

“Study of ER, PR & HER-2/NEU reactivity pattern in the patient of Breast Cancer in northern part of india”

Dr. Sumita A. Jain¹, Dr. Laxman Aggrawal¹, Dr. Atul Ameta,
Dr. Shraavan Nadkarni, Dr. Aashish Goyal, Dr. Ranjan, Dr. Kusum Gaur²

¹(Professor, Dept. of surgery, s.m.s. medical college, jaipur.)

²(Professor, Dept. of P.S.M., s.m.s. medical college, jaipur.)

Abstract: ER, PR, and HER2 represent the most acceptable factors for predicting prognosis, response or resistance to treatment, and potential use of newer drugs such as trastuzumab in the case of HER2 over-expression

Objectives- To find out ER, PR, & HER2/neu reactivity in breast cancer patient.

Methodology- This descriptive type of observational study included 203 cases of breast cancer. After confirming the diagnosis, either trucut biopsy or final biopsy specimen was employed to ascertain ER/PR status and HER2/neu receptor.

Results- In this study, 71(35%) out of 203 cases were HER2/neu positive & 132(65%) cases were HER2/neu negative. A significantly higher rate of HER2/neu protein over-expression was found in patients with poor prognostic factors (like large tumor size, high grade tumor and lymph node metastasis). Most of the patients who had HER2/neu protein over-expression were also ER-/PR-. This group (Her2/neu+, ER-, PR-) appeared to represent an aggressive form of breast cancer, presenting at a younger age with large tumor size & lymph node metastasis. **Conclusions-** HER2/neu testing along with ER/PR status should be performed routinely in all the patients with newly diagnosed breast cancer and therapy against Her2/neu (trastuzumab), should be considered to all patients with HER2/neu over-expression to increase D.F.S. and O.S.

Keywords: Breast cancer, ER, PR, Her-2/neu, Trastuzumab

I. Introduction

It has been documented that breast cancer is a heterogeneous disease with variable biological and clinical characteristics because of its different genetic make-up. It is well known that Proto-oncogenes and tumor suppressor genes are two classes of genes, that play a central role in the regulation of cell growth and differentiation. So any alterations in one or more of these genes appear to play an important role in the pathogenesis of most human malignancies. HER-2/neu proto-oncogene amplification and or over expression is one of the most important alterations encountered in breast cancer. HER-2/neu proto-oncogene (also called c-erbB2) is located on chromosome 17q11, which encodes for p185 a transmembrane glycoprotein with tyrosine kinase – Activity that belongs to the family of epidermal growth factor receptors.

HER2/neu proto-oncogene is amplified and or over expressed in approximately in 25- 30% of invasive primary breast cancers. An association have been found to exist between amplification and or over expression of HER-2/neu and a wide variety of different clinical and pathological features of breast carcinoma that include: Large tumor size, high grade, lack of steroid receptor expression, axillary lymph nodes metastasis, advanced stage, early relapse, and reduced overall survival.

From a clinical point of view HER-2/neu receptor has become important as a target for antibody-based therapy with trastuzumab (Herceptin). The interesting point of such a specific treatment is that only patients with tumors that over express HER-2/neu benefit from such a therapy. For that reason, the determination of HER-2/neu status in breast cancer is becoming of great interest, and recently this treatment has been shown to improve patient's outcome markedly.

Therefore, we plan to study this important genetic marker i.e. ER, PR, Her-2/Neu which could be used as a prognostic factor for the early management of this malignancy. This could hopefully help the clinicians better understand the disease manifestation in our patients, and, accordingly, help them develop a platform on which further disease investigation and clinical management strategies could be based.

II. Aims & Objectives

2.1 To Study ER, PR & Her-2/neu reactivity in the patient of breast cancer.

2.2 To determine the proportion of HER-2/ neu receptor positivity in patients of carcinoma breast.

III. Material and Methods

This study was done in the Deptt. of Surgery of S.M.S. Hospital and College, Jaipur. It is a descriptive type of observational study.

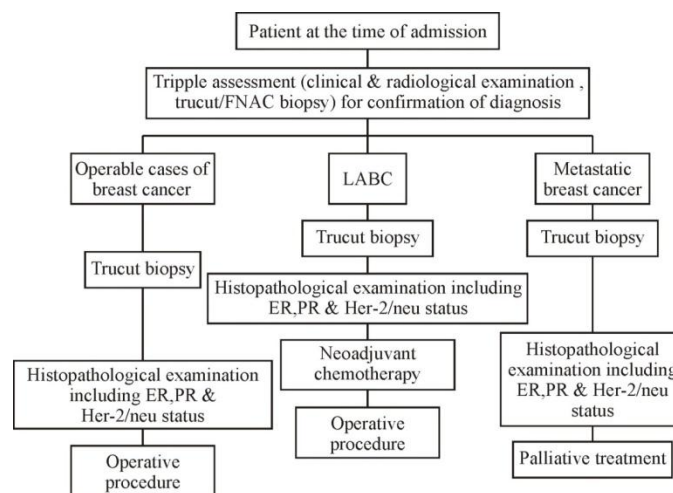
3.1sample size: 203 cases were selected randomly, after satisfying inclusion and exclusion criteria.

3.2Inclusion criteria: All operable and locally advanced & metastatic cases carcinoma breast admitted in the Deptt. of Surgery in S.M.S. Medical College, Jaipur

3.3Exclusion criteria: All patients who refuse for Hercep test (test for HER-s2/neu receptors) & ER, PR test. After confirming the diagnosis, either trucut biopsy or final biopsy specimen was employed to ascertain ER/PR status and HER2/neu receptor.

IHC staining for ER and PR was carried out and ER and PR positivity was defined as nuclear staining in more than 10% of tumor cells. HER2 protein expression was detected using DAKO Hercep Test.

3.4 Study design:

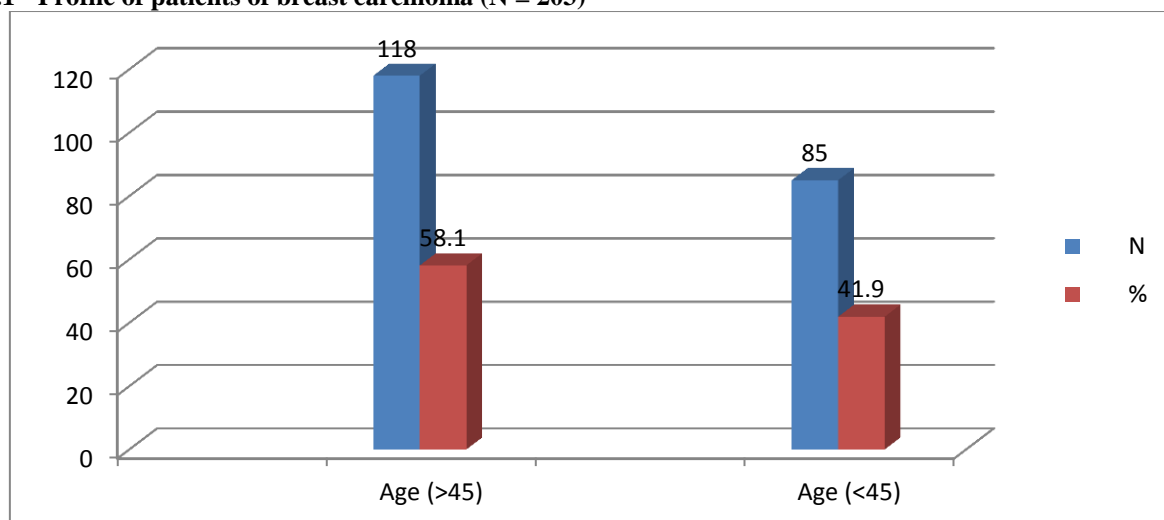


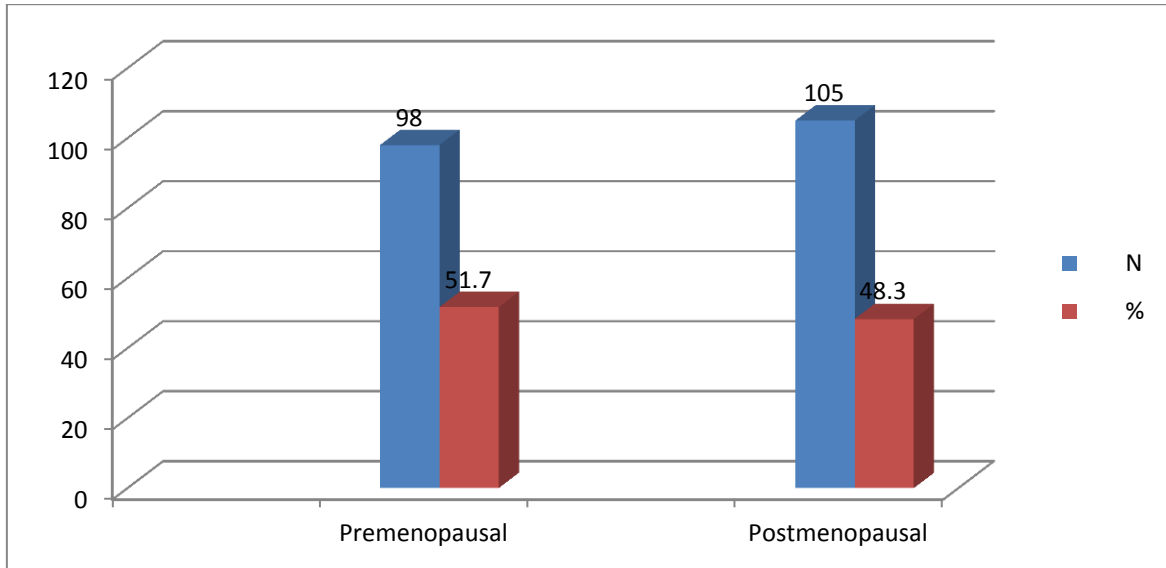
IV. Observation and Discussion

The association between Her-2 gene amplification and poor prognosis was first determined in 1987 by Slamonet *al.[1]*

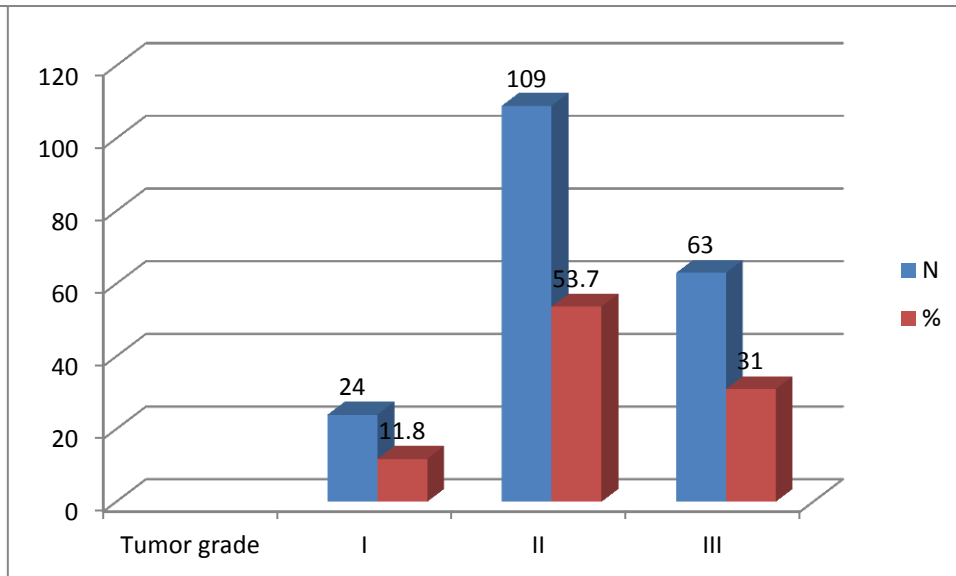
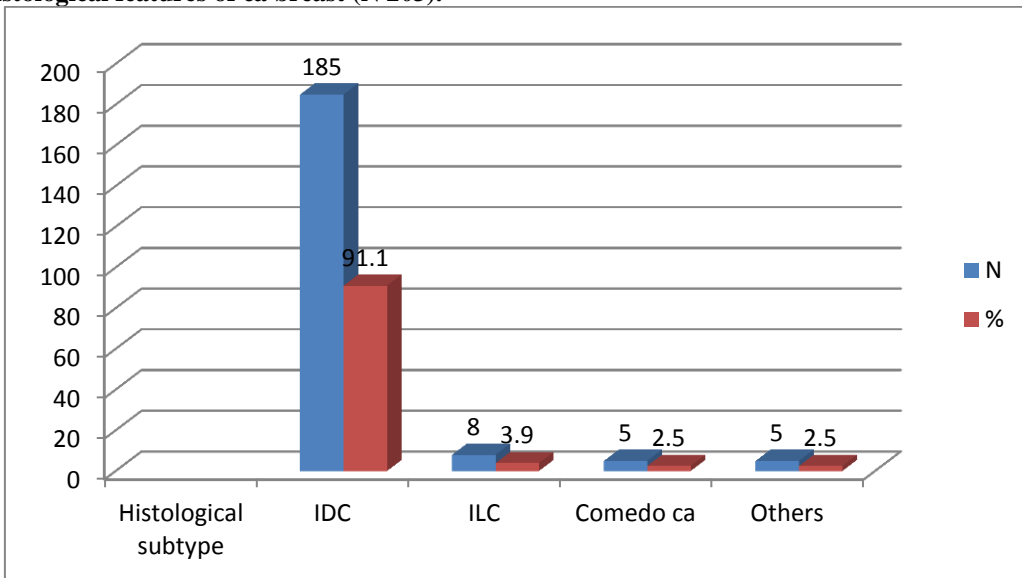
In our study of 203 patients of breast cancer, 58.1% (n=118) patients were >45years, while 41.9% (n=85) were ≤ 45 years of age with mean age of 48.4 years. Nidal M Almsari et al[2] had mean age of 47 years in their study with 37% patients within the age of 45 years. So now looking to the above ratio this is clear that more younger patients are coming with cancer breast in India.

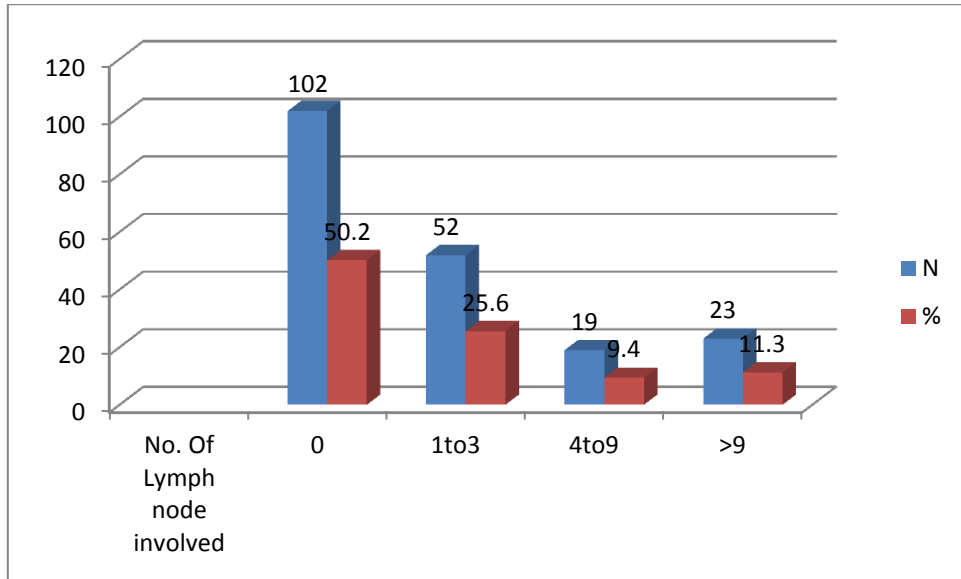
1.1 Profile of patients of breast carcinoma (N = 203)



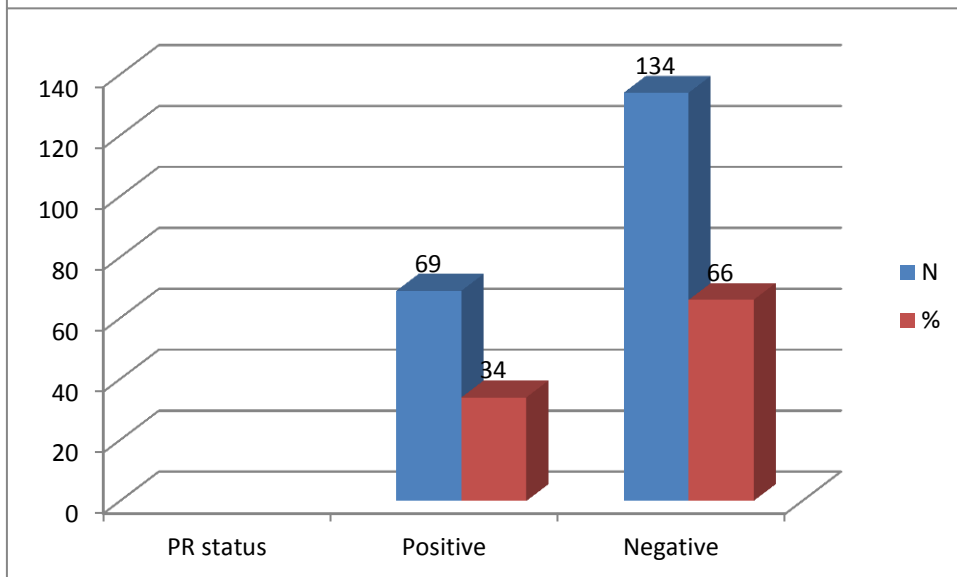
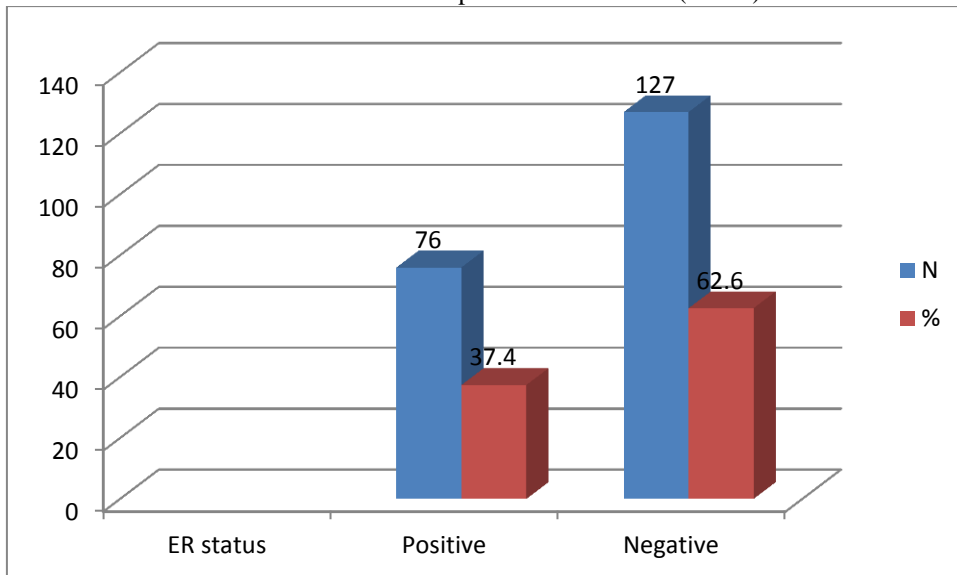


4.2 Histological features of ca breast (N 203).





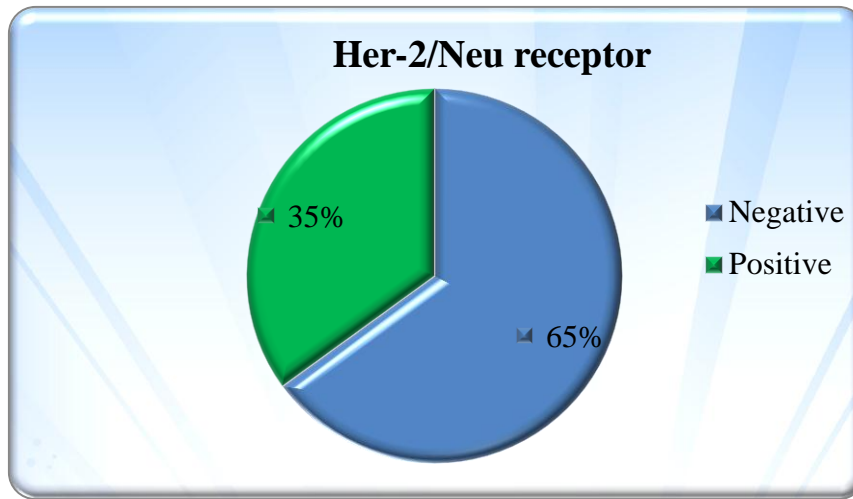
4.3 ER/PR status in patients of ca breast (N 203).



In our study 37.4% (n= 76) patients, had ER positive status and 62.6% (n=127) patients had ER negative status while 34% (n= 69) patients had PR positive status and 66% (n=134) patients had PR negative

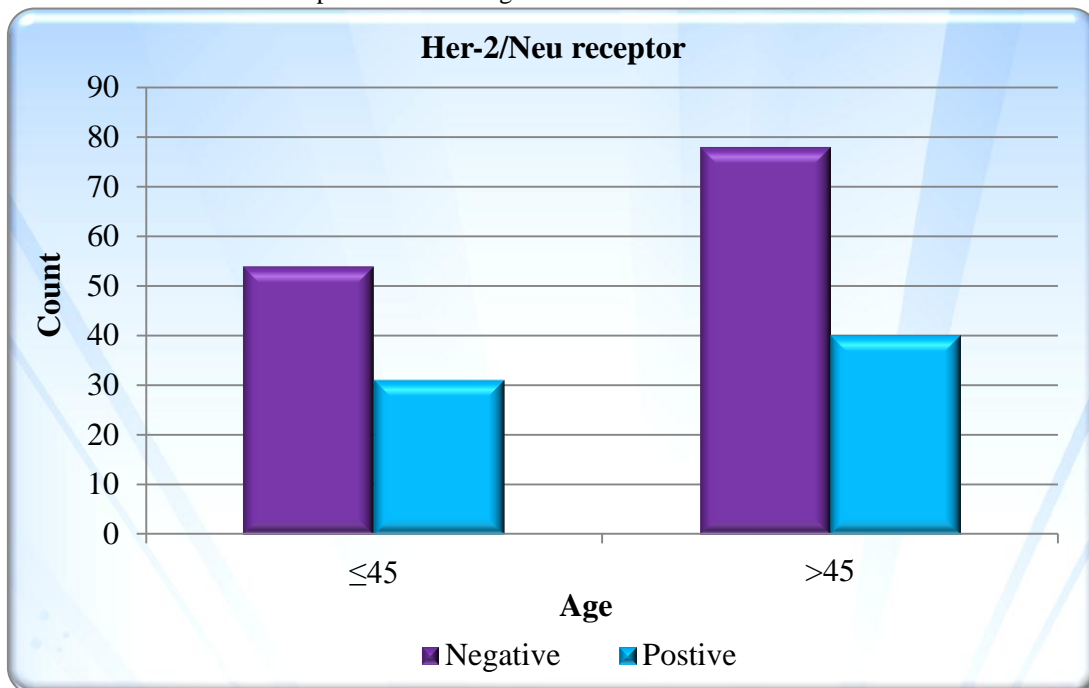
status. Nidal M Almasari (2) reported 53.4% ER positive, 46.6% ER negative, 52.3% PR positive & 47.7% PR negative patients.

4.4 Her-2/Neu receptor status in patients of ca breast (N 203).



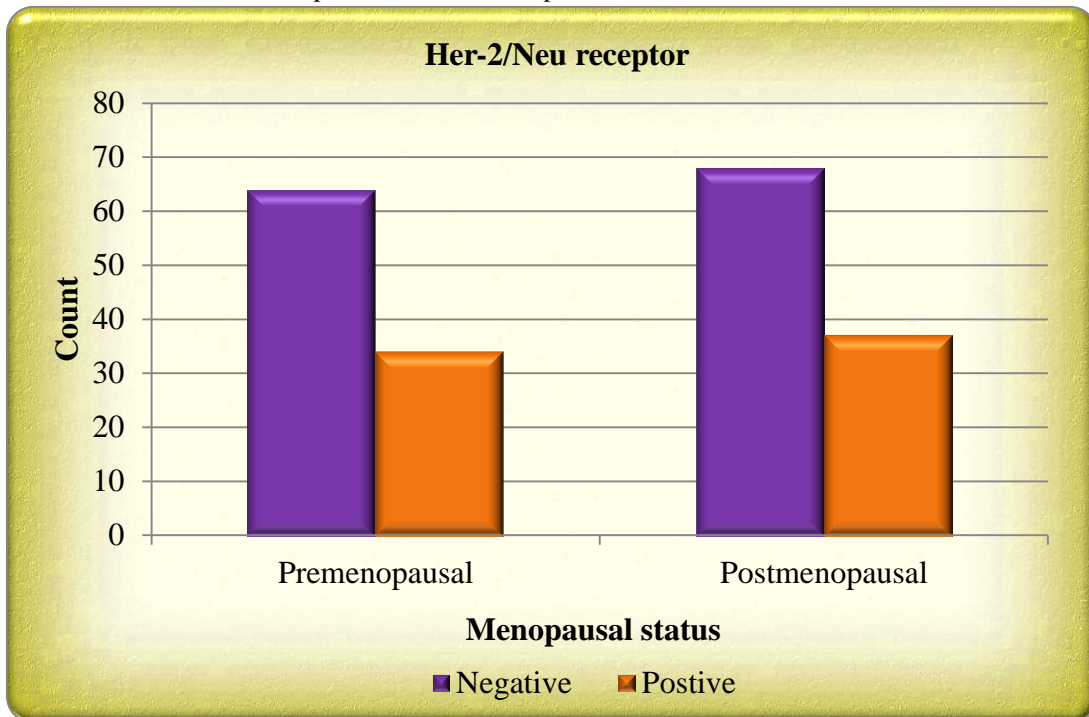
In this study, we found that 71 (35 %) out of 203 cases were HER-2/neu positive & 132 (65%) cases were Her-2/neu negative. Although there is a wide variation (15-35%) in HER-2/neu over-expression and amplification, our figure appears to be higher side of commonly accepted rate of 15 to 35% may be because of we were getting more patients of younger age group. Nidal M Almasari(2) had 25% Her-2/neu positive & 75% Her-2/neu negative patients in their study.

4.5 Association of Her-2/Neu receptor status with age



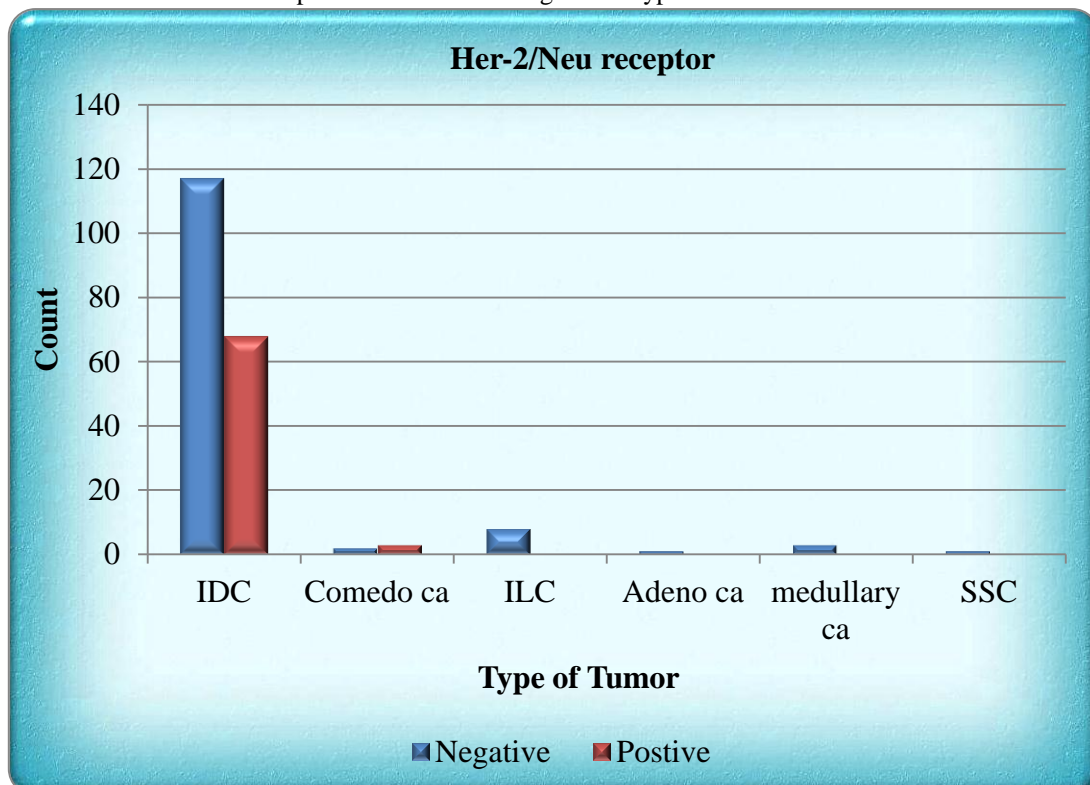
Her-2/neu protein over-expression was present in 31 out of 85 (36.5%) patients with age ≤45 years and in 40 out of 118 (33.9%) patients with age of > 45 years. (Chi- square = .144 with 1 degree of freedom ; p = .704) Franco Rilke [3] found that HER-2/neu over-expression is associated with young age; we also have high ratio of Her-2/neu over expression in young patients

4.6 Association of Her-2/Neu receptor status with menopausal status



Her-2/neu protein over-expression was present in 37 out of 105 (35.2%) post menopausal patients and in 34 out of 98 (34.7%) premenopausal patients. (Chi- square = .007 with 1 degree of freedom; p = .933)

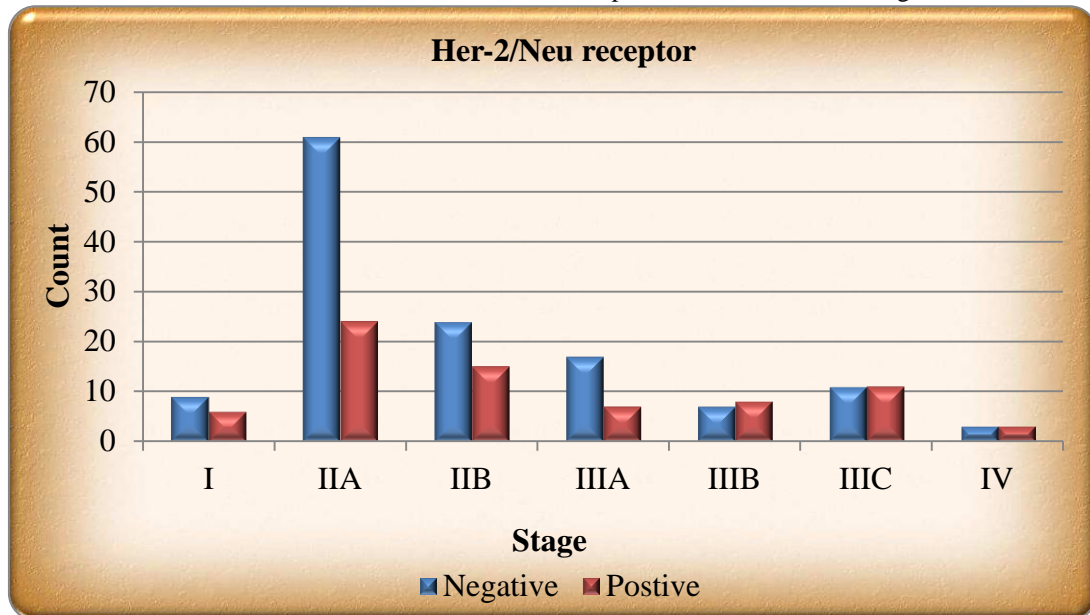
4.7 Association of Her-2/Neu receptor status with histological subtypes



Her-2/neu protein over-expression was present in 68 out of 185 (36.8%) patients with infiltrative ductal carcinoma and 3 out of 5 (60%) patients with comedo carcinoma and Her-2/neu protein over-expression was not found in any patients of infiltrative lobular carcinoma and other histological subtype which included three cases of medullary carcinoma, one case of adenocarcinoma and one case of squamous cell carcinoma of breast. (Chi-

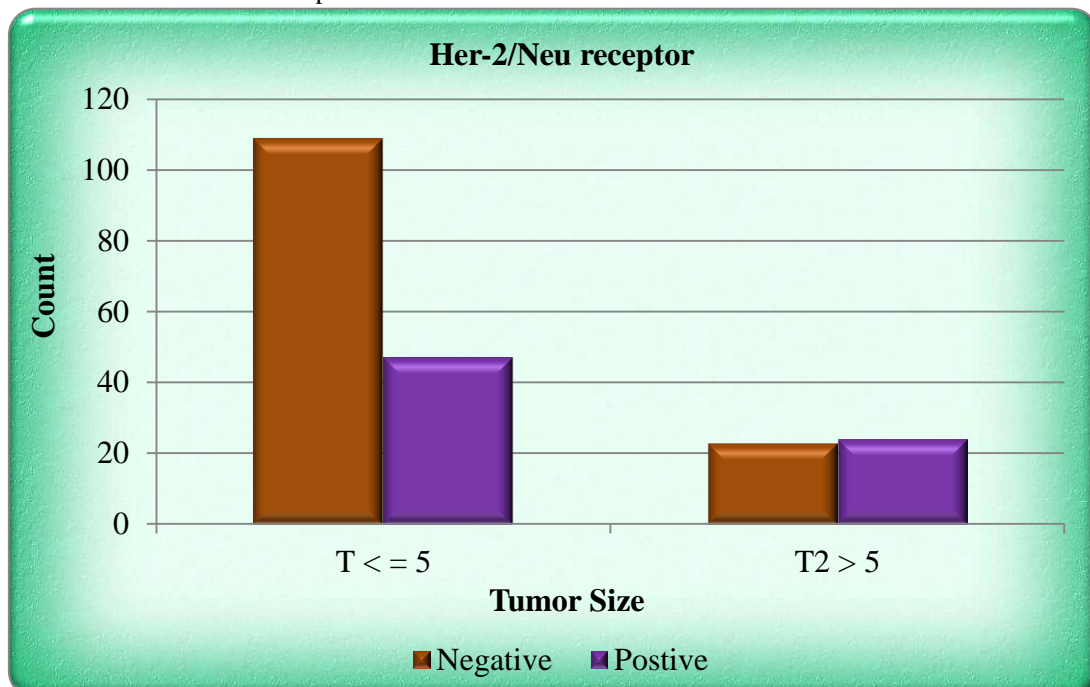
square = 8.627, Degree of freedom = 3, p value = .035). So Her-2/neu protein receptor over-expression was found in infiltrative ductal carcinoma & comedo carcinoma compare to other histological subtypes.

4.8 Association of Her-2/Neu receptor status with clinical stage.



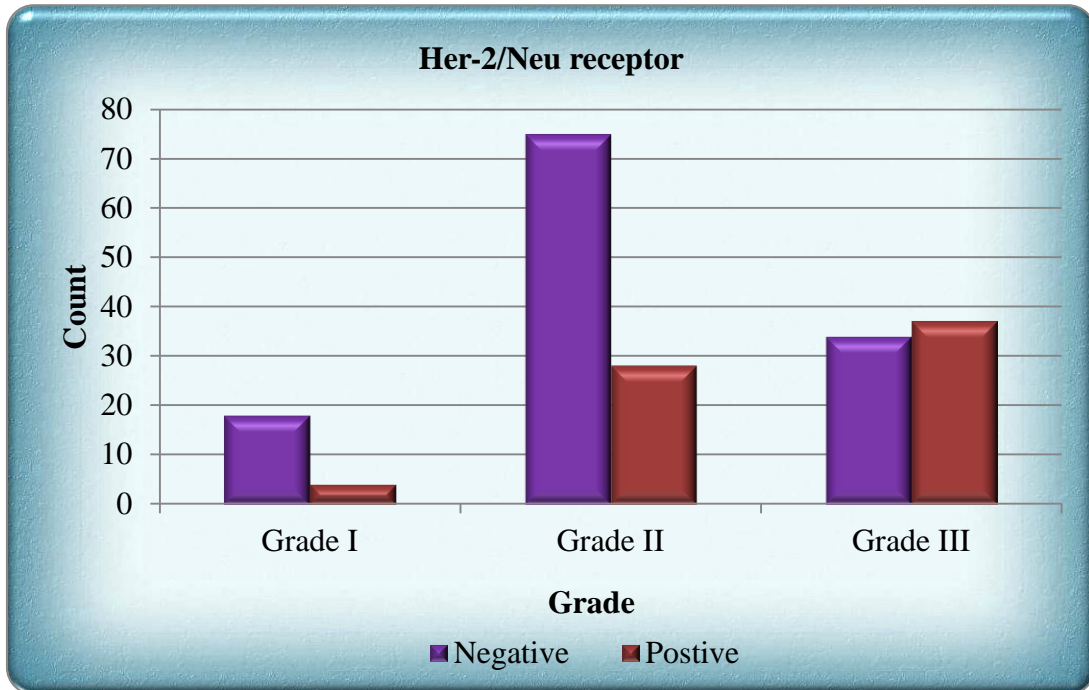
Her-2/neu protein receptor over-expression was present in 6 out of 15 (40%) stage I lesions, 31 out of 139 (31.2%) stage II lesions, 23 out of 58 (39.9%) stage III lesions, 3 out of 6 (50%) stage IV lesions. Tumor with strong Her-2/neu expression tended to be higher stage than those lacking over-expression. (Chi-square = 9.417, Degree of freedom = 6, p value = .151)

4.9 Association of Her-2/Neu receptor status with tumor size.



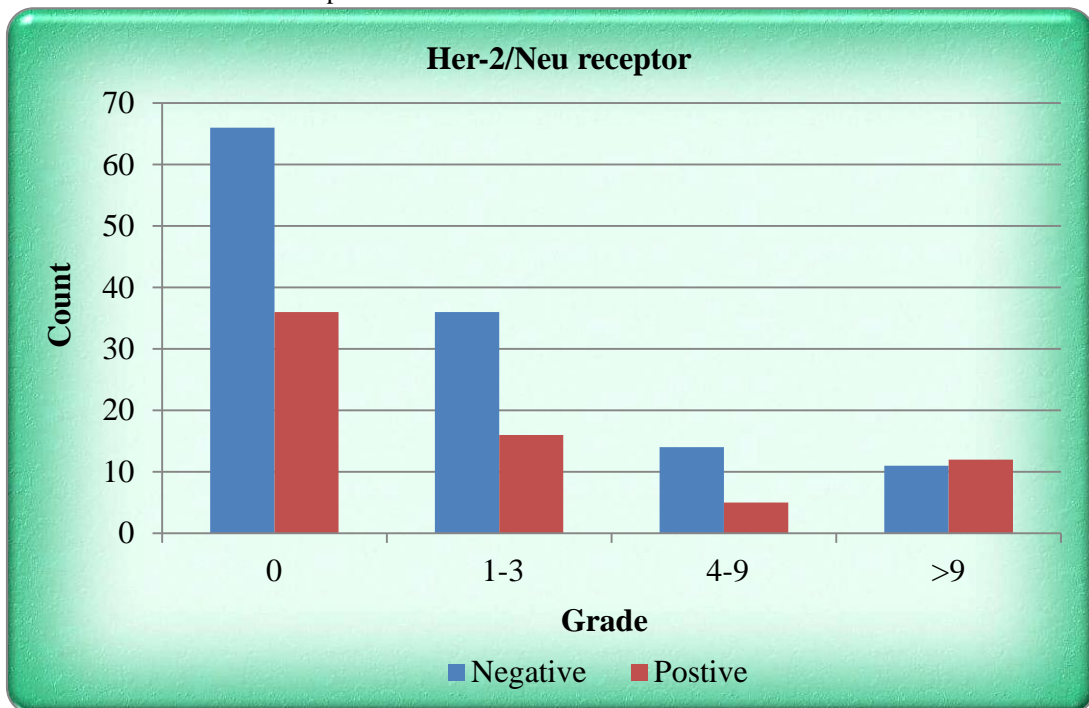
Tumor size is one of the most useful predictors of tumor behavior in breast cancer. Her-2/neu protein receptor over-expression was present in 10 out of 28 (35.7%) T1 lesions, 37 out of 128 (28.9%) T2 lesions, 13 out of 26 (50%) T3 lesions, 11 out of 21 (52.4%) T4 lesions (p value = .048). Her-2/neu protein receptor over-expression was present in 47 out of 156 (30.1%) patients had tumor size less than or equal to 5 cms, while 24 out of 47 (51.1%) with tumor size more than 5 cms in size. (p value = .008). The results was comparable to the study done by Nidam M almasari et al[2], who found Her-2 neu positivity in 35% patients with tumor >5cms.

4.10 Association of Her-2/Neu receptor status with tumor grade



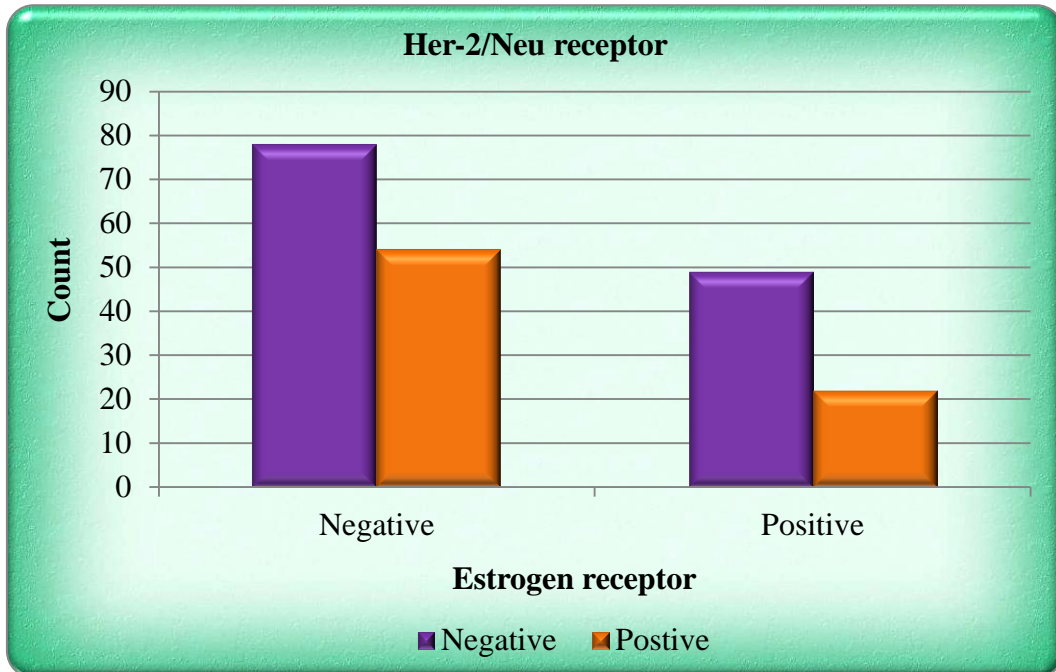
Her-2/neu protein receptor over-expression was present in 4 out of 22 (18.18%) grade I tumor, 28 out of 103 (27.18%) grade II tumors and 37 out of 71 (52.27%) grade III tumors. Her-2/neu protein receptor over-expression was high in high grade tumor which significant statistically. (Chi-square = 14.597, Degree of freedom = 2, p value = .001).In a study of Hoff et al[4], higher-grade tumors were more likely to demonstrate Her-2/neu amplification than lower grade ductal carcinomas ($p < 0.001$) which was also seen in our study. Similarly, Lobanaayadi et al[5] have also reported that 48.54% patients with grade III tumors and 30% patients with grade II tumors had increased rate of HER-2/neu positivity

4.11 Association of Her-2/Neu receptor status with no. of node involved.

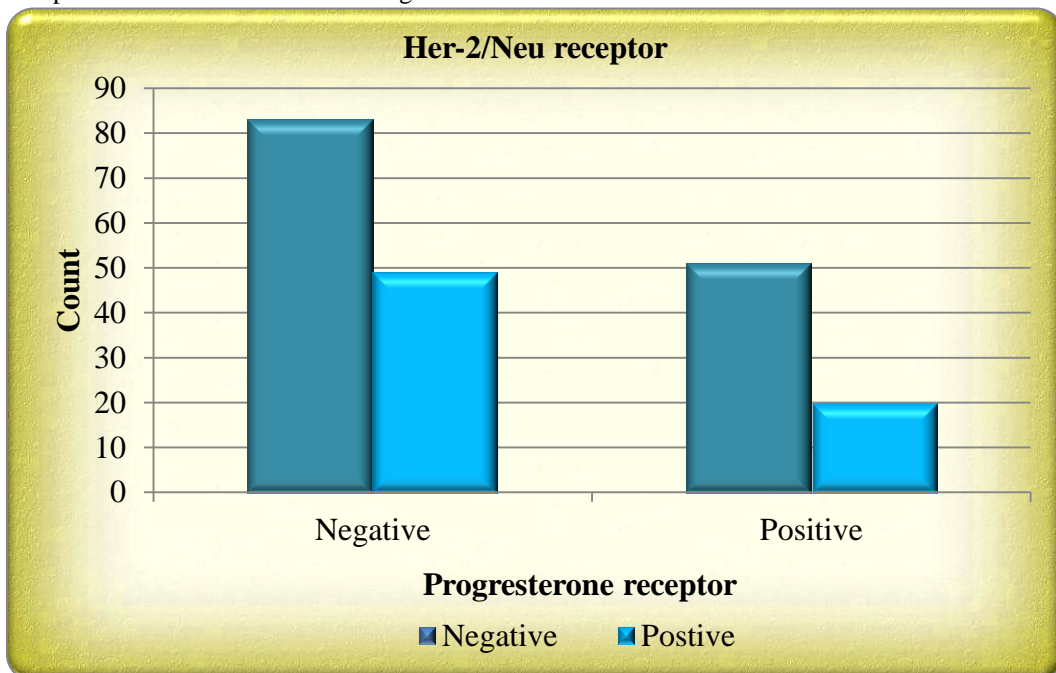


4.12 Association of Her-2/Neu receptor status with ER/PR status

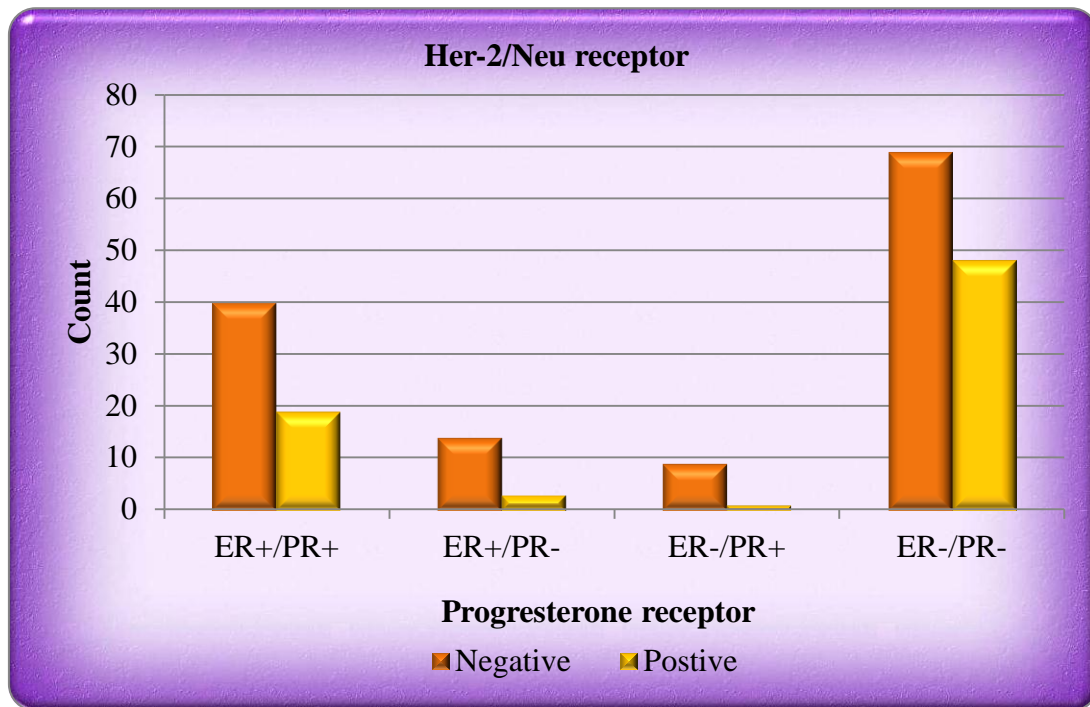
Her-2/neu protein over-expression was present in 22 out of 76 (29.9%) ER positive cases and in 49 out of 127 (38.6%) ER negative cases .In the study of Nidal M Almasari[2], Her-2/neu protein over-expression was present in 39% ER positive cases and in 42% ER negative cases.



Her-2/neu protein over-expression was present in 20 out of 69 (29%) PR positive cases and in 51 out of 134 (38.1%) PR negative cases. In the study of Nidal M Almasari[2], Her-2/neu protein over-expression was present in 65% PR positive cases and in 68% PR negative cases.



Most of the patients in our study who had Her-2/neu protein over-expression were ER-/PR-. This group appeared to represent an aggressive form of breast cancer, presenting at a younger age with large tumor size. Despite the great variation in levels of HER-2/neu positivity, nearly all investigators report a negative relationship between HER-2/neu status and steroid receptors levels [6,7,8,9]. This inverse association has been linked to the fact that estrogens and its receptor are required to suppress HER-2. This leads to lower or absent hormone receptors in women with HER-2/neu positive breast cancers. This is one of the reasons why women who express HER-2/neu may be resistant to tamoxifen[10].



In summary, in the study of 203 cases of breast carcinoma in which Her-2/neu protein receptor over-expression by IHC was performed, a statistically significant association was established between Her-2/neu protein receptor over-expression and large tumor size (p value <.05), which were further increased when tumor size was more than 5 cms in size, tumor grade (p value > .05), infiltrative ductal carcinoma and comedo carcinoma subtypes (p value <.05). Most of the patients in our study who had Her-2/neu protein over-expression were ER-/PR- but we did not get statistically significant value because significant number of patients had triple negative (ER-/PR-/Her-2/neu -ve) disease.

Her-2/neu protein receptor positivity was not significantly associated with age (p value >.05), menopausal status (p value >.05), number of lymph node.

V. Conclusion

HER-2/neu status in breast cancer is important because it provides valuable prognostic, predictive, and therapeutic information. The association of HER-2/neu with additional prognostic factors has always been of interest.

Her-2/neu over-expression tumor was shown to increase disease recurrence and metastasis and thus shorter survival. As over-expression of Her-2/neu protein and amplification of Her-2/neu gene is also associated with poor prognostic tumor characteristics such as high histological grade, high proliferative index, negative or lower estrogen receptor (ER) expression, lymphoid infiltration, p53 mutation, absence of bcl-2, and absence of lobular histology. Her-2/neu +ve and ER-/PR-ve group appeared to represent an aggressive form of breast cancer, presenting at a younger age with large tumor size.

We also found a significantly higher rate of HER-2/neu protein over-expression in patients with poor prognostic factor like large size tumor, high grade tumor and lymph node metastasis. We also found more Her-2/neu over-expression in patients with common histopathological tumor like invasive ductal carcinoma (IDC).

So, the final conclusion is that Her-2/neu testing along with ER/PR status should be performed routinely in all the patients with newly diagnoses breast cancer. Therapy against Her-2/neu (Trastuzumab) a humanized monoclonal antibody, should be considered to all patients whose tumor are strongly positive for Her-2/neu protein receptor because these patients have poor prognostic factors, higher tumor grade, larger size and carry poor prognosis and there is significant benefit in disease free survival and overall survival with concurrent trastuzumab administered over one year, as reported by Piccart et al [11]

References

- [1]. [Slamon DJ](#), [Clark GM](#), [Wong SG](#), [Levin WJ](#), [Ullrich A](#) and [McGuire WL](#). Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. [Science](#). 1987 Jan 9; 235(4785):177-82
- [2]. Nidal M Almasari and Mohammad Al Hamad et al. Immunohistochemical evaluation of human epidermal growth receptor 2 and estrogen and progesterone receptor in breast carcinoma in Jordan, *Breast Cancer Research* 2005
- [3]. Franco Rilke, Maria Ines Colnaghi, Natale Cascinelli, Salvatore Andreola, Maria Teresa Baldini, Rosaria Bufalino, Alessandro Testori. Prognostic significance of her-2/neu expression in breast cancer and its relationship to other prognostic factors. *International Journal of Cancer* Volume 49, Issue 1, pages 44–49, 19 August 1991. DOI: 10.1002/ijc.2910490109
- [4]. Hoff ER, Tubbs RR, Myles JL & Procop GW. HER-2/neu amplification in breast cancer. Stratification by tumor type and grade. *Am J ClinPathol* 2002;49:110-3.
- [5]. Lobna Ayadi, Abdelmajid Khabir, Habib Amouri, Sondes Karray, Abdallah Dammak, Mohamed Guermazi and Tahya Boudawara. Correlation of HER-2 over-expression with clinicopathological parameters in Tunisian breast carcinoma-*World Journal of Surgical Oncology* 2008, 6:112.
- [6]. Tatjana Ivković-Kapiclj, Slavica Knežević-Ušaj, Milana Panjković, Dragana Dilas-Ivanović et al. HER-2/neu over-expression in invasive ductal breast cancer – an association with other prognostic and predictive factors- *Arch Oncol* 2007;15(1-2):15-8.
- [7]. Mohammad Naeem, Amir Nasir, Zahid Aman, Tariq Ahmad and Ambreen Samad. Frequency of HER-2/neu receptor positivity and its association with other features of breast cancer- *J Ayub Med Coll Abbottabad* 2008; 20 (3).
- [8]. Traina A, Agostara B, Marasà L, Calabrò M, Zarcione M. HER2/neu expression in relation to clinicopathologic features of breast cancer patients. *Ann NY Acad Sci*. 2006 Nov; 1089:159-67.
- [9]. Ariga R, Zarif A, Korasick J, Reddy V, Siziopicou K. Correlation of Her-2/neu gene amplification with other prognostic and predictive factors in breast carcinoma. *Breast J* 2005;11:278-80.
- [10]. Tetu B & Brisson J. Prognostic significance of Her-2/neu oncogene expression in node-positive breast cancer. The influence of the pattern of immunostaining and adjuvant therapy. *Cancer* 1994;73:2359-65.
- [11]. Piccart-Gebhart MJ, Procter M, Leyland, Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 353:1659-1672, 2005.