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Lesions of uncertain malignant potential in breast: Role of multiparametric MRI and histopathological correlation

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ABSTRACT

Objectives: This study aims to retrospectively evaluate the role of multiparametric magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, in predicting the histopathological upgrade of B3 breast lesions. The primary objective is to calculate the mean ADC values for B3 and B5 lesions. The secondary objective involves evaluating the kinetic enhancement patterns of these lesions.

Materials and Methods: This retrospective analysis includes patients who underwent MR mammography between 2019 and 2023 in our institution and subsequently underwent trucut biopsy and histopathologically proven to be either B3 or B5 category breast lesions.

Results: Student's t-test was used to find out the significant difference in ADC between the two groups. B5 lesions had lower mean ADC value ($0.8 \pm 0.2 \times 10^{-3}$ mm^2/sec, $p = 0.026$), whereas B3 lesions had higher mean ADC value ($1.1 \pm 0.3 \times 10^{-3}$ mm^2/sec, $p = 0.026$).

Conclusion: The multiparametric MRI including DWI in high-risk breast lesions would help in predicting their pathological behavior non-invasively. Identifying the mean ADC value and MR morphological characteristics in these lesions may guide clinicians in reducing misdiagnosis and over-treatment.

Keywords: ADC, DWI, High-risk breast lesions, Kinetic enhancement pattern, Lesions of uncertain malignant potential

INTRODUCTION

Carcinoma breast is a significant health concern worldwide, with early and accurate diagnosis being vital for effective management and improved patient outcomes. The diagnostic pathway for suspected breast malignancies typically involves imaging studies followed by core needle biopsy. Histopathological evaluation of biopsy samples categorizes breast lesions on a spectrum from B1 (normal) to B5 (malignant) based on their histologic characteristics. Among these categories, B3 lesions, also referred to as lesions of uncertain malignant potential or high-risk breast lesions, present a diagnostic challenge due to their variable association with malignancy.

B3 lesions encompass a diverse group of breast pathologies, including atypical epithelial proliferation of ductal type (atypical ductal hyperplasia or ADH), lobular intraepithelial

neoplasia (LIN), complex sclerosing adenosis/radial scar, papillary lesions (PL), flat epithelial hyperplasia (FEA), and fibroepithelial lesions with cellular stroma (Phyllodes tumor). The malignancy risk associated with these subtypes varies, with ADH demonstrating the highest rate of malignancy at 20–30%.[1] Despite being non-obligate precursors to breast malignancy, these lesions often necessitate further surgical excision due to the uncertainty surrounding their malignant potential.[2]

The conventional approach of histopathological evaluation is invasive and not without limitations. There is a growing need for non-invasive imaging techniques that can accurately predict the histopathological upgrade of B3 lesions to guide clinical decision-making. Multiparametric magnetic resonance imaging (MRI), incorporating diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, has shown promise in this regard. MRI provides excellent soft tissue contrast and functional imaging capabilities, which can enhance the characterization of breast lesions.[3]

The accurate diagnosis and management of breast lesions, particularly those of uncertain malignant potential (B3 lesions), have been the area of interest for several studies over the past few decades. The review of these studies outlines the progression of research in this field, emphasizing the role of multiparametric MRI in improving diagnostic accuracy and predicting the histopathological upgrade of high-risk breast lesions.[4]

In the early 2000s, the investigators commenced researching the prospect of advanced imaging techniques in breast cancer diagnosis. Mammography and ultrasound were the primary imaging modalities used, but their limitations in distinguishing benign from malignant breast lesions were apparent.[5] The introduction of MRI offered a new dimension for breast imaging due to its superior soft tissue contrast and ability to provide functional imaging information.

By the mid-2000s, DWI evolved as a valuable tool in breast imaging. Various studies emphasized the ability of DWI to distinguish between benign and malignant lesions based on the ADC values. Malignant lesions typically revealed lower ADC values owing to their highly cellular nature, which restricts the diffusion of water molecules.[6]

The concept of multiparametric MRI, combining DWI with dynamic contrast-enhanced MRI (DCE-MRI), gained attention in the 2010s. This approach provided complementary information for precise lesion characterization and improved diagnostic confidence.[7]

Recent studies have continued to investigate the abilities of multiparametric MRI in breast imaging. Advances in MRI technology, including higher field strengths and improved imaging sequences, have further accentuated the ability to characterize breast lesions. Research has increasingly focused on the specific imaging features that correlate with malignancy risk, aiming to develop non-invasive tools for predicting the histopathological upgrade of high-risk breast lesions.[8]

This study aims to assess the role of multiparametric MRI, including DWI with ADC mapping, in predicting the histopathological behavior of high-risk breast lesions. Specifically, the identification of typical kinetic enhancement pattern and ADC values of these lesions provide a non-invasive diagnostic tool that can reduce the need for unnecessary biopsies and surgeries, thus minimizing patient morbidity and healthcare costs.[9] By improving the accuracy of breast lesion characterization noninvasively, MRI could guide the clinician to provide more customized and appropriate management options.[10]

MATERIALS AND METHODS

This is a retrospective study conducted to evaluate the role of multiparametric MRI, including DWI with ADC mapping and kinetic enhancement patterns, in predicting the histopathological categorization of high-risk breast lesions (B3) and malignant lesions (B5). The study population consists of patients who underwent MR mammography at our institution from 2019 to 2023. A total of 200 patients who had undergone MR mammography during this period were initially considered. During this period, 80 cases were interpreted as ACR MR BIRADS categories 3 and 4. Of these 80 cases, 41 cases that were histopathologically proven to be either B3 or B5 category lesions were included in this study. The imaging analysis of MRI examinations included DWI with ADC mapping, assessment of enhancement pattern, kinetic curve, and morphological characteristics of B3 and B5 category lesions.

All MR mammography examinations were performed using a 1.5T MRI scanner with a dedicated breast coil. The MRI protocol included axial T1 and T2 weighted images, DWI with b-values of 0, 600, and 1200 s/mm^2, and DCE-MRI performed after intravenous administration of gadolinium-based contrast agent.

The imaging analysis focused on the following parameters: ADC mapping, morphological characteristics of the breast lesions, and kinetic enhancement pattern. ADC values were calculated from the DWI images. Regions of interest (ROIs) were placed on the lesion (area of ROI: 30 mm^2), avoiding necrotic or hemorrhagic areas, to measure ADC values.

The enhancement patterns of the lesions were assessed on DCE-MRI. Kinetic enhancement curves were classified into three types: progressive or persistent (Type I), plateau

(Type II), and washout (Type III). The morphological characteristics of the lesions like size, shape, margin, and internal enhancement characteristics were also evaluated.

Histopathological examination of biopsy samples was performed using standard protocols. Lesions were categorized into B3 (high-risk) and B5 (malignant) based on histological characteristics. The study focused on the following subtypes of B3 lesions: ADH, LIN, complex sclerosing adenosis/radial scar, PL, FEA, and fibroepithelial lesions with cellular stroma (Phyllodes tumor).

Statistical Analysis

Descriptive statistics were represented with frequency (percentage) and mean ± SD for the categorical and continuous factors, respectively. The normality of the data was checked by using the Shapiro-Wilk test. Student's *t*-test/Mann-Whitney U test was used to determine the significant ADC difference between the two independent groups. Chi-square/Fisher's exact test determined the association between two independent categorical factors. *P*-value < 0.05 was considered as statistically significant. All the statistical analysis was done using the statistical software SPSS (IBM, 28.0).

RESULTS

The study included 41 patients with ACR MR BIRADS category 3 or 5 lesions, with the majority aged between 31 and 60 years. Histopathologically, 73.2% of lesions were classified as B3, while 26.8% of lesions were classified as B5 (malignant). Lesions predominantly had irregular shapes (41.5%) and irregular margins (46.3%), and the majority were ≤10 mm in diameter (46.3%). Most lesions displayed a mass-like enhancement pattern (90.2%) and type II kinetic curves (78%) [Table 1].

Table 1: Descriptive statistics.

Parameters	(*n*=41), *n*(%)
Age (in years)	
20–30	2 (4.9)
31–40	11 (26.8)
41–50	11 (26.8)
51–60	12 (29.3)
>60	5 (12.2)
Maximum diameter of the lesion	
≤10 mm	19 (46.3)
>10 mm	18 (43.9)
Non-mass enhancement	4 (9.8)
Shape	
Irregular	17 (41.5)
Oval	16 (39)
Round	4 (9.8)
Non-mass enhancement	4 (9.8)
Margin	
Irregular	19 (46.3)
Circumscribed	12 (29.3)
Spiculated	6 (14.6)
Non-mass enhancement	4 (9.8)
Enhancement pattern	
Mass like	37 (90.2)
Non-mass like	4 (9.8)
Kinetic curve	
Type I	5 (12.2)
Type II	32 (78)
Type III	4 (9.8)
Histopathological category	
B3-Lesion of uncertain malignant potential	30 (73.2)
B5-Malignant	11 (26.8)

Table 2 compares various morphological characteristics and mean ADC values between B3 (lesions of uncertain malignant potential) and B5 (malignant) histopathological categories among 41 patients. Significant differences were found in the maximum diameter of the lesion, with most B5 lesions being >10 mm (90.9%, $p = 0.001$), and lesion margins, with a higher proportion of irregular margins in B5 lesions (81.8%, $p = 0.047$). B5 lesions had lower mean ADC values ($0.8 \pm 0.2 \times 10^{-3}$ mm^2/sec, $p = 0.026$), whereas B3 lesions had high mean ADC values ($1.1 \pm 0.3 \times 10^{-3}$ mm^2/sec, $p = 0.026$). More number of malignant lesions were found in patients aged above 40 years. Most of the malignant lesions showed a type II pattern of kinetic curve, and two malignant lesions showed a washout (type III) pattern. The lesions of uncertain malignant potential (B3 category) were predominantly smaller in size (60% of the lesions measured ≤10 mm in maximum diameter), round or oval in shape (56.7%) with circumscribed margins (36.7%), and type II pattern of the kinetic curve (83.3%). Two of the B3 category lesions showed a washout pattern of kinetic curve. Morphological characteristics like size, shape, and margins were not analyzed for the lesions that showed non-mass enhancement on DCE-MRI.

DISCUSSION

Carcinoma breast is the second most common cause of cancer-related mortality.[11] During the evaluation of suspicious MR mammographic findings, a needle biopsy can reveal non-malignant breast lesions, atypia, carcinoma in situ, and invasive carcinoma. Histological examination of the lesions with uncertain malignant potential (B3) is important to aid early detection and treatment of breast cancer.[12] To prevent unnecessary surgical interventions for benign conditions, there is a need for a standardized imaging approach that can improve the accuracy of noninvasive diagnosis in clinical practice.[13] B3 lesions, although not definitive precursors to malignancy, can progress into high-grade lesions, primarily ductal carcinoma

Table 2: Comparison between parameters and histopathological category.

Parameters	Histopathological category, *n* (%)		*P*-value
	B3-Lesion of uncertain malignant potential (*n*=30)	B5-Malignant (*n*=11)	
Age (in years)			
20–30	1 (3.3)	1 (9.1)	0.312#
31–40	9 (30)	2 (18.2)	
41–50	6 (20)	5 (45.5)	
51–60	9 (30)	3 (27.3)	
>60	5 (16.7)	-	
Maximum diameter of the lesion			
≤10 mm	18 (60)	1 (9.1)	0.001#
>10 mm	8 (26.7)	10 (90.9)	
Not applicable for non-mass enhancement	4 (13.3)	-	
Shape			
Irregular	9 (30)	8 (72.7)	0.082#
Oval	14 (46.7)	2 (18.2)	
Round	3 (10)	1 (9.1)	
Not applicable for non-mass enhancement	4 (13.3)	-	
Margin			
Irregular	10 (33.3)	9 (81.8)	0.047#
Circumscribed	11 (36.7)	1 (9.1)	
Spiculated	5 (16.7)	1 (9.1)	
Not applicable for non-mass enhancement	4 (13.3)	-	
Enhancement pattern			
Mass like	26 (86.7)	11 (100)	0.559#
Non-mass like	4 (13.3)	-	
Kinetic curve			
Type I	3 (10)	2 (18.2)	0.380#
Type II	25 (83.3)	7 (63.6)	
Type III	2 (6.7)	2 (18.2)	
ADC			
Mean ± SD	1.1 ± 0.3	0.8 ± 0.2	0.026*
Range	0.6 – 1.9	0.6 – 1.1	
ACR MRI BIRADS category			
BIRADS 3	18 (60)	3 (27.3)	0.085#
BIRADS 4	12 (40)	8 (72.7)	

*Student's *t*-test/Mann-Whitney U test; #Chi-square/Fisher's exact test. ADC: Apparent diffusion co-efficient, SD: Standard deviation, ACR: American college of radiology, BIRADS: Breast imaging reporting and data system, MRI: Magnetic resonance imaging.

in situ (DCIS), and less commonly into low-grade invasive tumors. They also act as risk indicators, with atypia diagnoses increasing the likelihood of developing breast cancer in any part of the same breast or the opposite breast.[14]

Performing MR mammography in conjunction with core needle biopsy or vacuum-assisted breast biopsy (VABB) for patients diagnosed with high-risk lesions has been shown to significantly reduce the need for surgical intervention.[15] This strategy facilitates accurate characterization of the breast lesions and thereby reduces unwarranted surgeries. Multiparametric DCE-MRI provides ample information about the lesion's morphologic characteristics, kinetic enhancement pattern, and DWI, which helps in discerning benign lesions from malignant ones.[16] The utilization of DCE-MRI to analyze morphology and kinetic enhancement patterns of breast lesions and DWI with ADC mapping proposes paramount insight into the treatment planning of high-risk breast lesions.[17,18]

In 2014, Hussein *et al.*[3] conducted a study evaluating the role of DCE-MRI in assessing high-risk breast lesions. Their study could not demonstrate any statistically significant difference between the mean ADC value of high-risk breast lesions and malignant lesions. However, the study concluded that multiparametric DCE-MRI, including DWI and ADC mapping, provided complementary data crucial for analyzing high-risk breast lesions and predicting their histological upgrade rate.[3] This investigation emphasized the importance of incorporating multiparametric DCE-MRI to improve the precise assessment of high-risk breast lesions.

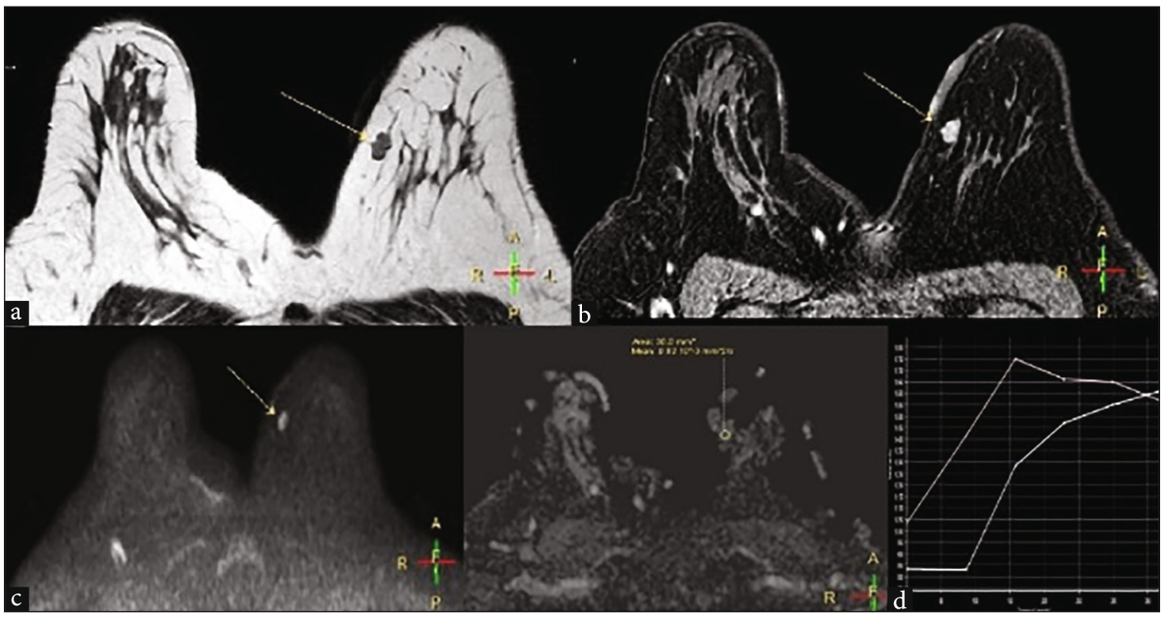

Figure 1: A 42-year-old female with a lump in the left breast and family history of breast cancer. (a) Axial T2WI and (b) Axial T1W fat-saturated post-contrast imaging show an irregular lobulated enhancing lesion in left breast—(yellow arrows), (c) Diffusion weighted imaging with apparent diffusion co-efficient value of 0.82×10^{-3} mm^2/sec (yellow arrow). (d) Type III kinetic curve pattern. Histopathology: invasive carcinoma with mucinous features—B5 category (Images not provided).

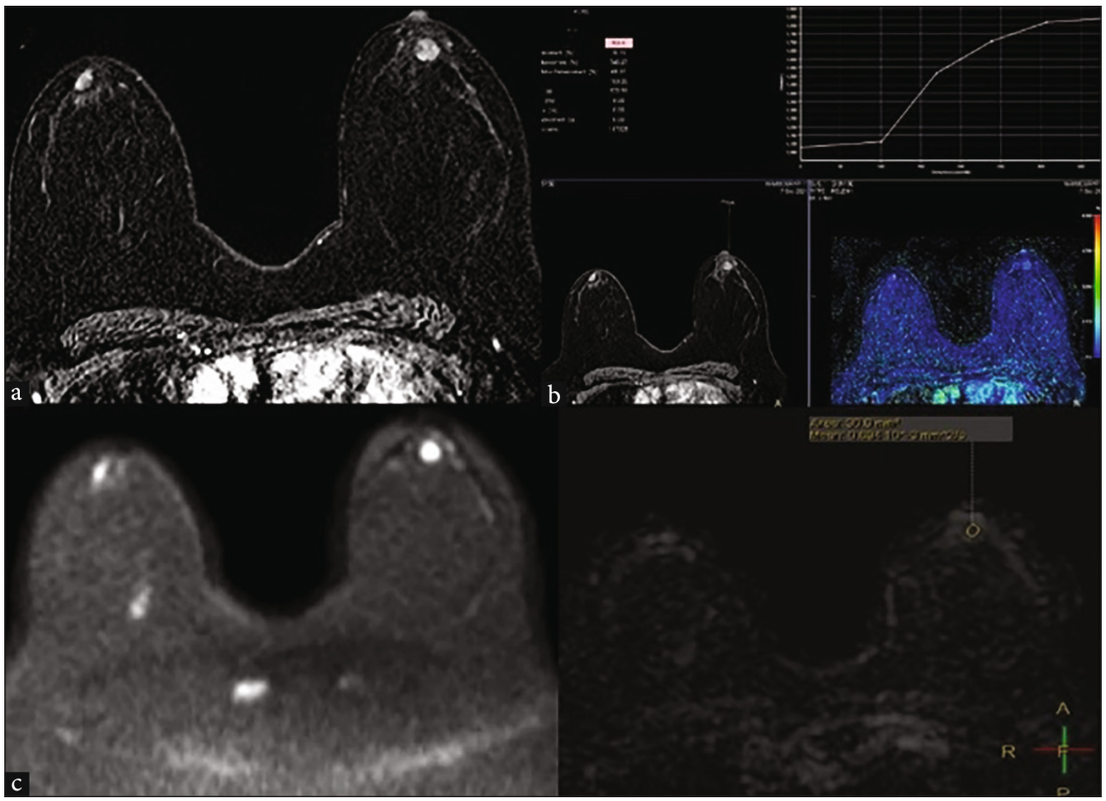

Figure 2: A 26-year-old female with complaints of bilateral breast lumps and a positive family history of breast cancer. (a) Axial T1W fat-saturated post-contrast imaging shows microlobulated enhancing lesion in the subareolar region of the left breast, (b) Type I kinetic curve pattern, (c) Diffusion weighted imaging with apparent diffusion co-efficient value of 0.69×10^{-3} mm^2/sec. Histopathology: ductal carcinoma in situ—B5 category (images not provided).

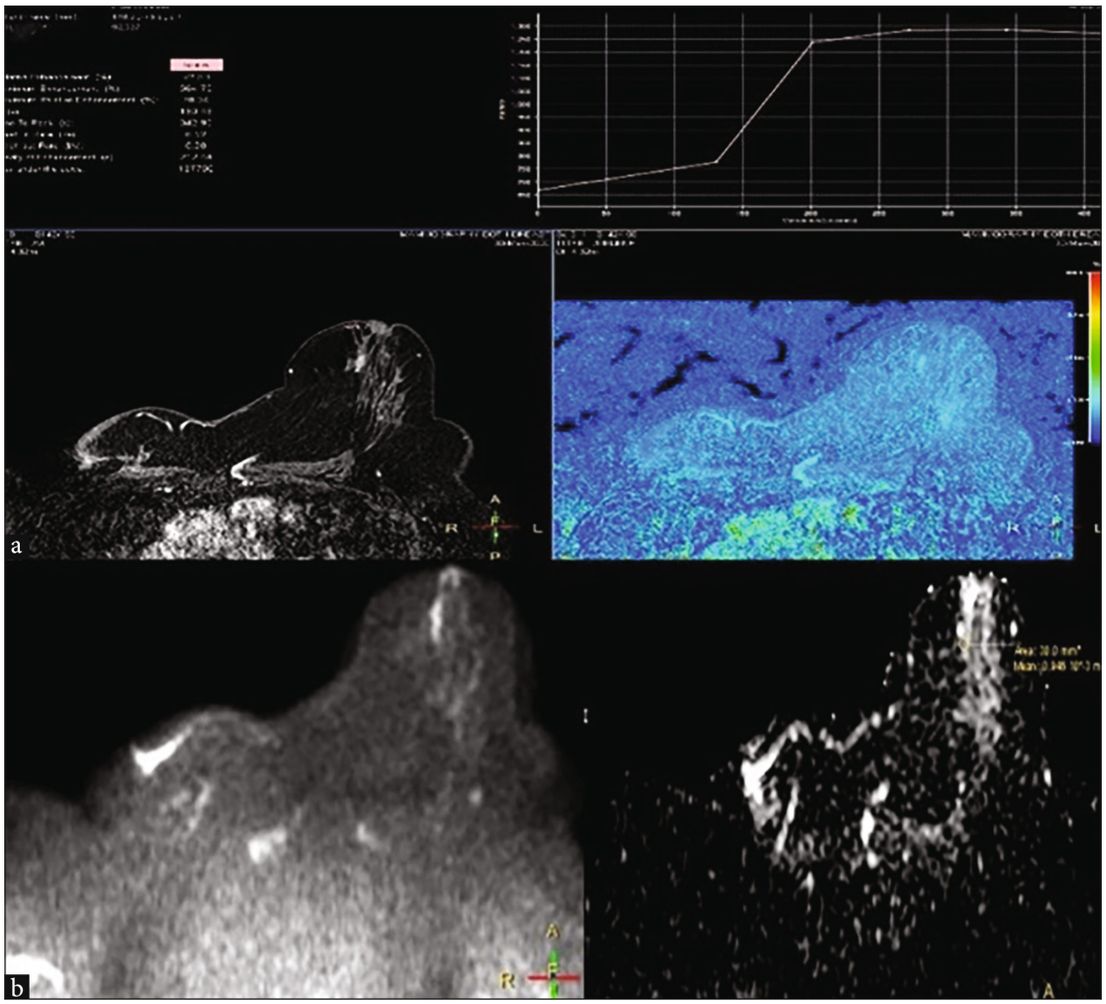

Figure 3: A 62-year-old patient with a past history of right breast malignancy status post-treatment, with complaints of left breast nipple discharge. (a) Axial T1W fat-saturated post-contrast imaging shows an enhancing lesion in the subareolar region of the left breast with type II kinetic curve pattern, (b) Diffusion weighted imaging with apparent diffusion co-efficient value of 0.94×10^{-3} mm^2/sec. Histopathology: intraductal papilloma with no significant atypia—B3 category (Images not provided).

The correlation between imaging features and histopathological outcomes has been a vital area of research. In 2016, Santucci *et al.*[4] analyzed the X-ray mammographic and MRI features of B3 category breast lesions and their histopathological correlation. Their analysis concluded that B3 lesions are associated with specific mammographic and MR imaging features. The ability to foresee the pathological behavior of B3 lesions noninvasively could greatly help clinicians provide customized treatment strategies.[4] This study underscored the prospect of imaging findings to guide clinical decisions and minimize the necessity of invasive procedures.

DWI and ADC are potentially useful in predicting the pathological behavior of high-risk breast lesions. Our study demonstrated that the mean ADC of high-risk breast lesions (B3) was significantly higher than that of malignant lesions (B5). Most of the malignant lesions in our study measured more than 10 mm in maximum diameter and had irregular size and shape, whereas B3 lesions were predominantly smaller in size (≤10 mm) with round- or oval-shaped and circumscribed margins. Our study could not demonstrate a statistically significant difference between the kinetic enhancement pattern of malignant lesions and lesions of uncertain malignant potential.

A few of the cases from our study with representative images have been described below. Figure 1 shows an irregular soft tissue signal intensity lesion in the 10–11 o'clock position of the left breast with lobulated margins and a type III time kinetic curve. The lesion measured approximately 15 mm in maximum diameter, and the mean ADC value was 0.82×10^{-3} mm^2/sec. It was reported as ACR MRI BIRADS

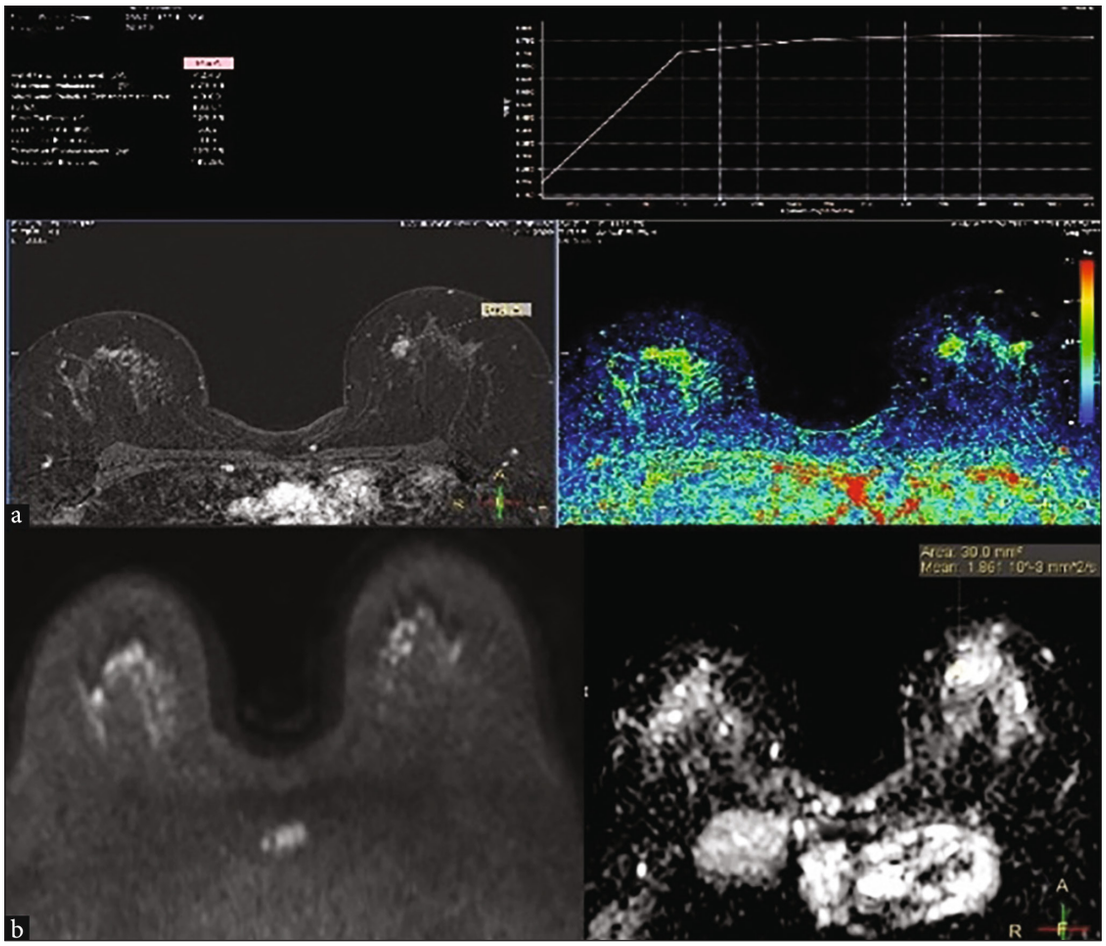

Figure 4: A 42-year-old female with a cluster of punctuate microcalcifications in the left breast on routine X-ray mammography. (a) Axial T1W fat-saturated post-contrast imaging shows a lobulated enhancing lesion in the 9 o'clock position of the left breast with type II kinetic curve. (b) Diffusion weighted imaging with apparent diffusion co-efficient value of 1.86×10^{-3} mm^2/sec. Histopathology: proliferative breast disease with fibrosis, sclerosing adenosis, and negative for in situ or invasive carcinoma—B3 category (Images not provided).

category 4 and was recommended for histopathology evaluation. Subsequently, the lesion was proven to be malignant on core needle biopsy, with histology being invasive carcinoma with mucinous features (B5 category).

MR mammography performed on another young female aged 26 years with complaints of lumps in both breasts revealed multiple bilateral nodular lesions demonstrating restricted diffusion and type I kinetic curve [Figure 2]. A few of the lesions showed internal cystic areas and microlobulated margins. MRI was suggestive of bilateral cellular fibroadenomata and categorized as ACR MRI BIRADS category 3. In view of the family history of breast cancer and the cellular nature of the lesions, histopathological correlation of lesion with microlobulated margins in the subareolar region of the left breast was recommended. The lesion measured 13 mm in maximum diameter, and the ADC value was 0.69×10^{-3} mm^2/sec. This lesion was later histologically proven to be ductal carcinoma in situ (B5 category).

Figure 3 depicts MR mammographic imaging of a 62-year-old patient who had a history of right breast malignancy—status post-right mastectomy and chemoradiation, presented with complaints of left breast nipple discharge. The MRI revealed a round intraductal lesion with smooth margins and a maximum diameter of 1.4 cm in the 9 o'clock position of the subareolar region of the left breast. The lesion showed a type II pattern of the kinetic curve on dynamic contrast-enhanced imaging and an ADC value of 0.94×10^{-3} mm^2/sec. It was reported as ACR MRI BIRADS category 3, and a trucut biopsy was performed in view of the history of malignancy in the right breast. The HPE of this lesion was suggestive of intraductal papilloma with no significant atypia (B3 category).

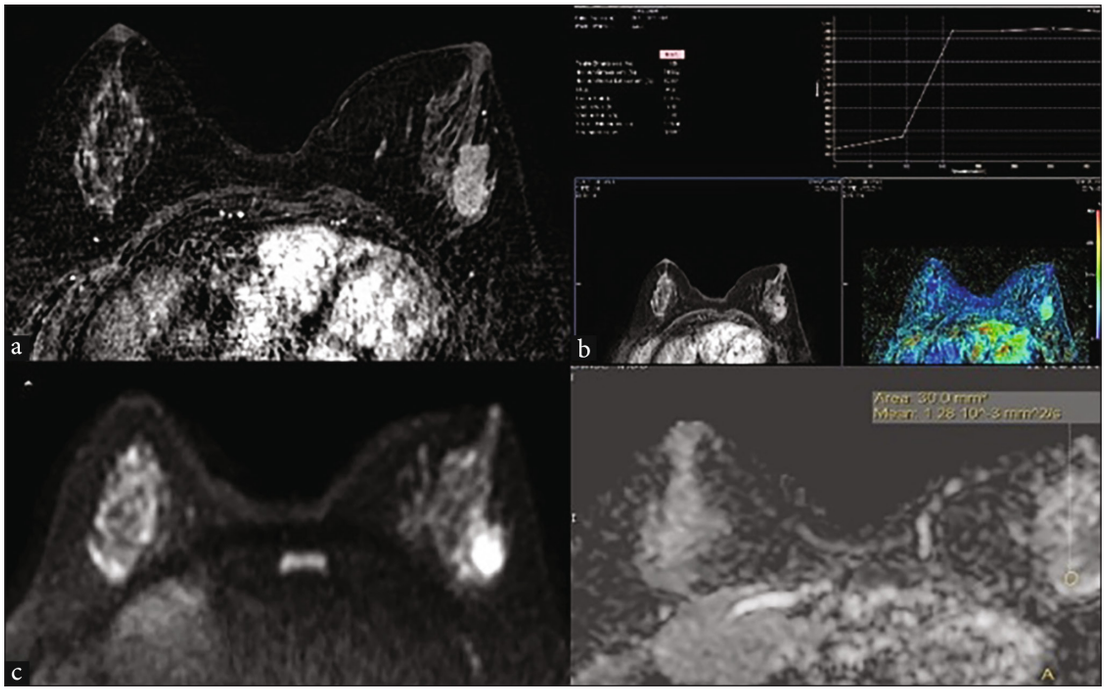

Figure 5: A 41-year-old patient who presented with a 2-month history of bleeding from the left nipple. (a) Axial T1W fat-saturated post-contrast imaging shows a lobulated enhancing lesion in 4 o'clock position of the left breast, (b) Type II kinetic curve, (c) Diffusion weighted imaging with apparent diffusion co-efficient value of 1.28×10^{-3} mm^2/sec. Histopathology: complex papillary epithelial proliferation with focal mild atypia—B3 category (Images not provided).

A 42-year-old patient underwent MR mammography in view of a cluster of punctuate microcalcifications in the left breast on routine X-ray mammography. A lobulated enhancing lesion with a maximum diameter of 13 mm, demonstrating restricted diffusion, and type II pattern of enhancement curve was observed in the 9 O'clock position of the left breast along the ductal course with adjoining duct ectasia. The ADC value was 1.86×10^{-3} mm^2/sec [Figure 4]. A biopsy was performed to rule out papillary lesions, and the histopathology was suggestive of proliferative breast disease with fibrosis, sclerosing adenosis, and negative for in situ or invasive carcinoma (B3 category).

Figure 5 demonstrates a 41-year-old patient who presented with a 2-month history of bleeding from the left nipple. MRI revealed a lobulated lesion of size 2.0 cm in the 4 o'clock position of the left breast with anterior ductal extension to nipple-areolar complex, type II kinetic curve, and ADC value of 1.28×10^{-3} mm^2/sec (ACR MRI BIRADS category 4). The histopathology of this lesion was suggestive of complex papillary epithelial proliferation with focal mild atypia (B3 category).

CONCLUSION

The correlation between imaging and pathological findings is essential for planning the appropriate management of high-risk breast lesions. Multiparametric dynamic contrast-enhanced MRI, incorporating DWI and ADC mapping, plays a significant role in noninvasively predicting the pathological behavior of high-risk breast lesions. These advanced and comprehensive imaging techniques, help us to design lesion-specific, customized treatment strategies to minimize the risk of misdiagnosis and prevent overtreatment.

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Ethical approval

The research/study approved by the IEC at Apollo Hospitals, Chennai, IEC-BMR application number: ASH-C-S-026/17-10-2023.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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