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Immuno-Histochemical demonstration of PCNA (Proliferating Cell Nuclear Antigen) expression in formalin fixed, paraffin wax embedded tissue sections in cases of carcinoma breast

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Abstract

Expression of PCNA has been shown to be of prognostic value in patients with certain types of cancer. Immuno-histochemical assessment of proliferative potential by the detection of nuclear proteins related to DNA replication is a promising approach. Documented study was conducted on 50 cases of carcinoma breast and 10 cases of benign breast lesions. Aim of the study was to compare the PCNA labelling index (LI) in benign and malignant breast lesions and to correlate it with tumor size, lymph node metastasis, histological type, histological grade and mitotic index. Significant correlation was observed between tumor size and PCNA index in carcinoma breast (t value=3.88, p value < 0.001).Significant correlation was also observed between histological grade, mitotic index and PCNA index. Statistical correlation between PCNA and histological grades I/III, II/III was found to be highly significant (p value <0.001). PCNA index showed a highly significant (p value <0.001) correlation with mitotic index with a linear correlation which was found to be directly and positively correlated (r = +0.9431). However, no definite correlation was seen between the metastatic lymphadenopathy and PCNA score (t value= 0.02 , p value >0.05). So PCNA served as a significant prognostic marker in the documented study.

Keywords: PCNA (proliferating cell nuclear antigen), immunohistochemical, labelling index, mitotic index, prognosis, carcinoma breast.

Introduction

Breast cancer is one of the most common cancers with greater than 1,300,000 cases and 450,000 deaths each year worldwide[1]. The development of breast cancer involves a progression through intermediate stages until the invasive carcinoma and finally into the metastatic disease[2].Variability in clinical progression in breast cancer requires identification of such markers that could predict the tumor behaviour[3].

The determination of tumor markers is a useful tool for clinical management in cancer patients assisting in diagnostic, staging evaluation of therapeutic response, detection of recurrence, metastasis and prognosis and development of new treatment modalities[4].Hormone receptors,HER-2 oncogene,Ki-67,PCNA, P53 proteins and genes for Hereditary susceptibility are various well established breast molecular markers with

prognostic or therapeutic value[5]. PCNA (proliferating cell nuclear antigen) and Ki-67 are two extensively studied proliferation related markers. PCNA is a useful antigenic marker in immunological studies of cellular proliferation. It is a 36 kD, non-histone protein involved in DNA synthesis, such as DNA polymerase delta, cell cycle control, DNA damage response and repair[6]. PCNA is variably present in late G 1,S and mitotic phase of dividing cell. In a number of tumors, the measurement of this protein was associated with mitotic activity and tumor grade[7]. The PCNA signal transduction has an important impact on growth regulation of breast cancer cells and is associated with poor overall survival[8]. PCNA has been called the ringmaster of the genome because it has been shown to be actively participating in a number of molecular pathways responsible for the life and death of the mammalian cell[9].PC10 antibody to this protein has been used to study its association with the proliferation kinetics. PC 10 has the property of specifically binding to PCNA in formalin fixed and processed histological material[10].

The potential value of IHC marker like PCNA can be assessed in formalin fixed tissues. This prompted us to evaluate PCNA expression in benign and malignant lesions of breast and to correlate it with other established prognostic markers like histological type, histological grade, mitotic index, lymph node status and tumor size.

Materials and Methods

This study was conducted in the Department of Pathology, Government Medical College, Amritsar. 50 cases of simple and modified Radical mastectomy specimens which were diagnosed clinically and confirmed histopathologically as carcinoma breast were included in this study along with 10 cases of benign breast diseases . Various details regarding size, site and lymph node status were recorded. Representative samples taken from grossing specimens were fixed in 10% formalin and were processed. Tissues were embedded in paraffin wax and blocks were sectioned with the help of rotary microtome into 4-6 micron thickness. Sections were stained with Haematoxylin and Eosin stain. Histopathologic typing of tumors was done according to WHO classification[11]. Out of 50 cases of carcinoma breast 37 cases were of IDC(NST) ,2 cases were diagnosed as DCIS, one with comedo pattern and other with cribriform pattern,9 cases were of DCIS with invasion,1 case of papillary carcinoma and 1 case of malignant phylloides tumor. Histological grading was done according to Nottingham Modification of Bloom Richardson grading system[12]. Mitotic index was calculated by counting mitotic figures in 1000 cells under 400x magnification in high proliferating areas with good cellularity away from the areas of necrosis.

For immunohistochemical demonstration of PCNA ,monoclonal antibody was used (DAKO Kits). Streptavidin biotin method including di-amino-benzidine (DAB) as chromogen was applied. 3-5µm thick sections were taken from paraffin blocks and fixed on to the freshly prepared poly-L-lysin coated slides. Sections were incubated at 37°C for 24 hrs. Deparaffinization and hydration was done followed by endogenous peroxidase blocking with 3% H_2O_2 for 20 min. After antigen retrieval in microwave for 20 min., tissues were incubated for 2 hrs with primary monoclonal antibody. Tonsil was taken as a positive control and in the negative control primary antibody was replaced by PBS buffer. After washings with PBS, sections were incubated with secondary biotinylated antibody for half an hour and then with Avidin Biotin Complex. Freshly prepared DAB was used and slides were washed with distilled water. Counter staining was done with haematoxylin.

PCNA immunoreactivity was calculated by counting total of 1000 cells under 400x magnification. The results were expressed as a ratio of stained nuclei to total nuclei (PCNA labeling index).

PCNA scoring was done as by Garcia et al (1989)[10]in this study.

PCNA Score	Percentage positivity
1	0-25%
2	26-50%
3	51-75%
4	76-100%

Observations

Histological examination of 60 cases of breast lump revealed malignant tumor in 50 cases and benign lesions in 10 cases. The peak incidence of the benign breast lesions was almost similar in 2nd and 4th decade i.e. 30% each while in 3rd and 5th decade, it came out to be 20% each. In carcinoma breast cases, maximum incidence was observed in 4th and 6th decade (88%). In malignant lesions 5 (10%) male patients were selected randomly for comparison, rest all (90%) being females. 90% of patients with benign breast lesions and 68% of the patients with malignant breast lesions had a short history of 1-6 months whereas very few cases were reported as late as > 12 months (10%). Left side of breast was involved in 90%of benign breast lesions and 54% of carcinoma breast cases. Skin involvement was seen in 18%of carcinoma breast cases and no skin involvement was seen in benign breast tumor.

Tumor size was also studied in the documented study and most of the patients (60%) with benign breast lesions as well as carcinoma breast (74%) were having tumor size between 2-5cm. Correlation between the tumor size of the benign with the malignant lesions was found to be insignificant with t value = 0.66 and p value > 0.05. The statistical correlation of tumor size with PCNA index in benign and malignant lesions was found to be highly significant i.e. t value = 3.88 and p value <0.001 (table1). No lymph node involvement was seen in benign breast lesions while 58% cases of carcinoma breast showed metastatic deposits in lymph nodes. A significant correlation was observed between tumor size and lymph node metastasis with p value < 0.05 but no definite correlation was observed between lymph node status and PCNA score with t value = 0.02 and p value >0.05 i.e. insignificant. In the documented study most common benign histological lesion was found to be fibrocystic disease along with sclerosing adenosis (50%), followed by fibroadenoma (30%) and phylloides tumor (20%). All the benign cases showed a low PCNA score of upto 2. Among the malignant breast lesions, the most common histological lesion encountered was IDC (NST)(74%) followed by IDC with intraductal component (18%), pure intraductal carcinoma (4%), papillary carcinoma (2%) and malignant phylloides (2%). High PCNA score of 1-4 was seen in IDC and DCIS along with IDC as compared to DCIS alone which showed PCNA score of upto 2. Malignant phylloides showed a higher PCNA score of 4 while papillary carcinoma showed a PCNA score of 2.

Table 1 Showing correlation between tumor size and PCNA score

	Tumor Size (cm)	No. of patients	Score1 (0-25%)	Score2 (26-50%)	Score3 (51-75%)	Score4 (76-100%)
Malignant	<2 cm	5	-	5	-	-
	2-5cm	37	7	20	4	6
	>5cm	8	-	3	3	2
Benign	<2cm	2	-	2	-	-
	2-5cm	6	6	-	-	-
	>5cm	2	1	1	-	-
	Total	60				

In the documented study, histological grading was done according to modified Nottinghams grading system and histologic grade was correlated with PCNA score. PCNA score showed an increase with an increase in the grade of tumor. Grade I tumor showed score of upto 2 while Grade III tumours had a higher PCNA score of 3 and 4(table2). Statistical correlation between PCNA and histological grades I/III , II/III was found to be highly significant i.e p value <0.001(table 3).

Table 2 Showing correlation of histological grade and PCNA score

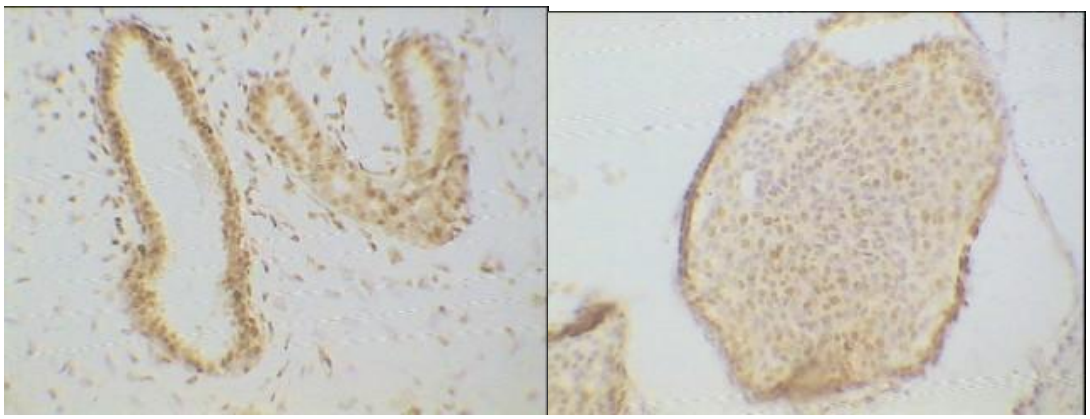
Histological Grade	No. of Cases	%age	PCNA Score1	PCNA Score2	PCNA Score3	PCNA Score4
Grade 1	14	28	6	6	-	2
Grade 2	25	50	2	20	3	-
Grade 3	11	22	-	1	3	7
Total	50	100	8	27	6	9

Table 3 Showing statistical correlation between histological grades and PCNA index

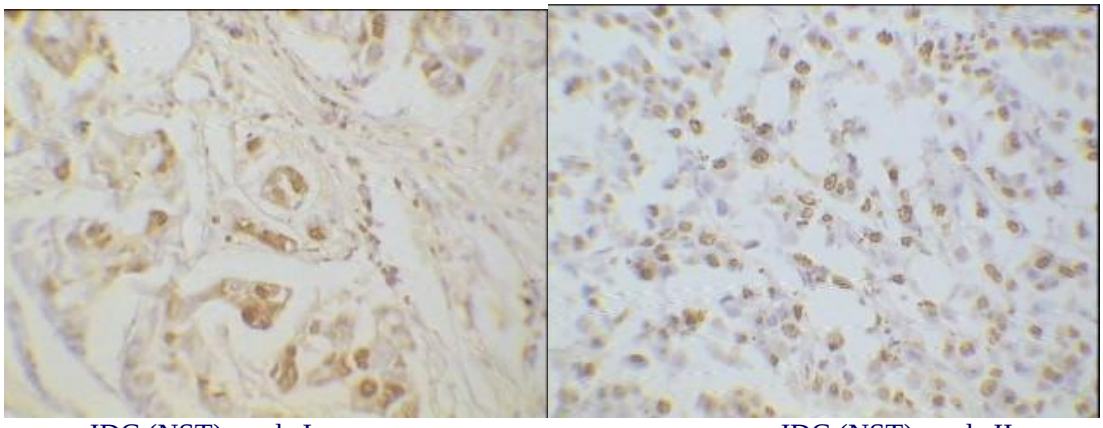
Histological Grade	No of Cases	PCNA index		Correlation	T value	P value
		Mean	S.D			
Grade 1	14	37.07	25.98	I/II	1.27	>0.05
Grade 2	25	44.48	10.71	I/III	4.49	<0.001
Grade 3	11	73.82	10.68	II/III	7.69	<0.001

Mitotic index of the malignant tumor varied markedly, however it was significantly higher (6-10/10 HPF) when compared to benign lesions (0-5/10 HPF). Statistical correlation of PCNA index between benign and malignant lesions was found to be highly significant (t value = 3.88, p value <0.001) while statistical correlation between Mitotic index (MI) and PCNA index was found to be directly and positively correlated (r = +0.9431) and highly significant i.e p value <0.001. Histological grade of the tumor was also correlated with the mitotic index and PCNA index. Statistical index correlation was found to be highly significant between grades I/III and II/III i.e p value <0.001.

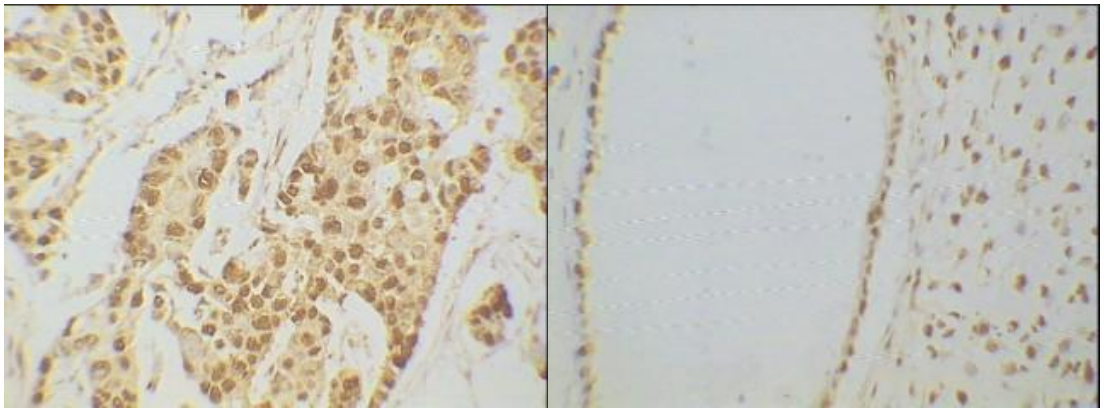
Photographs showing immunopositivity in benign and malignant breast lesions(400X)



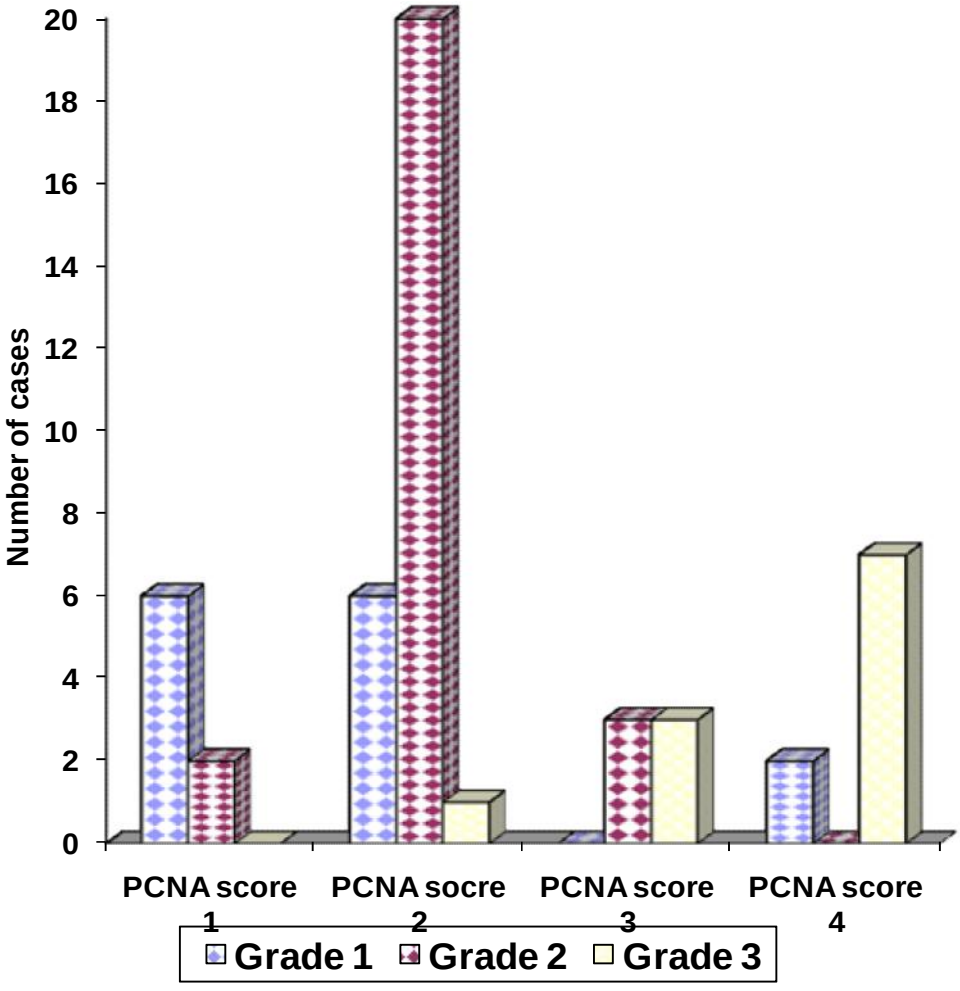
Fibroadenoma Ductal Carcinoma In Situ



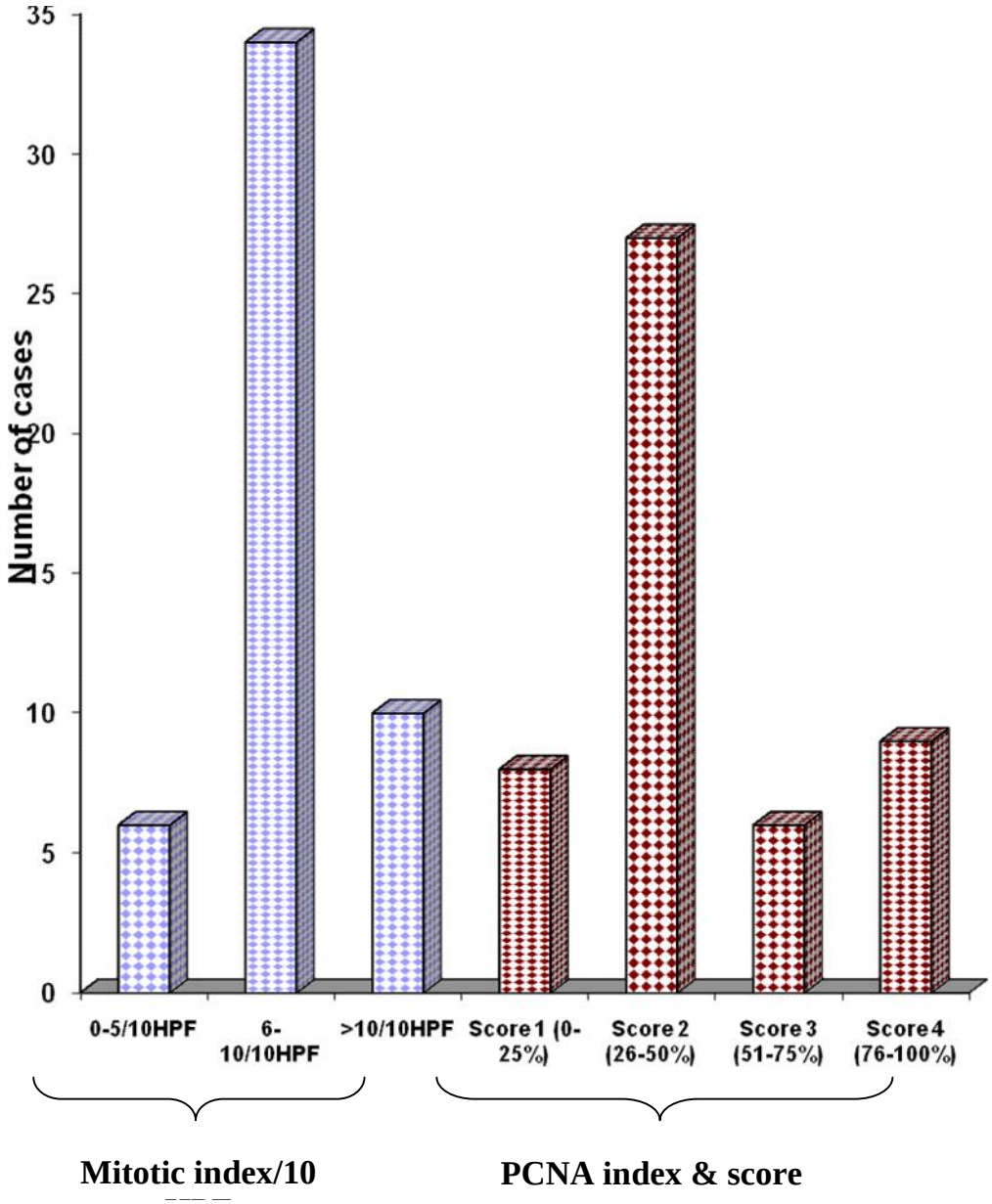
IDC (NST) grade I IDC (NST) grade II



IDC (NST) Grade III Malignant phylloides tumor



Graph I showing PCNA expression in breast carcinoma



Graph II showing distribution of breast carcinoma according to mitotic index and PCNA score

Discussion

Breast cancer is one of the most common and easily detectable human malignancies. It is the second leading cause of women mortality and morbidity worldwide and this cancer represents one of the most privileged malignancy regarding the use of markers with predictive values. A number of well established prognostic factors have been postulated to predict the clinical course of carcinoma breast. Cell proliferation is one of the most important single prognostic parameter in the breast cancer because uncontrolled ceaseless growth lies at the heart of neoplastic process[13]. Proliferative abnormalities precede the occurrence of morphological abnormalities and hence their measurement serves as a useful biomarker for chemotherapy trials and prognosis[14].PCNA is a useful antigenic marker in immunological studies of cellular proliferation whose synthesis reaches maximum during S –phase of cell cycle[15].

PCNA is widely used to assess cell proliferation in many malignancies but its expression in carcinoma breast is extremely variable and the prognostic significance is highly controversial.

The documented study assessed the immunohistochemical expression of proliferation marker PCNA in 50 cases of carcinoma breast and 10 cases of benign breast disease and also evaluated its association with the established independent prognostic parameters like tumor size, lymph node status, histological type, histological grade and mitotic index and correlated with PCNA score. Tumor size is one of the most powerful predictors of prognosis. An inverse relationship exists between the tumor size and survival rate[16]. Documented study showed a higher PCNA score of 2- 4 in patients with tumor size of > 2 cm. Statistical correlation of tumor size with PCNA index in benign and malignant lesions was also found to be highly significant (t value=3.88,p value <0.001) as observed by others[12,17,18,] Among the other prognostic factors, lymph node status is a very important influencing factor in predicting the prognosis of disease. The lymph nodes involved do have their impact on the survival rate as the patients having > 3 lymph nodes showing metastasis do have a sharp decline in the survival rate[19]. Documented study revealed no definite correlation between lymph node status and PCNA score (t value =0.02 , p value > 0.05).Surprisingly others[12,17] also observed no statistically significant correlation between PCNA index and lymph node status. Significant relationship exists between tumor size and lymph node metastasis and this relationship has direct reflection on survival[20] .In the documented study , statistical correlation between the tumor size and lymph node metastasis was found to be significant (p value <0.05).In the documented study, PCNA index showed significant correlation with the mitotic index. Tumors having higher mitotic index also showed higher PCNA index. On statistical evaluation, PCNA index was highly significant (p value <0.001) and showed a linear correlation which was found to be directly and positively correlated (r=+0.9431) as shown by other studies[12,17] .

Histopathology alone does not give enough information to the referring clinician to make decisions about the patient prognosis and treatment. Therefore scoring and grading systems have been developed which provide additional information[21]. Documented study also evaluated the applicability of Nottingham grading system as adopted by others[7,22]. A strong correlation of histological grade with prognosis has been observed[7]. Patients with grade I tumor have a significantly better survival than with grade II and III respectively. Significant correlation of histological grades with PCNA index was noticed in the documented study. Grade II and III tumors showed a higher PCNA index of >26% with PCNA scores of 2,3 and 4.Statistical correlation between the PCNA index and histological grades I/III and II/III was found to be highly significant (p value < 0.001)Similar findings were also observed by others[12,17,23].

Study by Masakuni Noguchi[24] on 91 patients of breast cancer showed no correlation of clinicopathological and biologic prognostic factors with PCNA expression.

Another study by K. Amit Kumar et al[25] in 2017 indicated that high grade tumors follow uncontrolled proliferative activity as a mechanism of tumor progression and showed significant positive correlation of PCNA LI with histological grade (p=0.041) but no correlation was observed with Ki-67 LI (p=0.232).This study also concluded that PCNA marker cannot substitute Ki-67 but may be used as an additional marker to assess proliferative activity along with other markers. This lack of association between PCNA and Ki-67 LI on breast carcinoma is surprising but similar result was also observed by Surowik et al[26].

PCNA is frequently over expressed in noncyclical cells in variable manner as compared to Ki-67 which is expressed only in cells actively involved in cell cycle. This discrepancy of PCNA LI may be due to its role in DNA repair in addition to cell proliferation. PCNA also has prolonged half life and its antigen persists in cells which have already completed cell cycle[27].

Recently, a molecular classification system has been proposed to categorize breast cancers into subtypes associated with optimal therapeutic modality which has also become widely used[28]. The St. Gallen International Expert Consensus 2011,recently refined at the 2013 conference proposed a new classification system for breast cancer in which a strong expression of progesterone receptors (PR) and Ki-67 level were both recognized as being important to surrogate definition of a Luminal A like disease. Luminal A subtype has high PR and low Ki-67 while Luminal B subtype has low PR and high Ki-67.

Studies by Zorka Inic et al[29] revealed that patients with Luminal B sutype will have a worse prognosis as well as a greater chance for local recurrence and survival than the Luminal A subtype. The prognostic and predictive value of Ki-67 was also evaluated by Luprosi et al[30] which concluded this marker as a prognostic factor for therapeutic decision, however, standardization of techniques and scoring methods are needed for integration of this marker in everyday practice.

PCNA protein is one of the central molecules responsible for decisions of life and death of a cell. It is an essential molecule in the life of single organisms[9]. PCNA immunoreactivity correlates well with the morphological features of cell proliferation as well particularly mitotic index and tumor grade and in breast tumors their expression is related to other markers of differentiation and prognosis[31]. The number of PCNA positive cells (G_1,S,G_2/M) is much higher than that of mitotic cells making the evaluation statistically more accurate (G_2/M)[32].PCNA is a marker of poor differentiation ie. maximum positivity is observed in grade 3 tumors of breast cancer (84%).[33] A high PCNA LI identifies patients who have a significantly shorter disease free and overall survival [34].PCNA index helps in the individual approach of the proliferation rate of each tumor, a parameter of potentially importance for predicting the biological behaviour of the tumor in association with other proliferation markers. It is an early indicator of ongoing cellular proliferation[35].It has an independent prognostic value.[36]So the study of histological type, histological grade, mitotic index, tumor size and lymph node status along with the proliferation marker PCNA in human breast cancer plays an important and promising role in determining the prognosis of the patients. PCNA can be a future candidate marker for prognosis and therapeutic responses in breast cancer evaluation as shown by Zhao et al[8] in his study which revealed that targeting phospho Y211 PCNA could be an effective strategy in breast cancer treatment.

Table 4 Showing statistical correlation of PCNA index with histological grade, mitotic index, tumour size and lymphnode status

Sr.no	Name of the Author	p value (HG Vs PCNA)	p value (MI Vs PCNA)	p value (Tumor size Vs PCNA)	p value (LN Vs PCNA)
1.	Frierson[37]	<0.0005	<0.0001	<0.03	NS
2.	Aggarwal et al[17]	<0.013	r=+0.74	<0.0001	< 0.17 (NS)
3.	Helal et al[23]	0.02 Chi sq	-	<0.03	+
4.	Documented study	<0.001	<0.01 (r = +0.94	<0.001	>0.05 (NS)

NS- Not Significant, HG- Histological Grade, MI- Mitotic Index, LN- Lymphnode

Conclusion

The documented study concludes that the proliferative abnormalities as detected by PCNA index precede the occurrence of morphological abnormalities. Proliferation plays an important role in predicting the clinical behaviour of the tumor. The correlation of PCNA index with other measures of cell proliferation like mitotic index or tumor aggressiveness that includes histological grade, tumor size and histological type in breast carcinoma supports the clinical significance of PCNA immunostaining because it is more sensitive prognostic marker than the usual prognostic parameters used to measure proliferation. It is cost competitive and can be determined easily even on paraffin embedded tissues. Measurement of PCNA index serves as a very significant marker for prognosis and a future candidate for therapeutic responses in breast cancer evaluation.

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