

A STUDY OF PROGNOSTIC MARKERS AND STAGE OF PRESENTATION OF BREAST CANCER IN SOUTHERN REGION OF KHYBER PAKHTUNKHWA, PAKISTAN

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ABSTRACT

Objective: To study prognostic markers and stage of breast cancer and their correlation, in patients of southern region of Khyber Pakhtunkhwa (KP).

Material and Methods: This study was done by retrospectively analyzing the data of all newly diagnosed patients of breast cancer registered from January 2006 till December 2008 at the Institute of Radiotherapy & Nuclear Medicine, Peshawar (IRNUM).

Results: There were 1358 new cases of primary breast cancer during the study period. The age range in these cases was 18-90 years with the median age group being in the 5th decade. From the available record of 933 cases, only 13.8% patients had grade I, 45.4% had grade II & 40.7% had grade III disease. Tumor size was documented in 923 cases. Among them, 42.45% had a T₃, 31.04% had a T₂ and 3.3% had a T₁ tumor. Stage of disease was documented in 1132 cases, of whom 38.8% had stage III, 33.7% had stage II, and 24.9% had stage IV disease. Only 2.7% were in stage I.

Conclusion: Patients with advanced stage of breast cancer have tumors of larger size and higher grade with extensive lymph node involvement. The majority of breast cancer patients in southern region of Khyber Pakhtunkhwa present with advanced disease. This translates into poor prognosis and outcome.

Key Words: Breast carcinoma, Tumor size, Grade, Lymph node status, Stage.

INTRODUCTION

Breast cancer is the most common cancer among women in both developed and developing countries^{1,2} is responsible for over a million of the estimated 10 million neoplasms diagnosed worldwide each year¹. Increasing incidence in low risk migrants (Asians) to high risk populations in USA can be accounted for by racial and genetic differences, cultural differences, as well as environmental exposures that vary throughout the world^{1,3,4}. Increasing trend of breast cancer in developing countries is mostly attributed to westernization of lifestyles¹. Carcinoma breast is also the most common cancer in the southern and northern regions of Pakistan (Karachi Tumor Registry and AFIP Tumor Registry). Data from the AFIP Tumor Registry showed 26% of all the malignancies to be breast cancer⁵. The important prognostic markers in invasive breast

cancer include size of the primary tumor, microscopic grade, axillary lymph node metastasis, skin and nipple invasion, vascular invasion and necrosis⁶. Treatment depends on these prognostic markers. This study was done to determine the prognostic markers and stage of breast cancer at presentation in patients of Southern region of Khyber Pakhtunkhwa (KP), and to correlate the two.

MATERIAL AND METHODS

This retrospective study was conducted by collecting data of all newly diagnosed patients of carcinoma breast registered from January 2006 to December 2008 at the Institute of Radiotherapy & Nuclear Medicine, Peshawar (IRNUM). This included both primary and metastatic cases. The patients registered at IRNUM belong to the Southern region of KP, FATA and also include Afghans. The variables recorded were age, gender, tumor size, tumor type, grade, lymph node & skin involvement and stage of the disease from the histopathological reports on a proforma. For all tumor characteristics, missing or unknown features were labeled as unknown for descriptive purposes and were excluded from further

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analysis. All male patients were also excluded from the study.

The histopathological reporting was done either locally, at Shaukat Khanum Memorial Hospital or Aga Khan Hospital, Karachi. Grading was according to the Nottingham Modified Bloom Richardson scoring system. Staging was done according to TNM classification system. Data interpretation was done using SPSS16.

RESULTS

The relevant tumor parameters were recorded from the histopathological reports in each case. During the 3 years study period 1358 newly diagnosed cases of primary breast cancer were registered. The age range was 18-90 years and the median age group was in the 5th decade. The highest number of cases (31.1%) were in their 5th decade, followed by 28.4% in their 4th, and 20.6% in their 6th decade. The majority of patients (51.1%) belonged to rural areas and 26.3% of the patients were from the Afghan community.

Tumor grade was documented in 933 cases. Only 13.8% patients had grade I, 45.4% grade II & 40.7% had grade III disease. The record of tumor size was available in 923 cases. The majority of patients (42.45%) had a T₃ tumor (size >5 cm) while 31.04% had a T₂ tumor (size 2-5 cm). Only 3.3% had a T₁ tumor (size <2 cm). Skin/muscle involvement was seen in 24.5% cases. There was no lymph node involvement (pN0) in 38.4% patients, while in 16.9% cases no lymph node was retrieved from the surgical specimen. Of the 607(44.7%) cases with lymph node involvement, 59% had pN1 lymph node status (1-3 positive lymph nodes), 23% had pN2 (4-8 positive lymph nodes) and 17.8% had a pN3 status (>8 positive lymph nodes). The record of stage was available in 1132 cases, of whom the maximum 38.8% were in stage III, followed by 33.7% in stage II and 24.9% in stage IV.

The majority of patients who belonged to stage III or IV of the disease had a tumor size of >5cm and quite a large number of patients showed skin and muscle involvement. A large number of patients who belonged to stage II had a tumor size of 2-5 cm. (Table 1). The majority of cases who had stage IV disease, had a grade II & III tumor. A large number of patients who had stage III of the disease, had grade III & II tumor. While the maximum patients who had stage II disease, had grade II tumors (Table 2). The majority of Stage III cases had metastasis involving either 4-8 or more than 8 lymph nodes. Paradoxically, a large number of stage IV patients had no lymph node metastasis. Patients with stage II mostly had 1-3 lymph node positive for metastatic disease. (Table 3).

Patients from rural areas mostly presented in stage III disease, followed by stage II & IV. This pattern was also seen among the Afghans. Patients from

Table 1: Size of tumor vs stage of tumor

Size of Tumor vs Stage of Tumor*				
Size of tumor	Stage of Tumor			
	Stage 1	Stage 2	Stage 3	Stage 4
	No. (%)	No. (%)	No. (%)	No. (%)
Upto 2cm	30(100)	24 (8.05)	4 (1.1)	—
2cm-5cm	—	149 (50)	67 (18.4)	35 (20.7)
>5cm (T3)	—	125 (41.9)	146 (40.1)	73 (43.2)
Any tumor size/muscle involvement (T4)	—	—	147 (40.4)	61(36.1)
Total	30 (100)	298 (100)	364 (100)	169 (100)

*Data of those patients in whom record of both tumor size and stage were available=861

Table 2: Grade of tumor vs stage of carcinoma breast

Grade vs Stage of tumor				
Grade	Stage of tumor			
	I	II	III	IV
	No. (%)	No. (%)	No. (%)	No. (%)
I	14(30.4)	54(18.5)	30 (9.7)	15 (10.2)
II	30(65.2)	147 (50.3)	130 (41.9)	74 (50.3)
III	2(4.4)	91 (31.2)	150 (48.4)	58 (39.5)
Total	46(100)	292(100)	310(100)	147(100)

Data of those patients in whom record of both stage and grade were available=795

Table 3: Lymph node metastasis vs Stage of Carcinoma breast

Lymph node metastasis Vs stage				
Number of Lymph node	Stage			
	Stage I	Stage II	Stage III	Stage IV
	No. (%)	No. (%)	No. (%)	No. (%)
1-3 (pN ₁)	0	134(78.8)	137(49.1)	57(52.3)
4-8(pN ₂)	0	20(11.8)	77(27.6)	30(27.5)
>8 (pN ₃)	0	15(8.8)	65(23.3)	22(20.2)
Total with positive lymph nodes	0(100)	170(100)	279(100)	109(100)
pN0	30 (100)	142(38.5)	100(23.3)	118(43.9)
Total cases with available record	30(100)	311(100)	379(100)	227(100)

Data of patients in whom both lymph node status and record of stage of the tumor were available = 947

urban areas mostly had stage II disease, followed by III & IV. The histopathological diagnosis in the majority (93%) was invasive ductal carcinoma. Lobular carcinoma was found in 2.7%, ductal carcinoma in situ (DCIS) in 1%, malignant phyllodes in 1% and sarcoma in 1.3%. The frequency of papillary carcinoma, malignant fibrous histiocytoma and non Hodgkins Lymphoma was 0.48- 0.5% each.

DISCUSSION

During the study period (2006-2008), 1358 new cases of primary breast cancer were registered at IRNUM. The age range was 18-90 years with a majority of patients 422 (31.1%) presenting in the 5th decade. This was followed by 384 (28.4%) patients in their 4th decade and 280 (20.6%) patients in their 6th decade. In the West, the median age at presentation is 61 years^{5,6}. The number of patients younger than 35 years was 258 (19.1%). Agarwal G⁷ has reported the proportion of young patients (< 35 years) to be 10% in developed nations and 25% in developing Asian countries. The same was reported in a study by Saba Sohail⁹. The U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) showed that black women had breast cancer at a younger mean age (57.6 years) than white women (62.6 years)⁸. A disproportionately high occurrence rate of breast cancer was found in immigrant Asian Indian/Pakistani women younger than 40 years and a lower percentage was found in the above 50 year age group. Young patients showed predominance for ER-negative breast cancers⁸. Bray F¹ reports the mean age at diagnosis in developing countries to be lower than European and American populations. The rapid rate of increase in breast cancer incidence before the age of menopause (40-50 years) subsequently slows down probably due to reduced levels of estrogen¹. These results correspond to our study but further studies are required to find out the reasons for increased incidence of carcinoma breast at a younger age in our population. The estrogen receptor status could not be assessed in our study and only 1.4% of the patients had a hormonal assay report.

These age-specific patterns may reflect differences in detection, but may be due to the differences of certain age-related exposures³. India, with a similar social and cultural background of a young age at first child birth and breast feeding practices, has an incidence rate lower than ours. This may be attributed to differences in genetic and dietary factors⁸. Our study showed that a majority of our patients have large tumors, mostly T₃, when they first seek medical advice. Large sized tumors and advanced stage disease are also seen in African American women at presentation⁶. Large tumors and advanced stage disease is common in women who use estrogen and progestins than those who do not⁷. The record of HRT use was not available in our study. Tumor size is one

of the important prognostic markers in breast carcinoma and there is an increased incidence of axillary lymph node metastasis in these patients⁶.

The reasons for late presentation or presentation when the tumor has attained a large size, are thought to be due to a number of reasons: ignorance, superstition, self-denial, fear of mastectomy, socioeconomic variables, cultural beliefs and unavailability of treatment facilities⁹⁻¹⁶.

When the grade was correlated with the stage of the disease, patients who had stage III disease, of them majority were of grade III & II tumors disease, while cases of stage II disease, the majority had grade II. Ahmad Z et al⁶ also reports an association between tumor grade and stage.

In our study, 607 (44.7%) patients had axillary lymph node metastases. The record may be incorrect as the possibility is that the lymph nodes were not recovered at the time of surgery, the pathologist did not look for them or the samples were of biopsy or lumpectomy. Only 724 (53.3%) out of 1358 cases had undergone a mastectomy. Among the patients with axillary lymph node metastases, 558 had undergone formal staging. Of these 558, the majority (50%) had stage III disease, 30.5% had stage II diseases and 19.5% had stage IV disease. The maximum number of positive lymph nodes i.e pN2 (4-8 positive lymph nodes) or pN3 (more than 8 positive lymph nodes) was seen in patients with stage III and IV disease. Patients with pN1 status (1-3 positive lymph nodes) mostly had stage II disease. (Table 3) It was also observed that higher grade and larger tumor size were associated with increased frequency of metastatic axillary lymph nodes. Axillary lymph node metastasis is one of the important prognostic markers in carcinoma breast influencing survival rate⁶.

Stage at diagnosis is critical in breast cancer since it is curable in early stages. Various studies have shown that Asian Indian/Pakistani women are diagnosed at a more advanced stage of breast cancer suggesting a need to raise awareness of screening in this ethnic group^{7,8,9,10}. In Pakistani females, breast cancer occurs at a younger age with patients having larger sized tumors at presentation with a greater frequency of metastasis to the axillary lymph nodes. The disease is predominantly a high grade invasive ductal carcinoma^{11,12,13,14}. This was also observed in our study. The majority (51.1%) of patients belonged to rural areas. Afghans constituted 26.3% (n=357) of the study group. They also have a lack of access to healthcare. These patients were seen to present with more advanced diseases compared to the urban population. The statement that women from a deprived background often present with advanced stage of the disease^{15,16} holds true in our study.

CONCLUSION

In our region, patients present with advanced breast cancer and the majority has bad prognostic signs. There is a definite correlation between the two. Unfortunately, we lack an organized approach to fight the commonest of malignancies. There is a need to carry out public awareness programs for regular self breast examination and advising yearly sonography for women under the age of 40 and mammography every second year for women above the age of 40 years.

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