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Zubair Ahmad

Aga Khan University, zubair.ahmad@aku.edu

Amna Khurshid

Aga Khan University

Asim Qureshi

Aga Khan University

Romana Idress

Aga Khan University, romana.idress@aku.edu

Nasira Asghar

Aga Khan University

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Authors

Zubair Ahmad, Amna Khurshid, Asim Qureshi, Romana Idress, Nasira Asghar, and Naila Kayani Naila Kayani



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Breast carcinoma grading, estimation of tumor size, axillary lymph node status, staging, and nottingham prognostic index scoring on mastectomy specimens

[Zubair Ahmad](#), [Amna Khurshid](#), [Asim Qureshi](#), [Romana Idress](#), [Nasira Asghar](#), [Naila Kayani](#)

Department of Pathology and Microbiology, The Aga Khan University, Hospital, Karachi, Pakistan

Click [here](#) for correspondence address and email

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Abstract

Introduction: Breast carcinoma is the most common malignant tumor and the leading cause of cancer death in women. In western countries, a sharp increase in the detection of breast carcinoma, largely due to widespread use of mammography, has recently led to a fall in breast cancer mortality. This, however, is not true for less developed countries, in which mortality continues to rise. **Objective:** The aim of this study was to acquire information about the extent and spread of breast carcinoma in our patients by grading the tumors, determining the tumor size, and axillary lymph node status, staging of the tumors and Nottingham Prognostic Index (NPI) scoring on the available material. **Materials and Methods:** One hundred and twenty consecutive mastectomy specimens with axillary lymph node sampling removed for breast carcinoma and received in the section of histopathology, Aga Khan University, in the year 2005, were included in the study. Standard protocols were used for the processing of the specimens, and reporting was done using a standard format incorporating all relevant tumor parameters. NPI was applied to the cases. **Results:** Out of the 120 cases, 5 (4.17) were grade 1, 91 (75.83) were grade 2, and 24 (20%) were grade 3. Also, 9 cases (7.5%) were T1 (4 were T1b, and 5 were T1c); 53 (44.16%) were T2; 50 (41.66%) were T3; and 8 (6.66%) were T4. Axillary lymph nodes were available in 107 cases. In 13 cases, no lymph nodes were recovered. Out of 107 cases 27 (25.23%) lymph nodes were negative for metastases pN0; 29 (27.10%) cases were pN1; 26 (24.30) were pN2; and 25 cases (23.36%) were pN3. Extranodal spread was present in 56 (70%) out of the 80 cases in which lymph nodes were positive. The average microscopic size of nodal metastasis was 1.7 cms. Significant statistical association was found between the number of positive nodes and perinodal extension ($P = 0.001$). Tumor necrosis was present in 76 out of 120 cases (63.33%). Vascular invasion was present in 43 out of 120 cases (35.83%). NPI scores were greater than 5.4 in 60 out of 107 cases (56.1%) indicating poor prognosis. **Conclusion:** The large majority of the cases were grade 2 tumors. Most cases (all grades) were T2 or T3, and were axillary lymph node positive. Large majority of cases with nodal metastases showed extra nodal spread. The majority of patients had NPI scores greater than 5.4 indicating poor prognosis. Significant statistical association was found between the number of positive nodes and perinodal extension ($P = 0.001$). The findings show extensive and advanced disease trends in our patients.

Keywords: Breast carcinoma, mastectomy, tumor size, grade, axillary lymph node status, stage, Nottingham Prognostic Index

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Introduction

Carcinoma of the breast is the most common malignant tumor and the most common cause of death from carcinoma in females. [1] In the West, widespread use of mammography has resulted in a marked increase in early detection of this carcinoma, when it is still localized and small in size. [2] As a result of early detection and improvement in therapy, breast carcinoma mortality is now beginning to fall. [3] This, however, unfortunately is not the case for developing countries in which breast cancer mortality is still rising. [4]

The therapy for carcinoma of the breast includes surgery (mainly mastectomy along with axillary lymph node sampling) hormonal therapy and chemotherapy [5] depending on the extent of the disease.

The most important morphologic prognostic factors in invasive carcinoma of breast include size of the primary tumor, microscopic grade, axillary lymph node metastases, blood and lymph vessel emboli, tumor necrosis, skin invasion, and nipple invasion.

Thus, a pathologist on receiving a mastectomy specimen must report all the above mentioned parameters, in order to provide adequate information to the clinician. The aim of this study was to acquire information about the extent and spread of invasive breast carcinoma in our patients, by incorporating all the important prognostic factors mentioned above, and to see how extensive and advanced the disease is in our population. The Nottingham Prognostic Index (NPI) [6] was constructed for patients with primary, operable breast cancer. We also applied the NPI in our cases to get an idea of the position of females suffering from breast cancer in our population stand in terms of chances of cure following mastectomy.

Materials and Methods

A total of 120 consecutive mastectomy specimens, received in the Section of Histopathology of a major referral center during the year 2005, were included in the study. All specimens were fixed in 10% buffered formalin and allowed to stay overnight. Specimens were grossed the next day, and representative sections were submitted according to established protocols. The sections were processed under standardized conditions for paraffin embedding. Section were then cut, and stained with Hematoxylin and Eosin using standard procedures. The reporting was done using a standard format incorporating all relevant tumor parameters. Grading and staging were done according to the Nottingham modification of the Bloom and Richardson Grading System [7] and TNM staging system, [8],[9] respectively. Cases were scored according to the NPI.

Data was analyzed using SPSS version 14.0.

Results

Age range of the patients was between 22-75 years (mean age, 47 years). Out of the 120 cases, there were 113 cases of infiltrating ductal carcinoma, NOS. There were two cases of invasive papillary carcinoma, one case of metaplastic carcinoma, two cases of invasive lobular carcinoma (including one case of pleomorphic lobular carcinoma, and one case of mixed ductal and lobular carcinoma), and one case of apocrine carcinoma [Figure 1], [Figure 2], [Figure 3], [Figure 4].

The tumor size ranged from as large as 13 X 12 cm² to as small as 1 X 1 cm²; average tumor size was 5 X 4 cm².

Out of the 120 cases, five cases (4.17%) were grade 1, 91 (75.83%) were grade 2, and 24 (20%) were grade 3.

The staging of the tumors was done according to the TNM system. The results of the T and N components are given in [Table 1].

Out of the 80 cases in which axillary lymph nodes were positive for tumor, extranodal spread was present in 56 cases (70%). The average microscopic size of the largest lymph node metastasis was 1.7 cm² in the largest dimension.

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Tumor necrosis was present in 76 out of 120 cases (63.33%). Vascular invasion was present in 43 out of 120 cases (35.83%).

No statistically significant association was seen between tumor size and microscopic size of the largest lymph node metastasis ($P = 0.384$); or between size of the tumor and number of positive lymph nodes ($P = 0.314$). Similarly, there was no significant statistical correlation between tumor size and perinodal extension of metastatic tumor ($P = 0.310$); or between the number of positive nodes and the microscopic size of the largest node metastasis ($P = 0.085$). However, significant statistical association was found between the number of positive nodes and perinodal extension ($P = 0.001$).

NPI was applied to 107 cases (in which lymph nodes were present). The results are shown in the [Table 1].

Discussion

Cancer statistics of 2005 and 2006 [10],[11] compiled by the American cancer society, rated breast cancer as the most common cancer in females. Similarly, multiple studies done in Pakistan [12],[13],[14],[15] showed breast cancer to be the most common cancer in the females in India. One of these studies comprised 32% of all cancers in women. [12] A study conducted in our own department showed that breast cancer is the most common cancer comprising a staggering 33.5% of all cancers in the women, and dwarfing the next most common i.e., carcinoma of the oral cavity (7.06%). [16] Another study in our department showed that breast cancer is so common that the absolute number of cancers is greater in females than males in the fourth, fifth, and sixth decades. [17] These studies emphasized the importance of breast cancer as a leading cause of cancer morbidity and mortality in our population. As shown above, mortality from breast cancer in developing countries is still rising. [4]

Various studies have shown that the gross size of tumor is one of the most significant prognostic factors in breast carcinoma and there is increased incidence of axillary lymph node metastases and decreased survival with increasing size of the tumor. [18],[19] In our study, as shown in the results, most tumors were T2 (44.16%) or T3 (41.66%).

According to TNM staging system for breast carcinoma, [9] T2 are tumors greater than 2 cm² but not more than 5 cm² in greatest dimension; while T3 are tumors greater than 5 cm² in the greatest dimension. Only 7.5% tumors were T1 (i.e. tumors 2 cm² or less in the greatest dimension), while 6.66% were T4 (4.17% T4b and 2.5% T4d). T4b are tumors of any size with direct extension to the skin of breast causing ulceration; while T4d are inflammatory carcinoma, tumors of any size with dermal lymphatic permeation on microscopic examination (a sign of ominous prognosis). These results show that in the large majority of our patients, the tumors are already of large size when women first seek medical attention.

As shown in our results, axillary lymph nodes were positive in 80 out of 107 cases in which these were recovered i.e., 74.77%, while in 27 cases (25.23%), lymph nodes were negative for metastases. Of the 80 cases with positive lymph nodes: 27.10% were pN1a (metastasis in 1 to 3 axillary lymph nodes); 24.30% were pN2a (metastasis in 4 to 9 axillary lymph nodes); and 23.36% were pN3 (metastasis in 10 or more axillary lymph nodes). These results show that in the large majority of our cases, axillary lymph nodes are already positive for metastatic tumor when the patients first seek medical attention, and in fact, majority of patients with positive nodes have pN2 or pN3 disease. The positivity of axillary lymph nodes for metastases is one of the most important prognostic parameters in carcinoma of breast [20] with sharp differences in survival rates between those with negative and positive nodes. In addition, the absolute number of nodes involved, the presence or absence of extranodal spread, and the amount of carcinoma in the positive nodes (measured by the microscopic size of the largest nodal metastases) are also prognostically important with survival rates falling with increased number of nodes involved (less than 4 versus 4 or more), presence of extranodal spread and increased amount of tumor in positive nodes. [21],[22],[23],[24] In our study, extranodal spread was present in 56 out of 80 cases with axillary node metastases (70%), and the average microscopic size of largest lymph node metastases was 1.7 cm², which is quite significant. Again, these findings show that disease is already present in advanced stage in the majority of our patients when it first comes to clinical attention.

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. [25],[26]

Histologic grade has also been found to be useful predictor of prognosis in patients with different stages of disease especially among those with negative axillary lymph nodes. [26] It has been found to be significantly related not only to increased recurrence and death in breast carcinoma patients, 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. [27] For these reasons, accurate grading of invasive breast carcinomas is extremely important and our cases have been graded according to the modified Bloom and Richardson grading system [7] which measures three parameters i.e. tubule formation, nuclear pleomorphism, and mitotic rate. Each of these is given a score of 1 to 3; final grade is determined by adding scores of all three categories i.e., grade 1 (score 3-5), grade 2 (score 6 or 7), grade 3 (score 8 or 9).

In our study, as shown in the results, only 4.17% cases were grade 1, while the large majority were grade 2 (75.83%) or

grade 3 (20%). Among tumors of all histologic grades, the majority were T2 or T3 with positive axillary lymph nodes, and increasing number of positive nodes with high grade tumors. Similarly, perinodal extension was more commonly seen in the tumors of higher grades.

Tumor necrosis, especially when extensive, correlates with increased histologic grade, increased incidence of lymph node metastases and decreased survival rates. [28] It was present in a large percentage of our cases (63.33%).

Vascular invasion shows, according to several studies, a high correlation with grade of the tumor, tumor size, and lymph node status. [29],[30] It was also present in a significant percentage (35.83%) of our cases.

The NPI has been widely adopted as a prognostic tool in breast cancer. [6] 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. These three subsets are: good prognosis (score up to 3.4) comprising 29% patients with 80% five year survival; moderate prognosis (score 3.4 to 5.4) comprising 54% patients with 42% five year survival; and poor prognosis (score greater than 5.4) comprising 17% patients with 13% five year survival. [6] Various studies have shown its usefulness and utility in predicting outcome in treated patients with breast cancer. [31],[32],[33],[34] D' Eredita *et al.* [34] conclude that their improved survival rates may be attributed to the administration of adjuvant therapies to a larger number of patients after applying NPI. They argue that NPI allows them to accurately predict prognosis and recommend its more common use.

According to our results [Table 1], surprisingly, 56% patients are in the poor prognosis category with NPI scores greater than 5.4. Less than 3% are in the good prognosis category. This further emphasizes the advanced nature of disease and poor prognosis for this most common cancer in our population.

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Correspondence Address:

Zubair Ahmad

Department of Pathology and Microbiology, Aga Khan University, Hospital, Stadium Road, PO Box 3500, Karachi 74800

Pakistan

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