



ORIGINAL ARTICLE

Histological Grading, Staging and Nottingham Prognostic Index Scoring of Breast Carcinoma: A Hospital Based Observational Study

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Abstract

Background and aims: Breast cancer besides being a global cancer burden comprises a complex and heterogeneous group of diseases at clinical, morphological, and molecular levels. Among all the clinico-pathological-molecular prognostic factors available in decision making about suitable treatment options for breast cancer, Nottingham prognostic index (NPI) is the most simple, powerful integrated and reproducible index. This study was aimed to evaluate the NPI in a group of breast cancer patients and to correlate NPI with other clinical and histomorphological features. **Materials and Methods:** A cross-sectional observational study of mastectomy specimens with axillary lymph node sampling was done for a period of three years. The diagnosis was made using WHO classification. Grading and staging was done using Modified Bloom Richardson score and TNM system respectively. The prognosis was scored by applying Nottingham Prognostic index. **Results:** Out of the 63 patients, most belonged to the age group of 41 to 50 years. The most common histologic type was Invasive Carcinoma of No Special Type (49 cases; 77.78%). Majority of the patients (69.84%) belonged to Bloom Richardson (BR) Grade II. Lymph node biopsy was reviewed with 57.14% of the patients showing nodal metastasis. Significant correlation was noted between NPI score and tumor size, positive lymph nodes and BR grade. The mean NPI score was found to be 4.53 ± 1.04 . **Conclusions:** NPI serves as an essential and powerful prognostic indicator, relying on relatively simple data of primary tumour size, lymph node stage and histological grade which act as a hard copy for clinicians to decide treatment modalities for the patient and in follow up as well.

Keywords

Carcinoma Breast, Tumour Grade, Nottingham Prognostic Index

Introduction

As per the Global Cancer Statistics 2020, breast cancer with an estimated 2.3 million new cases has surpassed lung cancer as the most commonly diagnosed cancer. It accounts for 1 in 4 cancer cases and for 1 in 6 cancer deaths.^[1] Breast cancers attribute to 25% of the female cancer cases in India with an increased incidence of the disease in younger women (between the ages of 30 and 40).^[2] There's also an increase prevalence of breast

cancer risk factors due to dramatic changes in lifestyle and an increase in the proportion of women in the industrial workforce area.^[1] Lack of awareness and ignorance in self-examination of breast leads to the presentation of breast cancer at a later stage.^[3] Although invasive carcinoma of the breast was clinically regarded as a single entity in the past, histologic and molecular analysis have demonstrated that breast cancer is a heterogeneous disease, composed of morphologically and genetically

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distinct entities with different molecular profiles, behaviour, and response to therapy. Clinically, invasive breast cancer is classified according to primary tumor size, lymph node status, and local extent and presence of distant spread. The favourable prognosis of certain histologic types of invasive carcinoma of the breast is now well.^[4] Numerous other factors are known to have independent prognostic value. Hence, there have been attempts at incorporating all these factors into meaningful indices. The most widely used of which is the Nottingham prognostic index (NPI), first described in 1982, which incorporates tumor size, lymph node stage and histological grade.^[5] Histologic grading has now been widely accepted as a powerful indicator of prognosis in addition to providing an overview of the intrinsic biologic characteristics of the tumours. Nottingham modification of Bloom Richardson grading system has been used for histologic grading of breast carcinoma and is based on semiquantitative evaluation of the morphological characteristics of the tumour, the degree of nuclear pleomorphism and the mitotic figures. In the current study we aim to acquire information about the extent and spread of breast carcinoma in our patients by grading the tumors, determining the tumor size, axillary lymph node status and Nottingham Prognostic Index (NPI) score.

Materials and Methods

The present study was conducted after obtaining ethical approval from Institutional ethical review committee (IEC/GMC/CAT C/2021/527 dated 24/052021). The present study was conducted from February 2018 to February 2021. This is a hospital-based retrospective study involving retrieval of archival records and tissue-paraffin blocks of cases histologically documented as breast carcinoma. A total number of 71 breast carcinoma cases were reviewed. However histological report of the resected specimen confirming the diagnosis and nodal status were present in only 63 (n=63) cases which were further included in the study. Fresh thin sections measuring about 3-5 μ m in size were cut from the retrieved tissue blocks and stained using hematoxylin and eosin staining technique for histologic analyses. The reporting was done on the stained sections incorporating all relevant tumor parameters. Tumours were classified according to World Health Organization (WHO). Histologic grading of the tumors was accomplished by Nottingham modification of Scarf-Bloom-Richardson-Method and staging was reported based on the TNM system. Nottingham Prognostic Index was used to score the prognosis of the patient. Cases were further scored according to the Nottingham prognostic index.

NPI was calculated as:

$$\text{NPI} = 0.2 \times \text{Tumour size (cm)} + \text{Lymph node stage (I/II/III)} + \text{Tumour grade (1/2/3)}$$

Thus calculated NPI was classified as low (NPI <3.4), intermediate (NPI 3.41-5.4) and high NPI (>5.4). The data obtained was coded and entered in Microsoft Excel Spreadsheet and reported in percentage (frequency) and proportion using descriptive statistics. The correlation using t-test was calculated using Epi Info statistical software.

Results

A total of (n = 63) histologically documented breast cancers cases with complete information were identified from February 2018 to February 2021. In the present study, age of the patients ranged between 29-72 years (mean 48.41 \pm 12.26), most of them aged between 41-50 years in which the most of the patients presented with left sided carcinoma breast 36 patients (57.14%). Among tumour characteristics, the most common histologic subtype of breast carcinoma seen in our study was of infiltrating ductal carcinoma, NOS (*Fig 1*) (49 cases; 77.78%). There were 6 cases (9.58%) of invasive lobular carcinoma, followed by 4 cases (6.35%) of malignant phyllodes (*Fig 2*). The uncommon types recorded were two cases (3.17%) of metaplastic carcinoma (*Fig 3*) and one case (1.59%) each of mucinous and medullary carcinoma (*Table 1*) (*Fig 4*).

The tumor size varied from 1.5 to 8 cm in largest dimension (mean 4.12 \pm 1.90 cm) with majority (74.60%) of the cases in the size range of 2-5 cm. Three (4.76%) cases had tumor size \geq 2 cm and were classified as tumor size Stage 1 (pT1). The mean NPI scores in patients with tumor size \geq 2.0 cm, 2.01 to 5.0 cm and $>$ 5 cm was noted as 4.05 \pm 0.57, 4.37 \pm 0.93 and 7.27 \pm 0.72 respectively. We did comparison of mean of tumour size and NPI score by employing t-test using statistical software epi Info and it was found to be statistically significant (p <0.050) (*Table 2*).

According to modified Bloom-Richardson tumor grade, majority of the cases were Grade II (73.01%), 20.63% were Grade III and 6.34% were Grade I. Comparison of mean of grade and NPI score difference was found to be statistically significant (p <0.050)

To record possible note on metastasis of individual cases, lymph node biopsy was reviewed with 57.14% of the patients showing nodal metastasis. The dissected lymph nodes ranged in size from 0.5-3.5 cm in largest diameter. The highest number of positive lymph nodes were 6 (stage 3, pN2). 42.86% cases were negative for the malignancy (pN0). Only three cases (4.76%) had lymph node positivity of $>$ 3 (pN2). Comparison of mean of lymph node status and NPI score was done employing t-test at

Table 1. Histologic types of Breast Carcinoma included in the study

Histologic type	No. of patients (N)	Percentage (%)
infiltrating ductal carcinoma, NOS	49	77.78
Invasive lobular carcinoma	6	9.58
Malignant Phyllodes	4	6.35
Metaplastic carcinoma	2	3.17
Medullary carcinoma	1	1.59
Metaplastic carcinoma	1	1.59

Table 2 Showing Classification

Tumor size (cm)	No. of patients (N)	Mean NPI score	
		Mean	SD
T1 (=2.00)	3	4.05	0.57
T2 (2.10-5.00)	47	4.37	0.93
T3 (>5.00)	13	7.27	0.72
P value		<0.05	
BR grade			
Grade I	4	2.5	0
Grade II	46	4.49	0.89
Grade III	13	5.29	0.8
P value		<0.05	
Number of lymph nodes involved			
0 (no lymph nodes involved)	27	3.75	0.65
1 to 3	33	5.08	0.57
>3	3	6.5	0.56
P value			

BR- Bloom-Richardson

NPI- Nottingham Prognostic Index

95% confidence interval of the difference and the p-value came upto <0.05 so, it was statistically significant (Table 2).

Cases were reported using tumor node metastasis (TNM) staging, showing predominance of stage II (69.84%) cases at diagnosis followed by stage III (23.80%). Four cases (6.34%) were found to be stage I at the time of diagnosis. NPI was applied to all the 63 cases. The mean NPI±SD was 4.58 ± 0.98 (range 2.5-7) and median value 4.7 which is equivalent to maximum number of cases in the moderate prognostic group (n=38, 60.31%). NPI score >5.4 (poor prognosis group) constituted 15.87% of the cases.

Summary of characteristic of carcinoma breast patient included in study is tabulated in (Table 3).

Discussion

Breast cancer is a major contributor to global cancer burden and a significant public health issue. With expansion of novel therapeutic options and a greater potential of recovery, breast cancer remains most widely researched malignancies in the past twenty years. In our three year study period, there were a total of 63

cases of breast cancer with complete histologic as well as lymph nodal status details. The age of the patients ranged from 29-72 years with a mean value of 48.41±12.26 which is very similar to study conducted by Hamza *et al.* ¹⁶ where the age range was 16 - 80 years with mean value of 46.5± 13. Similarly, in studies conducted by Shukla *et al.* ¹⁷ and Prabhu *et al.* ¹⁸ the mean age was 51.18±11.94 years and 52.05 years, respectively.

Left breast (n=36, 57.14%) was more commonly involved in the present study. Similar slight left side involvement was noted in studies of (58%) Pradhan *et al.* ¹⁹ and Randale *et al.* ¹¹⁰

Invasive ductal carcinoma, NOS (49 cases; 77.78%) was the most common histologic subtype of breast carcinoma seen in our study which is in concordance with the literatures. ^{14, 11, 12}.

There were 6 cases (9.58%) of Invasive lobular carcinoma, followed by 4 cases (6.35%) of malignant phyllodes. The uncommon types noted were metaplastic carcinoma (3.17%), mucinous (1.59%) and medullary carcinoma (1.59%) (Fig 6). This is in agreement with study by Soni *et al.* ¹³¹ and Oluogun *et al.* ¹⁴⁴

Studies have found, gross tumour size of the breast

Table 3. Characteristics of 63 breast cancer patients included in the study

Variables	Observations
Mean age	48.41 ± 12.26 years
Side involved	Left side
Most common histological type	Infiltrating ductal carcinoma, NST
Mean tumor size	4.12 ± 1.90 cm
Number of cases with Axillary lymph node involvement	36 (57.14%)
BR grading	Grade 1 – 4 patients (73.01%) Grade 2 – 46 patients (20.63%) Grade 3 – 13 patients (6.34%)
Stage according to TNM staging	Stage 4 (69.84%)
Mean NPI index	4.58±0.98

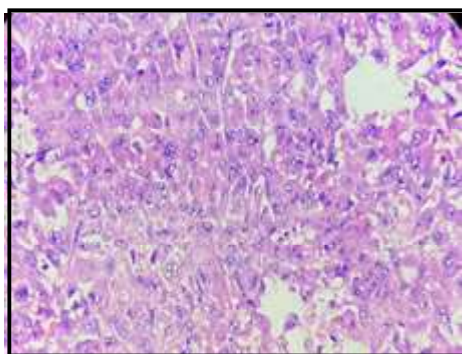


Fig. 1. Photomicrograph of Invasive ductal carcinoma no special type grade III IDC NST - III (H and E, ×400)

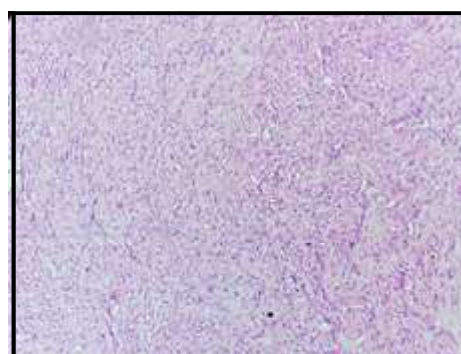


Fig. 2 Photomicrograph of Malignant Phyllodes tumour (H and E, ×100)

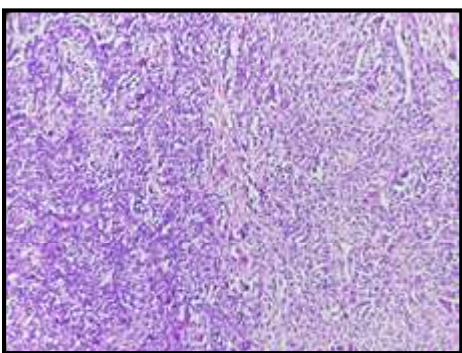


Fig 3. Photomicrograph of Metaplastic breast carcinoma (H and E, ×400)

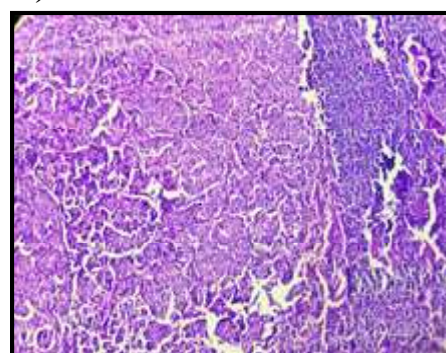


Fig.4 Photomicrograph of medullary carcinoma breast Syncytial sheets of tumor cells with peripheral lymphocyte infiltrate (H & E, ×100).

cancer to be an important independent, significant prognostic variables. Study by Rakha *et al.* ^[15] and Sundquist *et al.* ^[16] showed independent prognostic significance for small size tumors. Tumour size has been incorporated in the Nottingham prognostic index and in TNM staging system due to its independent prognostic significance. ^[4] The tumor size varied from 1.5 to 8 cm in largest dimension. Study conducted by Ahmad *et al.* ^[17] showed the size of tumor ranged from 1-13 cm in diameter which is very close to our study. The smallest tumor size was seen in a case of infiltrating ductal carcinoma NOS

and the largest tumor was seen in a case of metaplastic carcinoma. Patients were stratified according to primary tumor size into three groups (according to TNM classification): group A (pT1), 2 cm; group B (pT2), larger than 2 cm to 5 cm; and group C (pT3), larger than 5 cm. Highest numbers of cases were detected in the T2 stage i.e. with size varying between 2 - 5 cms (74.60%). Meanwhile, only three cases in group A (4.76%) were included which would require ancillary investigations such as mammogram and breast ultrasound for detection.



Mean tumour size (4.12 ± 1.90 cm) in our study which is similar to a study by Shukla *et al.*^[7] with mean value of 4.65 ± 1.89 cm and lie within the range reported in the literature^[6, 18]

Histologic grading system was first introduced by Greenhough in 1925. Since then, it has been revised by many authors over a period of years. The current, widely adopted system is the Nottingham modification of Scarff-Bloom-Richardson system which measures three parameters: tubular or glandular differentiation, nuclear pleomorphism and mitotic rate. Independent poor prognostic value of microscopic grading has been validated since many years in multiple studies. Study conducted by Rakha *et al.*,^[19] demonstrated good reproducibility of histologic grade which in combination with tumor size, lymph node involvement, and the NPI offers best and remarkable stratification for management of these patients. Grade been found to be significantly related not only to increased recurrence but also to disease free interval and overall length of survival after mastectomy regardless of clinical stage with early treatment failures occurring more commonly in high grade tumors. Our observation on overall grading showed, majority of the cases were grade II (73.01%), 20.63% were grade III and 6.34% were Grade I. Shukla *et al.*^[7] and Ahmad *et al.*,^[17] also demonstrated majority of the cases were grade II (62%) and (75.83%) respectively.

Orang *et al.*^[20] found in his study that as the tumor size increased, more lymph nodes were involved. The present study thus assessed the number of lymph node biopsied and the number that were positive with 57.14% of the patients showing nodal metastasis. 42.86% cases were negative for the malignancy (pN0). Axillary lymph node metastasis is one of the most important prognostic factor in carcinoma breast with sharp differences in survival rates between those with negative and positive nodes.^[17] Majority (52.38%) of the cases showed Group II metastasis (metastasis in 1 to 3 axillary lymph nodes). This is in agreement with others.^[6, 21]

The stage at presentation of breast cancer is more advanced with only 6.34% cases presenting at stage I reflecting delay in seeking medical attention. Predominance of stage II (69.84%) was seen as in other studies by Hamza *et al.*^[6] and Ahmad *et al.*^[17]

The positivity of axillary lymph nodes for metastases is one of the most important prognostic parameters in carcinoma of breast with sharp differences in survival rates between those with negative and positive nodes.^[14, 18] As shown in our results, axillary lymph nodes were positive in 52 (94.5%) out of 55 cases and lymph nodes were negative for metastases in only 3 (5.5%). Of the

52 cases with positive lymph nodes: 43.6% were Group II.

The main strength of NPI score is that it can be calculated from the routine histopathology report given by pathologist. The NPI scoring has been widely adopted as a prognostic tool for assessing the prognosis in primary operable breast carcinoma patients.^[18] According to Thangiam *et al.*^[22] NPI serves as simple clinicopathological prognostic tool which not only gives accurate prediction of prognosis but also offer guidance for administration of adjuvant therapies. In our study out of 63 cases, 10 cases (15.9 %) were of good prognostic group, 38 cases (60.3 %) from moderate prognostic group and 15 (23.8 %) in poor prognostic group. The NPI score ranged between 2.5 to 7. The mean NPI score was found to be 4.58 ± 0.98 . The findings were consistent with a study by Shukla *et al.*, and Foo *et al.*, reported mean NPI as 4.9, 4.76 and 4.6 respectively.^[7, 23] In the present study, majority of the patients (60.3%) had NPI score between 3.4 to 5.4 suggestive of moderate prognosis followed by poor prognosis (23.8 %) and good prognosis (15.9 %). In the present study, majority of the patients (64%) had NPI score between 3.4 to 5.4 suggestive of moderate prognosis followed by poor prognosis (32%) and good prognosis (4%). These findings were in agreement with a study by Shukla *et al.*, Randale *et al.*, and Pradhan *et al.*, reported moderate prognosis in 64%, 55.9%, 61.3% and 53.6 % of the patients.^[7, 10, 9] In contrast to the observations of present study, Ahmad *et al.* and Hamza *et al.* reported that, 56.1 % and 48% of the patients had a poor prognostic index respectively.^[17]

Studies by Ahmad *et al.*, by Shukla *et al.*, and Randale *et al.* observed that NPI index increases with increase in tumor size, positive lymph nodes and BR grade ($p < 0.05$) which is in accordance with results our result.^[17, 7, 10]

Most metaplastic tumors of the breast are poorly differentiated having high grade, are highly cellular with mitotically active pleomorphic spindle cells.^[24]

Conclusion

In the study presented herein, we demonstrated clinicopathological aspects of breast cancer along with the use of Nottingham Prognostic Index (NPI) based on relatively simple data which can be provided in routine histopathology report of carcinoma as a powerful and reproducible integrated index for assessing prognosis in patients of breast cancer in advanced resources deprived institute. The patient population is representative of the general breast cancer population in relation to the mean age at diagnosis and number of patients in the different NPI risk groups The most common type of breast carcinoma was of invasive carcinoma of NST. Majority



of the cases showed grade II of Nottingham modification of Bloom Richardson system with maximum number of cases having moderate Nottingham prognostic index. Authors considered this study to hold importance as it was conducted in the tertiary health care centre of North India and the patient population is representative in relation to the mean age and number of patients in the different NPI risk groups stressing on the importance to incorporate the three strongest determinants in breast cancer which further help clinicians to decide treatment modalities for the patient and in follow up as well.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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