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RESEARCH ARTICLE

METASTATIC BEHAVIOUR OF SUBTYPES IN LOCALLY ADVANCED CARCINOMA BREAST.

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Abstract

Introduction:-Prognostic factors have been known to predict the incidence of metastasis in carcinoma breast but the study of subtypes classification based on molecular markers may help in providing more personalized and individualized patient care with a more focused treatment and follow up of patients with high probability of metastasis at different sites.

Methods:- Patients with breast cancer (tissue biopsy proven) diagnosed between 2011 and 2013 were included. Subtypes were defined on the basis of molecular markers (ER, PR and Her 2 Neu) in five categories. (Luminal A, Luminal B, Luminal HER2, HER2 enriched and Basal). Distant sites for metastasis were classified as brain, liver, lung, bone, distant nodal, pleural/peritoneal, and others. Association between the site of relapse and subtype was assessed in multivariate models using logistic regression.

Results:- Mean age of diagnosis of patients in the study was 50.71 years (SD-11.493) with 41-50 years(31.5%) being the most common age group. Most of the patients in the study were locally advanced at the time of presentation (69.6%).Incidence of metastasis at the time of presentation was (38.7%) with bone being the most common site. Patients were divided on the basis of molecular subtypes with Basal(27.3%) being the most common subtype closely followed by luminal A(25.2%). Highest incidence of metastasis was seen in Basal subtype (33%) followed by Luminal HER (18.4%) and HER2 Enriched (18.1%). On subset analysis, Bone was the most common site of recurrence in Luminal A (61.5%) and Luminal B (58.8%). Basal and Luminal HER subtypes had Brain as the most common site of metastasis while HER2 Enriched had equal metastasis in liver and brain.

Conclusion:- Breast cancer subtypes are associated with distinct patterns of metastatic spread with a high probability of metastasis at the time of presentation as well as later in the life time. Hormone negative tumours had more incidence of metastasis than hormone positive tumours. Moreover, hormonal negative tumours were dominated by visceral metastasis than bony metastasis. It is important to understand the nuances of these subtypes to predict metastatic behavior, for early imaging and adequate individualized treatment and follow up.

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Introduction:-

Breast cancer is the most common cancer among Indian females after carcinoma cervix. It is the major cause of mortality among females. Most of the patients present in locally advanced stage, more prone to distant metastasis as risk of recurrence are influenced by stage at initial presentation and the underlying biology of the tumour. Approximately 10–15% of patients with breast cancer has an aggressive disease and develops distant metastases within 3 years after the initial detection of the primary tumour. However, the manifestation of metastases at distant sites 10 years or more after the initial diagnosis is also not unusual[1]. Patients with breast cancer are therefore at risk of experiencing metastasis for their entire lifetime. The heterogeneous nature of breast cancer metastasis makes it difficult not only to define cure for this disease, but also to assess risk factors for metastasis. Despite advances in treatment around 20-30% patients relapse during their disease course. Tumour size, nodal involvement, grade, lymph vascular invasion, and estrogen receptor[2] and human epidermal growth factor receptor[3] status are all independent risk factors for relapse. The propensity of breast cancer to give to distant metastasis depends on molecular type of cancer and these subtypes have preferential sites for distant relapse. A better understanding of patterns of metastatic spread may influence adjuvant therapy and surveillance decisions and determine which investigations and therapies are appropriate once distant disease has been diagnosed. The aim of this retrospective analysis was to identify any association with the site of metastasis to the molecular subtypes based on ER, PR, and HER2Neu status.

Methods and materials:-

Patients with locally advanced breast carcinoma diagnosed in between 2011 to 2013 were analyzed retrospectively. Metastatic disease at initial presentation was also included in the study. A total of 248 patients were seen out of which 10 patients were excluded due to non-availability of biopsy report. All patients had adequate tissue biopsy for histo-pathological diagnosis in form of core biopsy, if inoperable, or surgical specimen. Patients were evaluated for the receptor status i.e. ER, PR, HER2Neu and Ki-67. On the basis of these receptors, patients were further classified into subtypes as follows (Table 1):-

Receptor status Subtypes	ER	PR	HER 2	Ki-67
Luminal A	Positive	Positive	Negative	<14%
Luminal B	Positive	Positive	Negative	>14%
Her 2 Enriched	Negative	Negative	Positive	Any
Luminal Her2	Positive Negative	Negative Positive	Positive Positive	Any
Triple Negative	Negative	Negative	Negative	Any

Patients received the standard treatment of Adriamycin based neoadjuvant chemotherapy followed by surgery and radiation for locally advanced and systemic chemotherapy +/- radiation for metastatic disease. All the patients were followed up to the appearance of any metastasis or period of their last follow up.

Results:-

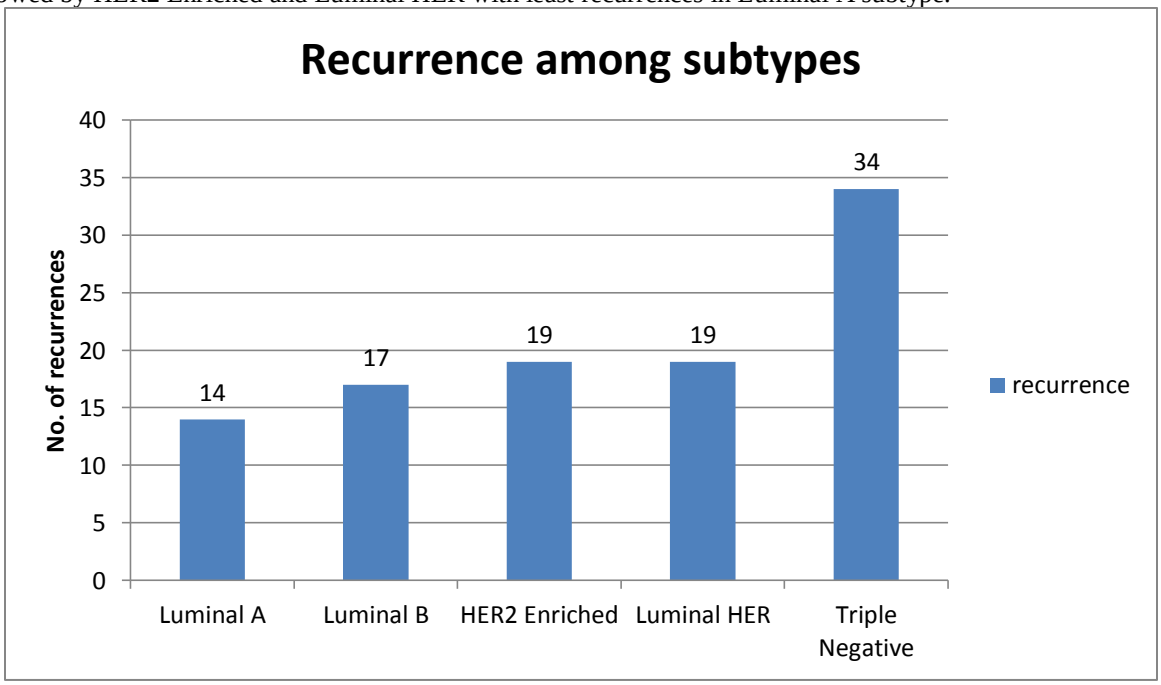
A total of 248 patients were taken out of which 10 patients were excluded before the analysis. 12 more patients were excluded from the analysis due to altered chemotherapy schedule given or prior treated patients. Results were analyzed using SPSS Software version 20. Mean age of the study group was 50.71 +/- 11.4 years with 41-50 years as the most common age group. Most of the patients were locally advanced stage while 35% had metastatic disease at presentation. Among the eligible 226 patients (Table 2), maximum patients were triple negative (27.4%) closely followed by luminal A (25.2%) while 18.1% were Luminal B, 14.2% HER2 Enriched and 15% Luminal HER2.

Subtypes		number	percentage
	LUMINAL A	57	25.2
	LUMINAL B	41	18.1
	HER2 ENRICHED	32	14.2
	BASAL	62	27.4
	LUMINAL HER2	34	15.0
	Total	226	100.0

Out of all patients with metastatic disease at presentation (Table 3),Bone (44.6%) was the most common site of metastasis followed by liver (22.9%) and lungs (14.5%).

	Bone	Liver	Brain	Lung	Other distant metastasis	total
Luminal A	14	3	0	4	1	22
Luminal B	6	4	0	3	0	13
Her2 Enriched	3	3	2	1	3	12
Luminal HER	8	6	0	2	2	18
Triple Negative	6	3	1	2	3	15

A total of 38.9% patients underwent upfront surgery with total mastectomy with axillary clearance (94.6%). After neoadjuvant chemotherapy in non-metastatic patients, 75 patients were amenable to surgery and underwent total mastectomy with axillary clearance (97.8%). The pattern of recurrence among the non-metastatic patients was different from the metastatic patients. Triple negative subtype (Graph 1) had the maximum number of recurrences followed by HER2 Enriched and Luminal HER with least recurrences in Luminal A subtype.



Bone continued as the most common site of metastasis in patients having recurrence followed by brain (Table 4).

	Bone	Liver	Brain	Lung	Other distant metastasis	Total
Luminal A	8	2	1	1	1	13
Luminal B	10	1	1	3	1	16
HER2 Enriched	1	5	5	4	2	17
Luminal HER	2	3	5	3	2	15
Triple Negative	3	7	9	7	2	28

Brain was the most common site of recurrence in Triple Negative subtype followed by lung and liver with least number of bone metastasis.

Discussion:-

The understanding of molecular subtypes of carcinoma breast is limited to early breast cancer and very little is known about the relapse at the different metastatic sites. This retrospective study intends to look into the pattern of spread among the different subtypes of locally advanced carcinoma breast. On analysis it was found that breast cancer subtypes are associated with unique patterns of metastatic spread with notable differences in survival after relapse. The observations illustrate the potential of locally advanced disease to seed on the metastatic disease process and have clinically relevant implications.

The study illustrated different pattern of metastatic spread among subtypes as Luminal A (ER+/PR+) having the least recurrence rate among the treated patients. In ER/PR positive tumours, bone was the most common site of metastasis with fewer visceral metastases. This result appears in accordance to the studies in literature[4,5]. The exact reason for this finding is beyond the scope of this paper and the answer might lie in the further molecular or translational level (SNAI1 Protein). SNAI1 protein is a zinc finger transcriptional repressor of CDH1which encodes E-cadherin. Down regulation of E-cadherin activates the "epithelial-mesenchymal transition" crucial for cancer cell dissemination and invasion which might augment breast cancer metastasis in bone[6]. The high rate may point to the central role that the bone marrow plays as a common homing organ for metastatic breast cancer cells, independent of the pattern of overt metastasis[7].

A proven fact about the poor prognostic factor of HER2 positivity is clearly depicted in the study with the significant association of visceral metastasis in these patients[8,9]. Patients who were HER2 positive mainly relapsed in liver, lungs and brain. Experimental mouse models suggest that EGFR is important for tumour cell motility and invasion and HER2 for tumour cell intravasation[10]. An important other reason for this finding can be the lack of use of Trastuzumab[11,12,13] as most of the patients attending the hospital belong to low socioeconomic strata. But unexpectedly, HER2 tumours didn't have the highest number of metastasis as they should have been.

The reason might be due to the high number of Triple Negative patients in the study group. The high percentage of triple negative cancer patients may be attributed to a higher level of awareness among the young females (mean age < 45 years) leading to early diagnosis. Among the triple negative subgroup, Brain was the most common site of metastasis which was reported in other studies.[14,15] Visceral metastasis accounts for a higher percentage in these patients making it the subtype having poor prognosis among all the subtypes.

With the knowledge of these subtypes and the pattern of spread among these subtypes, early imaging and diagnostic investigations should be done in order to detect any metastasis. A further consideration is that conventional imaging would not necessarily detect all metastatic disease, with subclinical metastases being missed simply because no or inappropriate imaging was performed. So appropriate imaging with high sensitivity and specificity should be done at the time of diagnosis.

Also, follow-up recommendations for patients with locally advanced breast cancer should be changed over time, and the diagnosis of metastases should not be still based on history and physical examination. A major limitation of the study is inadequate sample size and the non- usage of trastuzumab could be a confounding factor in the outcome of the study results.

Conclusion:-

The study done demonstrates the different patterns of relapse, in terms of different sites, among the subtypes based on ER, PR and HER2Neu.Hormone positive tumours have more tendencies to have bony metastasis while hormone negative tumours have more of visceral metastasis. A better knowledge of these patterns among subtypes may help in early detection and better suspicion of having these metastasis. An adaptation of imaging may be warranted to stratify follow-up of patients by breast cancer subtype, given the variation in distant metastasis sites and outcomes.

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