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PROGNOSTIC CLASSIFICATION OF BREAST CARCINOMA ON MOLECULAR BASIS USING ER, PR, HER-2/NEU AND KI67: A STUDY CONDUCTED ON 56 PATIENTS IN RIMS, RANCHI, JHARKHAND, INDIA

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ABSTRACT

Objective: To classify the cases of breast carcinoma coming to RIMS, Ranchi into Luminal A, B, Her-2/neu and basal like using IHC Markers- ER, PR, Her-2/neu and ki67

Materials and methods: In our study on 56 patients with breast carcinoma, were taken into account and the expression of Hormonal, markers ER, PR, Her-2 and ki67 were determined by immune-histo-chemistry and classification into Luminal A, B, Her-2 and Basal like were done subsequently.

Results: During the study period a total of 56 cases of Breast carcinoma were subjected to immune-histo-chemistry. The maximum number of patients was in the age group of 51-60 years of age. The study comprised mainly of females with a male to female ratio of 1:28. Histologically, 51 cases (91.07%) were invasive ductal carcinoma NOS. As per Bloom Richardson grading, 23 patients (41.07%) were of Grade I, 19 patients (33.92%) of Grade II and 14 patients (25%) of Grade III. Out of 14 cases of Bloom Richardson Grade III, 9 had high ki67 index (64.28%). A low Ki67 index was present in 40 cases of Grades I and II (95.23%)

P Value using Fisher's Exact Test = 0.0001 (statistically high significant correlation).

Depending on IHC markers ER, PR, Her-2/neu, and Ki67, molecular subtyping into Luminal A patients were 43 (76.78%), Luminal B were 10 (17.85%), Her-2/neu enriched-1 (1.78%) and Basal like-2 (3.57%).

KEYWORDS : Breast cancer, Immuno-histo-chemistry, molecular classification, Luminal A, B

I. Introduction:

Breast carcinomas is the most common cancer in women worldwide contributing about 20% of cancer deaths in women and are notably among the most significant concern for any women in today's world. Carcinomas of the breast show marked variation in regard to clinical presentation, biological behavior, and response to therapy. For the past several decades, the classification and management of breast carcinoma were primarily based on clinico-pathologic (morphology, size, grade, nodal status, etc.) characteristics. Even among histologically similar tumors, these characteristics could not always offer accurate prognostic and predictive information. Over the last few decades, the immune-pheno-typical profile of a breast carcinoma has achieved a greater prognostic and predictive importance. In this study we have attempted to classify 56 breast carcinoma samples coming to RIMS, Ranchi, India into Luminal A, B, Her2/neu and Basal like for better prognostic outcome of the patients.

II. Discussion:

The aim in modern medicine is to identify patients who have an unfavorable prognosis – or even better, to identify patients who may be capable of benefiting from an improved prognosis associated with a specific form of treatment. Similar to other carcinomas of various anatomic sites, the development of invasive breast carcinoma also involves multiple genetic alterations and this has long been exploited for prognostication.[1,7] The pioneering molecular classification system for breast carcinoma was developed by Perou et al in 2001. Depending on the intrinsic gene expression pattern using cDNA Microarray, four molecular subtypes of breast carcinomas were identified: "luminal", "HER2-enriched, "basal-like' and "normal breast-like'. The "luminal group" of carcinomas were largely hormone receptor[1,5] and express luminal epithelial genes-traits similar to those of normal luminal epithelial cells. The "HER2-enriched group" was mainly composed of breast carcinomas with amplification of the HER2 gene. The "basal like group" was ER (-ve), and frequently corresponded to the triple negative breast carcinomas (TNBCs, i.e., ER(-ve), PR(-ve), and HER2(-ve). This group of tumors was immune-reactive for cytokeratin (CK) 5/6 and CK17, similar to the reactivity pattern observed in myo-epithelial cells of the normal breast epithelium (i.e., "basal" cells, hence the term applied to this group). The category of tumors called "normal breast-like" had a gene expression pattern similar to that observed in normal breast tissue. It later became evident that the last subtype is most likely an artifact rather than a genuine type of breast cancer, resulting from contamination of tissue samples with high levels of normal breast tissue and paucity of the tumor, and may not exist at all. Luminal group was further divided into "A" and "B" depending on the proliferative rate.[2] Luminal B tumors responded less to hormonal therapy, and more to chemotherapy, relative to luminal A tumors.[3,4] In general, luminal B tumors had a poorer prognosis than did luminal A tumors[4]. Triple negative breast cancers have the worst prognosis overall.[1,6] Table no. 1 shows the chief features of the molecular subtypes. The various molecular classifications of breast carcinomas attempt to capture the intrinsic biologic variances among these tumors and stratify them into clinically relevant groups beyond those possible by ER/PR/HER2 testing. Most significantly, molecular classifications seek to stratify breast carcinomas into molecularly distinct subtypes with an aim to employ "druggable" targeted therapy. Using ER, PR, Her2/neu and Ki67 markers, molecular classification of Breast carcinoma into Luminal A, B, Her2 enriched and Basal like was done in this study and the results are shown in table 2. This clearly implicates that 76.78% of Luminal A patients can benefit only from hormonal therapy alone and neo-adjuvant chemotherapy is not required. Classifying breast carcinoma into luminal B is also helpful as we can understand that these patients will not benefit from hormonal therapy and chemotherapy will be required. Furthermore, these patients will have a poorer prognosis as there are increased chances of relapse. By use of one extra IHC marker that is Ki67, better or worse outcome can be easily predicted in a patient of breast carcinoma and the type of therapy required can also be predicted.

Table 1- Chief features of molecular sub-typing of Breast carcinoma

	Luminal A	Luminal B	Her2/neu enriched	Basal like
Immunoprofile ER,PR HER2 and Ki67	ER and/or PR +ve Her2/neu – ve Ki67 index<14%	ER and/or PR+VE Her2+/-ve Ki67index>14%	ER and PR-ve Her2+ve High proliferative rate	ER,PR-ve Her2- ve High prolifration rate
Prognosis	Good	Intermediate	Poor	Poor
Distant relapse	Distant relapse Peak at 4 y, and risk of relapse prolongs	Distant relapse Peak at 4 y, and risk of relapse prolongs	Peak at 4-6y, but risk persistent over 10-15 years.	Peak at 2years, then reduced to minimal over 10 years.
Response to hormonal therapy	Good	Poor with Hormonal therapy only	No response	No response
Response to chemotherapy	Poor	Intermediate	Good, better with trastuzumab	Good
Histologic grade	Low to intermediate	Intermediate	High	High

Table 2- Results as obtained after using IHC markers on 56 patients

Molecular subtype	No. of patients	Percentage
Luminal A	43	76.78%
Luminal B	10	17.85%
Her2 enriched	1	1.78%
Basal like	2	3.57%

III SUMMARY AND CONCLUSION

This was a prospective study of 56 patients of breast carcinoma coming to RIMS, Ranchi. Immuno-histo-chemical markers – ER, PR, Her2/neu, and Ki67 were applied on each case for prognostication.

A significant correlation was obtained when Ki67 histological grade (p value = 0.0001) were considered. A high Ki67 labeling index was associated with high histological grade which in turn shows a grave prognosis.

Using these four immune-histo-chemical markers, molecular classification of breast carcinoma into Luminal A, B, Her2/neu enriched and Basal like was done and it showed that 76.78% of patients fall in Luminal A category. These patients benefitted only from hormonal therapy alone and neo-adjuvant chemotherapy was not required, and have an overall good prognosis. Neo-adjuvant chemotherapy is required in 21.42% patients belonging to Luminal B and Basal like category and they had an overall poorer prognosis. Trastuzumab therapy can be started in Her2/neu enriched subtype.

A beforehand knowledge of these immune-histo-chemical markers can help onco-therapist to initiate a correct form of treatment and improve the survival rate in breast carcinoma patients.

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