A Study of Hormone Receptor Status in Breast Carcinoma and Their Histopathological Correlation

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Abstract
Introduction: *Hormone receptors ER, PR, and Her2/neu status are now widely accepted as a prognostic marker and decide therapeutic modalities in breast carcinoma. The study aimed to analyze receptor status in breast carcinoma with histopathological characteristics of the tumor.*

Purpose: *To correlate the expression of prognostic factors such as patients' age, menopause, tumor size, number of lymph nodes, and histological grading with oestrogen, progesterone, and He2/ neu receptor status.*

Material and Methods: *In this study, 71 specimens of breast carcinoma after modified radical mastectomy, simple mastectomy, and lumpectomy were sent to the pathology department for immunohistochemical and histopathological examination to know the hormonal status well as histopathological characteristics.*

Result: *Seventy-one breast carcinoma specimen reports were received from the pathology department after immunohistochemical testing of ER, PR, and Her2/neu. The study showed only 39.43% cases were ER+ PR+, 15.49% cases were ER+, PR+ and Her2/neu+. 9.85% of cases were Her2/neu +, 5.63% cases ER+, and29.57% cases were ER-/ PR-/ Her2/neu negative (triple-negative).*

According to this study's data, a statistically significant correlation of ER, PR, and Her2/neu was found with menopausal status, tumor size, number of lymph nodes, and tumor grade.

Conclusion: *ER, PR, and Her2/ neu receptor status are critical predictor factors in cases of carcinoma of the breast, which necessitates the routine evaluation of hormonal receptor status for better management of the disease.*

Keywords: *Breast carcinoma, Oestrogen receptor, Progesterone receptor, Her2/neu, Menopause status, Lymph node involvement.*

Introduction

Breast carcinoma is the second most common carcinoma in women and accounts for 22% of all female cancer, which is more than twice the prevalence of cancer in women at any other site[1]. It is the most common site-specific cancer in

women and is the leading cause of death from cancer for women aged 30- 60 years[2]. It accounts for 26% of all newly diagnosed cancer in females and is responsible for 15% of all cancer-related death in women[3]. The incidence of breast cancer has increased globally over the last several decades; the most significant increase has been seen in Asian countries[4]. In Asia, breast cancer incidence peaks among women in their forties, whereas in the United States and Europe, it peaks among women in their sixties[5]. India accounts for nearly 6% of death. One in every 22 women in India is diagnosed with breast carcinoma every year, with premenopausal patients constituting about 50% of all patients[6,7]. Although breast cancer incidence is low in India compared to western countries, it is associated with poor prognosis and high mortality, which may be due to late presentation when it is in the advanced stage[3]. Numerous variables such as histological type and grade, tumor size, lymph nodes status, the status of hormonal receptors- oestrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor-2 (Her2/neu) of tumor influence the prognosis and management of breast carcinoma[4]. With the advent of adjuvant hormonal or chemotherapeutic regimens determination, the ER, PR, and human epidermal growth factor receptor-2 (Her2/neu) receptor status in breast cancer has become a practice as positive receptor status confer a survival advantage in these patients[2,5]. It is well known that strong ER-positive cases benefit from endocrine therapy alone[4,5].

PR status is also independently associated with overall and disease-free survival. Patients with ER, PR positive tumor have a better prognosis than patients with negative expression [6].

Hormonal receptor study is not routinely measured as it is expensive and is still considered a research tool in many parts of our country. This could adversely impact decision-making regarding treatment protocol, and sometimes patients are treated empirically with tamoxifen, which is not always required. The present study was planned to keep in mind the predictive importance of receptor status for the prognosis of illness and appropriate therapy. The objective was to determine receptor status and its correlation with histopathological characteristics of the tumor in an Indian population.

Material and Method

This Hospital-based study was conducted on patients with carcinoma breast admitted to the Department of General surgery in MBS Hospital attached to Government Medical College, Kota (Rajasthan) for the last year. A total of 71 patients with breast carcinoma were included in the study. Operated cases had the samples of modified radical mastectomy, simple mastectomy, and lumpectomy. The specimen was sent for HPE and ER, PR, and Her2/neu status, and clinical details were obtained from the indoor tickets of the patients.

Results

The 71 cases of breast carcinoma were ascertained for ER, PR, and Her2/neu status concerning histological characteristics of the tumor. In the present study, female patients were aged between 26-75 years, with the youngest being 26 years and the oldest 75 years. The mean age of the carcinoma of the breast was 50.28 years, with a standard deviation of $\pm$ 12.83 years [Table 1]. The majority (53.52%) were in the age group of 35 to 54 years. The morphological characteristics were infiltrating duct carcinoma, not otherwise specified (53 cases-74.64%) followed by infiltrating duct carcinoma-comedo (13 cases-18.30%), mixed, ductular and lobular (2 cases-2.81%), mucinous adenocarcinoma (2 cases-2.81%), and medullary carcinoma (1 cases-1.40%) [Table 2]

Table 1: Age distribution of carcinoma of the breast

Age (years)	Number of patients
25-34	06
35-44	20
45-54	18
55-64	15
65-74	09
>75	03

Table 2: Morphological characteristics of a tumor

Morphology	No. of cases	% of cases
Infiltrating duct carcinoma-N	53	74.64
Infiltrating duct carcinoma-c	13	18.30
Mixed-ductular/lobular	02	02.81
Mucinous adenocarcinoma	02	02.81
Medullary carcinoma	01	01.40

Table 3: Histological grade and hormone receptor status

Grade	ER+/PR+	ER+/PR+/Her2/neu	ER+	Her2/neu+	ER-/PR-/Her2/neu-
I	10	01	02	00	01
II	13	05	02	02	12
III	06	04	00	04	09

Table 4: Comparison of age and hormone receptor status

Age	ER+ /PR+	ER- /PR-	ER+	Her2/neu+	ER+/PR +/Her2/neu +	ER-/ PR-/Her2neu
25-34	04	00	00	00	01	02
35-44	15	00	01	00	04	04
45-54	07	00	01	04	04	06
55-64	05	00	01	02	00	06
65-74	04	00	01	01	00	04
>75	03	00	00	00	00	00
	38-53.52%		4-5.63%	7-9.85%	9-12.67%	22-30.98%

Table 5: Menopausal status and hormone receptor status

Menopausal Status	ER+ / PR +	ER+/PR +/Her2/neu +	ER-/ PR-/ Her2/neu-	ER +	Her2/neu+
Premenopausal-33	18	06	07	19	08
Postmenopausal-38	20	04	15	23	09

Table 6: Tumor size and hormone receptor status

Tumor Size	ER+ / PR +	ER / PR/ Her2/neu +	ER-/ PR-/ Her2/neu-2 -	ER +	Her2/neu+
< 2 CM-20	15	02	04	01	03
2-5 CM-31	13	04	09	01	04
>5 CM-20	09	05	09	01	02

Table 7: No. of lymph node and hormone receptor

No. of Lymph Nodes	ER +/ PR +	ER+ / PR+ /Her2neu +	ER- / PR -/Her2/neu -		ER+	Her2/neu+
0-24	13	03	08		14	05
1-2-12	07	03	03		08	04
3-5-16	07	01	06		08	03
>6-19	11	03	05		12	05

The most frequent tumor grade was grade 2 (47.88%), followed by grade 3 (32.39%) and grade 1 (19.71%). In this study, most of the cases were grade 2, and hormone receptor positivity decreased as the tumor grade increased. Total grade 1 case was 14 (19.71%) out of which 13 cases (92.85%) were receptor-positive; in grade 2, total cases were 34 (47.88%), out of which 22 cases (64.70%) were receptor-positive, and in grade 3, total cases were 23 (32.39%) out of which 14 cases (60%) were receptor-positive [Table 3].

The result of this study showed that only 53.52% (38) cases were ER+/PR+, 12.67% (09) of cases ER+/PR+/Her2/neu+, 30.98%(22) cases ER/PR/Her2/neu-. The mean age of ER+/PR/Her2/neu+ was 46.10 years with ±12.44 years, the mean age of ER-/PR-/Her2/neu- was 52.27± of 12.82 years.

Here, the hormone receptor positivity/negativity was compared with the age of patients. A definitive positive correlation could not be made as the number of patients as a whole was more in the age group of 35-44 years (19 patients) [Table 4]. A total of 38 cases were postmenopausal out of which ER+/PR+ cases were 20 (34.21%), 4 cases (10.52%) were ER+,PR+, and Her2/neu+, 9 cases (13.15%) were only Her2/neu+, 23 cases (32.39%) were only ER+, and 15 cases (21.12%) were hormonereceptor negative. So, in our study, 33 cases (65.78%) were hormonereceptor-positive, and 15 cases (34.21%) were hormonereceptor-negative in the postmenopausal age group. In premenopausal age, total cases were 33 (46.47%) out of which 18 cases (48.48%) were ER+/PR+, 6 cases (15.15%) were ER+/PR+/Her2/neu+, 8 cases (24.24%) were only Her2/neu+, and 19 case (57.57%) was only ER+. So in the premenopausal age, total hormonereceptor-positive cases were 32 (45.07%), and 09 cases (12.67%) were hormonereceptor-negative. Hence it was seen that postmenopausal cases had more receptor positivity [Table5].

In this study, most tumors were of size 2-5 cm, and as the tumor size increased, hormone receptor negativity also increased. The mean tumor size in the ER+/PR+ group was 4.01cm. In tumors less than 2cm, 80% of the patients were receptor-positive, and 20% were receptor-negative. In tumor size 2-5 cm, hormone receptor positivity was 67.74%, and hormone receptor negativity was 32.25%. And with tumor size >5 cm, hormonereceptor positivity was 57.14%, and negativity was in 42.85% of cases. Our study showed that as the tumor size increases, the hormone receptor negativity also increases [Table 6].

In most cases, the lymph node number was between 2-5, and they were mainly hormone positive. The mean number of ER+/PR+ lymph nodes was 4.13 [Table 7].

Discussion

Carcinoma breast has known risk factors, each of which was correlated separately with ER, PR, and Her2/neu receptor status.

Age and Hormonal Receptors

Fisher et al., in 1980, studied 178 invasive breast cancer cases.

Well-differentiated tumors were more frequently ER-positive in older women[14]. Mohammed et al., in 1986, received 490 consecutive human breast biopsy and mastectomy specimens which were correlated with ER and PR content of the tissue. 63% of the patients with grade 4 infiltrating duct carcinoma were younger than 53 years (p<0.001). The patients who were younger than 53 years with grade 2 and 3 infiltrating Duct carcinoma also had significantly lower levels of ERs, but not PRs, than those older than 53 years of age[15].

Amaral and Sergio, in 2001, studied 306 patients with infiltrating duct carcinoma and found that both ER and PR were significantly associated (p<0.05) with patient's age (<60 years vs. >60 years).

When the association was studied between different levels of positivity for hormone receptor (+++ vs. ++vs.+vs. negative) and patients age

(<60 years vs.>60 years), significant P value(p<0.01),for both ER and PR, was found[17].

Alvarez Goyanes et al., in 2008, examined 1509 tumors from Cuban women diagnosed with breast cancer. Analysis of age at the time of diagnosis showed that ER expression was more significant in patients in the group aged >50 years (P <0.05)[19].

In our study (Table 4), out of 71 cases of carcinoma of the breast, who were from 26 to 75 year of age (mean age 50.28 ± 12.83), ER+ and PR+ cases were 29 (40.84%), ER+, PR+, and Her2/neu+ were 09 (12.67%). As age increased, ER and PR positivity increased.

Menopausal Status and Hormonal Receptors

Mohla et al., in 1982, studied 146 black women with breast cancer and found that postmenopausal patients and primary tumors showed higher ER+ than premenopausal patients and metastatic site. [23]

Amarlal and Sergio, in 2001, found a statistically significant positive association observed between PR, and this same variable was small and not statistically significant (P=0.37) [17].

Ruder et al., in 1989, found that patients who are at a postmenopausal stage, or older at menopause, or given first birth showed a positive correlation with ER and a negative correlation with PR[16].In this study, postmenopausal cases had more ER, PR receptor positivity,like the findings as that of Mohla and Eisenberg but not as that of Ruder, who found a negative correlation with PR menopausal status.

Tumour size and Hormonal Receptors

Amarlal and Sergio et al. found a statistically significant association between ER+

and PR + tumour and tumour size < 4.0 cm(p <0.005)[17]. Alveraz Goyanes et al. found that ER expression was associated with low nuclear grade and histological grade and similar tumor size (P0.05)[19]. Pourzand et al. found that younger women had tumors that were more likely to have a higher stage, larger size, and PR+(p = 0.05)[20].

In our study, as the size of the tumor increased, the ER and PR negativity has increased, which was statistically significant and is per the above studies.

Lymph node number and Hormonal Receptors

Stierer et al. and MacGrogan et al. showed that the presence of hormonal receptors (ER and PR) was not associated with nodal status[24,25].

Amaral and Sergio did not find any association with the hormonal receptors[17].

Ahmed et al. found a significant positive association between ER or PR expression with lymph node involvement (P=0.004 and P=0.022, respectively)[21].

Pourzand et al. found that 59.6% of ER+ patients had lymph node involvement; 60.4% of ER– patients had involved nodes; the difference was not statistically significant (P=0.88).Similarly, 57.1% of PR positive patients had lymph node involvement than 64.2% of PR negative patients, and it was also not statistically significant 9P=0.42)[20].

In this study, a significant association between lymph node status and ER /PR receptor was found. As we found that number of nodal involvements increased, the positivity of hormonal receptors also increased.

Histological Grade and Hormonal receptors

Fishers et al. (1980) found positive to be significantly associated with high nuclear and low histological grade[14].

Mohla et al. also found a significant correlation between the ER+ and tumor grade[23].

Mohammed et al. studied the ER and PRs in human breast cancer and correlation with histological subtype and degree of differentiation. Of the four grades of differentiation, the less differentiated grade 3 and 4 tumors showed a significantly lower level of ER and PRs in infiltrating ductal and lobular carcinoma (p <0.001). Patients are younger than 53 years of age with grade 2, and 3 infiltrating ductal carcinomas also had significantly lower levels of ERs, but not

of PRs, than those patients older than 53 years of age(p <0.001)[15].

Amaral and Sergio et al. Found a statistically significant association between ER and PR + tumor and low histological grade (p <0.01)[17].

Alvarez Goyanes et al. also found a significant association between ER and PR + tumors and low histological grade(p <0.01)[19].

In this study, the grade 1, 2, and 3 tumors showed receptor positivity of 92.85%, 64.70%, and 60.00%, respectively. We found that as grade increases, receptors positivity decreased.

Conclusion

This study conducted at MBS Hospital Kota evaluated the ER, PR, and Her2/neu status and correlations with other prognostic factors.

According to the data of this study, a statistically significant correlation of ER, PR, and Her2/neu was found with age, menopausal status, tumor size, number of lymph nodes, and histological grade of tumors. In our study, ER/PR, positive cases were 40.84%, and ER/PR/Her2 neu positive were 12.67% and mean age 50.28+- 12.83 years. As age increased, ER, PR positivity increased.

The postmenopausal case had more ER/PR positivity, like that of Mohali and Eisenberg. As the size of the tumor increased, ER/PR negativity has increased.

In this study, a significant association between lymph node status and ER/PR receptor was found. We found as the number of nodal involvements increases, the positivity of hormonal receptors also increases.

In this study, grade 1, 2, and 3, the tumor shows receptor positivity of 92.85%,64.70%, and 60%, respectively, so we found that as grade increased, receptor positivity decreased.

To conclude, ER, PR, and Her2/neu status is a significant predictor in the case of carcinoma of the breast, which necessitates a routine evaluation of the hormonal receptors' status to manage the disease better.

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