CORRELATION BETWEEN ULTRASOUND BI-RADS 4 BREAST LESIONS AND FINE NEEDLE CYTOLOGY CATEGORIES IN A SAMPLE OF IRAQI FEMALE PATIENTS

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KORELACIJA IZMEĐU ULTRAZVUČNIH BI-RADS 4 LEZIJA DOJKI I CITOLOŠKIH KATEGORIJA DOBIJENIH TANKOM IGLOM NA UZORKU PACIJENTKINJA IZ IRANA

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Received/Primljen: 22.03.2021.

Accepted/Prihvaćen: 19.06.2021.

ABSTRACT

Background: Breast cancer is the most common malignancy in female and the most registered cause of women's mortality worldwide. BI-RADS 4 breast lesions are associated with an exceptionally high rate of benign breast pathology and breast cancer, so BI-RADS 4 is subdivided into 4A, 4B and 4C to standardize the risk estimation of breast lesions. The aim of the study: to evaluate the correlation between BI-RADS 4 subdivisions 4A, 4B & 4C and the categories of reporting FNA cytology results. Patients and Methods: A case series study was conducted in the Oncology Teaching Hospital in Baghdad from September 2018 to September 2019. Included patients had suspicious breast findings and given BI-RADS 4 (4A, 4B, or 4C) in the radiological report accordingly. Fine needle aspiration was performed under the ultrasound guide and the results were classified into five categories. The biopsy was performed for suspicious, malignant or equivocal FNA findings. Results: This study included 158 women with BI-RADS 4 breast lesions with the mean age of (44.6 years); There was a highly significant association between BI-RADS 4 breast lesion and FNA results ($p < 0.001$); 51.9% of BI-RADS IV-C had C5 FNA results. There was a highly significant association between BI-RADS 4 lesion and the final diagnosis ($p < 0.001$); 41.2% of BI-RADS 4 B had a malignant breast lesion, while 37.3% of BI-RADS 4 C had a malignant lesion. Conclusion: A clear relationship was observed between BI-RADS 4 subcategories and the fine needle aspiration cytology subgroups. BI-RADS 4-B is helpful in the discrimination between benign and malignant breast lesions; furthermore BI-RADS 4C has more acceptable validity in the diagnosis of breast malignancy. Therefore, BI-RADS subcategories are encouraged to be included and mentioned in the ultrasound report for more accurate estimation of the lesion nature.

Keywords: BIRADS 4 breast lesion, ultrasound, fine needle aspiration cytology.

SAŽETAK

Sažetak: Kancer dojke je najuobičajenija vrsta maligniteta kod žena i najveći registrovani uzrok mortaliteta kod žena širom sveta. BI-RADS 4 lezije dojki su povezane sa izuzetno visokom stopom benigne patologije dojki i kancerom dojki tako da su BI-RADS 4 dalje podeljene na 4A, 4B i 4C da bi se standardizovala procena rizika lezija dojki. Cilj studije: proceniti korelaciju između BI-RADS 4 podkategorija 4A, 4B i 4C i kategorija iz izveštaja rezultata FNA citologije. Pacijenti i metode: Studija serije slučajeva je sprovedena u nastavnoj bazi za onkologiju u Bagdadu od septembra 2018 do septembra 2019. Uključeni pacijenti su imali sumnjive nalaze na dojkama i BI-RADS 4 (4A, 4B, ili 4C) u radiološkom izveštaju shodno tome. Aspiracija finom iglom je izvedena uz ultrazvuk i rezultati su klasifikovani u pet kategorija. Biopsija je urađena kod sumnjivih, malignih ili nesigurnih FNA nalaza. Rezultati: Ova studija je uključila 158 žena sa BI-RAD 4 lezijama dojki između BI-RADS 4 lezija dojki i FNA rezultata ($p < 0.001$); 51.9% od BI-RADS IV-C su imale C5 FNA rezultate. Postojala je veoma značajna povezanost između BI-RADS 4 lezije i konačne dijagnoze ($p < 0.001$); 41.2% od BI-RADS 4 B su imale maligne lezije dojki, dok je 37.3% od BI-RADS 4 C imalo maligne lezije. Zaključak: Jasan odnos se može primetiti između BI-RADS 4 subkategorija i citoloških podgrupa dobijenih finom iglom. BI-RADS 4-C je od pomoci u razlikovanju između benignih i malignih lezija dojki; osim toga BI-RADS 4C ima prihvatljiviju validnost u dijagnozi maligniteta dojki. Stoga, BI-RADS podkategorije bi trebalo uključiti i pomenuti u ultrazvučnom izveštaju zbog preciznije procene prirode lezije.

KLjučne reči: BIRADS 4 lezije dojki, ultrazvuk, aspiraciona citologija finom iglom.

INTRODUCTION

Breast cancer is the most common malignancy in females and the most registered cause of women's mortality worldwide (1,2). Ultrasound has been an essential imaging modality for evaluation and characterization of breast lesions.

The fifth edition of the Breast Imaging Report and Data System (BI-RADS) was delivered by the American College of Radiology (ACR) (3) in order to standardize the risk estimation of breast lesions. In the ACR BI-RADS US lexicon, breast lesions of the category 4 have a 3–94% rate of malignancy and were subdivided into 4A, 4B and 4C. The category 4A may be used for a breast lesion that needs an intervention but has a low risk of malignancy (3–10%), the category 4B lesions has a moderate risk of malignancy (11–50%), The findings in this category need careful radiologic and pathologic correlation. Suggested follow-up with a benign result will rely on concordance. The category 4C lesions has a high probability for malignancy (51–94%) but it is not highly suggestive of breast cancer. This implies that BI-RADS 4 breast lesions are associated with a greatly variable risk of benign and malignant breast lesions (4), which might lead to a high rate of unnecessary biopsies.

US is the main diagnostic and screening tool for breast lesions. However, breast lesions with BI-RADS 4 assessment category tend to have an overlapping appearance and are sometimes difficult to identify (5,6), which may result in a high false positive rate, and subsequently unneeded biopsies and treatment (7).

There aren't many literature data evaluating the Correlation of BI-RADS 4 subcategories with FNA cytology results categories but there are many studies evaluating the correlation in general. A recent study by Zonderland et al showed that breast cancer was the biopsy result in (52.7%) of BI-RADS 4 lesions (8). Another study by Orel et al. revealed that 34% of BI-RADS 4 breast lesions proved to be cancer by guided biopsy (9). The PPV of BI-RADS 4 lesions in the previous literature data ranged from 6.2% to 52.7% (8,10,11).

By subdividing the category 4 lesions into 4A, 4B and 4C, it becomes possible to demonstrate significant probabilities for malignancy within this category so the patient and her physician can give an optimal decision regarding the management (12).

Fine needle aspiration cytology (FNAC) has become an important tool in the preoperative evaluation of breast pathology, and it has revealed high sensitivity, specificity and accuracy. It became popular and frequently needed due to its easy and quick approach, being cheap, and can be done without complications. The main indication for FNA cytology is to differentiate malignant from benign lesions (13). However, in some situations; the differentiation of benign and malignant breast lesions is difficult and sometimes not possible in FNA cytology. This difficulty arises when a specimen is

deficient or if there is overlapping in the morphological features of benign and malignant lesions (for example, low-grade carcinoma in situ and atypical ductal hyperplasia). Consequently, the cytological reporting was classified for further standardization and the characteristic features are demonstrated in cytological terms in order to overcome these challenging situations. The five-tier system was the most commonly used categorization, which includes five categories from insufficient materials (C1), benign category (C2), atypical finding (C3), suspicious for malignancy (C4), or frankly malignant (C5) (14). This cytological reporting system enables the cytopathologists to define the indeterminate areas, and the referring clinicians to recommend an additional investigation for example, excisional biopsy.

In the study of Sehgal et al ,37.5% of C3 cases were found to be malignant during the histopathological evaluation ("false negative") (15) . Also in other literature data, C3 category revealed a malignant diagnosis in 8.6–52% cases. Sehgal et al reported that 87.5% of C4 category cases had a malignant diagnosis, and 12.5% cases revealed a benign diagnosis during the histopathological examination. Many other studies showed that C4 breast lesions were found to have a malignant diagnosis during the histopathological study in the range of 81% to 97% (16, 17, 18).

The aim of the study: is to evaluate the correlation between BI-RADS IV subdivisions 4A, 4B & 4C and the categories of reporting FNA cytology results.

PATIENTS AND METHODS

Study design, location and patient selection

This case series study was conducted in the Oncology Teaching Hospital /medical city from September 2018 to September 2019. The study included 158 female patients who attended the Breast Clinic in the Oncology Teaching Hospital either for screening or diagnostic purposes. Those patients had suspicious findings and given BI-RADS 4 in the breast ultrasound report.

Sonography technique and lesion characterization

Each patient underwent the breast ultrasound using GE machine (Voluson E6 with linear transducer that had frequency of 7.5-12 MHz). The patient lies in the supine position with their hands on their heads. Both breasts and axillary regions are examined by the ultrasound for each patient. The suspicious breast findings were assessed by two expert radiologists and given BI-RADS 4. BI-RADS 4 are classified into BI-RADS 4A, 4B and 4C according to the descriptors of breast US BI-RADS lexicon 2013 that was mentioned in the introduction. The lesion characteristics include the mass, heterogeneous area, architectural distortion and peripheral ductal dilatation. The breast mass was assessed for its shape, margin, echogenicity and associated findings as skin thickening, nipple retraction, etc...

Fine needle aspiration technique and interpretation

Fine needle aspiration was performed for all patients under the ultrasound guide using 21-gauge needle. The site of the entry point on the skin was cleaned, then, the needle was inserted. The vacuum or negative pressure was generated in the needle and with in and out movement of the needle, the sample was taken. The material was placed on the slide then. The slide was stained with modified Papanicolaou stain. Then, the slides were reviewed on the microscope (Human Scope Premium 2006) by two cytopathologists.

The results of FNA cytology were classified into five categories from C1 to C5.

When the results of FNA are suspicious, malignant or equivocal, the biopsy was performed, then, the results of ultrasound and FNA were compared and analyzed.

Ethical consideration

The approval was taken from the scientific committee of the University of Baghdad

Written informed consent was taken from all included patients.

Statistical analysis

The collected data were analyzed statistically by the Statistical Package of Social Sciences software version 22. The Chi square and Fischer's exact tests were applied for analyzing the data as suitable. Two by two tables were used to acquire the validity findings of US-BIRADS in comparison to the final diagnosis. The level of significance (p value) was regarded statistically significant if it was 0.05 or less.

RESULTS

This study included 158 women presented with the mean age of (44.6 years) and range of 15-77 years; 27.8% of women were in the age group <40 years, 33.5% of them were in the age group 40-49 years, 19% of them were in the age group 50-59 years and 19.6% of them were in the age group of 60 years and more.

The ultrasound examination revealed that BI-RADS 4 A category was the most common category type which was found in (67.7%). The hypoechoic texture of the breast mass was the most common appearance found in about (52.5%). The right sided breast lesion (found in 50.6% of tumors) was more present than the left sided one. The upper outer quadrant was the most common site affected in breast (affected in 57%). Other ultrasound characteristics of breast lesions were illustrated in table 1.

Table 1. Ultrasound characteristics of women with BI-RADS 4 breast lesion.

Variable		No.	%
US-BI-RADS			
4A		107	67.7
4B		28	17.7
4C		23	14.6
US description of breast lesion			
Mass	Hypoechoic	83	52.5
	Heterogeneous	38	24.1
	Isoechoic	11	7.0
	Complex	9	5.7
Peripheral duct dilation		8	5.1
Intraductal pathology		7	4.4
Complicated cyst		2	1.3
Side			
Right		80	50.6
Left		78	49.4
Site			
Upper outer quadrant		90	57.0
Lower outer quadrant		13	8.2
Upper inner quadrant		25	15.8
Lower inner quadrant		9	5.7
Retroareolar		21	13.3
Total		158	100.0

The fine needle aspiration has results for women with a shown breast lesion C1 (5.1%), C2 (7%), C3 (59.5%), C4 (11.4%) and C5 (17.1%). According to the FNA results, mild atypia was observed in (23.4%), moderate atypia in (15.2%), severe atypia in (5.1%), mild to moderate atypia in (18.4%), mammary carcinoma in (17.7%), intraductal papillary lesion was present in (3.8%), fibroadenoma in (7%), fibrocystic changes in (2.5%) and granulomatous mastitis in (7%). The final diagnosis revealed a benign breast lesion in 67.7% of women and a malignant breast lesion in 32.3% of women.

No significant differences were observed between women with a benign breast lesion and women with a malignant breast lesion regarding their ages (p=0.1). (**Table 2**)

Table 2. Distribution of women's age according to the final diagnosis.

Variable	Final diagnosis				P
	Benign		Malignant		
	No.	%	No.	%	
Age					0.1 ^{NS}
<40 years	33	30.8	11	21.6	
40-49 years	39	36.4	14	27.5	
50-59 years	19	17.8	11	21.6	
≥60 years	16	15.0	15	29.4	

There was a highly significant association between US-BIRADS 4 breast lesion and the final diagnosis ($p<0.001$); 41.2% of BI-RADS 4B women had a malignant breast lesion, while 37.3% of BIRADS 4C women had a malignant lesion. A highly significant association was observed between a hypoechoic breast mass and malignancy ($p<0.001$). (**Table 3**)

Table 3. Distribution of ultrasound characteristics according to the final diagnosis.

Variable	Final diagnosis				P
	Benign		Malignant		
	No.	%	No.	%	
US-BIRADS					<0.001 ^s
4A	96	89.7	11	21.6	
4B	7	6.5	21	41.2	
4C	4	3.7	19	37.3	
US-lesion description					<0.001 ^s
Hypoechoic	43	40.2	40	78.4	
Heterogeneous hypoechoic mass	32	29.9	6	11.8	
Isoechoic	10	9.3	1	2.0	
Complex mass	5	4.7	4	7.8	
Peripheral duct dilation	8	7.5	0	-	
Intraductal pathology	7	6.5	0	-	
Complicated cyst	2	1.9	0	-	
Side					0.2 ^{NS}
Right	51	47.7	29	56.9	
Left	56	52.3	22	43.1	
Site					0.3 ^{NS}
Upper outer quadrant	62	57.9	28	54.9	

Variable	Final diagnosis				P
	Benign		Malignant		
	No.	%	No.	%	
Lower outer quadrant	6	5.6	7	13.7	
Upper inner quadrant	16	15.0	9	17.6	
Lower inner quadrant	6	5.6	3	5.9	
Retroareolar	17	15.9	4	7.8	

S=Significant, NS=Not significant.

There was a highly significant association between C4 and C5 FNA results of women with a breast lesion and malignancy ($p<0.001$). A highly significant association was observed between mammary carcinoma by the FNA results and the final diagnosis of breast cancer by biopsy ($p<0.001$). (**Table 6**)

Table 4. Distribution of cytology results according to the final diagnosis

Variable	Finaldiagnosis				P
	Benign		Malignant		
	No.	%	No.	%	
FNA results					<0.001 _s
C1	8	7.5	0	-	
C2	10	9.3	1	2.0	
C3	89	83.2	5	9.8	
C4	0	-	18	35.3	
C5	0	-	27	52.9	
FNA results					<0.001 _s
Mild atypia	37	34.6	0	-	
Moderate atypia	12	11.2	12	23.5	
Severe atypia	0	-	8	15.7	
Mild to moderate atypia	26	24.3	3	5.9	
Mammary car- cinoma	0	-	28	54.9	
Intraductal lesion	6	5.6	0	-	
Fibroadenoma	11	10.3	0	-	
Fibrocystic changes	4	3.7	0	-	
Granulomatous mastitis	11	10.3	0	-	

S=Significant, NS=Not significant.

The validity findings of BI-RADS 4 breast lesions (4A, 4B, 4C) in regard to the final diagnosis were demonstrated in table 5.

Table 5. The validity findings of US-BIRADS 4 subdivisions in comparison to the final diagnosis.

BIRADS	Sensitivity	Specificity	+ve PV	-ve PV	Accuracy
BIRADS 4A	21.6%	10.3%	10.3%	21.6%	13.9%
BIRADS 4B	41.2%	93.5%	75%	76.9%	76.5%
BIRADS 4C	37.3%	96.3%	82.6%	76.3%	77.2%

There was a highly significant association between BI-RADS 4 breast lesion and the FNA results ($p < 0.001$); 51.9% of BI-RADS 4C women had C5 FNA results, while 100% of BI-RADS 4A women had C1 FNA results. (**Table 6**).

Table 6. Distribution of the ultrasound BI-RADS 4 categories according to the FNA results categories.

Variable	FNA results										P
	C1		C2		C3		C4		C5		
	No.	%	No.	%	No.	%	No.	%	No.	%	
US-BIRADS											<0.001 ^s
4A	8	100.0	9	81.8	82	87.2	6	33.3	2	7.4	
4B	0	-	2	18.2	8	8.5	7	38.9	11	40.7	
4C	0	-	0	-	4	4.3	5	27.8	14	51.9	

S=Significant.

Figure 1. 45-year old female. On her breast ultrasound, there is a lobulated hypoechoic mass given BIRADS 4A. FNA was done and it shows a benign finding (C2).

Figure 2. 50-year old female on regular follow up. Her breast ultrasound showed an oval shaped hypoechoic mass with an indistinct margin given BI-RADS 4 A. FNA was done from the lesion and revealed mild atypia (C3).

Figure 3. 31-year old female with a family history of breast cancer. Her breast ultrasound showed a small ill-defined hypoechoic mass with an indistinct margin measuring (6x4mm) and given BI-RADS 4B. FNA was done and revealed suspicious findings (C4) and then proved to be malignant by a subsequent biopsy.

Figure 4. The breast ultrasound of 57-year old female showed an ill-defined hypoechoic mass in the UUQ of the right breast and given BRADS 4B. FNA of this lesion revealed malignant cells and proved to be malignant by a subsequent biopsy.

DISCUSSION

Breast carcinoma is the most common type of females' malignancies all over the world (19,20). Breast cancers represented 25% of all cancers and the main mortality cause for women. An early diagnosis of breast cancer is very important in the treatment that varies from lumpectomy to mastectomy. This precise diagnosis is mainly essential in the prevention of overtreatment or undertreatment with a poor prognosis (21).

The present study revealed a highly significant association between BI-RADS 4 of women with a breast lesion and the FNA results ($p < 0.001$); 51.9% of BI-RADS 4 C women had C5 FNA results, while 100% of BI-RADS 4A women had C1 FNA results. This finding is similar to the results of Khaleel et al., a retrospective study in Iraq, which found a significant correlation between the ultrasound and the fine needle aspiration cytology findings in BI-RADS 4 breast lesions (22). The fine needle aspiration was commonly

introduced for the assessment of palpable breast masses and it is done under the ultrasound guidance that made it as a novel diagnostic tool of a breast mass (23). Recently, the ultrasound guided-FNA is the main molecular diagnostic technique for breast cancer (24), while the morphological diagnosis of breast tumors was more valid by the core needle biopsy (25). The ultrasound imaging enables clinicians to recognize the nature and extent of a breast mass especially lesions with difficult localization by mammography and also the ultrasound is regarded as a complement imaging tool for mammography (26). Our study found higher validity findings of the ultrasound BI-RADS 4C for the diagnosis of breast cancer as compared to BI-RADS 4A and 4B (the accuracy was 77% as compared to 13.9% and 76.5%, respectively). These findings are in agreement with the results of Filho et al study in Brazil which reported higher validity records of the ultrasound BI-RADS 4C in the diagnosis of breast carcinoma (27). Raza et al study in the USA documented that

these subcategories helped in providing more informative internal audit, improving the radiologic-pathologic correlation and improving the image-directed research (28). Additionally, Mustafa study in Iraq showed high agreement with the likelihood of malignancy after the application of BI-RADS terms in the category 4 and 5 (29).

In the current study, a benign breast lesion was finally detected in 67.7% of women and a malignant lesion in 32.3% of them. This malignancy proportion is lower than the results of Abedarahman et al study in Iraq which found that 87.3% of suspicious benign lesions were a malignant breast mass as detected by histopathology (30). However, another Iraqi study carried out by Mustafa et al revealed that only 1.1% of women with suspicious lesions had a malignant breast mass (31). The ultrasound BI-RADS 4A was common BI-RADS in the present study with a highly significant association between BI-RADS 4C and breast malignancy. This finding is consistent with the results of Park et al study in South Korea which reported a significant concordance between BI-RADS 4C and a malignant breast mass in women with the negative mammography findings (32). Our study showed that a highly significant association was observed between a hypoechoic mass of women with a breast mass and malignancy ($p < 0.001$). Similarly, Gokhale study in India reported that a hypoechoic mass is linked commonly with breast malignancy (33). Inconsistently, Kim et al study in South Korea stated that not all hypoechoic masses indicate breast malignancy, some benign breast lesions are characterized by hypoechoic lesions (34).

The fine needle aspiration found that a common breast lesion was C3 (59.5%) with a highly significant association between C4 and C5 FNA results of a breast lesion and malignancy ($p < 0.001$). These findings are in agreement with the results of Arul et al study in India which found an obvious difference between FNA C3 and C4 results regarding benign and malignant breast lesions (35). In spite of these findings, the discrimination between FNA C3 and C4 is not easy due to the lack of specific diagnostic criteria (16). The present study revealed that the FNA results were commonly as mild atypia (23.4%), mild to moderate atypia (18.4%) and mammary carcinoma (17.7%), with a highly significant association between mammary carcinoma by FNA and the final diagnosis by biopsy ($p < 0.001$). This finding coincides with the results of Mendoza et al study in China (36).

CONCLUSION

A clear relationship was observed between BI-RADS 4 subcategories and the fine needle aspiration cytology subgroups. BI-RADS 4-B is helpful in the discrimination between benign and malignant breast lesions; furthermore BI-RADS 4C has more acceptable validity in the diagnosis of breast malignancy.

Therefore, BI-RADS subcategories are encouraged to be included and mentioned in the ultrasound report for more accurate estimation of the lesion nature.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

FUNDING SOURCE

This paper has no funding source

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