RESEARCH ARTICLE

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The Rush to Evaluate Response at the End of Treatment in Breast Cancer Patients Who Received Neoadjuvant Treatment: Which Tests are Effective in The Selection of Surgical Technique?

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Abstract

Introduction: Evaluating the treatment response after neoadjuvant therapy (NAT) is essential for determining the surgical approach and planning adjuvant therapy. A variety of imaging methods are available to monitor tumor response. Mammography (MG) and breast ultrasonography (US) combined with physical examination are the most commonly used assessment methods. Our study investigates the impact of imaging techniques used during the NAT process on selecting surgical techniques after NAT. **Materials and Methods:** Patients who underwent surgery after NAT for breast cancer at the Etlik City Hospital Surgical Oncology clinic were retrospectively reviewed. These patients had local and systemic imaging performed using similar methods during before and after NAT. Radiological assessment was performed by examining changes in mammography, breast US, breast MRI, and PET findings before and after NAT. The study examined changes in planned surgical techniques before NAT and the influence of different imaging modalities on these decisions after NAT. **Results:** In patients who were converted back to mastectomy, MRI was found to be the most effective imaging method. In patients converted to lumpectomy, MG and USG were most effective The axillary US stood out as the most effective examination modality for the decision to perform an axillary intervention. PET had no impact on the choice of surgical technique for the breast. Among the 4 patients who were decided to undergo axillary dissection based on PET, none showed lymph node metastasis. **Conclusion:** In patients who have undergone NAT and are making decisions regarding surgery, PET imaging cannot be used to guide the surgical decision or approach for the primary tumour and axilla. In addition, PET is unsuitable for axillary staging.

Keywords: Breast cancer imaging- neoadjuvant therapy response evaluation- positron emission tomography imaging

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Introduction

Neoadjuvant chemotherapy is recommended in patients with locally advanced breast cancer without distant metastasis. Neoadjuvant treatment (NAT) is administered before surgery to reduce T and N stages of tumours. NAT is increasingly used in the treatment of breast cancer. Distinct regression was observed with NAT in specific histological subtypes, such as triple-negative and HER2-positive breast cancers. For patients with breast cancer who require mastectomy, NAT provides an opportunity for breast-conserving surgery (BCS). By reducing the volume of tissue that must be removed, NAT can increase the surgeons' options for local treatment. Additionally, NAT can prevent axillary dissection in patients with lymph node metastasis before treatment [1-3].

Evaluation of the response to treatment after NAT is crucial, as it plays a significant role in determining the surgical method and adjuvant therapy. Achieving a complete tumor response after NAT is associated with improved disease-free and overall survival rates. Although a physical examination is important for assessing the response to treatment, it can be misleading. Various imaging methods are available to track the tumour response. Mammography (MG) and breast ultrasonography (US) combined with physical examination are the most commonly used assessment methods [4]. Medical oncologists apply their own imaging algorithms when deciding whether to continue systemic therapy. However, imaging methods that can guide surgical techniques at the end of NAT have not been sufficiently clarified.

Our study investigates the impact of imaging techniques used during the NAT process on selecting surgical techniques after NAT.

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Materials and Methods

Patients who underwent surgery after NAT for breast cancer at the Etlik City Hospital Surgical Oncology clinic were retrospectively reviewed. These patients had local and systemic imaging performed using similar methods during before and after NAT.

Demographic and tumour-related data of the patients, including age, menopausal status, T and N stages, grade, and biological subtype, were recorded. Patients who underwent MG, breast US, breast magnetic resonance imaging (MRI), and positron emission tomography (PET) before and after NAT were included in the study. The physical response to NAT was documented in patient files, with pre- and post-NAT examinations conducted by the same team.

Radiological assessment was performed by examining changes in mammography, breast US, breast MRI, and PET findings before and after NAT. Treatment response was evaluated using RECIST criteria. According to RECIST 1.1, a complete response is defined as the disappearance of all target lesions and reducing any pathological lymph nodes to less than 10 mm. A partial response was defined as at least a 30% decrease in the sum of the diameters of the target lesions from baseline values. Progressive disease was defined at least a 20% increase in the sum of the diameters of the target lesions or if a new lesion greater than 5 mm appeared. Lesions that remain stable but do not meet the specified criteria are categorised as stable diseases [5].

The study examined changes in planned surgical techniques before NAT and the influence of different imaging modalities on these decisions after NAT. Descriptive statistics for categorical variables were presented as numbers and percentages, while quantitative variables were presented as means. Logistic regression analysis was performed to evaluate the impact of radiological imaging methods on the previously determined surgical treatment approach in the post-NAT period. Effect sizes of the variables were calculated using odds ratios. The SPSS v25 software package was used for the analysis, and a p-value of <0.05 was considered statistically significant.

Ethical approval for this study was obtained from the Ethics Committee of Ankara Etlik City Hospital (approval number: AESH-BADEK-2024-243).

Results

This study included 148 patients with an average age of 42 ± 4.1 years. Among them, 104 (70%) were premenopausal, and 44 (30%) were postmenopausal. Prior to NAT, mean tumour size was 3.3 ± 1.2 cm. Tumour sizes were classified as T1 in 24 patients (16%), T2 in 70 patients (47%), and T3 in 54 patients (37%). Regarding axillary status, 78 patients (53%) were N0, and 70 patients (47%) were N1. The histological grades were as follows: 16 patients (11%) were grade 1, 48 (32%) were grade 2, and 84 (57%) were grade 3. Regarding biological subtypes, 76 patients had luminal A/B, 32 had triple-negative (TN), and 40 had HER2+ (Table 1).

Ninety-seven patients (66%) underwent BCS/oncoplastic surgery (OPS), 14 (9%) underwent nipple-sparing mastectomy (NSM) / skin-sparing mastectomy (SSM), and 37 (25%) underwent mastectomy and reconstructive surgery. Among the 38 patients (39%) who underwent BCS, 15 (39 %) underwent the racket technique, inferior/superior pedicled reduction mammoplasty (29 patients, 30%), vertical mammoplasty (15 patients, 15.5%), fusiform/radial mammoplasty 15 patients (15.5%) techniques were used.

Regarding the axillary approach, sentinel lymph node biopsy (SLNB) alone was performed in 84 patients (57%); axillary dissection (AXDX) in 50 patients (34%) following a malignant finding in the SLNB frozen section; and direct AX DX in 14 patients (9%) owing to persistent clinical axillary positivity after NAT. Final postoperative pathology revealed a complete response to NAT in 40 patients (27%), a partial response in 89 patients (60%), and stable disease in 19 patients (13%). None of the patients experienced disease progression following NAT (Table 2).

Eight patients who were scheduled for BCS before NAT underwent mastectomy after NAT. Breast MRI (six patients) and MG (two patients) were primarily effective. Six patients scheduled for mastectomy before NAT were selected to undergo BCS after NAT. MG (three patients) and breast US (three patients) were primarily effective in this decision. The initially planned oncoplastic technique was modified after NAT in seven patients. MG (three patients) and breast US (four patients) were primarily effective in this decision. Three patients who were scheduled for NSM or SSM before NAT underwent mastectomy after NAT. Based on this, breast MRI was determined to be the most effective. Four patients scheduled for mastectomy before NAT underwent NSM or SSM. MG (three patients) and breast US (one patient) were primarily effective in this decision. Two patients scheduled for NSM before NAT were selected to undergo SSM after NAT. Based on this, MG and breast MRI were the most effective. Two patients scheduled for SSM before NAT were selected undergo NSM after NAT. MG (one patient) and breast US (one patient) were primarily effective in this decision. Fourteen

Table 1. General Characteristics of Patients Before NAT

Characteristic		Value (Percentage %)
Age		42 ± 4.1
Menopausal Status	Premenopausal	104 (70%)
	Postmenopausal	44 (30%)
Tumor Size (T Stage)	T1	24 (16%)
	T2	70 (47%)
	T3	54 (37%)
N Stage	N0	78 (53%)
	N1	70 (47%)
Grade	Grade 1	16 (11%)
	Grade 2	48 (32%)
	Grade 3	84 (57%)
Biological Subtype	Luminal A/B	76 (51%)
	Triple-Negative (TN)	32 (22%)
	HER2+	40 (27%)

Table 2. Surgical Methods and Technique Data

Surgical Method	Technique	Number of Patients (Percentage %)
Breast-Conserving Surgery (BCS) / Oncoplastic Surgery (OPS)	In all	97 (66%)
	Racket Mammoplasty	38 (39%)
	Inferior/Superior Pedicled Reduction Mammoplasty	29 (30%)
	Vertical Mammoplasty	15 (15.5%)
	Fusiform/Radial Mammoplasty	15 (15.5%)
Nipple-Sparing Mastectomy (NSM) / Skin-Sparing Mastectomy (SSM) + Reconstruction		14 (9%)
Mastectomy ± Reconstruction		37 (25%)
Axillary Approach	Sentinel Lymph Node Biopsy (SLNB)	84 (57%)
	SLNB + Axillary Dissection (AX DX)	50 (34%)
	AX DX	14 (9%)
Response Evaluation After Neoadjuvant Therapy	Complete Response	40 (27%)
	Partial Response	89 (60%)
	Stable Disease	19 (13%)
	Progressive Disease	0

patients were scheduled for AXDX before NAT underwent SLNB. Breast US (twelve patients) and breast MRI (two patients) were the most effective. Consequently, SLNB was performed if lymph nodes marked with clips before NAT were removed. Eight patients were scheduled for SLNB before NAT underwent AXDX. Breast US (four patients) and PET (four patients) were primarily used (Table 3).

The established regression model explains 23.8% of the variability in surgical modification based on the included variables, according to Nagelkerke R^2. The regression model is statistically significant ($\chi^2 = 13.889$, $p = 0.008$). Among the imaging methods, USG and MG statistically significantly increase the likelihood of predicting a change in the planned surgical procedure by 4.011 and 2.81 times, respectively. The impact of radiological imaging methods on surgical intervention modification is presented in Table 4.

In patients who were converted back to mastectomy, MRI was found to be the most effective imaging method. In patients converted to lumpectomy, MG and USG were most effective. None of the patients who were initially decided to undergo mastectomy and later received a decision for MKC/OPC after NAT, no re-excision was required. The axillary US stood out as the most effective examination modality for the decision to perform an axillary intervention. PET did not affect the technique used to apply to the breast. Among the 4 patients who were decided to undergo axillary dissection based on PET, none showed lymph node metastasis. Considering AXDX, only 2 of the 12 patients who decided to undergo SLNB with axillary US required dissection.

Discussion

Pathological evaluation remains the gold standard for assessing responses to NAT. However, the optimal imaging method for assessing the response remains unclear. Breast ultrasound is commonly used to assess the response to NAT. This is the most useful method for assessing the axilla following NAT [6]. In our study, breast US was the most effective imaging method for

Table 3. Changes in Surgical Planning Data According to Imaging Methods After NAT

Change in Surgical Plan	After The Imaging Method				
	MG	US	MRI	MG+MRI	PET
From Lumpectomy to Mastectomy	2		6		
From Mastectomy to Lumpectomy	3	3			
Changes in Oncoplastic Technique	3	4			
From NSM/SSM to Mastectomy			3		
From Mastectomy to NSM/SSM	3	1			
From NSM to SSM				2	
From SSM to NSM	1	1			
From AXDX to SLNB		12	2		
From SLNB to AXDX		4			4

MKC, lumpectomy; OPC, oncoplastic surgery; NSM, nipple-sparing mastectomy; SSM, skin-sparing mastectomy; AXDX, axillary dissection; SLNB, sentinel lymph node biopsy; MG, mammography; US, ultrasonography; MRI, magnetic resonance imaging; PET, positron emission tomography

Table 4. Logistics Regression Analysis

Variables	β	S.E.	Odds Ratio	P value
Constant	-1.330	0.579	0.264	0.022*
MG	1.443	0.929	2.81	0.04*
MRI	-1.044	0.592	0.352	0.078
US	1.389	0.663	4.011	0.026*
PET	-1.330	0.054	1.073	0.190

Model significance χ^2=13.889, p=0.008*; Nagelkerke R^2=0.238; Hosmer goodness-of-fit tests χ^2=7.822, p=0.451; MG, mammography; US, ultrasonography; MRI, magnetic resonance imaging; PET, positron emission tomography

significantly altering the surgical plan of axillary surgery. Additionally, PET imaging had no impact on determining the surgical approach and could potentially lead to overtreatment by misguiding the surgeon regarding the axillary plan. Therefore, PET does not play a role in surgical planning after NAT.

Accurately assessing the response to NAT offers crucial insights into the biology and prognosis of breast cancer following systemic therapy [7]. Clinical examination of the breast and lymph nodes, imaging, and pathological assessment following surgery were performed to evaluate the response to treatment after NAT. After completing NAT, the patient should be assessed through physical examination and imaging tests to determine the clinical response and guide the surgical approach. MG, US, and/or MRI are the most frequently used imaging methods [1]. These imaging techniques, performed during or after NAT, not only guide the selection of treatment regimens by evaluating tumour response and reducing unnecessary toxicity from ineffective regimens but also assist in making clinical decisions regarding breast surgery. Evaluations performed before and after NAT will also guide the choice of surgical technique. The treatment responses revealed by the final pathological results will undoubtedly determine the course of adjuvant therapy [8].

MG and breast US are the most commonly used imaging methods for initial staging and evaluation of responses after NAT. The primary goal is to measure the tumour volume comparatively. Mammography assessments rely on density measurements and architectural distortion; unclear tumor boundaries can, however, make it misleading. Reductions in tumour size and density in the MG are indicators of treatment response. The effectiveness of MG in evaluating responses in tumours with microcalcifications is high. The accuracy of mammography increases when tumor boundaries are well-defined, with noticeable differences in density and echogenicity [4, 7]. In our study, changes in the planned surgical technique were observed after NAT based on MMG results: mastectomy was planned for three patients while BCS was chosen, and for two patients, BCS was initially planned, but mastectomy was performed. Additionally, changes were made to the OPC technique in three patients. MG performed after NAT can influence the surgical plan and the selected technique.

Breast US is a valuable imaging method for evaluating tumour response after NAT and assessing the status of lymph nodes in the axilla. Since NAT can lead to the regression of axillary staging in patients, the question arises as to whether less invasive procedures, such as sentinel node biopsy or targeted removal of pretreated marked lymph nodes, could be recommended instead of axillary dissection for these patients. US improves the prediction of axillary response to treatment compared with physical examination and serves as a reliable guiding tool for marking target lymph nodes before the start of treatment. This is crucial for patient selection for less invasive surgery [9]. US is effective as breast MRI in providing information about the residual tumour size after neoadjuvant chemotherapy. The US offers advantages such as portability, low cost, convenient follow-up, and detection without radiation exposure [6]. In contrast, MRI is time-consuming, expensive, and requires contrast agent injection, which reduces its popularity in developing countries [3, 8]. NAT can reduce the axillary stage of the disease (N stage); 74% of clinically node-positive patients can achieve axillary pathological complete response after NAT, depending on the biological subtype of the cancer [10]. This situation can be assessed using non-invasive axillary staging techniques. Breast MRI and PET have low sensitivity and specificity for the evaluation of the axilla. Breast and axillary ultrasound are the most valuable imaging methods that can safely and efficiently assess the axilla during NAT, particularly in patients with N1 disease [11].

This study demonstrated that monitoring the morphological characteristics of lymph nodes and tumour size in the US is crucial for predicting axillary lymph nodes' status after NAT and evaluating the axillary response. Post-NAT axillary US is the imaging method with the highest diagnostic performance for assessing the axilla [12]. In our study, although axillary dissection was planned for 12 patients before NAT, post-NAT axillary US revealed LN regression of lymph nodes. Consequently, SLNB was performed on these patients. Verification of the lymph nodes marked with clips before NAT revealed no metastasis to any of the lymph nodes during SLNB. After SLNB, only two patients required AX or DX-based on postoperative pathology results. Detecting the axillary response with the US protected patients from unnecessary dissection. Evaluating the breast and axillary regions using the US before and after NAT is necessary for surgical planning.

When evaluating the response to NAT, the imaging characteristics of tumour subtypes vary. Although MRI can accurately measure the response to chemotherapy in some subtypes (triple-negative and HER2+), it is inadequate for assessing the largest subgroup (ER-positive/HER2-negative). MRI frequently identifies non-mass lesions, complicating size assessment, and may reveal additional suspicious foci, potentially prompting unnecessary mastectomies. Respiratory movements can also lead to misleading results in axillary evaluation. For these reasons, using MRI according to tumour subtype to assess the NAT response is recommended, but not for most common subtype, ER+/HER2- [11-14]. In our study, the decision for mastectomy was made for six patients initially planned for BCS following MRI. However, the final pathology did not reveal multicentric foci, which led to the decision to perform a mastectomy based on imaging. Consistent with the literature, we found that MRI led to unnecessary mastectomies in some patients.

PET is a metabolic functional imaging method based on the principle of increased glucose metabolism in malignant tumours. It can show changes in tumour metabolism early during NAT. Response rates in the metabolic evaluations varied between 16.3% and 55.6%. No consensus exists on the precise timing of PET imaging, specifically whether it should be performed later in the treatment process [15].

In PET imaging, patients are exposed not only to the PET radiopharmaceutical but also to X-rays produced by CT. The dose received by patients after PET is higher than that from many traditional diagnostic radiology examinations. Therefore, before an 18F-fluorodeoxyglucose (FDG) whole-body PET scan, all efforts should be made to justify and carefully consider the risk-benefit ratio clinically. For this reason, in patients who have a clinical response determined by physical examination and breast ultrasound after NAT, performing a post-NAT PET scan has no benefit in treatment planning and leads to additional radioactive exposure [16]. The meta-analysis indicated that the metabolic response detected using PET imaging after NAT was significant for both DFS and overall survival. PET appears to be effective for the risk stratification of patients with breast cancer patients [17]. In our study, PET had no impact on any patient's selection and planning of surgical methods. Regarding the axillary approach, dissection was performed instead of SLNB in four patients due to PET-positive findings. The pathological evaluation of the lymph nodes in these patients showed that all were reactive. Directly proceeding to dissection based on PET findings led to the overtreatment of patients.

Many studies have been conducted on the cost-effectiveness of PET. In one study, PET imaging of early-stage breast cancer detected distant metastases in 2.3% of the cases, whereas no distant metastases were found in 97% of the cases. Given its cost-effectiveness and the additional radiation dose to patients, PET imaging is considered inappropriate for early-stage breast cancer [18]. For patients who already have a clinical and radiological response as assessed using mammography and breast ultrasound at the end of NAT, PET imaging does not provide any additional benefits for surgical planning.

The limitations of the study include its retrospective nature and the limited number of patients.

In conclusion, in patients who have undergone NAT and are making decisions regarding surgery, PET imaging cannot be used to guide the surgical decision or approach for the primary tumour and axilla. In addition, PET is unsuitable for axillary staging. For patients undergoing NAT, PET can be a valuable tool for interim evaluation to determine the treatment response. However, disadvantages such as potential delays in surgery, high costs, and high radiation doses exists. Post-NAT PET should be reserved for patients where continuation of systemic therapy is being considered.

Author Contribution Statement

L.D. planning the study, M.O.K. wrote the article, and all authors contributed to the collection and evaluation of data..

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Statement of Ethics

Ethical approval for this study was obtained from the Ethics Committee of Ankara Etlik City Hospital (approval number: AESH-BADEK-2024-243).This study was conducted in accordance with the Declaration of Helsinki with informed consent from eligible participants.

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Data Availability Statement

The data in this study were obtained from Ankara Etlik City Hospital database where restrictions may apply as information could compromise the privacy of research participants. Datasets may be requested from the corresponding author (M.O.K.)

Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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