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CLINICOPATHOLOGICAL ASSESSMENT OF BREAST CARCINOMA IN MASTECTOMY SPECIMENS IN A SAMPLE OF IRAQI PATIENTS

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ABSTRACT

Background: In Iraq, breast cancer constituted the majority (37.9%) of documented female cancers in 2020 with 7,515 newly diagnosed cases and 3,019 deaths. **Aim of study:** assess the clinicopathological characteristics of women with breast cancer presenting with breast lumps and to compare the findings with other studies. **Methodology:** This is a cross sectional study that included 100 cases of breast cancer. The study was conducted in Iraq in the period from 2021-2022. **Results:** Most of the studied sample were in the age group (50-59 years). Regarding histopathological type, the majority were of invasive ductal carcinoma without in situ (67.0%). As for TNM staging, (36%) and (37%) were of pT2 and pT3; respectively and (40%) of pN3. Concerning Nottingham system grading, (54%) were of grade III. In terms of molecular classification, luminal A type was seen in (23.0%), followed by luminal B (26%). A significant association was detected between histopathological type and each of age, pT staging, pN staging, grading. Moreover, there was a significant association between Paget disease and pT staging. While no significant association was detected between histopathological type and neither molecular classification, multicentricity, laterality, and the affected.

KEYWORDS: Clinicopathological, assessment, breast carcinoma, mastectomy, Iraqi patients.

INTRODUCTION

According to the global cancer observatory, breast cancer is the most common cancer in females with an incidence of 2,261,419 cases diagnosed in 2020 and 684,996 deaths.[1] In Iraq, the situation is not different as the global cancer observatory documented that breast cancer constituted the majority (37.9%) of documented female cancers in 2020 with 7,515 newly diagnosed cases(22%) according to Iraqi cancer registry and 3,019 deaths.[2] Breast cancer generally develops in silence, and the vast majority of cases are diagnosed by regular screening.[3] Although non-metastatic early-stage illness is treatable in 70-80% of cases, existing treatments are not effective against advanced disease with distant metastasis.[4] Thus, if breast cancer is left untreated, the mean survival of patient is about 3 years after clinical presentation and more than 5-year survival rate is only one in twenty.[5]

Breast cancer is a complex disease with a wide range of molecular subtypes; which include activation of hormone receptors (progesterone and estrogen receptors), HER2 receptor, and/or BRCA mutations. Treatment strategies differ according to molecular subtype.[4]

Breast cancer is connected with a number of well-known risk factors, of which the most important is age. The family history is very important, as the presence of first-degree relative family history increases the risk of acquiring breast cancer of 3-4 times. However, the chance of acquiring breast cancer may be heightened if a person has a large number of second-degree relatives who have had the disease.[6] Besides family history, nulliparity, early menarche (age 12 or under), late menopause (age 50 or older), and the use of hormone replacement therapy are all risk factors for breast cancer.[7]

A palpable lump is the most prevalent symptom of a breast lesion. Every woman who has a breast lump, discomfort, or unusual discharge from the nipple is required to undergo proper clinical, radiological, and histopathological assessment.[8,9]

Important clinical parameters, such as tumor size, nodal status, stage distribution at first diagnosis, hormone receptor status, and the percentage of women presenting with distant metastases, are not well documented in Iraqi hospital records; and hence the need for scholarly publications regarding histopathological types of breast cancer and their parameters in order to improve regional management practices.

This study aims to assess the clinicopathological characteristics of women with breast cancer presenting with breast lumps and to compare the findings with other studies.

MATERIALS AND METHODS

This is a cross sectional including analysis of 100 randomly selected patients with breast carcinoma in Baghdad collected from private labs from January 2021 to January 2022. The data The cases involved were female patients who underwent mastectomies due to breast cancer and needed histopathological assessment to confirm the diagnosis. The study inclusion criteria enrolled all malignant breast lesions that presented clinically as lumps during the study period. The exclusion criteria was as the following:

- Cases with recurrent breast cancer.
- Patients on chemotherapy, radiotherapy or hormonal therapy.
- Male breast cancer.

Study material included specimens from mastectomies. In 50 suspicious cases, 4 micrometer tissue pieces sections were taken from representative areas and exposed to step wise processing and paraffin embedding, while other 50 cases are were taken from paraffin embedding blocks. Routine Hematoxylin and Eosin staining was done. Revision of histopathological diagnosis was done by two independent pathologists.

The clinicopathological data that were collected from patients' pathology report included

- Age.
- Histopathological type.
- pT staging (According to TNM classification system).
- pN staging (According to TNM classification system).
- Tumor grade (According to Elston/Nottingham modification of Bloom-Richardson system, based on (a) tumor tubule formation, (b) number of mitotic figures in most active areas and (c) nuclear pleomorphism).
- Molecular subtype: Luminal subtypes include luminal A (ER+ [strong], PR+, HER2-) and luminal B (ER+ [weak / moderate], PR-, sometimes HER2+), Basal like=triple negative (ER-, PR-, HER2-)
- Affected breast quadrant.
- Breast side.
- Presence of multicentricity.
- Paget's disease (Nipple involvement by invasive ductal carcinoma).

All statistical analyses were performed utilizing SPSS, version 26 and including mean, standard deviation, frequency and percentage using Yates Chi square with p. value <0.05 regarded as statistically significant.

RESULTS

A total number of 100 cases were investigated. Concerning age group distribution, most of the studied sample were in the age group 50-59 years (41.0%), followed by the age group 40-49 years (35.0%); as shown in table (1). The clinical characteristics are shown in table (2). Regarding histopathological type, the majority were of invasive ductal carcinoma without in situ (67.0%). As for TNM staging, (36%) and (37%) were of pT2 and pT3; respectively and (40%) of pN3. Concerning Nottingham system grading, (54%) were of grade III. In terms of molecular classification, luminal A type was seen in (23.0%), followed by luminal B (26%); The left side was the most common site (63.0%). The upper outer quadrant was the most common (52.9%) as illustrated in table (2).

Table 1: Age group distribution of the studied sample. Distribution of malignant breast lesions according to histopathological type, pT staging, pN staging, tumor grade, molecular classification, breast quadrant, multicentricity, and Paget's disease.

Age group	Frequency	Percentage (%)
20-29 years	2	2.0
30-39 years	7	7.0
40-49 years	35	35.0
50-59 years	41	41.0
60-69 years	12	12.0
70-79 years	3	3.0
Total	100	100.0
Clinical characteristics	**Frequency**	**Percentage (%)**
Histopathological type (Total=100)		
Invasive ductal carcinoma of no special type (NST) without invasive ductal carcinoma in situ	67	67.0
Invasive ductal carcinoma of no special type (NST)	13	13.0

with invasive ductal carcinoma in situ		
Lobular carcinoma	12	12.0
Mucinous carcinoma	8	8.0
Total	100	100.0
pT staging (Total=100)		
Tis	13	13.0
T1	9	9.0
T2	36	36.0
T3	37	37.0
T4	5	5.0
Total	100	100.0
pN staging (Total=100)		
pN0	29	29.0
pN1 (1-3 lymph nodes)	12	12.0
pN2 (4-9 lymph nodes)	19	19.0
pN3 (≥10 lymph nodes)	40	40.0
Total	100	100.0
Tumor grade* (Total=87)		
Grade III (Poorly differentiated Invasive ductal carcinoma)	54	62.1
Grade II (Moderately differentiated Invasive ductal carcinoma)	25	28.7
Grade I (Well differentiated Invasive ductal carcinoma)	8	9.2
Total	87	100.0
Molecular subtype (Total=87)**		
Luminal A	46	52.9
Luminal B	20	23.0
Her2-enriched	8	9.2
Basal-like	13	14.9
Total	87	100.0
Affected quadrant (Total=87)		
Upper outer quadrant	46	52.9
Lower outer quadrant	25	28.7
Upper inner quadrant	7	8.0
Lower inner quadrant	9	10.3
Total	87	100.0
Breast side (Total=100)		
Right	37	37.0
Left	63	63.0
Total	100	100.0
Multicentricity (Total=100)		
Yes	32	32.0
No	68	68.0
Total	100	100.0
Paget's disease (nipple involvement by Invasive ductal carcinoma) (Total=67)		
Yes	5	7.5
No	62	92.5
Total	67	100.0

*Grading by Nottingham system, also known as Scarff-Bloom-Richardson.
**Luminal subtypes include luminal A (ER+ [strong], PR+, HER2-) and luminal B (ER+ [weak / moderate], PR-, sometimes HER2+)Basal like=triple negative (ER-, PR-, HER2-).

A significant association was detected between histopathological type and each of age, pT staging, pN staging, grading. Moreover, there was a significant association between Paget disease and pT staging. While no significant association was detected between histopathological type and neither molecular classification, multicentricity,bi laterality, and the affected quadrant; as shown in tables (3-11).

Table (2): The relation between age group, pT staging, pN staging, grading and histopathological type (p value<0.001).

Age group	Histopathological type				Total	P value
	Invasive ductal carcinoma	Invasive ductal carcinoma in situ	Lobular carcinoma	Mucinous carcinoma		
20-29 years	1	1	0	0	2	<0.001
	1.5%	7.7%	0.0%	0.0%	2.0%	
30-39 years	4	3	0	0	7	
	6.0%	23.1%	0.0%	0.0%	7.0%	
40-49 years	23	4	8	0	35	
	34.3%	30.8%	80.0%	0.0%	35.0%	
50-59 years	37	1	2	1	41	
	55.2%	7.7%	20.0%	10.0%	41.0%	
60-69 years	2	4	0	6	12	
	3.0%	30.8%	0.0%	60.0%	12.0%	
70-79 years	0	0	0	3	3	
	0.0%	0.0%	0.0%	30.0%	3.0%	
Total	67	13	10	10	100	
	100.0%	100.0%	100.0%	100.0%	100.0%	
pT staging	**Histopathological type**				**Total**	**P value**
	Invasive ductal carcinoma	**Invasive ductal carcinoma in situ**	**Lobular carcinoma**	**Mucinous carcinoma**		
Tis	0	13	0	0	13	<0.001
	0.0%	100.0%	0.0%	0.0%	13.0%	
pT1	9	0	0	0	9	
	13.4%	0.0%	0.0%	0.0%	9.0%	
pT2	24	0	6	5	35	
	35.8%	0.0%	60.0%	50.0%	35.0%	
pT3	29	0	4	5	38	
	43.3%	0.0%	40.0%	50.0%	38.0%	
pT4	5	0	0	0	5	
	7.5%	0.0%	0.0%	0.0%	5.0%	
Total	67	13	10	10	100	
	100.0%	100.0%	100.0%	100.0%	100.0%	
pT staging	**Histopathological type**				**Total**	**P value**
	Invasive ductal carcinoma	**Invasive ductal carcinoma in situ**	**Lobular carcinoma**	**Mucinous carcinoma**		
Tis	0	13	0	0	13	<0.001
	0.0%	100.0%	0.0%	0.0%	13.0%	
pT1	9	0	0	0	9	
	13.4%	0.0%	0.0%	0.0%	9.0%	
pT2	24	0	6	5	35	
	35.8%	0.0%	60.0%	50.0%	35.0%	
pT3	29	0	4	5	38	
	43.3%	0.0%	40.0%	50.0%	38.0%	
pT4	5	0	0	0	5	
	7.5%	0.0%	0.0%	0.0%	5.0%	
Total	67	13	10	10	100	
	100.0%	100.0%	100.0%	100.0%	100.0%	
pN staging	**Histopathological type**				**Total**	**P value**
	Invasive ductal carcinoma	**Invasive ductal carcinoma in situ**	**Lobular carcinoma**	**Mucinous carcinoma**		
pN0	7	13	0	9	29	<0.001
	10.4%	100.0%	0.0%	90.0%	29.0%	
pN1	11	0	0	1	12	
	16.4%	0.0%	0.0%	10.0%	12.0%	
pN2	15	0	4	0	19	

	22.4%	0.0%	40.0%	0.0%	19.0%	
pN3	34	0	6	0	40	
	50.7%	0.0%	60.0%	0.0%	40.0%	
Total	67	13	10	10	100	
	100.0%	100.0%	100.0%	100.0%	100.0%	
Grading	**Histopathological type**				**Total**	
	Invasive ductal carcinoma	**Lobular carcinoma**	**Mucinous carcinoma**			
Poorly differentiated invasive ductal carcinoma	47	6	0		53	
	70.1%	60.0%	0.0%		60.9%	
Moderately differentiated invasive ductal carcinoma	14	2	10		26	
	20.9%	20.0%	100.0%		29.9%	<0.001
Well differentiated Invasive ductal carcinoma	6	2	0		8	
	9.0%	20.0%	0.0%		9.2%	
Total	67	10	10		87	
	100.0%	100.0%	100.0%		100.0%	

Table 3: The relation between Molecular subtype, affected, quadrant multicentricity, breast side and histopathological type (p value = 0.068).

Molecular subtype	**Histopathological type**			**Total**	**P value**
	Invasive ductal carcinoma	**Lobular carcinoma**	**Mucinous carcinoma**		
Luminal A	30	8	9	47	0.068
	44.8%	80.0%	90.0%	54.0%	
Luminal B	16	2	1	19	
	23.9%	20.0%	10.0%	21.8%	
Her2-enriched	8	0	0	8	
	11.9%	0.0%	0.0%	9.2%	
Basal-like	13	0	0	13	
	19.4%	0.0%	0.0%	14.9%	
Total	67	10	10	87	
	100.0%	100.0%	100.0%	100.0%	
Affected quadrant	**Histopathological type**			**Total**	**P value**
	Invasive ductal carcinoma	**Lobular carcinoma**	**Mucinous carcinoma**		
Upper outer quadrant	36	6	4	46	0.461
	53.7%	60.0%	40.0%	52.9%	
Lower outer quadrant	19	4	2	25	
	28.4%	40.0%	20.0%	28.7%	
Upper inner quadrant	5	0	2	7	
	7.5%	0.0%	20.0%	8.0%	
Lower inner quadrant	7	0	2	9	
	10.4%	0.0%	20.0%	10.3%	
Total	67	10	10	87	
	100.0%	100.0%	100.0%	100.0%	
Multicentricity	**Histopathological type**				**Total**	**P value**
	Invasive ductal carcinoma	**Invasive ductal carcinoma**	**Lobular carcinoma**	**Mucinous carcinoma**		

		in situ				
Yes	16	3	6	5	30	0.053
	23.9%	23.1%	60.0%	50.0%	30.0%	
No	51	10	4	5	70	
	76.1%	76.9%	40.0%	50.0%	70.0%	
Total	67	13	10	10	100	
	100.0%	100.0%	100.0%	100.0%	100.0%	
Breast side	**Histopathological type**				**Total**	**P value**
	Invasive ductal carcinoma	**Invasive ductal carcinoma in situ**	**Lobular carcinoma**	**Mucinous carcinoma**		
Right	24	4	5	4	37	0.076
	35.8%	30.8%	50.0%	40.0%	37.0%	
Left	43	9	5	6	63	
	64.2%	69.2%	50.0%	60.0%	63.0%	
Total	67	13	10	10	100	
	100.0%	100.0%	100.0%	100.0%	100.0%	

Table (4): The relation between Paget's disease and pT staging of cases with invasive ductal carcinoma (p value <0.001).

Paget disease	Histopathological type				Total	P value
	pT1	pT2	pT3	pT4		
Yes	0	0	0	5	5	<0.001
	0.0%	0.0%	0.0%	100.0%	7.5%	
No	9	24	29	0	62	
	100.0%	100.0%	100.0%	0.0%	92.5%	
Total	9	24	29	5	67	
	100.0%	100.0%	100.0%	100.0%	100.0%	

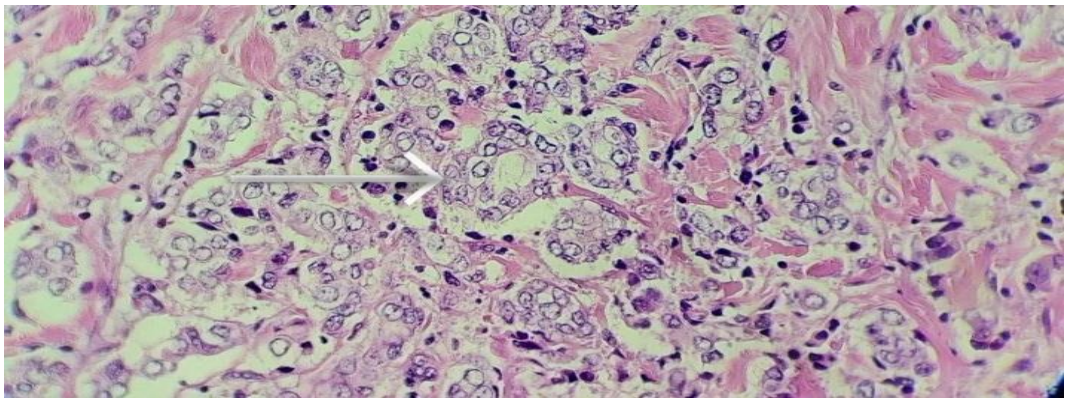

Fig. 1: Low grade invasive ductal carcinoma,grade-I with tubular formation >75% with small, regular uniform nucleus with low mitotic count <5/10hpf.(H and E stain 10x).

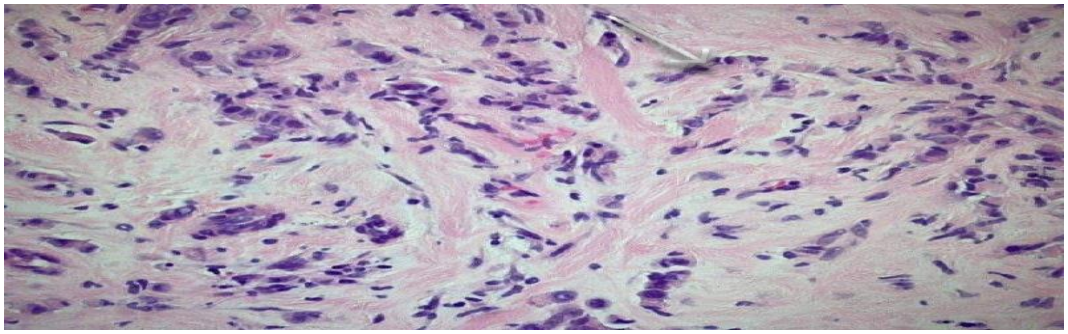

Figure 2: section show lobular breast carcinoma with tumor cells arranged in single file (indian file pattren) other cells arranged in discohesivewith monomorphic features and lacking marked atypia, (H and E, 40x).

DISCUSSION

Since the prognosis and response to breast cancer therapy are affected by a number of factors, including the tumor's size, grade, extent of lymphatic spread and receptor status;[11] this study assessed the tumor clinicopathological parameters of breast malignancy in Iraq. In the present study, invasive ductal carcinoma was the most common histopathological type in 80% (67.0% without in situ and 13.0% in situ), which is in concordance with other studies, such as (Mjali et al., 2022) in Karbala (91.8%),[12] (Al-Isawi et al., 2016) in Western Iraq (88%),[13] (Molah et al., 2015) in North Iraq (92.8%),[14] and (Khabaz et al., 2014) in Saudi Arabia (88.8%).[15] However, lower frequencies were reported in the US by (Sperry et al., 2020) and Turkey by (Ozmen et al., 2014) (75% and 78.7%, respectively).[16,17] This difference in prevalence of invasive ductal carcinoma between Arab countries on one hand, and the US and Turkey on the other hand; can be attributed to several factors, such as the late age of first birth and the use of hormone replacement therapy, which are proven risk factors for invasive lobular carcinoma. The present study has shown that lobular carcinoma was the second most common type (12.0%), which is expected given that invasive lobular carcinoma is the second most common histologic form of breast cancer, representing 5% to 15% of all invasive breast cancers.[18] The present study, has shown that breast malignancy was maximum at the 5th and 6th decades of life, with 9.0% of the studied sample being <40 years at diagnosis. Globally, 6.6% of all breast cancer diagnoses were made in women under the age of 40.[19] The study by (Isawi et al., 2016) in western Iraq revealed that 33.56% of breast cancer patients were ≤40 years old, and concluded that the presentation was significantly earlier than the worldwide age, including other Arab nations.[13] Concerning the reasons behind the rising frequency of early age breast cancer, genetic and environmental factors are to be considered including effects of consanguinity marriage that characterizes Iraqi community, role of hormonal replacement therapy, wars effect with use of unknown weapons, effects of parity, age of first pregnancy, length of reproductive life and prevalence of certain genes that are related to breast cancer in the Iraqi females, all these factors are to be investigated by a multifactorial study for more explanation.[13] It is noteworthy to mention that risk factors for early breast cancer Notable risk factors for early breast cancer include a low body weight and the recent use of an oral contraceptive. Young age is considered an independent negative predictor of cancer-specific survival. Moreover, breast cancers in very young women tend to be aggressive due in part to an overrepresentation of high-grade, triple-negative tumors.[20] Moreover, breast tumor of women under 40 years tend to with larger size and higher nodal status, due to the lack of regular screening programs in this age group.[21] In the present study, no cases were diagnosed in pT0 and 29 cases in pN0 stages. Moreover, 36% were diagnosed at stage pT2 and 37% at pT3. This indicates that a majority of cases are not detected at an early stage, which is common in developing countries. In Western Iraq, (Al-Isawi et al.) showed that only (2.4%) cases were detected at stage pT0 and pT1, and (2.9%) at pN0 and pN1.[13] These findings of the current study are in accordance with other studies, such as (Najjar & Easson) which included 12 Arabic countries and concluded that most cases of breast cancer in these countries are detected at late stages.[22] These findings of Arab countries are also in line with those of other third world countries; for example, the study by (Kumbjakar et al., 2021) in India found that 54.9% had a late diagnosis (Stage IIIA and above).[23] Concerning the causes of higher stage presentation, a systematic review by (Alhurishi et al., 2011) in the Middle East found that It was discovered that advanced age and poorer educational level had significant influence in explaining late presentation. It was observed that having a negative familial history of breast carcinoma had a moderate impact on breast cancer's delayed manifestation.[24] In the present study, Grade III was the most common histological grade (62.1%), this is in accordance with the study by (Kumbhakar et al., 2021) in India, who reported Grade III in (75.6%) of patients.[23] Other Iraqi studies also reported larger figures of grade III breast cancer (although lower than the present study) such as (Al-Isawi et al.) and (Nada Alwan), who reported percentages of 42.8% and 40%; respectively.[13,25] As for grade II, it was found in 29.9%. This is extremely less than what was found by (Mjala et al., 2022) in Karbala, Iraq (50.3%)[12] and (Shomaf et al., 2013) in Jordan (48%)[26] and Jangid et al., 2020) in India.[8] It is noteworthy to mention that histopathological grading of breast cancer has been widely studied.[27] It has been found that it has a prognostic significance that is of the same value as the lymph node status (pN staging) and a greater value than the tumor size (pT staging).[28] For example, In contrast to individuals with grade III tumors without any lymph node metastases, those with grade II tumors with 1-3 positive lymph nodes had a better prognosis.[27] The present study demonstrated that the majority were classified as luminal A (52.9%), which offers the best prognosis of all subtypes. It is close to what was reported by (Salhia et al.) in Egypt (44.3%)[29] and by (Ben Abdelkrim et al.) in Tunis (51.5%).[30] While a higher percentage was reported in by (Shomaf et al.) in Jordan (60%).[26] Compared to other subtypes, patients with luminal-A breast cancer have a far better prognosis. Bone metastases are more prevalent than those in the liver, lungs, or central nervous system, and recurrence is common despite the prevalence of hormone therapy.[31] Luminal B was the second most common (23%), which is close to the findings of (Salhia et al.) in Egyptian women (24.6%).[29] Lower frequencies were reported by (Mjali et al., 2022) in Karbala (15.8%),[12] (Khabaz et al., 2015) in Saudi Arabia (14.5%),[15] and (Shomaf et al.) in Jordan (13%).[26] It is worth mentioning that Luminal B tumors are prognostically less favorable than luminal A tumors, as they have a higher recurrence rate and lower survival rates after relapse compared to luminal-A subtype.[32] The HER2-neu subtype was detected in

(9.2%), which is in exact concordance with (Mjali et al., 2022) in Karbala (15.33%).[12] Studies conducted in Jordan, Saudi Arabia; reported rates of (12%), (12.3%)[15,26], HER2 is associated with more aggressive biological and clinical behavior. HER2-positive cancers have a poor prognosis without therapy. They are more susceptible to certain cytotoxic drugs like doxorubicin, have a lower hormonal sensitivity, and are more likely to spread to other organs, such as the brain.[33] The aggressive basal type was detected in (15%), which is also in exact similarity to the findings in Karbala (15.11%).[12] Studies conducted in Jordan, Saudi Arabia; reported rates of (15%), and (14.8%).[15,26] Basal-like cancers are associated with high histological and nuclear grade, poor tubule formation and the presence of central necrotic or fibrotic zones, pushing borders, conspicuous lymphocytic infiltrate and medullary features with exceptionally high mitotic and proliferative indices.[33] As for the affected quadrant; the upper outer quadrant was the most common site (53%), followed by the lower outer quadrant (32%). (Jangid et al.) showed that the most common site of the malignant lesion in breast was upper outer quadrant with 30.43% of the cases followed by lower outer quadrant with 21.16%.[8] The study by (Al Saad et al., 2022) in Bahrain found that the most common tumor location was in the UOQ (51.5%), followed by the UIQ (15.6%), LOQ (14.2%), and LIQ (14.2%).[34] In the present study, there was a left side predominance with left to right ratio of 1.7:1; which is in line with the study by (Al-Isawi et al., 2016) who reported a left to right ratio 1.58:1. A large study by (Al-Saad et al., 2022) found that right-sided breast cancer was associated with a higher positive family history of malignancy and an increased ratio of locally advanced and metastatic disease, and a reduced 5-year survival in relation to size and stage. Left-sided breast cancer was associated with higher early tumor stage.[35] The current study has shown Paget's disease in 4% patients, which is significantly higher the study by (Jangid et al., 2020) in India.[8] However, this is conceivable given the higher stage at presentation that was detected in the present study. It noteworthy to mention that all cases of Paget's disease were in patients with a tumor size of pT4 (nipple involvement).

CONCLUSION

From the findings of the present study, it can be concluded that the vast majority breast cancer cases in Iraq are of invasive ductal carcinoma type and generally present at a later stage, where poorly differentiated invasive ductal carcinoma grade-III was the most common grade type ,with Luminal A being the most common molecular subtype and the left side with upper outer quadrant was the most common location. The incidence of breast cancer peaked at the 6th decade of life.

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