



COMPARISON OF OUTCOME IN HETEROGENOUS RECEPTOR POSITIVITY VERSUS HOMOGENOUS RECEPTOR POSITIVITY IN BREAST CANCER PATIENTS.

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KEYWORDS :

INTRODUCTION

In recent years there has been increase in the cases of cancer worldwide among which breast cancer is leading cancer in females and has been known to be an endocrine related cancer¹. Carcinoma of breast is most common cancer in females that has now surpassed carcinoma of lung as leading cause of cancer in year 2020 with an estimated 2.3 million new cases in developed country². In developing countries breast cancer remains second most common cancer after cervical cancer in females but recent trends are showing reversal, where breast cancer is surpassing cervical cancer.

In India, it is the commonest cancer among females in urban area accounting for approximately 30% of all the cancers². In breast cancer steroid hormone receptors i.e Estrogen receptor (ER) and Progesterone receptor (PR) have been shown to be important prognostic factors and predictive markers for response to endocrine therapy in treatment of breast cancer³.

About 70% of breast cancers are hormone receptor positive tumors (HR+)³. PR is an estrogen regulated gene, ER+ve tumors are usually also PR+ve, whereas ER-ve tumors are usually PR-ve. Therefore single HR+ve tumors represent a minority of breast cancer³. The presence of ER and PR is associated with various histological and cellular kinetic features that suggest a favourable prognosis⁴. Breast cancer patients with tumors that are estrogen receptor positive and/or progesterone receptor positive have lower risk of mortality after their diagnosis compared to women with ER-ve and/or PR-ve disease⁵.

Some tumors are single hormone receptor positive (ER+ve/PR-ve or ER-ve/PR+ve) and are thought to be biologically and clinically different from double hormone receptor positive subtypes, although the cause of single hormone receptor positive breast cancer remains unclear⁶. Patients with single hormone receptor positive tumors have an intermediate prognosis between double hormone receptor positive (best survival) and double hormone negative (worst survival) tumors, whereas there is no survival difference

between patients who have ER+ve/PR-ve tumors and patients who have ER-ve/PR+ve tumors⁶.

Studies have shown that the absence of PR expression has a powerful prognostic value in ER+ve breast cancer patients, emphasizing the importance of reevaluating PR status as a biological marker for poor prognosis⁸. Previous studies have suggested that single hormone receptor positive tumors have poor prognosis as the characteristics of this tumors is not well known³.

Therefore in order to understand the exact clinical characteristics and prognosis of single hormone receptor positive breast cancer we compared ER+ve/PR-ve tumor with double hormone receptor positive as well as hormone negative tumors and stratified the results.

Aims and Objectives

- To assess the histopathological report of the patients with single hormone receptor positive tumors with double hormone positive tumors and hormone negative tumors.
- To evaluate the pattern of recurrence and metastasis in both the arms.

MATERIAL AND METHODS

Based on immunohistochemistry report (IHC) 30 patients were recruited in each arm

Arm 01: - ER+ve PR-ve Her2Neu -ve

Arm 02: - ER+ve PR+ve and ER-ve PR-ve. Her2Neu+ve or -ve.

This is a prospective study conducted after written consent of the patients. The parameters taken for the study were age, sex, stage at the time of presentation, laterality of tumor, histological type, estrogen receptor, progesterone receptor, human epidermal growth factor 2 (Her2) neu status, site of metastasis, post operative histopathological report.

During recruitment thorough analysis of the patients was done with complete metastatic workup which included blood investigations, Chest Xray, Ultrasound Abdomen+pelvis,

mammography, Contrast enhanced CT scan (Thorax + Abdomen+ Pelvis) or PET CT Scan, 2D Echo, IHC report. Based on IHC report patient were selected in respective arms and statistical analysis was done between these two arms. Most of the patients received neoadjuvant chemotherapy protocols which included inj Doxorubicin 60mg/m² and inj Cyclophosphamide 600 mg/m². inj Epirubicin 100 mg/m² and Inj Cyclophosphamide 830 mg/m². Inj Cyclophosphamide 600 mg/m² + Inj Doxorubicin 60 mg/m² + inj 5FU 600 mg/m². Inj Cyclophosphamide + Inj Epirubicin 100 mg/m² and inj 5FU 500 mg/m².

After completing neoadjuvant chemotherapy patients were reassessed clinically and radiologically for response and accordingly subjected to Breast Conservative surgery (BCS) or Modified radical mastectomy (MRM). Post operatively further cycles of chemotherapy were given which included Inj Paclitaxel 175mg/m² with inj Trastuzumab 8mg/kg loading dose and then from 2nd cycle, Inj Trastuzumab 6 mg/kg (Trastuzumab was added when Her2Neu receptor was positive) and radiation protocol included 40Gy/16# / 3.5 weeks using 6MV Photon Intensity Modulated Radiation Therapy (IMRT). After completing chemotherapy and radiation therapy hormonal medications were given according to hormone receptor status which included Tab Tamoxifen 20 mg PO. OD, Tab Anastrozole 1 mg PO OD, Tab Letrozole 2.5 mg PO OD as per the menopausal status of the patient. The patients then where kept on follow up with clinical and radiological investigation every 3 monthly.

RESULTS:-

ARM01:-

Majority of age groups were between 41-55 years i.e 16% followed by 23% each of age group 25-40 years and 56-70 years. Most of patients were postmenopausal 56% with most common left breast involvement. Among 30 patients 53% (16) patients underwent MRM and 40% (12) patients underwent BCS. 98% of patients required Neoadjuvant Chemotherapy due to locally advanced disease at presentation and after completing chemotherapy majority patients had ypT2, ypT3 and ypN0, ypN1 disease. The histopathological report included:-

Histopathology	
Ductal carcinoma in situ	3%
Invasive breast carcinoma	50%
Lobular carcinoma	0%
Medullary carcinoma	0%
Invasive ductal carcinoma	43%
Others	3%
No of axillary lymph node positive	
<10	86%
>10	14%
Extracapsular extension	
Present	74%
Absent	26%
Lymphovascular stromal extension	
Present	76%
Absent	24%
Margins	
Close	43%
Positive	16%
Free	40%

Most of the patients completed more than 1 years follow up i.e 63% of patients and upto 13% of patients had follow up of more than 2 years. As far as pattern of recurrence that were seen in this group included bone mets with highest number of cases (13%) followed by liver mets and local recurrence each at 6%, brain mets and lymph nodal mets at 3% each. 10% of the patients developed multiples metastasis. Average duration of developing mets was after 10 months of completing the treatment.

ARM02:-

In this arm 46% of patients were in 41-55 years of age group with 70% of patients in postmenopausal age group above 55 years. 53% of patients had left sided breast cancer. The percent of patients undergoing BCS or MRM was equal i.e 50%.

Only 33% of patients received NACT in this arm and postoperative HPR showed majority of the patients in ypT2, ypN0 and ypN1 disease. The histopathological report included:-

Histopathology	
Ductal carcinoma in situ	3%
Invasive breast carcinoma	56%
Lobular carcinoma	6%
Medullary carcinoma	0%
Invasive ductal carcinoma	26%
Others	6%
No of axillary lymph node positive	
<10	90%
>10	10%
Extracapsular extension	
Present	30%
Absent	70%
Lymphovascular stromal extension	
Present	60%
Absent	40%
Margins	
Close	20%
Positive	03%
Free	77%

Most of the patients in this arm completed follow up of more than 1 year (72%) out of which 46% of patients had follow up of more than 2 years. After completing the treatment majority of the patients developed metastasis after 15-20 months with most common site being Liver mets 6% followed by local recurrence, lung mets, skeletal mets and multiple mets each at 3%.

As compared to arm 01 the pattern of recurrence changed from skeletal mets been most common to liver mets (visceral mets) in this arm.

Thorough statistical analysis was done of postoperative histopathological report which showed that p value significance was since in extracapsular extension p<0.05. The significance was also seen in pattern of recurrences and metastasis in these patients p<0.05. In locally advanced breast cancer significant number of patients required NACT with p value<0.05 suggestive of arm 01 patients presenting to hospital in later stages of cancer. No p value significance was seen in Lymphovascular extension and number of lymph node dissected.

In this study we tried to correlate single hormone positive status of patient with age of menarche, menstrual health, body mass index, overall stress level, dietary habits, number of pregnancy, miscarriages, preterm delivery, age at first pregnancy, treatment for infertility and chronic use of any medication however no statistical significance was found.

DISCUSSION AND RESULTS

In our study we have evaluated in detail the biological characteristics and prognosis of single hormone receptor positive tumor through comparison with other hormone positive tumor and hormone negative tumor.

At the time of presentation majority of the patients with single hormone receptor positivity were diagnosed in locally advanced stage requiring some form of neoadjuvant chemotherapy (NACT) to downstage the disease. 98% of

patients in arm 01 received NACT as compared to 33% of patients in arm 02.

The postoperative histopathological report showed that 40% of patients even after receiving neoadjuvant treatment had ypT3+ disease whereas only 30% of patients in arm 02 had ypT3+ disease.

In terms of disease free period, in arm 01 only 13% of patients had a follow up of more than 2 years whereas in arm 02, 46% of patients had more than 2 years of follow up period.

We studied the pattern of metastasis and recurrences in these arms and found that most of the patients in arm 01 had metastasis in skeleton within a period of 10 months from start of treatment followed by liver mets and local recurrence rate each of 6% of study population. In arm 02 6% of patients developed liver mets followed by 3% each of skeletal mets, local recurrence and lung mets.

Our study is consistent with previous large studies by Soo Youn Bae et al, demonstrating that single hormone receptor positive tumors have more aggressive features³.

Single hormone receptor positivity and the site of recurrence had a major influence. Observing a tendency for metastasis at favourable site "BONE" for ER+ve tumors and "VISCERA" for other hormone positive or hormone negative tumors⁴.

Hormone receptor positive breast cancer with loss of progesterone receptor helps to identify high risk patients which would help to segregate them for aggressive therapeutic strategies so as to improve the survival and decrease the metastasis in such patients³.

CONCLUSION

We conclude that ER+ve PR+ve tumors although are quite rare in incidence these tumors tend to act aggressively. Further character analysis of these patients is required as their behaviour is different from both ER/PR+ve group of breast cancer. For a good control and management of such cases we would require to first of all identify such patients in early stages of cancer and go for aggressive management with long term follow up to pickup recurrences and metastasis.

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