Mammographic and Sonographic Criteria of Contralateral Breast Cancer versus the Index Cancer

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ABSTRACT :

BACKGROUND:

contralateral breast cancer (CBC) exists in two forms: synchronous and metachronous. Screening for CBC is important on initial cancer diagnosis because it allows for informed surgical decision making.

OBJECTIVE:

To assess the clinical, mammographic and sonographic features of CBC and to compare contralateral breast cancer features with those of index cancer.

METHODS:

A case series study conducted in Breast clinic, Oncology Teaching Hospital. The medical records of patients who visited the center during the period between 2018 and 2020 were reviewed. A total of 29 cases with bilateral breast cancer were collected. Twelve of them were with synchronous contralateral breast cancer and 17 have had metachronous breast cancer. Mammographic films and high-quality US images were reviewed to record lesion characteristics and BI-RADS category classification.

RESULTS:

Patients' mean age at the time of index tumor diagnosis was 49.7 (±9.87) ranged between 22-70 with 34.49% were 45 years and younger. 51.7% of them reported positive family history of breast cancer. 62.1% of the CBC were non-palpable lesions diagnosed during follow up in contrast to index tumor which were palpable l in 86.2%, P<0.0001. In mammography, microlabulated margin was seen in 71.4% of CBC mass whereas speculated mass was the dominant shape of the index cancer (63%), P=0.037. By sonography, non-mass hypoechoic area constituted 41.4% of CBC compared to 6.9% of index cancer, P=0.005. Moreover, CBC lesions were significantly smaller than index tumors with mean diameter of 15.3 (±9.5) vs 27.95 (±11.9), P <0.0001. 51.7% of CBC were irregular with 24.1% had indistinct margin compared with 44.8% of index cancers which exhibited speculated margin, P=0.027.

CONCLUSION:

CBC has mammographic and sonographic feature different from index tumor. Careful contralateral whole breast examination of patients newly diagnosed with breast cancer is essential particularly in younger patient and those with family history.

KEYWORDS: contralateral breast cancer, metachronous cancer, synchronous cancer, mammography, whole breast ultrasound.

INTRODUCTION:

Contralateral breast cancer (CBC) is the most common second tumor in primary breast cancer patients. In breast cancer survivors, the risk of developing CBC is 1.5- 5 fold higher than the risk of primary breast cancer in the general population [1, 2]. In the United States, the incidence of bilateral breast cancer after an ER-positive first cancer estimated to be: 0.45 for first cancers diagnosed before age 30 years and 0.25 to 0.37 for age 30 years or older.

Rates after an ER-negative cancer were higher: 1.26 before age 30 years, 0.85 for age 30 to 35 years, and 0.45 to 0.65 for age 40 or older [3].

Bilateral breast carcinomas exist in 2 forms; synchronous and metachronous [4]. A synchronous breast cancer is diagnosed more or less simultaneously in both breasts in the same patient. The cut-off for synchronicity described in the literature has usually been between 3 and 6 months [5].

Evidence supports viewing the two tumors in synchronous breast cancers as two primary lesions and not as one disease with metastatic spread [6].

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Metachronous cancer diagnosed in a sequential time interval following the primary tumor, usually more than 6 months [4].

The identification of patients who are at increased risk for CBC is essential in order to determine which patients should be routinely screened for CBC using additional radiological modalities and/or offered preventive measures as described in the next section. Characterization of CBC imaging findings has been the focus of many studies particularly with the improved precision of imaging modalities to ensure early detection and improve patient outcome [7,8]. The aim of this study was to assess the clinical, mammographic and sonographic features of contralateral breast cancer and to compare contralateral breast cancer features with those of index cancer.

METHODS:

This is a cross sectional retrospective study conducted in the National Center for Early Detection of Breast Diseases in Oncology Teaching Hospital, Baghdad Medical City. The study was approved by Medical City Directorate and Oncology Teaching Hospital ethical committees. Informed verbal consents were given by all participants.

The medical records of patients who visited the National Center for Early Detection of Breast Diseases during the period between 2018 and 2020 were retrospectively reviewed. A total of 29 patients with bilateral breast cancer with age range of 22- 70 years were collected, 12 were with synchronous contralateral breast cancer and 17 have had metachronous breast cancer. The lesions were considered synchronous if they were diagnosed within 6 months of initial diagnosis of the index tumor. When bilateral tumors were diagnosed simultaneously, the palpable lesion was considered as index [9,10]. Patients' demographic data, history, clinical parameters were retrieved form the records. Inclusion criteria included patients with synchronous breast cancer diagnosed during the complete assessment of the index tumor or within 6 months of the initial diagnosis and patients with metachronous tumor diagnosed after 6 months of the initial index breast cancer diagnosis. Patient with image confirmed CBC but histopathological confirmation was not available were excluded from the study.

Mammography was performed with Full-Field Digital Mammography System ($1941^{x}2294$ senograph DS).

Standard examination of the breast consists of a mediolateral oblique (MLO) and craniocaudal (CC) view of each breast. Both CC and MLO views were were assessed for the breast composition, symmetry, mass characteristics and architectural distortion and assigned according BI-RADS classification

Bilateral whole-breast sonography high-quality images were obtained with modern ultrasound equipment (GE LOGIC S8) sonography. Higher frequency 4–15 MHz linear transducer was used. The patient is examined in the supine oblique position. The side being examined is raised and the arm placed above the head to ensure that the breast tissue is evenly distributed over the chest wall. High-quality US images in patient records were reviewed to lesion characteristics and BI-RADS category classification.

Patients phone numbers were retrieved form breast clinic records and all patient were contacted to collect histopathological reports for the first and second tumors. The mean disease-free period was 27.1 months ranged from 0-147 months. Two patients were deceased in 2020, all the others were alive.

Statistical analyses

All statistical analyses were carried out using Statistical Package for Social Sciences (IBM SPSS) software version 25. Continuous variables were expressed as mean+SD, and range when required. Statistical comparisons were performed using Chi-square test or Fisher's exact tests for as appropriate to assess proportions of nominal/ ordinal variables in different groups. Student t test was used to compare parametric continuous data. A P value of less than 0.05 was considered statistically significant.

RESULTS:

The demographics of study cohort

The mean age of the patients at the time of index tumor diagnosis was 49.7 (±9.87) years ranging between 22-70 years, patients' demographics and characteristics are summarized in Table 1. Synchronous CBC was diagnosed in 12 patients, 10 out 12 (83.3%) were diagnosed simultaneously during the complete assessment of the index tumor. The other 2 cases were diagnosed within 2 months of the initial diagnosis. Metachronous breast cancer represented 17 of all cases which have been developed after 9-147 months of index tumor diagnosis.

Table 1: Demographics and characteristics of patients with contralateral breast cancer.

Patients' characteristics	No	(%)
Age		
<35	2	6.89
35-45	8	27.6
46-50	7	24.1
>50	12	41.4
Marital status		
Married	25	86.2
Not married	4	13.8
Reproductive status		
Premenopausal	13	44.8
Postmenopausal	16	55.2
Family history of breast cancer		
Positive	15	51.7
Negative	14	48.3
Family history of other cancers		
Positive	3	10.3
Negative	26	89.7
Type of operation		
Mastectomy	26	89.7
BCS	3	10.3

Abbreviations: BCS, breast conservative surgery

Clinical and pathological features of contralateral breast cancer

As shown in Table 2, 62.1% of the CBC were diagnosed during screening, this was significantly different (P<0.0001) compared with index tumor whom 89.7% of them were referred for diagnostic imaging either with a palpable mass (86.2%) or other symptoms (13.8%) such as pain in two (6%), skin changes one (3%) and nipple discharge in another (3%) of the patients.

Invasive ductal carcinoma was the dominant tumor type in both index and CBC. Invasive lobular carcinoma was the type of three index tumors and two CBC. CBC appeared to be of a of lower tumor grade compared to the index tumor however statistically, the difference was not significant. Ductal carcinoma in situ was seen in 44% of the index tumors and approximately one third of CBC with no any LCIS reported in the 58-cancer encountered. There was a significant difference between the stage of index and CBC (P=0.019). Six (20.7%) of the CBC were presented with distant metastasis (stage IV tumors), 3 out of 6 did not follow the regular surveillance after index tumor diagnosed.

Table 1:Clinical and pathological characteristics of index and contralateral breast cancer.

	Index tumor	%	Contra-lateral tumor	%	P
Referral screening Diagnostic	3 26	10.3 89.7	18 11	62.1 37.9	<0.0001
Clinical examination palpable lump No palpable lump	25 4	86.2 13.8	11 18	37.9 62.1	<0.0001
Histology type Invasive ducal ca Invasive lobular ca Others	25 3 1	86.2 10.3 3.4	27 2 0	93.1 6.9 0	0.67

Tumor grade I II III	 0 19 10	 0 65.5 34.5	 2 23 4	 6.9 79.3 13.8	0.075
Presence of in situ component No DCIS LCIS	 16 13 0	 55.2 44.8	 21 8 0	 72.4 27.6 0	0.274
Stage I II III IV	 4 17 8 0	 13.8 58.6 27.6 0	 7 13 3 6	 24.1 44.8 10.3 20.7	0.019
Total	29	100	29	100	

Abbreviations: DCIS, ductal carcinoma *in situ.* LCIS, lobular carcinoma *in situ*.

Radiological features of contralateral breast cancer Mammography findings

Mammographic findings of index and CBC are summarized in Table 3. The composition of breast at the time of index and CBC diagnosis was heterogeneously dense in 48.3%. Breast composition did not change at the time of diagnosis of the CBC.

Table 2:Mammography Findings and BI-RADS Category for 58 bilateral Breast Cancers.

US findings	Index tumor (n=29)	%	Contra-lateral tumor (n=29)	%	P
Composition Homogenous Heterogenous	 6 23	 20.7 79.3	 15 14	 51.7 48.3	0.014
Type of lesion Area Mass	 2 27	 6.9 93.1	 12 17	 41.4 58.6	0.005
Size in mm (SD)	27.59 (11.9)	-	15.3 (9.5)	-	<0.0001
Mass margin Irregular Angulated Indistinct Speculated	 6 2 8 13	 20.7 6.9 27.6 44.8	 15 3 7 4	 51.7 10.3 24.1 13.8	0.027
Echo pattern Hypoechoic Heterogenous	 27 2	 93.1 6.9	 17 12	 58.6 41.4	0.005
Other features Skin thickening Distortion	 10 25	 34.5 86.2	 4 29	 13.8 100	-
Suspicious lymph node Absent Present	 10 19	 34.5 65.5	 12 17	 41.4 58.6	0.588
BI-RADS 4b 4c 5	 3 10 16	 10.3 34.5 55.2	 8 16 5	 27.6 55.2 17.2	0.009

A mass was detected in 48.3% of CBC compared with 93.1% of Index cancers (P<0.0001). Significant difference was seen between mass shape of index and CBC (P=0.037). Microlabulated margin was seen in 71.4% of CBC mass whereas speculated mass was the dominant shape of the index cancer (63%). Associated architectural distortion was more frequently seen in index tumors (75.9%) compared to 20.7% of CBC, (P=<.0001).

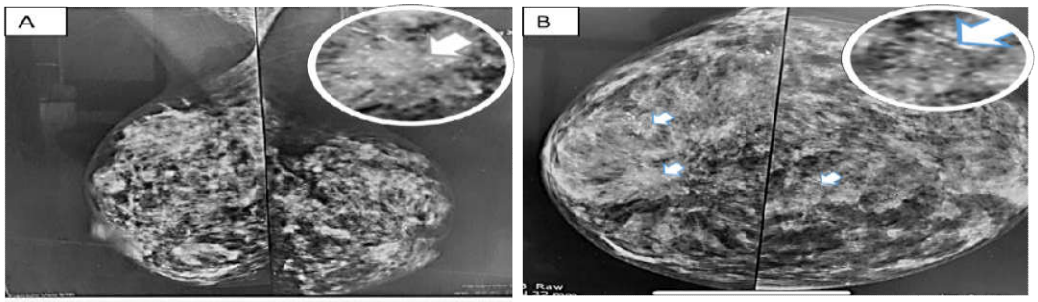

Figure 1: Mammography of a 45 years female with a synchronous breast cancer showing microcalcifications. A) MLO and B) CC mammography views showing multiple groups of micro calcifications seen in retro areolar area of right breast and two grouped of pleomorphic macrocalcification of left breast, both breasts associated with architecture distortion

Table 3: Ultrasound Findings and BI-RADS Categories for 58 bilateral Breast Cancers.

US findings	Index tumor (n=29)	%	Contra-lateral tumor (n=29)	%	P
Composition					
Homogenous	6	20.7	15	51.7	0.014
Heterogenous	23	79.3	14	48.3	
Type of lesion					
Area	2	6.9	12	41.4	0.005
Mass	27	93.1	17	58.6	
Size in mm (SD)	27.59 (11.9)	-	15.3 (9.54)	-	<0.0001
Mass margin					
Irregular	6	20.7	15	51.7	
Angulated	2	6.9	3	10.3	0.027
Indistinct	8	27.6	7	24.1	
Speculated	13	44.8	4	13.8	
Echo pattern					
Hypoechoic	27	93.1	17	58.6	0.005
Heterogenous	2	6.9	12	41.4	
Other features					
Skin thickening	10	34.5	4	13.8	-
Distortion	25	86.2	29	100	
Suspicious lymph node					
Absent	10	34.5	12	41.4	0.588
Present	19	65.5	17	58.6	
BI-RADS					
4b	3	10.3	8	27.6	0.009
4c	10	34.5	16	55.2	
5	16	55.2	5	17.2	

Mass density, associated calcification and lymph nodes were not significantly difference between the two groups (Figure 1). Mammographical BI-RADS classification for more than a half of index tumors was V compared to 27.6% of CBC in the same category. There was up to 27% of CBC in BI-RADS IVb category compared to only 6.9% of index cancer in the same category. The difference in BI-RDS (M) category, however, was not significant.

Sonography findings

Sonographic findings of CBC were significantly different from those of index cancer as summarized in Table 4. More than three quarters of index breast were of heterogenous composition compared to less than half of the contralateral breast (P=0.014). Nonmass hypoechoic area constituted 41.4% of CBC compared to 6.9% of index cancer (P=0.005); Figure 2.

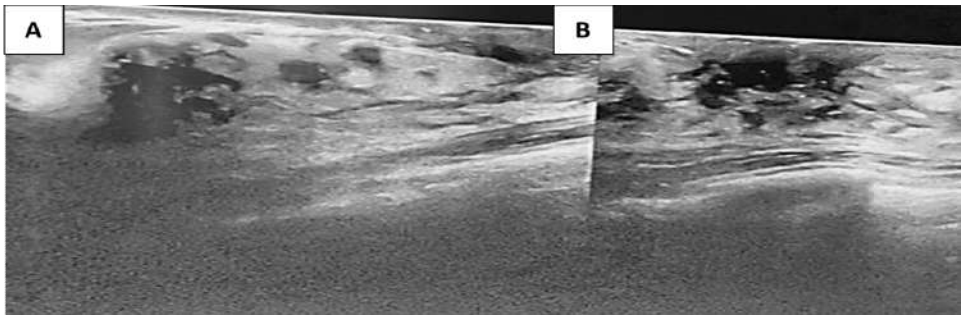

Figure 2 :Sonography of the synchronous breast cancer in figure 1. A) Right breast showing thick edematous skin with more than one hypoechoic area associated with retroareolar architecture distortion and UOQ ductal dilatation; B) Left breast showing two irregular outline hypoechoic area associated with architectural distortion.

Moreover, CBC lesions were significantly smaller than index tumors with mean diameter of 15.3 (9.54) vs 27.95 (11.9), P <0.0001. 51.7% of CBC were irregular with 24.1% had indistinct margin compared with 44.8% of index cancers which exhibited speculated margin, P=0.027. Heterogenous echo patten was more prevalent in CBC, 41.4% vs 6.9% of index cancer, P=0.005. Architectural distortion was a feature of all CBC with or without skin thickening which was also seen in 86% of index cancers. Axillary LN involvement was comparable in both groups. BI-RADS (US) classification of CBC included 17% category V compared to more than half of index tumor in the same category P=0.009.

Clinical, pathological and imaging characteristics of synchronous and metachronous cancers

Among women with synchronous breast cancer, the mean age at the time of diagnosis was 56.25 ranged (46-70) years, whereas the mean age of women with metachronous CBC at the time of index tumor diagnosis was 45.12 ranged between (22-61) years (P=0.001) with a mean disease-free period of 3.8 years.

Family history of having breast cancer was relatively similar in both types. Both synchronous and metachronous were more prevalent in the upper outer quadrant of the breast and the vast majority were of invasive ductal type. There was no significant difference between tumor grade or stage between the two types, however, 29.4% of metachronous were presented with distant metastasis at the time of diagnosis. Mammography and sonography BI-RADS classification was not significantly different between synchronous and metachronous CBC.

DISCUSSION:

The incidence of synchronous and metachronous CBC varies between the studies as a result of different definition used [8,1,12]. Radiological features of CBC were the focus of several studies to enable early diagnosis and better patient outcome [7, 8]. To our knowledge, this is the first study in Iraq comparing the radiological criteria of CBC to index breast cancer.

Young age, a breast cancer family history, and aggressive lobular tumors are CBC risk factors [13, 14]. In this study, more than one third of women with CBC were younger than 45 years when they

were diagnosed with the index tumor and more than half of them had a first-degree family member with breast cancer and 10% had lobular type index tumor. Women with synchronous breast cancer were 56.25 (46-70) when diagnosed. Mean age of women with metachronous CBC at index tumor identification was 45.12 (22-61) years with a 3.8-year disease-free duration. The typical age at initial diagnosis of metachronous illness is 52 years, according to Ozturk et al. [10] by Kheirelseid et al., [15], Diaz et al. [4], Liang et al (16). Patients with synchronous CBC in the same studies were much older. Our cohort's metachronous CBC patients were younger than reported. Alwan et al. revealed that breast cancer patients in Iraq are younger than in western nations, which may be due to biological and environmental causes[17,18].

Tumor type other than invasive ductal carcinoma constituted 13.4% of the index tumors. Lobular type which had a higher risk CBC, constituted 10.3% of index and 6.9% of the CBC. This was in the range of previously reported rates which range between 6%-13% [9,10,19]. Notably, the type and grade of synchronous and metachronous tumors were not usually consistent with those of index tumor confirming the different clonality and second neoplastic growth rather than a metastatic from the primary [20].

Approximately 86% of women sent for diagnostic imaging for their index tumor had a palpable breast lump, compared to 62.1 percent of CBC with no palpable mass and substantially lesser size. 11/29 (37.9%) of the CBC had a palpable lump, although three missed follow-up imaging and were diagnosed with distant metastases or locally progressed CBC. The lack of a screening program in Iraq and limited breast awareness among high-risk Iraqi women explain the high occurrence of diagnostic palpable index lesion. A South Korean study without breast cancer screening revealed similar results [9]. All synchronous CBC were nonpalpable lesions discovered by imaging at the index or early follow-up. In metachronous CBC, 8/17 (47%) had palpable lumps, underlining the necessity of clinical assessment with imaging in follow-up of patients after initial breast cancer therapy [21].

Mammographic surveillance of contralateral breast after mastectomy is recommended annually according to ACR guideline [21]. The role of mammography in early detection of CBC is established and many studies have previous looked into the CBC characterization of metachronous CBC in comparison to primary breast cancer. The mammographic density, in particular, has been proposed as a risk factor predictor for the development of CBC and may help in direct follow up and treatment plans. Sandberg et al.in their case control study proposed that more than 10% decrease in absolute mammographic density within the first two years after first diagnosis is associated with a significantly reduced risk of CBC [22]. Our results showed that more than half of the patients with CBC had heterogeneously dense breast, and as would be expected a mass was detected in only 48.3% of all CBC. Moreover, there was no obvious change in the breast composition at the time of metachronous CBC compared to primary diagnosis.

Although less than index tumor, mammograph was able to detect a mass in 48.3% of the cases. This could be due to 1) the significantly smaller size of CBC particularly in those on regular follow up 2) the high density of the CBC that obscure the small mass. Negative mammography is a common finding in CBC as previously reported[9]. Other studies pointed out that the mammographic signs of the index cancer were not consistently similar to the appearance of CBC [23]. In agreement with this, we found that the CBC margin appeared significantly different than index cancer. Microlobulation in 71.4% of CBC in contrast to 63% of index tumor which was speculated and associated with more architectural distortion.

Suspicious calcification whether pleomorphic linear or amorphous was more frequently seen in CBC (34.7%) compared to (13.8%) in index tumors although not significant, this finding was in line with other studies and confirming the important role of mammography [9].

Several studies examined the role of ultrasonography in diagnosing synchronous or metachronous CBC [25-29]. Sonography had a 60% sensitivity for identifying CBC before BI-RADS [28]. In 2008, another research confirmed the usefulness of whole breast US in finding CBC early, with 0.06 % false-negative results and 41.0 % PPV of biopsy referral rate (29). Recent research on the sonographic appearance of synchronous CBC found that it is similar to that of the index cancer, except for its posterior echogenicity and lower BI-RADS impression [9, 26]. Most US features were different from the index

tumor with reduced BI-RADS suspicion. Lesions on the contralateralbreast were smaller and more hypoechoic. For mass lesions, CBC had a heterogeneous echo pattern and irregular or indistinct margins. This underscores the necessity of careful entire US in breast cancer patients and looking for subtle suspicious findings during sonography [30].

CONCLUSION:

CBCs were prevalent in patients under 50 and with a breast cancer family history. Mammography and sonography found most CBC instances. Most of CBC cases were unpalpable when detected by mammography and or sonography. Most CBC masses had microlobulated margins and architectural distortion on mammography. Sonography shows CBC lesions as hypoechoic, irregular lumps.

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