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# Clinical and Diagnostic Study of Breast Cancer in Women and its Relation with Periodontal Disease

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## **ABSTRACT**

**Background:** Breast cancer (BC) is a common type of malignancy in females in Iraq. This study investigated BC's clinical and diagnostic features in 30 women and displayed its relationship with periodontal disease.

**Methods:** This cross-sectional study comprised 30 BC patients diagnosed in 2023. The clinical signs, ultrasound, biopsy, histopathology and Immunohistochemistry, treatment modules, and clinical signs of periodontal disease were reported and analysed.

**Results:** The mean and standard deviation of patients' age was 51.73±11.41. The location of Breast Cancer lesions was on the left and right sides in 11 (36.66%) and 19 (63.33%) patients, respectively. All patients showed various sizes of non-painful lumps with well-defined masses in different areas of the breast tissue with regular or irregular borders in ultrasound and MRI. The gross and histopathological changes of cancerous tumors differed according to conditions, stage, and interaction with the cancer receptors in Immunohistochemistry. The percentage of metastases was 100% (in 30 cases) for the lymph nodes and 66.66% (in 20 cases) for the rest of the other organs. Different treatment modules were used, including chemotherapy, surgery, radiation, and hormonal therapy. The cases suffering from mild, moderate, and severe periodontal disease were 7 (23.33%), 2 (6.66%), and 21 (70%), respectively.

**Conclusion**: The clinical signs, histopathological, IHC, and occurrence of periodontal disease in 30 women with breast cancer were documented in this study. The authors recommend further studies on breast cancer to support its early diagnosis and prevention strategies.

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# INTRODUCTION

The most prevalent cancer in women globally is breast cancer. It is diagnosed in 157 countries in women and accounts for 1 in 4 cancer cases. In 2022, an estimated 2.3 million new cases of breast cancer were reported, and around 1 in every nine cancers for both sexes worldwide. It is also considered the most frequent cancer in males and females and is the

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Department of Basic Sciences, College of Dentistry, Al-Iraqia University, Iraq, Baghdad, Adhamiyah, Hibat Katon, Street 22, District 308. Postbox: Kaifa: 7266. Email:kama18\_akool@aliraqia.edu.iq foremost cause of death from cancer in women, with case fatality rates being the highest in low-income countries.<sup>1</sup> Breast cancer is a common type of malignancy in females in Iraq. It is the most common cancer with a percentage of (23.1 %) and a cumulative risk of 6.0 among cancers in women, accounting for 8626 (40.0 %) from 21558 newly reported cancer cases according to The Global Cancer Observatory, Globocan 2022.<sup>2-4</sup> According to the latest Iraqi Cancer Registry, breast cancer is ranked first for women's death with a percentage of 3372 (15.7%) and Cum. Risk of 2.5 in 2022, with a five year prevalence of 24995 and 120.1 props (per 100 000).<sup>3,4</sup>



Thus, is has been showed that breast cancer is the foremost cancer site in the Iraqi population, especially women.

Furthermore, about 20-30% of breast cancer cases are the risk factors for other malignancies due to transformation and BC metastasis.5 A chronic inflammation of the soft tissues surrounding the teeth with the gradual destruction of the bone and teethsupporting structure is called Periodontal disease,<sup>6,7</sup> which leads to tooth loss. Initially, periodontal disease starts as dental plaque that attacks the periodontal immune system protection line of periodontal tissue, leading to inflammation and disease. The clinical manifestations of periodontal disease include gingiva bleeding, periodontal pocket, bone resorption, and, consequently, tooth loss if untreated.8 Periodontal disease is proven to be associated with a variety of diseases such as diabetes<sup>9</sup>, Rheumatoid arthritis<sup>10</sup>, cardiovascular system<sup>11</sup>, depression<sup>12</sup>, chronic obstructive pulmonary disease<sup>13</sup>, and Alzheimer's disease.<sup>14</sup>

Additionally, there are an increasing number of studies reporting a significant relationship between periodontitis and different kinds of cancers like head and neck cancer. 15 A literature review regarding breast cancer and its relation with periodontal disease in Iraq revealed a shortage of publications. Therefore, this study was designed to study the incidence of periodontal disease in 30 women diagnosed in 2023 with various stages of breast cancer. In addition, it describes the various aspects of these patients, including the clinical signs, ultrasound, histopathological changes, immunohistochemistry, and treatment modules.

## **METHODS**

Sample collection and inclusion and exclusion criteria

Simple random sampling was used in this study. Also, a non-biased strategy was used to select the participants. This method ensures that each individual in the target population has an equal chance of being chosen for the study and has the same probability of being included within the sample. This ensures that the sample was representative of the population and produced more reliable results. Only women diagnosed with breast cancer were included in the study, while normal women at examination were excluded from the study.

# **Participants**

This cross-sectional study focused on women who were diagnosed with breast cancer at the breast cancer unit at Al Hussein Teaching Hospital, Samaw, Al Muthanna governorate. During 2023, thirty women diagnosed with breast cancer were included in the

current study. The age of each patient at diagnosis was reported by asking about the date of birth displayed in the Iraqi National identity. Additionally, the location of the lesion (left or right), Metastasis to other body organs, Lymph node involvement, earlier clinical signs, ultrasound investigation, biopsy, histopathological features, immunohistochemistry, and treatment modules were reported. The patients also filled out a data collection form that included questions regarding oral health and factors associated with periodontal disease, such as smoking, chemotherapy, radiotherapy, hormonal therapy, and other initial clinical signs of periodontal disease.

# Periodontal disease investigations

The same dentist did all oral clinical examinations for all the subjects. The following data were recorded for each patient: the total number of teeth, plaque score for full mouth (number of plaque sites with detectable dental plaque divided by the total number of sites per mouth X 100), the score of gingival bleeding for full mouth on probing (the number of sites with gingival bleeding on probing divided by total number of sites per mouth multiplied by 100), the score of periodontal lesion of the entire mouth (the number of sites with a probing depth  $4 \ge \text{mm}$  divided by the total number of sites per mouth multiplied by 100), and the mean probing attachment level.

## Data and statistics analysis

Various patient records were analysed and presented as Mean  $\pm$  SD and percentages, and displayed in Tables.

## **RESULTS**

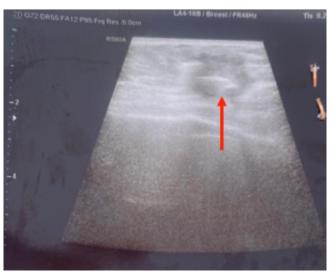
The mean and standard deviation of the patients' age was  $51.73\pm11.41$ . The participants were placed in two groups: the age of the participants in the first group (3.33%) were as follows: 67, 65, 58, 57, 52, 50, 48, 47, 43, 41, 33, 32, 29, & 26, and the age of the participants in the second group (6,66 %) were as follows: 71, 64, 56, 55,54, 53, 51, and 49.

Also, 11 lesions were on the left (36.66%) and 19 (63.33%) on the right side (Table 2). All patients showed obvious clinical signs, including various sizes of non-painful lumps. Additionally, the cases with metastasis showed clinical signs of respiratory system lesions.

The ultrasound and MRI results showed well-defined masses of various sizes in different areas of the breast tissue with regular or irregular borders (Figure 1, 2) (Table 1).



**Figure 1.** Shows the Ultrasound image of right-side breast cancer lesion



**Figure 2.** Shows the Ultrasound image of left-side breast cancer mass

**Table 1.** The age and clinical signs and IV Contrast/ MRI for all breast cancer patients

No.	Age	Clinical signs	CT with IV contrast / MRI
1	71	Feeling an abnormally large swelling in the right breast with pitting of the skin	A mass lesion in upper quadrant of right breast. The mass showed lobulate margins and heterogenous enhancement (Figure 4).
2	71	Painless lump on the right breast and changing in the skin and nipple appearance.	A mass lesion in upper quadrant of right breast. The mass showed lobulate margins and heterogenous enhancement
3	67	Feeling a large lump measuring 5X5x3 CM, no nipple, no ulceration	
4	65	A large mass, no nipple, no ulceration	A mass lesion in upper quadrant of right breast. The mass showed lobulate margins and heterogenous enhancement
5	64	A large mass on the left side with a respiratory problem	A phenotype consistent with a primary breast cancer
6	64	At the right breast, a large lump measuring $170 *160 *45$ mm. with skin attachment including nipple and areola with separated axillary tail.	Irregular large mass
7	58	Breast mass intra areolar regions, true cut biopsy under	A phenotype 1.5X1.5 cm mass consistent with a primary
		U/S guide was done	breast cancer.
8	57	A painless left breast mass	Irregular lobulated mass measuring 11 mm in aggregate diameter.
9	56	A large lump measuring 2.4 x 2.2 cm with skin attachment including nipple and areola with separated axillary tail.	Pet scan showed an FDG-avid lesion in the right breast upper slightly inner quadrant, measuring 2.4 X 2.2 cm with SUV max 8.2, related to the known malignancy.
10	56	A painless left breast mass	A mass lesion in upper quadrant of right breast.
11	55	A painless left breast mass	A phenotype consistent with a primary breast cancer
12	55	A painless left breast movable palpable mass about 3.5 X 3 X 1.7 cm	3 An irregular large mass measuring 1 cm
13	54	A painless left breast mass	An irregular large mass (Figure 5).
14	54	A painless lump on the right breast and changing in the skin and nipple appearance.	A large irregular lesion in upper quadrant of right breast. The mass showed lobulate margins and heterogenous enhancement
15	53	A painless left breast mass	A large irregular lesion in upper quadrant of right breast. The mass showed lobulate margins and heterogenous enhancement
16	53	A painless right breast large mass	A large irregular lesion in upper quadrant of right breast. The mass showed lobulate margins and heterogenous enhancement
17	52	A painless left breast large mass	An irregular lobulated mass measuring 4.5x 2.1 mm in aggregate diameter.



No.	Age year	/Clinical signs	CT with IV contrast / MRI
18	51	A painless multiple mass with skin attachment.	An irregular lobulated mass measuring 4.5x 2.1 mm in aggregate diameter.
19	51	A painless large mass measuring (17X4X6 cm ) with axillary tail measuring 12X6 cm $$	An irregular large mass (17X4X6 cm) with axillary tail measuring 12X6 cm on upper medial quadrant and away from posterior margin (2 cm /
20	50	A large palpable mass on the right site with enlargement of axillary lymph nodes.	
21	49	Large palpable mass on the right site with enlargement of axillary lymph nodes a	An irregular large mass (100X 180X50 mm) with axillary tail measuring 12X6 cm on upper medial quadrant and away from posterior margin (2 cm
22	49	A right breast malignant lesion showing a large palpable mass on the right site with enlargement of axillary lymph nodes.	An irregular large mass
23	48	Left large breast cancer and axillary enlargement	An irregular left large mass of 260*130*70 mm, located at lower outer quadrant (LOQ), about 5mm from deep margin.
24	45	A right breast malignant lesion showing a large palpable mass on the right site with enlargement of axillary lymph nodes.	An irregular shaped mass measuring 70 mm located in the UOQ, upper outer quadrant and about 20mm from deep margin.
25	43	A right breast malignant lesion showing a large A palpable mass on the right side with enlargement of axillary lymph nodes.	
26	41	A right breast malignant lesion showing a large palpable mass on the right side with enlargement of axillary lymph nodes.	
27	33	A right breast malignant lesion showing a large palpable mass measured 35x20x 15 on the right side with enlargement of axillary lymph nodes.	An irregular large mass on the right side
28	32	A right side palpable large mass with enlargement of axillary lymph nodes.	An irregular large mass on the right side
29	29	A right side palpable large mass with enlargement of axillary lymph nodes.	An irregular right breast mass measuring 19*16*7 cm with skin ellipse (18* 11 cm), centered by unremarkable nipple, axillary tail (20* 8cm) is attached. Tumor size 2.5 cm in the greatest dimension, tumor showing two foci of invasive carcinoma. The second focus is located beneath the nipple, and consists of a rigid whitish area rather than a discrete mass. It is composed of invasive and in situ carcinoma of similar morphology admixed with fat necrosis and foreign body and giant cell reaction. Ductal carcinoma in situ is present in the mass and in breast tissue. Tumor extends to the skin and nipples are negative for tumor infiltration, with lymph vascular invasion being present. Perineural invasion is not identified Margin (about 17 cm distant).
30	26	Left large breast cancer and axillary enlargement	An irregular right breast mass measuring 19*16*7 cm with skin ellipse (18* 11 cm), centered by unremarkable nipple, axillary tail (20* 8cm) is attached.

The gross and histopathological changes of cancerous tumors differed according to the disease conditions and stage of the disease and the interaction with different cancer receptors for IHC. Table 2 shows all the details for each disease condition. Most of the tissue sections taken from breast cancer lesion samples after local tumor resection or mastectomy

showed the infiltration of epithelial cells through nests of cords and multiple and different-shaped tubes mixed with increased activity of infrequent mitotic figures with a transformed lining.

#### **Table 2.** The histopathological features and results of immunohistochemistry No. Histopathology Immunohistochemistry 1 An infiltrating epithelial tumor composed of nest, cords and numerous ER, PR: Positive (intensity 3, tubules of moderately pleomorphic cells admixed with infrequent proportion 4, Allred score 7, Her-2: mitotic figures, surrounded by desmoplastic stroma. positive (Score 3+) A section from mastectomy specimen shows an infiltrating epithelial ER, PR: negative, 2. Her-2: negative tumor composed of nest, cords and numerous tubules of moderately (Score 0). pleomorphic cells admixed with infrequent mitotic figures, surrounded by desmoplastic stroma. A section from nipple shows dermal lymphatic invasion by tumor cells. The section from deep margin is free of hyperplasia with no tumor deposits. The second histopathological features are: Florid epithelial hyperplasia, fibrosis, chronic inflammation with foci of giant cells reaction, no in situ or residual carcinoma. A grossly cut right modified radical mastectomy, breast tissue with CK: +ve (Strong, diffuse), ER: +ve, axillary tail measuring 30X12X3 cm, tissue attached to skin measuring CD34: -ve, 22 cm, no ulceration, slicing mass relatively well defined, measuring 3.5 CM, white firm. Microscopical features showed partially infiltrative breast mass consisting of bland looking glandular epithelium exhibit squamous metaplasia and atypical round to oval epithelial cells with mild to moderate atypia, scattered mitotic activity ( > 5/10 HPF) and heavy stromal chronic inflammation. Moreover, the tumor showed cystic degeneration, myxoid changes, hemorrhage, stromal hyalinization, extending to one of the peripheral margin (Inked). 4 A section from mastectomy specimen shows an infiltrating epithelial Estrogen receptor: intensity score + tumor composed of nest, cords and numerous tubules of moderately proportion score: 3+4=7/8 (positive), pleomorphic cells admixed with infrequent mitotic figures, surrounded progesterone receptor intensity score by desmoplastic stroma. The section from nipples shows dermal +proportion score: 1+2=3/8 (weak positive), HER2/ Neu \*\* Score: + 3 lymphatic invasion by tumor cells. The section from deep margin is free of hyperplasia with no tumor deposits. The second histopathological positive. \* Allred scoring for ER/ PR features are: Florid epithelial hyperplasia, fibrosis, chronic receptors: Positive with total score inflammation with foci of giant cells reaction, no in situ or residual (PS+15) is 3-8 carcinoma. Breast carcinoma is confirmed. An infiltrating epithelial tumor composed of nest, cords and numerous Strongly positive for estrogen, negative tubules of moderately pleomorphic cells admixed with infrequent for progesterone, Her 2 positive (+3). mitotic figures, surrounded by desmoplastic stroma. The section from nipple shows dermal lymphatic invasion by tumor cells. Florid epithelial hyperplasia, fibrosis, chronic inflammation with foci of giant cells reaction, no in situ or residual carcinoma. Breast carcinoma is confirmed. Grossly cut sections show a tumor lesion located between the lower and ER, PR: positive, Her-2 Negative upper quadrant, measuring 35 mm in maximum dimension with firm (Score 0). grey whitish surfaces and located about 10 mm from deep margin. Sections from mastectomy specimen show an infiltrating epithelial tumor composed predominantly of tubules and occasional nests and sheets o mildly pleomorphic cells intermingled with infrequent mitotic figures, embedded in desmoplastic stroma. At foci, features of usual, atypical hyperplasia and low grade in situ components. Sections from nipple and deep margin are free of tumor. 7 Sections of breast tissue cores showed invasive cords, nests and acini of ER, PR: positive, Her-2 positive (Score atypical epithelial cells with desmoplastic stroma in between. 8 Three grossly cut irregular fragments of grey yellow fibrofatty tissues ER, PR: positive, Her-2 positive measuring 11.0 mm in aggregate diameter. Cut sections of the largest fragment show an irregular grey white lesion measuring 22 mm in maximum dimension and located about 15 mm from nearest margin.

cords, sheets and minimal tubules embedded in moderately desmoplastic and chronically inflamed stroma. Lymph vascular

invasion by tumor cells are noted.

Sections from breast tissue show a moderately differentiated epithelial tumor composed of moderately pleomorphic epithelial cells arranged in

# BC in relation to periodontal disease



- 9 Moderately pleomorphic epithelial cells arranged in cords and sheets. Minimal tubules embedded in moderately desmoplastic and chronically inflamed stroma. Tumor cells have invaded the lymph vessels.
- Sections from the nipples show dermal lymphatic invasion by tumor cells. Sections from deep margin is free of hyperplasia with no tumor deposits. The second histopathological features are: Florid epithelial hyperplasia, fibrosis, chronic inflammation with foci of giant cells reaction, no in situ or residual carcinoma, an infiltrating epithelial tumor composed of nest, cords and numerous tubules of moderately pleomorphic cells admixed with infrequent mitotic figures, surrounded by desmoplastic stroma.
- Sections of breast tissue cores showed invasive cords, nests and acini of atypical epithelial cells with desmoplastic stroma in between.
- 12 A grossly cut single piece of tissue measuring (3.5 X 3X 7 cm), cut sections showing an irregular grey mass measuring 1cm reaching the resection margin labeled by ink pieces from the mass. Destructed breast tissue infiltrated by sheets and nest of pleomorphic cells with hyperchromatic nuclei surrounded by desmoplastic stroma with the central area of necrosis. The growth shows infiltration to the margin.
- An infiltrating epithelial tumor composed of nest, cords and numerous tubules of moderately pleomorphic cells admixed with infrequent mitotic figures, surrounded by desmoplastic stroma. The section from the nipples shows derma.

- 14 Sections from mastectomy specimen show an infiltrating epithelial tumor composed of nest, cords and numerous tubules of moderately pleomorphic cells admixed with infrequent mitotic figures, surrounded by desmoplastic stroma. Sections from the nipples show derma.
- 15 Sections from mastectomy specimen show marked adenosis with numerous cystically dilated ducts lined by double layers of epithelial cells and exhibiting periductal inflammations. No evidence of residual tumor in the examined tumor deposits in one lymph node
- 16 Grade III tubular carcinoma.
- 17 Sections from mastectomy specimen show an infiltrating epithelial tumor composed of nest, cords and numerous tubules of moderately pleomorphic cells admixed with infrequent mitotic figures, surrounded by desmoplastic stroma. Sections from the nipples show derma. Sections of the ovaries show the infiltration of the ovarian stroma by malignant epithelia cells with glandular differentiation and desmoplastic stroma, with areas of cystically dilated malignant gland with papillary architecture (more prominent in large ovary).
- Fibrotic breast cores are infiltrated by sheets and nest of pleomorphic cells with hyperchromatic nuclei that have a high N/C ratio with focal ductal formation surrounded by desmoplastic stroma.

ER, PR: positive, Her-2 positive

ER: Proportion 2, intensity 2, total score 4 = positive. PR: Proportion 1 %, intensity 2, total score, 3 positive. Her-2/neu receptor proportion negative, intensity negative, total score= +1 negative.

ER: Proportion 3+4=7/8 (positive), PR: Proportion 1+2=3/8 (weak positive), Her-2/neu\*\* + 3 (Positive), intensity ER, PR: positive, Her-2 positive (Score

According to Allred scoring system for estrogen and Progesterone receptors: Progesterone receptor: proportion score (PS) = 2/5, intensity score (IS) = 1/3, total score (PS + IS) = 3/8 (Positive), Estrogen receptor  $\alpha$  (Clone EPI): Proportion score (PS): 4/5, Intensity Score= 3/3, Total Score (PS+ IS) = 7/8 (Positive). According to ASCO immunohistochemical scoring system for Her-2 receptor. Her-2 (c-erB-2 oncoprotein): Score 1 (Negative). Ki-67 expression is 60% ER, PR: positive, Her-2 positive (Score 3)

ER, PR: positive, Her-2: +ve 1 (negative).

ER: Proportion 2, intensity 2, total score 4 = positive. PR: Proportion 1 %, intensity 2, total score, 3 positive. Her-2/ neu receptor proportion negative, intensity negative, total score= +1 negative.

ER: positive, more than 90 % of the tumor cells are positive with strong intensity. PR: positive more than 90 % of the tumor cells with strong intensity, Her-2 negative / immuno score= zero, Gata 3: Positive, WTI: Negative.

ER, PR: Positive (intensity 3, proportion 4, Allred score 7, Her-2: positive (Score 3+)

- 19 Infiltration of the breast tissue by sheets of malignant ductal epithelial cell desmoplastic stroma and lympho vascular permeation and lymphocytic infiltrate (grade II morphology according to Nottingham nuclear grading). Sections from lymph nodes show reactive hyperplasia.
- 20 Sections from mastectomy specimen show an infiltrating epithelial tumor exhibiting histological features of Grade II infiltrating ductal carcinoma (Tubal formation Score 2, nuclear pleomorphism score 2, mitotic figures Score 2). Embedded in desmoplastic stroma. At foci, low grade in situ components are present. Sections of lymph nodes show the same histological features and located about 1 mm from the margin, with identified tumor deposits in 4 lymph nodes. Sections of the nipple are unremarkable.
- A grossly cut mastectomy specimen with attached axillary tail measuring 100X 180X50 mm. with unremarkable external surface; the serial cut sections show an irregular grey white lesion, with 8 lymph nodes noted in the axillary tail (5-20 mm). Mastectomy sections show an infiltrating epithelial tumor exhibiting grade II histological features and score 2 mitotic index, embedded in highly desmoplastic stroma. At foci, a low and high grade in situ component is present. Sections from lymph nodes show features of reactive follicular and sinus hyperplasia.
- 22 Invasive carcinoma of no special type (ductal). Histological Grade (Nottingham Histological Score: 2 Score of 7). Glandular (acinar) / Tubular differentiation: score 3, Nuclear pleomorphism: Score 3<br/>
  Mitotic rate score 1, Ductal carcinoma in situ: not identified, Lymph vascular invasion not identified
- Ductal Invasive carcinoma of no special type. Histological Grade. Glandular (acinar) / Tubular differentiation: score 3, Nuclear pleomorphism: Score 3< Mitotic rate score 1, Ductal carcinoma in situ: not identified, Lymph vascular invasion not identified
- Grossly cut mastectomy with attached axillary tail, measuring 220x 180x 110 mm. The cut sections show an irregular shaped grey white lesion measuring 70 mm in maximum dimension located in the UOQ upper outer quadrant and about 20 mm from the deep margin. Sections of mastectomy show an infiltrating epithelial tumor exhibiting the following histological features: Grade 11 infiltrating ductal carcinoma (Tubular formations = score 2, Nuclear pleomorphism = Score 2, Mitotic figures = Score 2), in desmoplastic stroma 2. Foci of low grade in situ and lymph vascular invasion by tumor cells. Sections from the nipple are unremarkable. Sections from the lymph nodes show tumor deposits in 4 lymph nodes.
- 25 Received right mastectomy specimen including skin with nipple and areolae and attached axillary tail. The whole specimen measured 290\*140\* 110 mm. The external surface is unremarkable. Serially cut sections show irregular shaped grey white lesion measuring 45 mm in diameter located about 5 mm from deep margin. 14 lymph nodes. Sections from mastectomy specimen show an infiltrating epithelial tumor composed of numerous tubules, nests and sheets of moderately pleomorphic cells intermingled in situ components are noted. Lymph vascular invasion by tumor cells is present. Sections from the nipple are unremarkable. Sections from the deep margin are 2mm from the tumor. Sections from identified lymph nodes show tumor deposits in 2 lymph nodes.
- 26 Multiple clusters of suspicious malignant epithelial cells.
- 27 Sections from breast tissues show an infiltrating malignant epithelial tumor composed of cords, nests, occasional tubules, cells configuration of mild to foci lobular in situ also noted.

ER, PR: Positive (intensity 3, proportion 4, Allred score 7, Her-2: positive (Score 3+)

ER, PR: positive, Her-2 positive (Score 3)

ER, PR: positive, Her-2: +ve 1 (score 1: negative). Ki-67 <14% positive tumor cells

Breast biomarkers results (CAP 2021 template) ER: Positive, nuclear positivity of cells is 90%, average intensity of staining is strong, PR: (PgR) Negative: the status of internal control cells present and stained as expected. Her-2 Positive 3+, Ki-67 index (40-50%)

ER, PR: positive, Her-2: +ve 2 Equivocal (Score 2). Incomplete and faint membrane staining in >30% of 3tumor cell, Ki-67 <14% positive tumor

ER, PR: positive, Her-2: +ve 1 (score 1: negative). Ki-67 <14% positive tumor cells

ER, PR: Positive (Allred total score 7), Her-2: Negative (Score 0)

ER, PR: positive, Her-2 positive (Score

ER, PR: positive, Her-2 positive



- A grossly cut fibrofatty piece of tissue measuring 8x6x6 cm with hemorrhagic cavity measuring 3cm and residual mass measuring 2cm. 1-4 mass. Sections show residual invasive ductal carcinoma, not otherwise specified, grade 2 with in situ component of solid pattern.
- 29 Glandular (acinar) / tubular differentiation score 3, Nuclear pleomorphic score 3, mitotic rate score 3.
- 30 Sections reveal sheets of moderately differentiated invasive ductal carcinoma, grade II, of non-otherwise specified type, showing marked fibro stromal and fat tissue invasion. A few foci of ductal carcinoma in situ of solid variant are seen. Sections of the skin are free of tumor.

ER, PR: positive, Her-2 Negative (Score 0).

ER, PR: positive, Her-2 Negative (Score 0).

ER, PR: positive, Her-2: +ve 1 (negative).

The nipple skin sections showed the infiltration of lymphocytes and cancer cells, in addition to some samples taken from deep lesions, with the presence of fibroblasts and inflammatory cells and giant cells. The immunohistochemistry results for ER, PR, Her-2, and Ki-67 receptors appear in Table 3.

Table 3. The scores of IHC for ER, PR, Her-2, and Ki-67 receptors

No	Degree of expression of Estrogen receptors	No	Degree of expression of Progesterone receptors	No	Her-2 Expression	No	Ki-67 Expression %
1	0	3	0	5	0	1	60%
1	2	0	1	7	1	1	50%
1	3	1	2	6	2	3	14%
27	4	2	3	12	3	25	0%

The results also showed the nature of the spread of cancer cells to local lymph nodes and regional lymph nodes. The number of metastases was 30 (100%) for the lymph nodes and 20 (66.66%) for the rest of the other organs (Tables 4 & 5). Table 6 shows the final diagnosis and the treatment program for each case.

**Table 4.** The number & percentage of metastasis to lymph nodes and invading other organs

Number and % of patients	Number and % of patients with			
with metastases to lymph	metastases to the other organs			
nodes				
30 (100%)	20 (66.66%)			

**Table 5.** The metastasis of breast cancer to lymph nodes and other organs according to each case

No.	Lymph nodes	Metastasis
1	Multiple enlarged right axillary LNs, the largest measures	No evidence of brain, liver and lung metastasis, there is a
	3.5cm suggestive of LN metastases. There is a hypodense	lytic lesion measuring 13 mm in T11 vertebra
	lesion measuring 2.6 cm in the right hilar region. Enlarged	
	hilar LN. There are enlarged mediastinal LNs, the largest	
	measuring13 mm in short axis diameter.	
2	8 right axillary lymph nodes were enlarged	No evidence of brain, liver and lung metastasis.
3	13 lymph nodes show reactive follicular hyperplasia, with no malignant deposit.	No evidence of brain, liver and lung metastasis.
4	10 lymph nodes show malignant deposit	Metastasis to liver, lung
5	Axillary, internal mammary, mediastinal or hilar	Evidence of bilateral lung nodules metastasis, a nodule in
	lymphadenopathy.	the right lung posteriorly measuring 2 cm with SUV max
		3,4 stable, a peri bronchi vascular nodule in the left lower
		lobe measuring 2X1.7 cm with SUV max 2.5 previously
		measuring 2.4 X 1.5 cm with SUV max 3.7. There is no
		radiotracer, pleural, or pericardial effusion.
6	9 lymph nodes are present in the axillary tail, ranging in	Evidence of lymph nodes involvement
	sizes from 5-20 mm. Sections from lymph nodes show	
	features of reactive lymphoid hyperplasia with no tumor	
7	deposits.	N 11 61 1 1 11 11 11 11 11 11 11 11 11 11
7	Sections of lymph nodes show tumor invasion	No evidence of brain, liver and lung metastasis, there is a
Ō	11111	lytic lesion measuring 13 mm in T11 vertebra
8	11 lymph nodes show reactive follicular hyperplasia, with no malignant deposit.	Evidence of lymph node invasion
9		
	metastatic; Pet scan shows FDG-avid enlarged right axillary	y metastasis.
	lymph node measuring 2.9 X 2.6 cm with SUV max 11.2	

cm.

No.	Lymph nodes	Metastasis			
10	Lymph nodes are present in the axillary tail, ranging in sizes No evidence of brain, liver and lung metastasis, distance				
	from 5-20 mm. Lymph nodes show features of reactive				
	lymphoid hyperplasia with no tumor deposits.				
11	8 lymph nodes are present in the axillary tail, ranging in No evidence of brain, liver and lung metastasis.				
	sizes from 5-20 mm. Lymph nodes show features of reactive lymphoid hyperplasia with no tumor deposits.				
12	3 first lymph nodes show invading cancer cells,	No evidence of brain, liver and lung metastasis.			
13	8 lymph nodes are present in the axillary tail; the nodes	No evidence of brain, liver and lung metastasis.			
	show features of reactive lymphoid hyperplasia with no	-			
1.4	tumor deposits.	To the control of the total to the total to the total total to the total			
14	11 lymph nodes show reactive follicular hyperplasia, with malignant deposit.	Evidence of liver metastasis, the right lob segment VII lesion shows hypo intense signal in T1& hyper T2			
	manghant deposit.	enhancing post contrast measuring 20 mm (metastasis).			
		However, no bone marrow lesion is seen, normal pancreas,			
		aorta, IVC, both kidneys and adrenal.			
15	One lymph node shows tumor deposits	Evidence of lymph node invasion			
16	11 lymph nodes show reactive follicular hyperplasia, with	Evidence of hepatic / liver metastasis. Adenocarcinoma in			
1.7	malignant deposit.	both ovaries.			
17	8 lymph nodes are present in the axillary tail, ranging in sizes from 5-20 mm. Lymph nodes s show features of	evidence of hepatic / metastatic adenocarcinoma in both ovaries			
	reactive lymphoid hyperplasia with tumor deposits.	Ovaries			
18	The 5 first lymph nodes are present in the axillary tail,	Sections from breast tissues show infiltrating tumor			
	showing features of reactive lymphoid hyperplasia with no	composed of solid nest, cords, sheets and occasional			
	tumor deposits.	tubules of moderately pleomorphic cells intermingled with			
		few mitotic figures and embedded in a desmoplastic stroma.			
19	30 lymph nodes are seen within the axillary tail, the largest				
	being 2.5X 2 cm.	7 1			
20		Evidence of lymph node invading			
21	(5-20 mm) 8 right axillary lymph nodes are enlarged	Evidence of lymph node invading			
22	8 right axillary lymph nodes are enlarged with tumor	Evidence of lymph node invading  Evidence of lymph node invading			
	deposit	7 1			
23	12 lymph nodes are noted attached to axillary tail (5-25	Sections from mastectomy show an infiltrating epithelial			
	mm)	tumor composed diffuse sheets, nests and tubules (45%) of			
		moderately pleomorphic cells (score 2) admixed with			
		infrequent mitotic figures (score 2) embedded in			
		desmoplastic stroma. At foci, high grade in-situ components are also present. Lymphovascular invasion by			
		tumor cells are noted. The section from the deep margin is			
		about 3 mm from the tumor. The section from the nipple is			
		unremarkable. Sections from the remaining breast tissues			
		show histological features of lactational changes. Sections			
		from the identified lymph nodes show tumor deposits in 5 lymph nodes			
24	17 lymph nodes are noted in the axillary tail (5-15 mm) with				
	evidence of tumor deposit.				
25	14 lymph nodes are noted in the axillary tail.	Evidence of lymph node invading			
26	8 right axillary lymph nodes are enlarged	Evidence of lymph node invading			
27	10 lymph nodes showed malignant deposit	Evidence of lymph node invading			
28	lymph nodes are present in the axillary tail, ranging in sizes	Totally, 16 lymph nodes free of tumor.			
	from 5-20 mm. Lymph nodes sections show features of				
29	reactive lymphoid hyperplasia with tumor deposits.  10 lymph nodes show malignant deposit	Evidence of lymph node invasion			
43	10 Tymph hodes show manghant deposit	Evidence of Tymph hode invasion			



30 8 lymph nodes are free of tumor deposit. Cross sectioning No evidence of brain, liver and lung metastasis. shows mass of solid whitish tissue at 12 O' clock, measuring 2.5 cm in the greatest dimension with about 1.7 cm distance from the inferior margin (the closest one). Also, another rigid area is seen beneath the nipple with no discreate mass. Regional lymph nodes: tumor present in the regional lymph nodes. The number of lymph nodes with macrometatases (greater than 2 mm) is 4; the number of lymph nodes with micrometastases (greater than 0.2 mm to 2 mm and / or greater than 200 cells) 0, the number of lymph nodes with isolated tumor cells (0.2mm or less 200 cells or less). The size of the largest nodal metastatic deposit: 2-4 cm, extranodal extension: not identified.

The results of the current study showed various degrees of periodontal disease. The results showed some patients suffered from the periodontal disease. Only one patient had no periodontal disease. Also,

Overall, 20 lymph nodes were examined.

23.33%<sup>7</sup> of the patients had mild periodontal disease, 6.66%<sup>2</sup> had moderate periodontal disease, and 70%<sup>21</sup> showed the severe form of the disease (Table 7).

Table 6. The final diagnosis for each case and the treatment modules.

No.	Diagnosis	Treatment module
1	Breast carcinoma grade III with bone metastasis	Taxol 130mg, Carboplatin 150mg Injection, mastectomy, radiotherapy, chemotherapy.
2 3	Residual moderate differentiated infiltrating ductal carcinoma Invasive lobular carcinoma/ Pathological stage: T2 N0 Mx.	ARIMIDEX tab 1 mg, mastectomy, radiotherapy, chemotherapy ARIMIDEX tab 1 mg, modified radical mastectomy,
_		radiotherapy, chemotherapy
4	Breast carcinoma	ARIMIDEX tab 1 mg, modified radical mastectomy, radiotherapy, chemotherapy; Zometa 4 mg.
5	Moderately differentiated adenocarcinoma with a mucinous component (50%)	Herceptin 600; modified left radical mastectomy and left axillary lymph node dissection, Right lung mastectomy and middle lobe segmentectomy.
6	Infiltrating ductal carcinoma, modified Bloom grade I, pT2N0Mx.	ARIMIDEX tab 1 mg, right mastectomy with attached skin including nipple and areola with separated axillary tail, radiotherapy, chemotherapy; Zometa
7	Invasive mammary carcinoma (mixed ductal& lobular), grade II .	Neupogen® (filgrastim), mastectomy, radiotherapy, chemotherapy.
8	Infiltrating ductal carcinoma, grade II	ARIMIDEX tab 1 mg, mastectomy, radiotherapy, chemotherapy
9	Invasive ductal breast cancer	ARIMIDEX tab 1 mg, mastectomy, radiotherapy, chemotherapy
10	Invasive carcinoma	ARIMIDEX tab 1 mg, mastectomy, radiotherapy, chemotherapy / Zantac, allermine, Plasit
11	Breast carcinoma grad II	ARIMIDEX tab 1 mg, mastectomy, radiotherapy, chemotherapy
12	Invasive ductal breast cancer / ductal grade II	ARIMIDEX tab 1 mg, lumpectomy, radiotherapy, chemotherapy
13	Luminal B1 breast cancer Subtype.	ARIMIDEX tab 1 mg, left mastectomy with attached skin including nipple and areola with separated axillary tail, radiotherapy, chemotherapy; Zometa
14	Breast carcinoma grad III	endoxan, adriamycin, NEUPOGEN® (filgrastim), Later: Zoladex 3.6 mg s/c and ARIMIDEX tab 1 mg
15	Malignant breast cancer	Taxol 130mg, Carboplatin 150mg Injection, Mastectomy and axillary Clearance.
16	Invasive ductal carcinoma, grade III	TYKERB® (lapatinib) tablets, Xeloda 500 mg, mastectomy, radiotherapy, chemotherapy
17	Breast carcinoma as primary site	Zometa®4 mg, ARIMIDEX tab 1 mg, mastectomy, radiotherapy, chemotherapy
18	Infiltrating ductal carcinoma, grade III (Modified Bloom-Richardson).	Trazimera, lumpectomy, Chemotherapy, radiotherapy.
19	Invasive ductal carcinoma of breast (NOS) of right breast, moderately differentiated, completely excised. Pathological stage is PT2 pN0 Mx.	ARIMIDEX tab 1 mg, Zoladex (S/C) right mastectomy with attached skin including nipple and areola with separated axillary tail, radiotherapy, chemotherapy; Zometa
20	Infiltrating ductal carcinoma, modified Bloom- Richardson grade II with lymph nodes metastasis, pT3N2M0	Trazimera, lumpectomy, Chemotherapy, radiotherapy.
21	Infiltrating ductal carcinoma, grade II	Taxol 130mg, mastectomy, radiotherapy, chemotherapy.
No.	Diagnosis	Treatment module
	··· · · · · · · · · · · · · · · · · ·	

- 22 Malignant invasive breast carcinoma
- 23 Infiltrating ductal carcinoma, modified Bloom- Richardson grade II with lymph nodes metastasis, pT3N2M0
- 24 Infiltrating ductal carcinoma, Modified Bloom-Richardson grade II with lymph nodes metastasis, pT3N2M0.
- 25 Infiltrating ductal carcinoma, modified Bloom grade II, pT2N1M0.
- 26 Malignant invasive breast carcinoma
- 27 Invasive lobular carcinoma
- 28 Stage T2pN0 invasive ductal carcinoma
- 29 Invasive carcinoma of no special type (ductal) with dense lymphoplasmacytic infiltrate. Histological grade (Nottingham histological score 3). Overall grade 3 (scores of 9) Glandular (acinar) / Tubular differentiation score 3. Mitotic rate score 3. Carcinoma in situ component not identified. Lymph vascular invasion is not identified. Pathological stage: pTNM, AJCC 8th Edition) pT2pN2a.
- 30 Moderately differentiated invasive ductal carcinoma Grade II (score 6 out 9 of Nottingham modification of the Bloom-Richardson system). T1N0Mx

Herceptin 600 mg, chemotherapy, Radio therapy

ZOLADEX injection, mastectomy and radiotherapy.

ARIMIDEX tab 1 mg, right mastectomy with attached skin including nipple and areola with separated axillary tail, radiotherapy, chemotherapy; Zometa

ZOLADEX injection, Arimidex, mastectomy and radiotherapy.

Herceptin 600 mg, mastectomy, chemotherapy, Radio therapy

ZOLADEX injection, Arimidex, mastectomy and radiotherapy. Taxol 130mg, Zoladex 3.6 Injection, Mastectomy and axillary Clearnce.

ZOLADEX injection, Tamoxifen, Right modified radical mastectomy and radiotherapy.

ARIMIDEX tab 1 mg, mastectomy, radiotherapy, chemotherapy

## DISCUSSION

Breast cancer is the most common cancer among women worldwide and in Iraq, and its incidence rate is estimated to reach 3.2 million in 2050. It is currently diagnosed and treated at an early stage in

most developed countries.<sup>18</sup> There are still significant differences in clinical symptoms and signs, the stage at which the disease is diagnosed in the patient, and the treatment module depending on the stage of the disease.<sup>18,19</sup>

**Table 7.** The incidence of the periodontal in the patients

No periodontal disease	Mild	Moderate	Severe
0 No signs of periodontal disease	7 (23.33 %) with signs o	of 2 (6.66%) with multiple	21 (70%) Showing multiple signs
(plaque, bleeding, loss of teeth)	plaque, bleeding, no loss	s signs of plaque	of plaque accumulation, severe
	of teeth	accumulation, bleeding,	bleeding, loss of many teeth and
		loss of few teeth	mobile of the others

The current study included a detailed finding of thirty breast cancer cases that were registered in the Breast Cancer Unit at Al-Hussein Teaching Hospital, in Al-Muthanna Governorate in 2023. Our results are consistent with those of previous studies in other Iraqi governorates.<sup>17,20–22</sup> It is also compatible with some studies<sup>22,23</sup> which showed variation of the age groups between affected women.

The current study also showed a high incidence of right breast cancer, 63.33%, compared to the left side, 36.66%. These results are consistent with some studies<sup>24</sup>, while they differ from other studies in terms of the incidence between the right and left breasts.<sup>25,26</sup> The results showed the nature of the spread of cancer cells to the local and regional lymph nodes. The rate of metastases was 100% for the lymph nodes and 66.66% for the rest of the other organs. These results are consistent with those of previous studies that recorded different observations regarding the rates of breast cancer metastases in Iraq and around the world. <sup>3,27–31</sup> Most studies recorded a high rate of metastases in the lymph nodes and in other organs, especially in

cases diagnosed in advanced stages of the disease. 32 The results of the current study also showed different clinical symptoms related to the site and the stage of the lump at the time of the first diagnosis. As for the clinical symptoms, most cases had palpable and painless tumours of different sizes, while in metastasis cases, other symptoms were accompanied by them, such as respiratory symptoms due to lung metastasis. The ultrasound and magnetic resonance imaging results were characterized by the appearance of the tumor mass in different areas of the breast, including those with regular and irregular edges. These results are consistent with those of thee previous studies <sup>33,34</sup>, which revealed different sizes of tumor mass in different locations. Also, the results of the current study showed differences in the gross and histological changes of cancer depending on its stage at the time of diagnosis and expression of receptors in IHC. These results agree with some previously published studies, which showed different histological changes, and various receptors expression. 35,36 In the current study, most of the



tissue sections of breast cancer samples showed nests of infiltrating epithelial cells in multiple cords and tubes and different shapes with an increase in infrequent mitotic figures and a transformed lining. In addition to the infiltration of lymphocytes and cancer cells in the nipple skin, deep lesions, fibroblasts, and inflammatory cells were present, along with giant cells. These results are consistent with those of some previously published studies in Iraq or the world. <sup>33,34,36</sup> The results of the IHC histochemical examination in the current study showed different reactions to ER, PR, Her-2, and Ki-67 receptors, and these results were consistent with previously published studies. <sup>35,36</sup>

The current study showed different types and stages of breast cancer which were diagnosed based on clinical symptoms, ultrasound and MRI images, gross and histological pathological changes, and the results of IHC histochemistry. Accordingly, the treatment program, which included chemotherapy, surgery, radiation, and hormonal therapy, was selected for each case. These results were consistent with previous studies. <sup>26,28,37</sup> In the current study, surgical treatment an important was Unfortunately, it included a radical option. mastectomy, which is still the standard surgical approach in Iraq and other Arab countries. 4,17,21,31 Many previous studies have reported low rates of mastectomy. <sup>38,39</sup> In a randomized clinical study, more than 50% of patients became eligible for surgery to remove the cancerous mass instead of total mastectomy, especially after neoadjuvant chemotherapy (NACT). 40

The incidence of breast cancer increased to 69% between 2013 and 2019. The BC rate increased from 40.4% to 62.6% in a prospective study conducted in Seoul, Korea, between 2014 and 2015. 40 In the Netherlands, the incidence of breast cancer increased from 43% to 57% between 2011 and 2016. 41 In a comprehensive study conducted in the Kurdistan Region in Iraq, 113 breast cancer patients were treated with NACT neoadjuvant chemotherapy. <sup>20</sup> The study showed an increase in the proportion of patients treated with NACT over time, from 13 (8.3%) in 2016 to 28 (14.2%) in 2021, which is in line with international trends. 41 Currently, systemic therapy is individualized according to each breast cancer subtype and NACT has been used instead of conventional chemotherapy. 41,42 The highest use of NACT was in HER2-enriched and TNBC in about 44% of patients, while luminal types accounted for 55.7% of patients. The Ki-67 proliferation index was 0.14 in 73.4% of patients, which was identical to the rates reported in the current study. 19

Currently, it is worth mentioning that the use of neoadjuvant therapy is associated with a reduced need

for extensive lymphadenectomy, especially axillary lymph node dissection. <sup>28,40</sup> Although most physicians prefer extensive lymphadenectomy, the majority of them had axillary lymph node dissection (ALND 94%) and only a minority had sentinel lymph node biopsy (SLNB 6%), which also reflects the need to change the treatment program in Iraq and Arab countries towards less aggressive axillary lymph node staging. SLNB reduces the number of lymph nodes removed, reduces surgical complications of ALND, and does not affect survival, which has been reported in previous studies. <sup>42,43</sup>

The results of the study showed a high percentage of patients with periodontal disease. A high percentage of 70 % of patients in this study showed severe periodontal disease. Meanwhile, the percentages of mild and moderate forms were 23.33 % and 6.66%, respectively. These results agree with those of a previously reported study<sup>43</sup>, which approved that tooth loss and chronic periodontal disease were highly prevalent in breast cancer survivors' postmenopausal women. They also mentioned that oral health evaluation should be done before breast cancer treatment.

The results of the current study are also compatible with a meta-analysis by Wang *et al.* (2022) <sup>8</sup>, which revealed a positive relationship between breast cancer, total cancer mortality, and periodontal disease. Additionally, they recommend a long follow-up period and multinational studies that improve the oral health of breast cancer patients.

Moreover, the current results also agree with the results of a previous study<sup>44</sup> which reported a significant statistical difference between females with breast cancer and healthy ones in clinical attachment loss. On the contrary, the prospective cohort study done by Jia *et al.*, (2020) <sup>45</sup> detected no clear relationship between breast cancer risk and periodontal disease and recommended further research.

# **CONCLUSION**

To our knowledge, this is the first study to offer a detailed description of breast cancer patients in Iraq. This study showed variation in the clinical, ultrasound, MRI, histological changes and IHC reaction for ER, PR, Her-2 and Ki-67 receptors in relation to the occurrence of periodontal disease for thirty patients diagnosed with breast cancer in Iraq. The authors recommend further studies on breast cancer to support its early diagnosis and prevention strategies.

# ETHICAL CONSIDERATIONS

The Helsinki Declaration and later amendments for human research were applied during all study procedures. Each patient received complete information about the nature and objectives of the study. All patients signed an informed consent form. This study has been approved by the Research and Ethical Committee (Ref.# 546 on 17th April 2023), College of Dentistry, Al-Iraqia University.

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## CONFLICT OF INTEREST

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