

**Original article:**

## **Role of Histological Grading & Mitotic Activity Index in Prognosis of Breast Cancer: A 2 Year Study in a Tertiary Care Health Centre**

<sup>1</sup>AmitVarma, <sup>2</sup>ShilpiDosi, <sup>3</sup>Kamal Malukani, <sup>4</sup>PriyankaKiyawat Jain, <sup>5</sup>Taiba Farooque ,  
<sup>6</sup>Garima Dhamnani

- 1.AmitVarma, MD (Pathology), Professor<sup>1</sup>
- 2.ShilpiDosi, MD (Pathology), Associate Professor<sup>1</sup>
3. Kamal Malukani, MD (Pathology), Professor<sup>1</sup>
- 4.PriyankaKiyawat Jain, MD (Pathology), Assistant Professor<sup>1</sup>
- 5.Taiba Farooque ,MBBS ,Junior resident <sup>1</sup>
6. GarimaDhamnani ,MBBS ,Junior resident<sup>1</sup>

Department of Pathology, Sri Aurobindo Medical College and Post Graduate Institute, Indore, Madhya Pradesh, India

Corresponding Author: Dr Shilpi Dosi

### **ABSTRACT**

**BACKGROUND:** The present study has been undertaken in view of rising incidence of breast carcinoma in Indian females. Histological grading is now recognized as a powerful prognostic factor .In the last few years evaluation of mitotic figures as a prognostic factor has attracted much attention because it helps in grading breast carcinoma.

**Aims & objectives:** To classify the histological typing and grading of breast carcinoma.

**Material & Methods-**This study comprised of 33cases of breast lesions reported during a last two year period from September 2015 to August 2017 in the department of Pathology,.From these specimens paraffin sections have been cut& stained with H&E for histological typing & grading.

**Results :**Out of 33 cases,87.88% were Infiltrating Ductal Carcinoma(NOS) and two cases (6.06 %) of invasive lobular and mucinous carcinoma each. Mitotic counts was 6-10/10HPF followed by 12 cases (36.36%) was more than 10/10HPF and in only three (9.09%) cases it was 0-5/10HPF .Grade was II in 48.49% cases followed by grade III in 30.30 % in remaining 21.21% cases grade was I.

**Conclusion:** mitotic activity index and histological grade are quite significant prognostic markers for breast carcinomas.

**Key words**-Breast carcinoma, Infiltrating Ductal carcinoma, Lobular carcinoma,Histological grade

---

### **INTRODUCTION**

Carcinoma of the breast is the most common malignant tumor and the leading cause of death from carcinoma in females all over the world.<sup>1</sup> Breast cancer is proportionately on the increase in a few metropolitan areas of India. This appear to be related to late marriage, late birth of first child, fewer children, shorter period of breast feeding, which are common among the educated urban women. Common denominator for most of these factors is strong and prolonged estrogen stimulation, operating on a genetically susceptible background. Genetic predisposition with familial breast carcinoma –

- BRCA-1 gene located on chromosome 17q

- BRCA-2 gene located on chromosome 13q

Commonest neoplasm of breast is tumour arising from epithelial component of glandular element of breast. Infiltrative ductal carcinoma being the most common type of carcinoma (70%), lobular carcinoma is the second most common followed by smaller groups such as medullary, mucinous, comedo carcinoma, paget's disease, papillary, tubular and inflammatory carcinoma.<sup>2</sup>

In recent years, interest in prognostic factors has been stimulated by the success of systemic adjuvant therapy for early stage in breast cancer. Histological grading is now recognized as a powerful prognostic factor and should be included as a component of the minimum data set for histological reporting of breast cancer. Assessment of histological grade has become more objective with modifications of *Patley and Scarff (1928)*<sup>3</sup> method first by *Bloom & Richardson (1957)*<sup>4</sup> and more recently by *Elaston and Ellis (1991)*<sup>5</sup>.

#### **AIMS :**

- \_ To establish histological type of breast malignancy.
- \_ To carry out mitotic activity index and histological grading of malignant breast lesions.

#### **MATERIAL AND METHODS:**

This study comprised of 33 cases of breast lesions reported during a last two year period from September 2015 to August 2017 in the department of Pathology, From these specimens paraffin sections have been cut & stained with H&E for histological typing & grading.

All H&E stained tissue sections were classified according to WHO and then histological grading were done.

#### **Histological grading of invasive carcinoma**

Invasive ductal carcinomas and all other invasive tumors are graded based on an assessment of tubule/gland formations nuclear pleomorphism and mitotic counts. Assessment of histological grade has become more objective with modifications of the *Patley and Scarff (1928)*<sup>3</sup> method first by *Bloom and Richardson (1957)*<sup>4</sup> and more recently by *Elaston and Ellis (1991)*<sup>5</sup>

#### **Method of grading**

##### **Tubules and glands formation**

when evaluating tubules and acini only structure exhibiting clear central lumina are counted.

##### **Nuclear pleomorphism**

It is assessed by reference to the regularity of nuclear size and shape of normal epithelial cells in adjacent breast tissue. Increasing irregularity of nuclear outlines and number and size of nucleoli are useful additional features in allocating scores for pleomorphism.

##### **Mitotic figures-(Van Diest et al )<sup>6</sup>**

The total number of mitoses per 10 high power fields. Mitotic counts /10 Hpf Clear hairy extension of nuclear material without nuclear membrane Counting done in most cellular region at tumour periphery

Field selection for mitotic scoring should be from the peripheral leading edge of the tumour. If there is heterogeneity, regions exhibiting a higher frequency of mitoses should be chosen. Must count only defined mitotic figures; hyperchromatic and pyknotic nuclei are ignored since they are more likely to represent apoptosis than proliferations. Mitotic counts require standardization to a fixed field area or by using a grid

system. Semiquantitative method for assessing histological grade in breast from *Elaston and Ellis (1991)*.<sup>5</sup>

**Feature Score**

*Tubule and gland formation*

Majority of tumor (>75%)	1
Moderate degree (10-75%)	2
Little or more (<10%)	3

*Nuclear pleomorphism*

Small, regular uniform cell	1
Moderate increase in size and variability	2
Marked variation	3

*Mitotic counts*

Dependent on microscopic field area 1-3

Examples of assignment of points for mitotic counts for 3 different field areas.

Field diameter (mm)	0.44	0.59	0.63
Field area (mm <sup>2</sup> )	0.152	0.274	0.312
Mitotic count			
1 point	0-5	0-9	0-11
2 point	6-10	10-19	12-22
3 point	>11	>20	>23

The three values are added together to produce score of 3 to 9, which the grade is assigned as follows :

Grade I	Well differentiated	3-5 points
Grade II	Moderately differentiated	6-7 points
Grade III	Poorly differentiated	8-9 points

**RESULTS**

In present study, 26 cases (78.79%) were belonged to rural area and remaining 7 cases (21.21%) were belonged to urban area. All of the cases were female, no single case in male was found.

out of 33 cases maximum cases (51.52%) were in the age group of 41-50 years followed by 27.27% of age group 51-60 years.(Table -1)

As most common clinical presentation of breast carcinoma is palpable lump . Maximum 23 cases (69.70%) presented with lump in breast followed by 5 cases (15.15%) with pain. Four cases (12.12%) presented with axillary mass. In only one case (3.03%) nipple discharge was seen. Left side was more common 17/23 than right side 6/23.(Table -2)

As evident from study in 22 out of 33 cases we found lymph nodes. Out of these 22 cases, 17 (77.28%) were positive for metastasis and 5 (22.72%) were negative .(Table –3).

Out of total 33 cases studied, maximum (87.89%) cases were of invasive ductal carcinoma (NOS), followed by 2 (6.06%) cases of invasive lobular carcinoma and 2 (8.06%) cases of mucinous carcinoma .( Table- 4)

Out of 33 cases in 18 (54.55%) cases mitotic counts was 6-10/10HPF followed by 12 cases (36.36%) was more than 10/10HPF and in only three (9.09%) cases it was 0-5/10HPF . (Table- 5).

Out of 33 cases , 16 (48.49%) cases were grade II with score 6-7 followed by 10 (30.30%) cases were grade III with score 8-9. Only seven (21.21%)cases were grade I with score 3-5 . (Table – 6)

There is a significant relationship between histological grading and histological type.

## DISCUSSION

The large number and variety of papers published on carcinoma of the breast, the treatment, prognosis and associated factors, are an index of the complexity of the problem and indeed of the study of any tumour (*Chevallier et al 1990, Du-Toir et al 1990*).<sup>(7,8)</sup>

Out of the 33 cases studied, maximum patients were in age group 41-50 years (51.52%) followed by 27.27% patients were from 51-60 years of age group. 15.15% patients were from above 60 years and 6.06% patients were from 31-40 years of age group . This is in accordance with study of *Hussain et al (1994)*, who found peak incidence between age of 41-50 years.<sup>(9)</sup>

Out of 33 cases maximum cases (69.70%) clinically presented with lump in breast followed by pain in 5 cases (15.15%). Four cases (12.12%) presented with axillary lump and in only one case (3.03%) nipple discharge was seen. These findings are in accordance with the study of *Blamey (1998)*, who noticed frequency of symptoms of women presenting in a breast clinic with lump 60-70% followed by pain 14-18%, nipple problems 7-9%, deformity 1% and inflammation 1%.<sup>(10)</sup>

In our study, out of 23 cases presented with breast lump, 17 (73.91%) cases with lump were localized on left side while in 6 (26.09%) cases were localized on right side (Table IV). This was in accordance with the study of *Haagensen (1986)* who showed that there is slight higher frequency of invasive breast cancer in the left breast with a reported left to right ratio of approximately 1.07:1.<sup>(11)</sup>

As observe in our study that in 16 cases (48.48%) tumor size varied between 2-5 cm followed by 13 cases (39.40%) with size more than 5cm and in only 4 cases (12.12%) size was less than 2cm . This is in accordance with the study of *Patel et al (2002)* studied 100 cases and distributed cases in 3 groups according to tumor size with less than 2cm approximately in 8 cases, 2-5cm in 64 cases and more than 5cm in 28 cases.<sup>(12)</sup>

As evident from our study that out of 33 cases, 22 (66.66%) had undergone radical mastectomy or having lymph nodes and out of these 22 cases 17 (77.28%) were positive for metastasis and 5 (22.72%) were negative . According to *Wartgotz and Norris (1990)* about one third of the reported cases had lymph node metastasis. The five year survival rate is 70%, similar to, or better than, patients with ordinary infiltrating carcinoma.<sup>(13)</sup>

Out of these 33 cases, all (100%) were invasive carcinomas of epithelial origin . These findings were in accordance with the study of *Hussain et al (1994)* who noticed in his study that there was 97.6% of epithelial and 2.4% of stromal tumours. <sup>(9)</sup>

Out of these 33 of invasive carcinomas (epithelial), 29 (87.88%) were of invasive ductal CA (NOS), two cases were (6.06%) of Invasive lobular CA and two cases were (6.06%) of mucinous carcinoma . Similar findings were noted by Berg and Hutter (1995).<sup>(2)</sup>

Out of 33 cases in 18 (54.55%) cases mitotic counts was 6-10/10HPF followed by 12 cases (36.36%) was more than 10/10HPF and in only three (9.09%) cases it was 0-5/10HPF. This is in accordance with the study of Patel et al (2002) studied 100 cases and found 0-5 mitotic figures /10 hpf in 43 cases, 6-10 mitotic figures /10 hpf in 30cases and more than 10 mitotic figures /10 hpf in 27 cases.<sup>(12)</sup>

In this study, all invasive epithelial tumours were graded according to the Modified Bloom Richardson Grading by Elaston and Ellis (1991).<sup>(5)</sup> Out of the 33 cases of invasive ductal carcinomas, 48.49% were Grade II, 30.30% were Grade III and remaining 21.21% were Grade I .Our results closely matched with the study of Doussal et al, 1989. In his study of 1262 patients 11 to 14% were grade I, 55 to 57% were grade II and 29 to 34% were grade III.<sup>(14)</sup>

Similar findings were observed in the study of Zubair Ahmad et al, 2009<sup>(15)</sup> who studied 120 cases of invasive breast carcinoma to acquire the information about the extent and spread of breast carcinoma by grading the tumors (based on modified Bloom and Richardson grading system), determining the tumor size & axillary lymph node status, tumor staging and Nottingham prognostic index (NPI) scoring. Out of 120 cases, 5(4.17%) were grade I, 91(75.83%) were grade II, and 24(20%) were grade III, concluding that the large majority of the cases were grade II tumors.

However the number of cases in present study is small and long follows up is required to reach any definitive conclusion. Ultimate goal of each study is how it can be beneficial to the society. Any research by itself on breast carcinoma is useful because of the sheer numbers of women worldwide who suffer morbidity & mortality due to this disease.

## CONCLUSION

It is concluded from this study ,high mitotic activity index , and high grade of tumor indicate the bad prognosis for breast carcinomas. These parameter are very useful where advanced studies like flowcytometry and immunohistochemical studies of the cell proliferation marker are not available.

Age group (in years)	No. of cases	Percentage
0-10	-	-
11-20	-	-
21-30	-	-
31-40	02	06.06
41-50	17	51.52
51-60	09	27.27
>60	05	15.15

**Table – 1: Age wise distribution of cases**

Clinical features	No. of cases	Percentage
Left breast lump	17	51.52
Right breast lump	06	18.18
Pain	05	15.15
Axillary mass	04	12.12
Nipple discharge	01	03.03

**Table -2: Clinical presentation wise distribution of cases**

Metastasis	No. of cases (n=22)	Percentage
Lymph node positive	17	77.28
Lymph node negative	05	22.72

**Table -3: Distribution according to metastatic lymph nodes**

Histological type	No. of cases	Percentage
Invasive ductal carcinoma (NOS)	29	87.88
Invasive lobular carcinoma	02	06.06
Mucinous	02	06.06

**Table 4 : Distribution of cases according to histological type**

Mitotic count/10HPF	Score	No. of cases	Percentage
0-5/10HPF	1	03	09.09
6-10/10HPF	2	18	54.55
>10/10HPF	3	12	36.36

**Table -5 : Distribution of cases according to Mitotic counts /10HPF**

Grade	Total score	No. of cases	Percentage
Grade I	3-5	07	21.21
Grade II	6-7	16	48.49
Grade III	8-9	10	30.30

**Table -6: Histological grade wise distribution of cases**

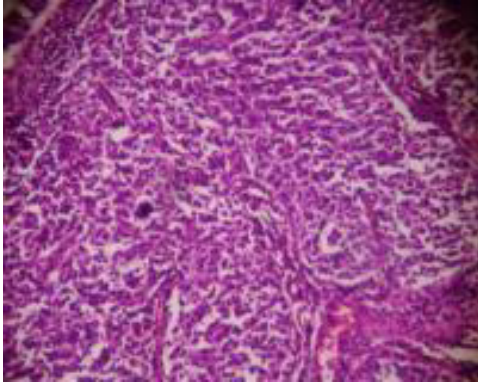


Figure 1: Photomicrograph showing infiltrating ductal carcinoma (H & E ,10 x 10X)

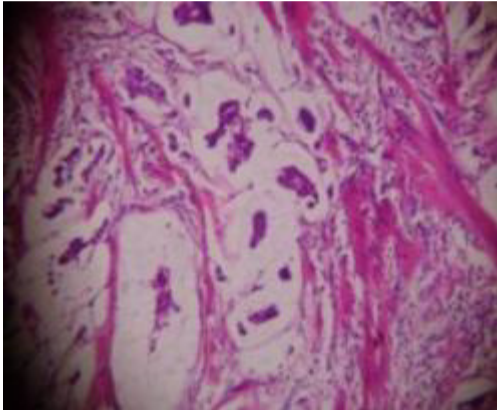


Figure 2: Photomicrograph showing mucinous carcinoma (H & E ,10 x 10X)

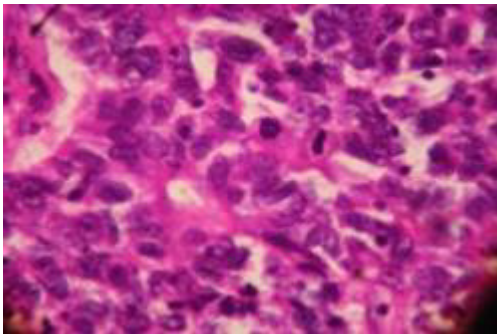


Figure 3: Photomicrograph showing high and abnormal mitotic figures IN infiltrating ductal carcinoma (H & E ,40 x 40X)

#### REFERENCES:

- 1 Jemal A, Murray T, Ward E, Samuels RC, Ghatgeer A, et al. Cancer statistics, 2005. *CA cancer J Clin* 2005;55:10-30
- 2 Berg J W & Hutter RVP : Breast Cancer, *Cancer* 75, 1995 : 257- 269.
- 3 Patley D. H Scarf , The position of histology in the prognosis of carcinoma breast .1928:801-804
- 4 Bloom H J, Richardson W W , Histological grading and prognosis in breast cancer. *Br. J. Cancer* 11, 1957: 359-77

- 5 Elaston C.W. & Ellis IO: Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long term follow up. *Histopathology*, 1991; 19:403-410.
- 6 Diest van PJ, Baak JPA, Matze-Cok P, Wisse-Brekelmans ECM, Galen CM van, Kurver PHJ, Reproducibility of mitosis counting in 2,469 breast cancer specimens: Results from the Multicenter Morphometric Mammary Carcinoma Project. *Hum Pathol* 23:603–607, 1992
- 7 Chevallier B, Mosseri V, Dance JP, Bastet P, Julian JP, Asselain B : A prognostic score in histological node negative breast cancer. *N Engl J. Med.* 309,1990: 1343-1347.
- 8 Du-toir RS, Locker AP, Ellis IO, Elstan CW, and Blamley RW: Evaluation of the prognostic value of triple node biopsy in early breast cancer.(1990) *Br. J. Surg* 77: 163-167.
- 9 Hussain MA, Ali S. Tyagi SP, Reza H. Incidence of cancer breast at Aligarh. *J Indian Med Asso*, 1994 Sep, 92(9): 296-7.
- 10 Blamey RW .Clinical aspects of malignant breast lesions in: systemic Pathology,CW Elaston,IO Ellis (eds).3<sup>rd</sup> ed,1998:501-513
- 11 Haagensen CD .Diseases of Breast .WB Saunders,Philadelphia,3<sup>rd</sup> ed.1986
- 12 Patel Chanrakant, Sindhu K P, Shah M.J.,Patel S.M. :Role of mitotic counts in grading and prognosis of the breast cancer.*Indian J Pathol.Microbiol*,july ,45(3),2002:247-254
- 13 Wargotz ES, Norris HJ, Austin RM et al. Fibromatosis of the breast: a clinical and pathological study of 28 cases. *Am J Surg Patho* 1987;11(1);38-45
- 14 Doussal V, Tubiana M, Friedman S, Hace K, Burnet M: Prognostic value of histologic grade nuclear components of scarf Bloom Richardson (SBR) - An improved score modification based on multivariate analysis of 1262 IDCS. *Cancer* 64: 1914-1921, 1989.
- 15 Zubair Ahmad,Amna Khurshid,Asim Qureshi,Romana Idress,Nasira Asghar,Naila Kayanj,Indian Journal of Pathology and Microbiology,2009,volume 52 ,Issue 4:477-481