Relationship of Her-2 Neu with Estrogen and Progesterone receptors & a brief description of Histological features in breast cancer.

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Abstract:

Background: Ca breast is the most common malignancy among women in the world. The receptor status of breast cancer including ER, PR and HER-2 Neu play a crucial role in planning the management of the disease.

Aims: Assessment of the hormone receptor (ER, PR and HER-2-Neu) expression in carcinoma breast is the primary aim and comparison of receptors with clinicopathological parameters: Age, histological type, grade of tumor and lymph node metastasis is also being focused in this study.

Methods: All the patients of breast cancer with known hormone receptors status were included in the study from Nov.2018-Oct.2019.

Results: Amongst 90 cases, 84.4% belong to invasive carcinoma of no special type (NST). The percentage of ER, PR and Her-2 Neu expression were 57.7%, 37.7%and 25.5% respectively. Mean age for HER-2Neu (+) and Her-2 Neu (-) were 53.4 and 52.04 respectively. Mean age for ER + and ER- were 56.42 and 47.56 respectively. Mean age for PR+ and PR- were 53.6 and 54.29 respectively. Patients with ER+, PR+ usually have lower grade1 tumor whereas patients with HER-2 Neu expression presented with higher grade tumor. There was an inverse relationship between ER, PR expression and HER-2 Neu expression (p-value<0.05). There was significant association between lymph node metastasis and Her-2 Neu and PR positivity.

Conclusion: ER and PR expression were inversely related to Her-2 Neu receptor expression. Elder patients (age>45 years) have more ER and PR positivity than younger patients (age<45 years). Her-2 Neu expression is associated with higher tumor grade (Grade 2 and 3) and probability of metastasis to the axilla is more in cases with HER-2 Neu overexpression .

KEYWORDS: Estrogen receptors, Progesterone receptors, c-erbB-2(Her-2-Neu), Carcinoma breast, Hormone receptor status in breast.

INTRODUCTION:

Breast cancer is the most common malignancy and the leading cause of cancer related deaths among women all around the world[1]. In India,breast cancer was the second most common cancer in women prior to 1990 (Takiar and Srivastava,2008). Mean age of Indian breast cancer patients is lower as compared to Western countries with an average difference of one decade[2,3]. In developed countries, majority of the patients have a negative lymph node status[4,5]. Indian and Asian studies have documented a greater percentage of breast carcinomas with lymph node metastasis compared to western figures[6,7]. For the early detection of the disease and for increasing the survival of the patients, several advancements in the management of breast cancer has been made[8,9]. Estrogen receptor, progesterone receptor (ER,PR) and HER-2Neu receptor have their own importance in the prognosis and management of the breast cancer[10].

Estrogen receptors, progesterone receptors and Her-2 Neu expression are crucial in the biology of breast cancer. It is known that ER and PR expression are the only predictive factors with proven usefulness in selecting patients who are likely to respond to adjuvant endocrine therapy[11]. Hormone receptors in tumor tissue correlates well with the response to hormone therapy and chemotherapy[12]. Patients lacking these receptors tend to have shorter disease free survival and earlier recurrences than those expressing these receptors. Her-2-Neu receptor or c-erbB-2 is the receptor whose overexpression is associated with adverse prognosis[13].

Correlation between ER,PR and HER-2-Neu has an important role in management of breast cancer. Ca breast patients overexpressing Her-2-Neu do not respond to Tamoxifen therapy[14]. The prognostic effects of Her-2-Neu expression appear to be stronger in node positive carcinomas than in node negative carcinoma[15]. Based on HER-2-Neu overexpression, humanized monoclonal antibody known as Trastuzumab has been introduced which is very effective in the treatment of cases in which this oncogene product is overexpressed[16].

MATERIALS AND METHODS:

The study was carried out in Government Medical College, Jammu, a tertiary care hospital . The present study included 90 cases of breast cancer. This is a prospective study and the duration of the study was 1 year extending from November 2018- October 2019.

The histological type, tumor grade, lymph node involvement ,estrogen and progesterone receptor and HER-2 Neu receptor expression were assessed. Biopsy specimens[either trucut biopsy or post op mastectomy specimens] were sent to pathology lab where they were processed and analysed for histopatholological examination ,status of ER/PR/HER-2/Neu and its pathological grading.Hormone receptor assay wasdone using immunohistochemistry.

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Tumor tissue was submitted in paraffin embedded block and heated incitrate buffer (pH=6.0) at approx 120°C and then Cooled for 10 minutes. Slides are loaded on autostainer and stained with haematoxylin and Eosin. Immunoreactivity is evaluated by estimating the percentage of positively stained nucleus for ER and PR and membranous staining for HER-2/Neu receptors.

For interpretation of Her-2 Neu staining, following scoring system was used.

Score 0: No staining is observed or membrane staining is observed in <10% of tumor cells.

Score 1+: Faint /barely perceptible membrane staining is detected in any population of tumor cells.

Score 2+: A weak to moderate complete membrane staining is observed in>10% of tumor cells. It is considered as weak positive.

Score 3+: Strongly positive. A strong complete membrane staining is observed in >30% of tumor cells. Score 3+ was considered as strong positive immunostaining for Her-2 Neu.

The ER and PR results were screened and interpreted according to the published guidelines by the the American Society of Clinical Oncology and College of American Pathologist (ASCO/CAP).

RESULTS:

Over a period of 1 year,90 patients with breast carcinoma were studied. Most of the cases (84.4%) belong to invasive carcinoma of no special type(NST), also known as invasive ductal carcinoma or ductal NOS. Four patients had invasive Lobular Carcinoma, six patients Medullary Carcinoma, two patients Papillary Carcinoma and two patients Metaplastic Carcinoma.

The mean age for HER-2 Neu (+) and Her-2 Neu (-) were 53.4 years and 52.04 years respectively. The mean age for ER (+) and ER (-) were 56.42 years and 47.56 years respectively. The mean age for PR (+) and PR (-) were 53.6 years and 54.29 years.

Amongst ER+ patients, 11.5% were <45 years of age whereas 88.4% were >45 years of age and among PR+ patients, 17.6% were <45 years of age and 82.3% were >45 years of age.

Table 1: Receptor positivity of patients in different age groups.

Age (in years)	HER2-NEU (+)	HER-2 NEU (-)	ER+	ER-	PR+	PR-
15-24	Nil	1	Nil	1	1	Nil
25-34	3	7	2	7	2	5
35-44	2	8	4	6	3	5
45-54	6	22	17	10	10	12
55-64	7	16	14	8	12	14
65-74	5	13	15	4	6	12
Mean Age	53.41	52.04	56.42	47.56	53.62	54.29

In our study, ER,PR and HER-2 Neu positivity were seen in 57.7%,37.7% and 25.5% of patients respectively.

Table 2: Receptor positivity of patients.

Receptor	Reactivity	Number	Percentage
Estrogen Receptor	Positive	52	57.7%
	Negative	36	40%
Progesterone receptor	Positive	34	37.7%
	Negative	48	53.3%
HER-2-Neu receptor	Positive	23	25.5%
	Negative	67	74.4%

In our study, 24.44% of patients were of tumor grade 1, 53.33% of patients were of tumor grade 2 and 22.22% of patients were of tumor grade 3. Amongst grade 2 and grade 3 tumors,51.47% were ER+, whereas 77.27% of grade 1 tumors were ER+. Amongst grade 2 and 3 tumors, PR positivity was 29.41% as compared to 63.63% PR positivity for grade 1 tumor.Amongst grade 2 and 3 tumors, 30.08% were positive for Her-2 Neu, whereas in Grade 1- Her-2- Neu positivity was seen in 9.09% of patients.

Table 3: Correlation of ER, PR and Her-2 Neu Receptors with Tumor grade

Tumor Grade	HER-2 Neu(+)	HER-2 Neu (-)	ER+	ER-	PR+	PR-
1	2	20	17	4	14	5
2	7	37	19	29	14	32
3	14	10	16	3	6	11

Table 4: Correlation of ER, PR with HER-2 Neu Receptors

Hormone receptor	HER2NEU+	HER2Neu-
ER+	7	45
ER-	16	20
PR+	3	31
PR-	20	28

In our study an inverse relationship was found between HER 2-Neu positive tumors and ER and PR positive tumors. Out of 23 Her-2 Neu + cases;67% were ER(-)and 87%werePR(-) (p-value<0.05).

Table 5: Relationship of Lymph node metastasis with Receptors

	Her-2 +	Her-2-	ER+	ER-	PR+	PR-
No L.N. Metastasis	5	32	16	10	4	16
1-3 L.N. involvement	4	18	18	12	8	14
>3 L.N. involvement	14	17	18	14	22	18

Among Her-2 Neu (+) patients 78.26% had ≥1 lymph node involvement whereas52.23 % of her-2 Neu (-) patient had≥1 lymph node involvement(**P Value<0.05**).

Among PR(+) patients 88.23% have ≥1 lymph node involvement and 66.66% of PR (-) patients had ≥1 lymph node involvement (**P Value<0.05**).

 Among ER (+) patients 69.23% of patients had ≥1 lymph node involvement where as among ER (-) patients 72.22% of patients had ≥1 lymph node involvement(**P Value>0.05**).

Discussion:

Breast cancer is commonly diagnosed dangerous disease in women and major cause of mortality globally. Prognostic parameters of Ca breast include hormone receptor status, histological grade, nodal metastasis, tumor size, vascular invasion and presence of tumor necrosis. These parameters also foretell whether there is need for adjuvant therapy.

Estrogen receptors, progesterone receptors and Her-2 Neu expression are of fundamental importance regarding breast cancer. ER and PR expression are the only predictive factors with proven usefulness in selecting patients who are likely to respond to adjuvant endocrine therapy[5]. Patients lacking these receptors tend to have shorter disease free survival and earlier recurrences than those expressing these receptors(Lancet.,1998).

Our study included about 90 cases and 84.4% belong to invasive carcinoma of No Special Type (NST). The percentage of Estrogen receptor was 57.7% whereas the percentage of Progesterone and Her-2-Neu were 37.7% and 25.5% respectively.

Patients with ER+, PR+ usually have lower grade1 tumor whereas patients with HER-2 Neu expression presented with higher grade tumor. There was found to be an inverse relation between ER, PR expression and HER-2 Neu(pvalue<0.05).HER-2 Neu positive patients (93.55%) presented with higher tumor grade (grade 2 and 3) compared to Her-2 negative patients (69.49%).In present study we also concluded that 78.26% of her-2 Neu (+) patients had ≥1 lymph node involvement. Whereas 52.23% of her-2 Neu (-) patient had≥1 lymph node involvement.(P Value=0.0007(<0.05). 88.23% of PR(+) patients have ≥1 lymph node involvement and and 66.6% PR (-) patients have ≥1 lymph node involvement.(PValue=0.042(<0.05).69.23% of ER(+) patients have ≥1 lymph node involvement whereas 72.2% of ER(-) patients have ≥1 lymph node involvement.(P Value=0.935(>0.05).

Conclusion:-

Breast cancer is a major public health problem and it is most prevalent cancer in women. Globally, Ca breast is the most common malignancy in women with nearly a half million deaths each year(IARC Globocan,2008).

In our study,the most common age group to get affected from Ca breast was 40-60 years. Most of the cases belong to invasive carcinoma of no special type(NST). ER and PR expression were inversely related to Her-2 Neu receptor. Her-2 Neu expression is associated with higher tumorgrade(Grade 2 and 3) and higher rate of axillary metastasis. As compared to grade 3,lower grade 1 tumor show higher number of ER and PR positivity.

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