

## The Clinicopathological Features of Breast Carcinoma Cases in Aldiwaniyah Province in Iraq

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**Abstract:** In Iraq, invasive ductal carcinoma is common and the disease is frequently diagnosed in late stages making the prognosis of the tumor bad in a significant portion of affected women. The prognosis of breast cancer is determined by a long list of prognostic factors such as stage of the disease, grade of the disease, presence of lymphatic invasion, presence of distant metastasis, size of tumor, age of patients and many other characteristics. Treatment of the disease includes surgical removal, chemotherapy, radiotherapy and biological treatment. The treatment of disease depends on a number of modifying factors and of these factors is the immunohistochemical expression of estrogen receptors (ER), progesterone receptors (PR) and her2neu.

**Aim of the study:** The objective of the present cross sectional study was to give an account about estrogen receptor (ER), progesterone receptor (PR) and her2neu receptor immunohistochemical expression in Iraqi women with breast carcinoma in Aldiwaniyah Province.

**Materials and methods:** Histopathological reports were retrieved from the archive of the central laboratories of Al Diwaniyah teaching hospital for the last 4 years. The duration of search was limited to the period January the 1<sup>st</sup> 2019 to January the 1<sup>st</sup> 2023. Information about clinical presentation, age, histopathological type, grade, number of lymph nodes, and immunohistochemical study were reported. Statistical description was based on reporting number, percentages, mean, range and standard deviation

Statistical package for social sciences (SPSS, Chicago, USA, IBM, version 26) was used to do statistical description and analysis and  $p \leq 0.05$  was the level of significance.

**Results:** The research included reports of 39 women with breast carcinoma having an age range of 25 -85 years and a mean age of  $53.31 \pm 15.96$  years. The mean size of tumor mass was  $3.24 \pm 1.34$  cm with a range of 0.5 -8 cm. The frequency distribution of patients according to molecular classification was as following: there were 16 cases (41 %) of luminal A group, 8 cases (20.5 %) of luminal B group, 8 cases (20.5 %) of HER2/neu group and 7 cases (17.9 %) of basal like group. There was no significant difference in mean age, mean size of tumor, mean number of lymph nodes and mean number of involved lymph nodes ( $p > 0.05$ ).

**Conclusion:** The most common molecular type was luminal A followed by luminal B and HER2/neu and lastly by basal like type. This molecular classification has no significant impact on clinicopathological characteristic of the disease.

**Key words:** Breast carcinoma, immunohistochemical, Iraq

## Introduction

Malignant neoplastic disorders are considered the big challenge for every health system worldwide because of the substantial rates of morbidity and mortality in association with these disorders (1-3). In women, breast cancer is one of the most common malignant diseases encountered and it is associated with gloomy prognosis in a significant portion of women (4-6). From pathological perspective, breast cancer is not a single disease, but it is represented by a heterogeneous group of malignant disease arising from variety of tissues (7). Some of these tumors are originating from soft tissues and are known sarcomas (8), some of them are attributed to monoclonal lymphoid tissue proliferation and are called lymphomas (9), others are originating from melanocytes and are known as malignant melanomas (10); malignant neoplasms of epithelial tissues are however by far the most common form of malignancy affecting the breast tissue (11).

Epithelial neoplasms affecting breast tissues can be benign such as fibroadenoma (12), whereas, malignant epithelial tumors can take different types of histological shapes, but, the basic two of histological forms are the ductal and the lobular type (13). Those two types are either limited by the basement membrane (in situ type) or associated with stromal infiltration and breaching of basement membrane (invasive type). Therefore, malignant epithelial tumors of breast can be in situ ductal, in situ lobular, invasive ductal or invasive lobular carcinoma (14). The most common type of breast carcinoma is the invasive ductal carcinoma not otherwise specified (NOS) (15).

In Iraq, invasive ductal carcinoma is common and the disease is frequently diagnosed in late stages making the prognosis of the tumor bad in a significant portion of affected women (16-18). The prognosis of breast cancer is determined by a long list of prognostic factors such as stage of the disease, grade of the disease, presence of lymphatic invasion, presence of distant metastasis, size of tumor, age of patients and many other characteristics (19, 20). Treatment of the disease includes surgical removal, chemotherapy, radiotherapy and biological treatment (21). The treatment of disease depends on a number of modifying factors and of these factors is the immunohistochemical expression of estrogen receptors (ER), progesterone receptors (PR) and her2neu (22-24).

Estrogen receptor and progesterone receptor expression in breast cancer is so far the most useful predictive marker (25). ER and PgR are intercellular steroid hormone receptors and have been frequently demonstrated in breast carcinoma. ER and PR expression has been found in majority of cases of invasive ductal carcinoma (26). Tumors expressing ER and PR receptors show a good response to hormonal therapy and chemotherapy leading to a better prognosis, good survival, and less mortality (25).

Other than hormonal receptors, the most promising biomarker in breast cancer is HER2. This is a protein that is overexpressed in a minority of breast cancers and has prognostic as well as predictive value (25). Tumors expressing HER2 are histologically high grade, are most likely to metastasize, and have a worse prognosis (27). However, HER2 overexpression also predicts a good response to anti-HER2 agents, including trastuzumab and lapatinib (25).

Breast carcinoma with the same histologic type, grade, and stage may show different outcomes and different responses to therapy. Evaluation of prognostic and predictive biomarkers ER, PgR, and HER2 is recommended in every case of breast carcinoma. Immunohistochemistry (IHC) is the most widely employed method to determine the status of ER, PgR, and HER2 in formalin-fixed paraffin-embedded tissue samples of breast cancers (25).

The objective of the present cross sectional study was to give an account about estrogen receptor (ER), progesterone receptor (PR) and her2neu receptor immunohistochemical expression in Iraqi women with breast carcinoma in Adiwaniyah Province.

### **Materials and methods**

Histopathological reports were retrieved from the archive of the central laboratories of Al Diwaniyah teaching hospital for the last 4 years. The duration of search was limited to the period January the 1<sup>st</sup> 2019 to January the 1<sup>st</sup> 2023. Information about clinical presentation, age, histopathological type, grade, number of lymph nodes, and immunohistochemical study were reported. There was no need for patients' consent because the study was retrospective; however, ethical approval was issued by the ethical committee of the health directorate. Statistical description was based on reporting number, percentages, mean, range and standard deviation. Statistical package for social sciences (SPSS, Chicago, USA, IBM, version 26) was used to do statistical description and analysis and  $p \leq 0.05$  was the level of significance.

### **Results**

Clinical and pathological characteristics of women with breast carcinoma are demonstrated in table 1. The research included reports of 39 women with breast carcinoma having an age range of 25 - 85 years and a mean age of  $53.31 \pm 15.96$  years. The mean size of tumor mass was  $3.24 \pm 1.34$  cm with a range of 0.5 - 8 cm. The mean number of surgically removed lymph nodes was  $9.05 \pm 2.70$  and the

range 5 -16 and the mean number of lymph nodes which are involved by malignant tumors was  $2.31 \pm 2.17$  with a range of 0-8. According to grade there were 6 (15.4 %) and 33 (84.6 %) cases of moderate differentiation and poor differentiation, respectively. Based on histological subtypes, there were 36 (92.3 %) and 3 (7.7 %), invasive ductal and invasive lobular cases, respectively.

Results of immunohistochemical investigations concerning estrogen receptors (ER) are shown in table 2. Results of immunohistochemical investigations concerning progesterone receptors (PR) are shown in table 3. Results of immunohistochemical investigations concerning her2neu receptors are shown in table 4. The frequency distribution of patients according to molecular classification following the immunohistochemical staining of estrogen receptors (ER), progesterone receptors (PR) and her2neu receptors is shown in figure 1. There were 16 cases (41 %) of luminal A group, 8 cases (20.5 %) of luminal B group, 8 cases (20.5 %) of HER2/neu group and 7 cases (17.9 %) of basal like group.

Comparison of clinical and pathological characteristics of patients categorized according to results of molecular classification is shown in table 5. There was no significant difference in mean age, mean size of tumor, mean number of lymph nodes and mean number of involved lymph nodes ( $p > 0.05$ ). The association of molecular classification to grade of tumor and histological type was also shown in table 5, but p-value could not be calculated because more than 20 % of cells have expected count of less than 5, thus, chi-square test was not carried out.

**Table 1:** Clinical and pathological characteristics of women with breast carcinoma

Characteristic	Result
<b>Number of cases</b>	39
<b>Age (years)</b>	
Mean $\pm$ SD	53.31 $\pm$ 15.96
Range	25 -85
<b>Size (cm)</b>	
Mean $\pm$ SD	3.24 $\pm$ 1.34
Range	0.5 -8
<b>Number of LN</b>	
Mean $\pm$ SD	9.05 $\pm$ 2.70
Range	5 -16
<b>Number of positive LN</b>	
Mean $\pm$ SD	2.31 $\pm$ 2.17
Range	0 -8
<b>Grade</b>	
II (Moderate)	6 (15.4 %)
III (Poor)	33 (84.6 %)

**Histological type**

Invasive ductal	36 (92.3 %)
Invasive lobular	3 (7.7 %)

**SD:** standard deviation; **LN:** lymph nodes

**Table 2:** Results of immunohistochemical investigations concerning estrogen receptors (ER)

Characteristic	Result
<b>ER</b>	
None	10 (25.6 %)
Weak	2 (5.1 %)
Moderate	2 (5.1 %)
Strong	25 (64.1 %)
<b>ERIS</b>	
None	10 (25.6 %)
Weak	2 (5.1 %)
Intermediate	9 (23.1 %)
Strong	18 (46.2 %)
<b>ERPS</b>	
0	10 (25.6 %)
1/100	2 (5.1 %)
1/10	4 (10.3 %)
1/3	11 (28.2 %)
2/3	10 (25.6 %)
1	2 (5.1 %)

**ER:** estrogen receptors; **ERIS:** estrogen receptors intensity score; **ERPS:** estrogen receptors proportion score

**Table 3:** Results of immunohistochemical investigations concerning progesterone receptors (PR)

Characteristic	Result
<b>PR</b>	
None	17 (43.6 %)
Weak	1 (2.6 %)
Moderate	2 (5.1 %)

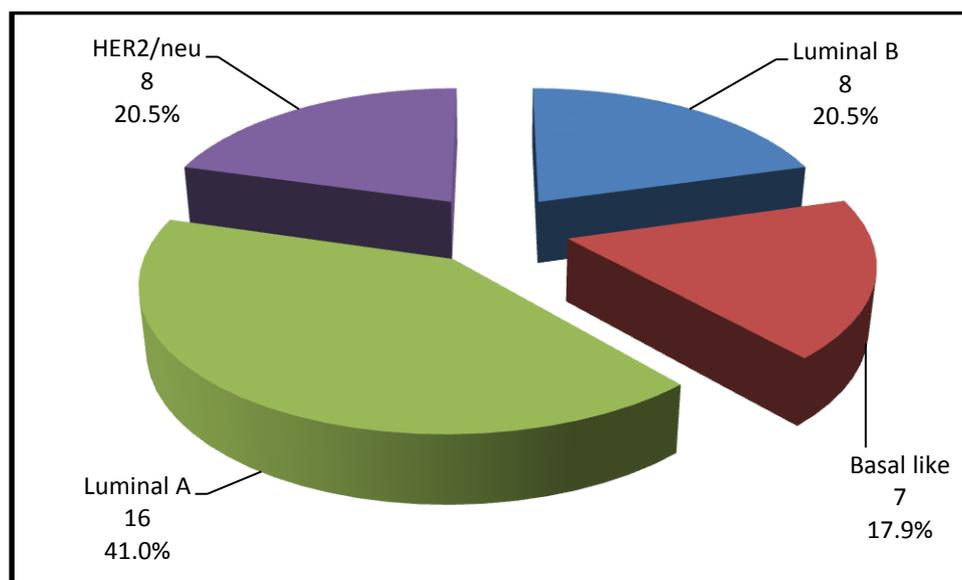
<b>PRIS</b>	Strong	19 (48.7 %)
	None	17 (43.6 %)
	Weak	2 (5.1 %)
	Intermediate	4 (10.3 %)
	Strong	16 (41 %)
<b>PRPS</b>	0	17 (43.6 %)
	1/100	2 (5.1 %)
	1/10	4 (10.3 %)
	1/3	6 (15.4 %)
	2/3	9 (23.1 %)
	1	1 (2.6 %)

**PR:** progesterone receptors; **PRIS:** progesterone receptors intensity score; **PRPS:** progesterone receptors proportion score

**Table 4:** Results of immunohistochemical investigations concerning her2neu receptors

Characteristic	Result
<b>Her2/Neo</b>	
Negative	23 (59 %)
Equivocal (moderate staining)	1 (2.6 %)
Strong (complete staining)	15 (38.5 %)
<b>IHC</b>	
ER-PR	14 (35.9 %)
Her2/neu	3 (7.7 %)
Her2neu +ER	5 (12.8 %)
Triple negative	7 (17.9 %)
Triple positive	8 (20.5 %)
ER	2 (5.1 %)

**ER:** estrogen receptors; **PR:** progesterone receptors



**Figure 1:** Pie chart showing the frequency distribution of patients according to molecular classification following the immunohistochemical staining of estrogen receptors (ER), progesterone receptors (PR) and her2neu receptors

**Table 5:** Comparison of clinical and pathological characteristics of patients categorized according to results of molecular classification

Characteristic	Luminal B <i>n</i> = 8	Basal like <i>n</i> = 7	Luminal A <i>n</i> = 16	HER2/neu <i>n</i> = 8	<i>p</i>
Age (years)	48.75 ±18.99	59.29 ±17.44	54.81 ±14.27	49.63 ±15.63	0.548 O NS
Size (cm)	3.25 ±1.13	3.00 ±1.66	3.14 ±1.00	3.63 ±1.94	0.821 O NS
Number of LN	7.88 ±2.17	9.14 ±2.19	9.69 ±3.30	8.88 ±2.17	0.498 O NS
Number of positive LN	2.00 ±1.77	2.57 ±2.23	2.19 ±1.80	2.62 ±3.29	0.928 O NS
<b>Grade</b>					
II	1 (12.5 %)	1 (14.3 %)	1 (6.3 %)	3 (37.5 %)	---
III	7 (87.5 %)	6 (85.7 %)	15 (93.8 %)	5 (62.5 %)	---
<b>Histopathological type</b>					
Invasive ductal	8 (100.0 %)	7 (100.0 %)	14 (87.5 %)	7 (87.5 %)	---
Invasive lobular	0 (0.0 %)	0 (0.0 %)	2 (12.5 %)	1 (12.5 %)	---

Data were presented as mean ±standard deviation or number (percentage); LN: lymph node; O: one way ANOVA; NS: not significant

## Discussion

Malignant disorders affecting breast is a common clinical problem seen daily in our health institutes. Reducing the mortality rate cause by that disease and improving the quality of life are the major aims of every health system dealing with this clinical problem. The diagnosis of the disease is becoming easier and faster because of the availability of clinicians with subspecialty of oncology and laboratory facilities to examine tissue biopsies and fine needle aspiration samples.

The real problem is with the prognosis of the disease and treatment approach. The late diagnosis of the disease is actually due to lack of proper screening tests to make early detection of suspicious lesions. The accurate classification of breast cancer lesions is an important determinant of type of surgical approach and chemo and radiotherapy. Previous well known approaches reside of the staging of disease clinically and pathologically. Evolution of approaches enrolled immunohistochemical technique in further categorization of cases of breast cancer and planning of type treatment based on the results of immunohistochemical study.

Breast cancer is currently classified molecularly into five groups: luminal A, luminal B, HER-2, basal, and normal breast-like. These subgroups may need to be further grouped together. A recent division of the HER-2 subgroup into three clinically distinct groups, one of which is said to exhibit particularly aggressive behavior, has been published. Due to these variations, efforts have been made to find variables that can explain variations in the prognosis of patients with HER-2 (28). Based on these research, it is anticipated that in the near future, the topic of prognosis differences despite therapy plans targeted with molecular indicators that offer data on tumor molecular identity, prognosis, and tailored treatment will become even more prominent. Possible causal processes were examined, for instance, based on HER-2 patients who relapsed after treatment or were resistant to treatment with monoclonal antibodies (Herceptin) targeting the extracellular domain (29-31).

A subset of HER-2 positive breast cancer patients with a poor prognosis have been shown to express p95HER2, a heterogeneous collection of HER2 carboxy-terminal fragments (30). The HER2 oncogene, 611-CTF, is one of these segments. Thus, it was determined that the status of the 611-CTF gene was definitely important for the development of p95HER2 positive cancers. Additionally, the production of the delta 16HER2 HER2 isoform, which encodes a receptor missing exon 16, is now acknowledged as one of the trastuzumab resistance mechanisms (32).

in our study, we found that the most common molecular subtype was luminal A in which ER and PR are positive and HER2/neu is negative, followed by luminal B in which all receptors are positive then HER2/neu type and lastly basal like type. These figures are in accordance with other previous reports and disagree with others (33). Indeed, in our study we found no correlation between clinicopathological characteristics and molecular classification. However, it should be better to correlate these molecular classes to response to treatment modalities, but data about such responses were difficult to collect.

## Conclusion

The most common molecular type was luminal A followed by luminal B and HER2/neu and lastly by basal like type. This molecular classification has no significant impact on clinicopathological characteristic of the disease.

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