ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2017; 3(1): 98-100
www.allresearchjournal.com
Received: 15-11-2016
Accepted: 16-12-2016

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Study of KI 67 expression in carcinoma breast

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Abstract
Introduction: Breast cancer is the second most common malignancy in India. It is a disease with unpredictable aggressiveness. Various treatment options are available for management of these patients. Many clinicopathologic prognostic factors play an important role in predicting responses to these treatment modalities. Commonly ER, PR and Her2/neu status is studied in all breast cancers. Of all the other markers, Ki 67 is one marker which reflects the proliferation potential of breast cancer. This can be used as an independent biomarker to know the response of tumor cells to chemotherapy. In the present study Ki 67 expression was studied and correlated to various clinicopathologic prognostic factors.
Aims and Objectives: Study of Ki 67 expression in breast cancer. To correlate Ki 67 expression with clinico pathological factors.
Methodology: 60 modified radical mastectomy specimens were studied. Histopathological examination followed by Immunohistochemistry study for Ki 67 expression was done and correlated with various clinicopathological factors.
Results: High Ki 67 expression was seen in 6(33%) cases in age group of 41- 50 years and all other age groups showed low expression of Ki 67. No statistically significant association between Ki 67 expression and age was noted in this study (p value=0.375). 3(5%) tumors with size < 2cms showed low expression of Ki 67 whereas 42(70%) cases with size > 2cms showed variable but high expression of Ki 67 and was statistically significant (p value = 0.002). Out of 18(30%) cases without lymph node involvement 17 showed low expression, 1 case showed high expression and out of 42(70%) cases with metastasis 38(90%) showed high expression (p value = 0.004). Grade 1 cases showed low expression Grade 2 and 3 cases showed high expression of Ki 67 which was statistically significant (p value = 0.022).
Conclusion: Ki 67 can be a valuable independent predictive and prognostic biomarker in breast cancer and it helps in management of these patients.

Keywords: Cell proliferation, Ki -67, Prognostic Factors, Chemotherapy

1. Introduction
Breast cancer is the second most common cancer among women in India [9]. It is seen more in 40 to 50 years of age and presents with palpable cancer [9]. Many of these patients will have lymph node metastasis at the time of diagnosis. It is an important public health problem draining the resources. Clinical management of breast cancer depends on many pathological and clinical prognostic markers. Lymph node status, size, type and grade of the tumour were used as the prognostic indicators. Recently, hormone receptor status of estrogen, and Her2/neu over expression is universally used as biomarkers for breast cancer [6, 7, 8]. These marker studies have become mandatory for deciding on the type of treatment. Ki 67 is one of the markers which reflect the proliferative index of tumour cells and helps to determine response to chemotherapy. This study attempts to determine the expression of Ki 67 in breast cancer patients and its correlation with other clinicopathological parameters.

2. Methods
The present study included 60 modified radical mastectomy (MRM) specimens received in department of Pathology, Mysore Medical College and Research Institute between Dec 2014 and May 2016, All MRM specimens diagnosed histopathologically with breast cancer were included. Sections were then taken from these specimens for immunohistochemistry to determine Ki 67 expression. All other patients' data were obtained from medical records.

Ki 67 immunohistochemical staining was done using paraffin blocks. 3µm sections were taken deparaffinised and rehydrated. Antigen retrieval was done and peroxide block performed using 3% hydrogen peroxide. Sections were incubated with primary antibody as per manufacturer's instructions. DAB (Diaminobenzidine) substrate was applied and incubated. Later the sections were counterstained with hematoxylin for visualization. Ki scoring was done and scored as low if ≤ 10% of tumor cells stained and as high for all other intensities.

Statistical analysis was done using R software. Ki 67 expression and its association with clinicopathological parameters were determined using Chi Square tests. P value was calculated for each parameter and p value of ≤ 0.005 was considered as significant.

3. Results

60 cases of breast cancer were studied. The age ranged from 26 to 76 years and the mean age was 48 years. Breast cancer was more common in premenopausal women 40 (60%). In 3 (5%) cases the tumor size was <2 cm and in 57(95%) cases it was > 2 cm. On histopathological typing 56 (93.2%) cases were infiltrating ductal carcinoma NOS. Other 4 cases included invasive lobular carcinoma, metaplastic carcinoma, medullary carcinoma and mucinous carcinoma. 42 (70%) of these cases showed lymph node metastases and 28(46%) cases showed lymphovascular invasion. As per NSBR (Nottingham Modified Scarff Bloom Richardson) grading, 12 (20%) cases were in Grade 1, 30(50%) were in Grade 2 and 18(30%) were in Grade 3. In 18(30%) cases no lymph node metastasis was seen. 42(70%) cases showed lymph node metastasis.

Ki 67 expression along with important clinicopathological parameters is shown in Table 1. Cases were categorised as High reactive (Fig 1) and as low reactive (Fig2). Cut-off of ≤ 10 tumor cells reactive was taken as low and > 10 tumor cells expressing was taken as high. Ki 67 expression was seen in 6(33%) cases in age group of 41- 50 years and all other age groups showed low expression of Ki 67. No statistically significant association between Ki 67 expression and age was noted in this study (p value=0.375). Tumor size < 2cms 3(5%) cases showed low expression of Ki 67 whereas of all other 57 cases, 42(70%) cases showed variable but high expression of Ki 67 and was statistically significant (p value = 0.002). Out of 18(30%) cases without lymph node involvement 17showed low expression 1 case showed high expression and out of 42(70%) cases with metastasis 38(90%) showed high expression (p value = 0.004). Grade 1 cases showed low expression Grade 2 and 3 cases showed high expression of Ki 67 which was statistically significant (p value = 0.022).

Table 1: Correlation of Ki 67 with clinicopathological parameters

Parameters	Low Ki 67	High Ki 67	P- value
Age(years)			
21-30	4	0	
31-40	11	4	
41-50	12	6	0.375
51-60	9	2	
61-70	8	2	
>70	1	1	
Tumor Size			
<2 cms	3	0	0.002
>2cms	15	42	
Lymph node			
No	17	1	0.004
N1,N2,N3	14	28	
NSBR Grade			
Grade 1	12	0	0.022
Grade2	23	7	
Grade 3	10	8	

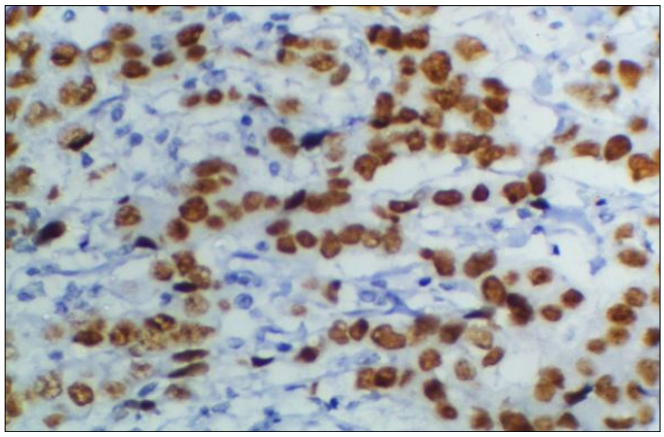

Fig 1: High reactive Ki 67 expression

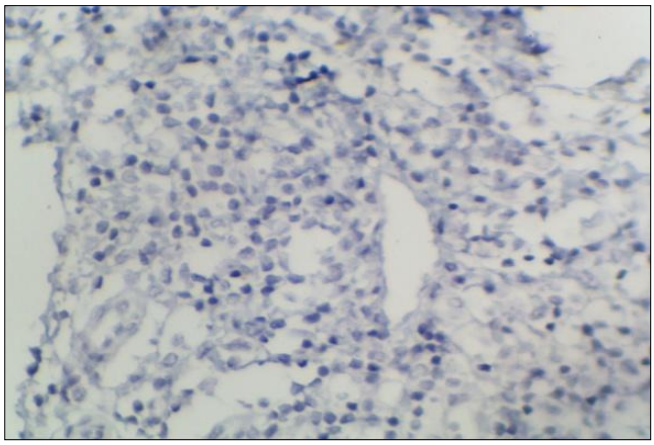

Fig 2: Low reactive Ki 67 expression

4. Discussion

In the present study the mean age of 48 years correlated with the studies of Yadav *et al.* [5] and Zineb Bouchbika *et al.* [8]. Likewise, the tumor size, in our study, ranging from 1 to 10 cm and similar observations were made by Yadav *et al.* [5] and Thiyagarajan *et al.* [6]. The most common histologic type of infiltrating ductal carcinoma NOS was seen in 56 cases in this study which compares well with similar findings by Thiyagarajan M *et al.* [6] and others. 30 cases in this study were categorised to be in NSBR Grade 2, followed by Grade 3 seen in 18 cases and 12 cases were in Grade1.Similar results were observed by Thiyagarajan M *et al.* [6] and Geetamala *et al.* [9]. Lymph node stage in this study comprised of ! 8(30%) cases in N0 and 42 (70%) cases in N2 and N3. Nodal involvement in our study compared well with Thiyagarajan M *et al.* Bhagat vasuda M *et al.* and Daehoon *et al.* [6, 7, 3].

In this study Ki 67 expression and its association with tumor size, lymph node stage and NSBR grading was statistically significant with P value <0.05. Similar findings were noted in Mohammad A *et al.* [1] Ki 67 expression in our study was not significantly associated with age and histologic subtype which is similar to many studies in literature [4, 10]. Thus, independently Ki 67 therefore is more expressed in highly metastasizing tumors, in tumors of high grade and tumors of relatively larger sizes. This probably is due to the high proliferative capacity of tumor cells and also carries poor prognosis [10]. This proves that Ki 67 can be a good prognostic marker as it reflects high proliferative potential in breast cancer. However as there are no proper standards in measurement, no proper defined techniques and prescribed cut-off limts its use as an independent biologic marker can be unreliable in at least few cases [2]. Recommendations by Breast Cancer Working Group must be followed for determination of Ki67 which helps for better standardization [2].

5. Conclusion

As a cell proliferation marker Ki67 can be an independent predictive and prognostic marker in managing breast cancer patients. Easy availability in all laboratories and better standardization are required for its routine use.

6. Acknowledgement

We acknowledge Dr. Bharathi M, Professor & HOD, Department of Pathology, Mysore Medical College and Research Institute, Mysore for her support

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