Original Research Article

Correlation of axillary lymph nodes involvement and Nottingham prognostic index with various histopathologic prognostic factors in invasive breast carcinoma

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ABSTRACT

Background: Breast cancer is the commonest cancer of urban Indian women and the second commonest in the rural women. The clinical management of this tumor relies on various prognostic factors, most importantly lymph node stage, tumor size and histologic grade. There have been attempts at integration of these factors into meaningful indices. The most widely used of these is the Nottingham prognostic index (NPI), this study was aimed to evaluate the NPI in a group of breast cancer patients and to correlate NPI with other clinical and histo-morphological features.
Methods: This was a two-year prospective, observational study was done in the Department of Surgery, Tertiary Care Teaching Hospital of Maharashtra, India. A total of 50 patients who presented with invasive carcinoma of breast from October 2016 to October 2018 were enrolled.
Results: Most of the patients belonged to the age group of 41 to 50 years (34%) and the mean age of patients in study was 51.18 ± 11.93 years. Left breast was more affected (62%) than the right breast (38%). Majority of the cases had tumor size of <5 cm (70%) and the mean size of was 4.65 ± 1.89 cms. Majority of the patients (62%) belonged to Bloom Richardson (BR) Grade II and 24% of the patients were ER and PR positive. Lymphovascular invasion was present in 74% of the patients. There was significant positive correlation between tumor size and lymph node involvement. Significant correlation was noted between NPI score and tumor size, positive lymph nodes and BR grade. The mean NPI scores in patients with lymphovascular invasion were noted as 4.92 ± 1.05, compared to 4.83 ± 0.93 among the patients in whom lymphovascular invasion was absent (p=0.779). The mean NPI scores in patients with ER-, PR- were slightly high (4.91 ± 0.94) compared to ER+, PR+ patients (4.76 ± 1.19) (p=0.778).
Conclusions: NPI is an essential and valuable prognostic indicator, which should be incorporated in breast cancer reporting by the histopathologists and also primary tumor size, lymph node stage and histological grade which provides further guideline to treating clinicians to choose treatment modalities for the patient and in deciding to follow up plan as well.

Keywords: Axillary lymph node involvement, Carcinoma breast, Nottingham prognostic index

INTRODUCTION

Breast carcinoma is one of the leading causes of cancer related mortality in females.[1] The clinical management of this tumor relies on various prognostic factors, most importantly lymph node stage, tumor size and histological grade.[2] Numerous other features have been independently shown to have prognostic value. Hence, there have been attempts at integration of these factors into meaningful indices. The most widely used of these is the Nottingham prognostic index (NPI), first described in 1982, which incorporates tumor size, lymph node stage and histological grade.[3]

Prognostic factors influence the design, conduct, and analysis of clinical trials of breast cancer. These factors can be used to distinguish patients likely to have recurrences after treatment of their primary tumor from those with low risk of recurrence and those likely to benefit from adjuvant therapy from those whose disease is likely to be resistant to treatment.[4] In clinical practice, it must show a wide separation in the outcome of the groups identified and select adequate numbers in each group. Hence, no single prognostic factor satisfies all the above criteria.[5]

The Nottingham Tenovus Primary Breast Cancer Study (NTPBCS) was set up in 1974 to evaluate a wide range of potential prognostic factors in a single cohort of patients.[6] Then, after it was soon established that the three most powerful factors were tumor size, lymph node status and histological grade and these were incorporated into the Nottingham Prognostic Index (NPI).[1,6-8] These results were greeted initially with considerable scepticism.[6]

Now NPI is widely accepted index to reflect metastatic behavior, growth rate and genetic instability of breast cancer, and to accurately predict survival patterns in accordingly stratified groups with follow up period after primary diagnosis of breast cancer.[1,5,8] Most importantly, NPI offers a responsive and sensitive means of modelling a continuum of clinical aggressiveness, indexing the outcome likelihood of invasive breast cancer patients. NPI can define 3 subsets of patients with different probabilities of dying from breast cancer, good ($\leq$3.4), moderate (3.41-5.4) and poor (>5.4) prognosis groups.[1] It is considered by many to be the gold standard by which novel prognostic factors are judged.[6] The aim of this study was to evaluate the correlation of axillary lymph nodes involvement and Nottingham prognostic index with various histopathologic prognostic factors in invasive breast carcinoma.

METHODS

The present study was conducted in the Department of General Surgery, Acharya Vinoba Bhave Rural Hospital, Sawangi, Meghe, Wardha, Maharashtra, India from October 2016 to October 2018.

The study was two year prospective, observational study conducted at Department of Surgery, Acharya Vinoba Bhave Rural Hospital, Sawangi, Meghe, Wardha, Maharashtra, India, a teaching hospital attached to Jawaralal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi (Meghe), Wardha, Maharashtra, India conducted for a period of two years from October 2016 to October 2018.

Patients admitted with carcinoma breast in the Department of Surgery Acharya Vinoba Bhave Rural Hospital, Sawangi Meghe, Wardha, Maharashtra, India. Total 50 patients who were admitted with breast carcinoma were included in the study.

The female patients regardless of their age, with a carcinoma of the breast proven by either cytological or histopathological confirmation were included.

The patients with benign breast problem, male patients, pregnant females, inoperable carcinoma breast and recurrent carcinoma breast were excluded.

Ethical clearance

Prior to the commencement, according to the tenets of the declaration of Helsinki, the study was accepted by the Ethical and Research committee, Datta Meghe Institute of Medical Sciences, Sawangi (Meghe), Wardha, Maharashtra, India.

Procedure

Patients were interviewed and demographic data along with clinical presentation was noted. These patients underwent clinical examination. Further, these patients underwent modified radical mastectomy (MRM) and other details including axillary lymph node status, tumor size, lymphovascular invasion and histopathological grade (Bloom Richardson grade (BR grade)) were assessed. These findings were recorded on a predesigned proforma.

Study variables

Nottingham Prognostic Index (NPI)

Calculation of the Nottingham Prognostic Index (NPI) was done by using the three factors which were tumor grade, number of lymph nodes involved and size of the tumor.

Tumor grade (G) given a score 1-3 based on BR grading, lymph node involvement (L) given a score as 1 if no node, 2 if 1-3 nodes and 3 if >3 nodal involvement with tumor size in cm (S).

NPI was worked out using internationally accepted formula as below.

NPI= (0.2 × tumor size (cm)) + lymph node stage (I/II/III) + tumor grade (I/II/III) or score, prognostic group and 5 years survival can be calculated online from http://www.pmidcalc.org.

In addition, ER and PR receptor status of specimen was also obtained.

Statistical analysis

The data obtained was coded and entered in Microsoft Excel Spreadsheet. The data was analysed by statistical software SPSS version 20.0. The categorical data was expressed as rates, ratios and percentages and comparison was done using chi-square test or Fisher's exact test.

Continuous data was expressed as mean±standard deviation. The comparison of more than two means was done by one-way ANOVA test at 95% confidence interval (CI), a probability ('p') value of less than or equal to 0.05 was considered as statistically significant.

RESULTS

This two-year prospective, observational study was done in the Department of Surgery, Acharya Vinoba Bhave Hospital, Sawangi, Maharashtra, India. 50 patients who presented with carcinoma of breast from October 2016 to October 2018 were studied.

The data obtained was analysed and the final results were tabulated and interpreted. In the present study, most of the patients were aged between 41-50 years (mean 51.18±11.94), in which the tumor size varied from 2.1 to 5 cm in the larger dimension mean tumour size was noted 4.65±1.89 cm whereas most of the patients presented with left sided ca breast 31 patients (62%) , lymph node metastasis was present in 58% of the patients. Out of 50 cases majority of the cases were Grade II (62%), 22% were Grade III and 16% were Grade I. Vascular invasion was observed in 37 cases (74%). The ER, PR negative status was observed in 33 cases (66%) and ER, PR positive status was observed in 12 cases (24%) (Table 1).

Table 1: Characteristic of Ca breast patient included in study.

Variables	Observations
Mean age of patient	51.18±11.94 (years)
Side involved in Ca breast	Left sided 31 (62%) patient
Mean tumor size	4.65±1.89 cm
Axillary lymph node involvement	29 (58%)
BR grading	Grade (II) 31 patients (62%) Grade (III) 11 patients (22%)
Presence of lympho-vascular invasion	37 (74%)
ER-, PR-	33 (66%)

In the present study the mean NPI scores in patients with tumor size ≤2.0 cm, 2.01 to 5.0 cm and >5 cm was noted as 4.35±0.64, 4.67±1.08 and 5.55±0.53 respectively. This difference was statistically significant between tumor size and NPI score (p <0.050) (Table 2).

As evidenced from Table 2 that there is increase in NPI score with increase in BR grade and the difference is statistically significant (p <0.050) (Table 3).

In the present study, the mean NPI scores in patients with no axillary lymph node involvement was 4.15±0.78, in patients with 1 to 3 positive lymph nodes was 4.96±0.66 and in those with involvement of >3 lymph nodes was

5.90±0.68. This difference was statistically significant (p<0.050) (Table 4).

Table 2: Correlation of tumor size and mean NPI score.

Tumor size (cm)	No. of patients (N)	Mean NPI score	
		Mean	SD
T1 (≤2.00)	2	4.35	0.07
T2 (2.10-5.00)	35	4.67	1.08
T3 (>5.00)	13	5.55	0.53
P value		<0.050	

Table 3: Correlation of BR grade and mean NPI score.

BR grade	No. of patients (N)	Mean NPI score	
		Mean	SD
Grade I	8	4.10	1.07
Grade II	31	4.94	0.95
Grade III	11	5.36	0.89
P value		<0.050	

Table 4: Correlation of number of positive lymph nodes involved and mean NPI scores.

Number of lymph nodes involved	No. of patients (N)	Mean NPI score	
		Mean	SD
0 (no lymph nodes involved)	21	4.15	0.78
1 to 3	14	4.96	0.66
>3	15	5.90	0.68
P value		<0.050	

In the present study, the mean NPI scores in patient's lymphovascular invasion were noted as 4.92±1.05, compared to 4.83±0.93 among the patients in whom lymphovascular invasion was absent. However, this difference was statistically not significant (p >0.050) (Table 5).

Table 5: Correlation of lymphovascular invasion and mean NPI scores.

Lyphovascular invasion	No. of patients (N)	Mean NPI score	
		Mean	SD
Present	37	4.92	1.05
Absent	13	4.83	0.93
P value		>0.050	

In the present study, majority of the patients had moderate prognosis (64%). The mean NPI score were 4.90±1.02 and median NPI scores were 4.9 with range 2.4 to 6.9 (Table 6).

Table 6: Distribution of patients according to the prognosis bases on NPI scores.

Prognosis (NPI scores) (rate of survival)	Distribution (n=50)	
	Number	%
Good (>2.4 to ≤3.4) (85%)	2	4.00
Moderate (>3.4 to ≤5.4) (70%)	32	64.00
Poor (>5.4) (50%)	16	32.00
Total	50	100.00
Mean±SD (Median, Range)	4.90±1.02 (4.9, 2.4-6.9)	

DISCUSSION

Breast cancer has a low prevalence in India but the number of cases of breast cancer is rising. Breast cancer is the most common carcinoma presenting in urban population and the second most commonly diagnosed carcinoma in rural population. In spite of its relevance, majority of breast cancer cases are diagnosed at an advanced stage, attributed by the lack in awareness among the rural population and absence of screening program. The treatment of the cancer relies on various findings like tumor size at the time of presentation, the number of positive lymph nodes and the histopathological grading. There have been studies to integrate these prognostic factors to get a more meaningful prognostic index. Most widely used prognostic index to find the outcome of patients with carcinoma breast is the Nottingham prognostic index. It was first introduced in 1982. It is based on the tumor size at the time of presentation, the lymph node stage and the histopathological grading.[15-19]

Correlation of lymphovascular invasion with NPI

In this study, the mean NPI scores in patients with lymphovascular invasion were noted as 4.92±1.05, compared to 4.83±0.93 among the patients in whom lymphovascular invasion was absent. However, this difference was statistically not significant (p>0.050). These finding suggest a lack of relationship between LVI and NPI. More recently Agarwal et al, studied the role of LVI as a prognostic marker and commented that, LVI was associated with higher NPI but its authenticity can be established only with the application of IHC for the endothelial markers.[20]

Correlation of positive lymph node according to tumor size

In present study, there is a statistically significant positive correlation between the tumor size and lymph node metastasis. Yadav et al, found in their study that there was a positive relation between lymph node involvement with increasing tumor size.[21] Orang et al, found in his study that as the tumor size increased, more lymph nodes were involved, which correlates with this study.[22] Michaelson et al, similarly found increasing fraction of lymph node involvement with growth in tumor size.[23] Colleoni et al, found a linear relation between lymph node involvement and increasing tumor size.[24]

Correlation of axillary lymph node status and BR grade

In the present study, the mean number of axillary lymph nodes involved in patients with grade I, II and III was noted as 2.25±3.58, 3.09±3.81 and 2.18±4.44 respectively (p >0.050) and no significant difference was noted between mean number of axillary lymph nodes involved and BR grade suggesting lack of relationship between mean number of axillary lymph nodes and BR grading. Microscopic grading system has been an important prognostic factor since many years and its prognostic value has been validated in multiple independent studies. Study conducted by Rakha et al, demonstrated that grade is an important determinant of breast cancer outcome and complimentary to lymph node (LN) stage.[2] However, the reproducibility of histologic grading has been questioned earlier and studies have been conducted to demonstrate reproducibility.[14] Various studies have analyzed the importance of histologic grade (based on the Modified Bloom and Richardson grading system) as a prognostic factor in carcinoma of the breast. It has been shown that patients with high grade tumors treated by mastectomy have significantly high frequency of lymph node metastases with four or more positive nodes, develop more systemic recurrences, and more of such patients die of metastatic disease compared to patients with low grade tumors.[2]

Correlation of NPI scores with tumor size, BR grade and positive axillary lymph node involvement

Various studies have shown that the gross size of tumor is one of the most significant prognostic factors in breast carcinoma and similar observations were noted in the present study. As the mean NPI scores in patients with tumor size ≤2.0 cm, 2.01 to 5.0 cm and >5 cm was noted as 4.35±0.64, 4.67±1.08 and 5.55±0.53 respectively. This difference was statistically significant between tumor size and NPI score (p <0.050). These findings suggest that, the mean NPI score significantly increases with tumor size and there is a strong correlation between NPI with size of the tumor. A study by Rekha et al, Kollias et al, and Sundquist et al, showed independent prognostic significance for small size tumors.[2,25,26] Various studies by Carter et al, and Russo et al, have shown that the gross size of tumor is one of the most significant prognostic factors in breast carcinoma.[27,28]

In the present study, the mean NPI scores in patients with no axillary lymph node involvement was 4.15±0.78, in patients with 1 to 3 positive lymph nodes was 4.96±0.66 and in those with involvement of >3 lymph nodes was 5.90±0.68. This difference was statistically significant (p <0.050). Various studies by Carter et al, and Russo et al, have shown that there is increased incidence of axillary lymph node metastasis and decreased survival.[27,28] The

positivity of axillary lymph nodes for metastasis 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.[4,8,29] The positivity of axillary lymph nodes for metastasis 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.[28] In addition, the absolute number of nodes involved, the presence or absence of extra nodal spread, and the amount of carcinoma in the positive nodes (measured by the microscopic size of the largest nodal metastasis) are also prognostically important with survival rates falling with increased number of nodes involved (less than 4 versus 4 or more), presence of extra nodal spread and increased amount of tumor in positive nodes.[30-33] However, in this study, extra nodal spread was not assessed. A study by Kwatra et al, showed that patients in higher NPI group had more frequent lymph node metastasis (85%).[12] This was in consonance with an earlier study by Albergaria A et al, which showed association between high NPI and lymph node involvement.[4] The findings of the present study were consistent with the studies by Kwatra et al, and Albergaria et al.[4,12] Histological grade provides important prognostic and management information.[5] It is extremely important to grade invasive breast carcinoma accurately. Modified Bloom and Richardson Grading System used to grade tumors measuring three parameters i.e. tubule formation, nuclear pleomorphism and mitotic rate.[13] In this study, the mean NPI scores in patients with grade I, II and III tumor were noted as 4.10 ± 1.07, 4.94 ± 0.95 and 5.36 ± 0.89 respectively showing significant increase in NPI score with increase in BR grade (p <0.050). These findings were consistent with a study by Kwatra et al, who reported that, the histological tumor grade, as defined by modified Bloom-Richardson grading system showed significant association with NPI.[12] Similar results have been found in earlier studies by Albergaria et al.[4] Other histological features like nuclear pleomorphism and presence of necrosis are also correlated with higher NPI. The findings of the present study were consistent with the studies by Kwatra et al, and Albergaria et al.[4,12]

ER PR status and NPI

In the present study the mean NPI scores in patients with ER-, PR- (4.91 ± 0.94) were slightly low compared to those who were ER+, PR+ (4.76 ± 1.19) but the difference was statistically not significant (p >0.050), suggesting lack of association between ER PR status and NPI scores. In contrast to these observations, Mudduwa et al, reported that the NPI correlated well with the hormone receptor status.[34] Zhen et al, found in his study that there is closely significant association between molecular subtypes and NPI in breast cancer.[35] The overall analysis in his study confirmed that the molecular subtype was significantly correlated with the traditional NPI score, indicating poor prognosis positively correlated to higher NPI score.

Nottingham prognostic index score

The NPI has been widely adopted as a prognostic tool in breast cancer.[36] It was constructed for patients with primary operable breast cancer. Based on three factors (tumor size, tumor grade, and stage of the disease), the index defined three subsets of patients with different chances of dying from breast cancer.[10] In the present study, the NPI score ranged between 2.4 to 6.9. The mean NPI score was found to be 4.90 ± 1.02. These findings were consistent with a study by Miller DV et al, and Foo CS et al, who reported mean NPI as 4.6 and 4.75 respectively which was slightly low but comparable to the present study.[37,38] Hamza et al, who reported a mean NPI of 5.3 ± 1.45 which was slightly higher than the present study.[11] 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 Lokuhetty et al, who reported moderate prognosis in 53.6% of the patients but good prognosis was seen in 26.7%, and poor prognosis in 19.7%.[39] In contrast to the observations of present study, Hamza et al, reported that, 48.0% of the patients had a poor prognostic index.[11] Another study by Ahmad et al, also reported that, majority of the cases (56.1%) had poor prognosis.[10] However, Galea et al, in their study also showed majority of the cases with good prognosis (54%).[40]

In this study, it was observed that NPI index increases with increase in tumor size, positive lymph nodes and BR grade (p<0.05), Ahmad et al, similarly reported a positive correlation between tumor size, positive lymph node and BR grade with NPI score, which was in accordance with a study conducted by Kwatra A et al, concluding that tumor size, positive lymph nodes and BR grade showed an increase with NPI.[10,37]

CONCLUSION

Author considered this study to be of immense significance even though it has a smaller size in contrast with the other studies. Foremost, 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. Next, every patient in the study was diagnosed and treated by a multidisciplinary team. Based on the result, author can advocate that NPI is an essential and valuable prognostic indicator, which should be incorporated in breast cancer reporting by the histopathologists and also primary tumor size, lymph node stage and histological grade which provides further guideline to treating clinicians to choose treatment modalities for the patient and in deciding to follow up plan as well.

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