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Establishment of Correlation of Ki-67 Proliferative Index Expression in the Peritumoral Tissue with Tumor Mass in ER (Estrogen Receptor) Positive Breast Carcinoma

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Breast carcinoma is the second most frequently occurring malignant tumor. It usually arises in a multistep fashion from intermediary lesions to invasive cancer. Identifying such predominantly occurring lesions adjacent to malignancy and studying of Proliferative Ki-67 index and (ER) status in such lesions and substantiate their possible identity as a premalignant lesion. The study tries to establish the lesions which have the potential for progression to overt malignancy, thereby indicating early identification and appropriate treatment.
Aim: To establish a correlation in the expression of Ki-67 proliferative index in the peritumoral tissue with tumor mass of ER-positive breast carcinomas.
Objectives: 1.To study the expression of ER in breast tumor mass. 2. To study expression of Ki-67 proliferative index in breast tumor mass and peritumoral tissue. 3. To assess the expression of Ki-67 proliferative index in breast tumor mass and peritumoral tissue. Study design: Observational prospective study.

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Materials and Methods: 32 mastectomy specimens of diagnosed cases of breast carcinoma sent to the Histopathology Section are studied. Gross features are described and the histopathological section stained by (H & E) stain and immunohistochemistry using monoclonal antibody to (ER) and proliferation-associated antigen (Ki-67) are studied. Statistics: Chi-square test, Spearman's rank-order correlation coefficient, and software used in the analysis were SPSS 22.0 version and Graph Pad Prism 6.0 version and $p<0.05$ is considered as the level of significance.

Results: In this study out of 32 ER-positive cases, 24 showed positivity for Ki-67 in tumor mass and 22 cases showed high Ki-67 in peritumoral tissue. Maximum lesions were proliferative lesions with atypia like ADH and DCIS.

Conclusion: Ki-67 is an accurate nuclear proliferative marker to assess cell proliferation status. In breast carcinoma adjacent peritumoral lesions show a high proliferative index which suggests a link and a trail of generation of premalignant lesions converting to invasive carcinoma. Proliferative lesions with and without atypia, moderate epithelioid, atypical ductal hyperplasia, and DCIS more or else equals IDC for Ki-67 proliferative index. Such cases should be regularly followed up for progression of these lesions to malignancy.

Keywords: Breast carcinoma; estrogen receptor; peritumoral; Ki-67.

1. INTRODUCTION

In women following cervical carcinoma, breast carcinoma stands as the most commonly occurring solid epithelial tumor. Nowadays it is not a rarely diagnosed condition causing deaths. Worldwide in developed and developing countries, it is a leading cause of death in the female population [1]. Breast carcinomas are observed to progress in a multistep fashion, ranging from benign to lesions with intermediate potential, to finally invasive carcinoma [2,3]. These before malignant lesions should thus be identified at an early stage to prevent progression to malignancy. Breast lesions are described as proliferative and neoplastic. Estrogen is a hormone responsible for proliferative activity and progression of the tumor. Estrogen Receptor (ER) status and proliferative index (Ki-67) are important markers of disease progression and prognosis [4]. Hence they are useful prognostic factors predicting survival free from disease in these patients [5,6].

Different lesions are seen in the same breast, the area in proximity to malignancy, justifying the multistep progression to malignancy [1,2]. Benign breast disease (BBD) is a group of lesions like atypical ductal hyperplasia, atypical lobular hyperplasia, ductal and lobular carcinoma in situ seen on histopathology. These have further been categorized into three broad pathologic categories: non-proliferative, proliferative without atypia, and proliferative with atypia [7]. Benign proliferative breast disease is an extremely complex and interrelated group of proliferative disorders of the breast parenchyma. They do not necessarily mean neoplastic lesions, rather they are a result of hormone-induced hyperplastic processes. Thus studying such lesions adjacent to malignancy and knowing Ki-67 proliferative index (MIB-1 index) and Estrogen receptor (ER) hormonal status in these cases would help us identity premalignant lesions in the respective patient.

The proportionate correlation between ER positivity and the Ki-67 index has been established in this study by learning their expression. The study identifies the lesions possessing potential for progression to frank malignancy. Thus early identification shall help to target therapy and ultimately reduce the incidence of breast cancers.

2. METHODS AND MATERIALS

The study was done from 1st August 2017 to 31st July 2019 in the histopathology division of the Department of Pathology in association with the Surgery department, JNMC Sawangi (Meghe), Wardha, Maharashtra. It is an observational prospective study.

2.1 Sample Size [8]

The sample size came out as 30, derived from the formula,

$n=Z\alpha/2^2 . P.(1-P)/d^2$,

where

"Z a/2" is the level of significance at 5 % that is 95 % confidence interval.

"p" is the prevalence of oral squamous cell carcinoma.

"d" is the desired error of margin.
"n" is the sample size.

2.2 Inclusion Criteria

1. Female patients reported as IDC of the breast on FNAC
2. Patients who underwent a modified radical mastectomy.
3. De-novo diagnosed cases of breast malignancy.
4. Patients are not on any other treatment.

2.3 Exclusion Criteria

1. All benign lesions and non-carcinomatous pathology of the breast were diagnosed on FNA.
2. Cases where only true-cut biopsy or lumpectomy or quadrantectomy has been done, as in such cases all the parameters will not be available for assessment.
3. Histopathological diagnosis of IDC without lymph node metastasis.
4. Known cases of breast malignancy undergoing follow-up.
5. Cases where neoadjuvant chemotherapy is already taken by the patients.
6. Subtypes of breast cancer other than IDC [NOS].

3. METHODOLOGY

Consent in a well-informed manner was taken from all the patients who came with complaints of a breast lump. Clinical assessment and proper history were obtained from these patients who were inpatients of the surgery department. FNA or true-cut biopsy was performed in most of the cases and diagnosed breast carcinoma patients were chosen for the study. These patients were subjected to MRM. Tissue specimens obtained from MRM procedure were received in the division of Histopathology, Department of Pathology, and kept overnight for fixation.• In the next step the grossing of specimens as per the standard method given in protocol. Sections from the tumor mass and peritumoral tissue were taken.

Definition of peritumoral tissue–It is defined as the closest point where invasion by tumor is not seen on examination [8]. These sections were subjected to tissue processing. After tissue processing was completed, routine Harris hematoxylin and eosin staining was done. Histomorphological assessment of the sections was done. Those cases reported as (IDC) invasive ductal carcinoma (NOS type) were recruited for the study. Grading of the tumor mass was carried out using the Modified Scarff Bloom Richardson grades [9].

- 3-5 score: Grade I (well-differentiated)
- 6-7 score: Grade II (moderately differentiated)
- 8-9 score: Grade III (poorly differentiated)

The predominant lesions in the peritumoral tissue were categorized as under:

A. Benign non-proliferative lesions:
   i. Fibrocystic changes

B. Benign proliferative lesions without atypia:
   i. Moderate epithelioid
   ii. Usual ductal hyperplasia
   iii. Fibroadenoma

C. Benign proliferative lesions with atypia
   i. Atypical ductal hyperplasia
   ii. Ductal carcinoma in situ

- Later the sections from the tumor mass and peritumoral tissue were studied for immunohistochemistry for ER and positive cases were chosen and subjected to Ki-67 staining. • The findings of IHC status for Ki-67 were compared between the tumor mass and the peritumoral tissue and the results were noted.
- Dako pharm DXTM Immunohistochemistry kit was used. ER score was calculated of each individual case using Allred scoring system. Thirty-two ER positive cases were chosen and sections from tumor mass and peritumoral areas of these cases were further subjected to immunohistochemistry for Ki-67 antigen.

4. RESULTS

Age distribution of cases: Maximum numbers of patients (32%) fell under the age group 41-50 years. The least patients (7%) were of the age group of 71-80 years. Quadrant wise distribution of lumps: Maximum numbers of cases (44%) were seen having lumps in upper and outer quadrant of the breast. Distribution of the lumps according to tumor size: Maximum cases (46%) belonged to T1 category. Distribution of the cases according to BR Grading: 56% of cases belonged to a poorly differentiated category.

Table 1. Histomorphological assessment of the lesions in the peritumoral area

	Category		No. of cases	Percentage
A	Benign non proliferative lesions=01	Fibrocystic change	01	03%
B	Proliferative lesions without atypia=17	Fibroadenoma	01	03%
		Usual Ductal hyperplasia	04	12%
		Moderate epitheliosis	12	38%
C	Proliferative lesions with atypia and lesions with in situ changes=14	Atypical Ductal Hyperplasia	08	25%
		Ductal Carcinoma In Situ	06	19%
	Total Cases (n)		32	100%

Proliferative lesions were more common than non-proliferative lesions. The commonest histomorphological change observed was of Moderate epitheliosis i.e. 12 cases (38%) while the least evident finding was of fibrocystic change accounting for a single case (03%).

Out of 32 ER, Ki-67 positivity in tumor mass was seen in 24 cases and in peritumoral tissue in 22 cases.

The highest Ki-67 expression was seen in the category of proliferative changes with atypia and in situ changes that included cases of ADH and DCIS (Fig. 1).

Thus, proliferative lesions were more common than non-proliferative lesions. The commonest histomorphological change observed was of Moderate epitheliosis i.e. 12 cases (38%) while the least evident finding was of fibrocystic change accounting for a single case (03%).

The expression of Ki-67 was high particularly in cases of ADH and DCIS (Fig. 2).

Fig. shows high Ki-67 proliferative index with discrete nuclear immunostaining (IHC 10x) (Cut off value: >30% cells).

Table 2. Correlation of Ki-67 index in peritumoral lesion and ER Score according to the range

		ER Score (Allred system)		Total
		2 to 5	≥6	
Ki-67 index in peritumoral lesion	Low	5(15.63%)	5(15.63%)	10(31.25%)
	High	11(34.38%)	11(34.38%)	22(68.75%)
Total		16(50%)	16(50%)	32(100%)

50% cases had ER score range of 2-5 and the remaining 50% cases had >5

Table 3. Distribution of cases according to Ki-67 proliferative index expression

			No. of cases	Percentage
Ki-67 Proliferative index	LOW	Tumor mass (<14%)	08	25%
		Peritumoral tissue (<30%)	10	32%
	HIGH	Tumor mass (>14%)	24	75%
		Peritumoral tissue (>30%)	22	68%

Table 4. Correlation of Ki-67 index in tumor mass and peritumoral lesion chi-square test

		Ki-67 in tumor mass		Total	ϰ2-value
		Low	High		
Ki-67 index in peritumoral lesion	Low	5(15.63%)	5(15.63%)	10(31.25%)	9.32
	High	1(3.13%)	21(65.63%)	22(68.75%)	P=0.002,S
Total		6(18.75%)	26(81.25%)	32(100%)	

p-value observed was 0.002

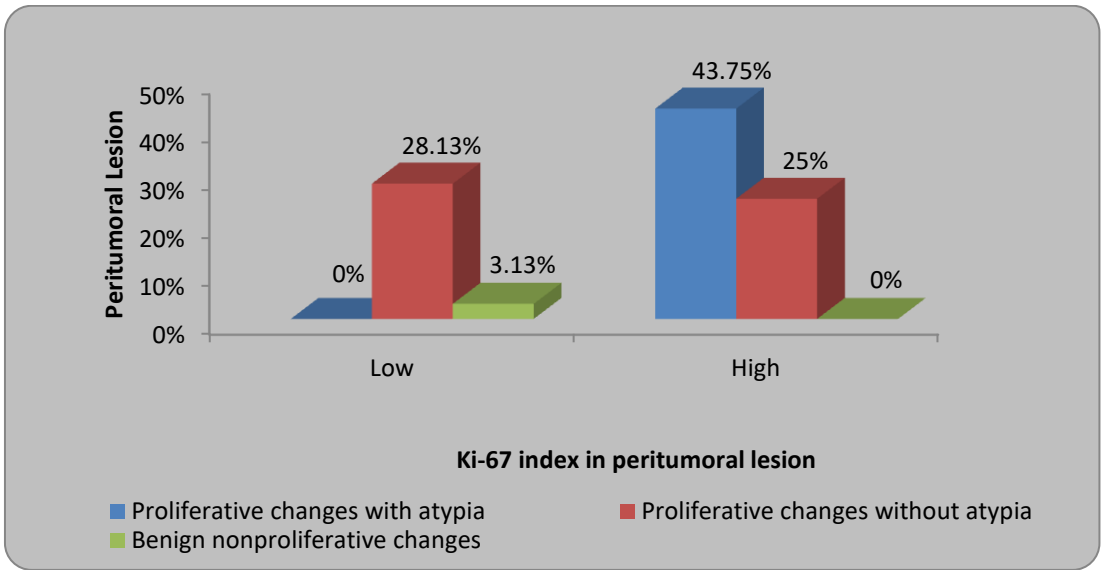

Fig. 1. Correlation of Ki-67 index in peritumoral lesions based on their categories

Table 5. Distribution of cases according to an individual histomorphological lesion

	Category	Lesions morphology	No. of cases	High Ki-67 in PT	Percentage
A	Benign non proliferative lesion	Fibrocystic change	01	00	00%
B	Proliferative lesions without atypia	Fibroadenoma	01	00	00%
		Usual Ductal hyperplasia	04	00	00%
		Moderate epitheliosis	12	08	25%
C	Proliferative lesions with atypia and in situ changes	Atypical Ductal Hyperplasia	08	08	25%
		Ductal Carcinoma in Situ	06	06	18%
	Total Cases (n)		32	22	68%

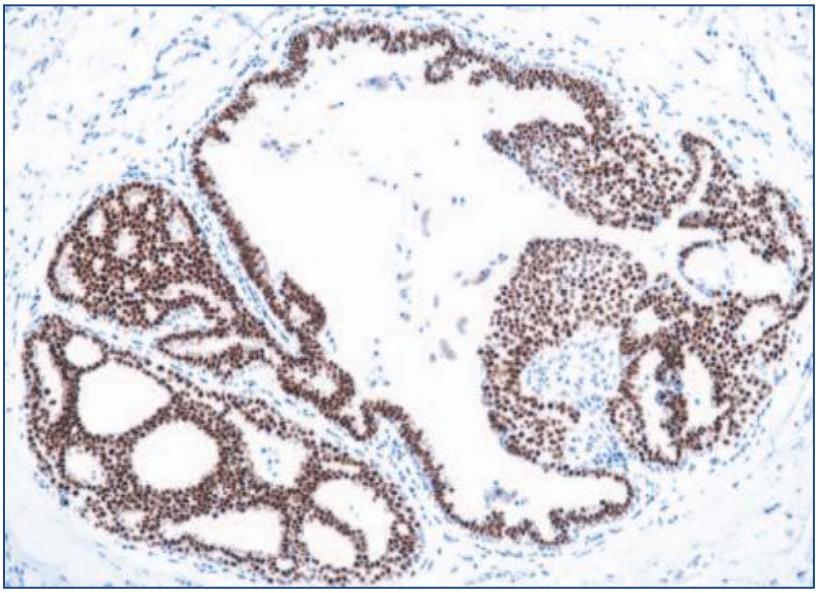

Fig. 2. Peritumoral tissue- atypical ductal hyperplasia

Table 6. Correlation of Ki-67 index expression in individual peritumoral lesion chi-square test

		Peritumoral Lesion						Total
		ADH	**DCIS**	**Fibroadenoma**	**Fibrocystic Changes**	**Mod Epitheliosis**	**UDH**	
Ki-67 index in peritumoral lesion	Low	0(0%)	0(0%)	1(3.13%)	1(3.13%)	4(12.50%)	4(12.50%)	10 (31.25%)
	High	8(25%)	6(18.75%)	0(0%)	0(0%)	8(25%)	0(0%)	22 (68.75%)
Total		8(25%)	6(18.75%)	1(3.13%)	1(3.13%)	12(37.50%)	4(12.50%)	32 (100%)
א2-value		19.58,p-value=0.001, significant.						

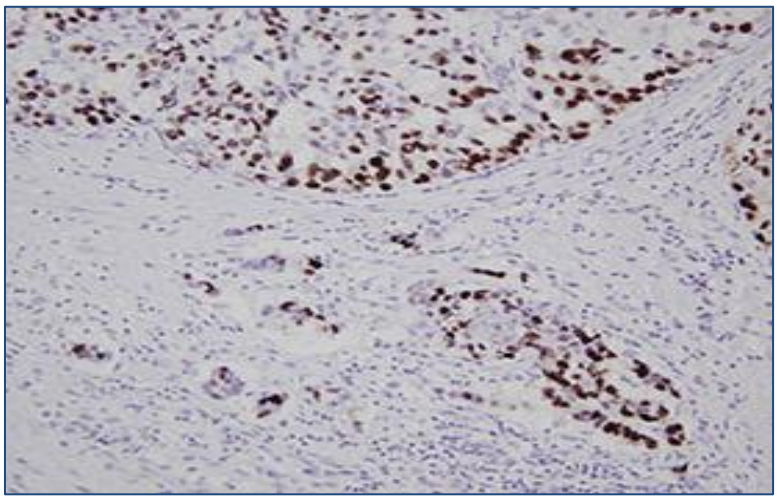

Fig. 3. Peritumoral tissue- ductal carcinoma in situ on IHC staining

Fig. shows high Ki-67 proliferative index with discrete nuclear immunostaining for Ki-67, Cut off value: >30% cells (IHC 10x).

4.1 Statistics

Statistical analysis was carried out by using descriptive and inferential statistics using chi-square test, Spearman's rank-order correlation coefficient and software used in the analysis were SPSS 22.0 version and GraphPad Prism 6.0 version while $p<0.05$ is taken as the level of significance.

The p-value for ER positivity and Ki-67 positivity in tumor mass was found to be 0.002 which is significant. p-value drawn for the Ki-67 proliferative index in peritumoral lesions was also found to be 0.001, which was significant irrespective of the histomorphological lesions within its categories.

5. DISCUSSION

Shashikala et al. [10] in their study, proliferative fibrocystic lesions in association with carcinoma breast- Study of mastectomy specimens, have a maximum number of cases accounting 65%, to undergo the diagnosis and subsequent mastectomy for IDC in the age range of 41-60 years. The present study has a concordant observation regarding the age range for the diagnosis of the IDC. Niikura et al. [11] in their study too had a mean age of presentation as 51 years.

The BR scores of the studies Klintman et al. [12] and Niikura et al. [11] were similar to the BR scores of the present study where peritumoral tissue assessment of the ER-positive breast is done, maximum number of patients belonged to BR Grade 2 (Moderately Differentiated) i.e. 18 cases (57%).

The consistent peritumoral area histomorphology has also been reported in the studies of Shashikala et al. [10] and Sathyalakshmi et al. [8].

Zhou [13], studied ER and Ki-67 expression in 56 cases, that constituted all proliferative lesions with and without atypia like UDH, ADH and DCIS.

Table 7. Histomorphological lesions in peritumoral tissue in different studies and the present study

Lesions in peritumoral tissue	Shashikala et al.	Sathyalakshmi et al.	Present study
Non proliferative benign	27 cases (27%)	05 cases (25%)	01 cases (04%)
Proliferative lesions without atypia	18 cases (18%)	08 cases (40%)	17 cases (53%)
Proliferative lesions with atypia and in situ changes	20 cases (20%)	07 cases (35%)	14 cases (43%)

Sathyalakshmi et al. [8] studied ER-positive breast carcinoma for peritumoral histomorphology and Ki-67 proliferative index. A total of 09 cases showed ER positivity. Increased ER positivity was commoner in proliferative lesions with atypia including in situ lesions. Most of the proliferative lesions without atypia were negative for ER and some came with little ER positivity, which is in concordance to our study.

The similar observation for Ki-67 proliferative index for ER positive IDC for the tumor mass has been quoted in the studies of Sathyalakshmi et al. [8] 7 cases of proliferative lesions with atypia and 8 cases of proliferative lesions without atypia showed Ki-67 positivity. The Ki 67 positivity was seen very high in patients with lesions such as ADH and DCIS. While only one case showed low Ki-67 expression and that belonged to benign non-proliferative category. These findings are in concordance with the present study. Ki-67 proliferative index for peritumor tissue in the agreement of the observation of present study has also been recorded in the studies of Zhou [11], where lesions showing ER positivity with high Ki-67 proliferative index mainly were proliferative lesions, especially ones with atypia and in situ lesions. These included following lesions- UDH, ADH, and DCIS. Similar related studies were reported [14-17]. Studies reported by Yeola et al. [18,19] Anand et al. [20] were reviewed.

The present study also made a similar observation to that of Sathyalakshmi et al. [8] where high Ki-67 proliferative index in addition to ER positivity was observed with situations of atypical ductal hyperplasia and DCIS.

6. CONCLUSIONS

1. The peritumoral area of the IDC show the definite histomorphological alterations which can be broadly classified as benign non-proliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia and in situ changes which are linked to the primary pathology of IDC.
2. The ER positive IDC in its peritumoral area shows higher percentage of categories B and C histomorphological alterations which include moderate epitheliosis, usual ductal hyperplasia, atypical ductal hyperplasia, and DCIS.
3. Ki-67 proliferative index in peritumoral tissue was observed to vary for the category B and C histomorphological lesions in ER positive IDC cases.
4. The Ki-67 proliferative index of tumoral area was concluded to be 24 out of 32 ER-positive IDC which was higher for the peritumoral one.
5. It is further concluded that proliferative lesions with and without atypia, moderate epitheliosis, atypical ductal hyperplasia and DCIS more or else equals IDC for Ki-67 proliferative index. Such cases should be closely monitored for and regularly followed up to note the progression of these lesions to recurrence of malignancy.
6. Peritumoral changes in category C of atypical ductal hyperplasia and DCIS with high Ki-67 proliferative index requires to be put to the watchful eyes to decrease the incidence of breast cancer by initiating appropriate therapy.

7. LIMITATIONS

The comparative statistics for Ki-67 proliferative index in the lesions observed in the peritumoral tissue available in the literature is less. The observations made in the present study therefore could not be compared extensively. The follow-up studies of histomorphological alterations in the peritumoral tissue of ER positive IDC too are not in plenty in published literature. Therefore one of the limiting factor for the present study is the follow-up of such cases even though it is one time Ki-67 estimated is high.

8. RECOMMENDATIONS

The reporting protocol of the mastectomy specimen should include the assessment of histomorphological alterations in the peritumoral tissue with its specified category and lesions within it. ER positive IDC should undergo Ki-67 proliferative index in the tumor as well the peritumoral tissue so that the proliferating potential can be predicted for recurrence and subsequent metastasis in the case of IDC.

CONSENT

Informed consent was taken from the target patients.

ETHICAL APPROVAL

The study was proceeded with, after the approval of the Institutional Ethics Committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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