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Expression of Ki-67 in Breast Cancer Cases – A Study

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Abstract
In the course of tumor development, the phenotypic of breast cancer constantly changes. Breast cancer is a clinically and biologically/pathologically heterogeneous illness, and this may be a contributing factor. It is crucial to have accurate prognostic data when counseling patients and formulating treatment strategies. While factors like age and menopausal status can be used as prognostic indicators in clinical parameters, crucial prognostic indicators in histology include tumour size and extent, histological type, histological grade, and the presence or absence of lymph node involvement.

1. Introduction
The complicated molecular nature of breast cancer is only partially reflected in the disease's diverse phenotype. In industrialized nations, breast carcinoma is the most common cancer in females. It is the second most frequent kind of cancer among Indian females. [1] The anticipated yearly number of cases is around 80,000, with incidence rates ranging from 16 to 25 per 100,000 of the population, adjusted for age. [2] In Asia, people between the ages of 40 and 50 are most likely to be diagnosed with breast cancer, while in the West, people between the ages of 60 and 70 are more likely to be diagnosed. High-grade malignancies and cancers

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lacking hormone receptors are common in Indian patients. [3]

Besides from being excellent predictors of the final result, additional factors also help focus medicines toward their intended biological targets. All of these things:

(i) **Progesterone Receptors (PR) and Estrogen Receptors (ER) :**Better results are associated with these nuclear hormone receptors, which are also a key indicator of how well hormonal (anti-estrogen) therapy will work. Chemotherapy is less likely to work on tumors that are ER positive. Less than 10% of tumors that do not express ER or PR are likely to react to hormone therapy, but these tumours are more likely to respond to chemotherapy. [5]

(ii) **The HER_2/neu (c-$erbB_2$) :**Transmembraneprotein HER_2/neu overexpression is predictive of response to medicines that target the protein, and is primarily associated with poor outcome and survival (e.g. Trastuzumab or Herceptin). [5]

(iii) **Rate of proliferation :**One of the main characteristics of cancer is sustained proliferation, which is crucial to the growth and progression of the disease. The most used technique is immunohistochemical evaluation of the Ki-67 antigen. High proliferation rate carcinomas are known to have a poor prognosis, albeit they respond better to chemotherapy. [5]

(i) **Aim:** To research the degree of Ki-67 expression in cases of breast cancer using immunohistochemistry.

(ii)

2. Review of Literature

Breast cancer is a collection of heterogeneous tumors that are located in the same anatomical location and cannot be viewed as a single, homogeneous disease. [15] Breast epithelial or mesenchymal tissue serves as the site of origin for breast cancers. In order to classify breast cancer histologically, the World Health Organization's (WHO) atlas is used, taking into account the morphological characteristics of the tumor. [16] The epithelium is the source of the vast majority of malignant breast cancers. The most prevalent kind is Invasive Breast Carcinoma No Special Type (IBC-NST), which is followed by Invasive Lobular Carcinoma and a number of "special types" include Tubular, Medullary, Mucinous, Micropapillary, Metaplastic Carcinoma, etc. [17]

(iii)

(iv)

(v)

By using cDNA microarray analysis, the pioneer investigations have suggested a novel description of the diverse group of breast tumors at the molecular level, going beyond the conventional hormone receptor (HR)+ and HR - types to identify many molecular/intrinsic subtypes. [18,19]

A classifier for breast cancer subtypes is the PAM50 study (Prosigna). It evaluates a patient's risk for a distant recurrence of the illness as well as the possibility that neoadjuvant chemotherapy will be effective. [29,30] These are some details on the many molecular subtypes of breast cancer:

Luminal A : The majority of newly diagnosed breast cancer cases are of the molecular subtype Luminal A, which is also the most prevalent.[31]

Luminal B: 20% to 30% of invasive breast cancer instances fall within this category. [36]

HER2+ :15% to 20% of breast cancer cases with recent diagnoses are represented by it. [40] A high expression of HER2 (> 10%), negative for ER (1%) and PR (20%), and a high expression of Ki-67 (> 20%) are the defining characteristics of this subtype.[32]

Triple-negative breast cancer (TNBC) :10% to 20% of all cases of breast cancer are caused by this group of tumors. [25] "This subtype is distinguished by the absence of the hormone receptors ER (1%), PR (20%), and the oncoprotein HER2 (10%) with Ki-67 index (> 30%)." [32]

TNBC tumors can be further broken down into the following seven different entities:

Two basal-like kinds (BL1 and BL2) that have a basal pattern of gene expression but differ in their immunological responses.

"Luminal Androgen Receptor type (LAR), which exhibits differential expression of genes involved in androgen metabolism"

"Significant variations in the expression of genes involving immunological signaling pathways are shown by the immunomodulatory type (IM)."

Claudin-low kinds (CL), identified by a lack of cellular junction protein expression (claudins 3, 4 and 7, in addition to E-cadherin)

The signaling of genes linked to stem cells and angiogenic factors differs between two types of mesenchymal tissue, namely "mesenchymal itself (M) and mesenchymal stem-like (MSL). Both exhibit positive regulation of the signaling pathways involved in EMT".

3. Material and Methods

This was a prospective type study of two years duration from June 2018 to May 2020 which was carried out at the Department of Pathology and Department of Molecular Biology and Genetic lab in our hospital with

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attached tertiary care centre. The study included all the cases of lumpectomy and modified radical mastectomy received for routine histopathological evaluation at histopathology section Department of Pathology and were further evaluated classifying breast cancer cases according to the WHO 2019 along with the evaluation of Ki-67 expression in breast cancer cases and their correlation with ER, PR and Her2-neu receptor and various other prognostic factors.

Inclusion criteria:

(i) All the breast cancer cases undergoing lumpectomy and modifiedradical mastectomy were included in this study.

Exclusion criteria:

(i) Tru cut biopsy were excluded.

(ii) Carcinoma with extensive tumor necrosis without sufficient viable

(iii) tumor were excluded.

(iv) Post chemotherapy and recurrence cases were excluded.

Nature of Specimens Received:

(i) Lumpectomy

(ii) Modified Radical Mastectomy

(iii) Toilet Mastectomy

Method of Data Collection:10% formalin preserved specimens were received after scrutiny of patient demographic, clinical details and laterality of the specimen along with details of surgical procedures performed viz lumpectomy or mastectomy. The specimens were oriented according to the laterality of the same and serial sliced at 1 cm distance and fixed in 10% NBF (Neutral buffered formalin) for 8 -12 hours. Proper care was taken so that specimen was not left in formalin for more than 24 hours as antigen retrieval procedure of IHC staining gets affected with over fixation.

4. Results and Discussion

Total 113 breast cancer cases were obtained within a period of 2 years from June 2018 to May 2020, which was a hospital based study.

Distribution of Ki-67 expression in breast cancer cases:

Table 1: Distribution of Ki-67 expression in breast cancer cases:

Sr. No.	Category	<20% Number of Cases (%)	>= 20% Number of Cases (%)	Total No. of Cases
	Ki-67	56 (49.56%)	57 (50.44%)	113

Out of 113 cases, cases of breast cancer showed low (<20%) expression of Ki-67 and cases showed high (>=20%) expression of Ki-67.

Table 2: Age distribution of breast cancer cases:

Sr. No.	Age	Number of Cases (%)
1	31-40	14 (12.38%)
2	41-50	35 (30.97%)
3	51-60	33 (29.20%)
4	61-70	18 (16.81%)
5	71-80	10 (8.845)
6	81-90	3 (1.8%)
7	Total	113 (100%)

"The youngest patient was 33 years old and oldest was 90 years of age. Maximum numbers of cases (35/113, 30.97%) were in the age group of 41 – 50 years. Out of the total 113 cases studied, 43% were below 50 years while the remaining 57% cases were above the age of 50 years."

Correlation of expression of Ki-67 with Age distribution in breast cancer cases

Table 3: Correlation of Ki-67 LI with Age distribution in breast cancer cases

Sr. No.	Age in Year	Ki- 67 Expression		
		<20% Number of Cases (%)	>= 20% Number of Cases (%)	Total No. of Cases
1	31-40	7 (50%)	7 (50%)	14
2	41-50	15 (42.85%)	20 (57.15%)	35
3	51-60	17 (51.56%)	16 (48.44%)	33
4	61-70	9 (50%)	9(50%)	18
5	71-80	7 (70%)	3 (30%)	10
6	81-90	1 (33.33%)	2 (66.67%)	3

X2 = 2.67 p value = 0.7508

"Ki-67 expression was individually correlated with prognostic factors like age, tumor size, histological type and grade, axillary lymph node metastasis, lymphovascular invasion (tumor emboli), tumor necrosis, hormone receptors viz estrogen receptor (ER) and progesterone receptor (PR), Her-2/neu status and molecular subtypes (Luminal A, Luminal B, Her 2/neu enriched and triple negative) of breast cancer cases."

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Distribution of gender in breast cancer cases: Out of the total of 113 breast cancer cases 112 cases (99.11%) were females and 1 case (0.89%) was of a male breast carcinoma.

Distribution of surgical procedures in breast cancer cases: Out of the total of 113 breast cancer cases in 15 cases (13.27%) underwent lumpectomy and the remaining 98 cases (86.73%) underwent Modified Radical Mastectomy (MRM).

Distribution of menopausal status in breast cancer cases:

Table 4: Distribution of menopausal status in breast cancer cases:

Sr. No.	Menopausal Status	Number of Cases (%)
1	Premenopausal	31 (27.67%)
2	Postmenopausal	82 (72.33%)

Out of the total of 112 breast cancer cases, 31 cases (27.67%) were premenopausal and 82 cases (72.33%) were postmenopausal.

Correlation of expression of Ki-67 with menopausal status in breast cancer cases:

Table 5: Correlation of Ki-67 LI with menopausal status in breast cancer cases:

Sr. No.	Menopausal Status	Ki- 67 Expression		
		<20% Number of Cases (%)	>= 20% Number of Cases (%)	Total No. of Cases
1	Premenopausal	13 (41.93%)	18 (58.07%)	31
2	Postmenopausal	42 (51.85%)	39 (48.15%)	81

X2 = 0.88 p value = 0.35

In our study out of 112 cases, maximum expression of Ki-67 was seen in premenopausal cases (18/31, 58.07%).

Mucinous Carcinoma

In the present study we had 3 cases of Mucinous Carcinoma of breast.

Table 6: Mucinous Carcinoma Breast Cases

Sr. No.	Histological type	Age/ Gender	Lymph node Involvement	ER	PR	Her2neu	Ki-67
1	MucinousCarcinoma Hypercellular	75/F	1/14	Positive	Positive	Negative	25
2	Mucinous Carcinoma Hypocellular	60/F	0/9	Positive	Positive	Negative	10
3	Pure Mucinous Carcinoma	45/F	0/13	Positive	Positive	Negative	10

Age of presentation of the 3 cases were 75 years, 60 years and 45 years. All the cases had left sided laterality. They were diagnosed as Mucinous Carcinoma – Hypercellular variant, Pure mucinous Carcinoma and Mucinous Carcinoma. Two cases showed low Ki-67 LI and 1 case showed high Ki-67 LI. All the cases were of the Luminal A molecular subtype showing ER+, PR+ and her2/neu-. Both pure mucinous carcinoma and Mucinous carcinoma has no nodal involvement along with low Ki-67 expression and The Mucinous carcinoma hypercellular variant showed high Ki-67 expresseion and had a node involvement. Thus, increased Ki-67 LI was observed in hypercellular variant of mucinous carcinoma.

Distribution of tumor emboli in breast cancer cases:

Table 7: Distribution of tumor emboli in breast cancer cases:

Sr. No.	Tumor Emboli	Number of Cases (%)
1	Present (+)	20 (18%)
2	Absent (-)	93 (82%)

Out of the 113 cases in our study lymphovascular emboli was present in 20 cases (18%) and absent in 93 cases (82%).

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5. Discussion

Sustained proliferation is essential in cancer growth and progression and is one of the key hallmarks of cancer.[6] "It may be assessed by various methods like counting mitotic figures in stained tissue sections, labeled nucleotides incorporation into DNA, and flow cytometric evaluation of cell fraction in the S phase. The most common method being Immunohistochemical assessment of Ki-67 antigen."

"Ki-67 expression was individually correlated with prognostic factors like age, tumor size, histological type, and grade, axillary lymph node metastasis, lymphovascular invasion (tumor emboli), tumor necrosis, hormone receptors viz estrogen receptor (ER) and progesterone receptor (PR), Her-2/neu status and molecular subtypes (Luminal A, Luminal B, Her 2 neu enriched and triplenegative) of breast cancer cases. he youngest patient was 33 years old and oldest was 90 years of age. Maximum numbers of cases were in the age group of 41 – 50 years followed by 51 – 60 years of age group." Out of the 113 cases studied 43% were below 50 years while the remaining 57% were above the age of 50 years. Mean age of patient was 54.92 years.

In present study, high Ki-67 expression was seen in the age group of 41 – 50 years i.e. in 20 cases (57.15%) followed by 51 – 60 years of age group i.e.16 cases (48.44%). A high Ki-67 LI significantly correlated with younger age was observed by Madani, Seyed-Hamid et al. [156]

In the present study, breast cancer was more common in postmenopausal women with 81 cases (72.33%) as compared to premenopausal women 31 (27.67%). However, high expression of Ki-67 was seen in more number of premenopausal women with breast cancer i.e. 18 cases (58.07%).

In a study by Bhagyashri R Hungund et al. (2019) on Indian cohort showed 53 cases were premenopausal and 35 cases were menopausal. Among the menopausal 37.7% cases (n=20) show Ki-67 LI < 15%, Among the premenopausal, 37.3% and 34.3% cases had Ki-67 of 15 -30 % and >30% respectively. However, this was statistically not significant (p value = 0.95)

Tumor size <2cms consisted of 10 cases. Out of the 10 cases, 8 cases (80%) showed low Ki-67 LI and 2 cases showed high Ki-67 LI. Whereas in cases having tumor size of 2 to 5 cms i.e. 63 cases, 34 cases showed low expression of Ki-67 and 29 cases showed high expression of Ki-67. Tumors with size > 5cms constituted 40 cases, out of which 14 cases showed low Ki- 67 LI and 26 cases showed high Ki-67 LI.

"Out of the total 113 cases of breast carcinoma in this study, maximumnumber of cases i.e. 76 cases (67.26%) were in the histological type of Invasive Breast Carcinoma – No Special Type (IBC-NST)," followed by Mixed IBC-NST 11 cases (9.74%), IBC with Medullary features 10 cases (8.85%), Invasive Lobular Carcinoma 6 cases (5.31%), IBC with Neuroendocrine features 3 cases (2.66%), Mucinous carcinoma 3 cases (2.66%) and 1 case each of Apocrine Carcinoma, Clear cell Carcinoma, Metaplastic Carcinoma and Glycogen Rich Clear Cell Carcinoma with 0.88% each respectively.

In present study we had 6 cases of Invasive Lobular Carcinoma (ILC) out of which 4 cases (66.66%) showed low Ki-67 LI as compared to 2 cases (33.34%) which showed higher expression. Thus, in Lobular carcinoma low Ki-67 LI was observed which in turn can also match with the overall good prognosis that is known about Lobular carcinoma of breast.

In a study by Hashmi et al. (2019)[170] which had a total of 91 cases of lobular carcinoma, 46 cases (50.5%) showed Ki-67 LI <15%, 20 cases (22%) showed Ki-67 LI 15 – 24%, 13 cases (14.3%) showed Ki-67 LI 25 – 44% and 12 cases (13.2%) showed Ki-67 LI >44%. Thus, in this study also maximum number of cases of lobular carcinoma showed low expression of Ki-67. Similar finding was observed in our study as well.

Another Indian cohort research done by Jain, R. et al. (2016)[167] found that "all cases were associated with low Ki-67 expression in Grade I tumor, while 92.31 percent of cases were associated with high Ki-67 expression in Grade III tumor. The high expression of Ki-67 was significantly associated with advanced stages and poorly differentiated tumors [p<0.0001]."

Study done by Sharath Kumar et al. (2017)[161] on Indian cohort, 18 cases had no lymph node metastasis of which maximum 17 cases showed low KI-67 LI and 1 case had high Ki-67 LI whereas 42 cases that had lymph node metastasis present of which maximum cases (28/42, 66.66%) showed high Ki-67 LI. (p=0.004)

Molino et al.[111] found that there was a positive relationship with nodal status as node negative tumor are more likely to have a low proliferation index. Jain, R. et al. (2016)[167] observed that in terms of nodal status, high Ki-67 expression was observed in 71.05% and 15.63% of cases of positive lymph node and negative lymph node breast tumors, respectively. Thus, as the tumor's nodal status increased, Ki-67 expression

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also increased. This finding was highly significant ($p<0.0001$).

"Out of the, 113 cases, 52 cases were PR positive and 61 cases were PR negative. In the present study, high expression of Ki-67 was seen in a greater number of PR negative (43/61, 70.50%) cases whereas more number of PR positive cases (38/52, 73.07%) showed low KI-67 LI." Thus, we observed a statistically significant inverse relationship between Ki-67 expression and PR status. Ki-67 was highly expressed in PR negative breast cancer cases as opposed to PR positive breast cancer cases. In a study done by Yin, Yongxiang et al. (2014)[173] "there were also significantly more PR positive patients in low Ki-67 positive group (35/49, 71.5%) than that in the high Ki-67 positive group (27/98, 27.5 %)."

The Luminal A molecular subtype of breast cancer cases in the current study consisted of 50 cases, of which 38 cases (76%) had low Ki-67 LI and 12 cases (24%) had high Ki-67 LI. The maximum number of subtype Luminal A cases i.e. 76%, showed a low proliferation of Ki-67. A study was done by Soliman et al. (2016) [157] containing 107 breast cancer cases. 44 cases were of Luminal A molecular subtype. All of the cases showed low expression of Ki-67.

The Luminal B subtype in the present study consisted of 10 cases, 6 of which were Luminal B - Her2neu negative and 4 of which were Luminal B - Her2/neu positive.

All 4 cases showed a high Ki-67 LI in the Luminal B - Her2/neu positive subtype.

Study by Bhagyashri R Hungund et al. (2019) [159] on Indian cohort of 88 breast cancer cases, Luminal B subtype consisted of 17 cases. of which 7 cases (41.2%) had Ki-67 <15%, 3 cases (17.65%) had Ki-67 of 15 - 30% and 7 cases (41.2%) had Ki-67 of >30%.

In the present study Her2/neu molecular subtype comprised of 17 cases, out of which 6 cases (35.29%) showed low Ki-67 LI and 11 cases (64.71%) showed high Ki-67 LI. The maximum number of Her2/neu molecular subtype cases (64.71%) showed a high Ki-67 proliferation index.

In a study done by Nguiessan Alphonse Aman et al (2018) [166] showed that maximum cases (13/15) within the Her2 positive molecular subtype had high Ki-67 LI > 30%.

When we compared the Ki-67 LI among different Breast cancer molecular phenotypes, we found that the TNBC subtype the highest (80.56%) cases showing high Ki-67 LI, followed by the Her2/neu enriched i.e. 64.71% cases, followed by luminal B i.e. 50% cases. Whereas Ki-67 LI was the least in luminal A subtype i.e. 24% cases.

Comparing the Ki-67 PI in the 2 luminal groups, Luminal A subtype showed more cases (38/50, 76%) with low Ki-67 LI. In contrast Luminal B subtype which had (5/10, 50%) cases with high Ki-67 LI. Compared to the Luminal B and the other 2 subtypes, Luminal A subtype tumors have a much lower activity for cell proliferation. The data in the present study indicate that the more aggressive the cancer is, i.e. the lower hormone receptor expression levels (ER, PR) or the higher HER2 expression, the higher the Ki-67 LI value. "In addition, compared to low Ki-67 LI in ER/PR+HER2- patients, the triple negative breast cancer (TNBC) and HER2+ subtypes were associated with a high Ki-67 score. This is confirmed by various studies done by Wang et al. (2014) and Sun et al. (2015)." [181,182]

Our above finding was in concordance with the study done by Hashmi et al. (2019)[170] The highest Ki-67 LI (mean 50.9 ± 23.7%) was observed in triple negative breast cancers (TNBC), which was followed by "Her2neu subtype (mean 42.6 ± 21.6%) and luminal B subtype (mean 34.9 ± 20.05%). On the contrary, Luminal A cancers showed the lowest Ki-67 LI (mean 23.6 ± 19.7%)."

6. Conclusion

Ki-67 index values are shown to be associated with breast cancer prognosis. Ki-67 expression reveals gradual increase with disease severity. Ki-67 Labelling Index "showed a statistically significant positive correlation with duration of lump, tumor size, tumor grade, lymph node status and ER, PR, Her2/neu status. Thus, supporting its role as a prognostic biomarker. The strong correlation of Ki-67 with molecular subtypes suggest that Ki-67 helps predict response to chemotherapy." Recent advances in molecular biology research is useful for further subtyping the histological types of breast carcinoma cases which is helpful for prognosis, treatment and better outcome.

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