

Correlation of Apparent Diffusion Coefficient Value Factor with Different Molecular Subtypes of Invasive Breast Carcinoma

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Abstract

DWI is a non-invasive technique that represents the biological character of the mainly Brownian movement of protons in bulk water molecules in vivo. To evaluate the role of the apparent diffusion coefficient (ADC) value in different molecular subtypes of invasive breast cancer. Prospective study of 30 patients with mean age of 45.5, diagnosed with breast cancer. Evaluated during the period from September 2018 to September 2019. DWIs and quantitative analysis of ADC maps was done, the mean ADC value of the breast lesions was calculated and correlated with the different prognostic factors. There was a significant difference between the mean ADC value of luminal A and HER-2 positive groups ($p= 0.001$); and between luminal B and HER-2 positive groups ($p= 0.001$). There was a significant difference between the mean ADC value of luminal A and TNBC groups ($p= 0.001$); and between luminal B and TNBC groups ($p= 0.001$). There was a significant difference between the mean ADC value of HER-2 positive and TNBC groups ($p= 0.001$); However, there was no statistical difference between luminal A and luminal B groups ($p= 1$). Lower ADC value is noted with high Ki-67 tumours ($0.91 \times 10^{-3} \text{ mm}^2$), while high ADC value is noted in low Ki-67 tumours ($0.99 \times 10^{-3} \text{ mm}^2$). Yet no statistically significant difference is noted in-between ($p=0.365$). DWI is a contrast-free modality that allows for both morphological and quantitative analysis. ADC value may not be the proper modality to use for identifying the degree of aggressiveness in breast cancer, yet it could be a good predictor of breast cancer cells that would respond to chemotherapy.

Keywords: Diffusion, ADC factor, Breast, Cancer, Prognosis, Magnetic resonance imaging.

1. Introduction

Diffusion-weighted MRI (DWI) need as of late been incorporated under those standard breast MRI to separation for favorable and threatening breast lesions got for progressive contrast-enhanced MRI [1].

DWI may be a non-invasive procedure that speaks to those living character of the principally brownian development for protons on mass water particles in vivo. Clear dissemination coefficient (ADC) values are quantified eventually Tom's perusing estimation for intend diffusivity along three orthogonal directions, which need aid influenced by cellulite of the tissue, liquid viscosity, film permanganic corrosive what's more blood stream [2].

A few investigations about DWI of the breast bring accounted altogether bring down ADC qualities done threatening tumours, compared with benevolent breast lesions also ordinary tissue [3].

Excellent prognostic markers, including tumor measure and grade, what's more lymph hub status clinched alongside patients with breast cancer, also sub-atomic markers, including estrogen receptor (ER), progesterone receptor (PR), Ki-67 index, human Growth element receptor 2 (HER2) protein Furthermore angiogenic sub-atomic markers, have been accounted for [4].

2. Patient and methods

2.1 Patients

This study included 30 patients. Cases were referred from general surgery departments in private centers and they were subjected to primary sonomammogram evaluation and MRI scanning including pre-contrast, dynamic post contrast as well as diffusion weighted sequences. Tumor grading was established by mean of open or core needle biopsy (considered as the gold standard reference).

2.2 MR imaging

Dynamic MR imaging was performed with high field strength 1.5 Tesla on Philips Achieva XR using SENSE breast coil 7 elements, with the patient in the prone position. Total study time ranged from 20 to 30 minutes.

2.3 Contrast medium

Magnevist (gadopentetate dimeglumine) is adjusted according to body weight as 0.2 mL/kg (0.1 mmol/kg) administered intravenous, by power injector at a rate of 2 mL/sec.

2.4 MRI imaging protocol

The MRI breast examination consisted of: Dynamic contrast enhanced MRI sequence was performed with high field strength 1.5 using dedicated double breast coil with eight channels. Sagittal T1 weighted spin echo

sequence was carried out for localization purpose and followed by plain sequences as follows : Axial T1-weighted spin echo (TR / TE = 500 / 5.3 msec.).Sagittal and Axial T2 weighted images spin echo (TR / TE = 120 / 4.9 msec.).Axial “Short Time Inversion Recovery” (STIR) (TR / TE = 80 / 6.5 msec).Pre-contrast images were obtained over a 512×192 matrix in the axial plane with a slice thickness of 4 mm without gap, flip angle=90° and FOV=34-37 cm.DWI was performed before the DCE-MRI acquisition using a diffusion-weighted “Echo-Planar Imaging” (EPI) sequence with parallel imaging ; using the following parameters: TR/TE = 5000/77 msec ; slice thickness = 5 mm and 1 mm interslice gap; matrix = 124 × 100,b-values (0, 850, 1000 s/mm²); and the diffusion image was supplied from “Spectral Adiabatic Inversion Recovery” (SPAIR) MR sequence. Respiratory triggering was used for better resolution. The T1W imaging done before and immediately following IV bolus contrast administration, to ensure that the early phase of enhancement (i.e., the time window between maximal enhancement of malignant lesions and the subsequent more delayed enhancement of background breast parenchyma and benign lesions) is sampled.Six dynamic acquisitions were taken: one before and five after intravenous injection of contrast material, using the dynamic “T1 High Resolution Isotropic Volumetric Examination” (THRIVE) sequence with the parameters (TR/TE 2.8/9 msec) and slice thickness = 1.5 mm.

2.5 Image post processing and analysis

Post processing image subtraction was obtained between the post contrast imaging showing maximum enhancement and pre-contrast images (in the same axial plane), using the software subtraction function available on the work station.Qualitative and quantitative analysis of the examined masses was done as follows:I-Qualitative analysis:Restricted diffusion was determined by visualization of abnormal bright signal intensity that became enhanced with increasing b values (0, 750, 1000) at “Diffusion weighted” (DW) images. The ADC map presented intermediate/low signal intensity (SI) that corresponded to the abnormality.II-Quantitative analysis:The ADC values were measured manually by applying ROI at areas of bright SI on DW images and intermediate/low SI on ADC maps/ most enhanced part within the lesion , avoiding cystic/necrotic areas.

2.6 Immunohistochemical analysis

Nottingham combined histologic grade are used for assessment of histological grades of IDC NOS using a numerical scoring system for tubule formation, pleomorphism and mitotic count. The total score could range from 3 to 9, with a total score of 3–5 representative of grade 1, a total score of 6 or 7 representative of grade 2 and a total score of 8 or 9 representative of grade 3 [5] .

Immunohistochemical analysis performed for ER, PR, HER2 and Ki-67. The status of ER and PR considered to be negative if expression is less than 10% and positive if expression is 10% or greater. Results for HER2 expression will scored as negative, 1+, 2+ or 3+, according to the manufacturer’s recommendations. Tumours with 0 or 1+ will classified as HER2 negative and 2+ or 3+ were HER2 positive. Ki-67staining of >20% is considered high expression and<20% is considered low expression.

In our study; Immunohistochemical analysis will performed for ER and PR according to the Allred scoring system considering only nuclear staining .

Evaluation of HER2/neu Status: HER2/neuimmunostaining results are estimated according to the HER2/neu scoring system used to evaluate the Hercep Test .MR Imaging

MRI was conducted on a 3.0T MR scanner (Philips Achieva, Philips Medical Systems; Netherlands) equipped with a phased-array torso surface coil.

2.7 Statistical methods

Data were coded and entered using the statistical package SPSS version 24. Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test when comparing 2 groups and analysis of variance (ANOVA) with multiple comparisons post hoc test when comparing more than 2 groups [6].P-values less than 0.05 were considered as statistically significant.

3.Results

3.1 Correlation of the mean ADC value with the molecular biomarkers of the tumor

There were 29 lesions (80.6%) ER-positive, 25 (69.5%)PR-positive and all the PR-positive lesions showed also ER positivity, and 5 (13.9%) HER-2-positive Fig (1).

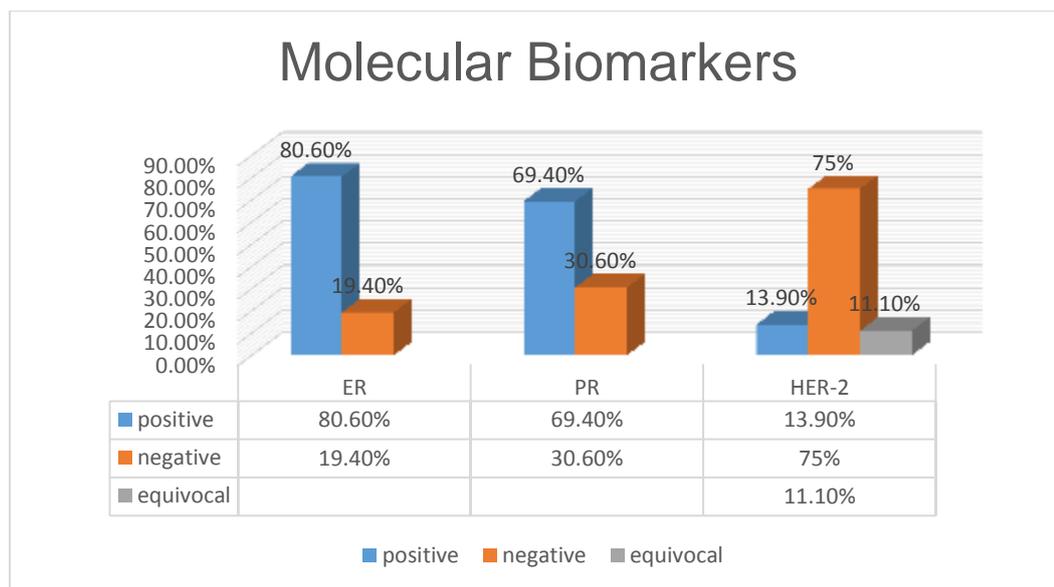


Fig (1) showing distribution of each molecular breast biomarkers of examined lesions

All lesions (100%) showed persistent high signal on DWI with low to intermediate signal on ADC map denoting restricted diffusion.

ADC values ranged from 0.90 to 1.2 × 10⁻³ mm²/s (mean 0.97 ± 0.9 × 10⁻³ mm²/s)

ER status, PR status and extent of HER2 expression were evaluated. The following table Table (1) shows the correlation of ADC value with each of them

Table (1) correlation of the molecular biomarkers with the mean ADC value.

		Mean dADC value ---x 10-3 mm		P value
		Mean	Standard Deviation	
ER	positive	.93	.03	< 0.001
	negative	1.14	.05	
PR	positive	.93	.02	< 0.001
	negative	1.08	.10	
HER2	positive	.98	.01	0.385
	negative	.98	.10	
	equivocal	.91	.00	

– Mean ADC of ER-positive cancers (0.93 × 10⁻³ ± 0.03 × 10⁻³ mm²/s.) was significantly lower than that of ER-negative cancers (1.1 × 10⁻³ ± 0.05 × 10⁻³ mm²/s.), p=0.001.

– Mean ADC of PR-positive cancers (0.93 × 10⁻³ ± 0.02 × 10⁻³ mm²/s.) was significantly lower than that of PR-negative cancers (1.08 × 10⁻³ ± 0.1 × 10⁻³ mm²/s.)

However, Mean ADC of HER 2- positive tumours (0.98 x 10⁻³ mm²) showed no statistically significant difference than mean ADC value in HER 2 - negative tumours (0.98 x 10⁻³ mm²) (p=0.385).

Ki-67 positivity was observed in 7/30 (23.3%) of the cases. Of the total, 3 (42.9%)

patients displayed higher than 14% Ki-67 expression, while 7 (57.1%) displayed less than 14% Ki-67 expression.

Lower ADC value is noted with high Ki-67 tumours (0.91 x 10⁻³ mm²), while high ADC value is noted in low Ki-67 tumours (0.99 x 10⁻³ mm²), Yet no statistically significant difference is noted in-between (p=0.365).

II-Correlation of the mean ADC value with the molecular subtypes of the lesion

By combining immunohistochemical markers in profiles recapitulating the intrinsic subtypes, we identified 20 lesions (55.6%) Luminal A tumours, 4 lesions (11.1%) Luminal B tumours, 5 lesions (13.9%) HER2-enriched tumours and 7 lesions (19.4%) triple negative tumours Fig (2).

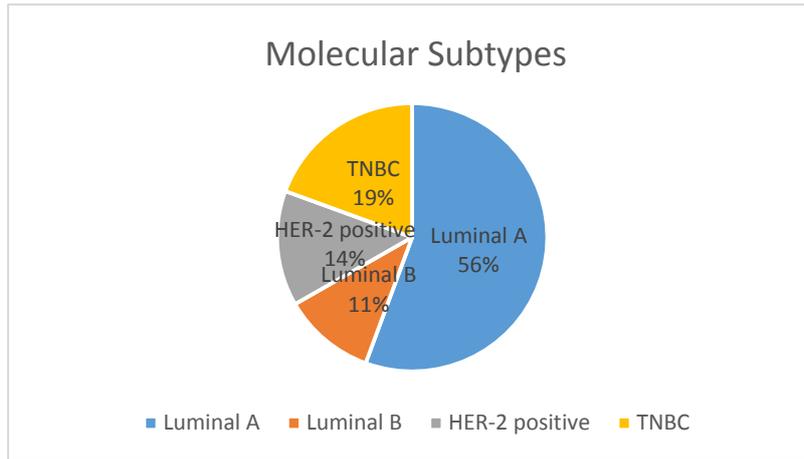


Fig (2) pie chart shows molecular subtypes of examined breast lesions

Molecular subtypes were evaluated. The following table Table (2) shows the correlation of ADC value with each of them Fig (3).

Table (2) correlation of the lesion molecular subtypes with the mean ADC value.

	Mean Standard Deviation	classification				P value
		Luminal A	Luminal B	HER2 positive	TNBC	
Mean dADC value ---x 10-3 mm		.92	.91	.98	1.14	< 0.001
		.01	.00	.01	.05	

- Correlation of the mean ADC value with the molecular classification of the tumor revealed:
 - o The mean ADC value of luminal A group was $0.92 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{s}$.
 - o The mean ADC value of luminal B group was $0.91 \pm 0.00 \times 10^{-3} \text{ mm}^2/\text{s}$.
 - o The mean ADC value of HER2-poistive group was $0.98 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{s}$.
 - o The mean ADC value of TNBC group was $1.14 \pm 0.05 \times 10^{-3} \text{ mm}^2/\text{s}$.

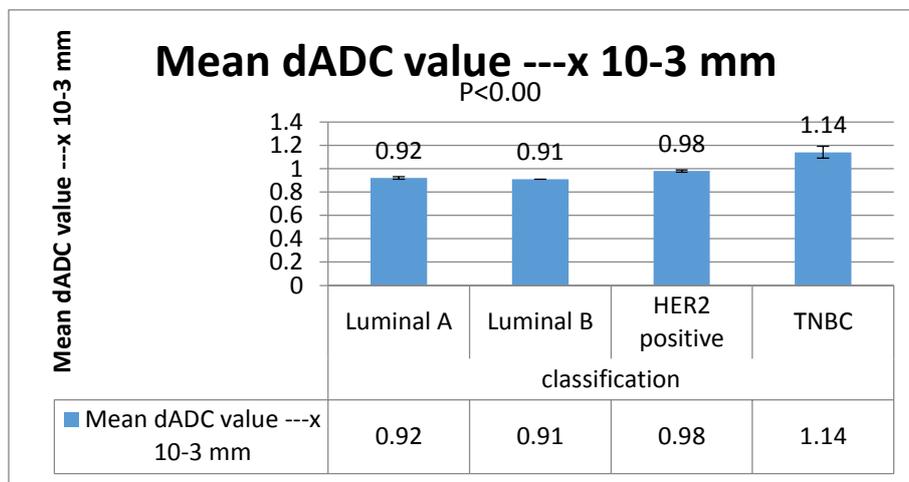


Fig (3) showing mean dADC value in different molecular subtypes.

- There was a significant difference between the mean ADC value of luminal A and HER-2 positive groups ($p= 0.001$); and between luminal B and HER-2 positive groups ($p= 0.001$).
- There was a significant difference between the mean ADC value of luminal A and TNBC groups ($p= 0.001$); and between luminal B and TNBC groups ($p= 0.001$).

- There was a significant difference between the mean ADC value of HER-2 positive and TNBC groups ($p=0.001$);
- However, there was no statistical difference between luminal A and luminal B groups ($p=1$).

4. Discussion

A few investigations need accounted that threatening tumours Typically indicate higher sign power ahead DWI, compared for Favorable lesions Also typical fibroglandular tissue, bringing about easier ADC qualities. It need been proposed that those diminished ADC esteem for harmful tumours might be expected on their expanded cellularity, bigger cores for a greater amount abundant macromolecular proteins, Furthermore lesquerella extracellular space [7], [2],[8]. In this study, we found that the intend ADC of the concentrated on breast threatening massenet might have been $0.97 \pm 0.9 \times 10^{-3} \text{ mm}^2/\text{s}$. This will be comparative of the imply ADC values news person Eventually Tom's perusing different past studies[9]; The imply ADC values of the individuals obtrusive ductal carcinomas $0.98 \pm 0.23 \times 10^{-3} \text{ mm}^2/\text{s}$ versus $(0.89 \pm 0.16 \times 10^{-3} \text{ mm}^2/\text{s})$ from claiming the individuals obtrusive ductal carcinomas not Overall specified.

Different investigations [10],[11] accounted An marginally higher mean ADC worth measuring $1.02 \times 10^{-3} \text{ mm}^2/\text{s}$ What's more $1.03 \times 10^{-3} \text{ mm}^2/\text{s}$.

ADC values went starting with 0.90 should $1.2 \times 10^{-3} \text{ mm}^2/\text{s}$ Previously, our investigation and so, it didn't surpass the cut off esteem between Favorable What's more harmful breast lesions set Eventually Tom's perusing past investigations [12],[13] the primary assessed An cutoff ADC esteem from claiming $1.23 \times 10^{-3} \text{ mm}^2/\text{s}$ with separate harmful starting with benevolent diseases, and the second found that those cut-off ADC qualities to considerate What's more harmful lesions were $1.21 \times 10^{-3} \text{ mm}^2/\text{s}$ to $b = 500 \text{ s/mm}^2$ What's more $1.22 \times 10^{-3} \text{ mm}^2/\text{s}$ for $b = 1000 \text{ s/mm}^2$, separately.

Prognostic factors of living markers, including estrogen receptor (ER) status, progesterone receptor (PR) status & human epidermal development variable receptor 2 (HER2) statement were broke down Furthermore associated for the imply ADC worth done our study.

To general, harmful breast lesions presentation an easier ADC worth due to secondary cell division thickness that brings about confinement of dissemination from claiming water atoms [14], However, former investigations [12] have found that TNBC need a higher imply ADC esteem over

different breast tumor subtypes because of TNBC's necrotic parts.

A portion investigations have accounted that the er influenced those ADC worth due to restraint of the angiogenic pathway Furthermore prompted a diminishing clinched alongside perfusion. An additional consider news person that ER-positive tumours demonstrated secondary cellulite. [15]. This discovering corresponds for our results, we found that ER-positive cancellous and PR sure cancellous indicated essentially bring down intend ADC values, compared with negative ones ($p=0.001$).

However, Despite HER2-positive outflow needed a All the more harmful phenotype, to our study; no statistically critical distinction might have been watched the middle of the intend ADC quality in the HER2 negative and sure bunches ($p=0.389$).

This will be similar with [15] who accounted that no correlations were watched the middle of the imply ADC quality Also HER2 outflow.

In spite of the fact that those clear dissemination coefficient worth in our examine might have been bring down for secondary Ki-67 list tumors over to easier Ki-67 list tumors, those contrasts were not statistically critical (p worth = 0.365). Aftereffect Might be a evidence that expanded Ki-67 list may be a marker of expanded cellulite Furthermore associated for more level ADC values.

Thus, variable discoveries need aid seen On expositive expression in regards those connection between hormonal receptor status Also ADC values.

This variability On comes about may be expected of the contrasts in the tumor span Also examination technique utilized for example, decision of imaging sequence, determination about separate b-values, and the strategy utilized for estimation from claiming ADC if attributed with restriction or measure for ROI. Also, those little test size about our study might be a reason for this error.

Those mean ADC quality of the diverse atomic subtypes for breast tumors incorporated done our study might have been $0.92 \pm 0.01 \times 10^{-3} \text{ mm}^2/\text{s}$, $0.91 \pm 0.00 \times 10^{-3} \text{ mm}^2/\text{s}$, $0.98 \pm 0.01 \times 10^{-3} \text{ mm}^2/\text{s}$ Furthermore $1.14 \pm 0.05 \times 10^{-3} \text{ mm}^2/\text{s}$ to luminal A, luminal B, HER2 enriched Also TNBC gatherings individually.

We discovered a noteworthy Contrast the middle of those imply ADC quality about

luminal A and TNBC bunches ($p=0.001$); Also the middle of luminal B Furthermore TNBC bunches ($p=0.001$). However, there might have been no Factual Contrast the middle of luminal A Furthermore luminal B Assemblies.

In understanding for investigation that discovered whole-lesion ADC Investigation uncovered ADC kurtosis to a chance to be higher done TNBC over those ER-positive subtype, demonstrating that it might be a functional list to differentiating TNBC from different breast tumor subtypes. [16]. This may be unique in relation to the comes about found that those base ADC for luminal A might have been essentially higher over that about luminal B (HER2-negative) (0.83 vs. 0.74×10^{-3} mm²/s; $p < 0.025$). [17]. Clinched alongside our study; triple negative needed those most elevated intend ADC worth (1.14×10^{-3} mm²/s), compared for alternate immunohistochemically characterized innate tumor subtypes.

This may be comparable on affirmed discoveries from claiming higher intend ADC esteem ($P < 0.001$) to TNBC to a univariate analysis, investigations have discovered that TNBC need a higher imply ADC quality over other breast tumor subtypes because of TNBC's necrotic components, reflecting a additional Combative malady course. [16]. Also accounted that triple-negative tumors demonstrated a higher ADC contrasted with non triple-negative tumors. [12]. In our contemplate we news person that imply ADC esteem for HER2-enriched tumours might have been fundamentally higher over that for luminal A ($p=0.001$), luminal B ($p=0.001$). Also we Figure the statistically noteworthy distinction the middle of intend ADC worth for HER2 enriched and "triple-negative subgroup" might have been ($p=0.001$).

Furthermore in understanding about our result study news person that the ADC esteem to HER2-enriched tumours might have been fundamentally higher over that about luminal A ($p=0.004$), What's more luminal B/ HER2-negative ($p=0.008$). A pattern towards measurable noteworthiness might have been also seen for the Contrast with luminal B/ HER2-positive tumours ($p=0.018$). [18].

5. Conclusion

DWI is a contrast-free modality that allows for both morphological and quantitative analysis. ADC value may not be the proper modality to use for identifying the degree of aggressiveness in breast cancer, yet it could be a good predictor of breast cancer cells that would respond to chemotherapy.

5.1 Conflict of interest

The authors declare that they have no conflict of interest.

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