Grades of Breast Tumor in Different Receptors (Estrogen, Progesterone & Her-2/Neu) Categories and Age Groups among Women with Breast Cancer

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ABSTRACT

Objectives: To evaluate the tumor grades in different receptors (Estrogen, Progesterone and Her-2/neu) categories and age groups among women with Breast Cancer.

Study Design: An observational cross-sectional study.

Place and Duration of Study: Oncology department, Jinnah Postgraduate Medical Center, Karachi, from Jul 2017 to Dec 2018.

Methodology: Total of 450 patients were enrolled in this study using non-probability consecutive sampling technique. The Receptors Status of Estrogen, Progesterone and Her2/neu was resolved into 4 different categories as i) Triple Positive (ER+PR+HER2+), ii) Triple Negative (ER-PR-HER2-), iii) ER+PR+Her2-, iv) ER–PR-Her2+. Age-wise, patients were divided into 3 groups.

Results: The mean age of patients was 46.57 years ± 10.82. No patient was observed with Grade I tumor while 240 with Grade II and 210 with Grade-III. 164/450 patients were observed in the ER+PR+Her2- category. Out of 164, 68.3% were Grade-II and 31.7% were Grade-III (p<0.001). In Triple-Negative category, 94 patients were observed, 31.90% were Grade-II while 68.10% were Grade-III (p<0.001). The patients, age with tumor Grade also showed statistically significant correlation (p<0.001).

Conclusion: This study sheds light on the tumor characteristics of our local population. Majority of our patients had ER+PR+Her2– phenotype/category dominantly having Grade-II tumors followed by Triple Negative typically showing Grade-III. Many of our patients were young (aged less than 36 years) having largely Grade-III tumors while older patients of age above 51 years dominantly showed Grade-II.

Keywords: Breast carcinoma, Estrogen receptor, Grade, Her-2/neu, Progesterone receptor.

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INTRODUCTION

Worldwide, breast cancer was the most common cause of cancer death in women, and it accounted for 521,817 of the total estimated 8.2 million cancer related deaths in 2012.[1]

The histologic grading system for breast cancer is a semi quantitative evaluation of morphologic features, based on which pathologists grade breast tumor into 3 categories of well (G I) to moderate (G II) to poorly differentiated (G III). The higher the tumor grade, the worse the prognosis.[2] Several grading systems have been accepted for breast cancer, namely the Modified Bloom Richardson and the Nottingham one. These systems have been validated in multiple studies demonstrating a correlation between disease free survival and breast cancer specific survival with tumor grade.[3,4]

Approximately 50-85% of breast malignancies exhibit ER or PR positivity and are referred to as hormone receptor-positive cancers having a better prognosis and these patients benefit from endocrine therapy.[5,6]

HER-2/neu is a proto-oncogene amplified and over-expressed in 15-20% of breast cancer cases in women. It is a good predictor of response to Trastuzumab, but also accounts for the aggressive behavior of the disease and poor prognosis.[7] Her2 status is defined by ASCO/CAP (American Society of Clinical oncology/College of American Pathology) guidelines.[8]

Younger patients have significantly higher tumor grade and now, it is well-known that age is an important prognostic factor with younger women having a poorer outcome in comparison with older women.[9,10]

In this study, we focused on these above-mentioned important prognostic and predictive factors such as Grades of tumor, Receptors status and Age of patients in our local population. Histological grades of breast tumor were evaluated in 4 different receptors (Estrogen, Progesterone and Her-2/neu) categories/ combinations and in 3 different age groups. Up to the

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best of our knowledge, no study has done such evaluation of grades of tumor in different receptors categories, locally.

METHODOLOGY

This was an observational cross-sectional study which was conducted in Oncology Ward of Jinnah Postgraduate Medical Center, the largest public sector tertiary care hospital in Karachi. The ethical approval from Institutional Review Board with IRB No. (F-2-81/2017-GEN/429/JPMC)was obtained from JPMC Research Department. A sample size of 450 was calculated using Select Statistics Sample size calculator, keeping a prevalence of breast cancer of 23% from previously published data,[11] a confidence interval of 98%, and the margin of error of 4.6%. The sample was recruited through non-probability consecutive sampling technique. All patients referred to the Oncology ward of Jinnah Postgraduate Medical Center, Karachi, Pakistan between July 2017 to December 2018 for the diagnosis and management of breast cancer participated in the study. The inclusion criteria into the study was patients with biopsy proven breast cancer reports mentioning grades of tumor and having complete receptors status (ER, PR, HER2/neu) tests done and those breast cancer patients not having these relevant tests reports were excluded from the study. Thus total 450 patients fulfilling our criteria were included in the study using non-probability consecutive sampling method. We collected information on all cancer cases including patient demographics, histological type, and grade of tumor and receptors status.

Estrogen, Progesterone and Her2/neu Receptors Status was resolved into 4 different categories/combinations as Triple Positive (ER + PR + HER2 +), ii) Triple Negative (ER-PR-HER2-), iii) ER + PR + Her2-, iv) ER-PR-Her2+. Subjects were also categorized into 3 age groups i.e. younger age group of 18-35 years, middle age group of 36-50 years and older age group of 51 years and above. Distribution of histological grades was statistically evaluated in these 4 receptors categories and 3 age groups via analyzing the data through SPSS version 20 using the Chi-Square test to observe statistical significance.A statistical value of less than 0.05 was considered significant.

RESULTS

A total of 450 subjects were included with ages ranging from 18-80 years of age. The mean age ± SD of patients was found to be 46.72 ± 10.82 years. 240 patients out of 450 (53.30%) were diagnosed with Grade II and 210 (46.70%) with Grade III tumor grade. No patient was observed with Grade I tumor. The most common histological breast cancer type was Infiltrating Ductal Carcinoma, Not Otherwise Specified (IDC, NOS) and its variants as shown in Table-I.

Table-I: Tumor characteristic (histology, receptors status and grade) and distribution of patients as per 3 age groups (n=450).

Variables	n (%)
Age (years)	
18-35	73 (16.2%)
36-50	233 (51.8%)
51 and above	144 (32%)
Tumor Type	
Invasive Ductal Carcinoma (Not Other vise Specified) and its variants	430 (95.6%)
Infiltrating Lobular Carcinoma	10 (2.2%)
Metaplastic Carcinoma	5 (1.1%
Infiltrating mixed Ductal & Lobular	1 (0.2%)
Invasive micropapillary carcinoma	1 (0.2%)
Invasive mucinous carcinoma	3 (0.7%)
Tumor Grade	
Grade I	-
Grade II	53.3% (240)
Grade III	46.7% (210
Receptor Status	
Estrogen Receptor +ve	276 (61.3%)
Estrogen Receptor -ve	174(38.7%)
Progesterone Receptor +ve	240(53.3%)
Progesterone Receptor -ve	210(46.7%)
Her2 +ve	149(33.1%)
Her2 -ve	301(66.9%)

Distribution of Tumor Grade II and Grade III was analyzed in 4 different receptor categories/combinations. It was found that total 386 patients fell into these 4 categories out of 450. Majority of our patients, 164/450 (36.5%) had the ER+PR+Her2- category/phenotype. Out of 164 cases, 68.3% were having Grade II tumors and 31.7% were Grade III with a significant $p<0.001$. Similarly, in the Triple Negative category, 94/450 (21%) patients were observed. Out of 94 patients, 31.90% were having Grade II while 68.10% were with Grade III with a p-value of <0.001.

For the remaining 2 categories, the p-value was >0.05, rendering it as statistically insignificant. These results are shown in Table-II.

Table-II: Tumor grades distribution in 4 different receptor categories (n=386).

Hormone Receptor Status/Categories	Grade-II	Grade-III	*p*-value
Triple Positive (64)	29 (45.3%)	35 (54.7%)	0.165
Triple Negative (94)	30 (31.9%)	64 (68.1%)	<0.001
ER+PR+Her2- (164)	112 (68.3%)	52 (31.7%)	<0.001
ER-PR-HER2+ (64)	31 (48.4%)	33 (51.6%)	0.397

In the present study, tumor grades were also evaluated with subject's age at the time of diagnosis. It was discovered that in patients with age group 18-35 years, total 73/450 (16.3%) patients were observed. Out of these 73 patients, 27 (37.0%) subjects had Grade II, while 46 (63.0%) were having Grade III tumors. The highest numbers of patients i.e 233/450 (51.7%) were observed in the age group 36-50 years, 120 (51.5%) were diagnosed with Grade II and 113 (48.5%) with Grade III disease. And similarly in the age group of 51 years and above, 144/450 (32%) patients were observed, out of which, 93 (64.6%) patients were diagnosed with Grade II and 54 (35.4%) with Grade III. Statistically age was significantly correlated (p<0.001) with tumor grades revealing that younger patients had significantly more Grade III tumor while older patients were diagnosed more with Grade II. These results are shown in Figure.

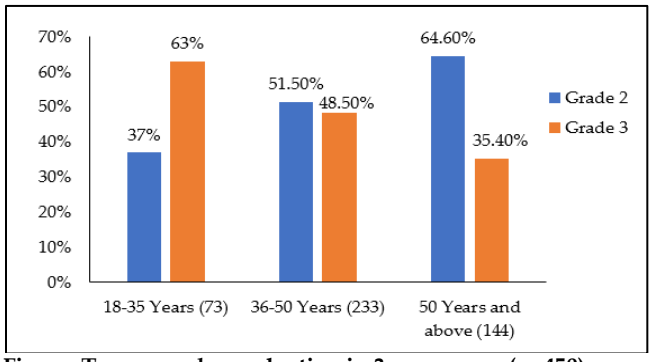

Figure: Tumor grades evaluation in 3 age groups (n=450).

DISCUSSION

The variation in the clinical behavior of breast cancer among patients is due to heterogeneity in the breast cancer biology which is itself determined by many factors including Grades of tumor, Receptors status of Estrogen, Progesterone and Her 2/neu and age of patients. Having this rational in background, the present study focused on these important deterministic factors to be analyzed in our patients and so the pattern of histological grades of breast tumor was evaluated in 4 different receptors categories and in 3 age groups. It was found out we have an extremely low frequency/prevalence of Grade I tumor, 0 case out of 450. Majority of our subjects were diagnosed with Grade II tumor i.e 240 (53.3%) while 210 (46.7%) identified as Grade III. In a study conducted at Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC), it was reported that out of a total of 4,366 cases of breast carcinoma, only 1.3% were Grade I, followed by 41.4% Grade II and Grade III with highest incidence of 49.6%.[12] A study conducted at the Agha Khan University Hospital Karachi showed Grade I tumor at the rate of 6.6%.[13] In contrast, a study from India, reported prevalence of Grade I breast carcinoma of 19% while that of Grade II and Grade III to be 54% and 27% respectively.[14]

In our study, The ER+PR+Her2- category showed the highest number of patients (164 out of 450) and histological Grade II dominated (68.30%) in this category vs Grade III (31.70%) with a p-value of <0.001. Our findings of having the highest number of patients in the ER+PR+Her2- category are similar to the study of SKMCH & RC, they also assessed the Receptor Status in four categories similar to us and reported the highest prevalence of patients (37.3%) in the category ER+PR+HER2-. However, unlike our study, they did not assess the grades of breast carcinoma within these 4 different receptors catego-ries.[12] The study conducted at the Aga Khan Hospital Karachi, in which patterns of hormone receptor status and HER-2/neu over expression was assessed in breast cancer patients and correlated with histologic grade, tumor size and lymph node metastasis, reported that patients with ER and PR positivity had dominantly Grade I and II tumors as compared to Grade III (p value<0.001).[13]

In the category of triple-negative, 94 patients were observed out of total 450 cases representing almost 21% of the total patients. The prevalence of triple negative phenotype as reported by the study at SKMCH & RC was 16.6%.[12] We found in our study that there was a preponderance of Grade III tumors in this category of triple negative at the rate of 68.10% with only 31.90% cases of Grade II tumors (p-value <0.001). It is well established that triple negative breast cancer is known to have a poorer prognosis and is characterized by high grade (Grade III) and thus an aggressive behavior as reported in literature.[15,16] Similarly, the prognostic significance of triple-negative breast cancer was explored in a cohort of 1,601 patients with breast cancer. It was found that subjects with triple negative cancer had an increased likelihood of distant recurrence (hazard ratio, 2.6; 95% confidence interval, 2.0-3.5; p<0.0001) and death (hazard ratio, 3.2; 95% confidence interval, 2.3-4.5; p<0.001) within 5 years of diagnosis as compared to other subjects in the cohort.[16]

In the present study, histological grade was also correlated with 3 different age groups. We reported a

significant correlation (p<0.001) between the tumor grade and age. The Grade III malignancy was most prevalent in the younger age group of 18-35 years while Grade II was more prevalent in older age group of 51 years and above. In the middle age group both grades were seen in almost equal proportions. These findings are in concordance with literature from other regions.[2,17] An American study reported similar findings that the younger subjects were significantly correlated with Grade III (p<0.001). The study concluded that younger women have a worse prognosis in comparison with the older patients in terms of recurrence rate, distant metastasis, and overall survival.[18] An another study published in the Journal of Clinical Oncology also reported similar findings to our study that younger patients were more likely to have higher-grade and a triple-negative hormone receptor status (p<0.001).[19]

CONCLUSION

This study looked at the tumor biology/characteristic of breast cancer in our local population. Majority of our patients showed ER+PR+Her- phenotype largely having Grade II tumor followed by Triple Negative phenotype typically showing Grade III. No patient with Grade I tumor was observed. The bulk of our patients were in age group of 36 to 50 years. A substantial number of our patients were of young aged 35 years or less, dominantly presentingwith Grade III tumors while older patients of age51 years and above mostly showed Grade-II tumor.

Conflict of Interest: None.

Author's Contribution

MIK: Disgn and concept, GH: Criticle review, KA: Supervision, SS: Statistical analysis and review, KA:, MA: Draft preparation, HS: Data collection and entry.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61(2): 69-90.
2. Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T. Breast cancer prognostic classification in the molecular era: the role of histological grade. Breast Cancer Res 2010; 12(4): 207.
3. Rakha EA, El-Sayed ME, Lee AH, Elston CW, Grainge MJ, Hodi Z, et al. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. J Clin Oncol 2008; 26(19): 3153-3158.
4. Pestalozzi BC, Zahrieh D, Mallon E. Distinct clinical and prognostic features of infil-trating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. J Clin Oncol 2008; 26(18): 3006-3014.
5. Early Breast Cancer Triallists Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials. Lancet 2011; 378(9793): 771-784.
6. Faheem M, Mahmood H. Estrogen receptor, progesterone receptor, and Her 2 Neu positivity and its association with tumour characteristics and menopausal status in a breast cancer cohort from northern Pakistan. Ecancermedi-calscience 2012; 6(1): 283.
7. Slamon DJ, Clark GM, Wong SG, Levin WJ. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987; 235(4785): 177-182.
8. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol 2014; 138(2): 241-256.
9. Adami HO, Malker B, Holmberg L, Persson I, Stone B. The relation between survival and age at diagnosis in breast cancer. N Engl J Med 1986; 315(9): 559-563.
10. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, et al. Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. J Clin Oncol 1994; 12(5): 888-894.
11. Sarwar MR, Saqib A. Cancer prevalence, incidence and mortality rates in Pakistan in 2012. Cogent Med 2017; 4(1): 1288773
12. Badar F, Mahmood S, Faraz R, Yousaf A, ul Quader A, Asif H, et al. Epidemiology of breast cancer at the Shaukat Khanum memorial cancer hospital and research center, Lahore, Pakistan. J Coll Physicians Surg Pak 2015; 25(10): 738-742.
13. Azizun-Nisa BY, Raza F, Kayani N. Comparison of ER, PR and HER-2/neu (C-erb B 2) reactivity pattern with histologic grade, tumor size and lymph node status in breast cancer. Asian Pac J Cancer Prev 2008; 9(4): 553-556.
14. Geethamala K, Murthy VS, Vani BR. Hormone receptor expression in breast carcinoma at our hospital: An experience. Clin Cancer Investig J 2015; 4(4): 511-515.
15. Lee JA, Kim KI, Bae JW, Jung YH. Triple negative breast cancer in Korea-distinct biology with different impact of prognostic factors on survival. Breast Cancer Res Tr 2010; 123(1): 177-87.
16. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007; 13(15): 4429-4434.
17. De La Rochefordiere A, Campana F, Fenton J, Vilcoq JR, Fourquet A, Asselain B, et al. Age as prognostic factor in premenopausal breast carcinoma. The Lancet 1993; 341(8852): 1039-1043.
18. Partridge AH, Hughes ME, Warner ET, Ottesen RA, Wong YN,. Subtype-dependent relationship between young age at diagnosis and breast cancer survival. J Clin Oncol 2016; 34(27): 3308-3314.