Available online at: http://www.iajps.com   *Research Article*

IMPACT OF HORMONE RECEPTOR STATUS (ER, PR, HER-2) ON PATTERNS OF METASTASIS IN BREAST CANCER AND ITS PHARMACEUTICAL MANAGEMENT IN TERTIARY CARE HOSPITAL: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract:
Despite the progress that has been made in diagnosis and treatment of early stage breast cancer a substantial proportion of patients still go on to develop incurable distant metastatic cancer. Estrogen receptors, progesterone receptors, human epidermal receptor-2 expression in breast cancer are associated with development of distant metastases. Most commonly observed site for distant metastases are liver, lung, bone, brain. The purpose of present study is to examine the hormone receptor status on development of distant metastases (liver, lung, bone, brain). The purpose of the present study focused mainly impact of hormone receptors such as estrogen receptor, progesterone receptor and human epidermal growth factor receptors in metastatic breast cancer were distant organs involved were liver, lung, bone, brain, recurrence and its pharmaceutical management based on receptor status in a tertiary care hospital. Based on the receptor presence and absence the treatment alters. Hence it is necessary to study the hormone receptor status which helps in management of disease and to prevent further progression of disease.
Key words:*metastatic breast cancer, hormone receptor status, estrogenreceptor(ER), progesterone receptor(PR), human epidermal receptor-2(HER2).*

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INTRODUCTION:

Cancer is the uncontrolled growth and spread of cells. It can affect almost any part of the body. The growths often invade surrounding tissue and can metastasize to distant sites (such as lung, liver, bone, brain). Many cancers can be prevented by avoiding exposure to common risk factors, such as tobacco smoke. In addition, a significant proportion of cancers can be cured, by surgery, radiotherapy or chemotherapy, especially if they are detected early.[1] The most common type of cancer is breast cancer, with 271,270 new cases expected in the United States in 2019.[2] Cancer cases in India (2010-2020) of NCRP indicate that there will be more than 100,000 estimated number of Breast Cancer cases annually in India based on the data from NCRP in Bangalore.[3]About two-thirds of breast cancers are hormone receptor positive, which means that they need female hormones (oestrogen and/or progesterone) to grow and reproduce.Hormones like estrogen and progesterone are chemicals produced by glands in the body. Normally, these hormones help regulate body cycles, like menstruation. However, sometimes these same hormones can cause cancer to grow. Cancer is called ER-positive (ER+) if it has receptors for hormone estrogen which receives the signals from estrogen and promotes its growth, just like normal cells. Similarly, the cancer is PR-positive (PR+) if it has receptors for hormone progesterone. Similarly, HER2-positive status of the breast carcinoma means that HER2 gene is making too many HER2 proteins. HER2 proteins are receptors on breast cells.The pathologist will perform tests on the breast cancer cells to determine if they have receptors that feed on estrogen or progesterone, stimulating their growth.

Immunohistochemical Scoring System for Estrogen Receptor, Progesterone Receptor, and Human Epidermal Growth Factor Receptor 2/Neu[4]

Allred system of scoring for estrogen receptor and progesterone receptor

ER and PR are nuclear receptors. In Allred system of scoring, score 0-5 is given to the cells depending on the proportion of cells which are stained (proportion score [PS]) and score 0-3 is given depending on the intensity of staining (intensity score [IS]) [Tables 1 and 2]. By adding the PS and IS, we can calculate the final Allred score (PS + IS = AS) [Table 3].

Scoring for human epidermal growth factor receptor 2/neu overexpression

HER2/neu is a cell membrane receptor and depending on the intensity of staining a score of 0-3 is given to the cells [Table 4].

Table 1: Proportion score

Score	Percentage of stained cells
0	No cells are ER positive
1	< 1% cells are ER positive
2	1-10% cells are ER positive
3	11-33% cells are ER positive
4	34-66% cells are ER positive
5	67-100% cells are ER positive

ER: Estrogen receptor

Table 2: Intensity score

Score	Intensity of staining
0	Negative
1	Weak
2	Intermediate
3	Strong

Table 3: Allred score (allred score=proportion score + intensity score)

Allred score	Effect of hormone therapy
0-1	No effect
2-3	Small (20%) chance of benefit
4-6	Moderate (50%) chance of benefit
7-8	Good (75%) chance of benefit

Table 4: The scoring of human epidermal growth factor receptor-2/neu depending on the intensity of staining of cells

Staining pattern	Score	HER2/neu protein overexpression assessment
No staining is observed, or membrane staining is observed in less than 10% of the tumor cells	0	Negative
A faint/barely perceptible membrane staining is detected in more than 10% 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 10% of the tumor cells	2+	Weakly positive/ equivocal
A strong complete membrane staining is observed in more than 30% of the tumor cells	3+	Strongly positive

HER2: Human epidermal growth factor receptor-2

AIM:
To study the prognostic effect of Hormone receptor status on pattern of metastasis in breast cancer and its pharmaceutical management.

OBJECTIVES:
To assess the hormone receptor status(ER, PR, HER-2) in metastatic breast cancer.

METHODOLOGY:
A prospective observational study was carried out in government general hospital, Guntur for duration of 6 months i.e., September 2018 to February 2019 after obtaining approval from institutional ethics committee. The patients were screened based on inclusion and exclusion criteria. Inclusion criteria includes Patients whose origin of cancer (primary lesion) involved is breast, Patients who are diagnosed with metastatic breast cancer, Breast cancer metastasis patients with either ER/PR/HER-2 positive or negative, Patients who are willing to participate in the study, Female patients with age >18yrs, Patients who are taking chemotherapy and hormonal therapy for metastatic breast cancer, Patients who are willing for regular follow up. Exclusion criteria includes Patients whose origin of cancer is other than breast, Patients with other than metastatic breast cancer, Patients who are <18yrs of age, Those who are not willing to participate in the study, Female patients with pregnancy, Patients who are not willing for regular follow up. Patients who satisfied inclusion criteria were included in the study. After including the subjects into the study the data was collected in the designed data collection form. The hormonal receptor status {ER/PR/HER-2} in metastatic breast cancer was assessed based on pathology reports. The data obtained was entered in advanced Microsoft excel spread sheet and evaluated. For statistical analysis, Graph Pad Prism 8.1.0 was used and one sample t-test and paired t-test was done with the 95% confidence interval at alpha value 0.05 and the p-values <0.05 are considered to be significant.

RESULTS:
Our study found that there is no significant association of family history in development of metastatic breast cancer as shown in table 5.

Table 5:Family history Vs Number of Subjects

Family history	Number of subjects (N=52)
Yes	3(5.77%)
No	49(94.23%)

Table 6: Age Vs No.of Subjects

The below table represents the information regarding distribution of subjects within the age groups 21-80.

Age of the subject	Number of subjects (N=52)
21-30	2(3.85%)
31-40	7(13.46%)
41-50	18(34.62%)
51-60	20(38.45%)
61-70	3(5.77%)
71-80	2(3.85%)

Table 7: Menstrual irregularities Vs number of subjects

Our study found there is no significant association of menstrual irregularities in development of metastasis in breast cancer.

Menstrual irregularities	Number of subjects (N=52)
Yes	19(36.54%)
No	33(63.46%)

Table 8: Metastatic site Vs number of subjects

The below table shows the information regarding the metastatic site which indicates the effected sites.

Type of metastasis	Number of subjects (N=52)
Bone	16(30.77%)
Liver	9(17.31%)
Lung	6(11.57%)
Brain	3(5.77%)
Recurrence	9(17.31%)
Bone, recurrence	1(1.92%)
Liver, recurrence	1(.92%)
Lung, bone	3(5.77%)
Liver, brain	1(1.92%)
Liver, lung	1(1.92%)
Bone, liver	1(1.92%)
Lung, bone, liver	1(1.92%)

Table 9: Hormonal receptor status in different metastatic breast cancer Vs Number of subjects

The below table shows the hormone receptor status in different metastatic breast cancer patients.

Types of metastatic site	$ER^+/PR^+/Her2^+$	$ER^+/PR^+/Her2^-$	$ER^-/PR^-/Her2^+$	$ER^-/PR^-/Her2^-$	$ER^+/PR^-/Her2^+$	$ER^+/PR^-/Her2^-$	$ER^-/PR^+/Her2^+$	$ER^-/PR^+/Her2^-$	Total (n)
Bone	3(18.75%)	8(50%)	2(12.5%)	2(12.5%)	0(0%)	0(0%)	0(0%)	1(6.25%)	16
Liver	3(33.33%)	3(33.33%)	1(11.11%)	2(22.22%)	0(0%)	0(0%)	0(0%)	0(0%)	9
Lung	1(16.67%)	2(33.33%)	0(0%)	2(33.33%)	0(0%)	0(0%)	0(0%)	1(16.67%)	6
Brain	0(0%)	1(33.33%)	0(0%)	2(66.67%)	0(0%)	0(0%)	0(0%)	0(0%)	3
Recurrence	1(11.11%)	5(55.56%)	2(22.22%)	1(11.11%)	0(0%)	0(0%)	0(0%)	0(0%)	9
Bone, recurrence	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1
Liver, recurrence	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1
Lung, bone	0(0%)	2(66.67%)	0(0%)	1(33.33%)	0(0%)	0(0%)	0(0%)	0(0%)	3
Liver, brain	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1
Liver, lung	0(0%)	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	1
Bone, liver	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1
Lung, bone, liver	0(%)	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	1

A p value (<0.0001****) was considered to extremely significant

DISCUSSION:

A non-experimental prospective observational study was carried out on- "**IMPACT OF HORMONE RECEPTOR STATUS (ER,PR,HER-2) ON PATTERN OF METASTASIS IN BREAST CANCER AND ITS PHARMACEUTICAL MANAGEMENT INTERTIARY CARE HOSPITAL.**" 52 patients met the inclusion criteria and were includedin the study. The data obtained was tabulated and analysed.The information regarding distribution of patients within age groups of 21 to 80 years.Majority of patients were found within 51 60 years (38.54%) followed by 41-50 years(34.62%), 31-40 years (13.46%) and 61-70 years (5.77%), 21-30 years (3.85%) , 71-80 years(3.85%). Based on the results obtained our study revealed that 16 (30.76%) subjects of the 52subjects the first distant metastasis was to bone.Out of the 18 subjects whose first metastasis wasto the viscera, the organ most often involved was the liver (n=9; 17.30%) followed by lung (n=6; 11.53%) and brain (n=3; 5.77%). These findings were in concordance with study doneby LindaVona-

Davisetal**.,** (2014) conducted a study on "Breast Cancer Pathology,Receptor Status, and Patterns of Metastasis in a Rural Appalachian Population."[5] And 9 out of52 subjects were diagnosed with recurrence(17.30%), remaining 9 subjects were diagnosedwith multiple site metastasis i.e., out of 9 (17.30%) 3 subjects were diagnosed with lung,bone (5.77%) and bone, recurrence(n=1 ;1.92%), liver, recurrence (n=1 ; 1.92%), liver, brain (n=1 ; 1.92%),liver, lung (n=1 ; 1.92%) bone, liver (n=1 ; 1.92%) lung, bone,liver(n=1; 1.92%).Our study main objective was to assess the hormone receptor status(ER, PR, HER-2) onpattern of metastasis in breast cancer. Tumors were grouped as HR-positive/HER2- positive(HR+/HER2+) , HR-negative/HER2-positive (HR /HER2+) , HR-positive/HER2- negative(HR+/HER2-) , HR-negative/HER2-negative (HR-/HER2-) and also estrogen receptornegative /progesterone receptor positive / HER2 negative (ER-/PR+/HER2-). We analysedhormonal receptor status by using t- test. Based on the results out of 52 subjects, 16 subjectswho

were diagnosed with carcinoma of breast with bone metastases in those hormonereceptor status is observed as HR+/HER2- (n=8 ;50%) , HR+/HER2+ (n=3 ; 18%) , HR-/HER2+ (n=2 ; 12.5%) , HR-/HER2- (n=2, 12.5%) and ER-/PR+/HER2- (n=1 ; 6.25%) (P=<0.0001). Out of 52 subjects, 9 subjects who were diagnosed with carcinoma of breast withliver metastases in those hormone receptor status is observed as HR+/HER2+ (n=3; 33.3%),HR+/HER2- (n=3; 33.3%), HR-/HER2-(n=2; 22.2%) HR-/HER2+ (n=1; 11.1%). Out of 52 subjects, 6 subjects who were diagnosed carcinoma of breast with lung metastasis in thosehormone receptor status is observed as HR-/HER2- (n=2; 33.3%) HR+/HER2- (n=2; 33.3%)HR+/HER2+ (n=1; 16.6%), ER-/PR+/HER2 (n=1; 16.6%) (P=<0.0001) and out of 52subjects, 3 subjects who were diagnosed with carcinoma of breast with brain metastasis inthose hormone receptor status is observed as HR-/HER2- (n=2; 66.6%) and HR+/HER2-(n=1; 33.3%) (P=<0.0001). Out of 52 subjects, 9 subjects who were diagnosed with breastcancer with recurrence in those hormone receptor status is observed as HR+/HER2- (n=5;55.5%), HR-/HER2+ (n=2; 22.2%), HR-/HER2- (n=1; 11.1%), HR+/HER2+ (n=1; 11.1%)(P=<0.0001%). Out of 52 subjects, 9 subjects who were diagnosed with multiple sitemetastasis, for bone, recurrence (n=1) HR/HER2+ (n=1; 100%) (P=0.0001). Liver,recurrence (n=1) with HR-/HER2+ (n=1; 100%) and 3 subjects diagnosed with lung, bonemetastasis having HR+/HER2- (n=2, 66.6%), HR-/HER2 (n=1; 33.3%) (P=<0.0001); liver,brain metastasis with HR-/HER2+ (n=1; 100%); liver, lung metastasis with HR-/HER2-(n=1;100%); bone, liver metastasis with HR-/HER2+ (n=1; 100%); Lung, bone, liver metastasis= with HR-/HER2- (n=1; 100%) (P=<0.0001).Our study also found that there is no significant association (94.23%) withfamily history for the development of metastasis in breast cancer and also there is nosignificant association (63.4%) with menstrual irregularities for the development ofmetastasis in breast cancer.

CONCLUSION:

Based on the results obtained our study concludes that bone is the major site of metastasis in breast cancer followed by recurrence, liver, lung, brain .in bone metastasis majority ofsubjects having receptor status HR+/HER2- (n=8; 50%) and in liver HR+/HER2+ (n=3;33.3%) HR+/HER2- (n=3; 33.3%) HR-/HER2- (n=2; 22.2%) was reported. In lungHR+/HER2-(n=2; 33.3%) HR-/HER2- (n=2; 33.3%), in brain majorly observed receptorstatus was triple negative HR-/HER2- (n=2; 66.6%), in recurrence condition HR+/HER2-(n=5; 55.5%) was majorly observed.In

case of multiple site metastasis i.e., bone, recurrence and liver, recurrence werewith receptor status HR-/HER2+ and in lung, bone with receptor status HR+/HER2- (n=2; 66.6%) and in liver, brain and bone, liver metastases HR-/HER2+ was observed. In liver,lung and lung, bone, liver metastasis the receptor status HR-/HER2- was found (P=<0.0001).

LIMITATION:

This study included only 52 patients to assess the "IMPACT OF HORMONE RECEPTOR STATUS (ER, PR, HER-2) ON PATTERN OF METASTASIS IN BREAST CANCER AND ITS PHARMACEUTICAL MANAGEMENT IN TERTIARY CARE HOSPITAL: APROSPECTIVE OBSERVATIONAL STUDY". 3 subjects were excluded because ofunavailability of hormonal receptor status .This study has to be further extended with morenumber of patients to derive at a better conclusion.

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