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 demonstrated to 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 seven female patients with local recurrence after mastectomy for invasive 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) 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, MBD was an independent risk factor for LR (p<0.001). Age and nodal status was near significant (p=0.07). **Conclusion:** mammographic breast density has 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.

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 changed by time and is affected by genetic factors. It decreases with age, and by menopause and multiparity. [2,3]

Breast density, refers to the appearance of radiographs of 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 and found 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 to Wolfe 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 multivariate analysis was assessed using logistic regression model. Mann-Whitney test used to evaluate the potential risk factors for LR. 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): 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%)	
N1	22 (25.3%)	6(26.1%)	16(25%)	
N2	26(29.9%)	3(13%)	23(35.9)	0.17
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 1 showed the correlation between patient's characteristics and MBD.

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 affecting LR

Factor	Mean time to local recurrence	P
Age≤50 years **>50 years**	35.74 50.71	**0.006**
Pathology Ductal Ca. Lobular Ca.	42.51 54.32	0.147
N stage Negative Positive	54.17 39.66	**0.014**
Mens. status Pre- Post-	38.79 48.04	0.090
LVI -ve +ve	49.00 38.13	**0.044**|
Her-2 +ve **-ve**	38.29 45.10	0.355
Tumor size< 5 **≥ 5**	47.32 38.82	0.125
Grade1-2 **3**	45.50 40.84	0.421
HRPositive negative	43.80 44.57	0.900
MBDLow High	67.59 35.52	**<0.001**
Ki67 Low high	53.53 38.45	**0.007**

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 cancer and loco regional recurrence in patients with invasive 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) 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 (table2), MBD was an independent risk factor for LR (p<0,001). Age and nodal status was near significant (p=0.07).

Tulin Cil 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 with local (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 of axillary lymph nodes involvement. So, they conclude that LN involvement is an intrinsic characteristic for molecular subtype of breast cancer. And Triple negative and Triple positive patients had the least and most incidence of LN metastases.

References

1. Jemal A, Bray F, Center MM, Ferlay J et al.: Global cancer statistics. CA Cancer J Clin 61:69–90, 2011.
2. Martin LJ, Boyd NF: Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. Breast Cancer Res 200810,2008.
3. Martin LJ, Melnichouk O, Guo H et al.: Family history, mammographic density, and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 19:456–463,2010.
4. McCormack VA, dos Santos Silva I: Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev15(6):1159–1169,2006.
5. Thurfjell E.: Breast density and the risk of breast cancer. N Engl J Med 347(12):866,2002.
6. Boyd NF, Rommens JM, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol6 (10):798–808, 2005.
7. Masarwah A, Auvinen P, Sudah M, et al.: Very low mammographic breast density predictspoorer outcome in patients with invasive breast cancer. Eur Radiol. 25(7):1875–82, 2015.
8. Masarwah A, Tammi M, Sudah M, et al.: The reciprocal association between mammographicbreast density, hyaluronan synthesis and patient outcome. Breast Cancer Res Treat. 153(3):625–34,2015.
9. Allred DC, Medina D.: The relevance of mouse models to understanding the development and progression of human breast cancer. J Mammary Gland Biol Neoplasia.13(3):279–88,2008.
10. Alowami S, Troup S, Al-Haddad S, et al.: Mammographic density is related to stroma and stromal proteoglycan expression. Breast Cancer Res. 5(5): R129–35,2003.
11. Hawes D, Downey S, Pearce CL, et al.: Dense breast stromal tissue shows greatly increased concentration of breast epithelium but no increase in its proliferative activity. Breast Cancer Res. 8(2): R24,2006.
12. Lahlou H, Muller WJ.: Beta1-integrins signaling and mammary tumor progression in transgenic mouse models: implications for human breast cancer. Breast Cancer Res. 13(6):229,2011.
13. van Dongen JA, Voogd AC, Fentiman IS, et al.: Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst. 92(14):1143–50,2000.
14. Poggi MM, Danforth DN, Sciuto LC, et al.: Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. Cancer. 98(4):697–702,2003.
15. Fisher B, Anderson S, Bryant J, et al.: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatmentof invasive breast cancer. N Engl J Med. 347(16):1233–41, 2002.
16. Yu-Sen Huang, Jenny Ling-Yu Chen, Chiun-Sheng Huang, et al: High mammographic breast density predicts locoregional recurrence after modified radical mastectomy for invasive breast cancer: a case-control study. Breast Cancer Research 18:120,2016.
17. Wolfe JN.: Risk for breast cancer development determined by mammographic parenchymal pattern. Cancer. 1976;37: 2486-2492,1976.
18. Tulin Cil; Eve Fishell; Wedad Hanna et al: Mammographic Density and the Riskof Breast ancer Recurrence After Breast-Conserving Surgery. Cancer December 15,: 5780-86,2009.

19. Louise Eriksson, Kamila Czene, Lena Rosenberg et al: Possible influence of mammographic density on local and locoregional recurrence of breast cancer. Breast Cancer Research 15: R56,2013.

20. Chengshuai Si, Yiting Jin, Hongying Wang, et al.: Association betweenmolecular subtypes and lymph node status in invasive breast cancer. Int J Clin Exp Pathol;7(10):6800-6806,2014.

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