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ORIGINAL ARTICLE

Relationship of Nottingham Prognostic Index with Prognostic Parameters of Breast Carcinoma

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ABSTRACT

Background: Breast cancer (BC) is the commonest malignancy in the female and it is gaining its significance due to worldwide rising incidence. It is also important due to 2.5% higher incidence in Pakistan as compared to neighbouring countries. Nottingham prognostic index (NPI) is an important prognostic factor of BC. It provides information about survival and morbidity. There are significant variations in different studies.
Aim: To carry out current study relating NPI with various histopathological parameters of BC.
Methods: This was a descriptive cross-sectional study. The study was done at the Department of Pathology, King Edward Medical University Lahore with the collaboration of four surgical units of Mayo Hospital Lahore from 2010 to 2019. Total 137 cases of breast carcinoma were included. Information about age, grade, primary tumor size, axillary lymph node status and stage was entered in the pre designed proforma. NPI was calculated as 0.2xtumor size(cm)+lymph node grade. NPI was scored as excellent, good, moderate and poor and its correlation was calculated against primary tumor size, lymph node grade, tumor grade and stage.
Results: We studied 137 cases of breast carcinoma with mean age 49.32±11.64 years. Mean NPI was 5.4±1.4 with range of 2.4 to 9.4. NPI scores in poor 65(47.4%) and moderate 61(44.5%) groups were significantly high as compared to good 10(7.3%) and excellent scores 1(0.7%). Most of the cases of poor NPI were in p T3 and p T4 whereas this was p T2 with moderate score. Poor score of NPI was significant in grade 3 which is in contrast to moderate score where grade 2 dominated the picture. Correlation of NPI with LNG was in favor of LNG 1 with good and moderate scores while LNG3 dominated in the poor group. In stage III, 49 cases (35.8%) were seen with poor score of NPI.
Conclusion: NPI is an important prognostic parameter and it can be studied with different histopathological parameters to see correlation between them. In the current study majority of the cases of NPI scored at poor and moderate levels. Correlation coefficient was linear, strong and positive especially with LNG. Mean NPI has ascending correlation with these parameters. Thus NPI can be used as a prognostic indicator when comparing with histopathological parameters of BC.
Keywords: Breast cancer, NPI, tumor grade, tumor stage, LNG

INTRODUCTION

Worldwide breast cancer (BC) is commonest in the females and it constitutes 23% of all malignancies and 41% of female cancer. According to WHO its incidence is on the rise in third world countries[1-2]. In Pakistan BC incidence is 1/9 in females this is 2.5 times higher than neighbouring countries of Iran and India[3] In other local studies it constitutes 38% and 45.9% of all cancers in females[4-5].

In developing countries BC is important because of younger age presentation, at higher stage and aggressive outcome which may be attributed to genetic and geographical variations. Mean age at presentation is 47±12, 47.57±12.02 while age ranges are 18-90 and 16-100 years.[2,6] BC peaks at 41-50(32%) and 40-49(60.3%) and 51-60(32.35%) years[7-9].

Invasive ductal carcinoma(IDC) is the commonest type of BC followed by Invasive lobular carcinoma(ILC) and others.[5] Different prognostic factors operates in BC which are tumor grade, stage, estrogen & progesterone receptors (ER&PR) and HER2 Neu. In different studies Nottingham Prognostic Index (NPI) was also used to predict possible outcome and clinical behaviour including the probability of mortality. NPI incorporates tumor grade, size and axillary lymph node metastases. Bloom Richerdson grading system is scored as grade 1, 2 and 3. Lymph node grade (LN) involvement is taken as 1= no lymph node positive, 2=1-3 lymph node positive and 3 =>3 lymph node positive. Tumor size is measured in centimeters. NPI is calculated as NPI=(0.2xtumor size(cm)+LN grade I,II,III+ tumor grade I,II,III). It is divided into three and in some studies into four prognostic groups as excellent ≤ 2.4, good >2.4 ≤ 3.4, moderate>3.4≤ 5.4, poor > 5.4. Different prognostic factors have been studied against NPI[10-11].

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In a local study by Farrukh Kamal and colleagues, significant numbers of cases 53.57% were of moderate NPI group followed by poor outcome as 35% and with good prognosis at 11.42%[12]. Almost similar trends with some variations were seen by a study in India with good, moderate and poor NPI groups indicating the outcomes results 14.7%, 60.29% and 25% respectively[9]. Yet another study from Morroco revealed some significant deviations and the NPI scores were good (5.1%), moderate (55.1%) and poor (39.8%)[11]. It is further to be mentioned that no significant of researches in Pakistan addressed the relationship of NPI scores with histomorphological parameters of BC.

Above researches showed significant variations. This necessitates to conduct a study relatively at large scale with NPI to see its relationship with morphological characters of breast carcinoma.

MATERIALS AND METHODS

This is a descriptive cross sectional study which was conducted in the department of pathology of King Edward Medical University with collaboration of general surgical units of Mayo Hospital Lahore. Ethical approval was granted by the secretary institutional review board. Non probability convenient sampling was used and 137 samples were incorporated in this research. Only modified radical mastectomy specimens fixed in 10% formalin were included in the study. Unfixed, patients less than 10 years of age and the specimens with history of neoadjuvant therapy were excluded.

Using computer software, records were retrieved and the information about age, diagnosis, prognostic factors including, grade, stage, p T(primary tumor), lymph node status and scoring of NPI were entered onto the proforma. SPSS version 22 was used for statistical analysis. Sample size of 137 cases was calculated taking confidence level at 95%, absolute precesion as 6% and prognosis of NPI score as 85%[10]. Quantitative variables like age

and NPI scores were calculated as mean±SD while qualitative variables LNG, tumor grade, stage and pT(primary tumor) were presented as frequencies and percentages. NPI scores were stratified against qualitative variables. Spearmann rank correlation and chi square tests were applied taking p value 0.05% as significant. Results thus obtained were compared with local and international studies.

RESULTS

NPI is an important prognostic indicator of breast carcinoma. Mean age was 49.32±11.64 years. Mean NPI was 5.4±1.4 with range of 2.4 to 9.4. Most of the NPI 65(47.4%) cases belonged to poor group followed by 61 cases(44.5%) in the moderate NPI category. Only 10(7.3%) cases were in the good NPI and unfortunately only 1(0.7%) was in the excellent NPI category. Significant numbers of p T3 and p T4 were seen in poor NPI score whereas in moderate NPI group p T2 dominated. Good and excellent NPI scores were unfortunately very few.(Table I). Correlation coefficient was positive and 0.237. We also studied NPI against breast carcinoma stage. In the poor NPI, 49(35.8%) were seen in stage III as compared to 14(10.2%) cases in stage II. This was reversed in moderate NPI where 43(31.4%) cases seen in stage II as compared to 17(12.4%) cases which were seen in stage III (Table II). Correlation coefficient was still strong and positive (0.463). Grade 3 was significant in poor category of NPI while grade 2 dominated in moderate NPI (Table IV). Correlation coefficient was 0.490 which is strong and positive. Same trend was seen in analysis of NPI against LNG however in the moderate group , majority cases were in grade 1 whereas in the poor group grade 3 outnumbered the others (Table V). Correlation coefficient was even more strong which was 0.663.

Mean NPI was seen in ascending order against tumor p T, tumor grade, stage and lymph node grade(Table III,VI). p value was less than 0.05 in all cases which is statistically significant.

Table I: Relationship of NPI with primary tumor

NPI			pT				Total
			T1	T2	T3	T4	
NPI	G	Count	2	4	1	3	10
		% of Total	1.5%	2.9%	0.7%	2.2%	7.3%
	M	Count	4	30	17	10	61
		% of Total	2.9%	21.9%	12.4%	7.3%	44.5%
	P	Count	1	19	22	23	65
		% of Total	0.7%	13.9%	16.1%	16.8%	47.4%
	E	Count	1	0	0	0	1
		% of Total	0.7%	0.0%	0.0%	0.0%	0.7%
Total		Count	8	53	40	36	137
		% of Total	5.8%	38.7%	29.2%	26.3%	100.0%

NPI=Nottingham prognostic index, p T= Primary Tumor, T= Tumor, G= Good, M=Moderate, P=Poor, E=Excellent

Table II: Correlation of Stage with NPI

NPI			Tumor Stage				Total
			I	II	III	IV	
NPI	G	Count	2	5	3	0	10
		% of Total	1.5%	3.6%	2.2%	0.0%	7.3%
	M	Count	1	43	17	0	61
		% of Total	0.7%	31.4%	12.4%	0.0%	44.5%
	P	Count	0	14	49	2	65
		% of Total	0.0%	10.2%	35.8%	1.5%	47.4%
	E	Count	1	0	0	0	1
		% of Total	0.7%	0.0%	0.0%	0.0%	0.7%
Total		Count	4	62	69	2	137
		% of Total	2.9%	45.3%	50.4%	1.5%	100.0%

NPI=Nottingham prognostic index, p T= Primary Tumor, T= Tumor, G= Good, M=Moderate, P=Poor, E=Excellent

Table III: Correlation of Primary tumor and stage with NPI

pT	Mean NPI	n	SD	Stage	Mean NPI	n	SD
T1	4.37	8	1.31	I	3.37	4	0.81
T2	4.77	53	1.08	II	4.65	62	1.02
T3	5.95	40	1.28	III	6.17	69	1.32
T4	6.03	36	1.62	IV	7.50	2	0.70

p T=Primary tumor, NPI=Nottingham prognostic index,
n=Number of patients, SD=Standard deviation

Table IV: Relationship of NPI with Tumor grade

NPI			Tumor Grade			Total
			G1	G2	G3	
NPI	G	Count	6	3	1	10
		% of Total	4.4%	2.2%	0.7%	7.3%
	M	Count	5	33	23	61
		% of Total	3.6%	24.1%	16.8%	44.5%
	P	Count	0	13	52	65
		% of Total	0.0%	9.5%	38.0%	47.4%
	E	Count	1	0	0	1
		% of Total	0.7%	0.0%	0.0%	0.7%
Total		Count	12	49	76	137
		% of Total	8.8%	35.8%	55.5%	100.0%

NPI: Nottingham prognostic index, G=Good, M=Moderate, P==Poor, E=Excellent
G=Grade

Table V: Relationship of NPI with lymph node grade

NPI			LNG			Total
			LN1	LN2	LN3	
NPI	G	Count	10	0	0	10
		% of Total	7.3%	0.0%	0.0%	7.3%
	M	Count	45	12	4	61
		% of Total	32.8%	8.8%	2.9%	44.5%
	P	Count	8	19	38	65
		% of Total	5.8%	13.9%	27.7%	47.4%
	E	Count	1	0	0	1
		% of Total	0.7%	0.0%	0.0%	0.7%
Total		Count	64	31	42	137
		% of Total	46.7%	22.6%	30.7%	100.0%

NPI=Nottingham prognostic index, LNG=Lymph node grade, G=Good, M=Moderate, P=Poor, E=Excellent, LN=Lymph node

Table VI: Correlation of tumor grade and LNG with NPI

Grade	Mean NPI	n	SD	LNG	Mean NPI	n	SD
G1	3.58	12	1.12	1	4.38	64	0.95
G2	4.73	49	0.99	2	5.51	31	0.65
G3	6.16	76	1.26	3	6.94	42	1.11

G=Grade, NPI=Nottingham prognostic index, LNG=Lymph node grade
SD=Standard deviation, n=Number of patients

Table VII: Comparison of NPI in different studies

NPI	Zaimi A[11]	Pradhan A et al[17]	Ahmad Z et al[18]	Gite K et al[16]	Kamal F at al[12]	Current study
Excellent	0.00%	6.45%	0.00%	0.00%	0.00%	0.7%
Good	5.1%	16.13%	2.8%	4.44%	11.42%	7.3%
Moderate	55.1%	61.29%	41.1%	46.66%	53.57%	44.5%
Poor	39.8%	16.13%	56.1%	48.88%	35%	47.4%

NPI=Nottingham Prognostic Index

DISCUSSION

Breast cancer is the most common cancer in the females and it constitute 38% of all female malignancies in Pakistan whereas in UK, Australia and United States it is 30%, 27% and 26%.[5] Different prognostic factors are used for BC including NPI which can be used to judge clinical aggressiveness.[10] NPI incorporates tumor stage in centimeter, grade and lymph node grade[13].

Current study showed significant high Mean NPI as 5.4±1.4 and the range was 2.4 to 9.4. This is in contrast to 2.3 to 7.2 with mean 4.7±1.2 in a study from Kwatra and associates[14]. Shukla A et al concluded NPI range 2.4 to 6.9 with mean 4.9±1.02 which is still low than ours.[10] Unfortunately we found significant numbers of poor (47.4%) and moderate (44.5%) groups of NPI whereas there were only 7.3% and 0.7% for good and excellent groups. Kwatra et al showed 54% cases in Moderate NPI while Shetty SM and associates in India noticed significant variation with 60.29%, 25% with moderate and poor NPI groups respectively. Good NPI was 14.7%[14,9]. In the same country another study revealed 12.5%, 58.3% and 29.2% as good, moderate and poor NPI which is again variation with respect to poor group[15]. Gite K et al came out with somewhat similar outcome like our study. Excellent, good, moderate and poor NPI groups resulted in 0%, 4.44%, 46.66% and 48.88%.[16] Table VII is showing some significant variation and similarities regarding NPI groups in different studies including the current one.

Above table shows important deviation from the study from Pradhan and associates with respect to moderate NPI whereas only 16.13% cases are in poor NPI group. Rest of the studies roughly parallels our study.

Ashish Shukla and associates compared tumor size, grade and lymph node involvement with NPI. He noticed increasing mean NPI score just like our case with ascending p T, tumor grade and lymph node involved. p value was less than 0.05% in both cases which is statistically significant. However frequency of NPI was quite variable with 64% and 32% cases against moderate and poor NPI groups in his study as compared to our 44.5% and 47.4%.[10] This could be due to some environmental and genetic variations. Kwatra et al also noticed significant correlation with ascending trend against grade, lymph node status and stage of the tumor.[14] Pradhan A et al also found statistically significant correlation between tumor size and NPI which is consistent with our finding.[17]

Strong correlations coefficients were noticed by Winzer and associates between NPI and tumor grade(0.70), no. of positive lymph nodes(0.71) and tumor size(0.59).[19] These findings are consistent and even more stronger than our results. Gite K et al also found strong but negative correlation coefficient between NPI and tumor grade which is further validating current research.[16]

Conclusion: Current research showed higher NPI against BC and unfortunately more numbers are seen in poor NPI group. Ascending trends of mean NPI were seen against p T, grade, stage and LNG which are statistically significant. It also concluded that NPI has strong and positive correlation coefficient with these parameters. We found some significant deviations regarding mean NPI when comparing other local and international studies which might be attributed to environmental and genetic variations. Further we recommend NPI scores to be studied against other variables like age, menopausal status, hormone receptors, skin and lymphovascular invasion.

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