Original Article

Grading, staging and Nottingham prognostic index scoring of breast carcinoma

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ABSTRACT

Background: Breast carcinoma is the most frequent malignant tumor in women accounting for approximately 15% of female cancer deaths. It is the second most common malignancy among women in Nepal. Our objectives were to study the extent and spread of different histological types breast carcinoma in the eastern region of Nepal, to grade and stage the tumors, score the prognosis.

Materials and methods: A cross-sectional descriptive study of mastectomy specimens with axillary lymph node sampling was done for a period of two years. Diagnosis was done using WHO classification. Modified Bloom Richardson score and TNM system was used to grade and stage the tumors. Nottingham Prognostic index was applied to score the prognosis.

Results: Out of 31 total cases, the most common histologic type was Invasive Carcinoma of No Special Type (67.74%). The largest tumor size was of 12cm which had poor NPI score. Most tumors were of grade II and T2. Out of 30 cases with lymph nodes, 13 were negative for metastasis pN0, 10 were pN1 and 7 were pN2. Extranodal spread was observed in 6 out of 17 cases with lymph node metastasis and was associated with higher grades and poor prognosis.

Conclusion: Higher grade tumors, lymph node metastasis and extranodal extension are associated with higher Nottingham Prognostic Index score.

INTRODUCTION

Breast carcinoma is the most frequent malignant tumor in women accounting for approximately 15% of female cancer

deaths. It is the leading cause of death in women aged 44-50 years. More than 1,000,000 cases occur worldwide annually. The incidence is high in North America and Northern Europe but low in most Asian and African countries.[1,2]

In Nepal, breast cancer is the second most common malignancy among women.[3,4] Widespread use of mammography has led to a sharp increase in the detection

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Table 1: Histologic types of Breast Carcinoma, age range and size of the tumors.

Histologic Type	No. of Cases	%	Age in years		Size of the tumor (cm)	
			Range	Mean	Range	Mean
Invasive Carcinoma of No Special Type (NST)	21	67.74	30-70	48.95	1.2-6.5	
Pleomorphic Lobular Carcinoma	1	3.23	56	56	4	4
Mucinous Carcinoma	1	3.23	70	70	1.5	1.5
Carcinoma with Medullary features	5	16.13	25-50	39	2.5-12	6.1
Carcinoma with apocrine differentiation	2	6.45	55-75	65	2.1-4	3
Intracystic Papillary Carcinoma	1	3.23	60	60	2.5	2.5

Table 2: Modified Bloom Richardson Grading scores in the study population

Modified Bloom Richardson Grade	No. of Cases	%
I	11	35.48
II	12	38.71
III	8	25.81
Total	**31**	**100**

of the breast cancer in the United States.[1,5] In Nepal, due to lack of awareness and limited facility of mammography, the detection of breast cancer is less at early stage.[4] Ignorance and reluctance in self-examination of breast lumps leads to the presentation of breast cancer at a later stage.[3] Breast cancer is more than 200 times more common in women than in men.

Breast examination, by the patients herself or by the clinician, is a very useful method of detection of palpable breast lumps. However, for non-palpable lumps, mammography has radically changed the diagnostic approach to breast cancer as only 60% of the tumors detected by mammography are palpable.[1]

Breast cancer is a heterogeneous disease with varying degree of microscopic types and has varying molecular behavior. This leads to variation in the response to treatment by different types of breast cancer. The prognosis of breast carcinoma is dependent on numerous clinicopathological factors including patient's age, types of gene mutation, presence of hormone receptors, size and type of the tumor, lymphovascular invasion, tumor necrosis, local invasion, metastasis, cytoarchitectural pattern, microscopic grade and many more. Histopathology has been a gold standard not only for the diagnosis of breast cancer but has also played a very important role as traditional prognostic factor. With the advent of vast majority of therapeutic strategies for breast cancer, it is important to identify the prognosis of the patient.[6]

Tumor size estimation provides prognostic information. It is incorporated in Nottingham Prognostic Index along with

other variables. It is used in TNM staging as categorical variable.[6] Lymph node status is one of the most important prognostic parameters for operable breast cancers. Lymph node staging is one of the variables used in Nottingham prognostic index as well as in TNM staging system.

One of the powerful prognostic indicators is the histologic grading. Nottingham modification of Bloom Richardson grading system has been widely used for histologic grading of breast carcinoma. It is based on the cytoarchitectural pattern and the proliferative index of the tumor. Glandular or tubular formation by the tumor cells is the first component of Nottingham modification of Bloom Richardson grading system which reflects the architectural pattern indicating the degree of differentiation of the tumors cells towards normal breast ducts and lobules.[6] Nuclear pleomorphism is the second component assessed which indicates the cytomorphology of the tumors cells. The third component assessed is the number of mitotic figures which is a measure of proliferation of tumor cells.

Amongst the various prognostic factors, the three strongest determinants in breast cancer are primary tumor size, lymph node stage and histological grade.[5] Hence, it is important to incorporate all the three prognostic parameters mentioned above on receiving mastectomy specimens and report it.[5]

There are various histologic types of breast carcinoma having their own prognostic significance. The most commonly used classification of breast cancer is of World Health Organization (WHO).The pathology report serves as a hard copy for clinicians on which various treatment modalities are based.

The aim of this study was to classify the various types of breast carcinoma in our institute and to use the traditional prognostic factors for assessment of prognosis for our patients as we don't have the facilities to assess the molecular prognostic factors. It is equally important to know the staging of the tumor.

MATERIALS AND METHODS

All the mastectomy specimens with axillary lymph node

Table 3: Association between tumor size and Nottingham Prognostic Index

	Size of tumor grossly (cm)				
NPI	Mean	N	Std. Deviation	Grouped Median	P value
0	2.000	2	.7071	2.000	
1	2.500	4	.6880	2.250	
2	4.195	19	1.6811	4.167	0.048
3	5.917	6	3.7204	5.250	
Total	**4.168**	**31**	**2.3158**	**3.714**	

Table 4: Association between tumor size and ECM

	Size of tumor (cm)				
Extranodal extension	Mean	N	Std. Deviation	Grouped Median	P value
0	3.779	24	2.3298	3.100	
1	5.500	6	2.0000	5.125	0.035
Total	4.123	30	2.3419	3.643	

Table 5: Association between ECM and number of positive lymph nodes

			Extranodal extension		Total	P value
			0	1		
No of positive nodes	≤4	Count (%)	24 (96.0%)	1 (4.0%)	25 (100.0%)	
	>4	Count (%)	1 (16.7%)	5 (83.3%)	6 (100.0%)	<0.001
Total		**Count (%)**	**25 (80.6%)**	**6 (19.4%)**	**31 (100.0%)**	

sampling submitted in the Department of Pathology during a period of two years was included in the study. The study was conducted from August, 2012 to July, 2014.

The specimens were fixed in 10% buffered formalin for overnight. Next day, the specimen was grossed and 5mm thin representative sections were submitted according to established protocols. Dehydration was carried out in ascending concentrations of ethanol; clearing was done in xylene and impregnation in paraffin wax. Tissue blocks were prepared and 5um thin sections were cut using rotary microtome and the slides were stained with haematoxylin and eosin and studied under microscope.

Histologic classification of tumors was done according to World Health Organization (WHO). Histologic grading of the tumors was done by Nottingham modification of Scarff-bloom-Richardson-Method. Staging was based on the TNM system adopted by both the International Union against cancer (UICC) and the American Joint Commission on Cancer Staging and End Results Reporting (AJC). Nottingham Prognostic Index was used to score the prognosis of the patient.

Collected data were entered in Microsoft Excel 2000 and converted it into SPSS PC+ 11.5 Version for statistical analysis. The descriptive statistics were presented in percentage, proportion, tabular forms and mean and standard deviation were calculated. For inferential statistics

odds ratio, chi square test with p-values were calculated at the level of significant at 95%, to find out the relationship between dependent variables and independent variables.

RESULTS

There were a total of 31 cases of breast carcinoma during the study period of two years.

Age distribution: The age of the patients ranged from 25-70 years with a mean age of 49.83 year (Table no. 1). Majority of carcinomas were seen in two peaks. The first peak was seen in 51-60 years of age followed by the second peak in 31-40 years of age.

The youngest patient was of 25 years with a case of carcinoma with medullary features. Cases of invasive carcinoma of no special type (NST), mucinous carcinoma and carcinoma with apocrine differentiation showed patients with older age groups. The oldest patient was of 75 years and was seen in case of apocrine carcinoma. Table no.1.

Involvement of side: Out of 31 cases, 15 cases showed involvement of right breast, while 16 cases showed left breast involvement.

Tumor size: Size of tumor ranged from 1.2cm to 12 cm in diameter. The smallest tumor of 1.2cm was seen in case of invasive carcinoma of NST. The largest tumor was of
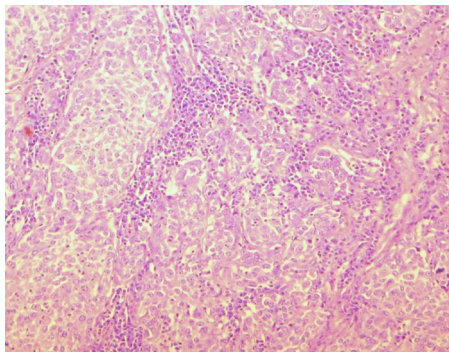
Figure 1: Carcinoma with medullary features revealing syntytial arrangement of tumor cells with prominent lymphoplasmacytic infiltration (HE stain, x40).
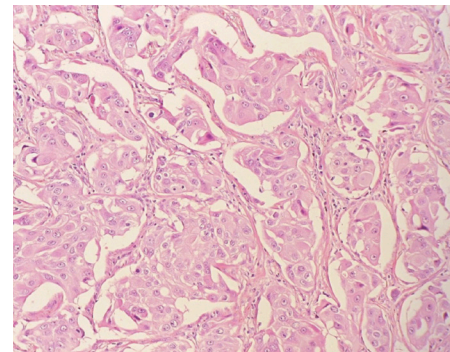
12cm and was seen in a case of carcinoma with medullary features. (Table 1)

Microscopic types: The most common type of breast carcinoma seen in our study was of invasive carcinoma of NST (21cases; 67.74%). This was followed by 5 cases (16.13%) of carcinoma with medullary features (fig.1). There were two cases (6.45%) of carcinoma with apocrine differentiation (fig.2) and one each (3.23%) of pleomorphic lobular carcinoma, mucinous carcinoma (fig.3) and intracystic papillary carcinoma. (Table 1)

12 out of 31 cases showed grade II score of Nottingham modification of Bloom Richardson system. Grade I was seen in 11cases and grade III in 8cases. (Table 2)

Nottingham Prognostic Index: Out of 31 cases, majority of them (19 cases; 61.29%) had moderate prognosis. Good and poor prognoses were seen in 5 cases (16.13%) each. There were two cases (6.45%) having excellent prognosis.

Lymph node involvement: Out of 31 specimens of mastectomy with axillary lymph nodes, only 17 cases showed lymph node metastasis. The size of dissected lymph nodes ranged from 0.2-2.8cm in diameter. The highest number of positive lymph nodes was 9. Extranodal spread or extracapsular metastasis (ECM) was observed in 6 out of 17 cases with nodal metastasis.

TNM Staging: The tumors were categorized according to TNM staging adopted by both the International Union against cancer (UICC) and the American Joint Commission on Cancer Staging and End Results Reporting (AJCC).

Primary tumor size (T): Majority of the cases (17) were in T2, followed by 8 cases in T3. There were 3 cases each in T1 and T4.

Pathological Lymph node metastasis (pN): Out of 31 cases, 14 were in pN0, 10 were in pN1, 7 were in pN2 and none were in pN3 stage. None of the cases showed distant metastasis (M0).

Figure 2: Carcinoma with apocrine differentiation showing cells having enlarged nuclei, prominent nucleoli and abundant eosinophilic cytoplasm (HE stain, x100).
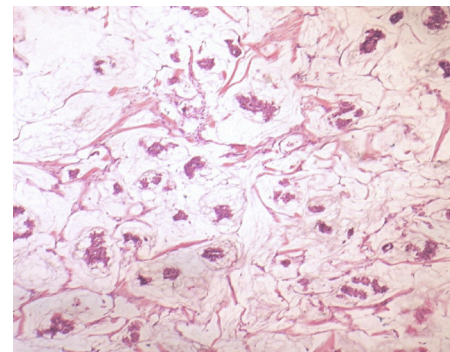

Figure 3: Mucinous carcinoma showing few clusters of carcinoma cells floating in lakes of abundant mucin (HE stain, x40).

No statistical significant association was seen between tumor size and microscopic grading (p=0.544) or between tumor size and number of positive lymph nodes (p=0.331). (Table 3) But a statistically significant association was observed between tumor size and NPI (p=0.048) and also between tumor size and ECM (0.035). (Table 3 & 4). Association between extracapsular metastasis (ECM) and microscopic grade (p=0.358) as well as between ECM and NPI (p=0.069) was non-significant statistically. But a statistically significant association was observed between ECM and number of positive lymph nodes (p=<0.001). (Table 5) Tumor necrosis was present in 15 out of 31 cases (48.38%). Vascular invasion was observed in 13 out of 31 cases (42%). There was a non-significant statistical association between tumor necrosis and microscopic grade (p=0.072). Similarly, association between tumor necrosis and NPI was also statistically non-significant (p=1.00).

DISCUSSION

Breast cancer is the most common carcinoma in women accounting for 23% of all cancers in women.[2] Though there is a lack of population based cancer registry system in Nepal, hospital based cancer registry published by Pradhanaga et al[7] revealed breast cancer as the second commonest cancer among Nepalese women after cervical cancer.

Breast cancer education, screening and breast examination by the patient herself or by the clinician are primary factors for detection of breast cancer.[3] Reluctance to self-examination and limited facilities of mammographic screening are the key factors leading to late detection of breast cancer in Nepal. A study conducted by Shrestha K[8] on breast cancer knowledge and screening practice among women visiting KIST medical college has revealed that 70% of women were unaware of breast cancer.

There were a total of 31 cases of breast cancer during a period of two years of our study period. The age ranged from 25-75 years with a mean age of 49.83 years which is very similar to study conducted by Ahmad et al where the age range was from 22-75 years with mean age of 47 years.[5] Similarly, in studies conducted Khan GM et al[9] and Jha AK et al[10] the mean age was 47.6 years and 47.30 years respectively. The age ranged from 50-59 years in a study conducted by Khan S at Nepalgunj Medical College.[4]

The tumor size ranged from 1.2cm to 12 cm in diameter in our study. The smallest tumor size was seen in a case of invasive carcinoma of NST and the largest tumor was seen in a case of carcinoma with medullary differentiation. In the study conducted by Ahmad et al[5], the size of tumor ranged from 1-13cm in diameter which is very close to our study. Tumor size is an important independent variable for prognostication. It has been incorporated in the Nottingham prognostic index and in TNM staging system.[6]

The microscopic types of breast carcinoma were classified according to WHO classification of breast cancer. The most common type found in our study was invasive carcinoma of NST which is in concordance with the literatures.[1,2,6,11] Similar result was seen in other studies.[5]

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 EA demonstrated that grade is an important determinant of breast cancer outcome and complimentary to lymph node (LN) stage.[12] However, the reproducibility of histologic grading has been questioned earlier[13] and studies have been conducted to demonstrate reproducibility.[14,15]

Microscopic grading system was first introduced by Greenhough in 1925. Since then, the grading system has been revised by many authors over a period of years. The adopted system now widely used in the Nottingham modification of Scarff-Bloom-Richardson system. It uses three components: tubular or glandular differentiation, nuclear pleomorphism and mitotic rate. The first component, tubular or glandular differentiation reflects degree of tumor differentiation and resemblance to the normal glandular tissue of breast. The second component, nuclear pleomorphism reflects the morphology of the tumor cells. The last component, mitotic count reflects the proliferative activity of the tumor cells.

Out of 31 cases, majority of the cases (38.71%) were grade II, 35.48% were grade I and 25.81% were grade III. Ahmad et al also demonstrated majority of the cases were grade II (75.83%).[5]

Nottingham prognostic index is widely accepted prognostic index which is a combination of various individual powerful prognostic variables. It was developed through multivariate analysis of a wide range of prognostic variables including time-dependent and biologic variables.[6,13] It is a combination of three strong individual prognostic factors; tumor size, lymph node stage and microscopic grade. NPI is used for stratification of patients for systemic therapy. It is based on traditional prognostic factors so it can be used easily on routine histologic sections.[6]

In our study, majority of the cases (61.29%) had moderate prognosis. In the study conducted by Ahmad et al, majority of the cases (56.1%) had poor prognosis. Galea MH et al in their study showed majority of the cases with good prognosis (54%).[16] Various studies have demonstrated that gene expression profiling can complement the classical NPI.[12,17] Study conducted by Kurshumliu F et al demonstrated that the original three-tiered NPI statistically correlates with the expression of prognostic immunohistochemical markers in breast carcinoma of NST.[18] Study conducted by Belle VV et al demonstrated increased 5-year prognostic accuracy by the addition of progesterone receptor and human epidermal growth factor receptor 2 (HER 2).[19] Tripple negative breast cancer (TNBC) is a clinicopathological classification which identifies a group of breast cancer with aggressive behavior and NPI is a truthful diagnostic tool in TNBC.[20]

Studies have shown that tumor size is an important and powerful prognostic factor and is associated with increased likelihood of lymph node metastasis.[20] However, our study could not demonstrate a statistical association between the two. But a statistically significant association was observed between tumor size and NPI (p=0.048) and also between tumor size and ECM (0.035).

According to TNM staging, majority of the tumors (54.84%) in our study were T2, i, e, size of the tumors was greater than 2cm but smaller than 5cm. 25.81% of the tumor were T3 with size greater than 5cm. 9.68% of the tumors were equally distributed in T1 and T4. T1 is tumor size less than 2cm and T4 means any size of the tumor but with extension to the overlying skin with ulceration.

Lymph node is one of the powerful prognostic factors. Out of 31 cases in our study, only 14 cases were pN0 as they did not show axillary lymph node metastasis.[10] cases were pN1 with metastasis in 1-3 axillary lymph nodes.[7] cases were pN2 with metastasis in 4-9 axillary lymph nodes. pN3 with metastasis in 10 or more axillary lymph nodes were not observed in our study.

Extra capsular metastasis (ECM) or extranodal extension

of tumor was observed in 6 out of 17 positive axillary lymph nodes. A statistically significant association was observed between ECM and number of positive lymph nodes (p=<0.001) in our study. It also showed a statistically significant association of ECM and tumor size (0.035). However, association between ECM and microscopic grade (p=0.358) as well as between ECM and NPI (p=0.069) was non-significant statistically.

CONCLUSION

This study was conducted with an aim to find out various types of breast carcinoma in the eastern region of Nepal and to use the traditional prognostic factors for assessment of prognosis for our patients. The most common type of breast carcinoma was of invasive carcinoma of NST. Most of the cases showed score of II of Nottingham modification of Bloom Richardson system, majority had moderate Nottingham prognostic index and were in T2 pN0. We could like to conclude by stressing on the importance to incorporate the three strongest determinants in breast cancer; primary tumor size, lymph node stage and histological grade while reporting breast carcinoma as the pathology report serves as a hard copy for clinicians to decide treatment modalities for the patient and in follow up as well.

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