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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.¹ It is also considered the most frequent cancer in males and females and is the foremost cause of death from cancer in women, with

case fatality rates being the highest in low-income countries.¹ 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 2022.²⁻⁴ 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).^{3,4} Thus, it has been showed that breast cancer is the

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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 teeth-supporting structure is called Periodontal disease,^{6,7} 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 diabetes⁹, Rheumatoid arthritis¹⁰, cardiovascular system¹¹, depression¹², chronic obstructive pulmonary disease¹³, and Alzheimer's disease.¹⁴

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 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 ± 11.41 . 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).

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.



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	A mass lesion in upper quadrant of right breast. The mass showed lobulate margins and heterogenous enhancement
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 U/S guide was done	A phenotype 1.5X1.5 cm mass consistent with a primary 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	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 /Clinical signs year	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.	An irregular large mass measuring 300*180*70 mm
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.	An irregular large mass on the right side
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.

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.

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 2.** The histopathological features and results of immunohistochemistry

No.	Histopathology	Immunohistochemistry
1	An infiltrating epithelial tumor composed of nest, cords and numerous tubules of moderately pleomorphic cells admixed with infrequent mitotic figures, surrounded by desmoplastic stroma.	ER, PR: Positive (intensity 3, proportion 4, Allred score 7, Her-2: positive (Score 3+)
2	A section from mastectomy specimen shows an infiltrating epithelial tumor composed of nest, cords and numerous tubules of moderately 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.	ER, PR: negative, 2. Her-2: negative (Score 0).
3	A grossly cut right modified radical mastectomy, breast tissue with axillary tail measuring 30X12X3 cm, tissue attached to skin measuring 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).	CK: +ve (Strong, diffuse), ER: +ve, CD34: -ve,
4	A section from mastectomy specimen shows 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 nipples 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. Breast carcinoma is confirmed.	Estrogen receptor: intensity score + proportion score: 3+4= 7/ 8 (positive), progesterone receptor intensity score +proportion score: 1+ 2= 3/8 (weak positive), HER2/ Neu ** Score: + 3 positive. * Allred scoring for ER/ PR receptors: Positive with total score (PS+15) is 3-8
5	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 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.	Strongly positive for estrogen, negative for progesterone, Her 2 positive (+3).
6	Grossly cut sections show a tumor lesion located between the lower and upper quadrant, measuring 35 mm in maximum dimension with firm 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.	ER, PR: positive, Her-2 Negative (Score 0).
7	Sections of breast tissue cores showed invasive cords, nests and acini of atypical epithelial cells with desmoplastic stroma in between.	ER, PR: positive, Her-2 positive (Score 3)
8	Three grossly cut irregular fragments of grey yellow fibrofatty tissues 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. Sections from breast tissue show a moderately differentiated epithelial tumor composed of moderately pleomorphic epithelial cells arranged in cords, sheets and minimal tubules embedded in moderately desmoplastic and chronically inflamed stroma. Lymph vascular invasion by tumor cells are noted.	ER, PR: positive, Her-2 positive



- 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. ER, PR: positive, Her-2 positive
- 10 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. 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.
- 11 Sections of breast tissue cores showed invasive cords, nests and acini of atypical epithelial cells with desmoplastic stroma in between. ER: Proportion 3+4= 7/8 (positive) , PR: Proportion 1 + 2= 3/8 (weak positive) , Her-2/ neu** + 3 (Positive) , intensity
- 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. ER, PR: positive, Her-2 positive (Score 3)
- 13 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. 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 α (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)
- 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. ER, PR: positive, Her-2: +ve 1 (negative).
- 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. 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.
- 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). 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.
- 18 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 (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. ER, PR: Positive (intensity 3, proportion 4, Allred score 7, Her-2: positive (Score 3+))
- 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. ER, PR: positive, Her-2 positive (Score 3)
- 21 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. ER, PR: positive, Her-2: +ve 1 (score 1: negative). Ki-67 <14% positive tumor cells
- 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< Mitotic rate score 1, Ductal carcinoma in situ: not identified, Lymph vascular invasion not identified 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%)
- 23 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 ER, PR: positive, Her-2: +ve 2 Equivocal (Score 2). Incomplete and faint membrane staining in >30% of 3-tumor cell, Ki-67 <14% positive tumor cells.
- 24 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 II 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. ER, PR: positive, Her-2: +ve 1 (score 1: negative). Ki-67 <14% positive tumor cells
- 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. ER, PR: Positive (Allred total score 7), Her-2: Negative (Score 0)
- 26 Multiple clusters of suspicious malignant epithelial cells. ER, PR: positive, Her-2 positive (Score 3)
- 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, Her-2 positive



28	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.	ER, PR: positive, Her-2 Negative (Score 0).
29	Glandular (acinar) / tubular differentiation score 3, Nuclear pleomorphic score 3, mitotic rate score 3.	ER, PR: positive, Her-2 Negative (Score 0).
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: +ve 1 (negative).

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 with metastases to lymph nodes	Number and % of patients with metastases to the other organs
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 3.5cm suggestive of LN metastases. There is a hypodense lesion measuring 2.6 cm in the right hilar region. Enlarged hilar LN. There are enlarged mediastinal LNs, the largest measuring 13 mm in short axis diameter.	No evidence of brain, liver and lung metastasis, there is a lytic lesion measuring 13 mm in T11 vertebra
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 lymphadenopathy.	Evidence of bilateral lung nodules metastasis, a nodule in 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 sizes from 5-20 mm. Sections from lymph nodes show features of reactive lymphoid hyperplasia with no tumor deposits.	Evidence of lymph nodes involvement
7	Sections of lymph nodes show tumor invasion	No evidence of brain, liver and lung metastasis, there is a 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	A few adjacent faintly avid sub-centimetric lymph nodes, metastatic; Pet scan shows FDG-avid enlarged right axillary lymph node measuring 2.9 X 2.6 cm with SUV max 11.2 cm.	No evidence of brain, liver and lung metastasis, distance metastasis.

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

No.	Lymph nodes	Metastasis
10	Lymph nodes are present in the axillary tail, ranging in sizes from 5-20 mm. Lymph nodes show features of reactive lymphoid hyperplasia with no tumor deposits.	No evidence of brain, liver and lung metastasis, distance metastasis.
11	8 lymph nodes are present in the axillary tail, ranging in sizes from 5-20 mm. Lymph nodes show features of reactive lymphoid hyperplasia with no tumor deposits.	No evidence of brain, liver and lung metastasis.
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 show features of reactive lymphoid hyperplasia with no tumor deposits.	No evidence of brain, liver and lung metastasis.
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 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 malignant deposit.	Evidence of hepatic / liver metastasis. Adenocarcinoma in 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 reactive lymphoid hyperplasia with tumor deposits.	evidence of hepatic / metastatic adenocarcinoma in both ovaries
18	The 5 first lymph nodes are present in the axillary tail, showing features of reactive lymphoid hyperplasia with no tumor deposits.	Sections from breast tissues show infiltrating tumor composed of solid nest, cords, sheets and occasional 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.	Evidence of lymph node invasion
20	15 right axillary lymph nodes are present with axillary tail (5-20 mm)	Evidence of lymph node invading
21	8 right axillary lymph nodes are enlarged	Evidence of lymph node invading
22	8 right axillary lymph nodes are enlarged with tumor deposit	Evidence of lymph node invading
23	12 lymph nodes are noted attached to axillary tail (5-25 mm)	Sections from mastectomy show an infiltrating epithelial 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.	Evidence of lymph node invading
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 from 5-20 mm. Lymph nodes sections show features of reactive lymphoid hyperplasia with tumor deposits.	Totally, 16 lymph nodes free of tumor.
29	10 lymph nodes show malignant deposit	Evidence of lymph node invasion



- 30 8 lymph nodes are free of tumor deposit. Cross sectioning 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 discrete mass. Regional lymph nodes: tumor present in the regional lymph nodes. The number of lymph nodes with macrometastases (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. Overall, 20 lymph nodes were examined. No evidence of brain, liver and lung metastasis.

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,

23.33%⁷ of the patients had mild periodontal disease, 6.66%² had moderate periodontal disease, and 70%²¹ showed a 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	Residual moderate differentiated infiltrating ductal carcinoma	ARIMIDEX tab 1 mg, mastectomy, radiotherapy, chemotherapy
3	Invasive lobular carcinoma/ Pathological stage: T2 N0 Mx.	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.

**Table 6.** The final diagnosis for each case and the treatment modules.(continued)

No.	Diagnosis	Treatment module
22	Malignant invasive breast carcinoma	Herceptin 600 mg, chemotherapy, Radio therapy
23	Infiltrating ductal carcinoma, modified Bloom- Richardson grade II with lymph nodes metastasis, pT3N2M0	ZOLADEX injection, mastectomy and radiotherapy.
24	Infiltrating ductal carcinoma, Modified Bloom-Richardson grade II with lymph nodes metastasis, pT3N2M0.	ARIMIDEX tab 1 mg, right mastectomy with attached skin including nipple and areola with separated axillary tail, radiotherapy, chemotherapy; Zometa
25	Infiltrating ductal carcinoma, modified Bloom grade II, pT2N1M0.	ZOLADEX injection, Arimidex, mastectomy and radiotherapy.
26	Malignant invasive breast carcinoma	Herceptin 600 mg, mastectomy, chemotherapy, Radio therapy
27	Invasive lobular carcinoma	ZOLADEX injection, Arimidex, mastectomy and radiotherapy.
28	Stage T2pN0 invasive ductal carcinoma	Taxol 130mg, Zoladex 3.6 Injection, Mastectomy and axillary Clearance.
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.	ZOLADEX injection, Tamoxifen, Right modified radical mastectomy and radiotherapy.
30	Moderately differentiated invasive ductal carcinoma Grade II (score 6 out of 9 of Nottingham modification of the Bloom-Richardson system). T1N0Mx	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.^{16,17} It is currently diagnosed and treated at an early stage in

most developed countries.¹⁸ 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.^{18,19}

Table 7. The incidence of the periodontal in the patients

No periodontal disease	Mild	Moderate	Severe
0 No signs of periodontal disease (plaque, bleeding, loss of teeth)	7 (23.33 %) with signs of plaque, bleeding, no loss of teeth	2 (6.66%) with multiple signs of plaque accumulation, bleeding, loss of few teeth	21 (70%) Showing multiple signs of plaque accumulation, severe bleeding, loss of many teeth and 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.^{17,20-22} It is also compatible with some studies^{22,23} 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 studies²⁴, while they differ from other studies in terms of the incidence between the right and left breasts.^{25,26} 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.^{3,27-31} 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 the previous studies^{33,34}, 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.^{33,34,36} 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.^{35,36}

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.^{26,28,37} In the current study, surgical treatment was an important option. Unfortunately, it included a radical 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.^{38,39} 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.²⁰ 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.^{28,40} 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.^{42,43}

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 study⁴³, 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)⁸, 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 study⁴⁴ 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)⁴⁵ 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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