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Correlation of HER-2/*neu* Status with Estrogen (ER) & Progesterone (PR) Receptor in Breast Malignancies

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ABSTRACT

Introduction: Prognosis and management of breast cancer are influenced by the classic variables such as histologic type and grade, tumor size, lymph node status, status of hormonal receptors- i.e. estrogen receptor (ER) and progesterone receptor (PR) of the tumor, and, more recently, HER-2/*neu* (Human Epidermal Growth factor Receptor-2) overexpression. Expression levels of the estrogen, progesterone and HER2/*neu* receptors which characterize clinically distinct breast tumours have been shown to change during disease progression and in response to systemic therapies. The interrelationship of ER, PR, and HER-2 has come to have a crucial role in the management of breast cancer. **Aims & Objectives:** To determine the ER, PR and HER2/*neu* status in breast malignancies. **Place and duration of study:** The study was conducted at Department of Histopathology, Federal Postgraduate Medical Institute, Shaikh Zayed Hospital Lahore, for the period of Six months. **Material & Methods:** 30 samples of diagnosed breast cancer were included in study. Formalin fixed paraffin embedded wax block were taken for immunohistochemical staining of ER, PR & HER-2/*neu*. **Results:** Out of 30 cases, racially 29 were Punjabi and 1 was Pakhtun. There were 23 mastectomy samples and 7 needle core biopsies. Out of 30 cases, 29 were Infiltrating Ductal Carcinoma. Grade I, II, III 13.3%, 66.7% and 20% respectively and only one case was of Carcinosarcoma ($p<0.01$). Overall immunoexpression for ER, PR and HER-2/*neu* were 33.3% ($p<0.01$), 56.7% ($p<0.05$) and 73.3% respectively. Triple positive (TP) cases were 23.3% and triple negative (TN) were 10 %. Regarding ER expression in infiltrating ductal carcinoma, 63.3% were ER negative and 33.3% were ER positive and comparison was statistically highly significant ($p<0.01$).PR expression in infiltrating ductal carcinoma showed 56.7% PR positive and 40% PR negative which was statistically significant ($p<0.05$).There is negative correlation of HER-2/*neu* positive and ER positive and positive correlation of HER-2/*neu* positive and PR positive cases.
Conclusion: There is inverse correlation of HER-2/*neu* positive and ER positive and positive correlation of HER-2/*neu* positive and PR positive cases.

Key words: ER, PR, HER-2/*neu*, Breast receptors, Breast carcinoma.

INTRODUCTION

Worldwide, breast cancer is the most common type of cancer and the most common cause of cancer-related mortality among women. In women, breast cancer accounts for 26% of new cases of cancer and 15% of cancer deaths, second only to lung cancer as a cause of cancer-specific death. Although incidence rates (all races combined) are substantially higher for women aged 50 and older (375.0 per 100,000) compared with women younger than 50 years (42.5 per 100,000), approximately 23% of breast cancers are diagnosed in women younger than 50 years, because those women represent 73% of the female population.[1]

In Pakistan as well, breast is the most common site of female cancer, accounting for one third of female cancer (age-standardized Rate=51.7). Bhurgri et al (2000) has reported for Karachi (Pakistan) the highest incidence of breast cancer for any Asian population except Jews in Israel.[2] Armed Force Institute of Pathology (AFIP), Rawalpindi is publishing regular cancer data in form of decade monographs.[3]

Prognosis and management of breast cancer is influenced by the classic variables such as histologic type and grade, tumor size, lymph node status, status of hormonal receptors- estrogen receptor (ER)

and progesterone receptor (PR) of the tumor, and, more recently, HER-2/*neu* status.[5] The histopathological examination of the breast cancer is based on the morphological features but more specific prognostic information about its biology are obtained from the immunohistochemical (IHC) testing of the human epidermal growth factor receptor HER2/*neu*, estrogen receptors (ER) and progesterone receptors (PR). Expression levels of the estrogen, progesterone and HER2/*neu* receptors which characterize clinically distinct breast tumors have been shown to change during disease progression and in response to systemic therapies.[6]

HER-2/*neu*, also known as c-erbB-2 (HER-2/*neu*), a proto-oncogene located on chromosome 17, is amplified and/or the protein (HER-2/*neu*) is over expressed in 15% to 25% of invasive breast carcinomas and is associated with a worse clinical outcome. In contrast, ER is expressed in 70% to 95% of invasive lobular carcinomas and in 70% to 80% of invasive ductal carcinomas, and PR is expressed in 60% to 70% of invasive ductal carcinomas.[4] Expression of ER and/or PR generally is associated with a better outcome. Survival and response to hormone therapy are most favorable among women with tumors positive for both ER and PR, intermediate for tumors discordant on receptor status, and least favorable for tumors negative for both.[7] The interrelationship of ER, PR, and HER-2/*neu* has an important role in the management of breast cancer. It has been shown that patients with breast carcinoma over expressing HER-2/*neu* do not respond to tamoxifen therapy. Although HER-2/*neu* expression is generally inversely correlated with ER and PR expression, the precise extent of its inverse relationship and its association with classic histologic prognostic indicators has not been studied systematically in a large series of cases.[8]

The hormone receptor expression measured by IHC is accepted as standard evaluation method all over the world, but the cutoff point in immune-histochemical (IHC) evaluation is still controversial.[9]

The randomized population coming to Shaikh Zayed Hospital is different (majority from Punjab) compared to any other tertiary care center in city. As no data is available from this institute on breast cancer receptor status, so this study may help to determine the behavior of breast cancer and their prognostic attributes in patients coming to Shaikh Zayed Hospital.

The Receptor Status: The receptor status of breast cancers has traditionally been identified by immunohistochemistry, which stains the cells based on the presence of estrogen receptors (ER), progesterone receptors (PR) and HER-2/*neu* receptors.[10]

Receptor status is used to divide breast cancer into several molecular classes:

- Basal-like (13% to 25% of NST carcinomas), which are ER-ve, PR-ve and HER-2/*neu*-ve (triple negative, TN). These tumors are generally high grade with high proliferative index and aggressive behavior. Most BRCA1 breast cancers are basal-like TN.[11]
- Luminal A (40% to 55% of NST carcinomas), which are ER and PR +ve, HER-2/*neu* negative and low grade. These tumors are generally slow growing and better respond to hormonal treatment.
- Luminal B (15% to 20% of NST carcinomas), which are ER+ ve, PR +ve and over expresses HER-2/*neu* (Triple Positive). These are major group of ER +vecancers with higher grade and higher proliferative rate, may respond to chemotherapy.[12]
- HER-2/*neu* Positive (7% to 12 % of NST carcinomas), which have amplified ERBB2, over express HER-2/*neu* protein and ER –ve. These cancers are often poorly differentiated and associated with high frequency of brain metastasis.

Claudin-low/ Normal breast-like (6% to 10% of NST cancers), a more recently described class that is often triple-negative but which may be distinct in that this subset of TN also has low cell-cell junction protein and has frequent lymphocytic infiltration. Usually well-differentiated ER +ve and HER-2/*neu* negative.[13]

MATERIAL AND METHODS

The study was conducted at Department of Histopathology, Shaikh Zayed Federal Postgraduate Medical Institute, Shaikh Zayed Hospital, Lahore. The specimens of the patients with breast malignancies received in Histopathology Department, Shaikh Zayed Hospital were enrolled in study. The patient were accessed in the relevant ward, explained the objective of study, benefits of tests, sought informed / written consent, the patient's specimen were enrolled in study for ER, PR and HER-2/*neu* status and these tests were carried out free of cost for the patient.

Inclusion Criteria

- Specimens of female patients (only) of reproductive age, peri-menopausal and post menopausal with invasive breast carcinomas diagnosed by histopathology as primary tumor.

- Tissue fixation should be done with 10% neutral buffered formalin for at least 6-72 hours.
- Needle core biopsy, Trucut biopsy, lumpectomy, mastectomy

Exclusion Criteria
- In situ carcinoma.
- Patients receiving neo-adjuvant therapy.
- Recurrent carcinoma.
- Cytological specimen/smear

Sample Size
The sample size were estimated by using 5% level of significance, 80% power of test with expected expression of ER 49.1% and 78.17%; and PR in 24.3% and 53.13% in HER-2 +ve and HER-2 -ve cases respectively. The estimated size was 30. Thirty (30) cases fulfilling the criteria were included.

Reagents and Procedure: A variety of detection kits are available in market, Super Senstive™ One-Step Polymer-HRP Detection System by "Biogenex", was used for this study following standard procedure of staining and demonstration.

Estrogen Receptor Ab-11 (Clone 1D5)
Ab-11 strongly stains the nucleus of epithelial cells in breast carcinomas.
Mol. Wt. of Antigen: 67kDa
Progesterone Receptor Ab-9 (Clone 1A6)
Description: Human progesterone receptor (PR) exists in two forms: 116kDa (B-form) and 81kDa (A-form).
HER-2/*neu*/c-erbB-2 (Clone SP3)
Clone SP3 is excellent for staining of formalin/ paraffin.
Cellular Localization: Cell membrane
Assessment of staining:
- **ER/PR Nuclear Staining Scoring:** Estrogen and progesterone receptors are located in the nucleus of breast epithelial and carcinoma cells. The percentage of tumor cells demonstrating positive reactivity, their intensity of staining results combined together and simple arithmetical number, either of these two methods has been previously in practice. Recently simpler 'Allred score' methods have been promoted which appear equally effective clinically. This uses either a direct count of the proportion of tumor nuclei that take up stain or a simple combination of % cells staining plus a measure of intensity of stain. The scoring system in table is a simple additive system giving a range from 0 to 8 (Minimum score 0, maximum score 8).

Allred Score system

Score for Proportion staining	Score for staining intensity
0 = No Nuclear staining	0 = No staining
1 = <1% Nuclei staining	1 = Weak staining
2 = 1 – 10% Nuclei staining	2 = Moderate staining
3 = 10 – 33% Nuclei staining	3 = Strong staining
4 = 33 – 66% Nuclei staining	
5 = 66 – 100% Nuclei staining	

- **HER-2/neu membranous Staining Score:**

Grading of the Immunohistochemical Staining for HER-2/*neu* Over Expression

Staining Pattern	Score	HER-2/neu over expression assessment
No staining is observed or membrane staining is observed in less than 30% of the tumor cells.	0	Negative
A faint/barely perceptible membrane staining is detected in more than 30% of the tumor cells. The cells are only stained in part of their membrane.	1+	Negative
A weak to moderate complete membrane staining is observed in more than 30% of the tumor cells.	2+	Weakly Positive
A strong complete membrane staining is observed in more than 30% of the tumor cells.	3+	Strongly Positive

If the results are either 3+ or 0, the determination can be safely stopped there, since the correlation with gene over expression or lack of it, respectively, as measured by FISH, is nearly 100%. If the immunotest gives instead a result of 1+ or 2+, the performance of FISH is recommended.

Statistical analysis:
Statistical analysis was conducted using SPSS version 16

RESULTS

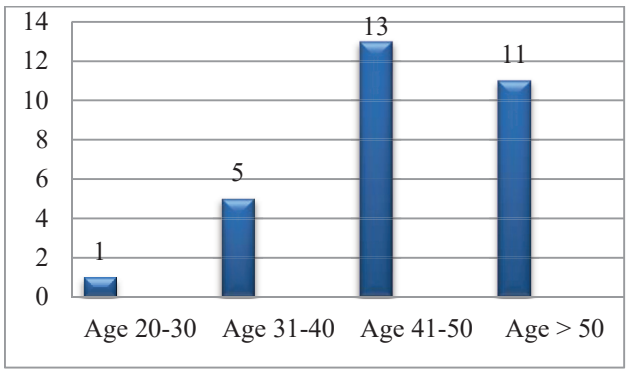

Fig-1: Age distribution of cases (n=30)

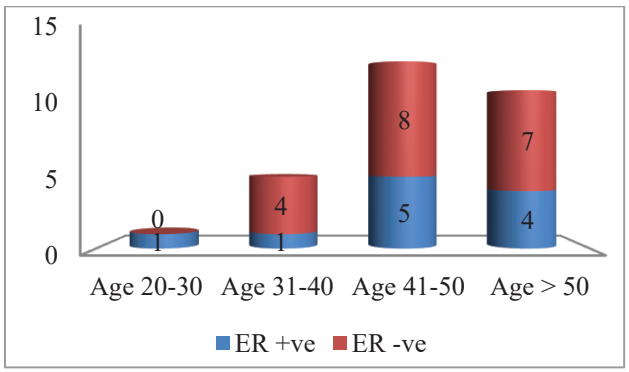

Fig-2: Estrogen receptor status, age distribution (n=30)

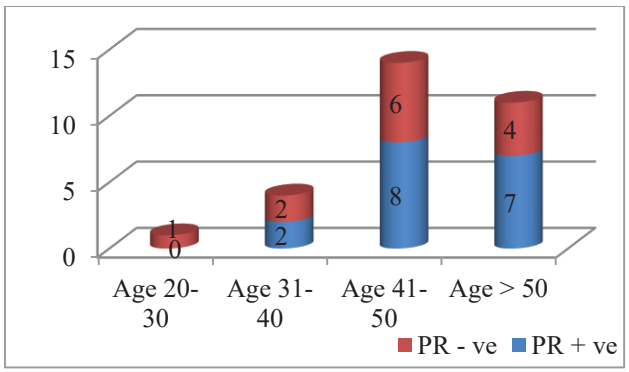

Fig-3: Progesterone receptor status, age distribution (n=30)

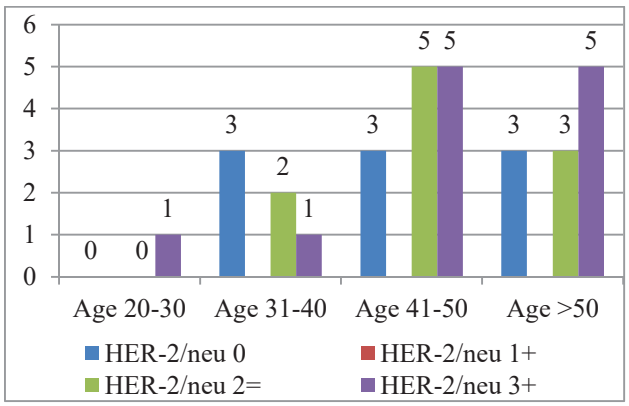

Fig-4: HER-2/*neu* over-expression with age distribution

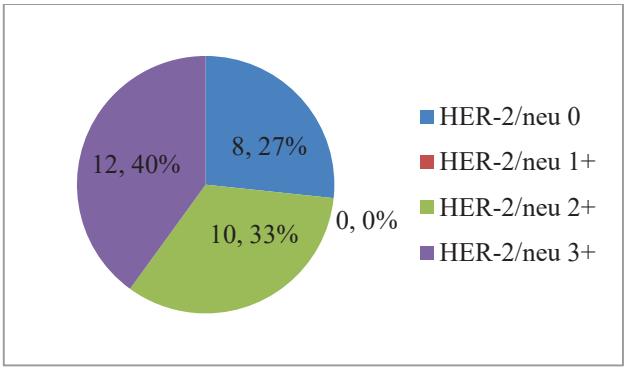

Fig-5: HER-2/*neu* score in breast carcinomas(n=30)

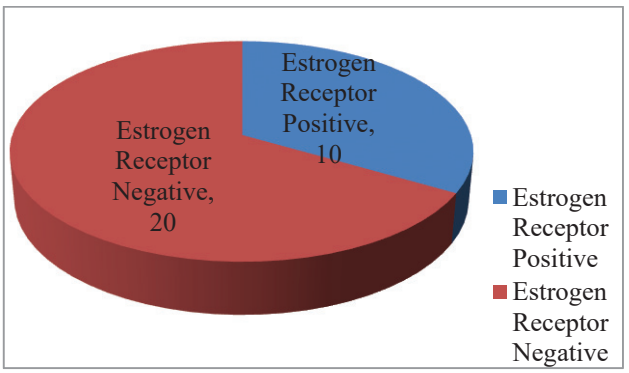

Fig-6: Estrogen receptor status of breast malignancies (n=30)

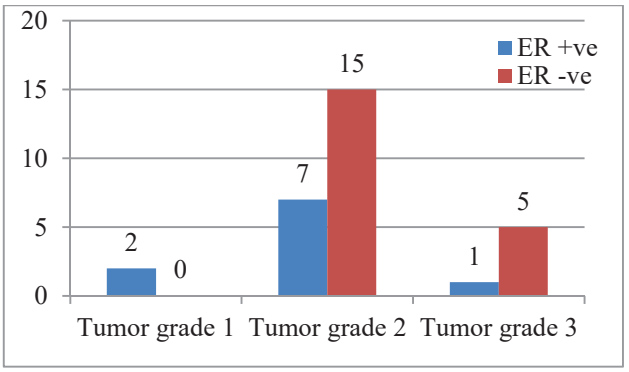

Fig-7: ER Status with tumor grades (n=30)

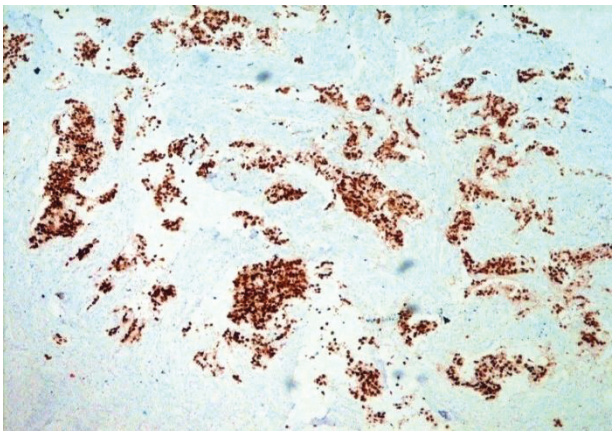

Fig-8: Photomicrograph Estrogen Receptor (ER) Positive, IH. 4x10

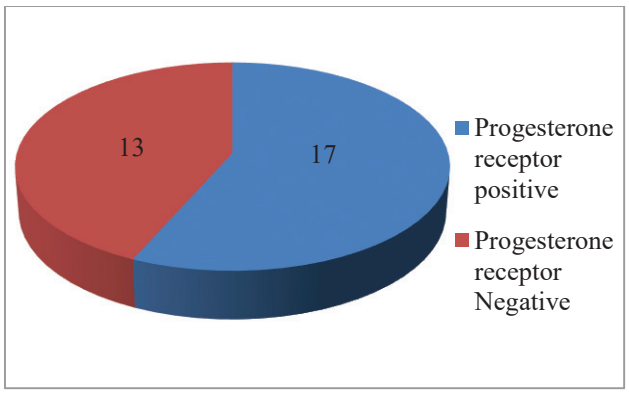

Fig-9: Progesterone receptor status in breast malignancies (n=30)

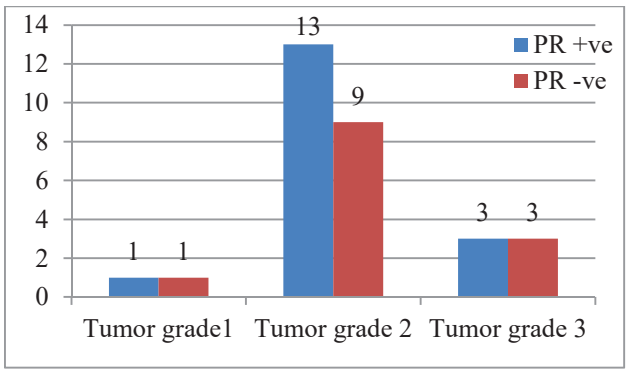

Fig-10: PR Status with tumor grades (n=30)

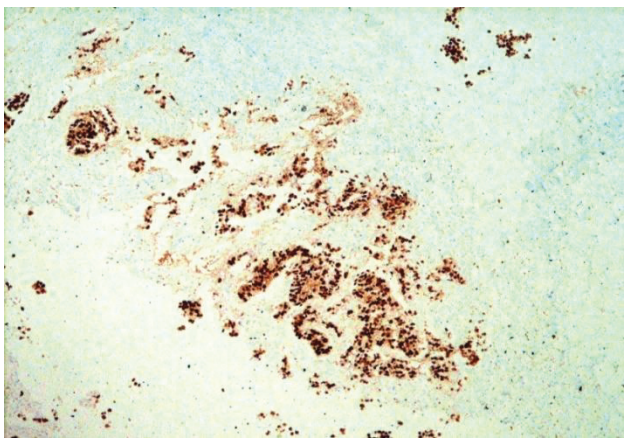

Fig-11: Photomicrograph Progesterone Receptor (PR) Positive, IH. 4x10

Histological Subtypes	HER-2/*neu*			ER		PR	
	Strong +ve	Weak +ve	-ve	+ve	-ve	+ve	-ve
Ductal Carcinoma	12* (40%)	09* (30%)	08 (26.7%)	10 (33.3%)	19* (63.3%)	17** (56.7%)	12 (40%)
Carcinosar-coma	--	01 (3.3%)	--	Nil	01 (3.3%)	Nil	01 (3.3%)
Total Subjects	12 (40%)	10 (33.3%)	08 (26.7%)	11 (33.3%)	19 (66.6%)	17 (56.7%)	13 (43.3%)

Table-1: Frequency of HER-2/*neu*, ER & PR in various histological types (n=30) (*P<0.01) (**P<0.05)

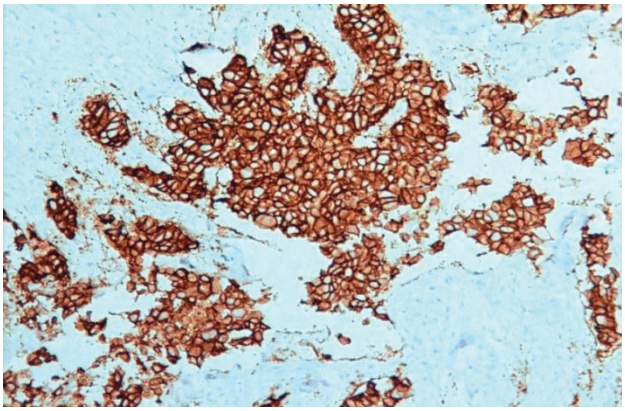

Fig-12: Photomicrograph 12: HER-2/*neu* 3+, IH. 10X10

Receptors	No. of cases	%age
ER/PR+ve,HER-2/neu +ve	07	23.3%
ER/PR+ve,HER-2/neu -ve	01	3.3%
ER/PR-ve,HER-2/neu +ve	08	26.7%
ER/PR-ve,HER-2/neu -ve	03	10%
ER/PR +ve	08	26.7%
ER/PR -ve	11	36.7%
ER+/PR-ve	02	6.7%
ER-/PR +ve	09	30%
HER-2/neu +ve	22	73.3%
HER-2/neu -ve	08	26.7%

Table-2: Receptor Status in Different Cases (P<0.01)

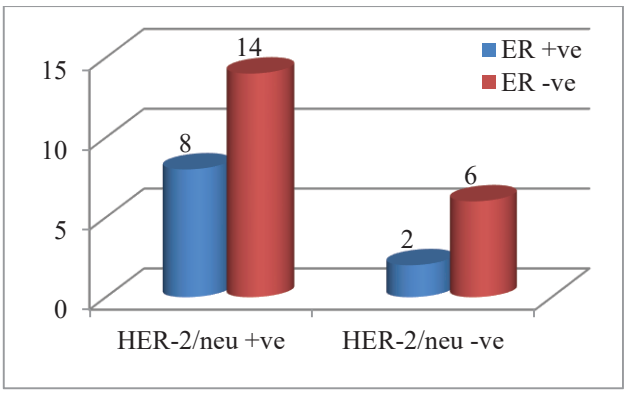

Fig-13: Comparison of Her -2/*neu* status with ER Status

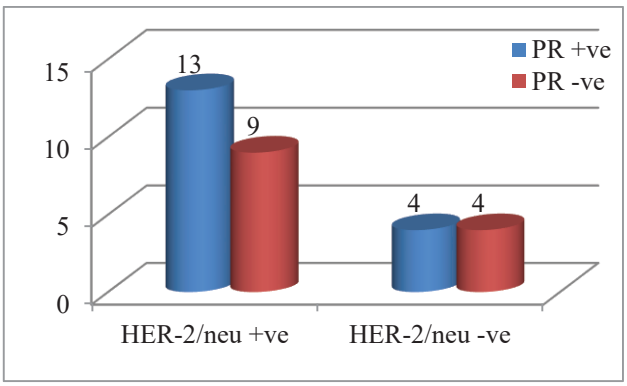

Fig-14: Comparison of Her -2/*neu* status with PR Status

	HER-2/*neu* +ve (n=22)	**HER-2/*neu* –ve (n=08)**
Total cases	22 (73.3%)	08 (26.7%)
Age (Mean)	49.2	48.6
Grades	1 02 (9.1%) 2 16* (72.7%) 3 04 (18.2%)	1 Nil 2 06* (75%) 3 02 (25%)
ER Expression	ER-ve 14*(63.6%) ER+ve 08 (36.4%)	ER-ve 06*(75%) ER+ve 02 (25%)
PR Expression	PR-ve 09 (40.9%) PR+ve 13*(59.1%)	PR-ve 04 (50%) PR+ve 04 (50%)

Table-3: Expression of HER-2/*neu* with ER/PR Status

Correlation with	**r value**	**Significance**
HER-2/neu +ve Vs ER +ve	(-0.682) -ve correlation	P< 0.01(HS)
HER-2/neu +ve Vs PR +ve	(0.821) +ve correlation	P<0.01(HS)

Table-4: Correlation of HER-2/*neu* positive with ER/PR expressions

DISCUSSION

In the study of Sofi at el (2012), the receptor status was available in 101 cases, 67 (66.3%) cases were ER positive, 64 (63.4%) cases were PR positive, 61 (60.4%) cases were both ER and PR positive, 31 (30.7%) cases were both ER and PR negative, 6 (5.9%) cases were ER positive and PR negative and 3 (2.9%) cases were ER negative and PR positive. While in this study, out of 30 cases, 10 (33.3%) were ER positive and 17 (56.6%) were PR positive, and in 8 (26.6%) were both ER and PR positive while 20 (66.7%) were ER negative, 13 (43.3%) were PR negative and 11 (36.7%) were ER, PR negative.[14] IDC (Infiltrating ductal carcinoma) was the predominant morphological category with IDC NOS (not otherwise specified). Modified Bloom Richardson Grading was applicable to 119 cases, of which 9 (7.6%) cases were grade 1, 62 (52.1%) cases were grade 2 and 48 (40.3%) cases were grade 3 (Sofi at el 2012).

While in this study, 29 (96.6%) were Infiltrating Ductal Carcinoma and 1 (3.3%) was carcinosarcoma. Regarding grade, 02 (6.6%), were in grade 1, 22 (73.3%) were in grade 2 and 6 (20%) in grade 3 and difference was highly significant when comparing grade 2 with other grades (p< 0.01).[14] Regarding HER-2/*neu* expression, out of 22 HER-2/*neu* +ve cases, 08(36.4%) were ER +ve and 13 (59.1%) were PR +ve. There is negative correlation of HER-2/*neu* +ve and ER+ve cases while +ve correlation of HER-2/*neu* +ve and PR +ve cases.

A retrospective analysis was performed on 267 cases of breast cancer referred for treatment at King Hussein Cancer Center, Jordan between the period of June 2003 and June 2004.[15] Standard immune stains were used for evaluation of hormone receptors and HER-2/*neu*. In addition, evaluation of HER-2/*neu* was done by FISH in selected cases. Of these 267 cases, 240 (89.9%) were ductal carcinomas of various histological grades, 122 (50.8%) of which were ER-positive, 138 (57.5%) PR positive and 42 (17.5%) HER-2/*neu*-positive. Twenty two (8.2%) of all cases were lobular carcinomas, 15 (68%) of which were ER-positive, 20 (90.9%) PR positive and 3 (13.6%) HER-2/*neu*-positive. Five (1.9%) of the total cases were of mixed lobular and ductal types, 4 (80%) of which were ER-positive, 3 (60%) PR-positive and none were positive for HER-2/*neu*

Another study was conducted at Department of Histopathology, Armed Forces Institute of Pathology, Rawalpindi. Out of 535 cases, there were 481 (89.9%) cases of infiltrating ductal carcinoma with mean age of 48 years and mean tumor size of 4.4 cm. Tumor grade II was seen in 68% cases and lymph node metastases were present in 65% cases. HER-2/*neu* expression was seen in 31% cases, while ER and PR expression was seen in 72.3% and 62.6% respectively. ER and PR showed inverse association with HER-2/*neu* while positive association was seen with lymph node metastases ($p<0.05$). No association was seen between tumor size and tumor grade. Joint ER and PR expression also showed a higher number (73.5%) of HER-2/*neu* negative cases.[16]

Study conducted at Department of Pathology and Microbiology, Aga Khan University Hospital; Mean age of the patients was 48.3 years. The left breast was more commonly involved (57%). Tumor size ranged from 0.3 to 15.0 cm; 12% were >2.0 and 35.3% were >5.0 cm in diameter. The predominant morphology was infiltrating ductal carcinoma (85.3%). The majority of the cases presented as grade II (55.3%) lesions with tumor necrosis (70%) and lymph node involvement (71.3%). ER and PR were positive in 32.7% and 25.3% cases respectively. HER-2/*neu* was positive (3+) in 24.7%. ER positivity increased and HER-2/neu positivity decreased with rising age. ER and PR expression was significantly lower in HER-2/*neu* positive as compared with HER-2/*neu* negative tumors (ER 83.8% vs 69.8%; PR 91.9% vs 77.8%). In the HER-2/*neu* positive tumors, ER and PR expression in high grade tumors was significantly

decreased compared with intermediate grade tumors (ER 5.6% vs 10.5; PR 0% vs 5.3%). ER expression in the HER-2/*neu* positive, large sized tumors was also significantly decreased compared with smaller tumors (ER 6.3% vs 11.8).

In regard to HER-2/*neu*, the results appear to be within the commonly reported rates of 20% to 30%. Less than 20% or more than 30% of HER-2/*neu* over-expression was reported by many studies.[17]

The overall co-expression of hormones receptors in another study were found as follow: ER +ve/PR +ve (39.41%), ER +ve/PR -ve(13.86%), ER-/PR+(0.72%) and ER-/PR-(45.98%). One of the interesting results in our study was that ER-/PR+ which found only in one case out of 137 malignant cases. Such finding was reported by Nicholas et al,[18] he found only one case out of 192 with ER-ve have PR+ve with weak positive immune staining.

These results were strongly challenged by Colomer et al.[19] they reported ER+/PR+, ER+/PR–, ER–/PR+, and ER–/PR– in 46%, 19%, 7% and 28%, respectively. In another study, 63.9% of white American women with breast cancer were ER+/PR+, 12.8% ER+/PR-, 3.6% ER-/PR+ and 19.8% ER-/PR- while among black American women 48.3% were ER+/PR+, 11.8% ER+/PR-, 5% ER-/PR+ and 34.8% ER-/PR-.

One well defined subtype of breast cancer is characterized by lack of ER, PR and HER-2/*neu* over-expression/ or amplification that's called TN tumors.[20] It constitutes 10% to 20% of breast cancer. The inverse association between hormones receptors and HER-2/*neu* 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 over-express HER-2/*neu* may be resistant to Tamoxifen.[21] These results confirmed that the presence of ER and PR receptors in human breast cancer cell lines resulted in a strong reduction of HER-2/*neu* protein over-expression. These findings are in agreement with other reports in the literature, which showed an inverse significant association between hormones receptors expression and HER2 over-expression.

Among the various proposed prognostic factors, HER-2/*neu* over-expression has been found to predict early metastasis, shortened disease-free survival, overall survival, poor clinical outcome with therapy and early recurrence in breast carcinoma. The association between amplified HER-2/*neu* gene and a shorter disease-free survival (DFS) as well as overall survival, has been confirmed by several studies. This subset of HER-2/*neu* positive breast cancer also shows resistance to certain forms of chemotherapy like CMF (cyclophosphamide, methotrexate and 5-Fluorouracil) and tamoxifen, while showing sensitivity to others like doxorubicin. HER-2/*neu* has been found to be associated with other poor prognostic factors including age, lymph node status, tumor size and histological grading. Trastuzumab, a humanized antibody to HER-2/*neu* protein is being used as a therapy for patients with advanced breast cancer.[21]

CONCLUSION

- Out of 30 cases 29 were Infiltraing ductal carcinoma, grade 1, grade 2, grade 3 were 02 (6.6%), 22 (73.3%) and 06 (20%) respectively.
- Only one case was that of carcinosarcoma grade 2
- HER-2/*neu* over expression was found in 73.3% (22).
- Age was found to be statistically associated with HER-2/*neu* positivity and young patients had HER-2/ *neu* positive breast carcinoma.
- 23.3 % (07) cases are triple positive disease and 10% (03) are with triple negative disease.
- Among HER-2/*neu* +ve cases, 72.7% (16) were of IDC grade 2.
- In HER-2/*neu* +ve cases, 36.4% (8) were ER +ve while 63.6% (14) were ER-ve.
- In HER-2/*neu* +ve cases, 59.1% (13) were PR +ve while 40.9% (09) were PR-ve.
- 63.6% (14) cases were with ER –ve in HER-2/*neu* +ve subjects.
- 59.1 % (13) cases were with PR +ve in HER-2/*neu* +ve subjects.
- There is inverse correlation of HER-2/ *neu* +ve and ER +ve subjects and positive correlation of HER-2/ *neu* +ve with PR +ve cases.
- In IDC, 21 cases were with HER-2/ *neu* +ve (12 cases +3 & 9 cases +2) and 08 cases were with HER-2/ *neu* –ve. 10 cases were with ER +ve and 19 cases were with ER –ve. 17 cases were with PR +ve and 12 cases were with PR –ve. Only one case of Non-IDC (Carcinosarcoma) is ER/PR –ve and HER-2/ *neu* +2 in this study.
- Out of 07 triple +ve cases, 05 were grade 2 IDC with age groups between 40-60 years. One triple +ve case was grade 1 IDC with age 45 years and one triple +ve case was grade 3 IDC with age 52 years.
- All 03 triple –ve cases were of IDC grade 2 with age group ≤ 50 years.

Limitation of study:

This study is based on immunohistochemical method for detection of estrogen receptor,

progesterone receptors and HER2/*neu* over expression. HER2/*neu* 2+ breast carcinomas on immunohistochemistry are equivocal in their estimation, for such cases florescent in-situ hybridization (FISH) is the standard method for HER2/*neu* over expression. This study by its very design is based on immunohistochemical method, so is deficient in conclusive and reliable expression of HER2/*neu* 2+ cases.

In this study for HER2/*neu* estimation membrane staining of >30% of tumor cells was employed, which has been recently revised to > 10% of tumor cells by College of American Pathologist (CAP) in its recent, "Template for reporting results of biomarker testing of specimen from patient with carcinoma of breast" version 1.3.0.0 posting date August 2019.

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