ISSN No:-2456-2165

Correlation between Histological Grade and Ki67 in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy

Sajid Ali
Medical Oncology, Hayatabad Medical Complex Peshawar

Ayesha Sadia
Mphil Hematology
KMU Peshawar

Shehryar Ahmad
Clinical Technologist Health Department, Khyber-Pakhtunkhwa

Abstract:

Background: Breast cancer (BC) is a heterogeneous disorder and is a major health related concern. Certain breast cancer indicators, such as the proliferative marker ki67 index, can also help predict the clinical prognosis of this complex malignancy. This study aims to find correlation between ki67proliferativeindex,with the histological subtype of breast cancer in the neoadjuvant setting.

Materials and Methods:

We collected data of 79 patients having age ranges between 23–67 years. The patients demographic data, their histo pathological subtype, ER,PR, HER2 receptor status and Ki-67 were analyzed. The Ki-67 values were divided at 20% cut off point into "low Ki-67 <_20%" and "high Ki-67 > 20%".

Results:The range of patients was between 23–67 years.About 89.87% patients have invasive ductal carcinomas (n=71), 7.59% have invasive lobular carcinoma(n=6), 1.2% each had mucinous carcinoma and DCIS.(n=1). Baseline Ki67 index was available for 62 biopsy specimens. There was significant correlation between Ki67 and histological grade in different histological subtypes of patients who were denovo at the time of presentation. Patients who received neoadjuvant chemotherapy9patients with grade II had complete pathological remission(pCR) while 6 grade 3 patients had pCR, similaly 7 patients with ki67<- 20 had pCR while 6 were > 20.

Conclusion: This study finds significant correlation between Ki67and Histological grade. Those who received neoadjuvant chemotherapy with grade II histological grade had complete pathological remission.

Keywords:- *Breast Cancer, Chemotherapy, Histological subtype, Ki67.*

I. INTRODUCTION

According to the American Cancer Society breast cancer is the most common tumor in female gender, making 30% of new cancer diagnosis in the year 2018.[1] As breast cancer is a heterogeneous disease, so it demands its adequate evaluation and categorization into different subtypes. Molecular testing is recommended in treatment decision and also has a prognostic utility. Molecular genetics due to its high cost are not routinely in clinical practice.On the contrary,Immunohistochemical (IHC) markers,being cost effective, to define breast cancer subtypes is routinely used in clinical decision making[2] . Breast cancer subtypes, in different studies, have an effect on the disease prognosis and predicts response to chemotherapy and endocrine treatment. The anti-HER2 therapy gives survivalbenefit to the Her2 positive breast cancer patients[3] .One of the most important prognostic factors is tumor proliferation. Ki-67 is nuclear protein which is found during the cell cycle in the late G1, S, G2 and M phases , reflecting the proportion of cellular proliferation[4] .Luminal breast cancers are subdivided by Ki-67 expression into luminal A and luminal B groups [5] . It has also been found that higher the nuclear protein expression , the higher relapse risk and decreased survival especially in early stage breast cancers [6]. Histological grade, the degree of cellular differentiation, is also a vital marker of breast cancer and predicts prognosis and to select the most suitable management plan for breast cancer patients [7] . Histological grade, in histopathological specimens, is calculated in accordance to the Nottingham modification of the Scarf-Bloom-Richardson (SBR) grading system. The tumor is graded by determiningthe morphological features (, nuclear pleomorphism, tubule formation and mitotic count). The grade of the tumor may be correlated to Ki-67 expression based on the mitotic count[8] however only few studies have elaborated correlation between histological grade and ki67 and how these two prognostic factors are predictive of the outcome of breast cancer patients with different IHC-based subtypes. In this study, breast cancer patients from oncology unit were enrolled to determine any possible interaction between histological grade and ki67 and their prognostic utility in different breast cancer subtypes based on IHC.

II. MATERIAL AND METHODS

We collected data of 79 patients diagnosed with breast cancers and treated in oncology setup of Hayatabad Medical Complex Peshawar, Pakistan during 2020-2022. Immunohistochemically (IHC) staining was used for determination of estrogen receptor (ER), progesterone receptor (PR), epidermal development factor receptor type 2 (HER2) and Ki67(IHC) and fluorescent insitu hybridization(FISH) if HER2 found to be equivocal i.e 2+.Classification of clinical pathological subtypes were defined as: Luminal A breast cancers are ER and/or PR good, HER2 negative, Histological grade 1 or 2; Luminal B subtype is ER and/or PR positive, HER2 positive or negative and/or grade 3; 3rd was triple negative (TN), ER, PR and HER2 negative independent of grade ; lastly the

ISSN No:-2456-2165

HER2 good, ER, PR negative and HER2 positive, independent of histological grade. Ki67 value of 14% was a cutoff point to divide between Luminal A and B tumors independent of the grade of tumor. Data were Analyzed using SPSS version 22 and presented in the form of graph. Chi-Square test of independence was used for determining possible interaction between histological grade and ki67 and their prognostic utility in different breast cancer subtypes based on IHCand whether their values dictate response to neoadjuvant chemotherapy. P value of <0.05 were considered statistically significant.

III. RESULTS

Median age was 52 years (26-72), with 89.87% invasive ductal carcinomas (n=71), 7.59% invasive lobular carcinoma (n=6), 1.2% each had mucinous carcinoma and DCIS.(n=1)as shown in Figure 1.

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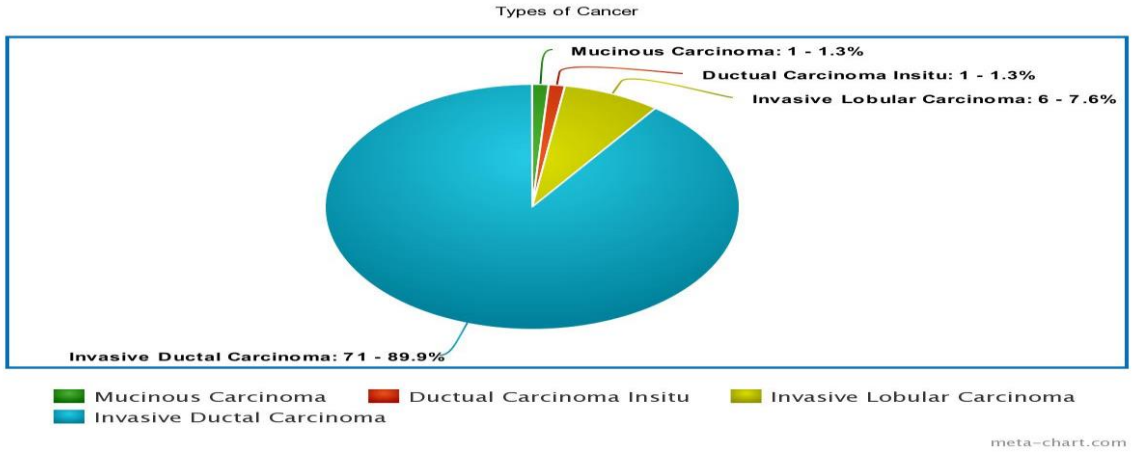

Fig. 1: Types of Cancer

Baseline Ki67 index was available for 62biopsy specimens. Lump in the breast was the chief presentation whereas the tumor size on physical assessment was 7 +/- 3.3 cm (2-15 cm) respectively. Data regarding Clinical stages of disease revealed 2 patientsin Stage I, 12 in stage II 35% , while 43 in stage 3 III 45.6% respectively whereas stage IV have only 14 patients 19.3% (Figure 2).

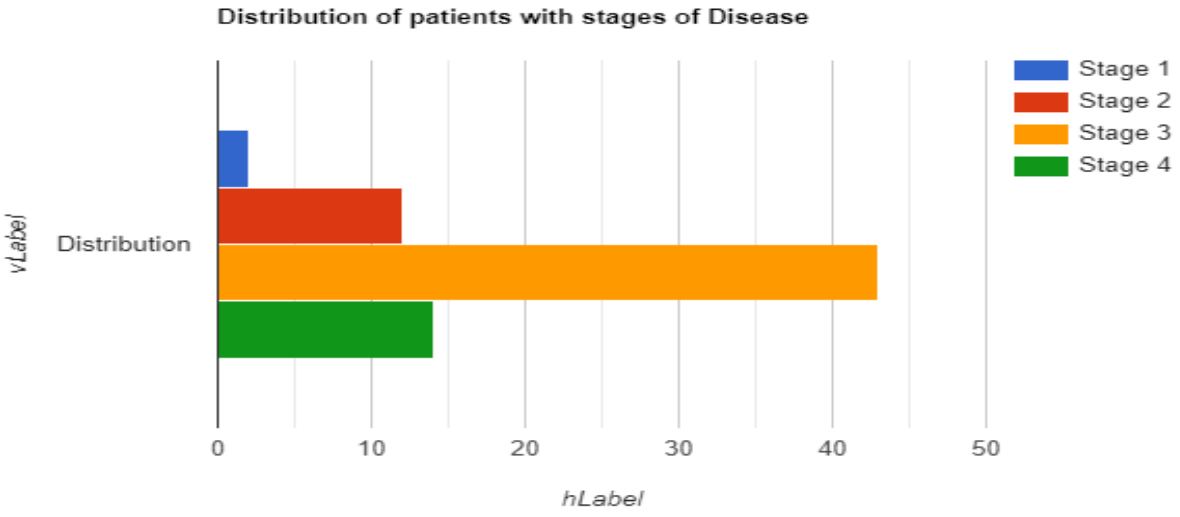

Fig. 2: Distribution of patients with stages of Disease

IHC for Ki67 was performed on 62 samples in the prechemotheraphy specimens. To find out the association between HG and Ki67, chi-square test was performed on 63 samples processed.we observed that Ki67 and Histological grade were correlated factors and p value obtained was <0.05 at 95 % confidence interval as shown in table 1.

Results						
	Ki67≤20	Ki67>20				*Row Totals*
Grade 1	1 (0.52) [0.43]	0 (0.48) [0.48]				1
Grade 2	28 (19.90) [3.29]	10 (18.10) [3.62]				38
Grade 3	4 (12.57) [5.84]	20 (11.43) [6.43]				24
Column Totals	33	30				63 (Grand Total)

The chi-square statistic is 20.0957. The *p*-value is .000043. The result is significant at $p < .05$.

Table1: Ki67 and Histological grade correlation

About 61.29% of all patients had ki67<-20(n=38), 38.70% had ki67>20. About 43.63% of the cases of IDC had ki67> 20(n=24).100% of ILC had ki67<- 20(n=6) and the only single mucinous histology also had ki 67 of 14(n=1). 87.5.16% grade II Had low Ki-67 (n = 28) while 12.5% of grade II had high Ki-67 (n = 4). 33.33% of grade III were with low Ki-67 (n = 10), 60.66% grade III with high Ki-67(n=20) Only 1 patient had grade 1 with no ki67 performed. Grade III was found to have higher incidence of high Ki-67 than any other histological grade group.

IV. DISCUSSION

Breast cancer, due to variable biomarkers, has a very heterogeneous disease course. These biomarkers affect the clinical behavior of the tumor. Choosing the most appropriate treatment can be carried out by the help of these clinical and molecular biomarkers. The Ki-67 nuclear antigen protein is associated with cell cycle, and can be detected in different phases of cell cycle division i.eG1-, S-, G2- and M-phase except G0 quiescent phase. (G0)[9]. Ki-67 expression testing is of utmost importance in early stage breast cancer patients, in adjuvant setting to decide about hormonal treatment vs chemotheraphy[10]. Different breast cancer subtypes have been identified based on estrogen receptor (ER), progesterone receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2). Out of these 4 major subtype,1st type which is of good prognostic value, is luminal type A, which is ER+ and/or PR+/ /HER2– status, low-grade tumour[11]. The 2ndsubtype, about 10% of breast cancers, is of luminal type B which is ER+ and/or PR/HER2– status[12]. The 3rd type is HER2 positive disease, with an immune histochemistry(IHC) profile of ER+, HER2 overexpression or amplification, and any value of Ki-67or PR [13]. The 4th entity is HER2 enriched breast cancers (HER2-2E), these tumors are HER2+, and has a high expression of ERBB2 and 17q genes amplicon, like GRB7, with ESR1,PGR are expressed in low to intermediate levels. Majority of these HER2 enriched tumors are usually hormone receptor-negative (HR-), but about 30% can be typically HR+[14]. Age of the patient, histological subtype of tumor, size of tumor , female gender, HER2 and hormonal status, lymph node status as well as Ki-67 proliferative index has both prognostic and predictive value in breast cancer treatment, more so in the loco-regional disease[15,16]. The grade of tumor is an important prognostic component of breast cancer prognostic tools and is being incorporated in the breast cancer staging assessment like in Nottingham Prognostic Index(NPI) to decide about choosing the most appropriate treatment forbreast cancer patients. The histological grade of the tumor is determined by the morphological features as nuclear pleomorphism, tubule formation and mitotic count. This may highlight the hypothesis that ki67 may be related to histological grade of carcinoma breast based on the mitotic count[8]. The small cohort of the study limits the study but the data collected help us to guide the importance of routine use of Ki-67 measurement in the diagnostic workup of breast cancer, as it may help in determining breast tumor histological subtypes and also to apply it as a predictive and a prognostic tool in the breast tumor management[17,18]. In the current study, the correlation between Ki-67 level and the grade of the tumor variables was analyzed. It was found that high ki67 was correlated with high tumor grade. GradeIII tumorswith a Ki-67 below 20% were uncommon. On the contrary majority of grade II tumors tend to had Ki-67 below 20%.

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