) in evaluating the feasibility of skin-sparing mastectomy.

	Study cohort $n = 30$
PreNAC stage	
IIIB	20 (66.7)
IIIC	10 (33.3)
PostNAC stage	
0	2 (6.7)
IA	6 (20.0)
IB	0 (0.0)
IIA	4 (13.3)
IIB	5 (16.7)
IIIA	5 (16.7)
IIIB	5 (16.7)
IIIC	1 (3.3)
Tumour receptor status	
ER+/PR+/HER2– (luminal A)	10 (33.3)
ER+/PR+/HER2+ (luminal B)	9 (30.0)
ER–/PR–/HER2+ (HER2-enriched)	6 (20.0)
ER–/PR–/HER2– (triple-negative)	5 (16.7)
Radiological response in PET	
Partial	25 (83.3)
Complete	5 (16.7)
Radiological response in MRI	
Partial	28 (93.3)
Complete	2 (6.7)
Histopathological response (Miller–Payne)	
1	2 (6.7)
2	10 (33.3)
3	9 (30.0)
4	6 (20.0)
5	3 (10.0)
Type of surgery	
Classical mastectomy	18 (60.0)
Breast-conserving surgery	10 (33.3)
Skin-sparing mastectomy	2 (6.7)
Tumour type	
Invasive ductal carcinoma	26 (86.7)
Invasive lobular carcinoma	1 (3.3)
Other	3 (10.0)
Axilla positivity	
PreNAC radiology	
PET	25 (83.3)
MRI	29 (96.7)
PostNAC radiology	
PET	9 (30.0)
MRI	14 (46.7)
Histopathology	20 (66.7)

Data presented as *n* of patients (%).
ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 2. Evaluation of skin involvement in patients ($n = 30$) with locally-advanced breast cancer who underwent neoadjuvant chemotherapy (NAC) and who participated in this study to investigate the role of positron emission tomography (PET) and magnetic resonance imaging (MRI) in evaluating the feasibility of skin-sparing mastectomy.

	Study cohort $n = 30$
PreNAC PET	14 (46.7)
PostNAC PET	3 (10.0)
PreNAC MRI	29 (96.7)
PostNAC MRI	12 (40.0)
Histopathology (final pathology)	16 (53.3)
Skin biopsy(before treatment)	20 (66,6)

Data presented as *n* of patients (%).

underwent classical mastectomy were histopathologically negative for skin involvement following surgery. Skin involvement was histopathologically negative in six of 10 patients who underwent breast-conserving surgery and in one of two patients who underwent skin-sparing mastectomy. Systemic and axillary recurrence was observed during follow-up in the one patient with skin involvement who underwent skin-sparing mastectomy. This patient's preNAC MRI and PET scans identified skin

Table 3. Assessment of concordance between radiological and pathological skin involvement assessments in patients ($n = 30$) with locally-advanced breast cancer who underwent neoadjuvant chemotherapy (NAC) and who participated in this study to investigate the role of positron emission tomography (PET) and magnetic resonance imaging (MRI) in evaluating the feasibility of skin-sparing mastectomy.

	Histopathology skin positivity	Statistical significance[a]
PreNAC PET	8 (57,1)	NS
PostNAC PET	2 (12.5)	$P = 0.001$
PreNAC MRI	15 (93,75)	$P = 0.001$
PostNAC MRI	10 (62.5)	NS

Data presented as *n* of patients (%).
[a]NS, no significant difference ($P > 0.05$). McNemar's test

Table 4. Assessment of the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the role of positron emission tomography (PET) and magnetic resonance imaging (MRI)for predicting skin involvement in skin biopsies prior to chemotherapy and final pathologies in patients ($n = 30$) with locally-advanced breast cancer who underwent neoadjuvant chemotherapy (NAC).

	PPV, %	NPV, %	Sensitivity, %	Specificity, %
PreNAC PET	85,7	50	60	80
PostNAC PET	66,6	48,1	12,5	92,6
PreNAC MRI	68,9	100	100	10
PostNAC MRI	83,3	66,6	62,5	85,7

involvement, but no skin involvement was observed on radiological imaging after NAC.

The mean duration of follow-up was 22.4 months. Local recurrence was observed in five (16.7%) patients. Both local and systemic recurrence occurred in one of these patients. Axillary recurrence occurred in three patients (10.0%). There was no significant relationship between postNAC MRI and PET or histopathological skin involvement and local or systemic recurrence (data not shown). There was no significant relationship between local and systemic recurrence and the type of surgery undertaken (data not shown). There was no significant relationship between the presence of ER, PR, HER2 receptors or Ki-67 protein and histopathological skin involvement (data not shown). As the Ki-67 values of patients are different and as it is not related to skin involvement, the Ki-67 data are not presented in Table 1.

Discussion

Neoadjuvant chemotherapy is accepted as the standard treatment approach in LABC.[8] Evaluation of the response to NAC in LABC is traditionally performed by ultrasonography or mammography. However, with these methods, it is not always possible to distinguish residual tumour from fibrosis. At present, ^{18}F-FDG PET/CT and MRI are frequently used in clinical practice. Several studies suggest the combined use of MRI and PET for the prediction of histopathological complete response after NAC.[24–29]

Determination of the presence and extent of residual tumour after NAC is also important in planning the surgical approach to be performed. Effective use of preoperative imaging methods allows appropriate surgery to be planned and successfully applied to the patient.[30] However, consideration should be given to which imaging method is more accurate at this stage.[31,32] A previous study that compared the efficacy of MRI to determine the histopathological response to NAC concluded that its sensitivity was 68% and specificity was 91%.[33] In this present study, these values were 100%/10% for MRI before NAC and 62%/85% for MRI after NAC, respectively. A previous study that investigated the efficacy of PET for predicting the histopathological response to NAC concluded that the

sensitivity was 80.5% and specificity was 72%.[34] In this present study, these values were 60%/80% for PET before NAC and 12%/92% for PET after NAC, respectively. PET may be able to demonstrate the presence of viable tumour cells more effectively, but it may be difficult to differentiate between the presence of inflammation and tumour cells. MRI can produce a false 'complete response' result when, despite tumour cell destruction by the chemotherapy, a residual tumour cell population remains. According to these results, considering the high sensitivity specivity and positive predictive value of PET before NAC and of MRI after NAC, it may be appropriate to use the two modalities together for effective and appropriate preoperative planning.

Skin-sparing mastectomy has become widely used in recent years, especially in patients undergoing prophylactic mastectomy or those with early-stage breast cancer. It was first described by Freeman in 1962[35] and modified by Toth and Lappert in 1991.[36] Using this method, as much skin as possible is spared while the nipple areola complex is resected with breast tissue. Sparing the natural skin covering also increases the aesthetic success of the reconstruction methods. However, there are still concerns about its success for oncological outcomes and its negative effects on local and systemic recurrence when compared with standard mastectomy.[37,38] However, studies have shown that breast-conserving mastectomy and classical mastectomy have similar local and systemic recurrence rates.[16,39] Despite the controversial application of skin-sparing mastectomy, especially in advanced breast cancer, successful results of recent applications in this group of patients have been reported.[39] A previous study that compared skin-sparing mastectomy and classical mastectomy demonstrated no significant difference in the local, regional, and systemic recurrence rates between these two techniques despite the fact that the local recurrence rate increases with increased stage.[40] Similarly, another study that evaluated skin-sparing mastectomy in LABC found that irrespective of the histopathological complete response rate, skin-sparing mastectomy was not associated with high local recurrence.[41] In NAC-treated patients undergoing breast-conserving surgery and classical mastectomy, both surgeries showed similar results for local recurrence.[11,12] Prospective studies that investigate the effect of different surgical techniques over longer follow-up periods may lead to more accurate findings. Predicting histopathological complete response, demonstrating axillary nodal involvement, and measuring biological markers have been widely applied in studies that have aimed to determine the effectiveness of the radiological methods used in the evaluation of treatment response after NAC.[42] However, to the best of our knowledge, no studies have specifically investigated the effectiveness of various radiological evaluation methods for predicting skin involvement. In this present study, the role of PET and MRI for identifying skin involvement preNAC and postNAC was investigated in order to demonstrate the feasibility of using skin-sparing mastectomy. When these modalities were evaluated separately before and after NAC, it was concluded that preNAC PET and postNAC MRI more accurately identified skin involvement.

This present study had several limitations. First, the number of patients was small. Secondly, the follow-up period was relatively short. Extending the follow-up period would allow for a more reliable evaluation of local and systemic recurrence rates to be made.

In conclusion, preNAC PET and postNAC MRI more accurately determined skin involvement, so it might be possible to use these two radiological evaluation methods together to assess patient suitability

for skin-sparing mastectomy in selected patients.

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Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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