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RESEARCH ARTICLE

Evaluation of Pathological Responses and Breast MRI Images in Breast Cancer Patients Who Have Received Neoadjuvant Therapy: A Single Center Experience

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ABSTRACT

Objective: In the present study, pre-operative magnetic resonance imaging (MRI) responses following neoadjuvant chemotherapy (NAC) administration were compared with postoperative pathological response rates. The study design was retrospective cross sectional method.

Materials and Methods: Breast MRI is helpful in determining treatment plans, responses, and prospective survival analyses in breast cancer patients receiving neoadjuvant chemotherapy. A total of 39 patients receiving NAC between January 2019 and June 2020 were analyzed in the hospital. Treatment responses after NAC in patients with locally advanced who had not received any treatment before were evaluated with MRI. The longest diameter was recorded as well as the transfers of the primary tumor and axillary lymph node. The correlation of response rates obtained with the MRI with pathological specimen results was also examined.

Results: When the pathological clinical response (pCR) was compared with the radiological response of the tumor and lymph node, the sensitivity was found to be 52.6% and 70.5%, and the accuracy was 64.1% and 51.2%, respectively.

Conclusion: The preferred MRI techniques and sequence intervals, and the histopathological characteristics of the tumor increase the accuracy rates in reaching pathological complete response rates.

Keywords: Breast cancer, MRI, neoadjuvant chemotherapy

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INTRODUCTION

The goal of neoadjuvant chemoterapies (NAC) are to prolong disease-free survival and overall survival by improving a pathological complete response (pCR).[1] The reduction in tumor size enables the preservation of breast volume and the prediction of the post-operative treatment response.[2]

Neoadjuvant therapy responses have been conducted with magnetic resonance imaging (MRI) to predict pCR in many studies. pCR has been a good predictor for prolonging survival.[3] The detection of the pathological axillary lymph node impacts chemotherapy, radiotherapy, and surgical options. Axillary lymph node response may prevent unnecessary axillary dissection.[4] The residual tumor may appear larger or smaller than anticipated after the NAC. MRI responses are related to tumor size, histological type, genetic heterogeneity, and the visual determination of the clinician.[5,6] Since the sensitivity and specificity of the tumor response in dynamic and diffusion MRI examinations are different, the development of new techniques is on the agenda.[7]

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The purpose of the study was to determine the breast cancer MRI response of the primary tumor and axillary lymph node with neoadjuvant therapy and also to determine its relation with pathological response rates.

MATERIALS and METHODS

Thirty-nine patients with locally advanced lymph node-positive invasive ductal breast carcinoma who received neoadjuvant chemotherapy were included in the study between January 2019 and June 2020. In these patients, treatment response was evaluated with MRI with contrast done before and after treatment. Previously treated patients, patients with metastatic disease, and those who refused treatment were excluded from the study. The chemotherapies with adriamycin, cyclophosphamide, and taxane were used for 24 weeks. The Luminal A group was not given hormonal treatment in the neoadjuvant period. MRI responses of the long axis and horizontal axis of the primary tumor and axillary lymph nodes were evaluated based on the Response Evaluation Criteria in Solid Tumor (RECIST) criteria.[8] Lymph node biopsy was performed in patients with breast cancer surgery (BCS) and axillary dissection was applied if necessary.

In patients receiving NAC, radiological complete response was abbreviated as rCR, partial response as rPR, stable disease as rSD, and clinical complete response as cCR, partial response was abbreviated as cPR, stable disease was abbreviated as cSD and progressive disease was abbreviated as cPD in the same cases.

Those with no pathological axillary metastases were classified as pathological complete response (pCR). Whether tumor size, lymph node, and pCR responses were related to age, Ki-67, estrogen receptor (ER), and progesterone receptor (PR) status, tumor subtype variables were shown by Chi-square test. MRI scans were carried out with 1.5T (Magnetom Area, Siemens Healthcare, Germany) 24-channel breast coil, and the images were acquired both before and after the administration of paramagnetic contrast agent (Gadopentetate dimeglumine). The first phase was obtained before the contrast agent injection, and the second phase 30 seconds after the injection. The images before the contrast were subtracted from post-injection images to obtain subtraction images. The study was conducted in accordance with the Declaration of Helsinki and permission was obtained from the Clinical Research Ethics Committee of Kanuni Sultan Süleyman Training and Research Hospital to conduct the study on 23 July 2020 with the number 2020.07.163. Informed consent was waived by the Institutional Review Board.

Statistical Analysis

Statistical analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc. Chicago, IL, USA). Breast cancers were classified according to the American Joint Committee on Cancer (AJJC) TNM staging system. Thirty-nine cases were taken considering age and Ki-67 index. Categorical variables were expressed as counts and percentages and measurable variables were expressed as mean and standard deviation (SD). Accurate positive result, specificity (or true negative rate) was measured as the was taken as radiological and pathological residual tumor tissue proportion of cases with an actual negative outcome. Radiologic partial response was identified as false positive in patients with no pathological residual disease, and the cases with cCR on MRI but no pathological response were determined as a false negative exact test. Diagnostic tests were used to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (Sensitivity=True positive/(true positive+false negative); Specificity= True negative/(true negative+false positive); PPV=True positive/(true positive+false positive); NPV=True negative/(true negative +false negative)). The Spearman's correlation test was used for correlation, and p-values <0.05 were considered to indicate a statistically significant Statistical differences between categorical variables were evaluated with Pearson Chi-square and Fisher's difference.

RESULTS

The mean years 48.92±11.30 in the study. Five of 39 patients were luminal A (12.8%), 19 were luminal B (48.7%), 8 were HER-2 positive (20.5%), and 7 were triple negative (17.9%) (Table 1).

Radiologically, at the end of NAC, 16 (41%) had complete response, 16 (41%) partial, and 7 (17.9%) stable response in the primary tumor. No progression was detected in any patient. Radiologically, the tumor was reduced by an average of 23%. Pathological complete response was obtained in the primary tumor in 19 (48.8%) of the patients. The rCR was found in 27 (69.2%) of 39 patients, rPR in 11 patients (28.2%), and stable lymph node images in 1 (2.6%). In the pathological evaluation of lymph nodes of 39 cases, 21 (53.8%) were metastatic and 18 (46.2%) were benign.

In the present study, the best radiological tumor response was found to be in luminal A 82% (Tumor (T) pre-NAC: 30.6 –Tpost NAC 5.5 mm); HER-2 positive 77.5 % (T preNAC 35-Tpost NAC 7.8 mm); triple negative 56.2% (Tpre –NAC 43-Tpost NAC 19.1 mm); min. luminal B 47% (Tpre-NAC 33-Tpost NAC 17.5 mm) (Fig. 1).

Table 1. Characteristics of patients

Characteristics	Patients (n=39)	
	n	%
Age		
Mean		48.9
<48	18	46.2
≥48	21	53.8
Clinical tumor stage		
1	2	5.1
2	22	56.4
3	6	15.4
4	9	23.1
Clinical lymph node stage		
0	3	7.7
1	19	48.7
2	15	38.5
3	2	5.1
Clinical stage		
2	16	41
3	23	59
Grade		
1	5	12.8
2	20	51.3
3	14	35.9
Ki-67		
≤14	8	20.5
>14	31	79.5
Estrogen receptor status		
Positive	23	59
Negative	16	41
Progesterone receptor status		
Positive	20	51.3
Negative	19	48.7
HER status		
Positive	16	41
Negative	23	59
Subtype		
Luminal A	5	12.8
Luminal B	19	48.7
Her-2	8	20.5
Triple-negative	7	17.9
Surgery		
Lumpectomy	21	53.8
Mastectomy	18	46.2

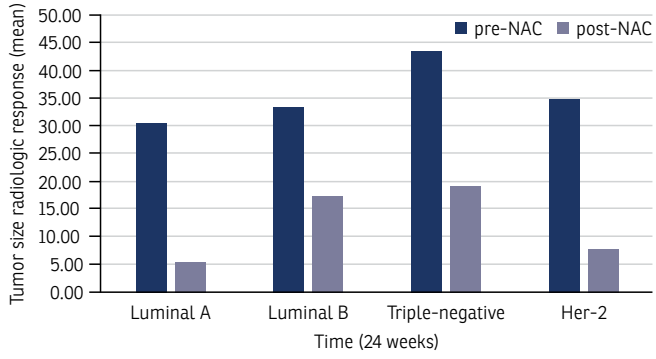

Figure 1. Radiologic response rates in tumor size according to subtypes of breast cancers

NAC: Neoadjuvant chemoterapies

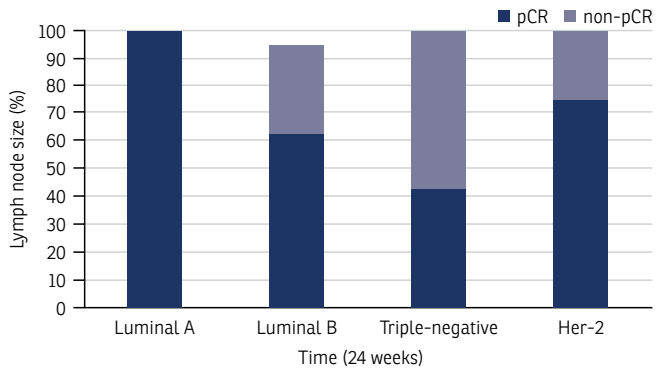

Figure 2. pCR ratio of axillary lymph nodes according to subtypes . They were 100%, 62%, 42%, 73% in luminal A,B, triple-negative and HER-2 positives, respectively

pCR: Pathological complete response

The receptor, age, tumor histological subtype, and Ki-67 percent were not found to be related with pCR (p=0.855, ER (+)/(-); p=0.595, PR(+)/(-); p=0.817, HER-2(+)/(-); p=0.703; p= 0.961; p=0.220, respectively) (Table 2). This is because of the small number of patients.

The radiological and pathological relevance of the axillary lymph node was found to be significant only in patients with Ki-67 >14 (p=0.02). pCR rates of the axilla were 100 % in the luminal A group, 62% in the luminal B group, 73% in the HER-2 group, and 42% in triple- negative group in our study (Fig. 2).

We found a weak correlation between the number of lymph nodes and size before neoadjuvant therapy and the tumor size at the end of treatment and Ki- 67 index(r=0.392, p=0.014; r= 0.366, p=0.022; r=0.411, p=0.009; r=0.366,

Table 2. Univariate analysis of concordant and discordant Tumor, Lymph node and pathological complet responses according to age, tumor subtype, receptor, Ki-67 variables at pre-and post MR imaging

Variables	Tumor response	Discordant		Concordant		p*
		n	%	n	%	
Age	<48.92	8	44.4	10	55.6	0.487
	>48.92	6	28.6	15	71.4	
Subtype	Luminal A	3	60.0	2	40	0.682
	Luminal B	7	36.8	12	63.2	
	Her-2	2	25.0	6	75.0	
	Triple negative	2	28.6	5	71.4	
Ki-67	<14	4	50.0	4	50.0	0.604
	>14	10	32.3	21	67.7	
Estrogen receptor	Negative	4	26.7	11	73.3	0.544
	Positive	10	41.7	14	58.3	
Progesterone receptor	Negative	6	31.6	13	68.4	0.831
	Positive	8	40.0	12	60.0	
Her-2	Negative	8	34.8	15	65.2	1.000
	Positive	6	37.5	10	62.5	
	Lymph node response					
Age	<48.92	8	44.4	10	55.6	0.863
	>48.92	11	52.4	10	47.6	
Subtype	Luminal A	5	100	0	0.0	0.118
	Luminal B	8	42.1	11	57.9	
	Her-2	3	37.5	5	62.5	
	Triple-negative	3	42.9	4	57.1	
Ki-67	<14	7	87.5	1	12.5	**0.02**
	>14	12	38.7	19	61.3	
Estrogen receptor	Negative	6	40.0	9	60.0	0.595
	Positive	13	54.2	11	45.8	
Progesterone receptor	Negative	7	36.8	12	63.2	0.260
	Positive	12	60.2	8	40.0	
Her-2	Negative	13	56.5	10	43.5	0.399
	Positive	6	37.5	10	62.5	
	Pathological complet response					
Age	<48.92	8	44.4	10	55.6	0.703
	>48.92	7	33.3	14	66.7	
Subtype	Luminal A	2	40.0	3	60.0	0.961
	Luminal B	8	42.1	11	57.9	
	Her-2	3	37.5	5	62.5	
	Triple-negative	2	28.6	5	71.4	

Table 2. Cont.

Variables	Tumor response	Discordant		Concordant		p
		n	%	n	%	
Ki-67	<14	5	62.5	3	37.5	0.220
	>14	10	32.3	21	67.7	
Estrogen receptor	Negative	5	33.3	10	66.7	0.855
	Positive	10	41.7	14	58.3	
Progesterone receptor	Negative	6	31.6	13	68.4	0.595
	Positive	9	45.0	11	55.0	
Her-2	Negative	8	34.8	15	65.2	0.817
	Positive	7	43.8	9	56.3	

p=0.022, respectively)p=0.392, p=0.366, p=0.411, p=0.366, respectively). In radiological terms, although there was a complete response in 16 (41%) primary tumor tissue cases, and in 27 (69.2%) lymph node cases; the pathological specimen was 46.2% in 19 cases (48.8%) in the primary tumor and 18 cases in the lymph node (Table 3).

Axillary pathological lymph node response was found to be 3.25±1.81.

The accuracy rate of the treatment response in MRI was found to be 64.1% primary tumor response in the breast and 51.2% in the lymph node, while 61.5% accuracy was found with pCR for all tumor subtypes (Table 4).

DISCUSSION

Neoadjuvant treatment response was found to be compatible with axillary pCR in cases with lymph node positive, hormone receptor (HR) negative, and Ki-67>30.[9] It was observed that the chemotherapy response in the lymph node was not compatible with the tumor subtype; however, it was significantly higher in those with Ki-67 ≥14 (Table 2, p=0.02). However, high Ki-67 did not provide adequate pCR rates. The low number of triple-negative and HER-2 positive tumors, the Ki-67 index being more than 50 % in only five cases, led us to believe that the pathological response was not only dependent on the proliferation index but also on intra-tumoral genetic changes.[10–12] Since a certain cut-off value was not obtained in our HR-positive cases, good neoadjuvant chemothearpy response cannot be associated with receptor levels.[13] It has been stated in the studies that the contrary findings may be due to incomplete suppression of the breast parenchymal plane.[14]

Table3. Distribution of radiological complete, partial response by MRI imaging and pathological complete response rates in lymph node and tumor tis

Response	Lymph node		Tumor size	
	n	%	n	%
r-Complete	27	69.2	16	41
r-Partial	11	28.2	16	42
r-Stable	1	2.6	7	18
Pathologic	18	46.2	19	48.8

r-Complete: Radiological complete; r-Partial: Radiological partial; r-Stable: Radiological stable

Table 4. Sensitivity, specificity, PPV, NPV, and accuracy of MRI in determining pCR according to all subtypes, c-T and c-N diameters

All subtypes	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
p-CR	43.7	73.9	53.8	65.3	61.5
r-T	52.6	75	66.7	62.5	64.1
r-N	70.5	36.3	46.1	61.5	51.2

PPV: Positive predictive value; NPV: Negative predictive value; MRI: Magnetic resonance imaging; pCR: Pathological complet response

The radiological and pathological response rates of the primary tumor and axillary lymph nodes are shown in Table 3 in our study. It was concluded that the radiological evaluation was more misleading, especially in the axillary lymph node (Table 4, NPV 61.5%). Axillary pathological lymph

node response was found to be 3.25±1.81 (range: 1.4–5.0). The shrinkage of the tumor and the response to chemotherapy in the axillary lymph node are different from each other because the tumor cellularity and membrane characteristics are different and the distribution of the contrast agent varies.[15] The treatment response also varies according to the metabolic changes in the tumor due to chemotherapy, the technical characteristics of MRI, and the timing of the imaging.[7,16]

MRI is performed before treatment in breast cancer today due to its higher sensitivity and specificity when compared to ultrasonography and positron emission tomography (PET-CT).[17] However, the role of MRI is limited in post-chemotherapy axillary staging, with sensitivity 43–50%, specificity 78–84%, and accuracy 68–72% were detected.[18] The accuracy of MRI findings increases in aggressive tumors such as HER-2 positive and triple-negative, and in advanced stages (the involvement of three or more axillary lymph nodes).[18–20] The mean sensitivity of MRI was 84.7%.,[20,21] and the negative predictive value was 95% in patients not receiving neoadjuvant chemotherapy. [20] When the radiological response of the tumor and lymph node was compared in our cases with the pCR, the sensitivity was 52.6% and 70.5%, 43.7% and accuracy 64.1% and 51.2%, 61.5% respectively (Table 4). Accuracy rates and sensitivity of post-chemotherapy breast MRI response assessment was found to be lower than literature. Perhaps the determination of tumor remnants with interim evaluations can be an alternative method to reach a pathological complete response to select new drugs or combinations. The sensitivity in subgroups could not be evaluated since 39 patients were included in our study.

The limitations of this study were the retrospective nature, the small number of patients, the evaluation of MRI results by one single radiologist, and decreased MRI sensitivity because of different narrowing patterns in the tumor and lymph nodes after neoadjuvant chemotherapy. Radiological signal characteristics differ according to tumor subtypes and chemotherapy options in radionic multiparametric MRI.[6]

CONCLUSION

MRI modality affects treatment options in patients who have breast cancer. It is widely used to evaluate the early response to neo-adjuvant therapy on an individual basis and to determine the surgical procedure to be selected. The sensitivity value will vary according to tumor subtype, chemotherapy chosen, and the MRI protocol.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences İstanbul Kanuni Sultan Süleyman Research and Training Hospital Ethics Committee (No: 2020.07.163, Date: 23/07/2020).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions: Concept: S.D., S.S., N.B.; Design: S.D., S.S., N.B.; Supervision: S.D., S.S., N.B.; Materials: S.D., S.S., N.G., N.B.; Data Collection or Processing: S.D., S.S., N.G.; Analysis or Interpretation: S.D., S.S., N.B.; Literature Search: S.D., S.S., N.B.; Writing: N.B.; Critical review: S.D., S.S., N.G., N.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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