

The Effectiveness of Radiological Methods in Predicting Pathological Complete Response After Neoadjuvant Therapy in Locally Advanced Breast Cancer Patients

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Abstract

Aim: The current innovations in breast cancer treatment have led to an increased utilization of neoadjuvant therapy. Pathological complete response (PCR) following neoadjuvant therapy is a crucial prognostic factor for predicting survival. The objective of this study is to demonstrate the efficacy of radiological methods in predicting PCR in our patients with locally advanced breast cancer.

Methods: The medical records of patients who received treatment for breast cancer at our hospital between January 2017 and January 2022 were retrospectively reviewed. The study included female patients over the age of 18 with locally advanced unifocal breast cancer who underwent neoadjuvant chemotherapy. Demographic information, menopausal status, molecular subtypes, radiological results, disease stage, treatment and surgical methods, and pathology results were recorded.

Results: A total of 4474 patients were treated for breast cancer out of which 94 patients met the criteria for this study. The mean age of the patients was 49.9 ± 11.1 years. Ultrasonography was performed on all patients, while FDG-PetCT was performed on 47 (50%) patients and magnetic resonance imaging (MRI) was performed on 31 (33%) patients for radiological response evaluation. The radiological complete response was highest in the FDG-petCT group (39.4%). The rate of pathological complete response was 35.1%.

Conclusion: Although FDG-PETCT has high sensitivity in predicting pathological complete response after neoadjuvant chemotherapy in locally advanced breast cancers, the common use of ultrasonography, FDG-PETCT, and magnetic resonance imaging is more advantageous due to their different benefits.

Keywords: Breast; breast cancer; neoadjuvant therapy

1. Introduction

Breast cancer is the most common malignancy among females and is the second most common cancer after lung cancer. With recent advancements, radical surgeries for the treatment of breast cancer have decreased and the use of minimally invasive surgeries has increased¹. Locally advanced breast cancers are classified as Stage 2b and Stage 3 tumors according to the TNM

2003 classification². Locally advanced breast cancer is a heterogeneous group of diseases that includes both aggressive and slow-progressing tumors. In developed countries, 5-25% of all breast cancers are classified as locally advanced, while in developing countries, this rate can be as high as 73%. The reason for this difference is thought to be due to differences in educational levels and lack of screening programs^{3,4}.

Although adjuvant chemotherapy (CT) and radiotherapy (RT) can be administered after surgery in operable locally advanced breast cancer patients, neoadjuvant chemotherapy (NACT) has become the standard treatment. This treatment offers advantages such as reducing the stage of the disease, rendering inoperable tumors operable, destroying micrometastases, and evaluating chemo-resistance.

Thanks to this treatment, patients who were candidates for mastectomy can undergo breast-conserving surgery⁵. In addition to the advantages of neoadjuvant therapy, there are also disadvantages such as changes in the biological characteristics of the primary tumor, overtreatment, increased risk of local recurrence, and disease progression during preoperative treatment. Furthermore, studies

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have shown that neoadjuvant therapy does not confer a survival advantage⁶. Many treatment guidelines recommend anthracycline-containing chemotherapy regimens as an initial treatment⁷.

The evaluation of response to treatment is based on anatomical changes observed through imaging methods. The "Response Evaluation Criteria in Solid Tumors (RECIST)" were updated by the World Health Organization in 2009⁸. Functional assessments of metabolic activity can be performed by positron emission tomography (PET). Positron Emission Tomography Response Criteria (PERCIST) for solid tumors were developed in 2009 in order to standardize this evaluation⁹. Positron emission tomography (PET) can be utilized for the functional assessment of metabolic activity. In 2009, Positron Emission Tomography Response Criteria (PERCIST) were developed to standardize the evaluation of solid tumors. The pathological response that occurs after neoadjuvant chemotherapy in patients with locally advanced breast cancer is the most significant prognostic factor for evaluating survival rates¹⁰. Several quantitative and categorical methods, such as the Chevalier Scoring System, have been developed to characterize the pathological response to neoadjuvant chemotherapy. In our study, we aimed to present the effectiveness of radiological methods in predicting pathological complete response (PCR) in patients with locally advanced breast cancer who were treated at our clinic, in the literature.

2. Materials and methods

2.1. Sample

For this study, the Baskent University Medical and Research Council's 22.03.2023 history and KA22/457 the protocol approval has been obtained and the study has been designed in accordance with the Helsinki Declaration. The medical records of patients who underwent treatment for breast cancer at our hospital from January 2017 to January 2022 were retrospectively reviewed. Female patients over 18 years old, diagnosed with locally advanced unifocal breast cancer, and who received neoadjuvant chemotherapy were included in the study. Breast cancer cases with multiple data deficiencies, except for multisentric and locally advanced breast cancer, were excluded from the study. After pre-treatment imaging of the patients, all of them received anthracycline and taxane-based neoadjuvant chemotherapy (NACT), and surgery was performed after radiological response evaluation. Following surgery, 50 Gy radiation therapy was administered to the breast/chest wall and axilla. Radiological complete response was defined as the absence of significant mass in the breast and the disappearance of abnormal features in the armpit lymph nodes. Pathological complete response was defined as the absence of residual invasive tumors in the breast or armpit nodes. Clinicopathological characteristics were documented for each patient, including demographic data, menopause status (the age range of 45 to 55 is considered as perimenopause), molecular subtypes, radiological results, disease stage, treatment and surgery methods, and pathology results.

2.2. Statistical analysis

The statistical analysis of the data was conducted using the Statistical Package for the Social Sciences (SPSS) version 25.0. The performance measures of radiological and pathological tests were evaluated through Receiver Operating Characteristic (ROC) analysis, and the statistical analyses were tested at a significance level of $p < 0.05$.

3. Results

A total of 94 female patients were included in the study, with a mean age of 49.9 ± 11.06 years. Most patients were in the premenopausal group of the patients (48.9%). Regarding their molecular subtyping, luminal b patients were the most common subgroups (51.1%). Stage 2B disease was 95.7% frequency (Stage2B/-Stage3:90/4). The least types of surgeries performed were modified radical mastectomy + axillary lymph node dissection (6.4%). (Table 1).

Table 1

Demographic and clinical characteristics of the patients

Patient Characteristics	n (%)	
The average age	49,96±11.06 year	
Menopause	Menopausal	27 (%28.7)
	Premenopausal	46 (%48.9)
	Postmenopausal	21 (%22.3)
Reseptor	Luminal A	15 (%16)
	Luminal B	48 (%51.1)
	Triple -	16 (%17)
Stage	HER +	15 (%16)
	Stage2B	90 (%95.7)
	Stage3	4 (%4.3)
Surgery	SM+SLN	43 (%45.7)
	BM+SLN	34 (%36.2)
	SSM+SLN	11 (%11.7)
	MRM+AD	6 (%6.4)

SM:Segmental Mastectomy SLN:Sentinel Lenf Node Biopsy BM:Basic Mastectomy SSM:Skin Sparing Mastectomy MRM:Modifiye Radical Mastectomy AD:Aksiller Dissection

Table 2

Statistical evaluation of pathological and radiological complete response

Chevalier	USG	MRI	Fdg-PET
AUC	0.61	0.66	0.61
%95 confidence range	0.51 – 0.71	0.45 – 0.87	0.51 – 0.72
p	0.033	0.163	0.028
Sensitivity	0.46	0.60	0.94
Spesifity	0.77	0.71	0.29
PPV	0.52	0.50	0.41
NPV	0.72	0.79	0.90

AUC: Area under the curve, PPV:Positive predictive value, NPV:Negative predictive value

Ultrasonography (USG) was performed on all patients, FDG-PetCT was performed in 47 (50%) patients and magnetic resonance imaging (MRI) was performed in 31 (32.9%) patients for radiological response evaluation. In terms of radiological complete response evaluation, FDG-petCT showed the most complete response (39.3%). In terms of pathological complete response evaluation, 34 (36.1%) patients achieved PCR. The performance of complete response for pathological and radiological tests was evaluated using ROC analysis (Table 2). The AUC value for ultrasonographic radiological response evaluation was 0.61 (p=0.033) (Figure 1), and the success rate of determining complete response for the test was 46%, with a success rate of determining no response of 77%.

Those who had a complete response in radiology actually had a 52% probability of having a pathological complete response (positive predictive value=PPV), while those who did not have a complete response with USG actually had a 72% probability of not having a complete response in pathology (negative predictive value=NPV). The AUC value of magnetic resonance imaging was 0.66 (p=0.163) (Figure 2), the success of the test in determining the complete response was 60%, the success in determining no response was 71%. Those with a complete radiological response had a 50% probability of actually having a pathological complete response (PCR), while those without a response had a 79% probability of actually not having a response in pathology (NPV). The AUC value of FDG-PetCT was 0.61 (p=0.028) (Figure 3), the success rate of determining the complete response of the test was 94%, and the success rate of determining no response was 29%.

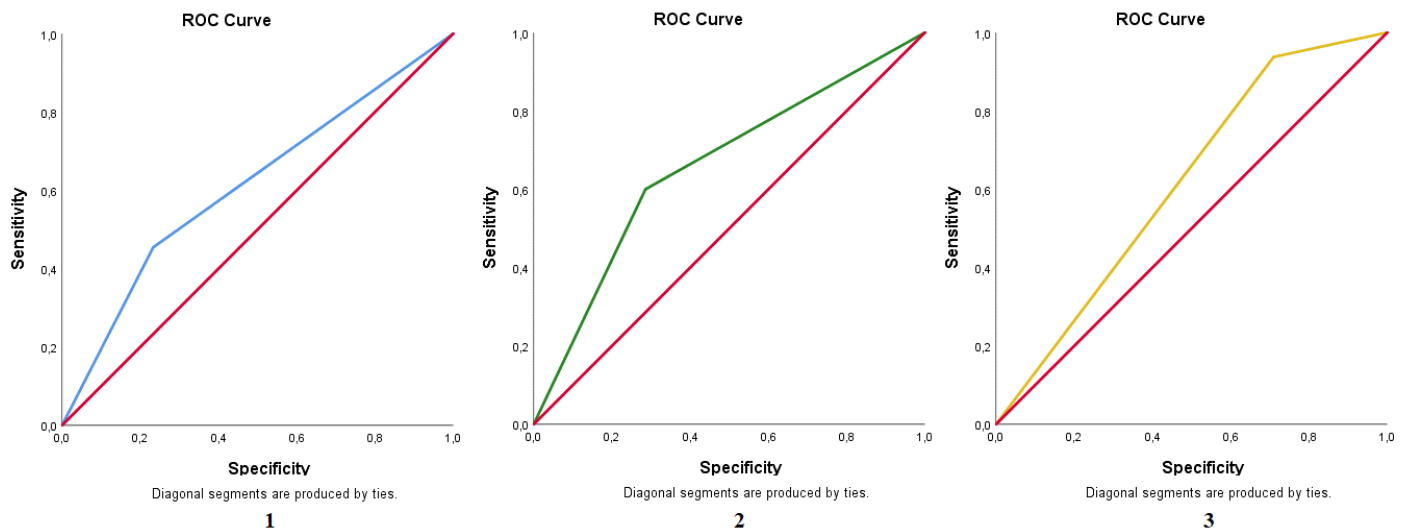
Table 3

Prediction of pathological response by USG

Chevalier-Usqp	Luminal B	Triple -	Her +
AUC	0.56	0.67	0.75
%95 Confidence range	0.41 – 0.72	0.42 – 0.92	0.57 – 0.94
p	0.423	0.17	0.008
Sensitivity	0.39	0.55	0.51
Spesifity	0.74	0.80	0.98

AUC: Area under the curve

The probability of pathological complete response for those with radiological complete response was 41% (PKD), and the probability of non-response not being a response in pathology was 90% (NKD) (Figure 1). When the evaluation was made according to the receptor status, it was possible to make an evaluation only in the USG group due to the number of samples. While there was no PTY in the Luminal A group, the results were statistically meaningless in the Luminal B group and the Triple group. In each 2+ group, the AUC value was 0.75 (p=0.008), the success of determining the complete response of the test was 51%, and the success of determining no response was 98% (Table 3).

**Figure 1-2-3**

1. Evaluation of radiological response with USG and ROC analysis of the relationship between pathological response (AUC:0.61)
2. Evaluation of radiological response with MRI and ROC analysis of the relationship between pathological response (AUC:0.66)
3. Evaluation of radiological response with FDG-petCT and ROC analysis of the relationship between pathological response (AUC:0.61)

Table 4
Pathological complete response rates

Author	Year	Patients number	PCR(%)	Worst response	Best response
Houssami N et al (17)	2012	11695	31.1	Luminal A	Her2+
Boughey JC et al (18)	2014	694	28	Luminal	Her2+
Haque W et al (16)	2018	13939	19	Luminal A	Her2+
Agrawal R et al (19)	2020	224	46	Luminal	Triple -
Müller C et al (20)	2021	205	47	Luminal A	Her2+

Table 5
Radiological complete response comparison

Author	Year	Patients number	Comparison	Result
Tateishi U et al (24)	2012	142	MRG/FDG-pet	FDG-pet sensitive ve spesifik
S You et al (28)	2015	139	USG/MRG/FDG-pet	All sensitive /FDG-pet spesifik
Ann YY et al (25)	2015	20	MRI/FDG-PET	MRI sensitive ve spesifik
Chen L et al (29)	2017	527	MRI/FDG-pet	FDG-pet sensitive/MRI spesifik
Evans A et al (26)	2018	80	USG/MRI	MRI sensitive ve spesifik
Huimin Li et al (30)	2018	575	MRI/FDG-pet	MRI sensitive/FDG-pet spesifik
Sanei Sistani S et al (27)	2020	3248	USG/MRI	USG=MRI

USG:Ultrasonography MRI:Magnetic Resonance Imaging

4. Discussion

Increasing preventive medicine activities in recent years have led to the detection of many malignancies at an early stage and increased survival rates. Due to this, although the rates of locally advanced breast cancer have decreased, the rates are still high in communities of people with low economic and sociocultural levels. Many studies have been conducted related to the treatment systematics of locally advanced breast cancer. As a result of these studies, it has been proven that neoadjuvant therapy has a positive effect on the results in appropriate patient groups. The compatibility of radiological response and pathological response is very valuable in the evaluation of response to treatment. In our study, we evaluated the follow-up and treatment results of locally advanced breast cancer patients treated in our clinic. Our correlation rates between the results were similar to those reported in the literature.

While the incidence of premenopausal breast cancer has risen in recent years, breast cancer is still more common in patients aged 50 and older. In our study, the median age of patients was 49.9 ± 11.06 , which is consistent with the literature. Early detection rates of breast cancer have increased in recent years due to improved screening methods. The number of premenopausal (38.2%) and perimenopausal (29.7%) patients was higher than that of postmenopausal patients. We believe that the increase in breast cancer frequency and improved early screening methods are contributing factors to this trend.

The response to neoadjuvant chemotherapy in terms of pathological complete response rate is influenced by various factors, such as age, tumor size, nodal status, and receptor status¹¹.

According to a meta-analysis conducted by Von Waldenfels G. and colleagues in 2018, among 8,949 patients, the lowest pathological complete response rate was observed in patients over the age of 65 (11.7%), while the highest response rate was observed in patients under the age of 40 (20.9%)¹². In our study, we found that the pathological complete response rate was 18% in premenopausal patients, 9.5% in perimenopausal patients, and 8.5% in postmenopausal patients. These findings are consistent with the literature, indicating a decrease in response rate with increasing age. The results of the study were consistent with the literature, with the worst outcomes observed in the postmenopausal group.

Tumor receptor status is an important indicator of the biological function of the tumor, and different frequency rates have been reported in breast cancer patients based on receptor status in various studies in the literature. For instance, Caiyun et al. reported that patients with Luminal B tumors comprised 50% of all patients in their study with 220 patients in 2018, followed by Luminal A and other types¹². Akoz et al. found Luminal B (32.3%), Luminal A (24.5%), Triple-negative (14.1%), and HER2-positive (29%) in a different study conducted in 2018¹⁴. In a review study conducted in 2001, Chu and colleagues also found the ER+/PR+ patient group to be the most common molecular type, accounting for 63.9%¹⁵. In our study, we observed a similar distribution, with 15.9% of patients having Luminal A, 51% having Luminal B, 17% having Triple-negative, and 15.9% having HER2-positive breast cancer.

In a study conducted by W. Haque et al. on 14,000 patients, the overall PCR rate was 19%, with the lowest rate found in the Luminal A group (0.3%) and the highest rate in the Her2+ group (38.7%)¹⁶. A meta-analysis by Houssami et al. on 11,695 patients reported PCR rates of 8.3% for Luminal A, 18.7% for Luminal B, 38.9% for Her2+,

and 31.1% for Triple-negative breast cancer¹⁷. In our study, of the 34 patients who achieved PCR, 1 (7.6%) had Luminal A, 13 (26%) had Luminal B, 11 (68.7%) had Triple-negative breast cancer, and 9 (60%) had the Her2 molecular subtype, consistent with the literature (see Table 4).

In a study by Gajdos C et al. on 144 patients, it was shown that smaller tumors were more likely to respond to chemotherapy than larger tumors²¹. In another study involving 165 patients, Bonadonna and colleagues found an inverse relationship between the degree of response and tumor size for tumors larger than 3 cm.

A study by Smith et al.²² found that as tumor size increased, the response to treatment decreased. Among patients who received transplantation, pathological complete response was observed in 3 of the 6 patients with tumors larger than 5 cm, 34 of the 76 patients with tumors 2-5 cm, and 3 of the 12 patients with tumors 0-2 cm. When accounting for the excess number of Her2+ and Triple-negative breast cancer patients with treatment response, we believe that factors other than size may have contributed to these results.

Various imaging methods can be used to assess radiological complete response. Ultrasound (USG), computed tomography (CT), and magnetic resonance imaging (MRI) provide anatomical response evaluation, while FDG-PETCT is used to evaluate metabolic complete response²³. In a study by Tateishi et al., contrast-enhanced MRI and FDG-PETCT were compared, and the sensitivity and specificity values were found to be 45.5% and 85.5% for MRI, and 70.4% and 95.7% for PETCT, respectively²⁴. In another study by Yeng Yi Ann et al., the response to neoadjuvant chemotherapy was evaluated with MRI and FDG-PETCT. They found that contrast-enhanced MRI, diffusion-weighted MRI, and FDG-PETCT had the highest diagnostic performance, with contrast-enhanced MRI showing the best results. Although there was no statistically significant difference between FDG-PETCT and diffusion-weighted MRI, their combined use improved specificity²⁵. In their study of 80 patients, Evans et al. compared ultrasonography and MRI and found the sensitivity and specificity values to be 78%-81% and 91%-95%, respectively. The ROC analysis revealed AUC values of 0.91 for USG and 0.96 for MRI²⁶. Sheikhabaei et al. analyzed 10 different studies and showed that MRI has higher sensitivity (88% vs. 71%) than petCT imaging alone, but lower specificity (55% vs. 77%), with AUC values also found to be higher on MRI²⁷. In our study, PETCT (94%) was the evaluation method with the lowest specificity, although it had the highest sensitivity, making it the best test for detecting those with the disease. The best test for specificity was ultrasonography, which distinguished those who did not have the disease the best. Although MRI appeared to have the best value in test distinctiveness, this was not statistically significant.

In the evaluation of pathological complete response in receptor groups, PCR is higher in Triple-positive and Her2-positive tumors, while it is lower in luminal group tumors^{31,32}. Due to insufficient sample size and lack of data, statistical evaluation could not be performed according to receptor status in patients who underwent FDG-PET/CT and MRI. In the ultrasound group, there was no pathological complete response in the Luminal A group, and the results were statistically insignificant in the Luminal B and Triple-positive groups. The sensitivity was 51% and the specificity was 98% in the Her2-positive group.

Our study had limitations, such as a small sample size due to being a single-center retrospective study and the lack of standardization in radiological follow-up methods after treatment, resulting in insufficient data.

5. Conclusions

In conclusion a significant survival advantage has been achieved with the introduction of a multidisciplinary approach and chemoradiotherapy in the treatment of locally advanced breast cancer. Radiological evaluation performed after neoadjuvant therapy is of great importance in surgical planning. As a result of our study, although the MRI test seemed to be superior to the others in terms of its performance among the radiological evaluations after treatment, the results were not statistically significant. Although the sensitivity and specificity values of all three tests are not at the desired level, we believe that their combined use can improve the specificity of predicting pathological response.

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None.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by for this study, the Baskent University Medical and Research Council's 22.03.2023 history and KA22/457.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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