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Patterns of Metastatic Breast Cancer in Punjab Pakistan

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ORIGINAL ARTICLE

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ABSTRACT

Background: Breast cancer is the most prevalent type of cancer worldwide. It is uncontrollable growth of breast tissues or cells. In Pakistan, breast cancer cases show an increased number of metastasis due to late detection of cancer. Unawareness and carelessness about symptoms are the main causes of worse outcomes.
Objective: To explore the metastatic patterns of breast cancer in patients from Punjab, Pakistan.
Methods: A total of 296 Breast Cancer patient's data were retrieved from Oncology Department INMOL Cancer Hospital Lahore from Feb. to Dec. 2019. Bloom-Richardson Histological grading systems were used for tumor grading. ER, PR, HER2/neu immunohistochemistry markers were evaluated. Correlations were assessed with different factors including patient sign & symptoms, SGTNM grading system, and ECOG score. SPSS was used to analyze data.
Results: Stage 2 and grade 2 depicted the highest expression of ER, PR and Her2neu in the correlation of breast cancer stages with cancer receptor biomarkers. In correlation of TNM with breast cancer stages, 40.6% of patients have large tumors at stage 2, and 60% of patients have more lymph nodes that contain cancers at stage 2. The significance level of ECOG and grades was 0.015 while of ECOG and stages was 0.002, which shows its significant statistical importance.
Conclusion: Breast cancer spreads and proliferates most in grade 2 or stage 2 and 3. During these stages, the proliferative receptors are overexpressed to support cancer spread, tumor size increases, lymph nodes swell up and metastasis is initiated.

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Introduction

Breast cancer is one of the leading causes of death in women around the world and is seconded by ovarian cancer. It can be defined as uncontrolled cell growth in the breast tissue of the individual leading to a tumor or lump formation in the mammary gland that can sometimes cause pain, swelling and a bloody discharge [1]. It is normally referred only to women, but breast cancer is also reported in males in some cases [2].

In Pakistan, the leading type of cancer is breast cancer, and it presents a very small survival rate percentage. The reason for this is that most women are either unaware of the illness or do not take the symptoms seriously [3]. Mostly the problem is tried to be cured by self-medication or use of homeopathic medicine. Only when the disease has progressed to an elevated extent, a doctor or physician is consulted. Due to this reason, the survival rate of breast cancer patients is quite low in Pakistan. The majority of patients of the cancer are detected in late stages and very rarely the disease is caught in early stage of cancer [4].

Metastasis is the term use in cancer when the cancer has grown to such an extent that cancer has started to spread to other organs of the body. In terms of breast cancer, the

metastasis commonly starts with spread of cancer to lymph nodes present in the underarm region and spread the cancer to the lungs. Lymph node metastasis is the most common metastasis initiation site in breast cancer. Pakistani patients show an increased number of metastasis cases due to late detection of cancer [5].

Breast cancer can be classified into 5 stages based on the severity and intensity of cancer. The stages are given Roman numeral numbers to classify them. Stage 0 indicates that the cancer is just initial, stages I & II indicate that the cancer has spread and is still localized in the breast tissue while stages III &IV indicate that the cancer has metastasized and has spread to other organs of the body [6].

The TNM system is a standard method for grading breast cancer based on tumor size (T), lymph node involvement (N), and metastasis (M). It assesses disease severity, aiding oncologists in treatment decisions. Another tool, the ECOG performance status, developed by the WHO and the Eastern Cooperative Oncology Group, evaluates a patient's fitness for treatments like chemotherapy or radiotherapy, which are crucial but often toxic [7]. Patients with grades 3-4 are typically deemed unfit for curative treatments but may qualify for palliative care. Grade 2 patients can usually tolerate toxic therapies, while grade 1 includes most surgical candidates, though the ECOG scale lacks precision in determining surgical eligibility. Breast cancer is highly heterogeneous, with subtypes based on histology, stage, grade, hormone receptor status, and gene expression. Histological analysis categorizes patients into groups based on overexpression of receptors such as ER, PR, and HER-2, with increased receptor overexpression linked to greater cancer severity and metastasis risk [8].

This study examines metastatic patterns in breast cancer patients from Punjab, Pakistan, correlating these patterns with TNM status, ECOG performance, and histological classifications. The analysis considers patients of varying ages and stages to identify factors driving metastasis initiation and progression.

Methods

A total of 296 Breast Cancer patient's data were retrieved from Oncology Department INMOL Cancer Hospital Lahore from February 2019 to December 2019. Demographic studies were done from patients' history file. Out of 296 cases, 106 cases were analyzed for further testing include Grading, Staging and Hormonal Studies by accessing Histopathological samples of these patients as these samples were managed only.

All samples were subjected for routine histological examination, were stained with Haematoxylin and Eosin (H and E) staining and were reported according to standard protocol. Bloom-Richardson Histological grading system were used for tumor grading. Apart from tumor tissue were taken for Immunohistochemistry by using Peroxidase- antiperoxidase (PAP) technique. A slice of tissue was taken on positively charged slides. Antigen retrieval was done using EDTA buffer solution of pH 9.0 was used for antigen retrieval and slides were stained with monoclonal antibodies obtained from 'BIOCARE' medical company. ER (clone EP1), PR (clone EP2), HER2/neu (clone EP3) immunohistochemistry markers were used. ER, PR positivity was interpreted and reported using Allred scoring system which takes into account both intensity of nuclear staining and proportion of immuno-positive tumor cells. ER, PR is considered to be positive if ≥1% of tumor cell nuclei are immunoreactive. HER2/neu positivity was interpreted and reported using ASCO 2007 guidelines (American Society of Cancer Oncology) which takes into account the cytoplasmic membrane staining and the proportion of immuno-positive tumor cells. The data were analyzed on SPSS version 21. Results were showed as percentage, minimum and maximum. The level of significance was measured by using Pearson Chi Square.

Results

Age groups correlation with symptoms

The patients were divided into 5 age groups and their physical symptoms such as redness, swelling, pain and discharge were observed. Patients of age 20-30 were placed in group 1, 30-40 were placed in group 2, 40-50 were placed in group 3, 50-60 were placed in group 4 and 60-70 years of age patients were placed in group 5.

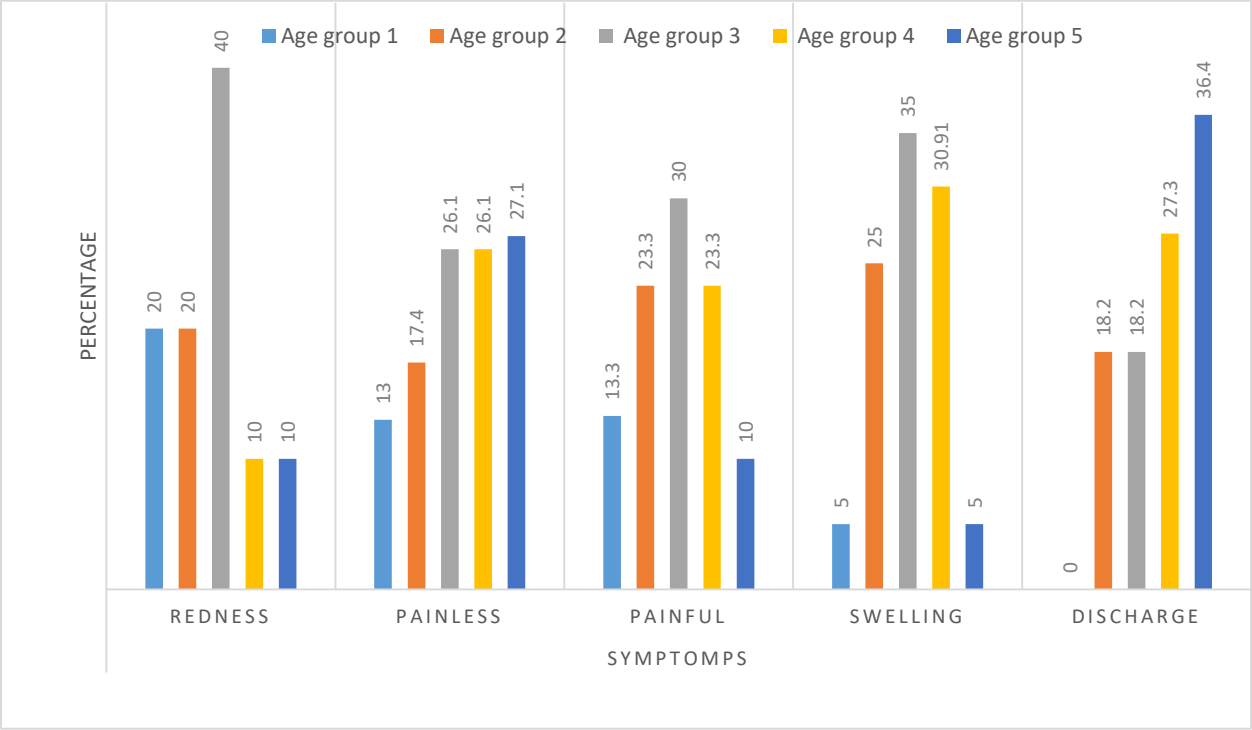


Figure 1: Descriptive graph of correlation of age with physical symptoms

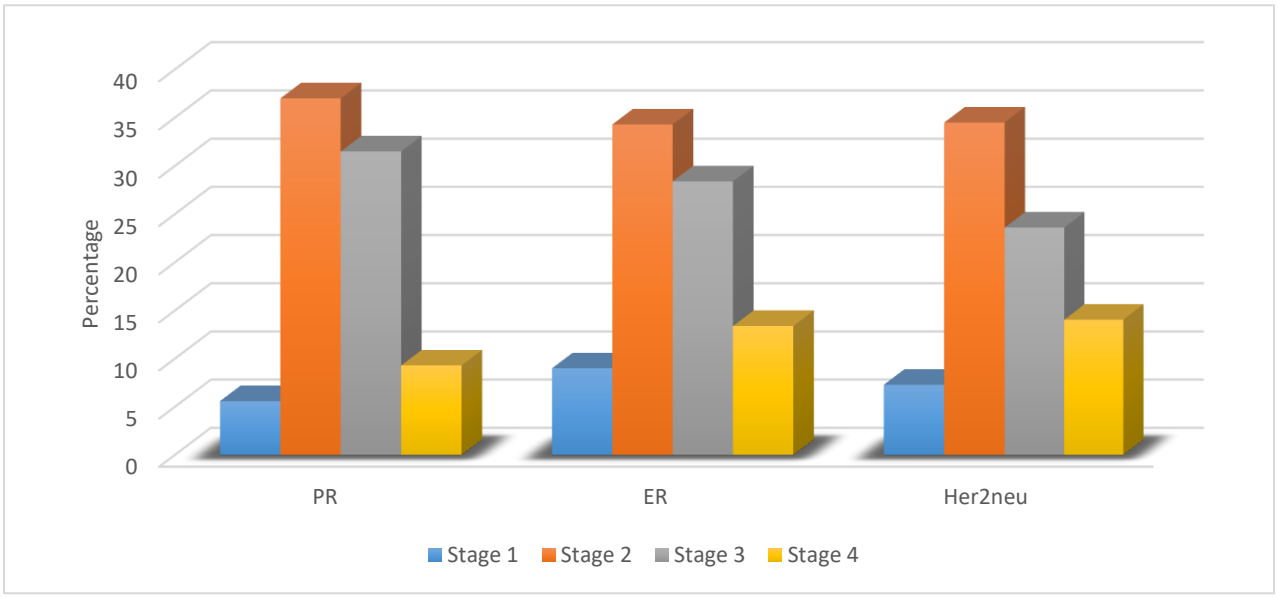


Figure 2: Expression of PR, ER and HER2 in stage 2 as compared to rest of the stages

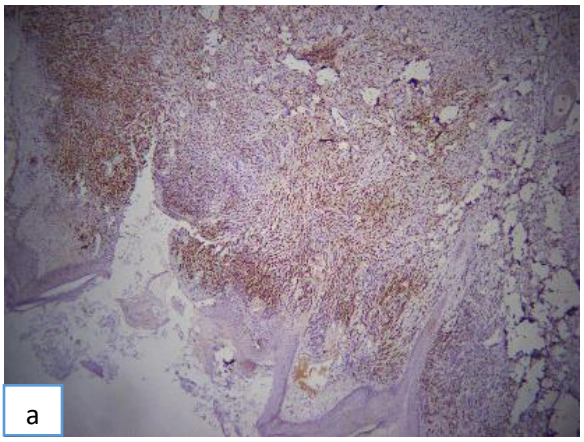
Of the 106 cancer patients, 40% of have more redness at age group 3. 26.1% of patients have painless symptoms at age group 2 and 3 as compared to other groups whereas belongs to age group bears 30% more pain rather than any other age group. Age group 3 patients have 35% more swelling but age group 5 shows 36.4% more discharge than any other group as shown in Figure 1.

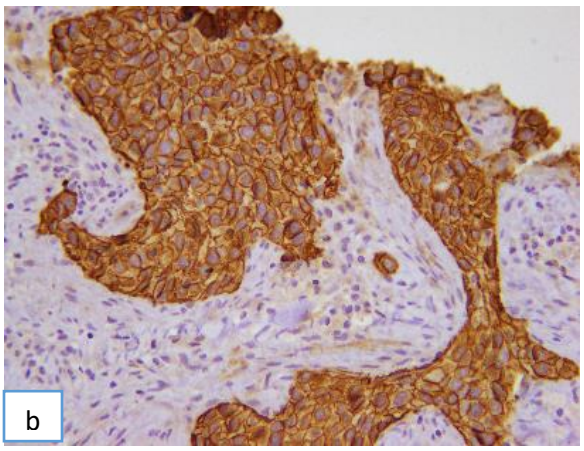
Correlation of stages of breast cancer with cancer receptor biomarkers

The level of Estrogen receptor (ER|), Progesterone receptor (PR) and epidermal growth factor receptor 2(HER2) receptor in cancer patients of different stages were checked to see the impact of overexpression of these receptors with the disease prognosis. Of the 106 cancer patients, 37% of patients have more PR expression level at stage 2. 34.3% of patients have more ER expression level at same stage as the PR and 34.5% patient's shows maximum Her2nue expression level at stage 2 as compared to other groups. As shown in Figure 2.

Immunohistochemical analysis of tumor samples for receptor identification

This analysis could be best explained in Figure 3. As a part showing cancer tissue sample positive for ER receptor expression, b part showing cancer tissue sample positive for PR receptor expression and c part showing cancer tissue sample positive for HER-2 receptor expression.





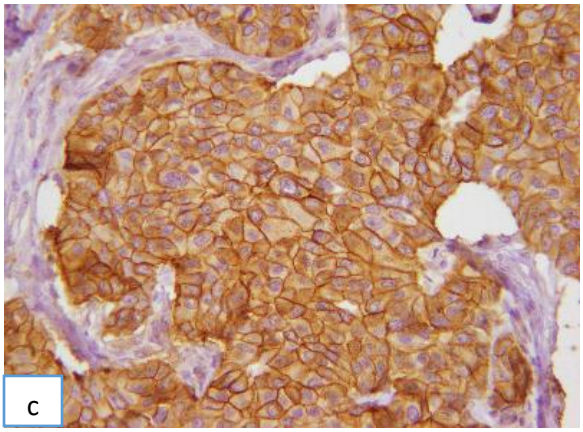


Figure 3: Immunohistochemical analysis of cancer biopsy samples for ER, PR and HER2 expression

Correlation of breast cancer grades with cancer receptor biomarkers

Upon inspection of different grades of breast cancer, it was observed that ER, PR and Her-2 showed more expression in Grade two breast cancer patients as compared to other grade breast cancer samples as shown in Table 1.

Of the 106 cancer patients, 50% of patients have more PR expression level at grade 2. 58.2% of patients have more ER expression level at same grade as the PR and 52.7% patient's shows maximum Her2nue expression level at grade 2 as compared to other groups.

Table 1: Positive and negative samples of ER, PR and HER2 receptor in different grades of breast cancer.

	PR	ER	Her2neu
Grade 1	1.9	3	3.6
Grade 2	50	58.2	52.7
Grade 3	44.4	35.8	41.8

Correlation of different stages of breast cancer with TNM status

Data was collected at different stages of breast cancer patients and was compared to TNM status of the patient. It was seen that out of the total patients 40.6% patients have large tumor size at stage 2 and 60% of patients have more lymph nodes that contain cancers at stage 2. Whereas 42.9% of patients have a cancer that is metastasize at stage 3. Further details are depicted in Table 2.

Correlation of ECOG pattern with different grades of breast cancer:

When patients with different stages of breast cancer were compared to the ECOG pattern observed in these patients grade one patient showed no ECOG pattern whereas the level of ECOG pattern increases in grade 2 and 3. From overall patient's activity analysis 75% of patients shows minimum activity at grade 3 as compared to other grades patients. Further details are shown in Table 3. While reading "Pearson Chi-Square" row χ (1) = 25.012, p = .015, statistically significant association between grade and ECOG.

Correlation of ECOG pattern with different stages of breast cancer

When ECOG pattern of different patients was compared to the stages of breast cancer in these patients it was seen that ECOG pattern was low in stage 1 whereas high ECOG pattern was observed in stage 2 and 3 whereas 50% decrease in ECOG pattern was observed in stage 4. On reading "Pearson Chi-Square" row $\chi(1)$ = 18.649, p = .002. This tells us that there is statistically significant association between stage and ECOG, see Table 4.

Table 2: TNM status in correlation with different stages of breast cancer.

Cancer Stages	T					N				M	
	0	1	2	3	4	0	1	2	3	0	1
1	0	25	3.1	4.2	13.3	7.3	8.8	0	20	6.7	14.3
2	33.3	25	40.6	37.5	23.3	34.1	32.4	16.7	60	34.8	24.4
3	44.4	25	21.9	25	40	34.1	20.6	50	10	28.1	42.9
4	11.1	12.5	21.9	8.3	10	7.3	23.5	16.7	0	14.6	7.1

Table 3: Correlation of different grades of breast cancer with ECOG pattern

Grades	ECOG			
	0	1	2	3
1	20	0	0	0
2	40	57.8	47.6	20
3	40	40.6	47.6	75

Table 4: Comparison of ECOG with different stages of breast cancer

Cancer Stages	ECOG			
	0	1	2	3
1	26.7	6.3	0	0
2	26.7	34.4	38.1	25
3	20	32.8	28.6	25
4	6.7	9.4	23.8	50

Discussion

Lumps may develop instantaneously and then grow over days and months and are primary indicative of breast cancer, while redness indicates the presence of any sort of infection against which body triggers and work to eliminate the foreign cells or abnormal cells. Self-examination for breast improves the survival rates in the patients with breast cancer family history and reduces the breast cancer worries [9]. Patients with painful, swelling and discharge symptoms show the high degree of breast cancer. It shows the highest significant ratio of RCC (0.522233) in age group of 40-50 years old patient which is followed by age group of >60 years old patients having RCC value of (0.484682). This data is compatible with (Mansha, Muhammad, et al) who wrote that high number of patients with 82.5% was found at the time of diagnosis with age factor of 46 years or more [9].While 17.5% diagnosed patients have the age less than 35 years. This study is also compatible with (Rambau, Peter F., et al) who reported the Tanzanian women median age diagnosis which was 46 years, patients with age interval 35-45 years having the percentage of 32.5% [10].

On the basis of SGTNM status maximum significance ratio of RCC (0.5068) in ECOG 1 was seen. Hormonal studies was also done which shows the heavy illness of patients was present with triple positive mean ER, PR,HER2/neu positive cases. HER 2/neu in approximately 15 – 30% of breast cancers' patients is over expressed and is also in coordination with shorter

disease-free interval. HER 2/neu amplification is also associated with the nodal metastasis and ER and PR receptors' absence [11]. Triple positive cases show high degree of illness with stage 4 patients followed by ER, PR positive cases which fall in stage 3 category. ECOG evaluation on the bases of hormones status have significant ratio of ECOG 1 (0.909). HER2 positive cancers further studies may also be necessary at subtype level in order to avoid the over treatment with understanding of their possible pathways for treatment [12]. There are some risk factors which effect hormones exposure to breast tissues. These include: obesity, early menarche, hormone use and late menopause [13]. Reproductive factors that affect increase or decrease in breast cancer ratio involves pregnancy, fertility drugs, breastfeeding, hormonal birth control and postmenopausal hormones [14].

Grades show the progression of cancer cells. TNM staging system also play role to describe the cancer types which shows the progression of cancer to other organs depending on the size of tumor which is indicated by T. To shows that tumor is of small size or may be its not present. While T4 shows that tumor is of large size maybe it grows to the other parts of the body like chest which indicate the high level of cancer. Patient's presentation in TNM staging system was higher with tumor presence which shows the high grade with enlarge tumor. Lymph node involvement shows the progression of tumor to lymphatics. Most of the studied patient was found below the age of 46 years with 52.4% and higher frequency of lymph node involvement was also studied in this group (p=0.012). 64% of patients were found at clinical stage 3 and more than 70% of patients have metastasis of lymphatics when they are diagnosed [10]. ECOG evaluation on the bases of hormones status have significant ratio of ECOG 1 (0.909). HER2 positive cancers further studies may also be necessary at subtype level in order to avoid the over treatment with understanding of their possible pathways for treatment [12]. ECOG patterns were correlated with grades according to degree of freedom of twelve and its significance was 0.015 and it's asymptomatic. This shows a great significant statistic correlation between ECOG and grades. ECOG patterns were correlated with stages according to degree of freedom of twelve and its significance was 0.002 and this shows a great significant statistic correlation between ECOG and stages. It is necessary to know the mode of treatment as well as the study at subset level. Moreover, population awareness may also play an important role to reduce the breast among females.

Conclusion

Analysis of data shows that maximum symptoms show at the age group of 40 to 51. PR, ER and Her2neu have maximum expression level at stage 2 and grade 2. It is observed that tumor size is large at Grade 3 and stage 3. Lymph nodes contain more cancer at grade 2 and stage 3 while metastasis at both grade 2, grade 3 and stage 3. Above analysis shows that with the increase in grade and stage of cancer decreased the physical activity of patient. This data suggests that maximum proliferation and spread of cancer takes place in grade 2/ stage 2, 3 type breast cancer and during these stages the proliferative receptors are overexpressed to support cancer spread, tumor size increases, lymph nodes swell up and metastasis is initiated. Therefore, controlling cancer in stage 2 and 3 is crucial to control the cancer spread and improve the prognosis of the patient.

Authors' contributions

ICMJE criteria	Details	Author(s)
1. Substantial contributions	Conception, OR	1
	Design of the work, OR	1,2
	Data acquisition, analysis, or interpretation	1,2
2. Drafting or reviewing	Draft the work, OR	1
	Review critically for important intellectual content	2
3. Final approval	Approve the version to be published	1,2
4. Accountable	Agree to be accountable for all aspects of the work	1,2

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The University of Management and Sciences' Ethics Committee gave its approval for the study, which was carried out by ethical standards. Before distributing the questionnaire, all participants gave their verbal and written informed consent, and participant confidentiality was rigorously upheld for the whole study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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