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Role of diffusion weighted imaging as an adjunct to dynamic contrast enhanced MRI in the characterisation of breast lesions

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Abstract
Water is the major composition of the body and MRI takes the advantage of the magnetic properties of the hydrogen nuclei (protons) in the body tissue. Magnetic resonance imaging applies magnetic fields to produce detailed cross-sectional images of tissue structures. A small portion of the protons in the patient body are brought into alignment with a strong magnetic field within the MRI scanner. MR examination was performed on a 1.5 Tesla Philips achieve MR scanner (Philips medical system, Netherlands) using a dedicated 8 channel bilateral breast coil with patients positioned prone and the breasts hanging freely into the cushioned openings which are surrounded by the specialized breast coil, which is a signal receiver and works with the MRI unit to create images. In our study, assessment of breast lesions by DCE MRI ALONE provided a sensitivity of 97.6%, specificity of 80%, positive predictive value was 91.1% and negative predictive value was 94.1%. P value <0.0001. In our study, breast lesions evaluated by a protocol incorporating DWI into conventional DCE MR showed a sensitivity of 100%, specificity of 90%, and Positive predictive value of 95.4% and negative predictive value of 100%. P value <0.0001. Measure of agreement (Kappa) is 0.92.

Keywords: Diffusion weighted imaging, dynamic contrast enhanced MRI, breast lesions

Introduction
The breast or mammary gland is a modified sweat gland that has an important function of milk production. An understanding of the development, anatomy, physiology and histology is important in the interpretation of breast MRI. With the understanding of the normal breast, one is able to correlate radiologic-pathologic entities better.

The hormone oestrogen captures a major role in the carcinoma development of the breast. Increased proliferation of cancer cells is the result of the expression of peptide growth factor, induced by oestrogen binding to the oestrogen receptor. In fact, about 60%-75% of premenopausal and postmenopausal women have oestrogen dependent carcinomas. Therefore, it is expected that anti-oestrogen selective receptor modulators will show reduced risk of breast cancer. However, especially the combination of oestrogen and progesterone increases breast cancer risk [1].

There are risk factors in every type of cancer. Many relative risk factors have been identified for developing breast cancer. Comparison of the incidence of breast cancer or its related death in women with a specified risk factor against those women without such factor is the relative risk. However, it has been shown that 70% of all women with breast cancer have no known risk factors [2].

A remaining problem is the lack of preventive measurements. Therefore, early diagnosis and treatment are considered the most promising approach to reduce breast cancer mortality.

Proliferation of cells is a tightly regulated process. In a normal state, cells proliferate in response to proliferation-promoting signals to fulfil a function such as replacing lost cells or repairing injured tissues. Once the proliferation is complete, proliferation-suppressing signals are activated. These proliferation suppressing signals promote cells to exit the proliferation cycle (cell cycle) by returning to the dormant state (Go), either by differentiating or by cell death (apoptosis). Each of these functions is carried out by a complex system of interacting proteins. Any mutation or a genetic change of any component of the proliferation-promoting system may induce uncontrolled, continuous proliferation.

The constitutively expressed component is called an oncogene [3].

Conversely, any mutation or a genetic change in proliferation-suppressing gene also results in uncontrolled, continuous proliferation, possibly leading to cancer. The lost gene is called a tumour suppressor gene. Similarly, expression of antiapoptotic genes may result in immortalization of the cell, which further induces many genetic changes resulting in occurrence of cancer. Loss of pro apoptotic genes may lead to similar results [4].

Water is the major composition of the body and MRI takes the advantage of the magnetic properties of the hydrogen nuclei (protons) in the body tissue. Magnetic resonance imaging applies magnetic fields to produce detailed cross-sectional images of tissue structures. A small portion of the protons in the patient body are brought into alignment with a strong magnetic field within the MRI scanner. Then the protons are exposed to brief pulse of the radiofrequency energy, which alters the magnetic vectors of the protons. As the protons relax and realign along the applied magnetic field energy is released. The return to equilibrium of the water protons is characterized by the T1 and T2 relaxation times. This electro magnetic resonance signal is detected and electronically processed by the scanner to construct an image exploiting the different "relaxation times" of the different tissues in the breast to generate the image contrast.

Compared with mammography and breast ultrasonography, contrast-enhanced MRI is a breast imaging technique that offers not only information on lesion cross-sectional morphology but also on functional features such as tissue perfusion and enhancement kinetics [5].

Methodology

Acquisition of MR images

MR examination was performed on a 1.5 Tesla Philips achieva MR scanner (Philips medical system, Netherlands) using a dedicated 8 channel bilateral breast coil with patients positioned prone and the breasts hanging freely into the cushioned openings which are surrounded by the specialised breast coil, which is a signal receiver and works with the MRI unit to create images.

All the patients were imaged with dynamic contrast enhanced MRI and diffusion weighted MRI.

MRI protocol

The conventional DCE MRI protocol included nonfat suppressed T2 weighted turbo spin echo (TR 2500-5000; TE-120ms; matrix-432; slice thickness -3mm); nonfat suppressed unenhanced and contrast enhanced fat suppressed 3D T1 weighted images in the axial plane. T1-weighted sequence parameters are TR 350-550; TE-10ms; matrix 160x222; slice thickness 3mm. Axial STIR "short tau inversion recovery sequence (TR 165-7447; TE 70ms; matrix 128x171; slice thickness 3mm) was also performed.

Diffusion weighted images were performed before contrast injection (to negate any possible effects of the presence of contrast agent may have on water diffusion within the tumour tissue and also to nullify any T2 shortening resulting from the contrast agent). Axial DWI using echo-planar imaging (EPI) (Shortest TR and TE; matrix 144x82 slice thickness-7mm; EPI factor 45) was performed with tri directional diffusion gradients by using b values: 0, 600 & 1200 mm^2/sec.

The ADC maps were created automatically by the scanner from the trace weighted images with b values of 600 and 1200 mm^2/sec.

Where the S2 and S1 are the signal intensities at b value of 1,200 and 600, respectively.

Intravenous injection of Gadolinium at a dose of 0.1 mmol/kg of body weight was administered at a rate of 2ml/sec with a power injector followed by a 20ml of saline flush and Contrast enhanced image acquisition started immediately after the bolus of saline. Six continuous dynamic contrast-enhanced images were performed.

MR image analysis

All the MRI images were interpreted using the American College of Radiology BI-RADS breast MRI lexicon incorporating morphologic and kinetic features. The palpable, sonographic or mammographically suspicious lesion was considered the index lesion. The index lesion was identified on subtracted and T2-weighted images. In patients with multiple lesions in one breast with similar MR imaging features, the lesion with the most suspicious MR features was considered as the index lesion. The MR images were analyzed for the morphologic features such as size, shape, signal intensity and enhancement pattern. On dynamic MR Images, a region of interest (ROI) was placed at the most enhancing area of the lesion and time signal intensity curves were obtained.

The index lesion was classified as either mass (three-dimensional space-occupying lesion) or non-mass like enhancement and morphologic features were analyzed. For the masses, shape, margins, type of enhancement and signal intensity on T1- and T2-weighted images were analysed. On T1w and T2w images masses were considered hypointense, hyperintense, isointense and heterointense relative to adjacent breast glandular parenchyma. The nonmass lesions were assessed for the distribution, internal enhancement pattern, and symmetry.

The dynamic scans were assessed for the degree of enhancement and time signal intensity curves which were acquired with the help of dedicated software on computer. The enhancement kinetics of the lesions were analysed based on two standpoints. First is the peak percentage increase of signal intensity in the early phase, (the first two contrast-enhanced acquisitions-wash-in rate) and the second is the shape of the curve after the early phase (wash- out kinetics). A wash-in rate of more than 80% was defined as fast or strong, between 50% and 80% as intermediate, and less than 50% as slow enhancement.

Three types of time signal intensity curves were obtained. Type-I (progressive) curve-enhancement continues to increase with each post contrast sequence. Type-II (plateau) curves; enhancement levels off after the first post contrast sequence. In the Type-III (washout) curve; enhancement decreases after initial rise. These curves were obtained by placing the region of interest (ROI) on the lesion.

In the morphologic analysis of the MR images, oval or round shaped masses or masses with smooth margins; presence of fatty signal within the lesion on T1 and T2 images, homogenous enhancement with non-enhancing internal septations, bilateral symmetric non- mass enhancement in any distribution; and unilateral, asymmetric non mass enhancements in local or regional distribution were considered negative for malignancy in our study.

Patients with benign findings at MR imaging were followed-up within 1 year with mammography or ultrasound

to ensure the stability of the lesion.
Irregular shaped masses with irregular or spiculated margins, heterogeneous or rim enhancement, and clumped type of non-mass like enhancement in ductal or segmental distribution were considered positive for malignancy.
In the kinetic analysis of the MR images, type-I curve (slow initial enhancement and persistent increase in uptake) was considered negative for malignancy. Type II and III curves (strong early enhancement with an ensuing plateau or wash-out time) were considered positive for malignancy.
Combined morphologic and kinetic analysis of dynamic contrast-enhanced MR images were interpreted according to the BI-RADS criteria. The lesions were classified into one of the five BI-RADS categories.

BI-RADS 1 (negative): No mass lesion or any contrast enhancement.

BI-RADS 2 (benign): Focal masses with round, oval, or macrolobular shape; smooth margins; nonenhancing internal septations; and a persistent type of enhancement.

BI-RADS 3 (probably benign): Focal masses with round, oval, or macrolobular shape; smooth margins and a persistent or plateau time course; and asymmetric, nonmass enhancements of local or regional distribution.

BI-RADS 4 (suspicious findings): Masses with suspicious morphology (for masses: irregular shape, irregular or spiculated margin, and
Heterogeneous or rim enhancement and for nonmass lesions: clumped and dendritic type enhancement at ductal and segmental distribution) or wash-out time course.

BI-RADS 5 (highly malignant): Masses with suspicious morphology, more than 90% wash-in rate, and plateau or wash-out time course.

ADC Measurement
Measurement of the ADC values were done on ADC maps which were generated automatically by the system from the trace weighted images with b values of 600 and 1200. T2-weighted and subtracted MR images were used as pilot images for localizing the lesion. Absolute ADC measurements were then recorded by manually placing the ROI (round ROI of area 2.5mm^2) within the solid portions of the lesion. Obvious cystic and necrotic areas were avoided. When a lesion was not hyper intense on DWI, the ROI was drawn at the corresponding location and size as reflected on DCE-MRI. At least three measurements were done for each lesion, and the lowest one was accepted as the ADC value.

Histopathological analysis
Final diagnoses were obtained with histopathologic analysis of the surgically excised specimen or core biopsy tissue specimen analysis. Ductal carcinoma in situ (DCIS) and any type of invasive carcinoma at histopathological diagnoses were considered as malignant. Patients with features of a benign lesion were followed-up within 1 year with mammography or ultrasound to evaluate the stability of the index lesion

Results

Table 1: Signal Intensity Characteristics of Index Mass Lesions on T2WI (n=62).

Signal intensity on T2 weighted images	Malignant	Benign	Total
Hypo/isointense	2/42 (4.8%)	2/20 (10%)	4/62 (6.5%)
Hyperintense	22/42 (52.4%)	15/20 (75%)	38/62 (61.3%)
Heterointense	18/42 (42.8%)	3/20 (15%)	20/62 (32.3%)

Table 2: Type of Enhancement in Index Lesions on MRI (n=62).

Type of enhancement	Malignant	Benign	Total
Homogenous	3/42(7.1%)	13/20(65%)	16/62(25.8%)
Heterogenous	31/42(73.8%)	7/20(35.0%)	38/62(61.3%)
Rim	8/42(19%)	0/20(0%)	8/62(12.9%)

In our study, heterogeneous enhancement was the most common pattern of enhancement (31/42, 73.8%) found in the malignant lesions. Rim enhancement pattern was the second common pattern of enhancement (8/42, 19%) in malignant lesions whereas 3 of the malignant lesions showed homogenous enhancement. Most of the benign lesions showed homogenous enhancement (13/20, 65%). Of the 13 benign lesions showing homogeneous enhancement, 7 had non enhancing internal septations. 7 benign lesions showed heterogeneous enhancement. None of the benign lesions showed rim enhancement. None of the index lesions presented as only non-mass type of enhancement.

Table 3: Type of time intensity curve (n=62).

Time intensity curve	Malignant	Benign	Total
Type i	0/42 (0%)	15/20 (75%)	15/62 (24.2%)
Type ii	12/42 (28.6%)	3/20 (15%)	15/62 (24.2%)
Type iii	30/42 (71.4%)	2/20 (10%)	32/62 (51.6%)

Five (25%) of the 20 benign and all the 42 (100%) malignant lesions revealed strong early enhancement. Of the 20 benign lesions 15 (75%) showed persistent, Three (15%) showed plateau and 2 (10%) showed washed out time course. Of 42 malignant lesions, 12 (28.6%) showed plateau, 30 (71.4%) showed wash out time course.

Table 4: BI-RADS Category of Index Lesions on MRI (n=62).

BI-RADS category	Frequency in All lesions	Frequency in benign lesions	Frequency in malignant lesions
2	14/62(22.5%)	14/20(70%)	0/42(0%)
3	4/62(6.4%)	2/20(10%)	2/42(4.6%)
4	4/62(6.4%)	2/20(10%)	2/42(4.6%)
5	40/62(64.5%)	2/20(10%)	38/42(90.4%)

Maximum number of patients (n=40) in our study were classified as BI-RADS
Category 5 on MRI and followed by BI-RADS category 2 (n=14). Most of the benign lesions (n=14) were classified as BI-RADS category 2. Four patients were classified each as BI-RADS category 4 and category 3.
In all 62 patients, we could localize and measure the ADC value of the index lesion.

Table 5: ADC analysis of index lesions (n=62).

ADC values	Minimum $x10^{-3}$ mm^2/s	Maximum $x10^{-3}$ mm^2/s	Mean $x10^{-3}$ mm^2/s	standard deviation	P value
Malignant	0.49	1.0	0.72	0.129	<0.0001
Benign	0.81	1.64	1.25	0.238	

The mean ADC value for malignant lesions in our study was $0.72\pm0.129x10^{-3}$ mm^2/s. Minimum and maximum ADC values for malignant lesions were $0.49x10^{-3}$ mm^2/s and $1.0x10^{-3}$ mm^2/s respectively (Range-$0.51x10^{-3}$ mm^2/s). P value <0.0001.
The mean ADC value for benign lesions in our study was $1.25\pm0.238x10^{-3}$ mm^2/s. Minimum and maximum ADC values for benign lesions were $0.81x10^{-3}$ mm^2/s and $1.64x10^{-3}$ mm^2/s respectively (Range -$0.83x10^{-3}$ mm^2/s).
Mean ADC value for malignant breast lesions were significantly lower than mean ADC values for benign breast lesions (P <0.0001).

Table 6: Mean ADC values of various grades of invasive ductal carcinoma (Nottingham modification of Bloom-Richardson system).

Mean ADC $x10^{-3}$ mm^2/s	Histopathologic grading			P value
	Grade i	Grade ii	Grade iii	<0.87
	0.77	0.74	0.69	

In our study we looked at correlating apparent diffusion coefficient (ADC) values of invasive ductal carcinomas with the histopathological grading using Nottingham modification of Bloom-Richardson system. The mean ADC value for grade I IDC was $0.77x10^{-3}mm^2/s$; mean ADC value for grade II IDC was 0.74 $x10^{-3}$ mm^2/s; mean ADC value for grade III IDC was $0.69x10^{-3}mm^2/s$. We observed that there was a tendency for progressive decrease in mean ADC values of the infiltrating ductal carcinomas with increasing histological tumour grades. Though there was a difference between the ADC values of different tumour grades, the difference was not statistically significant (P = 0.87).
Receiver operating characteristic curve for apparent diffusion coefficient (ADC) values. Upper left point on curve is cut-off value of ADC with highest sensitivity and specificity.
Receiver operating characteristic curve analyses: Area under the curve (AUC) was 0.979. AUC represents the probability that lesion a will be classified accurately as either benign or malignant. An ADC cut-off value of $1.0x10^{-3}$ mm^2/s provided optimal sensitivity of 100% and specificity of 90%.
All the malignant lesions were classified correctly using the ADC'S whereas two of the 20 benign lesions were misdiagnosed as malignant with ADC values alone. The resulting sensitivity and specificity of DWI were 100% and 90%, respectively.

Table 7: Histopathologic distribution of the index lesions.

Histopathology	Frequency	Percentage (%)
Malignant	42	67.7%
Benign	20	32.3%
Total	62	100%

Of the 62 lesions, 42 (67.7%) were malignant and 20 (32.3%) were benign.
Of the 42 (67.7%) malignant lesions, 34 (54.8%) were invasive ductal carcinomas (IDCs), 3 (4.8%) were invasive lobular carcinomas (ILCs), 1 (1.6%) were mixed invasive ductal and lobular carcinomas, 2 (3.2%) were Paget's disease, 2 (3.2%) were ductal carcinoma insitu. Invasive ductal carcinoma was the commonest malignant lesion. Of the 20 (32.3%) benign lesions: 14 (22.6%) were fibro adenomas; 2 (3.2%) were intraductal papillary lesions; 1 (1.6%) were fat necrosis; 1(1.6%) were ductal hyperplasia; 1 (1.6%) were chronic inflammation and 1 (1.6%) were fibrocystic changes. Fibro adenoma was the commonest benign lesion.

Table 8: DCE MRI - Histopathological correlation of index lesions (n=62).

	Histopathology			
DCE MRI	Malignant	Benign	Total	P Value
Malignant	41 (97.6%) True positive	4 (20%) False positive	45	<0.0001
Benign	1 (2.4%) False negative	16 (80%) True negative	17	
Total	42	20		

In our study, assessment of breast lesions by DCE MRI ALONE provided a sensitivity of 97.6%, specificity of 80%, positive predictive value was 91.1% and negative predictive value was 94.1%. P value <0.0001. Measure of agreement (Kappa) is 0.80.

Table 9: DWI-Histopathological correlation of index lesions (n=62).

Histopathology				
DWI	**Malignant**	**Benign**	**Total**	**P value**
Malignant	42 (100%) true positive	2 (10%) false positive	44	<0.0001
Benign	0 (0%) false negative	18 (90%) true negative	18	
Total	42	20	62	

In our study, assessment of breast lesions by DWI ADC alone showed a sensitivity of 100%, specificity of 90%, and Positive predictive value of 95.4% and negative predictive value of 100%. P value <0.0001. Measure of agreement (Kappa) is 0.92.

Table 10: DCE MRI +DWI -Histopathological correlation of index lesions (n=62).

Histopathology				
DCE MRI+DWI	**Malignant**	**Benign**	**Total**	**P value**
Malignant	42 (100%) True positive	2 (10%) False positive	44	<0.0001
Benign	0 (0%) False negative	18 (90%) True negative	18	
Total	42	20	62	

In our study, breast lesions evaluated by a protocol incorporating DWI into conventional DCE MR showed a sensitivity of 100%, specificity of 90%, and Positive predictive value of 95.4% and negative predictive value of 100%. P value <0.0001. Measure of agreement (Kappa) is 0.92.

Discussion

In our study heterogeneous enhancement was the most common pattern (31/42, 73.8%) found in the malignant lesions which was similar to studies by Kacl *et al*., [6], Liberman *et al*., [7] and Kim *et al*., [8] who reported heterogeneous enhancement as the most common enhancing pattern among malignant lesions. other types of enhancements in our study included rim enhancement in 8 of the malignant lesions and 3 malignant lesions showed homogenous enhancement. Homogenous enhancement was the most common pattern (13/20, 65%) found in benign lesions. Seven of the benign lesions showed heterogeneous enhancement. None of the benign lesions had rim enhancement. The above observations of our study are similar with the results of the previous studies.

Enhancement kinetic curves were also assessed in our study. Majority (30 of 42, 71.4%) of the malignant lesions showed wash out enhancement pattern which is a type III curve. 12 of the malignant lesions showed plateau curve, that is the enhancement levels off after the 2-3mins, which is type II kinetic curve constituting 28.6%. In benign lesions, 75% showed type 1, 15% showed type II and 10% showed type III curve kinetic curves.

A study done by Christiana Katharina Kuhl *et al*., [4] showed the distribution of different types of kinetic curves for breast cancer which were type I (benign type)-8.9%; type II (intermediate type)-33.6% and type III (malignant type)-57.4%. The distribution of curve types for benign lesions was type I-83%, type II-11.5% and type III-5.5%.

Kuhl *et al*., [4] also showed the importance of assessing the time enhancement curve as a way to increase the specificity of breast MRI. They studied 266 enhancing lesions in 230 patients, with 101 breast cancers. The likelihood of breast cancer association with Type 1, 2 and 3 curves was 6%, 64% and 87% respectively. Collective assessment of the morphological characters and kinetic curve shape provided an overall specificity of 83%, with 91% sensitivity. This study indicates the importance of assessing time enhancement curve along with the degree of enhancement so as to increase the specificity of breast MRI.

In our study DCE MRI alone provided overall sensitivity of 97.6%, specificity of 80% positive predictive value of 91.1%, Negative predictive value of 94.1% (P value <0.0001).

DWI provides information on the microstructure of the tissues and reflects changes in water molecule mobility caused by alterations in the tissue environment due to a pathologic process. The apparent diffusion coefficient (ADC) is a quantity derived from diffusion weighted images which quantifies the rate of diffusion of water molecule.

High apparent diffusion coefficient values indicate unimpeded diffusion whereas low apparent diffusion coefficient values imply restricted motion of molecules. Malignant tumours have lower ADC values than benign lesions. This is likely because of the increased cellularity, larger nuclei and less extracellular space in malignant tumours.

DWI is also influenced by tissue perfusion. At lower b values (less than 400s/mm^2) the effect of perfusion predominates. The increased perfusion rates in the malignant tumours than benign tumours may probably have effect on the ADC values and may increase the ADC values at lower b values. On the other hand, diffusion of the water molecules has greater influence on the ADC values and the malignant tumours have lower ADCs due to restricted diffusivity of the water molecules. The ADC values calculated using higher b values more effectively differentiates malignant tumours from benign lesions. Therefore, we considered using higher b values in our study [9].

In our study ADC values were calculated for all the lesions and the mean ADC value for benign and malignant lesions were calculated. The ADC values for malignant lesions ranged from $0.49x10^{-3}$mm/s to $1.00x10^{-3}$mm/s with the mean ADC value of $0.72\pm0.13x10^{-3}$mm/s. The ADC values for benign lesions ranged from $0.81x10^{-3}$mm/sec to $1.64x10^{-3}$ mm/s with the mean ADC value of $1.25\pm0.24x\ 10^{-3}$mm/s.

We found that, there was a significant difference in the mean ADC value of the benign and malignant lesions (P <0.0001) which was similar to Yong G *et al*., who did a study on 52 patients with histopathologically proven breast lesions to evaluate the value of diffusion weighted imaging (DWI) in distinguishing benign and malignant breast lesions. They found that the ADC's varied substantially

between benign ($1.57\pm0.23x10^{-3}mm^2/s$) and malignant breast lesions ($0.97\pm0.20x10^{-3}\ mm^2/s$).

In our study we used b value combination of 0,600 and 1200s/mm^2 and found that there was significant difference between the mean ADC's of benign and malignant lesions which was similar to Fernanda philadelphia arantes Pereira *et al*., who studied 45 women with 52 focal mass breast lesions to study the utility of diffusion weighted MRI in differentiating benign from malignant breast lesions by using different 'b' values (0, 250, 500, 750 and 1000s/mm^2). They found that mean ADC value was significantly lower for malignant lesions compared to benign lesions (p <0.0001) in all 'b' value combinations.

In our study, Diffusion weighted imaging using b values 0,600 and 1200s/mm^2 with an ADC cut-off value of $1.0x10^{-3}$ mm^2/s provided an optimal sensitivity of 100%, a specificity of 90%, Positive predictive value of 95.4% and negative predictive value of 100% (P value <0.0001).

Our study found similar results to a retrospective study conducted by Lalitha palle *et al*., [10] to evaluate the role of diffusion weighted imaging (DWI) and the apparent diffusion coefficient (ADC) for characterising breast lesions. They studied a total of 200 patients. Based on previous study results they considered, lesions with ADC values from 1.3 to 1.5mm^2/s as benign and lesions with ADC values ranging between 0.85 and 1.1mm^2/s as malignant. Their study showed a sensitivity of 97.22%, a specificity of 100%, and Positive predictive value of 100% and negative predictive value of 99%.

Our study results were also consistent with the study of Marwa E. Abdelrahman *et al*., [11] to assess the diagnostic value of DWI for detection and differentiation of suspicious breast lesions with histopathological correlation. The mean ADC values for malignant and benign lesions were 0.89 ± 0.183 and $1.83\pm0.462x10^{-3}mm^2$/sec respectively. In their study sensitivity of the DWI was 89.5%, specificity 100%; PPV 100%; and NPV 93.94%.

In a study done by Savannah C. Partridge *et al*., [12] to evaluate the apparent diffusion coefficient values for discriminating benign and malignant breast lesions and relation between the lesion size and ADC values. They studied 91 women with 116 breast lesions identified with dynamic contrast-enhanced MRI. Diffusion-weighted images were acquired at b values of 0 and 600s/mm^2. Similar to our study the mean ADC was significantly lower for malignant than for benign lesions for both mass lesions (mean difference, $0.49x10^{-3}mm^2/s$; p <0.001) and lesions with non-mass like enhancement (mean difference, $0.20x10^{-3}mm^2/s$; p= 0.02). And there was no relation (p >0.05) between ADC value and lesion size for benign or malignant lesions.

In our study there was one benign lesion with irregular shape, margins and heterointense signal on T2w images. It showed a type II kinetic curve on enhancement kinetics. There was diffusion restriction with low ADC value ($0.81x10^{-3}mm^2/s$). Both DCE MRI and DWI were interpreted as positive for malignancy. But on histopathological analysis it was chronic dense inflammation mimicking malignancy.

Both conventional breast imaging and breast MRI cannot reliably distinguish between the inflammatory and malignant cause of the breast inflammation (130,131) (case 6). Even DWI failed to precisely diagnose dense inflammation. With the availability of very less literature on the role of DWI in distinguishing inflammatory carcinoma and inflammation, the role of DWI in this respect is yet to be established.

In our study, there were two intra ductal papillary lesions, one of them was mimicking malignancy on both DCE MRI (irregular margins and type III curve) and DWI which showed restricted diffusion and the ADC value was $1.01x10^{-3}mm/s$. The other case was an intra-ductal papilloma which morphologically had benign characters whereas kinetic curve analysis showed type III curve and DWI showed restricted diffusion with ADC value of 1.09 x 10^{-3}mm/s. Due to increased cellularity and high vascularity of intra ductal papillary lesions, characterization of intra ductal papillary lesions on DCE MRI and DWI may create problems during interpretation of breast MRI. Both the intra ductal papillary lesions in our study showed restricted diffusion with borderline ADC values which could be due to the high cellularity of these lesions.

In our study there was one case of fibrocystic change presenting as non-mass like enhancement with type II kinetic curve, diffusion restriction and low ADC value ($0.85x10^{-3}mm/s$) all the features favouring towards a malignant lesion. There are only few studies on the MR imaging features of fibrocystic disease. A study done by Mariano *et al*., showed that FCC can present either as a mass or as a non-mass like regional enhancement. On MR imaging, fibrocystic changes may cause diagnostic problem, particularly non mass like enhancement and also there are case reports of fibrocystic changes presenting with low ADC values. Low ADC value in fibrocystic change can possibly be due to fibrotic and sclerotic changes and within the associated inflammation.

In our study there was one case of fat necrosis with irregular shape, margins and intralesional T1w hyper intensities which were suppressed on fat saturated images. The lesion showed progressive uptake of contrast resulting in type I curve and there was no restriction of diffusion on DWI, ADC value was $1.30x10^{-3}mm/s$. On MR imaging, fat necrosis is seen as a round or oval mass with hypointense T1-weighted signal on fat-saturated images with a peripheral enhancing rim. However, the peripheral rim may show irregular or spiculated margins possibly due to associated fibrosis.

There were 14 cases of fibro adenomas (mean ADC value $1.35x10^{-3}mm/s$) in our study and there was no difficulty in diagnosing fibro adenomas using DCE MRI and DWI due to their typical morphological and enhancement features.

Infiltrating ductal carcinomas (IDC) formed the majority (34/42; 6-infiltrating ductal carcinoma grade I; 15-infiltrating ductal carcinoma grade II; 13-infiltrating ductal carcinoma grade III) of malignant lesions in our study, all the infiltrating ductal carcinomas had irregular shape with spiculated or irregular margins and T2 heterointense signal intensity. On DCE MRI majority showed heterogeneous enhancement and Type III kinetic curve. All the lesions showed restricted diffusion.

In our study we also looked at correlating apparent diffusion coefficient (ADC) values of invasive ductal carcinomas with the histopathological grading using Nottingham modification of Bloom-Richardson system. The mean ADC value for grade I IDC was $0.77x10^{-3}mm^2/s$; mean ADC value for grade II IDC was $0.74x10^{-3}$ mm^2/s; mean ADC value for grade III IDC was $0.69x10^{-3}mm^2/s$. We observed that there was a tendency for progressive

decrease in mean ADC values of the infiltrating ductal carcinomas with increasing histological tumour grades. Though there was a difference between the ADC values of different tumour grades, the difference did not reach a statistical significance (P = 0.87).

There were 3 invasive lobular carcinomas in our study, all the three presented as irregular masses with 2 of them having spiculated margins and the other one had irregular margin. All three showed heterogeneous enhancement with 2 of them showing type II kinetic curve and the other one showed type III kinetic curve. With respect to the enhancement kinetics of the invasive lobular carcinomas there is limited literature on enhancement kinetics of ILC. Most of the invasive breast carcinomas show a typical pattern of rapid enhancement and washout, whereas invasive lobular carcinomas have a tendency to demonstrate delayed maximum enhancement, with only few of them exhibiting the washout kinetics.

There are two ductal carcinoma insitu (DCIS) cases in our study; both of them showed restricted diffusion with low ADC values like invasive carcinomas. In a study done by Kuroki Y *et al*., they reported higher ADC values in pure and predominant DCIS in comparison with IDC'S. So DWI may misdiagnose DCIS as benign.

In our study we assessed the adjunctive role of diffusion weighted imaging to DCE MRI. We used a protocol combining DCE MRI and DWI and obtained a sensitivity of 100%, specificity of 90%, positive predictive value was 95.4% and negative predictive value was 100% and there was an improvement of 10%, 2.4%, 4.3% and 5.9% (measure of agreement, kappa value of 0.924) in overall specificity, sensitivity, positive predictive values and negative predictive values of breast MRI. There was a significant increase (P value <0.0001) in the specificity over DCE MRI alone.

In our study, the addition of DWI to conventional DCE MRI provided similar results to previous studies. Hidetake Yabuuchi *et al*. conducted similar studies to evaluate the diagnostic accuracy of a combination of dynamic contrast-enhanced MR imaging (DCE-MRI) and diffusion-weighted MR imaging (DWI) in characterization of enhancing masses and non-mass like enhancement on breast MR imaging and to find the strongest discriminators between carcinoma and benign breast lesions. They studied 75 enhancing masses in 71 patients and found that irregular margin, heterogeneous internal enhancement, rim enhancement, plateau time–intensity curve (TIC) pattern, washout TIC pattern and ADC values less than $1.1x10^{-3}mm^2/s$ were the strongest indicators of malignancy. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 92%, 86%, 97%, 71% and 91% respectively. They also studied 22 non-mass-like enhancement lesions in 21 patients and found that segmental distribution ($P = 0.018$), clumped internal enhancement ($P = 0.005$), and ADC less than $1.3x10^{-3}mm^2/s$ ($P = 0.047$) were the strongest MR indicators of malignancy. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 87% (13/15), 86% (6/7), 93% (13/14), 75% (6/8) and 86% (19/22), respectively.

They concluded that the combination of DWI and DCE-MRI could produce high diagnostic accuracy in the characterization of enhanced mass and non-mass like enhancement on breast MR imaging.

Another study conducted by Sibel kul *et al*., [13] on 84 patients with breast tumors to evaluate the diagnostic value of an imaging protocol that combines dynamic contrast enhanced MRI and diffusion weighted imaging provided similar results with sensitivity of 95.7% and specificity of 89.2%. The specificity of breast MRI improved by 13.5% without a significant decrease in the sensitivity. Our study also provided similar results with improvement of 10% in specificity.

Savannah. C. Partridge *et al*., [14] conducted a retrospective study on 70 patients with 83 suspicious breast lesions to investigate whether adding DWI to DCE MRI could improve the PPV of breast MRI and results showed an improvement of 10% in positive predictive value. They concluded that DWI has potential for improving the PPV of breast MRI for lesions of varied types and sizes.

Our study results are promising in that DWI may play an adjunctive role in improving the diagnostic accuracy of the breast MRI. However, there were few limitations in our study. First, there was more number of malignant lesions relative to benign lesions because in our study majority of the breast MRI's were performed as a part of preoperative assessment in suspected breast cancers. Therefore, there was a higher tendency for inclusion of malignant lesions in our study with insufficient number of benign lesions.

Second the ADC values are influenced by the degree of diffusion sensitization (b-value) used in the study. In our study, we used b values of 600 and 1200 s/mm^2 and the ADC ranges for benign and malignant lesions obtained in our study may not be the same as that obtained at different b values.

Conclusion

In our study, we found that by using a MRI protocol combining dynamic contrast enhanced MRI and diffusion weighted imaging, the former known to have a good sensitivity and variable specificity in characterizing breast lesions, the overall diagnostic accuracy of breast MRI was improved along with increase in the specificity of the breast MRI. Thus, diffusion weighted imaging acts as a promising adjunct tool in the MRI assessment of breast lesions. With the improvements in image acquisition techniques, diffusion weighted imaging can be obtained easily and evaluation of ADC values derived from it, aids in differential diagnosis of breast lesions. And also adding an ADC threshold to the assessment of breast MRI improved the diagnostic accuracy of DCE-MRI. Further, diffusion weighted imaging helps in tumour detection without the use of the contrast. Our prospective study showed promising results that the addition of diffusion weighted imaging to dynamic contrast enhanced MRI has potential to improve the specificity of breast MRI.

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