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Research Article

Does Mammographic Density Predict Pathological Complete Response in Patients with Locally Advanced Breast Cancer Receiving Neoadjuvant Chemotherapy?

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Abstract

Objectives: We aimed to investigate the relationship between mammographic density (MD) category and pathological complete response (pCR) in patients with locally advanced breast cancer receiving neoadjuvant chemotherapy.

Methods: The study population consisted of 98 breast cancer patients. At the time of diagnosis, MD was categorised according to BIRADS 5th Edition. pCR was defined as the absence of residual tumour cells in the breast and axilla after completion of neoadjuvant chemotherapy (NACT).

Results: Patients with less dense breast density (MD category A+B) were significantly older than patients with more dense breast density (MD category C+D) (p=0.001). When patients were divided according to BIRADS classification (A/B and C/D), there was no statistical difference in performing pCR between patients with high MD and patients with low MD (p=0.684 ;%95 GA 0.67-0.69).

Conclusion: In previous studies, conflicting results were obtained in the relationship between MD value and treatment response. In our study, MD was not an independent predictor of response to breast cancer NACT.

Keywords: Breast Cancer, density, pathological complete response, mammographic density

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Breast cancer (BC) is the most common cancer in women worldwide. With more than two million new cases each year; it constitutes almost one in four cancer cases in women.[1] Many parameters such as estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor-2 (Her-2) status, Ki-67 level, tumour diameter, histological grade, lymphovascular invasion (LVI), histopathological subtype, TNM stage are evaluated together to determine the treatment modality in both localised and metastatic disease. These parameters also have prognostic significance as they give an idea about the clinical course.[2] Breast density refers to the ratio of fibroglan-

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dular tissue in breast tissue compared to adipose tissue in the breast. Wolf first described the relationship between mammographic breast density and cancer in 1976.[3] Subsequently, numerous studies have shown a strong risk association between mammographic density (MD) and BC.[4] Breast densitometry is important for breast cancer in two aspects. One is that a dense breast is an independent risk factor for the development of breast cancer. The other is that it is more difficult to detect tumours in dense breasts, so patients with dense breasts may be diagnosed later.[5] Mammographic density is among the risk factors for breast cancer, such as ageing and genetic mutations. Breast density is evaluated in four categories. Women with the highest breast density have a 4 to 6 times higher cancer risk than women with lower breast density.[6] The extracellular matrix and collagen organisation in the breast tissue of women with dense breasts are different from those of women with less dense breasts. Some metalloproteases that predispose to cancer are very high in women with dense breasts. Thus, a carcinogenic microenvironment is created in the dense breast structure.[7,8] Neoadjuvant chemotherapy (NACT) is a form of systemic treatment given preoperatively in BC. All systemic treatments used in breast cancer reduce the possibility of distant recurrence. Preoperative administration of these treatments reduces the surgical area width to be applied to the breast and axilla region as a result of tumour size reduction. Thus, breast-conserving surgery is performed instead of mastectomy, resulting in fewer postoperative complications and better cosmetic results. At the same time, neoadjuvant treatment provides an early evaluation of the effect of systemic therapy and control of micrometastatic disease.[9] The highest pathological complete response (pCR) rates are observed in HER2 positive and triple negative subtypes. Considering the pathological responses after NACT, there is no definite biomarker that predicts which patients will respond better to which treatment, except for the receptor status of the tumour. In studies using MD in search of biomarkers, conflicting results have been obtained regarding the relationship of MD value with treatment response.[10] Personalised cancer treatment requires predictive biomarkers, including image-based biomarkers. In our study, we aimed to evaluate the relationship between MD category and pCR in patients with locally advanced breast cancer who received NACT and to examine whether MD could be a predictor for NACT response.

Methods

The study population consisted of 202 patients who were admitted to Dokuz Eylül University Hospital Medical Oncology Polyclinic with a diagnosis of locally advanced BC between 2018 and 2021. Patients with a follow-up period of less than 12 months (n=50), patients whose clinicopathological data were not available (n=40), and patients who received systemic treatment for less than 1 month (n=14) have been excluded from the study. Patients with metastatic disease, neoadjuvant endocrine treatment, bilateral breast cancer, male breast cancer or patients who had previously received NACT for breast cancer treatment were excluded. A total of 98 BC patients were included in the study.

Mammographic density was categorised according to BI-RADS (Breast Imaging Reporting and Data Systems) 5th edition at the time of diagnosis.[11] The BI-RADS density category ranges from A to D. Category A stands for "breast almost completely "fatty", category B for "diffuse fibroglandular density", category C for "heterogeneous dense" and category D for "extremely dense breast". ER and PR cells were considered positive when >10% of the cells showed positive staining. Patients received NACT according to the standard appropriate to their clinical and pathological characteristics in accordance with the guideline recommendations. pCR was defined as the absence of residual tumour cells in the breast and axilla on pathological examination performed after NACT was completed and surgery was performed. Demographic data and clinical characteristics of the patients were obtained from the hospital database by retrospective review. According to BI-RADS classification, patients were categorised as A and B group densities and C and D group densities.

We summarised the demographic, clinical and pathological characteristics of the patients according to both BI-RADS classification and pCR. SPSS 25.0 (IBM Corporation, Armonk, New York, United States) was used to analyse the variables. The conformity of univariate data to normal distribution was assessed by Shapiro-Wilk test, the conformity of multivariate data to normal distribution was assessed by Mardia; (Dornik and Hansen omnibus) test and homogeneity of variance was assessed by Levene test. According to the normal distribution and homogeneity of variance of the data, appropriate parametric and nonparametric analyses were applied. Quantitative variables were expressed as mean ± standard deviation and median range (minimum-maximum) and categorical variables were expressed as n (%). Overall survival was estimated using the Kaplan-Meier method and results were compared using the log-rank test. Variables were analysed at 95% confidence level and p value less than 0.05 was considered significant.

Results

The status of 98 patients included in the study according to BI-RADS and tumour characteristics are presented in Table 1. The mean age of the patients was 53±13.3 years. Most of

Table 1. Characteristics of Patients According to Mammographic Density

	Mammographic Density				
	BIRADS-A Mean±SS.	**BIRADS-B Mean±SS.**	**BIRADS-C Mean±SS.**	**BIRADS-D Mean±SS.**	**p**
Age (year)	68.9±9.7	58.9±13.2	48.7±9.8	46.4±12.1	<0.001#
BMI (kg/m^2)	30.8±14.5	29.2±10	35±17.4	29±4.5	0.48#
	n (%)	**n (%)**	**n (%)**	**n (%)**	
Menopause Status					
Premenopause	0 (0)	14 (40)	31 (75.6)	9 (75)	0.001$^{\Phi}$
Postmenopause	10 (100)	21 (60)	10 (24.3)	3 (25)	
pCR					
Yes	8 (80)	28 (80)	31 (75.6)	6 (50)	0.36$^{\Phi}$
No	2 (20)	7 (20)	10 (24.3)	6 (50)	
BIRADS					
BIRADS 4	3 (30)	4 (11.7)	14 (34.1)	6 (54.5)	0.03$^{\Phi}$
BIRADS 5	6 (60)	29 (85.2)	25 (60.9)	5 (45.4)	
BIRADS 6	1 (10)	1 (2.9)	1 (2.4)	0 (0)	
Pathology					
Ductal	3 (30)	24 (68.5)	27 (65.8)	10 (83.3)	0.03*
Lobuler	5 (50)	7 (20)	7 (17)	2 (16.6)	
Other	2 (20)	4 (11.4)	7 (17)	0 (0)	
Molecular Sub-Group					
Luminal A	3 (30)	8 (22.8)	11 (26.8)	1 (8.3)	0.85$^{\Phi}$
LuminalB	3 (30)	11 (31.4)	12 (29.2)	5 (41.6)	
Her-2	2 (20)	13 (37.1)	10 (24.3)	4 (33.3)	
Triple negative	2 (20)	3 (8.5)	8 (19.5)	2 (16.6)	
ER					
Pozitive	8 (80)	25 (71.4)	28 (68.2)	6 (50)	0.52$^{\Phi}$
Negative	2 (20)	10 (28.5)	13 (31.7)	6 (50)	
PR					
Pozitive	5 (50)	19 (54.2)	21 (51.2)	4 (33.3)	0.66$^{\Phi}$
Negative	5 (50)	16 (45.7)	20 (48.7)	8 (66.6)	
T Stage					
1	5 (50)	15 (42.8)	19 (46.3)	3 (25)	0.65*
2	4 (40)	18 (51.4)	16 (39)	7 (58.3)	
3	1 (10)	1 (2.8)	3 (7.3)	2 (16.6)	
4	0 (0)	1 (2.8)	3 (7.3)	0 (0)	
Tumor Localization					
Right	5 (50)	19 (54.2)	18 (43.9)	7 (58.3)	0.85*
Left	5 (50)	13 (37.1)	20 (48.7)	4 (33.3)	
Bilateral	0 (0)	3 (8.5)	3 (7.3)	1 (8.3)	

#independent sample t test; *linear-by-linear association; $^{\Phi}$fisher's (exact) test; BMI: BodyMass Index; pCR: Pathological Complete Response; BI-RADS: Breast Imaging Reporting and Data Systems; ER: Estrogen Receptor; PR: Progesterone Receptor; TNM: tumour, node, metastasis

the patients were classified as intermediate (B+C) density breast. A total of 77.5% of the patients were categorised as BI-RADS B or C, only 10.2% as A and 12.2% as D. There were no premenopausal patients with MD category A. According to BI-RADS, the mean age decreased with increasing breast density and the number of premenopausal patients increased. Patients with less dense breast composition (MD category: A+B) were significantly older than patients with more dense breasts (MD category: C+D, p=0.001). There was no statistically significant relationship between body mass index and breast density (p=0.48). There was no statistically significant relationship between breast density categories according to BI-RADS and breast cancer subtypes. There was a statistically significant difference between luminal

A, luminal B, triple negative subtypes in terms of pCR rates (p=0.007). There was no statistically significant relationship between tumour size and MD. It was concluded that tumours in invasive ductal carcinoma pathology were collected in the B+C density group at a statistically significant rate when compared with other histopathological types. In our study, 25 (25.5%) patients had pCR following NACT. In 73 (74.5%) patients, pCR could not be obtained. According to BI-RADS A,B,C,D, 2, 7, 10 and 6 patients achieved pCR, respectively. No correlation was found between pCR and menopausal status and tumour localisation. Age was not found to be a factor in obtaining pCR (p=0.33). According to BI-RADS score, pCR was found to be statistically significantly higher in patients with a score of 4 (p=0.008). When patients were dichotomised according to BI-RADS classification (A/B vs. C/D), there was no statistical difference between patients with high MD and patients with low MD (p=0.68; 95% CI 0.67-0.69) (Table 2).

Discussion

Nowadays, neoadjuvant treatment has become a standard treatment modality in patients with locally advanced BC. As the use of neoadjuvant treatment increases, the response rate to treatment, the prognosis of the patients and the determination of the factors that may predict the treatment response become more important. In this study, the relationship between mammographic breast density and pCR was investigated. In our study, the pCR rate was 25.5% (25/98). This rate was higher than the rates reported in the literature. A similar high rate was observed by Spring et al. who obtained pCR after NACT in 53 (31.7%) of 170 patients.[12] Sasanpour et al. reported a very high pCR rate of 39.2% in a study conducted in Iran, which they attributed to the patients with higher negative ER/PR percentage in their study group.[13] In our study, patients with negative ER/PR percentage were in the majority. 76.6% of the patients were non-luminal type A. Approximately one third of the patients were in the HER-2 positive subgroup. The high number of HER-2 positive patients and especially the dual anti-Her-2 blockade applied in NACT in recent years may have affected the high pCR result. In our study, we observed that the pCR rates of patients with BI-RADS 4 were statistically significantly higher than those of patients with BI-RADS 5 and 6. This may be related to the fact that patients who will be diagnosed earlier will have a better prognosis. Throughout a woman's life, MD changes and is strongly associated with hormonal events. On the other hand, Martin et al. did not find any association between serum estrogen levels and MD in pre- or post-menopausal women.[14] Mammographic density; with increasing age, shows a sharp decrease in the perimenopausal period.[14] In our study, there was a statistical difference between premenopausal and postmenopausal patient groups in terms of MD (p=0.001) (Table 3). Some studies have examined MD during NACT and adjuvant chemotherapy.[15,16] A decrease in MD of more than 10% increases the risk of contralateral BC compared to those whose density remains unchanged or decreases less. MD decrease in young premenopausal patients receiving adjuvant chemotherapy is more marked than in postmenopausal patients.[17] A possible biological explanation for the decrease in MD after chemotherapy in premenopausal patients is lobular atrophy.[18] In a study, large tumour size was found to be associated with high MD.[19] Similarly, in our study, as the tumour size increased, the degree of MD was found to be increased. This may probably be due to the fact that the tumour is detected late in the dense breast. Meanwhile, no significant correlation was found between MD and PCR in our study. The pCR rate was 22.7% in the low-density group and 38.5% in the high-density group. There was no statistical relationship between these clinically significant values. Similarly, Skarping et al. in a study of 200 breast cancer patients who received NACT concluded that MD was not a predictive marker of Pcr.[20] In another study, the same group found that premenopausal women with MD category D were less likely to achieve pCR after NACT.[21] In a study by Cullinane et al. similar to our study, it was concluded that MD did not independently predict pCR after NACT.[22]

Our study has some limitations. One of the most important limitations is its retrospective design and limited number of patients. Another limitation is that although BIRADS categorisation is subject to certain standards, evaluation bias cannot be excluded because no single radiologist evaluated the mammographic imaging because of the retrospective design of our study.

Table 2. pCR Rates According to Mammographic Density Groups

	pCR			
	No n (%)	**Yes n (%)**	**Total n (%)**	**p**
Density				
A	8 (10.9)	2 (8)	10 (10.2)	0,62*
B	28 (38.3)	7 (28)	35 (35.7)	
C	31 (42.4)	10(40)	41 (41.8)	
D	6 (8.2)	6 (24)	12 (12.2)	
Grouped Densıty				
A+B	36 (49.3)	9 (36)	45 (45.9)	0,68ϕ
C+D	37 (50.7)	16 (64)	53 (54)	

*linear-by-linearassociation; ϕfisher's (exact) test; pCR: Pathological Complete Response.

Table 3. Distribution According to Menopausal Status

	Menopause Status			
	Postmenopause Median (IQR)	**Premenopause Median (IQR)**	**Total Median (IQR)**	**p**
Age (year)	64 (60.5-70)	46 (40-51)	53 (43-64)	<0.001#
Overall Survival (month)	56.5 (43.5-78.5)	48 (37-74)	51 (39-76)	0,49#
BMI (kg/m^2)	28.06 (22.78-39.55)	30.23 (24.84-36.28)	28.88 (22.86-36.92)	0,89#
	n (%)	**n (%)**	**n (%)**	
Density				
A	10 (22.7)	0 (0)	10 (10.2)	<0.001*
B	21 (47.7)	14 (25.9)	35 (35.7)	
C	10 (22.7)	31 (57.4)	41 (41.8)	
D	3 (6.8)	9 (16.6)	12 (12.2)	
Grouped Density				
A+B	31 (70.5)	14 (25.9)	45 (45.9)	<0.001$^{\Phi}$
C+D	13 (29.5)	40 (74.1)	53 (54.1)	
ER Pozitive	33 (75)	34 (62.9)	67 (68.3)	0,27$^{\Phi}$
Negative	11 (25)	20 (37)	31 (31.6)	
PR Pozitive	22 (50)	27 (50)	49 (50)	>0.05$^{\Phi}$
Negative	22 (50)	27 (50)	49 (50)	

#independent sample t test; *linear-by-linear association; $^{\Phi}$fisher's (exact) test; BMI: Body Mass Index; ER: Estrogen Receptor; PR: Progesterone Receptor

Conclusion

The results of this study showed that breast density is not an independent predictive marker for complete pathological response to neoadjuvant treatment. Large-scale studies based on larger subgroup analyses of MD as a biomarker are needed.

Disclosures

Ethics Committee Approval: Ethical approval was taken from Dokuz Eylül University Ethical Comittee: 20.07.2022; Number 2022/23-16.

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Conflict of Interest: None declared.

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