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Clinicopathological and molecular characteristics of breast cancers: a comparative study

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ABSTRACT
Objectives and Background: This is a retrospective research of 50 cases that uses immunohistochemistry to assess the expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor proliferation index in breast carcinomas. The purpose of this research was to apply molecular categorization to patient data, examine how that data compared to clinicopathological factors, and highlight the value of targeted therapy.
Materials and Methods: Specimens from April 2023 to July 2023 were collected at the tertiary care center in Telangana for analysis of the expression of the aforementioned markers following modified radical mastectomy. Infiltrating ductal carcinoma of undifferentiated type and its variants including medullary, papillary, metaplastic, lobular, mucinous, and apocrine carcinoma were identified in Hematoxylin. Fifty samples were chosen for immunohistochemistry investigation, thirty of which were IDC NST and thirty of which were unique variations.
Results: Among the 50 instances analyzed, 37% were determined to be of the luminal A type, while 8% each were of the luminal B and hybrid types. Grade III HER2 was the most common grade. Forty-eight percent of the 50 cases were considered successful. The HER2, Hybrid, and Basal subtypes each accounted for one death. When comparing the agreement between histopathological and molecular classification, a negative kappa value shows that the agreement is poorer than chance, lending credence to the necessity of molecular classification for targeted therapy.
Conclusion: Molecular subgroup research would open the way for "personalization" of treatment for breast tumors using the more practical and cost-effective technology of immunohistochemistry, which is important because breast cancers are heterogeneous and have varying clinical outcomes.

Keywords: Clinicopathological, molecular characteristics, breast cancers, comparative

INTRODUCTION

Breast carcinoma is one of the most frequently diagnosed tumors globally, accounting for 16% of all cases among female cancers. Although HPV has surpassed cervical cancer as the leading cause of cancer-related fatalities in underdeveloped nations, survival rates remain dismal. In India, it occurs in 30–33% of every 1,000,000 women, with a relative risk of 0.033. The death rate can be lowered significantly via early detection and treatment [1-3].

According to the type of cell from whence they originated, breast tumors are classified as either (i) ductal carcinoma or (ii) lobular carcinoma. Breast cancers can be divided into two main types: lobular (10-20%) and ductal (80-90%). When it comes to metastasis, recurrence, and therapeutic response, breast tumors exhibit a wide range of behaviors. Our knowledge of tumor behavior and therapeutic response has been greatly improved via the study of molecular features of tumors. Both their prognostic value and their ability to predict therapeutic success have increased the spotlight on these molecular markers in breast cancer. In particular, researchers are becoming more interested in the steroid receptors HER2 neu, CK5/6, Ki67, and ER/PR [4-6].

Malignant ductal epithelial tumors of the breast, known as invasive breast carcinomas, have a higher propensity for metastasizing to other parts of the body. Due to its obviousness, breast carcinoma is one of the cancers frequently recorded in historical texts. Breast cancer was first described in the Edwin Smith Papyrus, which dates back to around 1600 B.C. Imhotep recounted the earliest known case of breast cancer in 2650 BC. Leonides said that malignancies are like crabs since they stick to their surroundings so stubbornly [7, 8].

The new molecular classification of breast tumors is based on an algorithm, which has been made possible by recent developments in breast pathology that evaluate the RNA, DNA, and proteins of malignant cells. Gene expression

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profiling has helped researchers identify five distinct classes of gene expression patterns: Luminal A, Luminal B, HER2 type, Basal, and unclassified. This categorization is highly correlated with treatment outcomes and prognosis. Luminal A tumors had the best long-term disease-free survival rates. However, basal type and HER2 subtype cancers respond well to chemotherapy but have the lowest prognosis overall [9-11].

In this study of 50 cases, researchers attempted to use immunohistochemistry to determine the hormonal status and proliferation index of invasive ductal carcinoma of no special type and its special variants. There was also a correlation between the histology grade and additional prognostic variables. The study's primary goal was to characterize the demographic patterns in which breast cancer occurs [12, 13]. The purpose of this research was to examine the histomorphological characteristics of breast cancer, such as grade, lymph node status, lymph vascular invasion, lymphocytic response, and necrosis. The goal of this study was to examine invasive breast carcinomas for the presence of ER, PR, HER 2 neu, CK5/6, and Ki67. Where the terminal duct lobular unit has a small number of cancerous cells.

Materials and Methods

Specimens from April 2023 to July 2023 were collected at the tertiary care center in Telangana, analysis of the expression of the aforementioned markers following modified radical mastectomy. Infiltrating ductal carcinoma of undifferentiated type and its variants including medullary, papillary, metaplastic, lobular, mucinous, and apocrine carcinoma were identified in Hematoxylin. Fifty samples were chosen for immunohistochemistry investigation, thirty of which were IDC NST and thirty of which were unique variations.

Inclusion criteria:

- All breast cancer specimens from modified radical mastectomy, including invasive breast cancers of all types, as well as medullary, mucinous, papillary, apocrine, and metaplastic cancers, regardless of age or gender, were included in the study.

Exclusion criteria:

- Phylloides tumors,
- Benign breast lesions,
- All trucut biopsies,
- Tumors with pre-existing premalignant diseases, and tumors.
- Tumor recurrences.

Method of Data Collection

For the 50 cases included in the study that were reported during the study period, a detailed history of the cases including age, sex, menstrual history, side of the breast, type of procedure, history of neo adjuvant therapy, details of gross characteristics such as tumour size, nodal status details, and more was obtained from surgical pathology, surgical oncology, and medical oncology records. The tissue was treated, paraffin embedded, and sliced.

RESULTS

During the period spanning from April 2023 to July 2023, a grand number of 25,536 specimens were received. A total of 1012 breast specimens were obtained, of which 1020 instances were identified as breast tumors, representing 3.85% of all cases. The aggregate count of non-neoplastic instances, including both benign and malignant cases, was 190, with 370 cases classified as benign and 550 cases classified as malignant. The distribution of non-neoplastic breast lesions, benign tumors, and malignant tumors is presented in Table 1, with percentages of 20.46%, 33.42%, and 46.11%, respectively.

Table 1: The distribution of breast cancer cases

	Non neoplastic	Benign	Malignant
Breast	190	370	550

There were 370 radical mastectomy specimens among the 550 breast cancer cases. Among these 190 instances, 50 were included in this investigation, including 25 cases of Infiltrating ductal carcinoma NST and 25 cases of special variations, which included apocrine, medullary, mucinous, metaplastic, lobular, and papillary carcinomas (Table 2).

Table 2: The distribution of cases in the research

Sr. No.	Histopathological Classification	No of cases (%)
1.	Infiltrating ductal carcinoma no special type (IDC NST)	25
2.	Metaplastic carcinoma	5
3.	Papillary carcinoma	5
4.	Lobular carcinoma	5

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5.	Apocrine carcinoma	3
6.	Medullary carcinoma	5
7.	Mucinous carcinoma	2

All 50 cases had their data analyzed and scored for ER, PR, HER2, CK5/6, and Ki67. According to the results of the molecular analysis, the tumors were categorized as either luminal A, luminal B, HER 2, basal, or unclassified. Among the 50 cases, 22 were the most prevalent luminal A type, 14 were basal type, 8 were HER2 positive, 6 were unclassified, and 5 were a luminal B or hybrid. Per Table 3 below.

Table 3: The Molecular Subtype Distribution in the Present Investigation

Molecular subtypes	**Luminal A**	**Luminal B**	**HER 2**	**Hybrid**	**Basal**	**Unclassified**
No of cases	20	5	8	2	10	5

The eldest presenter was 75 years old, and the youngest was 26. This comparison was not statistically significant. Table 4 shows that the left side of the breast was more commonly impacted than the right side among the 50 cases included in this investigation.

Table 4: The relative contributions of different groups to molecular classification

	SIDE		
Molecular Classification (MC)	**Right**	**Left**	**Total**
Luminal A	10	12	22
Luminal B	2	3	5
HER2	1	5	6
Hybrid	2	2	4
Basal	5	2	7
Unclassified	5	3	8
Total	25	25	50

After looking at the distribution of cancers by side, we observed that 55% of luminal A tumors, 60% of luminal B tumors, 82% of HER 2 tumors, and 57% of basal tumors all occurred on the left side of the body. Three of the five cases of Hybrid tumors were located on the right side of the breast, while the number of cases of the unclassified kind was about the same on both sides. Table 5 shows there was no statistical significance.

Table 5: Location of tumors in relation to their molecular subtypes

Molecular Classification	**UOQ**	**LOQ**	**LIQ**	**CQ**	**Total**
Luminal A	11	3	3	4	21
Luminal B	4	0	0	0	4
HER2	5	1	0	3	9
Hybrid	2	0	1	0	3
Basal	2	0	0	5	7
Unclassified	2	2	0	2	6
Total	26	6	4	14	50

73% of luminal A, 80% of luminal B and hybrid, 79% of basal, 67% of unclassified, and 63% of HER 2 types were found to have fibrocystic disease as an associated lesion. The luminal A subtype accounts for 5 of 11 ductal carcinoma in situ instances, whereas the basal and unclassified subtypes each account for 27% and 18%, respectively. All 50 cases were evaluated for lymphovascular invasion, which is a poor prognostic indicator. Table 6 shows that it occurred 66.7% of the time and was absent 33.3% of the time.

Table 6: Lymphatic vessel invasion and its molecular subtype

Molecular Classification	**Present**	**Absent**	**Total**
Luminal A	10	9	19
Luminal B	3	2	5
HER2	4	1	5
Hybrid	2	2	4
Basal	10	3	13
Unclassified	1	3	4
Total	30	20	50

There was a significant uptick in the frequency of lymphovascular invasion across all molecular subtypes except the unclassified type. In contrast to the 60% of luminal tumors and hybrid instances that exhibited lymphovascular invasion,

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87% of HER 2 and 78% of basal tumors did.

DISCUSSION

Cancer of the breast, or breast carcinoma, accounts for 16% of all cancer diagnoses in women globally. In India, the rate of incidence is 30-33% per 100,000 females, with a corresponding relative risk of 0.033. Death rates can be lowered by early diagnosis and treatment. Fifty breast carcinomas were analyzed by immunohistochemistry, graded using the ASCO - CAP system, and used in the current investigation. Cases were assigned molecular subtypes based on the scores. Molecular categorization was compared to clinical characteristics, histological subtype, grading, and prognostic variables.

Using immunohistochemical markers, we assigned molecular classifications to 50 cases of breast carcinomas. The luminal A type was found to be the most prevalent, making up 37% of the total, while the luminal B type and the hybrid type both made up 8% of the total. The findings accord with those of Perou, sorlie, *et al*. Patients with breast cancer ranged in age from 25 to 85, with the average being 51.7. The incidence of breast cancer was highest in women aged 50 to 59. This agrees with the findings of the research conducted by Rajesh Singh Laishram*et al*. The HER 2 and basal kinds of the molecular categorization had patients that presented at younger ages. This agreed with what Lajos Pusztai *et al*. found in their research [14-16].

More tumors of luminal A, luminal B, HER2, and basal types were located on the left side of the body. More cancers occurred on the right side of the body in hybrid types. The incidence of tumors in the upper outer quadrant was highest across all molecular subgroups, followed by cancers in the middle quadrant. The majority of tumors were of the T2 size, which is consistent with the findings of the studies by Christine L. Carter *et al*. and Lakmini *et al*. T3 tumors larger than 5 cm were seen in Luminal B, HER 2, and unclassified kinds. Luminal A tumors were often of the T2 size. That fits with what bhumsukkaen *et al*. found. In contrast to infiltrating ductal carcinoma NST, the histological classification of 72% of luminal A cancers indicates that they correspond to histological variants of specific types. 40 percent of luminal A, 25 percent of luminal B, 42 percent of HER 2 basal, and 16 percent of unclassified are variations.

All but one of the five mucinous tumor patients tested positive for hormone receptors, and all were HER 2 negative. This agreed with the findings of the study by Lacorixtriki *et al*. Three of the five medullary tumor cases were triple negative, meaning they tested negative for both hormone receptors and HER 2 neu. This agrees with the findings of Jensen *et al* [17-19].

All five cases of papillary carcinoma tested positive for hormone receptors but negative for HER 2 neu, indicating that they all belonged to the luminal A subtype. Both the Chen *et al*. study and the Lotan *et al*. investigation came to similar conclusions. None of the five apocrine carcinomas were of the luminal A type. Luminal B accounted for one case, while basal and hybrid cancers made up the other two. This agrees with the findings of the study by Matsuo *et al*. GM Tse *et al*. conducted a study in which they categorized metaplastic carcinomas as triple negative tumors. However, in our investigation, none of the five cases of metaplastic tumors were of the basal type. Two were categorized as Luminal A, one as Luminal B, one as HER 2, and one as HER 3 [20-22].

In four out of the five lobular carcinoma cases, the tumors were classified as luminal A. Consistent with the findings of Weidner *et al*., several researchers have found that luminal A and B are the most prevalent molecular subtypes, while HER 2 and basal type are the least common. Contrary to this, the current investigation found that the basal molecular subtype was the most common among the 30 instances of invasive ductal carcinoma [23, 24].

Forty percent of grade I tumors in this analysis were of an unknown type. High-grade tumors made up 50% of the basal variety and 29% of the HER 2 variety. The percentage of grade II luminal A cancers was 18%. None of the hybrid or luminal A types were of the grade III variety. Rakha *et al*. found substantial variation in hazard ratio and likelihood of relapse over 10 years among ER-positive Luminal A tumors. A higher tumor grade was associated with a higher hazard ratio. The likelihood of recurrence after 10 years was statistically significant at 5% for grade 1 tumors, 24% for grade II tumors, and 43% for grade III tumors. Only 11% of the 27 cases of luminal tumors were classified as grade I, while 22% were classified as grade II, and 5% were classified as grade III. There was an elevated recurrence rate reported in grade III tumors after a year of follow up. The study also found that grade III tumors were more common in the HER2 and basal kinds. That fits in with what Rakha *et al*. found [25-27].

High-proliferating hormone receptor-positive cancers were classified as luminal B in the current analysis. Although both luminal A and luminal B tumors are positive for the estrogen receptor, the luminal B subtype is more likely to experience early relapse following endocrine therapy, supporting the findings of the study by Bentran and Philippe bedard *et al*. The risk of early distant metastases was found to be 2.86 times higher in luminal B subtypes than in luminal A tumors. Tumors with low hormone receptor expression, varying HER 2 expression, and a high proliferation index have

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been identified and separated from more placid luminal A tumors [28, 29].

Breast cancers that express a high proliferation index with ki67, a nuclear marker for cell proliferation, did not benefit much from adjuvant chemotherapy and were linked to the worst outcomes, regardless of the cancers' histological or molecular subtypes, according to a study by Maggie cheang *et al*. The prognostic value of the Ki-67 index was evaluated, and a threshold of 14% was established as being visually detectable. According to the research conducted by Maggie cheang *et al*., recurrence rates were higher for Luminal B and hybrid kinds. Their immunohistochemistry research of breast malignancies led them to the conclusion that recurrence-free survival and disease survival were low among patients with luminal B and luminal -HER 2 hybrid tumors who had been treated with adjuvant systemic treatment. All of the luminal B tumors in the current investigation were found to be alive and well after a year of follow-up, but only 60% of cases were disease-free in the luminal-HER2 hybrid and basal kinds. Therefore, determining whether tumors fall into the basal and hybrid classifications is crucial for treating them appropriately [31-33].

Breast cancer treatment is comprehensive, encompassing endocrine therapy, systemic chemotherapy, and Herceptin therapy based on histological classification. Whereas molecular classification of breast tumors allows for more precise treatment, reducing the number of patients exposed to medications they don't need while also cutting down on treatment costs and side effects. Histopathological and molecular classifications provide different information, and thus different therapeutic options. Because of this, evidence of discord between the two taxonomies is required [34-36].

The current study compared each molecular subtype to its corresponding histopathological categorization, and the results showed that there was substantial disagreement between the two systems, as evidenced by a negative inter rater agreement KAPPA value. The two systems' inconsistency demonstrates molecular classification's worth in the practice of targeted medicine. Some patients in the current study received treatment based on histological classification, whereas others received treatment based on immunohistochemistry examination of triple markers. Hess KR *et al*., Ayers M *et al*., and Gianni L *et al*. all reported that relapse rates dropped significantly when patients were given tailored therapy according to their cancer's molecular profile [35-37].

CONCLUSION

Our knowledge of tumor behavior and therapeutic response has been greatly improved via the study of molecular features of tumors. This study aimed to use immunohistochemistry to assess the hormonal status and proliferation index in 50 cases of invasive ductal carcinoma, including NST and its variations. Given the heterogeneity and variability in clinical outcomes associated with breast tumors, studies identifying molecular subgroups could open the way for "personalization" of treatment for the disease, using the more practical and cost-effective immunohistochemistry.

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Conflict of Interest None

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