Positive Predictive Value Assessment of Malignancy in BI-RADS 4B and 4C Breast Lesions in Indian Scenario: A Tertiary Center Study

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Abstract

Breast Imaging Reporting and Data System (BI-RADS) is a standardized method of reporting breast pathology identified in breast imaging which is classified into seven categories (0-6) of which category 4 covers a wide range of likelihood of malignancy in between from 2-95% likelihood of malignancy. To improve clinical audits, category 4 is sub-categorized into 4A, 4B, and 4C categories. The positive predictive value for malignancies of BI-RADS 4B and 4C lesions in correlation with pathological diagnosis. This was a retrospective study conducted from June to May 2021 in the Integrated Breast Care Centre (IBCC) in AIIMS, Rishikesh, India. A total of 77 patients were classified as BI-RADS 4B and 4C lesions, 33 were classified as BI-RADS 4B, and 4C as BI-RADS 4C sub-categories.

Keywords: BI-RADS; PPV; Breast; Carcinoma; Biopsy; Pathological techniques

Introduction

Breast disorders are the most commonly diagnosed diseases in females in the present era, especially in India. Hence the evaluation and diagnosis of breast-related problems have progressed significantly over the past 15-20 years due to recent advances in imaging technology and Pathological techniques as well as increased interdisciplinary management of breast problems. "Breast cancer is the most common cancer identified in the Indian women accounting for about 27.7% of all the cancers in Indian women according to Globocan 2018"[1].Breast Imaging Reporting and Data System (BI-RADS) is a standardized method of reporting breast pathology identified in Breast Imaging (Mammography, Ultrasound, and MRI) which is classified into seven categories, from category 0–6 [2]. In this classification, BI-RADS category 4 is reserved for imaging findings that do not have the classic features of malignancy but are sufficient enough to justify a biopsy to rule out malignancy. BI-RADS category 3 represents a less than 2% likelihood of malignancy, while category 5 represents a 95% or more likelihood of malignancy therefore, category 4 covers a wide range of likelihood of malignancy in between from 2-95% likelihood of malignancy [3].To improve clinical audits, inter-communication with surgeons, pathologists, and Image-directed research, many facilities subdivide category 4 into BI-RADS 4A, 4B and 4C especially with 4B and 4C lesions having moderate to high (10-95%) suspicion for malignancy. There are limited studies in the research literature evaluating the positive predictive values and pathological results of 4A, 4B and 4C subcategories [4,5].

Objectives

this study aims to correlate Radiological diagnosis with the Pathological diagnosis of BI-RADS 4B and 4C lesions to assess the positive predictive value for malignancies of BI-RADS 4B and 4C lesions in correlation with pathological diagnosis.

Materials and Methods

This was a retrospective observational study conducted from September 2018 to August 2019 for 12 months in the Integrated Breast Care Centre (IBCC) established exclusively for patients related to breast diseases at AIIMS, Rishikesh in September 2018 in collaboration with other departments like Breast Imaging, Onco-Pathology and Radiation Oncology.

In these 12 months out of a total of 2567 patients, 77 patients were classified as BI-RADS 4B and 4C lesions by Radiologists based on imaging findings of which 33 were classified as BI-RADS 4B and 4C as BI-RADS 4C sub-categories.

Patients who presented to Breast clinic OPD with various complaints underwent triple assessment with a clinical examination followed by radiological assessment with imaging modalities like mammogram and ultrasonography. Based on ACR guidelines, ultrasonography was performed for patients <35 years, and a mammogram was performed in patients >35 years of age. Complimentary mammography or ultrasonography was done when needed. The imaging features were analyzed accordingly and classified 0 to 6.

Ultrasonogram was performed using high-frequency (4-12 MHz) linear probe of Esaote MyLab 9 eXP Diagnostic Ultrasound System, Model: MyLab Nine eXP scanner, and Mindray Z6. Mammography was performed using Hologic Selenia Dimensions, Hologic (USA).

Patients who were identified with breast lesions of BI-RADS category 4 and above on imaging underwent pathological assessment (FNAC and Trucut Biopsy with 14 Gauge needle) after informed consent. All the procedures were performed under image guidance by experienced radiologists. Pathology reports were issued by two senior pathologists with significant experience in breast pathology. Patients who had not given consent for procedures and lesions categorized 0, 1, 2, 3; 4A and 5 were excluded from ourstudy.

The radiological diagnosis was analyzed in correlation with pathological diagnosis to establish the positive (PPV) for malignancy in BI-RADS 4B and 4C breast lesions.

Statistical analysis

Our statistical analyses were performed using the SPSS software package version 26. All continuous and categorical variables were assessed for the values normal di stribution. The descriptive data were given as means ± SD. The Pearson chi-square test was used for the analytic assessment and the differences were considered to be statistically significant when the p-value was <0.05. Calculations were done by simple percentage and Positive Predictive Value (PPV) was calculated by the formula:

PPV=True positive/Total positive × 100.

Summary of concordance analysis

• Fleiss Kappa (Concordance between all 3 taken together)=0.544 (p<0.001)

• Cohen's Kappa (For Pairwise Concordance):

• FNAC with Biopsy: Kappa=0.867, p<0.001

• Kappa value interpretation Landis and Koch (1977):

• <0 : No agreement

• 0-0.20 : Slight

• 0.21-0.40 : Fair

• 0.41-0.60 : Moderate

• 0.61-0.80 : Substantial

• 0.81-1.0 : Perfect

Results

Of all patients included in this study, the Mean+SD of age in patients with BI-RADS 4B lesions was 42.97 ± 13.99 and 4C lesions were 47.82 ± 10.93 respectively (4C>4B). Family or past surgical history related to malignancy was noted in 14 (42.4%) and 10 (22.7%) of patients with 4B and 4C lesions. The Mean+SD duration of complaints was around 11.44 ± 11.63 months and 7.72 ± 11.39 months in patients with BI-RADS 4B and 4C lesions respectively noting more duration of symptoms noted in patients with 4B lesions. On clinical examination, a lump in the breast was noted in 29 (87.9%) and 41 (93.2%) of patients with BI-RADS 4B and 4C lesions respectively. The Mean+SD size of the lump palpable in BI-RADS 4B and 4C lesions was 3.36 ± 1.43 cm and 9.17 ± 14.00 cm respectively. (Tables 1 and 2).

There was a significant difference between the various groups in terms of the distribution of Biopsy ($X^2=18.827$, $p=<0.001$).

In the BI-RADS 4B group, 69.7% and 30.3% proved to be benign and malignant, respectively on biopsy. Similarly in the BI-RADS 4C group, 20.5% and 79.5% of the participants proved benign and malignant on biopsy respectively as in Table 3.

There was a near perfect agreement between the two methods, and this agreement wasstatisticallysignificant (Cohen's Kappa=0.867, p=<0.001) as in Table 4.

The disagreements observed between the two methods were as follows

2 (2.6%) cases classified as benign by biopsy, were classified as malignant by FNAC. 3 (3.9%) cases classified as malignant by biopsy were classified as benign by FNAC. In the cases which came as benign on biopsy however malignant on FNAC, a repeat biopsy was done using VABB, which also showed benign pathology, hence they were kept on short-term follow-up. The lesions which came malignant on core biopsy and benign on FNAC were treated like malignant lesions.

DISCUSSION

The Breast Imaging-Reporting and Data System (BI-RADS) was developed in the year 1985 tostandardize breast lesions reporting on imaging and follow-up [6]. Each abnormality in the breast is assessed systematically correlating with the patient's history and imaging findings finally into 6 BI-RADS categories. BI-RADS 4 category assigned to suspicious lesions, for which, there is a 2 to 95% likelihood of malignancy. A biopsy is routinely recommended in these cases. Therefore, in the ACR BI-RADS atlas, the suggestion now is to subdivide category 4 into three subgroups (4A, 4B and 4C) to better inform the referring surgeons and pathologists of the degree of concern. These subcategories also serve to accomplish a more informative internal audit, to improve radiological/pathological correlation, and image-directed research.

Out of all BI-RADS categorized lesions, category 4B is appropriate for lesions considered to have a moderate (10-50%) suspicion, and the 4C category has high (50-95%) suspicion of malignancy. These lesions are further subjected to biopsy for confirmation of the type of lesion which influences the treatment modality to the patient. Follow-up and correlation of pathological results are of the greatest importance in this subgroup because the range of lesion types may be fairly evenly distributed between benign and malignant, which in turn change the fate of these patients.

According to ACR guidelines, positive predictive values for BI-RADS 4 lesions are 2-95% for malignancy, of which 10-50% PPV for BI-RADS 4B lesions and 50-95% PPV for BI-RADS 4C lesions [7]. In a study of 186 BI-RADS 4 lesions, where 73 (39%) of them were histologically proven for malignancy, the appearance of subcategories 4A, 4B and 4C were 19.5%, 41.5%, and 74.3%, respectively[8].In another study, 2,430 patients with BI-RADS 4 lesions who were subjected to biopsy, found a prevalence of 18.6% of cancer. The PPV for cancer was 7.6% for BI-RADS 4A lesions, 37.8% for 4B and 81.9% for 4C lesions.

These findings were found to be comparable with our findings [9]. In a study, they found positive predictive values for malignancy in the categories as follows: BI-RADS 2: 0%, 3: 2%, 4: 30%, 5: 97%[10].In our study, we observed Positive Predictive Values (PPV) similar to other studies. 30.3% of the participants in the group BI-RADS 4B had biopsy malignant and 79.5% of the participants in the group BI-RADS 4C had biopsy malignant as in (Figures 1 and 2). This was per the recommended ACR guidelines.

It was found that other diagnoses excluding malignancy in BI-RADS 4B lesions were 7(30.4%) phyllodes tumor, 9(27.2%) fibro adenoma, 1(4.34%) fibrocystic disease, 1(4.34%) fibro adenomas, 2(6.06%) granulomatous mastitis and 3(9.09%) inflammatory conditions. Similarly, 3(6.81%) cases were found to be phyllodes tumor, 2(4.54%) fibrocystic disease, 2(4.54%) granulomatous mastitis, and 2(4.54%) inflammatory conditions observed in BI-RADS 4C breast lesions. These conditions can mimic malignancy on imaging which will lead to false positivity diagnosis on imaging.

Discordant benign are those lesions that have imaging features highly suspicious for malignancy but results in benign pathology on core biopsy as in Figure 3. The reported percentages of imaging-pathology discordant lesions among breast CNB in the literature range from 2 to 19.2% [11-15]. Benign lesions with spiculated findings (granular cell tumor, sclerosing adenosis, postsurgical scar, fat necrosis, mastitis, diabetic mastopathy, and sarcoidosis) can mimic malignancy on imaging [16-17]. However, approximately 4 to 30.9% of discordant lesions after USG guided biopsy are confirmed as cancer by subsequent surgical excision as in Figure 4 [14,15].

If there is concern regarding a discordant benign core biopsy, the radiologist needs to discuss with the interpretingpathologist and communicate about the discrepancy in both diagnoses. Based on that discussion, the radiologist should communicate with the referring surgeon, patient, and discuss the need for a repeat biopsy. In addition to surgical biopsy, USG guided VABB is a valuable alternative to surgical biopsy for these discordant lesions and the reported upgrade rate ranges from 4.6% to 22.7% in various studies [18-20]. Therefore, both surgical biopsy and USG guided VABB can be recommended for repeated biopsies of discordant benign lesions at USG guided biopsy, and the best biopsy method for that particular type of lesion should be chosen based on interdepartmental discussions between the radiologist, pathologist, surgeon, and finally with the patient. In our study, we had done similar inter-departmental discussions and alternative procedures like VABB and surgical excisional biopsy were performed based on the feasibility and necessity of these lesions (Figures 5 and 6).

Conclusion

The Positive Predictive Value (PPV) for BI-RADS 4B and 4C lesions, found in our study were according to the current ACR guidelines. Hence, sub categorizing these lesions into BI-RADS 4B and 4C was justified in our study. The cause of discordant benignity in our study were various lesions that can mimic malignancy on imaging, such as phyllodes tumor, fibro adenoma, fibrocystic disease, fibroadenomas, granulomatous mastitis, and inflammatory conditions. Hence, the existence of such lesions mimicking malignancy justifies the need of classifying suspicious lesions into BI-RADS 4B and 4C and not into the BI-RADS 3 or 5 categories on imaging.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2018; 68: 394-424.
2. Spak DA, Plaxco JS, Santiago L, Dryden MJ, Dogan BE, et al. BI-RADS® fifth edition: A Summary of Changes. Diagnostic and Interventional Imaging 2017; 98: 179-190.
3. D'Orsi CJ, Newell MS. BI-RADS decoded: detailed guidance on potentially confusing issues. Radiologic Clinics of North America 2007; 45: 751-763.
4. Wiratkapun C, Bunyapaiboonsri W, Wibulpolprasert B, Lertsithichai P. Biopsy rate, and positive predictive value for breast cancer in BI-RADS category 4 breast lesions. Medical Journal of the Medical Association of Thailand 2010; 93: 830.

5. Sanders MA, Roland L,Sahoo S. Clinical implications of sub categorizing bi-rads 4 breast lesions associated with microcalcification: a radiology–pathology correlation study. The Breast Journal 2010; 16: 28-31.
6. Luo WQ, Huang QX, Huang XW, Hu HT, Zeng FQ, et al. Predicting breast cancer in breast imaging reporting and data system (BI-RADS) ultrasound category 4 or 5 lesions: a nomogram combining radionics and BI-RADS. Scientific Reports 2019; 9: 1.
7. Abdullah N, Mesurolle B, El-Khoury M, Kao E. Breast imaging reporting and data system lexicon for the US: interobserver agreement for the assessment of breast masses. Radiology 2009; 252: 665-672.
8. Elverici E, Barça AN, Aktaş H, Özsoy A, Zengin B, et al. Nonpalpable BI-RADS 4 breast lesions: sonographic findings and pathology correlation. Diagnostic and Interventional Radiology 2015; 21: 189.
9. Yoon JH, Kim MJ, Moon HJ, Kwak JY, Kim EK. Subcategorization of ultrasonographic BI-RADS category 4: positive predictive value and clinical factors affecting it. Ultrasound in Medicine & Biology 2011; 37: 693-699.
10. Luo WQ, Huang QX, Huang XW, Hu HT, Zeng FQ, et al. Predicting breast cancer in breast imaging reporting and data system (BI-RADS) ultrasound category 4 or 5 lesions: a nomogram combining radionics and BI-RADS. Scientific reports 2019; 9: 1-1.
11. Youk JH, Kim EK, Kim MJ, Kwak JY, Son EJ. Analysis of false-negative results after US-guided 14-gauge core needle breast biopsy. European Radiology 2010; 20: 782-789.
12. Mihalik JE, Krupka L, Davenport R, Tucker L, Toevs C, et al. The rate of imaging-histologic discordance of benign breast disease: a multidisciplinary approach to the management of discordance at a large university-based hospital. The American Journal of Surgery 2010; 199: 319-323.
13. Kim MJ, Kim EK, Lee JY, Youk JH, Park BW,et al. Breast lesions with imaging-histologic discordance during US-guided 14G automated core biopsy: can the directional vacuum-assisted removal replace the surgical excision? Initial findings. European Radiology 2007; 17: 2376-283.
14. Son EJ, Kim EK, Youk JH, Kim MJ, Kwak JY, et al. Imaging-histologic discordance after sonographically guided percutaneous breast biopsy: a prospective observational study. Ultrasound in Medicine & Biology 2011; 37: 1771-1778.
15. Soyder A, Taşkın F, Ozbas S. Imaging-histological discordance after sonographically guided percutaneous breast core biopsy. Breast Care 2015; 10: 33-37.
16. Cho SH, Park SH. Mimickers of breast malignancy on breast sonography. Journal of Ultrasound in Medicine 2013; 32: 2029-2036.
17. Kim MJ, Kim D, Jung W, Koo JS. Histological analysis of benign breast imaging reporting and data system categories 4c and 5 breast lesions in the imaging study. Yonsei Medical Journal 2012; 53: 1203-1210.
18. Li JL, Wang ZL, Su L, Liu XJ, Tang J. Breast lesions with ultrasound imaging-histologic discordance at 16-gauge core needle biopsy: can re-biopsy with 10-gauge vacuum-assisted system get definitive diagnosis?. The Breast 2010; 19: 446-449.
19. Wang ZL, Liu G, Li JL, Su L, Liu XJ, et al. Breast lesions with imaging-histologic discordance during 16-gauge core needle biopsy system: would Vacuum-Assisted Removal get Significantly More Definitive Histologic Diagnosis Than Vacuum-Assisted Biopsy?. The Breast Journal 2011; 17: 456-461.
20. Sohn YM, Yoon JH, Kim EK, Moon HJ, Kim MJ. Percutaneous ultrasound-guided vacuum-assisted removal versus surgery for breast lesions showing imaging-histology discordance after ultrasound-guided core-needle biopsy. Korean journal of radiology 2014; 15: 697-703.

Table 1: Pathology details of benign lesions.

S.No	Total (77)	4B (33)	4C (44)
	Benign	23 (69.7%)	9 (20.5%)
1	Phyllodes tumor	7 (30.4%)	3 (6.81%)
2	Fibro adenoma	9 (27.2%)	0
3	Fibrocystic disease	1 (4.34%)	2 (4.54%)
4	Granulomatous mastitis	2 (6.06%)	2 (4.54%)
5	Inflammatory conditions	3 (9.09%)	2 (4.54%)
6	Fibro adenomas	1 (4.34%)	0

Table 2: Pathology details of malignant lesions.

S.No	Total (77)	4B lesion (33)	4C lesion (44)
	Malignant	10 (30.3%)	35 (79.5%)
1	Invasive ductal carcinoma	8 (80%)	28 (80%)
(A)	DCIS	0	1 (3.57%)
(B)	Grade 1	1 (12.5%)	2 (7.14%)
(C)	Grade 2	1 (12.5%)	12 (42.8%)
(D)	Grade 3	6 (75%)	13 (46.4%)
2	Invasive carcinoma (NST)	1 (10%)	0
3	Papillary carcinoma	1 (10%)	4 (11.4%)
4	Malignant phyllodes	0	1 (2.85%)
5	Mucinous carcinoma	0	1 (2.85%)
6	Poorly differentiated carcinoma	0	1 (2.85%)

Table 3: Association between BI-RADS and biopsy (n = 77)

Biopsy	BIRADS			Chi-Squared Test	
	4B	4C	Total	X^2	P-Value
Benign	23(69.7%)	9 (20.5%)	32 (41.6%)	18.827	<0.001
Malignant	10 (30.3%)	35 (79.5%)	45 (58.4%)		
Total	33 (100.0%)	44 (100.0%)	77 (100.0%)		

Table 4: Comparison of FNAC with biopsy (n = 77).

Biopsy		Biopsy			Cohen's Kappa	
		Benign	Malignant	Total	k	P-Value
FNAC	Benign	30(39.0%)	3 (3.9%)	33 (42.9%)	0.867	<0.001
	Malignant	2 (2.6%)	42(54.5%)	44 (57.1%)		
	Total	32(41.6%)	45(58.4%)	77(100.0%)		

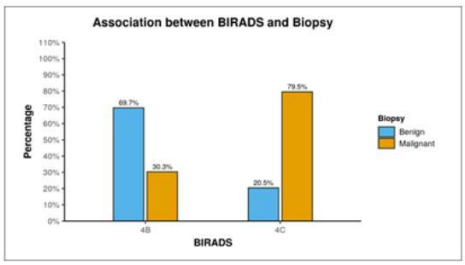

Figure 1 : Association between BI-RADS 4B and 4C lesions with biopsy.

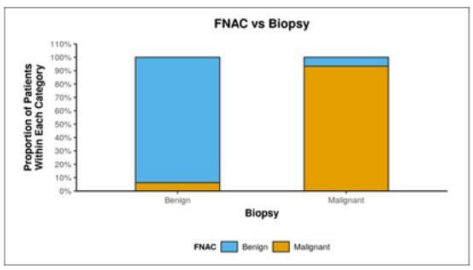

Figure 2 : Bar graph depicts the classification of cases by both the methods.

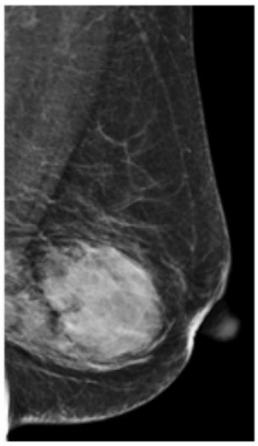

Figure 3 : Mammography and USG of BI-RADS 4B lesion (discordant benign).

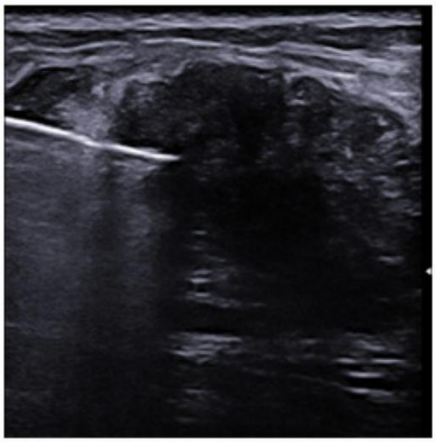

Figure 4 : Greyscale USG image shows a mult i-l obu ted, heterogeneously.

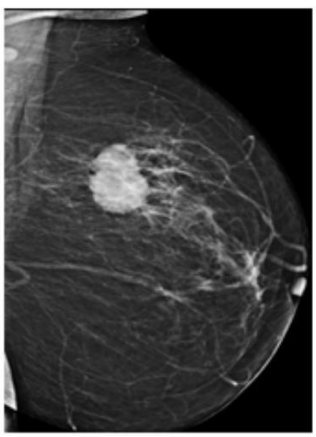

Figure 5 : Mammography and USG of BI-RADS 4C lesion (concordant malignant).

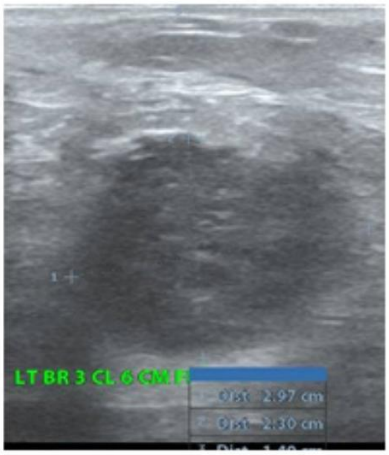

Figure 6 : Mammography and USG of BI-RADS 4C lesion (concordant malignant).