

Histopathological Evaluation of Carcinoma Breast with Significance of Histological Grading and other Morphological Prognostic Factors at a Tertiary Health Care Institute

Kavita Gite¹ and Rajendra Chaudhari^{2*}

¹PG Resident, Department of Pathology, Dr. Vasant Rao Pawar Medical College Hospital & RC, Nashik – 422003, Maharashtra, India; kavitaapgite@gmail.com

²Associate Professor, Department of Pathology, Dr. Vasant Rao Pawar Medical College Hospital & RC, Nashik – 422003, Maharashtra, India; drrajchaudhari@yahoo.co.in

Abstract

Background: Breast carcinoma is the second common malignancy among women. Pathological prognostic factors in breast cancer are now widely used to predict prognosis of breast carcinoma and to plan its effective management. **Aim and Objectives:** To analyze the spread and extent of various histological patterns of carcinoma breast, to do grading and staging of the tumors and to correlate above factors with the prognosis. **Material and Methods:** The present study was a prospective study of histopathological findings of modified radical mastectomy specimens received in the department of pathology of Dr. Vasant Rao Pawar Medical College, Hospital and Research Centre, Nashik over a period of 2 years and 3 months that is from June 2015 to September 2017. A total of 45 mastectomy specimens were analyzed in this period, using standard histopathology technique. Positive status of Axillary lymph nodes and other prognostic factors were analyzed. Nottingham Prognostic Index (NPI) was used to assess the prognosis. Follow up of all the patients was kept. **Results:** Out of 45 total cases, the most common histologic type was Invasive Ductal Carcinoma (NOS) (86.67%). The largest tumor size was 14.5cm. Maximum tumors were of Grade II. Out of the 45 cases, 31 (68.88%) cases showed tumor metastasis in axillary lymph nodes. 48.88% of the patients showed poor prognosis category with score greater than 5.4. **Conclusion:** After keeping follow up with the patients we came to a conclusion that, the lymph node status, tumor size, histologic pattern, histologic grade, necrosis and presence or absence of blood vessel invasion remains the best independent prognostic indicators.

Keywords: Carcinoma Breast, Modified Bloom Richardson Score, Nottingham Prognostic Index, TNM Staging

1. Introduction

“However, innocent be the breast lump, it can be malignant, unless proved other-wise”. Women are 100 times more likely to have breast cancer as compared to men and second cause of mortality by cancer on them¹.

Carcinoma breast is very rare below 25 years of age more common in 35 years to 75 years. Lump in the breast is the most common presentation.

It is the breast tissue in the upper outer quadrant which is most frequently involved (65%). Typically, it is hard and irregular, but it can also be firm. Fixation to the skin, ulceration, peau d'orange, fixation to pectoral is and chest wall occurs later.

Clinicopathological factors, patient's age, styles of genetic mutation, presence of hormone receptors, size and kind of the growth, lymphovascular invasion, tumour necrosis, local invasion, metastasis, structure pattern, microscopic

*Author for correspondence

grade and plenty of additional factors affect the prognosis of breast cancer². Histopathology has been an old customary for the designation of carcinoma and has additionally a really necessary role as traditional prognostic factor³.

With the development of numerous therapeutic strategies for breast carcinoma, it is important to identify the prognostic factors of the carcinoma. Prognostic information is provided by estimation of tumour size.

Nottingham Prognostic Index is employed along with different variables to determine the prognosis. For the operable breast cancers, lymph node involvement by carcinoma is one of the most important parameters for prognosis.

Lymph node staging is one in every of the variables employed in Nottingham prognostic index likewise as in TNM staging system^{4,5}.

One of the strong prognostic factors is that the histological grading. Nottingham modification of Bloom Richardson grading system has been used for histologic grading of carcinoma breast which considers the cytoarchitectural morphology and the proliferative potential of tumour. The first component considered is the glandular or tubular formation by the tumour cells associated with the architecture. Nuclear size and shape variation is the component assessed which denotes the cell morphology. The third component is the mitotic activity which measures the division of tumour cells. The primary tumour size, lymph node involvement and microscopic grade are the three factors for determining the prognostic variables.

These three prognostic factors must be taken into account when MRM specimens are received. There are various histologic patterns of breast carcinoma having their own prognostic importance. World Health Organization (WHO) is the most widely preferred classification of breast cancer⁶. The histopathology report helps the onco surgeons in deciding the treatment and further management of patients suffering from carcinoma breast.

2. Aims and Objectives

The aims and objectives of this study were to categorize the various types of breast carcinoma in patients admitted in our institute and to use the traditional prognostic parameters to arrive at the prognosis for our patients. Significance of histological grading as well as other morphological factors in prognosis of carcinoma breast carcinoma breast was determined.

3. Materials and Methods

The present study was a prospective study of histopathological findings of modified radical mastectomy specimens received in the department of pathology of a Dr. Vasantrao Pawar Medical College, Hospital and Research Centre over a period of 2 years and 3 months, that is from June 2015 to September 2017.

3.1 Eligibility Criteria

3.1.1 Inclusion Criteria

All females of age group 30-75 years diagnosed with ductal carcinoma on histopathological examination.

3.1.2 Exclusion Criteria

Patients diagnosed with Duct Carcinoma In Situ (DCIS) and In Situ/infiltrating lobular Carcinoma.

Methodology:

The present study was conducted in pathology department of our medical college and tertiary health care centre. A minimum of 45 patients fulfilling eligibility criteria are included. The detailed clinical history has been noted.

The material which has been included in the study was modified radical mastectomy specimens which were already diagnosed as breast carcinoma on biopsies.

The Modified Radical Mastectomy specimens received were kept for fixation in 10% fresh formalin. The specimen was examined grossly after proper fixation for 24 hours, the tumour part was identified and its dimensions were noted and necessary sections were obtained. The gross description of the Modified Radical Mastectomy specimen and the tumours comprise: size of tumour, location, gross appearance of tumour, distance of tumour against the resection margins, appearance of overlying skin and involvement of nipple areola complex by tumour. Number of lymph nodes dissected from axillary tail.

The sections submitted were then passed through ascending grade of alcohol and xylene and finally embedded in melted paraffin wax.

Then blocks were prepared, single block was made for each section, thin sections of 4 to 5 microns thickness were cut. Sections on slides were taken and stained by haematoxylin-eosin staining procedure.

Haematoxylin and eosin stained sections were examined under light microscope WHO criteria was applied for histological classification.

Nottingham modification of Scarff-Bloom-Richardson-Method was used for histological grading of the tumours. TNM system adopted by both the Union for International Cancer Control (UICC) and the American Joint Commission on Cancer was utilised to stage the tumors.

Prognostic scoring was done based on Nottingham Prognostic Index (NPI)². Microscopic examination revealed following tumor characteristics.

- a) Pattern and histological type of Carcinoma Breast
- b) Nottingham histologic score based histological grade of tumor

Three factors are considered in the scoring system and each is scored from 1 to 3.

The Percentage of Gland Formation

Score 1: >75% of tumor composed of glandular/tubular structure.

Score 2: 10% to 75% of tumor composed of glandular/tubular structure.

Score 3: <10% of tumor composed of glandular/tubular structure.

The Nuclear Characteristics or Nuclear Pleomorphism

Score 1: Small nuclei with mild increase in size compared with breast epithelial cells, regular nuclear membrane, evenly dispersed nuclear chromatin and size is more or less uniform.

Score 2: Cells are bigger than normal epithelial cell with open vesicular nuclei are moderately enlarged, visible nucleoli, and moderate irregularity in nuclear membrane.

Score 3: Nuclei are vesicular, often with distinct nucleoli, exhibiting severe variation in nuclear size and irregular nuclear membrane, seldom with very atypical and bizarre cells.

The Mitotic Activity of Malignant Cells visualized under Microscope

Score 1: 10 high power fields show less than or equal to 9 mitoses.

Score 2: 10 high power fields show 10-19 mitoses.

Score 3: 10 high power fields show equal to or more than 20 mitoses.

The final total score is derived from the three scores and the score varies from 3 to 9.

Grade 1: Tumor showing a 3-5 score

Grade 2: Tumor showing 6-7 score

Grade 3: Tumor showing 8-9 score

c) Lymphovascular emboli and perineural spread by the tumor cells.

d) Presence or absence of In situ duct carcinoma.

e) Status of lymph nodal involvement was determined as follows

N0 - No lymph nodes involved by tumor cells.

N1 - Involvement of 1 to 3 lymph nodes.

N2 - Involvement of 4 to 9 lymph nodes.

N3 - Involvement of 10 or more lymph nodes.

Nottingham Prognostic Index (NPI): NPI was used to assess the prognostic status of the patients.

The value was calculated for prediction of survival using three pathological characteristics: tumor size, lymph nodes positive for malignancy and grade of the tumor.

NPI was derived by applying the formula as follows:

$$NPI = [0.2 \times S] + N + G$$

Where,

S: is the size of the tumor in centimeters;

N: is the number of lymph nodes positive for malignancy:
0 = 1, 1-3 = 2, >3 = 3;

G: is the tumor grade: Grade I = 1, Grade II = 2, Grade III = 3

Score Survival for 5 years

>=2.0 to <=2.4 (93%)

>2.4 to <=3.4 (85%)

>3.4 to <=5.4 (70%)

>5.4 (50%)

4. Results

Age range of the patients included in the current study was between 30-75 years (mean age, 53.62 years).

4.1 Gross Examination

On gross examination 13 cases out of 45 cases showed involvement of skin of breast tissue by tumour/ulcer and 10 cases out of 45 cases showed involvement of nipple areola complex by tumour (Figure 1-3).

Out of 45 cases 3 cases showed solid and cystic pattern of growth grossly while majority tumors shows only solid pattern of growth (Figure 1-3).

4.2 Microscopic Classification

Breast carcinoma with most common pattern was that of Infiltrating Duct Carcinoma, Not otherwise specified (NOS) (Figure 4).



Figure 1. Specimen of carcinoma breast.



Figure 2. Cut section of Carcinoma Breast showing irregular tumour.



Figure 3. Image showing involvement of skin and nipple-areola complex by tumour.

Out of the 45 patients, there were 39 patients having Infiltrating Ductal Carcinoma, NOS. There were 2

patients having Neuroendocrine Carcinoma, 1 patient having Metaplastic Carcinoma, 2 patients having Mucinous Carcinoma and 1 patient having of Cribriform carcinoma (Table 1).

Table1. Microscopic types

Microscopic types	No. of Cases	%
Infiltrating ductal carcinoma, NOS	39	86.67%
Neuroendocrine carcinoma	2	4.44%
Mucinous carcinoma	2	4.44%
Metaplastic carcinoma	1	2.22%
Cribriform carcinoma	1	2.22%
Total	45	100.00%

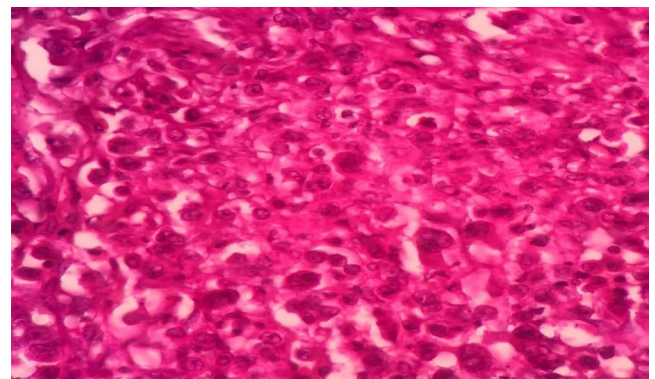


Figure 4. H&E x400 image showing infiltrating (ductal) carcinoma of NST.

The largest size of tumour was 14.5 x 9 cm, smallest was 2.5 x 1.6 cm; average tumour size being 5 x 4 cm.

Modified Bloom Richardson grading scores in the study population was applied: Out of the 45 patients, 2 patients (4.44%) were grade I, 31 patients (68.88%) were grade II, and 12 patients (26.66%) were grade III.

Out of the 45 patients, 31 (68.88%) patients showed tumor metastasis in axillary lymph nodes. Out of these 31 patients, perinodal spread was present in 25 patients (55.55%). The largest size of tumor metastasis was 4 cm. (Table 2)

29 out of 45 patients showed necrosis of tumour (64.44%).

Vascular invasion was present in 23 out of 45 patients (51.11%).

Perineural invasion was present in 18 cases out of 45 cases (40%).

In our study, T2 tumours were greater in number (Table 3).

NPI was applied to all cases. The maximum patients showed NPI score more than 5.4 suggesting poor prognosis (Table 4).

Table 2. Lymph nodes showing metastasis by tumor cells

Status of Lymph nodes (N)	Number of patients	Percentage
NX	1	2.22%
N0	14	31.11%
N1	11	24.44%
N2	15	33.33%
N3	4	8.89%
Total	45	100.00%

Table 3. TNM staging

Primary Tumor (T)	Number of patients	Percentage
T1	3	6.67%
T2	21	46.67%
T3	8	17.78%
T4	13	28.89%
Total	45	100.00%

Table 4. Nottingham Prognostic Index (NPI)

Score	Patients	Percentage	Prognosis
2 – 2.4	0	0.00%	Excellent
2.5 – 3.4	2	4.44%	Good
3.5 – 5.3	21	46.66%	Moderate
>= 5.4	22	48.88%	Poor
Total	45	100.00%	

Follow up of cases was done at the end of the study.

Out of 45 cases 5 had expired, these cases had Histologic grade III and NPI score of >5.4.

31 cases were disease free. These cases had Histologic grade I or grade II.

9 cases showed metastasis and recurrences. These cases had histologic grade II or grade III.

This indicates that histologic grade and NPI is significantly related to poor outcome of disease in patients with breast carcinoma. There is increased recurrence rate of breast carcinoma as well as increased morbidity and mortality. There is also decreased general survival after MRM, irrespective of clinical condition with unsuccessful early treatment taking place more commonly in tumours of high grade (Table 5 and 6).

Table 5. Prognosis

Prognosis	Survival 2		Total
	Death	Survived	
Good	0	2	2
Moderate	0	21	21
Poor	5	17	22
Total	5	40	45

Table 6. Outcome

Survival	Frequency	Percentage
Died	5	11.11%
Survived	40	88.89%
Total	45	100.00%

Table 7. NPI score and MRB grade correlation

Spearman's rank correlation method			
		NPI score	MRB grade
NPI score	Correlation Coefficient	1	-.885**
	Sig. (2-tailed)	.	0
	N	45	45
MRB grade	Correlation Coefficient	-.885**	1
	Sig. (2-tailed)	0	.
	N	45	45

**, Correlation is significant at the 0.01 level (2-tailed).

Logistic Regression for Dependent Variable: Outcome
Independent Variable: NPI, Lymph nodes, Skin involvement, Vascular Invasion

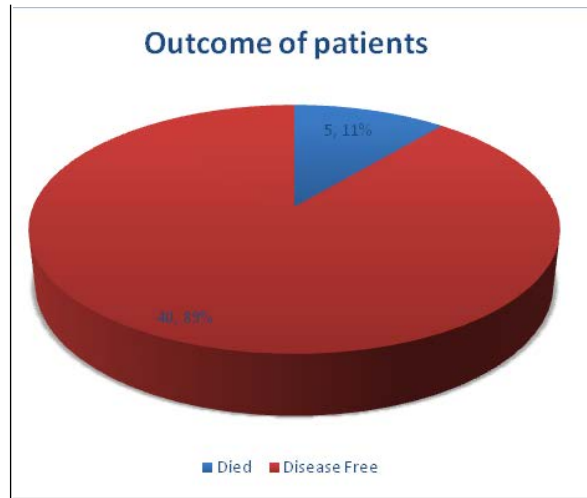


Figure 5. Spearman's rank correlation coefficient = -0.885 implies strongest negative correlation between NPI and prognosis.

Model Summary			
Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	24.401 ^a	.144	.287

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Therefore, the variation which can be explained in the dependent variable based on our study varies from 14.0% to 28.70% (Table 7 and Figure 5).

Table 8. Classification table

	Observed	Predicted			
		Survival 2		Percentage Correct	
		Died	Disease		
Step 1	Survival 2	Died	1	4	20.0
		Disease Free	1	39	97.5
	Overall Percentage				88.9
A. The cut value is .500					

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
								Lower	Upper
Step 1 ^a	NPI	-.412	.189	4.731	1	.030	.662	.457	.960
	Constant	4.667	1.325	12.402	1	.000	106.375		

a. Variable(s) entered on step 1: NPI.

Binomial logistic regression judges the probability of an event (in this study, having disease free) taking place. If the estimated probability of the event taking place is more than or equal to 0.5 (better than even chance), SPSS Statistics defines the event as occurring (e.g., disease free being present). If the probability is less than 0.5, SPSS Statistics defines the event as not taking place (e.g. died) (Table 8).

Statistical significance for each of the independent variables is decided by The Wald test («Wald» column). The statistical significance of the test is assigned in the «Sig.» column. NPI ($p = .030$) added significantly to the model.

5. Discussion

With increasing incidence, breast carcinoma has become the commonest carcinoma in Indian women.

5.1 Comparative Incidence of Mean Age of Breast Cancer

Table 9. Mean age of breast cancer: comparative incidence

Studies	Rajasekhar Reddy et al.	Pradhan A et al.	Present study
Mean age (years)	47.84	48.95	53.62

Table 10. Comparative incidence of tumor size (T)

Tumour Size (T stage)	Rajasekhar Reddy et al.	Pradhan A et. al.	Zubair Ahmed et al.	Present study
T1 (≤ 2 cms)	12.07 %	10.33%	7.5%	6.67%
T2 (> 2 cms - < 5 cms)	67.24 %	54.83%	44.16%	46.67%
T3 (≥ 5 cms)	12.64 %	25.80%	41.66%	17.78%
T4 (Any size of tumor with chest wall or skin infiltration)	8.46 %	10.33%	6.66%	28.89%

However in the current study the mean age of patient at the time of first treatment was 53.62 years. This shows a trend of late presentation of almost 3-4 years in the study population^{7,8} (Table 9).

In our study and other comparative studies⁷⁻⁹ T2 tumours were greater in number.

As per TNM staging system for breast carcinoma, T2 are tumour with size more than 2 cm but smaller than size 5 cm; while T3 are tumour measuring more than 5 cm in the largest dimension.

Only 7.5% tumours were found to be T1 (i.e. tumours 2cm or smaller in the largest dimension), while 6.66% were stage T4 (4.17% T4b and 2.5% T4d) (Table 10).

T4b are tumours of any size causing direct skin invasion and ulceration; while T4d are inflammatory carcinoma, tumours of any size with permeation of dermal lymphatics on light microscopy (a sign of bad prognosis).

Infiltrating Ductal cell carcinoma was the most common histological subtype in our study and also in study⁹⁻¹⁰.

In a study¹⁰ the histo-morphological patterns seen in breast cancer patients indicates that Infiltrating Ductal Carcinoma Not Otherwise Specified (IDC NOS) was the most prevalent type (88%).

In our study most of the cases (33.33%) were pN2 (metastasis in 4 to 9 axillary lymph nodes), where as in Zubair Ahmed et al study reported majority of cases with

N1 and Pradhan A et al study reported majority of cases with Number (Table 11).

Table 11. Comparative occurrence of tumor metastasis to lymph nodes (N)

Regional lymph nodes (N)	Zubair Ahmed et al.	Pradhan A et al.	Present study
NX	0%	0%	2.22%
N0	24.23%	45.16%	31.11%
N1	27.10%	32.25%	24.44%
N2	24.30%	22.58%	33.33%
N3	23.36%	0.01%	8.89%

Out of 45 cases, most of the cases (66.67%) belonged to grade II, 4.44% belonged to grade I and 28.89% belonged to grade III. Rajasekhar Reddy et al., Pradhan A et al and Z. Ahmad et al. also observed most of the cases belonging to grade II (75.83%) (Table 12).

Tumor necrosis, especially when massive, corresponds with escalating histologic grade, more incidence of metastasis of lymph nodes and reduced survival rate of the patient¹¹. It was there in a sizable number of our patients (64.44%).

Intravascular invasion shows, according to several studies, an increased correlation with tumor grade, size of tumor, and status of lymph nodes^{12,13}.

Table 12. Comparative occurrence of Nottingham modification of the Scarff-Bloom-Richardson grading system

Extent of differentiation	Grade (Score)	Rajasekhar Reddy et al.	Pradhan A et al.	Zubair Ahmed et al.	Present study
Well Differentiated	I (3 – 5)	8.62%	35.48 %	4.17%	4.44%
Moderately Differentiated	II (6 – 7)	81.61%	38.71 %	75.83%	66.67%
Poorly Differentiated	III (8 – 9)	9.77%	25.81 %	20%	28.89%

Table 13. Comparative incidence of NPI

NPI	Pradhan A et al.	Zubair Ahmed et al.	Present study	Prognosis
2 – 2.4	6.45%	0.00%	0.00%	Excellent
2.5 – 3.4	16.13%	2.8%	4.44%	Good
3.5 – 5.3	61.29%	41.1%	46.66%	Moderate
>= 5.4	16.13%	56.1%	48.88%	Poor

It was also there in a sizable number (51.11%) of our patients.

The NPI has been extensively used to determine the prognosis of patients of carcinoma breast¹⁴.

It was designed for patients with primary operable carcinoma breast. Depending on three factors (size of tumor, grade of tumor, and staging), the index showed three types of patients with different chances of mortality from breast cancer. These three types are: better prognosis (score up to 3.4) composed of 4.44% patients with 80% five year survival; average prognosis (score 3.4 to 5.4) composed of 46.66% patients with 42% five year survival; and bad prognosis (score greater then 5.4) composed of 48.44% patients with 13% five year survival.

According to our results 48.88% patients are in class with bad prognosis with NPI scores more than 5.4. Only 4.44% are in the better prognosis category.

This further denotes the progressive nature of carcinoma and bad prognosis for breast carcinoma in our population (Table 13).

6. Conclusion

This study was carried out with a target to evaluate breast carcinoma histopathologically (macroscopic as well as microscopic examination of received mastectomy specimens) in the Pathology department of Dr. VPMC Hospital and Research Centre, Nashik and to utilize the conventional prognostic factors for evaluation of prognosis for our patients. The maximum number of cases belonged to Infiltrating Ductal carcinoma of NST. Majority of the tumors had sizes between 2 cm and 5 cm (T2- 46.67%). Tumor necrosis was seen in a large percentage of our patients (64.44%). Most of the cases showed score of Grade II of Nottingham modification of Bloom Richardson system. In our study, 48.88% patients are in the category of bad prognosis with NPI scores greater than 5.4. Based on these findings, the Nottingham

Prognostic Index, derived from careful evaluation of size of tumor, grade on histology and status of lymph node involvement is currently the most practicable outcome criteria available, and the sole integrated index to have been assessed in independent prospective studies. We stress on the role of a standardized reporting protocol in learning the trends of breast carcinoma, a malignancy that has a poor social awareness despite many recent advances in management. The findings show progressive and adverse disease trends in our patients. After keeping follow up with the patients we came to a conclusion that: the involvement of lymph nodes, size of the tumor, histologic pattern, histologic grade, necrosis and presence or absence of intravascular invasion remain the best independent prognostic indicators. Histological grade, assessed shows a very firm correlation with prognosis; patients with grade I tumors have a proportionately better survival than those with grade II and III tumors. Finally, the treatment of patients with breast cancer should be done on a multidisciplinary pattern and therapeutic modalities should be decided at combined meetings with proactive participation by histopathologists.

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