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Original Research Article

Ki-67 Expression and Its Association with Conventional Prognostic Markers in Breast Carcinoma

Bhagyashri R Hungund[1], Prakash R Malur[2], Ashok S Godhi[3], Nares Kumar Tyagi[4], Arun V Joshi[5]

[1]Professor, Dept of Pathology, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Nehru Nagar, Belagavi, Karnataka, India.
[2]Consultant Pathologist, KLE's Dr Prabhakar Kore Hospital and Research Centre, Belagavi, Karnataka, India.
[3]Professor, Dept of Surgery, Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Nehru Nagar, Belagavi, Karnataka, India.
[4]Statistician and Head of Department, Dept of Epidemiology and Biostatistics, KLE Academy of Higher Education and Research, Nehru Nagar, Belagavi, Karnataka, India.
[5]Associate Professor, Dept of Community Medicine, BIMS, Belagavi, Karnataka, India.

Corresponding Author: Bhagyashri R Hungund

ABSTRACT

Background: Breast cancer is the most common malignancy among women with varied diagnostic and clinical outcomes. The proliferative markers are evaluated in various tumours including breast carcinoma. Ki-67 is one of the most reliable markers to assess the proliferative activity and has a promising role in evaluating the prognosis of breast carcinoma. Study of its association with other prognostic markers can help in planning of treatment strategies tailoring the therapeutic regimen.

Objective: The present study is conducted to evaluate the role of Ki-67 expression in breast carcinoma and to study its association with currently used clinical, histopathological, immunohistochemical prognostic markers and Nottingham prognostic index.

Materials and Methods: 88 patients of breast carcinoma were evaluated to study Ki-67 expression and its association with various clinical, histopathological features, hormone receptor status, HER-2/neu expression and Nottingham Prognostic Index. Distributions of the various variables were expressed as percentages. Chi-square and Fisher's exact test were used to study the association of Ki-67 expression and the other variables.

Results: Among 88 cases of breast carcinoma, 30 cases (34.09%), 32 cases (36.4%) and 26 cases (29.55%) showed proliferative index of <15%, >15%-30% and >30% respectively. Right sided tumors, duration of lump (>6months), higher histological grade, HER2/neu positivity and Triple negativity showed higher proliferation index ($p<0.05$). Majority of the tumors with proliferation index of >30% had poor prognosis as indicated by Nottingham Prognostic index of >5.4%

Conclusion: Study of Ki-67 expression helps in predicting the clinicopathological spectrum and outcomes in breast cancer patients.

Key words: Grade, Molecular markers, Nottingham Prognostic index, histopathology, Prognosis, Proliferation

INTRODUCTION

Breast cancer is the most common malignancy in women worldwide, with increasing trends seen in developing countries including India. [1] Breast cancer presentation varies widely with different

diagnostic and clinical outcomes. [2] There is a need to understand the biology of the disease to improve the treatment outcome and reduce the mortality. The currently used prognostic markers are age, axillary lymph node status, histopathological grade, lympho-vascular invasion, hormone receptor status and human epidermal growth factor receptor expression. [3,4]

Proliferation markers have been broadly evaluated as a prognostic factor for breast carcinoma. Various proliferative markers that have been evaluated include Ki-67, Proliferation cell nuclear antigen (PCNA), flow cytometrically determined cell cycle distributions based on DNA content, Bromodeoxyuridine (BrdU), p53 over expression, high S phase fraction, aneuploidy and high mitotic index. [5] Ki-67 is a nuclear protein which regulates the cell cycle and is expressed in all active phases of cell cycle and is not expressed in resting phase i.e. in G0 phase of cell cycle. Ki-67 is easily available, easy to detect, cost effective and more reproducible compared to other markers. The Ki-67 expression as detected by immunohistochemistry is one of the most reliable indicators of the proliferative status of cancer cells. [6]

It has been studied and used to stratify prognosis in invasive breast cancer and has been reported to correlate with clinical response to chemo therapy. [7] But, its routine use has not been implemented. St Gallen Consensus conferences in 2011 and 2013 recommended use of Ki67 for analysis of cellular proliferation and differentiating its expression in Luminal tumors. [8] However they are based on molecular genetic studies and molecular profile of the patients; the cost of these molecular assays would always be a limiting factor in the resource poor settings. [9]

This gives way to the development of surrogate markers which when used appropriately can help stratify the patients for appropriate management. Cheang et al recommended the use of Ki-67 along with ER, PR, HER-2/neu as a surrogate for molecular profiling which can be used in the resource poor setting. [9] Also studies have observed differences in frequency of high Ki-67 expression in different ethnic and racial groups. [10]

The present study was conducted to study Ki-67 expression in breast carcinoma and to study its association with currently used prognostic markers to assess the prognosis including the clinical, histopathological features, hormone receptor status, HER-2/neu expression and Nottingham Prognostic Index (NPI).

MATERIALS AND METHODS

Ethical clearance was obtained from the Institutional Ethical committee.

The study material comprised of medical records, histopathology blocks and slides of 88 consecutive patients of breast carcinoma whose operated samples were sent the department of Pathology attached to a tertiary care hospital in north Karnataka during the period of 5years(January 2007 to Dec 2011). Universal sampling was done.

The data obtained from the medical records included age, sex, religion menopausal status, family history, clinical presentation, duration of symptoms, side of the breast involved and type of surgery. The data pertaining to gross examination findings including size, quadrant involved, changes in nipple and areola were obtained from the grossing notes.

Hematoxylin and Eosin stained slides were archived from department of pathology and were evaluated for histological features including type, grade, presence or absence of necrosis, lympho-vascular invasion, fibrosis, in-situ changes and stromal reaction.

The histological grade was calculated using Nottingham's Bloom Richard grading system which uses degree of tubule formation, nuclear atypia, and mitosis as parameters of grading. [11] Nottingham prognostic index was calculated using the formula.[Size(cm)X 0.2]+[LN stage (1-3)]+[Grade(1-3)]. [12] Three prognostic groups with score of <3.4 ,>3.4-5.4, and >5.4 which indicated Excellent/

good, moderate and poor prognosis were made.

The representative blocks were cut in to 3-4micron thin sections for immune-histochemical staining with Estrogen receptor(ER), Progesterone receptor (PR), Her-2/neu and Ki-67 markers. Pre-diluted ready to use Anti-ER (Clone 1D5, Mouse, Biogenex), Anti-PR (Clone PR88, Mouse, Biogenex), Anti-Erb-2/Her-2 (Clone EP1045Y, Rabbit, Biogenex), Anti-Ki-67 Proliferating cell (BGX-297, Mouse, Biogenx) and Biogenex Super Sensitive detective systems were used for immune-histochemical staining. Positive and negative controls were run with each batch. Already known positive cases were used as positive control for ER, PR, HER-2/ neu. Lymph node was used as positive control for Ki-67 expression.

ER and PR stained slides were evaluated for the percentage of cells showing intra-nuclear staining of any intensity and was reported as positive when more than 1% of the cells showed intra-nuclear positivity as per American society of Clinical oncology/ College of American Pathologists Clinical Practice (ASCO-CAP) guidelines. [13] HER-2/neu expression was interpreted using ASCOCAP guidelines 2007 with membrane staining as 3+(Positive), 2+(unequivocal) and 1+ or less as negative. [14]

Ki-67 was evaluated as percentage of positive cells within the total number of malignant cells counted across the sections. Nuclear staining of any intensity within tumor cells was considered positive. Minimum 500 cells were counted for scoring. According to the recommendations at the St. Gallen conference, the tumors were classified as <15 %(Low), 16-30%(Intermediate), and > 30 %(High). [15] All the cases were classified according to the molecular subtypes depending upon the expression of hormonal receptors (HR) and Her-2/neu. Tumors that were positive for ER and negative for HER-2/neu were classified as Luminal A type; those positive for ER and HER-2/neu were Luminal B; those that were negative for ER and positive for HER-2/neu were classified as HER-2 disease; and those that were negative for both ER and HER-2/neu were classified as Basal type (Triple negative type). [16]

Statistical analysis was performed using SPSS Ver.20. The distributions of various variables were expressed in percentages. The averages were calculated wherever relevant. Chi square test and Fischer's exact test were used to study the association between the variables. P value of <0.05 was considered significant.

RESULTS

The 88 cases of breast carcinoma showed proliferative index of <15% in 30 cases (34.09%), 15% to 30% in 32 cases (36.4%) and >30% in 26 cases (29.55%) . The median Ki-67 index was 20%.

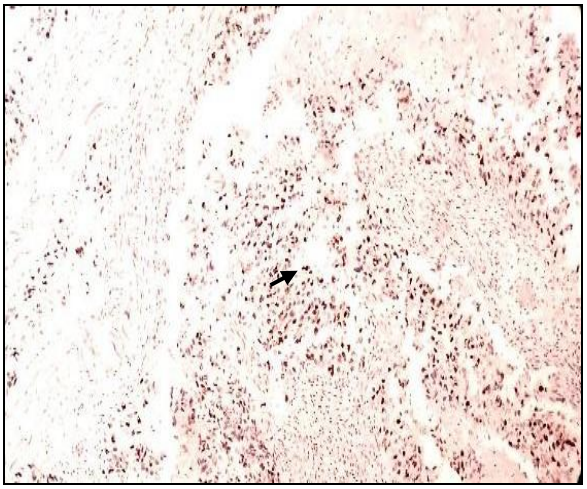

Fig 1: Showing Ki-67 expression with >30% proliferation index(X200)

It was observed that higher number subjects in the age group of 40-49 years had a higher (>30%) percentage of Ki-67 expression(38.5%)followed by 20-39 and 50 age groups. However this difference was not statistically significant. Menopausal status and religion did not show significant difference in the Ki-67 index. (Table1)

Table 1: Ki-67 index in breast carcinoma by age, menopausal status, and religion

	Ki-67 index expressed as percentage				
	<15 (%)	15-30(%)	>30 (%)	Total (%)	P value
	30(34.1)	32(36.4)	26(29.6)	88(100)	
Age					
20-39	4(26.7)	7(46.7)	4(26.7)	15	0.9
40-49	7(26.9)	9(34.6)	10(38.5)	26	
>50	19(40.4)	16(34.0)	12(25.5)	47	
Menopausal status					
Menopausal	20(37.7)	19(35.9)	14(26.4)	53	0.95
Premenopausal	10(28.6)	13(37.1)	12(34.3)	35	
Religion					
Hindus	27(35.1)	27(35.1)	23(29.9)	77	0.975
Others	3(27.3)	5(45.5)	3(27.3)	11	

Note: Two subjects were only with family history, hence, family history is not analyzed

Lump was the predominant symptom (75%) and majority presented with lump on left breast (48%). Right sided tumors had higher proliferation compared to left ($p<0.05$). Majority presented with lump of <6months duration.47% of tumors presenting >6 months had higher proliferation. Fixation to chest (41.7%), upper inner quadrant involvement and tumor had higher proliferation index.(Table 2)

Table 2: Ki-67 index in breast carcinoma by clinical presentation, side involved, duration of lump, fixation to the chest, quadrant involved and size of the tumor

	Ki-67 index expressed as percentage				
	<15 (%)	15-30 (%)	>30 (%)	Total (%)	
	30(34.1)	32(36.4)	26(29.6)	88(100)	p value
Clinical Presentation					0.1
Lump	22(29.3)	30(40)	23(30.7)	75	
Lump with other symptoms	8(61.5)	2(15.4)	3(23.1)	13	
Side					0.025
Left	22(45.8)	17(35.4)	9(18.8)	48	
Rt/Bilateral	8(20.0)	15(37.5)	17(42.5)	40	
Duration of lump*					0.025
<6months	22(31.9)	30(43.4)	17(24.6)	69	
>6months	8(42.1)	2(10.5)	9(47.4)	19	
Fixation to chest					0.9
Absent	25(32.9)	30(39.5)	21(27.6%)	76	
Present	5(41.7)	2(16.8)	5(41.7%)	12	
Quadrant					0.9
Lower inner	2(33.3)	3(50)	1(16.7%)	6	
Lower Outer	8(50.0)	3(18.8)	5(31.3%)	16	
Upper Inner	4(22.2)	6(33.3)	8(44.4%)	18	
Upper outer	9(29.03)	16(51.6)	6(19.4%)	31	
Others**	7(41.9)	4(23.5)	6(35.3%)	17	
Size of tumor in cm					0.201
<5	23(33.8)	19(27.9)	26(38.2)	68	
>5	3(20)	7(46.7)	5(7.4)	15	
Not known	3(60)	1(20)	1(20)	05	

Note:*: involving more than one quadrant

Among the various histological features, grade of the tumor showed significant association with proliferation index. 11cases (55%) of grade III tumors showed proliferation index of >30% while only 2cases (12.5%) and 13cases (25%) of grade II and grade I tumors respectively showed higher proliferation index. Presence of fibrosis, necrosis, fibrocystic change, lymphocytic infiltration did not show statistically significant difference in proliferative index.(Table 3)

Only Tumors with three or more lymph nodes positives had higher proliferation index. 13 cases (50% had proliferation index of >15 % and 8 cases had proliferation index of ≥30%. This difference was not statistically significant. However lymph node positivity with 1-3 lymph-nodes did not show increased

proliferation index compared to no lymph-node positivity.(Table 4)

Table 3: Ki-67 index in Breast carcinoma by histopathological features

	Ki-67 index expressed as percentage				
	<15 (%)	15- 30(%)	>30(%)	Total (%)	p value
	30(34.1)	32(36.4)	26(29.6)	88(100)	
Histological type					0.9
IDC NOS	21(30)	26(37.1)	23(32.9)	70	
Infiltrating Lobular	3(60.0)	2(40)	0	5	
Mucinous	2(100)	0		2	
Papillary	1(33.3)	0	2(66.7)	3	
Medullary	0	0	1(100)	1	
Others	3(42.9)	4(57.1)	0	7	
Grade*					0.05
GradeI	7(43.8)	7(43.8)	2(12.5)	16	
Grade II	21(40.4)	18(34.6)	13(25)	52	
GradeIII	2(10)	7(35)	11(55)	20	
Lymphovascular invasion					0.9
Absent	13(40.6)	11(34.4)	8(25)	32	
Present	17(30.4)	21(37.5)	18(32.1)	56	
Necrosis					0.9
Absent	14(36.8)	15(39.5)	9(23.7)	38	
Present	16(32)	17(34)	17(34)	50	
Fibrosis					0.9
Absent	3(21.4)	5(35.7)	6(42.9)	14	
Present	27(36.5)	27(36.5)	20(27.03)	74	
Fibrocystic change					0.9
Absent	22(32.4)	26(38.2)	20(29.4)	68	
Present	8(40)	6(30)	6(30)	20	
In-situ changes					0.9
Absent	12(40)	11(36.7)	7(23.3)	30	
Present	18(31.0)	21(36.2)	19(32.8)	58	
Lymphocytic infiltration					0.9
Absent	3(25)	6(50)	3(25)	12	
Present	27(35.5)	26(34.2)	23(30.3)	76	
PNI					0.9
Absent	29(34.1)	30()	26(30.6)	85	
Present	1(33.3)	2(66.7)	0(0)	3	

Note: IDC NOS; Infiltrating duct carcinoma Not otherwise specified
PNI: Perineural invasion

Table 4: Ki-67 index in breast carcinoma by lymph-node positivity

Lymph-nodes status	<15(%)	15-30(%)	≥30 (%)	Grand Total
	22(31.9)	30(43.5)	17(24.6)	69(100)
N0(<1)	11(34.4)	13(40.6)	8(25)	32
N1(1-3)	6(54.5)	4(36.4)	1(9.1)	11
N2/N3(>3)	5(19.2)	13(50)	8(30.8)	26
Grand Total	22	30	17	69
	P value=0.9			

Immunohistochemical expression of hormonal receptors did not show significant difference in proliferation index. 14 cases (36.9%) of HER-2/neu positive tumors showed proliferation index of >30 ($p<0.05$) (Table 5).

Table 5: Ki-67 index in Breast carcinoma by expression of Estrogen, Progestrone, HER2/neu receptors

	Ki-67 index expressed as percentage				
	<15(%)	15-30(%)	≥30 (%)	Total(N=88)	p value
	30(34.1)	32(36.4)	26(29.6)	88(100)	
ER					0.9
Negative	15(34.9)	12(27.9)	17(39.5)	44	
Positive	15(34.1)	20(45.5)	9(20.5)	44	
PgR					0.9
Negative	15(31.9)	15(31.9)	17(36.2)	47	
Positive	15(36.5)	17(41.5)	9(21.95)	41	
HER-2/Neu					0.025
Negative/Equivocal	16(34.04)	22(44)	12(25.5)	50	
Positive	14(36.84)	10(26.3)	14(36.9)	38	

Among the molecular subtypes 43.5% cases of Triple negative subtypes showed higher proliferation index followed by Luminal B(41.2%), HER-2/neu type and Luminal A(7.4%) and this difference was statistically significant ($p<0.05$).(Table 6)

Table 6: Ki-67 index by Molecular subtypes of breast carcinoma

Molecular subtype	<15(%)	15-30(%)	≥30 (%)	Grand Total
	30(34.1)	32(36.4)	26(29.6)	88(100)
Luminal A	8(29.6)	17(62.96)	2(7.4)	27
Luminal B	7(41.2)	3(17.65)	7(41.2)	17
HER-2/neu	7(33.3)	7(33.3)	7(33.3)	21
Triple Negative	8(34.8)	5(21.7)	10(43.5)	23
	p value<0.05			

Patients with >15 % and had moderate to poor prognosis. Majority of patients with proliferative index of <15% had Excellent/ good prognosis (56.2%) while only 1case (6.3%) of 17 cases with >30% proliferation had Excellent /good prognosis. However this difference was not statistically significant.(Table 7)

Table 7: Ki-67 index in breast carcinoma by Nottingham prognostic Index (NPI)

	Ki-67 labelling index expressed as percentage			
NPI	<15(%)	15-30(%)	≥30 (%)	Grand Total
	22(31.9)	30(43.5)	17(24.6)	69(100)
Excellent/good Prognosis	9(56.2)	6(37.5)	1(6.3)	16
Moderate prognosis	9(27.3)	16(48.4)	8(24.2)	33
Poor Prognosis	4(20)	8(40)	8(40)	20
Grand Total	22	30	17	69
	P value=0.1			

As there were very few cases that showed positive family history, bilateral involvement, showing perineural invasion and histological types other than infiltrating duct carcinoma-Not otherwise specified these variables were not analyzed separately.

DISCUSSION

Breast carcinoma is the most common malignancy worldwide. It has varied clinical outcomes due to its biological heterogeneity. Apart from various other factors, Ki-67 has been studied as a proliferative marker in various studies in diverse population groups. Various studies have used different cut off points for evaluation of its prognostic and predictive roles. However the as the recent recommendations suggested, the cut-off point of 15% has been used in the present study. [15]

A study [17] conducted among Iranian patients found significant association between Ki-67 expression and higher nuclear grade, Her-2-neu positivity with higher frequency among TN type similar to the present study.

A large study conducted in Japan [16] found the median value of 20%and they observed that DCIS, lobular carcinoma and mucinous carcinoma had lower Ki-67 values similar to the present study. .

In the above mentioned study, among the breast cancer subtypes luminal A was predominant and luminal B was the least frequent type. [16] Similarly in the present study Luminal A was the most predominant type. However TN was the next common subtype followed by HER2/neu rich and the Luminal B types. Another study conducted in Egyptian University observed a predominance of Luminal A subtype (44%), followed by triple negative (25%) Luminal B (23%) and HER-2/neu enriched. It was observed in their study that all the patients with Luminal A subtype had lower proliferation (<15%) while higher proliferation was observed in 69% of luminal B, 34% of HER-2neu type and 60% of Triple negative type. Patients with lower proliferation index displayed better overall survival than those with higher Ki-67 who also exhibited higher instances of metastasis and recurrences. [18]

The Japanese study also observed higher Ki-67 index in in patients with larger tumors, younger age, positive lymphnodes, higher nuclear grade negative ER/PgR expression and positive HER-2/neu expression which was statistically significant. [16] Similar observations were made by The Turkish study except for lymphnode status which was not found to be significantly associated. [8] A study done on Saudi population also demonstrated similar results..However tumor size, lymphovascular emboli, ER, PgR status did not show statistical significant association [19] similar to the present study.

A recent study in South India also observed statistically significant association between size, and grade of tumor. The present study observed significant association of proliferation index with higher grade, HER2-neu positivity and triple negativity.

In addition the South Indian study also observed significant association with NPI. The present study also observed that the proliferation index was higher in poor prognosis group. However this was not statistically significant. It is also noted that tumors with an increase in number of stromal lymphocytes showed lower proliferation which was also observed in our study.

Other prognostic factors like the menopausal status, lymphovascular invasion, necrosis, desmoplasia, presence of in-situ carcinoma component, nipple and areola involvement similar to the present study. [20]

CONCLUSION

Ki-67 can be used as an important supplement in the panel of prognostic markers to assess the prognosis of breast carcinoma.

Limitations: Follow up of the patients was not done in the patients which could have allowed us to measure the direct prognostic.

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