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Original Article

ER, PR & HER-2 RECEPTOR STATUS IN RECURRENT BREAST CANCER: ITS RELATION TO AGE & TIME OF RECURRENCE

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Abstract

Background: Malignant neoplastic lesions of the breast are one of the main causes of cancer death among women. In tumor cells the expression status of Estrogen receptor (ER), progesterone receptor (PR), and c-ERBB2 (HER2/neu) are therapeutically and prognostically important markers affecting the treatment approach, management and prognosis of breast carcinoma.

Objective: To explore the relation of receptor status in recurrent breast cancer to age and time of recurrence.

Methods: This study was conducted in National Institute of Cancer Research and Hospital (NICRH) and included 81 female patients between 20 to 75 years with recurrent breast cancer. Detection of receptor status of ER +ve/-ve, PR +ve/-ve, Her-2+ve/-ve was based on the immunohistochemistry staining of tissue samples of malignant neoplastic lesions prepared from tissue biopsies of patients with recurrent breast cancer. All the information were recorded through the pre-structured data collection sheet and analyzed.

Results: This study showed that most of the recurrent breast cancer patients were Triple negative breast cancer (TNBC) (39.5%) and among them most of them were younger patients. Younger patients with TNBC had increased risk of recurrence. Most of the recurrence occured within 1-2 years.

Conclusion: It can be concluded that the assessment of the expression of these biomarkers in recurrent tumors provides reliable information for the treatment approach of loco-regional tumors.

Key words: Recurrent breast cancer, Oestrogen, progesterone and HER-2 receptor status, Triple negative Breast cancer, IHT.

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Introduction

Malignant neoplastic lesions of the breast are the most common form of malignancy diagnosed in women. About 14% of cancer deaths among women are caused by breast cancer[1]. Recurrent breast cancer is a major clinical manifestation and represents the principal cause of breast cancer-related deaths. A number of researchers have tried to predict some sort of pattern for breast cancer recurrence.

Estrogen receptor (ER), progesterone receptor (PR), and c-ERBB2 (HER2/neu) are therapeutically and prognostically important markers in the management of breast carcinoma. About 60% to 70% of breast carcinomas express ER protein, and these tumors are associated with better prognosis[2]. ER status is important in predicting the response to adjuvant hormonal therapy. More than half of ER+ tumors express PR. Hence, simultaneous analysis of ER and PR gives more information regarding likely hormonal response. Some studies have reported the presence of PR as a better predictive marker of response to hormone therapy than quantitative ER[2]. Of breast carcinomas, 55% express both ER and PR, whereas 22% do not express either ER or PR. In addition, 20% of tumors are ER+ and PR−, and 3% are ER− and PR+[2, 3].

The HER2/neu receptor is a member of the epidermal growth factor receptor family of receptor tyrosine kinases, which are considered to be important mediators of cell proliferation and differentiation[4]. Overexpression of the HER2/neu oncogene is also important event in breast cancer tumorigenesis. It is activated in 20% to 30% of cases through amplification and overexpression of the oncogene. Overexpression of HER2/neu reflects an increased proliferative activity of the tumor. HER2/neu positivity has been reported to be a negative predictor of response to hormonal therapy, adjuvant radiotherapy, and adjuvant chemotherapy[5].

It appears that ER-negative breast cancers are associated with higher risk of recurrence during the initial 5 years after diagnosis, compared to ER-positive breast cancers. Thereafter, the risk of recurrence chronically increases in ER-positive breast cancers for the next 10 years, and at 15 years following diagnosis, the risk appears to be equal for both subtypes. In ductal carcinoma in situ, it has been analyzed that the ER-negative/PR-negative but HER2-positive cancers have higher risk of recurrence, compared to ER-positive/PR-positive/HER2-negative cancers[6]. The Triple negative breast cancer (TNBC), marked by absence of ER/PR/HER2, are generally associated with high risk of recurrence with particularly high risk of distant recurrences in brain and visceral metastases, compared to receptor positive tumors[7].

Materials and Methods

This cross-sectional study was carried out in the department of surgical oncology of NICRH from July 2014 to April 2016. Informed written consent was taken from each patient before their enrollment in the study. 81 patient with recurrent breast cancer admitted in the department of surgical oncology were included in the study. Detection of Estrogen receptor (ER), progesterone receptor (PR), and c-ERBB2 (HER2/neu) receptor status was based on the immunohistochemistry staining of tissue samples of malignant neoplastic lesions prepared from tissue biopsies of patients with recurrent breast cancer. All the information like history, clinical examination & relevant investigations including FNAC, Tru-cut biopsy from the lesion, IHT and also the imaging of common metastatic sites were recorded through the pre-structured data collection sheet and analyzed.

Results

81 patient with recurrent breast cancer were included in the study. The mean age of the patients was 41.68 (SD±9.309) years. Most of them were (54, 55.7%) younger age (≤40 years). It was found that 21 (51.2%) patients had TNBC out of 41 younger group patients and only 11(27.5%) patients had TNBC >40 years age group patients. But no significant association between receptor status. It was found that 32 (39.5%) patients had TNBC out of 81 patients and most of them recurrence occur within 1-2 years in TNBC & other groups.

Table 1: ER, PR & HER-2 status.

Variables	Frequency	Percent
Receptor status (n=81)		
ER,PR,Her2 +ve	10	12.3
ER,PR+ve,Her2-ve	21	26
TNBC	32	39.5
ER,PR-ve,Her2+ve	18	22.2
Age (n=81)		
≤40 years	41	50.61
>40 years	40	49.38

Table 2: Cross tabulation between age and Receptor status

Age	Receptor status				Total	P-value
	ER+ve,PR+ve; HER-2 +ve	ER+ve,PR+ve, HER-2-ve	ER- ve,PR-ve, HER-2-ve	ER- ve,PR-ve, HER-2+ve		
1 (≤40)	3	10	21	7	41	
2 (>40)	7	11	11	11	40	0.130
Total	10	21	32	18	81	

Table 3: Cross tabulation between receptor status and time of recurrence

Time of recurrence	Receptor status				Total	P-value
	ER,PR,HER -2 +ve	ER,PR+ve,HER -2-ve	ER,PR,HER -2-ve	ER,PR -ve,HER -2 +ve		
<1 year	4	2	6	2	14	
1-2 years	3	11	15	9	38	0.528
>2 years	3	8	11	7	29	
Total	10	21	32	18	81	

Discussion

This study explores the relation of receptor status in recurrent breast cancer to age and time of recurrence. Our data showed that the mean age of the patients was 41.68 (SD±9.3) years. Out of 81patients, 41 patients (50.61%) were (≤40 years) younger age group and 40 patients (49.38%) patients were (>40 years) older age group. So that most of the tumour recurrence occurred in younger age group. Age groups of 35 years or less and 40 years or less have been associated with an increased risk of locoregional recurrence after mastectomy[8]. A study reported a crude local recurrence rate of 67% for patients aged 20 to 29 years and 41% for patients aged 30 to 39 years in an early radical mastectomy series, whereas in women aged <40 years, local failure rates were 21% to 25%[9]. Another radical mastectomy series, observed a similar crude failure rate of 67% for ages 20 to 29 years and 46% for ages 20 to 39 years, compared with < 25% for those <40 years of age[10]. Mathews et al[8]. reported that the crude rate of locoregional failure after mastectomy doubled with younger age i.e. from 6% to 7% for ages > 35 years to 12% for ≤ 35 years. The locoregional failure rate at 5 years was only 7.4% after modified radical mastectomy in 140 patients aged ≤ 35 years[11].

In our study majority of the patients (32, 39.5%) were TNBC. ER, PR, Her2 +ve were (10, 12.3%), ER, PR +ve, Her2-ve were (21, 26%) & ER, PR -ve, Her2 +ve were (18, 22.2%). It was found that 21 (51.2%) patients had TNBC

out of 41 younger group patients and only 11(27.5%) patients had TNBC >40 years age group patients. But no significant association between receptor status. It was found that 32 (39.5%) patients had TNBC out of 81 patients and in most of them recurrence occurerd within 1-2 years in TNBC & in other groups. No significant association between receptor status & time of recurrence. The frequency of hormones receptor-positive breast cancer has been found to be high as in the western countries (65% to 80%)[12]. ER+ and PR+ tumors were more likely to be associated with younger age at diagnosis compared to ER− and PR− tumors. ER−, PR− tumors displayed features of a more aggressive biological phenotype than ER+, PR+ tumors. This evaluation allowed identification of patients with high-risk features for whom new treatments are needed[13]. HER2/neu levels are closely associated with adverse clinico-pathological and molecular factors. A study found that overexpression of HER2/neu correlated significantly with stages of disease, with lymph nodes and absence of ER, PR receptors[14].

HER2/neu positive tumors might be attributed to the low number of patients undergoing HER2/neu analysis, which limited the number of subgroups HER2/neu+ and HER2/neu− cases, engendering possible insignificant differences. Considering the importance of evaluating HER2/neu expression, we strongly feel that this issue should be further investigated taking into account patients' management and alternative therapeutic strategies[15]. The overexpression of HER2/neu reflects the activity of tumor cells and the clinical course of disease towards progression or regression. HER2/neu plays an important role in cell proliferation and differentiation, and its overexpression seems to correlate with an increase in the proliferative activity of breast cancer cells[16].

Analysis of all recurrent breast cancer patients for elevated HER2/neu levels can provide valuable information for patient management in both the HER2/neu positive and HER2/neu negative groups. ER signalling pathways in breast cancer and HER2/neu overexpression are associated with resistance to hormonal therapy which would take in consideration alternative therapeutic strategies as the number of HER2/neu targeted drug choices continues to increase.

Conclusion

Breast cancer in younger age groups, TNBC had more recurrence & is more aggressive than in older age groups. Most of the recurrence occurs within 1-2 years. Although negative progesterone receptor tumors were more likely to have HER-2 over expression, different biologic behavior of breast cancer in younger age groups may be due to progesterone receptor positive status. A combination of ER, PR and HER2/neu and prognostic factors could be of clinical value in defining subgroups in recurrent breast cancer patients that might benefit from more aggressive treatment. Assessment of the expression of these biomarkers in recurrent tumors provides reliable information for the treatment approach of loco-regional tumors.

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