Mammographic Breast Density as a Predictive Factor of Local Recurrence in Female Patients with Invasive Breast Cancer

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Abstract: Purpose: Mammographic breast density (MBD)is one of the strongest breast cancer risk factors. Dense breast tissue was demonstratedto increase the risk of local recurrence after modified radical mastectomy. The aim of this study was to evaluate MBD as a predictive factor for local recurrence in female patients with invasive breast cancer**. Methods**: Eighty sevenfemale patients with local recurrence after mastectomy forinvasive breast cancer were included in this study. Patient's data were recorded concerning mammographic density, age, menopausal status and tumor features (histological type, grade, size, nodal status, LVI, hormonal receptors status, Ki67 and Her-2/neu). **Results**:Among all patients, 23 (26.44%) patients had low dense breasts (<25%) while 64 (73.66%) patients had high dense breasts (≥25%). Analysis of risk factors associated with local recurrence according to the mean time (in months) showed a significant association between early local relapse (LR) andhigh MBD (p<0.001), age <50 (p=0.006), LVI (p=0.044), positive axillary nodes (p=0.014) and high Ki67 expression (p=0.007). In multivariate analysis, MBD was an independent risk factor for LR (p<0.001). Age and nodal status was near significant (p=0.07). **Conclusion:** mammographic breast densityhas a significant impact on local recurrence in female patients with invasive breast cancer. Further studies with large number of patients still needed to confirm the predictive value of MBD in the incidence of local recurrence in female patients with invasive breast cancer.

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1. Introduction

Breast cancer the most common leading cause of cancer related death and cancer in women.[1] Mammography one of the tools in the diagnosis of breast cancer and is currently considered to be the primary investigative modality.Mammographic breast density changedby time and is affected by genetic factors.It decreases with age, and by menopause and multiparity.[2,3]

Breast density, refers to the appearance ofradiographsof breast. [5,6]Radiolucent fat appears dark on a mammogram. Epithelial and fibrous stromal tissues, on the other hand, appear white or radio dense and are collectively referred to as mammographic density. High mammographic density is inversely associated with age and body weight and can be measured inquantitative and qualitative manners.[4].

Patients with very low density were associated with a poor prognosis.[7- 9]Density has many mechanisms that could affect prognosis. The MBD has consistently been associated with breast stromal composition, which is involved in tumor progression.[10-13]

The primary treatment for local breast cancer is modified radical mastectomy.[14,15]Nearly 10% of patients had MRM are at risk of locoregional recurrence (LRR), and a 25% of patients are at risk of developing distant metastases during follow up.[16] Huang et al evaluated MBD as a predictive for LRR in patients with invasive breast cancer andfound that dense breast tissue increased the risk of locoregional recurrence after MRM.[17]

2. Material and Methods

Eighty seven (87) patients with invasive breast were included out of diagnosed patients in clinical oncology department, Tanta university hospital in the period from December 2012 to December 2017. Patients with invasive breast carcinoma who experienced local relapse (LR) after modified radical mastectomy were included. Patients with unavailable pretreatment mammography were excluded. Information's were recorded concerning mammographic density, age, menopausal status and tumor features (histological type, grade, size, nodal status, LVI, hormonal receptors status, Ki67 and Her-2/neu).Mammographic density was calculated visually using the craniocaudal projections of the original diagnostic mammograms. To minimize error, tow radiologists share in the analysis. Patients were classified according toWolfe classification of mammographic.[10] they were classified as low (<25% density)and high (>25% density).

Statistical analysis:

Descriptive characteristics were compared using the chi-squared test.The multivariateanalysis was assessed using logistic regression model. Mann- Whitney test used to evaluate the potential risk factors forLR. Overall, a p value <0.05 was considered statistically significant. SPSS program version 21 was used.

3. Results

Among all patients, 23 (26.44%) patients had low dense breasts (<25%) while 64 (73.66%) patients had high dense breasts (>25%). Age < 50 (p=0.002), premenopausal women (p=0.013), tumor size >5cm (p=0.003), LVI (p=0.001), high Ki67 expression (p<0.001) and patients who received adjuvant radiotherapy (p<0.001) were significantly associated with more frequent high breast density.

Table 1 showed the correlation between patient's characteristics and MBD.

Table (1): Correlation between mammographic breast density and patients characteristics.

	Total (n = 87)	**Low (n = 23)**	**High (64)**	**P**
Age				
≤50	39(44.8%)	4(17.4%)	35(54.7%)	0.002*
>50	48(55.2%)	19(82.6%)	29(45.3%)	
Pathology				
Ductal	76(87.4%)	19(82.6%)	57(89.1%)	0.42
Lobular	11(12.6%)	4(17.4%)	7(10.9%)	
Menopause				
Pre	38(43.7%)	5(21.7%)	33(51.6%)	0.013*
Post	49(56.3%)	18(78.3%)	31(48.4%)	
N				
N0	26(29.9%)	10(43.5%)	16(25%)	0.17
N1	22 (25.3%)	6(26.1%)	16(25%)	
N2	26(29.9%)	3(13%)	23(35.9)	
N3	13(14.9%)	4(17.4%)	9(14.1)	
Grade				
G1&2	59(67.8%)	16(69.6%)	43(67.2%)	0.83
G3	28(32.2%)	7(30.4%)	21(32.8%)	
LVI				
Non	47(54%)	19(82.6%)	28(43.8%)	0.001*
Yes	40(46%)	4(17.4%)	36(56.2%)	
radiotherapy				
Yes	68(78.2%)	12(52.2%)	56(87.5%)	<0.001
No	19(21.8%)	11(47.8%)	8(12.5%)	
Ki67				
Low	32(36.8%)	15(65.2%)	17(26.6%)	0.001*
High	55(63.2%)	8(34.8%)	47(73.4%)	
Her-2				
Positive	14(16.1%)	2(8.7)	12(18.8%)	0.26
Negative	73(83.9%)	21(91.3%)	52(81.2%)	
Tumor size				
<=5	53(60.9)	20(87)	33(51.6)	0.003*
>5	34(39.1)	3(13)	34(39.1)	
Hormonal status				
+ve	64(73.6)	14(60.8)	50(78.1)	0.11
-ve	23(26.4)	9(39.1)	14(21.9)	

Table 2 showed analysis of risk factors associated with local recurrence according to the mean time (months) to local relapse. There were a significant association between early local relapse

(LR) and high MBD (p<0.001), age <50 (p=0.006), LVI (p=0.044), positive axillary nodes (p=0.014) and high Ki67 expression (p=0.007). In multivariate analysis (table3), MBD was an independent risk factor for LR (p<0.001). Age and nodal status was near significant (p=0.07).

Table (2) Univariate analysis for factors affectingLR

Factor	Mean time to local recurrence	P
Age		
≤50 years	35.74	**0.006**
>50 years	50.71	
Pathology		
Ductal Ca.	42.51	0.147
Lobular Ca.	54.32	
N stage		
Negative	54.17	**0.014**
Positive	39.66	
Menopause		
Pre-	38.79	0.090
Post-	48.04	
LVI		
-ve	49.00	**0.044**|
+ve	38.13	
Her-2		
+v	38.29	0.355
-ve	45.10	
Tumor size		
< 5	47.32	0.125
≥ 5	38.82	
Grade		
1-2	45.50	0.421
3	40.84	
HR		
Positive	43.80	0.900
negative	44.57	
MBD		
Low	67.59	**<0.001**
High	35.52	
Ki67		
Low	53.53	**0.007**
high	38.45	

Table (3) multivariate analysis for factor affecting LR

factor	HR (95% CI)	p-value
Age	0.623(0.372-1.042)	0.071
Nodal stage	1.640 (.960 – 2.800)	**0.070**
LVI	1.064(0.658-1.721)	0.800
MBD	1.687 (1.273 – 2.236)	**<0.001**
Ki67	1.042(0.630-1.724)	0.872

4. Discussion

Mammographic density is one of the risk factors for breast cancerandloco regional recurrence in patients withinvasive breast cancer.[20]in the present study there was correlation between patient's characteristics and MBD. Among 87 patients, 23 (26.44%) patients had low dense breasts (<25%) while 64 (73.66%) patients had high dense breasts (≥25%). Age < 50 (p=0.002), premenopausal women (p=0.013), tumor size ≥5cm (p=0.003), LVI (p=0.001), high Ki67 expression (p<0.001) and patients who received adjuvant

radiotherapy (p<0.001) were significantly associated with more frequent high breast density.

The analysis of risk factors associated with local recurrence according to the mean time (months) to local relapse showed a significant association between early local relapse (LR) andhigh MBD (p<0.001), age <50 (p=0.006), LVI (p=0.044), positive axillary nodes (p=0.014) and high Ki67 expression (p=0.007). In multivariate analysis (table2), MBD was an independent risk factor for LR (p<0,001). Age and nodal status was near significant (p=0.07).

Tulin et al 2009[19] evaluated the role of mammographic density as a risk factor for the development of local recurrence and found that patients with high mammographic density had a greater risk of local recurrence compared with the low dense breasts. Women who did not receive radiotherapy had a disease recurrence rate at 10 years of40% for patients with >50% density versus 0% for women <25% density (P < .0001). They concluded that mammographic breast density is an important risk factor for local breast cancer recurrence especially among women not receiving breast irradiation.

Louise et al 2013[20] found that (PD) was associated withlocal(p = 0.039) and locoregional recurrence (p = 0.033)for women with PD≥25%. They suggested that high mammographic density is an independent risk factor of both local and LRR.

Yu-Sen et al [17] evaluated patients with dense (50–75% density) and extremely dense (>75% density) breasts and found that those patients had an increased risk of locoregional recurrence. They also demonstrate that dense breast tissue (>50% density) increased the risk of LRR after modified radical mastectomy in patients with invasive breast cancer.

In a study carried out by Chengshuai et al [21], 814 patients with invasive breast cancer were evaluated on univariate and multivariate analysis. The tumor size and subtype show statistical significance with LN metastases. Luminal B type shows significant higher incidence ofaxillary lymph nodes involvement. So, they conclude that LN involvement is an intrinsic characteristic for molecular subtype of breast cancer. And triple positive patientshad the least and most incidence of LN metastases.

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