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ORIGINAL ARTICLE

Diffusion magnetic resonance imaging of breast lesions: Initial experience at Alexandria University

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Abstract *Objective:* The purpose of our study was to investigate whether adding diffusion weighted imaging (DWI) to dynamic contrast-enhanced MRI (DCE-MRI) could improve specificity and the positive predictive value (PPV) of breast MRI in differentiating benign and malignant focal breast mass lesions.
Materials and methods: The prospective study included 71 females with 103 focal breast lesions on DCE-MRI who underwent subsequent biopsy. DWI was acquired during diagnostic breast MRI using $b = 0$, 400 and 800 s/mm^2. Apparent diffusion coefficient (ADC) values were compared for benign and malignant lesions. Sensitivity and PPV were calculated for DCE-MRI alone (based on biopsy recommendations) and DCE-MRI plus DWI (adding an ADC threshold) for the same set of lesions.

Abbreviations: MRM, magnetic resonance mammography; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; CC, cranio-caudal; MLO, medio-lateral oblique; PPV, positive predictive value; DCE-MRI, dynamic contrast enhanced magnetic resonance imaging

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Results: On pathological basis, 57 out of 103 focal lesions were benign and the remaining revealed, 45 were malignant and one borderline. Malignant lesions exhibited lower mean ADC ($< 1.3 \times 10^{-3}$ mm^2/s) than benign lesions ($> 1.3 \times 10^{-3}$ mm^2/s). Applying an ADC threshold of 1.3×10^{-3} mm^2/s sensitivity increased (on conventional DCE-MRI basis) from 86.95% up to 93.47% and the specificity from 91.22% to 96.49% in detection of malignancy with PPV of 95.55% in comparison to 86.95% for enhancement kinetics alone, which would have avoided biopsy for 10.5% (6/57) of benign lesions without missing any cancers.

Conclusion: DWI shows potential for improving the PPV of breast MRI for detection of malignant breast lesions.

Recommendation: Furthermore, larger studies should be made to use it as a monitor for tumor response to chemotherapy.

1. Introduction

Radiologists who practice breast imaging have long known that the field provides observational and interpretative challenges second to no other area of radiology. The discipline of breast imaging is changing rapidly; the updates on the state-of-the-art technology as well as fortifying the basic concepts of breast imaging have been refined and improved over the prior 10–15 years.[1]

The medical imaging department at our institution, the Alexandria University, has first introduced the magnetic resonance mammography (MRM) 5 years ago. Ever since, it has been thoroughly under investigation particularly as it is an important component of a still ongoing national breast imaging program, which started in 2009 by screening for early detection of breast cancer using digital mammography, with special reflection on the population pool of the Alexandria district.

Magnetic resonance mammography (MRM) is emerging as an important tool for the detection and characterization of breast cancer.[2] Additional lesions seen by MRI that are not visible on the mammogram have been reported to be present between 27% and 37% of patients.[3] This value is derived primarily from the high sensitivity of contrast material enhancement in the detection of breast cancer. Still, the characterization of lesions as benign or malignant on the basis of MR imaging characteristics remains a challenge.[4,5]

Studies in varying patient populations, using different equipment, techniques, and interpretation criteria have yielded sensitivities generally greater than 90%, but greatly varying specificities.[6–8] The improved sensitivity of MRI over conventional imaging studies and clinical examination should allow more accurate delineation of cancers and better treatment planning. However, if the specificity is low, many additional biopsies—with the added cost and needless patient anxiety—will result.[9]

Diffusion weighted imaging (DWI), an MRI sequence, explores the random motion of water molecules in the body. Water molecules held in a container outside the body are in constant random Brownian motion. This uninhibited motion of water molecules is free from diffusion. By contrast, the movement of water molecules in biologic tissues is restricted because their motion is modified and limited by interactions with cell membranes and macromolecules. The apparent diffusion coefficient (ADC) values are measured to estimate the degree of diffusion. The degree of restriction to water diffusion in biologic tissue is inversely correlated to the tissue cellularity and the integrity of cell membranes. The motion of water molecules is more restricted in tissues with a high cellular density associated with numerous intact cell membranes.[10,11]

Malignant lesions, in general, have more tightly packed cells with a more compact architecture and, consequently, have lower ADC values as compared with benign lesions. There is inhibition of effective movement of water molecules and restricted diffusion in dense malignant lesions. The higher ADC values of cystic or necrotic areas reflect a lack of significant restriction of diffusion of water. False-negative values can be obtained in cystic/necrotic malignancies.[9,12–14]

Measurement of the ADC provides a quantitative estimate of the restrictive nature of the motion of water molecules within tissue for each voxel in a diffusion-weighted image. Several studies were designed to compare the ADC values between malignant and benign lesions in the breast as well as to study the change of ADC values in peri-tumor tissues, which would be helpful for the clinical surgeon to decide the scope and pattern of operation.[15]

Several attempts were made to quantify the ADC values of benign and malignant breast lesions in order to use them in conjunct with other criteria to reach a final diagnosis, several studies were done which concluded that the malignant lesions had a mean ADC value of $1.2 \pm 0.3 \times 10^{-3}$ mm^2/s while benign lesions had an ADC value of $1.7 \pm 0.5 \times 10^{-3}$ mm^2/s in comparison to the normal breast tissue with ADC value of $2.1 \pm 0.3 \times 10^{-3}$ mm^2/s. The wide range of ADC values together with the overlap between certain entities of benign and malignant lesions makes it difficult to standardize a sharp cut off value, still there is a consensus that an ADC of 1.2 or less is usually considered malignant, while an ADC value of 1.5 and more is considered benign with the intervening range being an overlap that can be considered as either according to the morphological and kinetics of the lesion at hand.[16–20]

The aim of our study was to determine the feasibility of diffusion weighted MRI sequence in increasing the MRM specificity and positive predictive value in differentiating benign and malignant focal breast mass lesions, thus alleviating the unnecessary biopsy of benign lesions as well as patients with equivocal post-therapy finding rather than undergoing the stress of re-biopsy.

2. Methods

2.1. Study population

Between January 2010 and December 2011, female patients who presented to the Oncology and Onco-Surgery Departments in the Alexandria Main University Hospital with suspected breast lump were referred to the Radiodiagnosis Department and prospectively assessed. The presence of a mass lesion had been suggested by clinical assessment and further proved by mammography and ultrasonography. Conventional DCE-MRI detected mass lesions in 71 patients with a total of 103 mass lesions; that were subjected to further assessment by DWI. Lastly, histo-pathological analysis revealed 57 benign lesions, 45 malignant lesions and one showing borderline result (fibroadenoma with cellular atypia), among the studied 71 patients six had mixed benign and malignant breast lesions. The females' age range was between 15 and 70 years with a mean of 45 years, with 51 newly diagnosed patients and 44 post-managed cases on follow-up with suspected recurrence/de novo lesions. All females signed a formal consent before undergoing the procedure and an approval from the medical ethics committee was attained before starting the research.

2.2. Imaging techniques

For newly diagnosed lesions mammography with standard cranio-caudal (CC) and medio-lateral oblique (MLO) views was obtained for both breasts. In case of already managed patients for breast cancer, the study was carried out accordingly, i.e. patients who underwent mastectomy, unilateral mammographic CC and MLO views were attained for the contra-lateral breast, while cases treated by lumpectomy or merely chemo- and radiotherapy, bilateral mammographic images were obtained.

Sono-mammography was carried out according to the condition at hand. It was performed either as a combination to mammography especially in equivocal cases usually addressed as BI-RADS 0 to reach a solid diagnosis prior to the magnetic resonance mammography, or on a separate setting in patients with a clear BI-RADS class based on mammographic findings.

2.3. MR imaging

Imaging was performed on a 1.5-T whole-body system; Magnetom Avanto, Siemens Medical Solutions (Erlangen, Germany), using a 4 channel phased array surface Breast Matrix Coil. The patient laid prone on the MR table with her breasts tightly fitted in the coil. Before the patient's positioning, an IV line was secured into the patient's arm, maintained with saline and connected to an automated power injector. Comfort of the patient is paramount. Every effort was made to ensure it by head, arm and leg supports and pillows, as this would improve compliance and prevent motion especially between the pre- and post-contrast sets of images avoiding mis-registration and sequence repetition hence reducing total scan time which was typically around 20 min.

2.4. Scanning protocols and parameters

The imaging protocol consisted of an initial rapid gradient-echo scout localization sequence acquired in all three orthogonal planes through both breasts. Non-contrast sequences of the breasts, axilla, and chest wall were acquired in the axial plane notably: T2-weighted, fat saturated sequence with TR = 5600, TE (59), FOV = 270–340 mm, acquisition matrix = 320 * 314, slice thickness = 4 mm and gap 20% = 0.8 mm in the axial plane. T1 – weighted, non-fat saturated sequence with TR = 8.6, TE = 4.7, FOV = 270–340, acquisition matrix = 448 * 323, slice thickness = 1 mm and gap −10% = −0.1 mm in the axial plane with trial to visualize the axillae as our machine lacks a separate axillary coil. Diffusion weighted echo-planar imaging (EPI) sequence is applied before contrast administration with TR = 4800, TE = 98, FOV = 270–340, matrix = 192 * 192, slice thickness = 4 mm and gap 50% = 2 mm in the axial plane, repeated with B-values 0, 400, 800 and automatically computer-generated ADC map. This was followed by a 3D T1-weighted gradient-echo sequence performed before and repeated five times after the intravenous administration of 0.2 mL of gadolinium chelate per kilogram of the body weight. The initial non-contrast phase with same parameters was acquired, to be used later on for subtraction. The contrast was administered using an automatic injector in a break of around 30 s. Post-contrast imaging phase was initiated thereafter, 3D gradient-echo sequence with a repetition time of 60 s. Imaging was performed with a 270–340 mm field of view over a minimum matrix of 448 * 322 and slice thickness of 1 mm or less with no gap and an overlap of around 10%. The number of sections acquired and the section thickness depended on the size of the breast. The total imaging time for this acquisition was required to be around 6.5 min. Fat suppression and image subtraction were used in all cases. Automatically generated MIP images in the axial, sagittal and coronal views as well as color coded wash-in, wash-out and perfusion equilibrium images were analyzed as an aid in reaching the diagnosis in some cases.

2.5. Image post-processing and interpretation

Image post processing techniques, using Syngo Siemens Medical Solutions software, were applied for every breast MRI exam, which adopted a systematic approach to review the MRM studies consisting of two parts:

2.5.1 Analysis of the conventional MRI sequences comprising both morphological and contrast dynamic curves. As a start evaluation of the breasts and any detected lesions was carried out. This included the lesion's signal intensity notably the T2 signal and fat content as well as its shape and margins, followed by enhancement kinetics analysis using the enhancement signal intensity versus time curves by manually plotting a ROI on the enhancing lesions generating the type I progressive enhancement, type II plateau and type III rapid wash in wash out curve patterns.

2.5.2 Generating apparent diffusion coefficient (ADC) maps for assessment of lesion's diffusion. The lesion was identified by comparing the contrast-enhanced MR images and diffusion-weighted images, the ADC values of mass or focal lesions were calculated accordingly. Since the cut off value of diffusion restriction is still under investigation, we decided to use the most specific cut off value for restriction till present which is ADC of 1.2 or less

Table 1 Enhancement pattern of detected focal lesions.

	Benign	Malignant	Borderline	Total
Type I curve	46	6	–	52
Type II curve	–	2	–	2
Type III curve	5	33	1	39
Mix of 3 curves	1	4		5
Non-enhancing	5	–	–	5
Total	57	45	1	103

(usually considered malignant), ADC value of 1.5 and more (considered benign) with the intervening range being an overlap or borderline. Non-mass lesions were excluded from the ADC analysis. The highest-signal portion of the lesion was visually identified on high-b-value images, and a circular region of interest (ROI) was placed manually on that portion of the lesion.

The final diagnosis was confirmed by histo-pathological analysis in all patients.

3. Results

Seventy-one cases had solid mass lesions with a total number of 103 masses on MRI analysis in comparison to only 81 focal masses on sonography (81/103 = 78.64%).

Morphological criteria were comparable on MRM and sonography, for the enhancement kinetics 52 lesions with type I progressive curve, 39 with washout type III curve and two lesions with type II curve, where a mix of all curve patterns is seen in five out of the 98 enhancing mass lesions while the remaining five lesions showed no preferential lesion enhancement after contrast administration other than the normal surroundings. Forty-six of the benign lesions had type I curve, one had a mix of three curve types, while six had type III curve. On the other hand six of the malignant lesions had type I curve, two had type II, 33 had type III and four had a mix of three curve types. The remaining borderline mass lesion had type III curve. Type III wash in wash out pattern and to a lesser extent type II plateau correlated with malignancy in 39/45 patients (Table 1).

Taking type III curve alone into consideration, obtained sensitivity was 73.33%, specificity was 91.22% and positive predictive value (PPV) was 86.95%, while adding type II plateau or mixed curve patterns to detect malignancy sensitivity rose up to 86.66%, while specificity went down to 89.47% and PPV did not vary much being 86.84%.

Adding the diffusion weighted imaging technique, all the examined lesions showed ADC values ranging from 0.5 to 3×10^{-3} cm^2/s. Forty-five lesions displayed restricted diffusion with a range from 0.5 to 1.2×10^{-3} cm^2/s. Borderline restriction (with ADC value of $1.3–1.4 \times 10^{-3}$ cm^2/s) was calculated in five lesions. The rest of the lesions (53 lesions) showed no

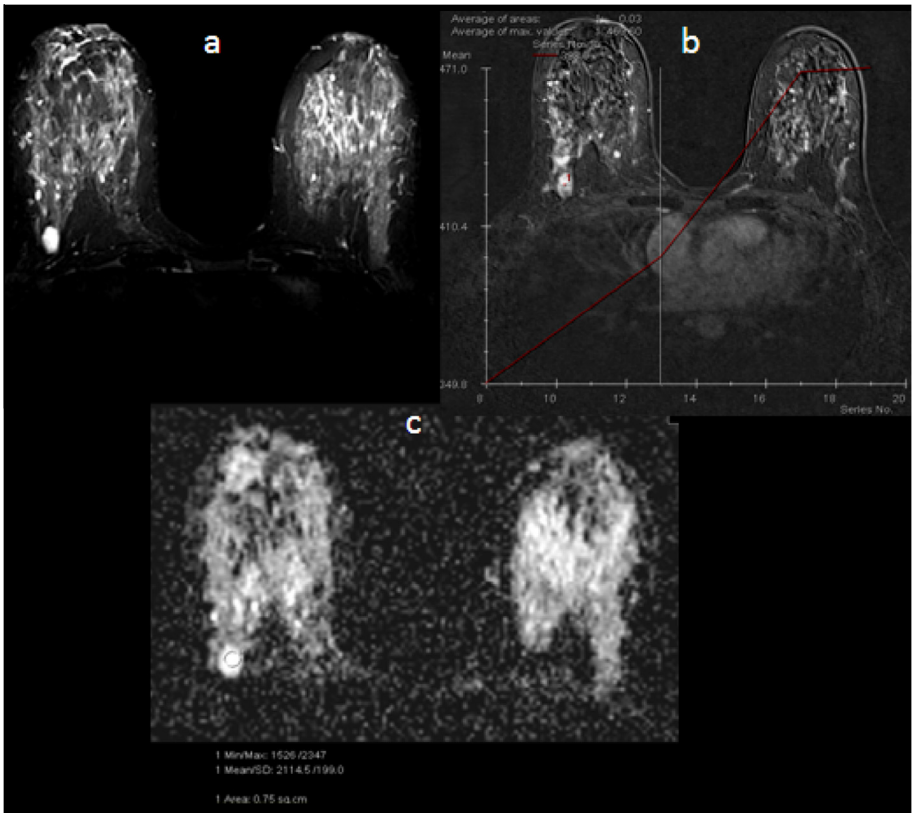

Figure 1 Forty five years old female with the right breast asymmetry and well-defined partially obscured opacities proved by US to be well-defined oval shaped lesion of probably benign nature, MRM confirmed its benign nature. (a) T2 fat suppressed axial image revealed T2 hyperintense right axillary tail lesion, (b) post-contrast subtracted image revealed type I curve pattern, while the ADC map (c) revealed no restriction with ADC value of 2.1 ($> 1.3 \times 10^{-3}$ mm^2/s).

Table 2 Diffusion weighted imaging values for detected focal mass lesions.

	Focal mass lesions			Total
	Benign	Malignant	Borderline	
Non-restricted ($>1.4\times10^{-3}$ mm^2/s)	51	2	–	53
Borderline restriction ($1.3–1.4\times10^{-3}$ mm^2/s)	4	–	1	5
Restricted ($<1.3\times10^{-3}$ mm^2/s)	2	43	–	45
Total	57	45	1	103

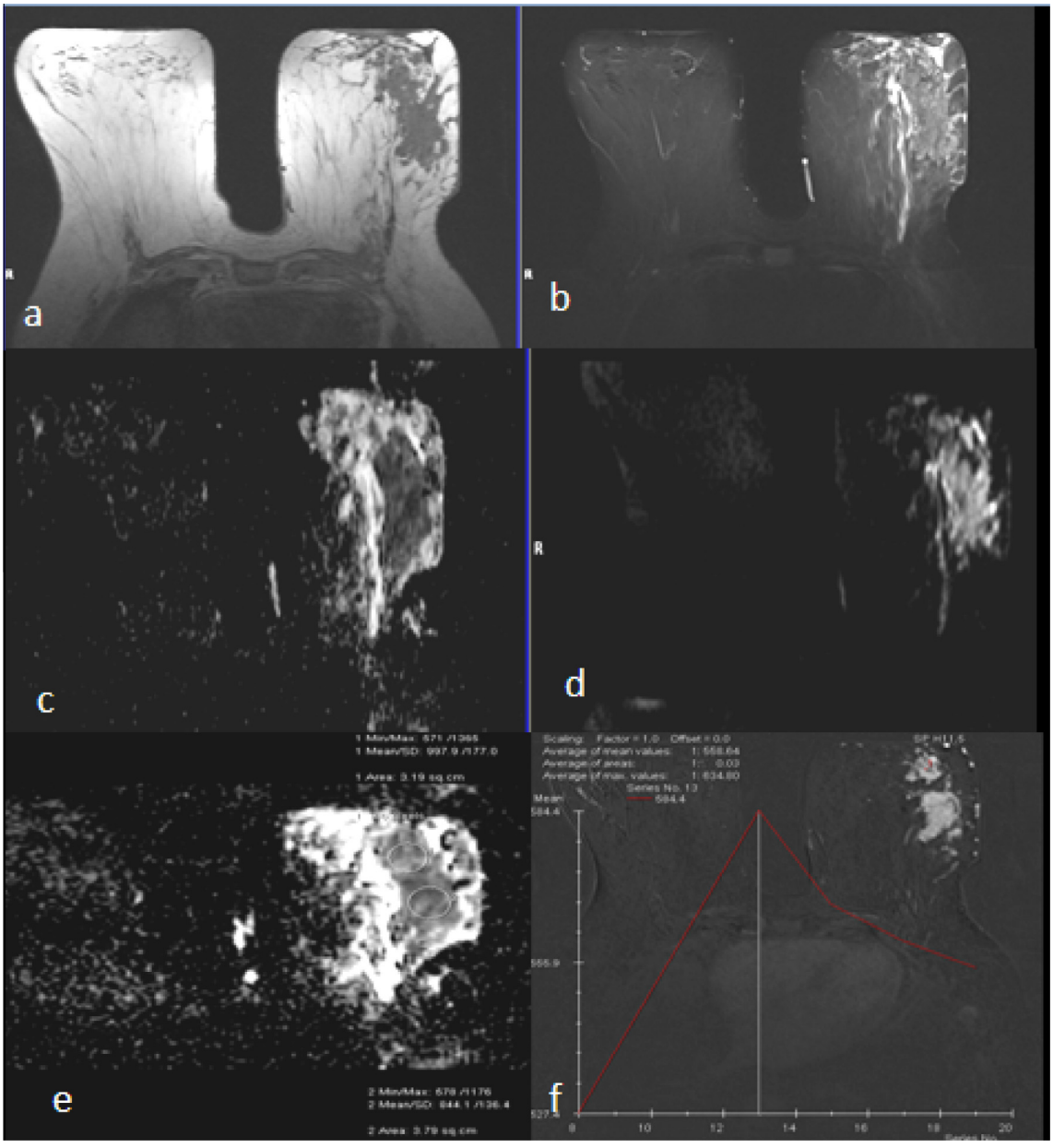

Figure 2 Sixty five years old menopausal female with the left breast asymmetry, infiltrative lesion on US and left axillary nodes with lost hilum and desmoplastic reaction, FNAC revealed granulomatous mastitis which was inconsistent with the MRM findings, re-biopsy, core type, revealed lobular carcinomatosis. T1 (a) and T2 fat suppressed (b) axial images revealing the left breast T1 and T2 hypointense lesions surrounded by edema reaching deep into the underlying pectoralis muscle appreciated on T2 fat suppressed image, diffusion analysis with ADC map (c) and b-800 value DWI (d), showing marked diffusion restriction (hypointense on ADC map and hyperintense on DWI), followed by the ADC values (e) of the lesion which was $<1.3\times10^{-3}$ mm^2/s), while (f) is post-contrast subtracted images showing type III rapid wash in wash out enhancement curve.

restricted diffusion with ADC values ranging from 1.5 to 3×10^{-3} cm^2/s (Fig. 1).

Out of the 45 lesions with restricted diffusion 43 proved to be malignant mass lesions, while the other two were benign lesions which proved to be inflammatory in origin with the breast abscess formation which was the scope of the ADC reading, for cases with borderline restriction, four proved to be benign while the remaining one proved to be borderline (cellular atypia). As for the remaining 53 non-restricted lesions, only two were already known as malignant lesions and were on chemotherapy, while the remaining 51 proved to be benign on histo-pathological analysis (Table 2) (Fig. 2).

Comparing the enhancement kinetics with the ADC values one noticed that four cases with progressive enhancement curve showed restricted diffusion, which proved to be malignant, four cases with borderline diffusion proved to be benign on histo-pathological analysis. Adding diffusion analysis to the fore mentioned enhancement kinetics criterion the sensitivity jumped from 86.95% up to 93.47% and the specificity from 91.22% to 96.49% in detection of malignancy with PPV of 95.55% in comparison to 86.66% for enhancement kinetics alone. Both specificity and PPV would be changed up to 100% respectively if the two breast abscesses were excluded since they are not true focal solid lesions. Furthermore, sensitivity would rise up to 97.72% instead of just 93.47% if we exclude the already known cases of malignancy.

Lymph nodes were detected in all cases, where 32 showed lost/eccentric hilum cases, 29 showed globular shape, three had infiltration into the surrounding tissue, one with central necrosis, 24 cases exhibited restricted diffusion ranging from 0.5 to 1×10^{-3} cm^2/ s ($< 1.3 \times 10^{-3}$ cm^2/ s), where 35 proved to be malignant and 36 benign on histo-pathology (Fig. 3).

4. Discussion

Reviewing the study's results we agreed with previous studies that MRI was superior to ultrasonography in detecting additional lesions mounting up to 21.35% (22/103), which concurs with the widely accepted concept that MRM is an established technique for improving the sensitivity of detecting breast cancer.[21,22,23]

However, breast MRI is still flawed for its relative low specificity compared to mammography and ultrasonography. Generally, several diverse techniques for breast MRI are used in a trial to overcome such drawback. Our study focused on the basic conventional dynamic-enhanced MRI which as previously mentioned increased sensitivity of detecting breast lesions in general, and added the DWI sequence testing its feasibility

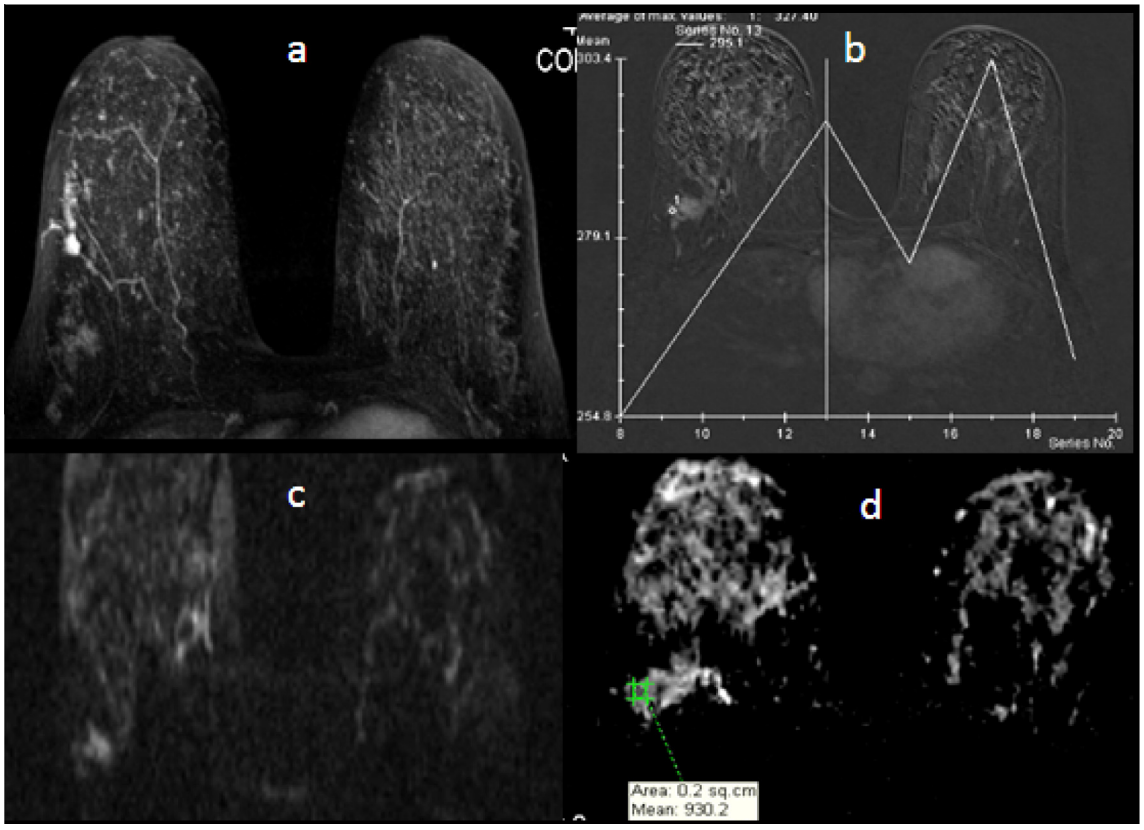

Figure 3 A 42 years old female with family history of breast cancer and microcalcification on follow-up (high risk) developed right axillary lump, altered texture but still no masses were identified on US, MRM revealed enhancing focus, still irreproducible on US, wire localization and biopsy revealed DCIS with invasive component (a): axial MIP image showing enhancing focus surrounded by clumped non-mass enhancement and level I axillary node, (b) post-processed subtracted enhanced image showing type III wash in wash out pattern along the node, diffusion analysis with b-800 value DWI (c) and ADC map (d) showing diffusion restriction (hypointense on ADC map and hyperintense on DWI), showing ADC values of $< 1.3 \times 10^{-3}$ mm^2/s) of the right axillary nodes.

as complimentary tool in increasing its specificity for labeling breast lesions as benign or malignant.

Summing up our diffusion analysis results; sensitivity was 93.47%, specificity 96.49% and PPV was 95.55% for malignancy detection, which concurred with several other studies.

In 2009, Kim et al. found the cancer detection rate for DWI was 92% in their study of 67 tumors, where DWI was able to detect mammographically and clinically occult breast carcinomas.[24]

Moreover, the performance of DWI to discriminate between benign and latent tumors also is very good, according to a 2009 study by Yili et al. The research had accuracy as high as 97% in differentiating benign from malignant lesions.[15]

Other studies used a lower ADC value threshold of $1.13 \times 10^{-3}\,mm^2/s$ as Tozaki et al. yielded a specificity of 67% (43/64) and sensitivity of 97% (61/63) for focal mass lesions, regardless of the lesion size.[20]

Such low specificity differed from ours due to the fact that we used a higher ADC cut off value, while sensitivity did not vary to that extent, which upgraded our cut off value and proved its significant higher accuracy.

Same conflict was faced when using a higher ADC cut off value as did Partridge et al. by applying an ADC threshold of $1.81 \times 10^{-3}\,mm^2/s$ for 100% sensitivity but produced a PPV of 47%, therefore, the stress of biopsying benign lesions increased, since many benign lesions exhibited ADC values below this cut off and therefore, they were regarded as suspicious by DCE-MRI and obviously by the high ADC cut off value suggested on DWI.[17]

Analyzing the study's results we would find that a total of 12 cases would be misplaced depending on the enhancement criterion alone.

Six cases with type III curve proved to be benign by biopsy, adding the DWI sequence with its ADC threshold to the assessment increased the PPV over DCE-MRI alone and would have prevented biopsy for those cases which account for 6/57 (10.5%) of benign lesions and 6/103 (5.82%) of the total number of lesions studied. The other six cases would have been missed as benign which is reflected in the sensitivity values difference.

In theory, if we omit the two complicated cysts with diffusion restriction since we should consider them as benign based on other criteria such as signal characteristics and the fact that they are liquefied rather than solid focal lesions, we would have both specificity and PPV surge to 100%, respectively.

On the other hand, the false negative lesions on DWI, were already on chemotherapy and non-restriction actually reflected the tumor response on a biological level to treatment, again excluding them from the calculations as they do not fit the criteria of being newly discovered lesions waiting to be classified, and the fact that they are biologically altered sequel to external factors, would raise the sensitivity of up to 97.72% instead of just 93.47%, taking into consideration that the false negative lesion by diffusion proved on histo-pathological analysis to be fibroadenoma with atypia (borderline), which should not be considered as frank malignancy in the first place. Hence further studies should be carried out to test the potential of diffusion weighted imaging and the use of ADC values in monitoring the response of cases with breast cancer on chemotherapy rather than considering it as a drawback of the current study.

Trying to explain the fact; that histo-pathologically borderline lesions might give non-restricted ADC values; DWI provides biological information about the composition of tissues, their physical properties, their microstructure and their architectural organization, which might not be at all disturbed to the extent that they might reflect on the DWI readings.[25]

Furthermore, DWI was found to be useful in detecting affected lymph nodes in conjunction to shape criterion, since three out of the 24 nodes showing restricted diffusion actually had preserved hilum which aids in identifying nodal affection earlier by biological behavior rather than waiting for morphological changes which reflects on the choice of line of treatment.

As for the size criterion of the lesions, we did not give it much weight, as our lesions' size was above 5 mm, which is sometimes used as a threshold of detection, since the ROI of assessment might include the neighboring tissue if less than that, which subsequently might give inaccurate, falsified readings. According to Partridge et al., whose study excluded foci, the difference in diagnostic performance of DWI for these very small (< 5 mm) lesions was not evaluated, as it was likely that the ADCs of foci were affected by the limited spatial resolution of DWI. Both, his study and ours, warrant further investigation of this area.[19]

Though our work was performed on a 1.5 T MRI machine, still our results concur with other studies, even those performed on 3 T machines. Matsuoka and colleagues evaluated 16 lesions and 13 patients who underwent MRI exams with both magnet strengths. The study found no significant difference for ADC values between the two MRI devices, the lesions less than 10 mm in size were more clearly visible and better delineated at 3 T. However, researchers noted that the exam protocol varied in this study, with thinner image slices acquired with 3 T compared with 1.5 T.[26]

5. Conclusion

Our data were comparable to others with no significant impact from the population pool. DWI revealed to increase the specificity for breast tumors detection in comparison to conventional MRI, with subsequent decrease in the rate of additional unnecessary biopsies. Still DWI should be performed in conjunction with contrast-enhanced MRI because it is evident that small breast lesions as well as non-mass enhancement are not seen on DWI.

Furthermore, DWI shows a promising potential for monitoring the response to chemotherapy even before the post-treatment morphological changes, further studies are advised to prove such hypothesis.

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