Original Article

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Frequency of Luminal A and Luminal B Breast Cancers in Pakistani Population

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ABSTRACT

Objective: To measure frequency of Luminal A and Luminal B breast cancers in hormone receptor positive cancers in Pakistani population. **Study Design:** Descriptive, Cross Sectional Survey. **Settings:** Pathology department, Fatima Memorial Hospital, Lahore. **Duration:** July 2016 to January 2017. **Methodology:** 110 cases of hormone receptor positive breast cancers were subclassified into luminal A and luminal B breast cancers by using immunohistochemical stain Ki67. The cut-off value of ki67 in our study was set as 14%. The selected cases were ER and PR positive which was determined by doing the immunohistochemical stain ER and PR and these cases were further subjected to the proliferation index marker ki67. The hematoxylin and eosin slides along with the immunohistochemical stains were interpreted by histopathologist. The collected information was analyzed by using computer software SPSS version 18. **Results:** The frequency of luminal A was 37% and luminal B as 63%. Age range was 22 to 80 years with an average of 49 years. Maximum number of cases were seen within range of 41 to 50 years. Ductal carcinoma was the most common subtype followed by lobular breast carcinoma. Grade 3 cancers constituted more than 50% of total cases. 48.8% of luminal A and 66.7% of luminal B cancers were grade 3 cancers. **Conclusion:** Frequency of luminal B breast cancer is greater than luminal A cancers in Pakistani population.

Keywords: Breast cancer, ER, PR, Ki67, Luminal, Immunohistochemistry.

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INTRODUCTION

Breast cancer is the most common cancer in women accounting for 23% of all cancer patients and account for 14% of cancer related deaths.[1] Incidence of breast tumors has increased in Asian population over last few decades.[2,3] Within Asia, the highest rate of breast cancer is seen in Pakistan. Every one in nine women suffer from breast cancer in Pakistan.[4,5]

Breast cancer is a heterogeneous group of diseases with diverse clinical, morphological, molecular and prognostic properties. This has led to many classifications based on different criteria over periods of time. With the advancing techniques like tissue micro-array technology and gene expression studies it is revealed that heterogeneity of breast cancers is due to genetic, epigenetic and transcriptional changes at the molecular levels. Thus, making it the basis of the variability of presentation, clinical behavior and response to therapeutic modalities.[6]

Broadly speaking the breast cancers are divided into hormone receptor (HR) positive and HR negative breast tumors. Molecular evidences show that deletions of 16q and gains of 1q are seen in HR positive breast cancers. Whereas more severe genetic alterations such as p53 mutations, BRCA1 mutations, Her2 amplification and high genomic instability are present in HR negative breast cancers.[7,8] The molecular classification divides the breast cancers into five distinct subtypes with each molecular subtype mapped with an immunohistochemistry (IHC) subtype. It helps in identifying the basic fundamental molecular differences of breast cancer, patients with, comparatively good prognosis, distinct clinical outcomes and avoiding un-necessary exposure to chemotherapy. The molecular subtypes are luminal A, luminal B, Her2 over-expression, basal and normal breast like tumors.[9,10] The luminal tumors express hormone receptors, luminal cytokeratin's 8/18 and genes associated with ER activation.[11]

The hormone receptor positive breast tumors are subtyped as luminal A and luminal B breast cancers on the basis of proliferation index ki67.[7] Ki67 is a nuclear non-histone protein present in all proliferating cells and in all active phases of cell cycle except G0. It is used as an effective proliferation marker measured as positively stained malignant cells using the most common anti-human ki67 monoclonal antibody MIB1. Generally between 500 to 2000 cells are counted in representative fields on hematoxylin and eosin stained slides. The positively stained malignant cells in the selected field are quantitatively measured using light microscope. The ki67 score is the positively stained tumor cells among the total malignant cells.[12,13] The cut-off value of ki67 in differentiating luminal A and luminal B is not exactly standardized. Initially in 2011, the cut off set in St. Gallen conference was 14% which was reviewed as 20% in 2013. Due to greater variability of ki67 within a given tumor and low reproducibility of ki67 in cancers with intermediate proliferation activity, the use of median ki67 of local laboratory was accepted in St Gallen conference held in 2015.[14,15]

Luminal A subtype constitutes 50-60% of all breast cancers. This subtype has low proliferation index, higher expression of ER-related genes as compared to luminal B and has favorable prognosis. The luminal A subtype has lower relapse rate over

period of 15 years after the diagnosis. It is responsive to hormonal therapy and does not require any chemotherapy.[16-19] Luminal B cancers account for 40% of breast tumors. They have high proliferation index; high histologic grade and they show higher expression of proliferative genes. Chemotherapy is added to hormonal therapy for treatment of luminal B cancers. They are associated with poorer prognosis as compared to luminal A breast cancer.[16,20]

OBJECTIVE:

To measure frequency of Luminal A and Luminal B breast cancers in hormone receptor positive cancers in Pakistani population.

METHODOLOGY

Study Design: Descriptive, Cross Sectional Survey.

Settings: Pathology department, Fatima Memorial Hospital, Lahore Pakistan.

Duration: July 2016 to January 2017.

Methods: Breast cancer specimens received at Fatima Memorial Hospital, Lahore, with demographic details such as name, gender and age were collected by non-probability consecutive sampling technique. These specimens were fixed in 10% buffered formalin, grossed, stained with Hematoxylin and Eosin and diagnosed by a histopathologist. Staining for ER, PR was performed according to the specifications given by the manufacturer including appropriate positive and negative controls for staining. 110 ER, PR positive breast cancer cases were included with 95% confidence level and 8% margin of error. Ki-67 immunohistochemical stain was performed on these cases and interpreted by a histopathologist. The cut-off value set for ki67 in our study was 14%.

Statistical Analysis: The collected information was analyzed by using computer software SPSS version 18. The quantitative variables like age, ER, PR and Ki-67 expression were presented as mean ± standard deviation. Frequencies and percentages were calculated for luminal A and luminal B. Data was stratified for age to address the effect modifiers. Stratification chi-square test was applied to check the significance with p-value ≤ 0.01 as significant.

RESULTS

Among 110 cases, age range was 22 to 80 years with an average age of 49 years. Maximum number of cases (n=38) were seen in age range of 41 to 50 years with 18 cases of luminal A and 20 cases of luminal B. Equal proportion of luminal B cancers (n=20) were seen in age group of 51-60 years. (Table-1)

In our study, frequency of luminal B is more than that of luminal A**.** Among all the cases, ductal carcinomas were 94% (n=103) and lobular carcinomas were 6% (n=7). 34% of luminal A and 60% of luminal B were of ductal type. 3% of luminal A and 3% of luminal B were of lobular type. Out of total 41 cases of luminal A, 2.4%, 48.8%, 48.8% were grade 1, grade 2 and grade 3 respectively. Among luminal B, 33.3% were grade 2 and 66.7% were grade 3. Only one case of grade 1 breast cancer was identified, which was of luminal A subtype. No grade 1 case was found among luminal B subtype. Overall grade 3 tumors constituted more than 50% of the total cases. 48.8% of luminal A and 66.7% of luminal B cancers were grade 3.

Table 1: Age distribution (n=110)

Age Range	Luminal A	Luminal B	Total	%
20 – 30	1	6	7	6.4
31-40	9	13	22	20.0
41-50	18	20	38	34.5
51-60	10	20	30	27.3
61-70	2	5	7	6.4
71-80	1	5	6	5.4

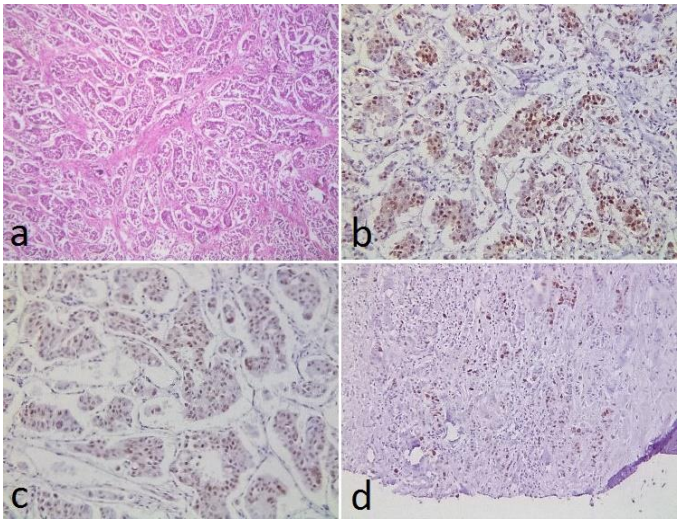

Figure 1: Luminal A phenotype: a) IDC 2, H&E, 200x. b) ER positivity. c) PR positivity. d) Ki-67 positive in < 14% of tumor cells

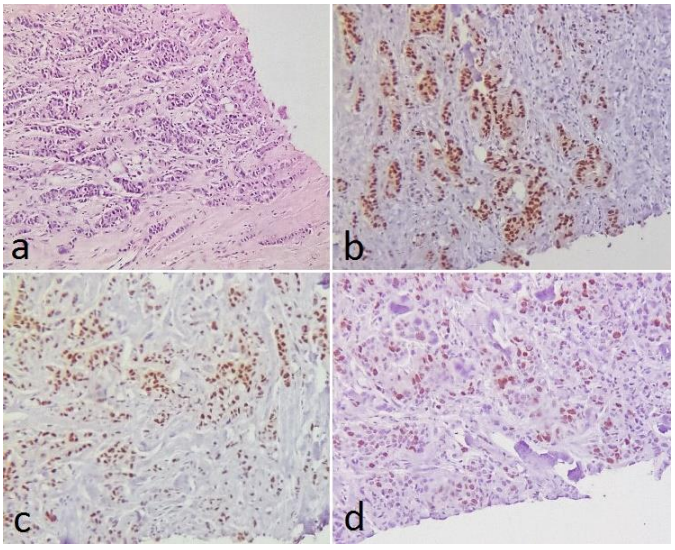

Figure 2: Luminal B phenotype: a) IDC 3, H&E, 200x. b) ER positivity. c) PR positivity. d) Ki-67 positive in >14% of tumor cells

Table 2: Comparison of luminal A and luminal B cancers

	Luminal A	Luminal B	Total
Frequency:			
	41 (37%)	69 (63%)	110 (100%)
Histological type:			
IDC	38 (34%)	66 (60%)	104 (94%)
ILC	3 (3%)	3 (3%)	6 (6%)
Histologic grade:			
Grade 1	1 (0.9%)	0 (0%)	0.9%
Grade 2	20 (18%)	23 (20.9%)	39.1%
Grade 3	20 (18%)	46 (41.8%)	60%

DISCUSSION

Breast cancer is most common cancer accounting for 18% of all cancers in Asian-Pacific region.[2] Breast cancer occurs at a younger age group in Asia as compared to the western women in which the common age of breast cancer is sixties. The postmenopausal increase of breast cancer is not seen in Asia where peak incidence of breast cancer is in their forties.[21] In our study similar results were found with majority of patients being within age range of 40-60 years.

Histologically the most common type of breast cancer is invasive ductal carcinoma (IDC) that makes up 80% of all breast cancers. Amongst special subtypes invasive lobular carcinoma (ILC) is the most frequently encountered tumor.[22,23] In our study the most common tumor was IDC followed by ILC.

Within luminal subtypes of breast cancer luminal A subtype is most frequent one constituting 50-60% of breast cancers.[9,11] However few studies done in Asian population contradict with these western results showing greater frequency of luminal B breast cancer. Our study is concordant to the studies showing higher frequency of luminal B subtype. Similar results were obtained by a study done by Hashmi et. al within Pakistani population showing higher frequency of luminal B breast cancer and relatively younger age group is involved more often.[24] A study done by Naveed *et al* in the Asian population and by Shokouh *et al* in Iran showed the higher prevalence of luminal B tumors.[25,26] Frequency of luminal A as 3.9% and luminal B as 16% was observed by Al Tamimi *et al* in Saudi population.[27] El Fatemi *et al* in Morocco and Juliana et. al in Colombia conducted the studies with same results of higher frequency of luminal B breast cancer.[28,29]

Luminal B subtype is more aggressive with high proliferation and high histological grade.[30] In our study most of luminal B tumors were high grade and no grade 1 tumor was found as luminal B. In comparison, the less than half of the cases of luminal A were grade 3 and a case of grade 1 tumor was identified in this group. The higher percentage of grade 3 corresponds to the reported aggressive behavior of luminal B as compared to luminal A cancers.

CONCLUSION

Luminal B breast cancer is more frequent tumor within the hormone receptor positive tumors in our population using ki67 cut-off value as 14%. However, there is need of extensive work to be done on the molecular sub-typing, their prognosis and response to the therapeutic modalities within Pakistan so that the benefit of the targeted therapies could be utilized for improving the long term survival of breast cancer patients.

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