Diffusion Weighted Magnetic Resonance Imaging Texture Biomarkers for Breast Cancer Diagnosis

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Abstract
Quantification of breast lesion heterogeneity by means of MRI texture contributes in differentiating benign from malignant breast lesions. This study investigates the diagnostic performance of1st and 2nd order Texture Analysis descriptors on Apparent Diffusion Coefficient (ADC) lesion maps.78 histologically verified breast lesions (40 benign, 38 malignant) of 67 patients undergoing DW-MRI at 3.0 T, were analyzed. ADC maps were generated for a slice representative of lesion largest diameter. A two-step segmentation approach was applied on high b-value diffusion image, based on Fuzzy C-Means (FCM) clustering and edge-based contouring, for defining the lesion region contour. Lesion contour was transferred to ADC map and subjected to texture analysis by means of twelve first-order and eleven second-order texture features. Logistic Regression Classifier was employed to assess the diagnostic ability of individual features and feature combinations. Diagnostic performance was evaluated by means of the area under Receiver Operating Characteristic curve (Az). The highest classification performance (Az=0.965±0.024) was achieved by the combined feature subset 25th Percentile (1storder) and Entropy (2ndorder),suggesting the diagnostic significance of accurately quantifying lesion heterogeneity by texture-based feature combinations on ADC maps. Combined 1st and 2nd order texture biomarkers provide accurate spatial information of lesion ADC heterogeneity and holds potential in differentiating benign from malignant breast lesion status.

Keywords: Texture Analysis, MR-Diffusion, Breast Cancer Diagnosis, Imaging Biomarkers

Introduction

Quantification of tumor imaging heterogeneity, has the potential to identify (radiomic descriptors) of disease diagnosis, prognosis and response to therapy, non-invasively and cost-effectively [1]. Breast MRI provides functional imaging of breast tumors derived from imaging sequences such as Dynamic Contrast Enhanced (DCE) and Diffusion Weighted Imaging (DWI), mapping tissue vascular permeability/angiogenesis and cellularity/microstructure, respectively. DWI-MRI, quantifies the mobility of water molecules with Apparent Diffusion Coefficient (ADC) maps. Quantitative DWI-MRI analysis has mainly exploited1st order Texture Analysis, highlighting features such as mean ADC value, achieving the highest classification accuracy (Az 0.90) between benign and malignant status [1-3].However, biophysical mechanisms for ADC heterogeneity among different lesions has been further exploited with multi-parametric MRI, combining DCE [4] and DWI image features [5, 6]. Nevertheless, no study has been reported considering 1st and 2nd order texture feature combina-

tions to quantify ADC map heterogeneity for predicting breast cancer clinical diagnosis.

The current study investigates the predictive power of individual 1st and 2nd order texture descriptors and their combinations on ADC lesion maps, in differentiating benign from malignant breast lesions. In order to enhance the proposed pipeline repeatability, image registration and semi-automated segmentation steps were considered.

1 Materials and Methods

1.1 Patient cohort and MRI acquisition

This retrospective study was approved by the Institutional Ethics Committee.78histologically verified breast lesions were analyzed, originating from 67 female patients undergoing DW-MRI at 3.0 T. Thirty-two female patients with40 benign findings and thirty-five female patients with 38 malignant breast tumors were included. Patients underwent breast MRI in a 3.0 T MR scanner(Signa HDx, GE Healthcare), with a dedicated breast coil. Imaging included axial T2-weighted fast spin echo sequence, axial short TI inversion recovery sequence, axial diffusion-weighted echo-planar imaging (DWI) sequence (DW-EPI, TR/TE, 6000/63.7 msec; slice thickness, 4 mm; spacing, 0 mm; matrix, 96x108; FOV, 360x360 mm). Sensitizing diffusion gradients were applied in three orthogonal directions with b values of 0 and 900 sec/mm^2. A three-dimensional fat-suppressed T1-weighted dynamic sequence was acquired once before and five times after the intravenous injection of 0.1 mmol/kg of gadopentate dimeglumine followed by a 20-mL flush of saline solution.

1.2 Image Analysis

In order to remove motion artifacts, a registration algorithm was adopted to map high-b value (b=900sec/mm^2) DW images to corresponding low b value DW images. The applied three-level multi-resolution registration scheme combines two levels of rigid and a final resolution level of b-spline transform, using a Gaussian smoothing pyramid. The applied optimizer is a stochastic gradient descent, while the similarity metric is Mutual Information [7]. The Elastix 4.5 [8] software for intensity-based medical image registration based on the open source software Insight Toolkit (ITK) version 4.0 [9] was used for implementation of the registration scheme.

A semi-automated Fuzzy C-Means (FCM) clustering algorithm [10], was adopted for lesion delineation, having demonstrated improved performance in breast MRI lesion segmentation. Initially, an experienced radiologist defined a loose rectangular region of interest (ROI), containing the whole lesion, in slices representative of lesion's largest diameter, on high b-value diffusion images. FCM was applied the ROI, to build the likelihood membership map (cluster number, 2; weighting exponent, 2; stop criteria, 0.0005; max iteration, 100). Subsequently, an edge-based segmentation model was applied for binarization of the membership map followed by morphological operations to derive the final lesion contour, subsequently transferred to Apparent

Diffusion Coefficient (ADC) map (Fig. 1), generated according to the mono-exponential model [2, 3].Texture Analysis (TA) of ADC lesion maps included two feature sets, composed of twelve 1st order and eleven 2nd order texture features. ADC maps and first order texture analysis were implemented with in-house code in MATLAB R2017b, while second order TA was achieved by MaZda package v4.6 [11]. ADC lesion maps were re-binned to 6 bits/pixel and grey-level normalized ($\mu \pm 3\sigma$) for second order TA. Eleven features from Grey Level Co-occurrence Matrices-GLCM were calculated, considering a distance of one pixel and four directions (0°, 45°, 90° and 135°), averaged in order to obtain rotationally invariant features.

The discriminating ability of extracted features was investigated employing univariate and multivariate Logistic Regression Classifiers, using the publicly available data mining and machine-learning software Weka [12]. The area under Receiver Operating Characteristic (ROC) curve (Az index) was used for evaluating classification performance, employing a 10-fold cross validation training/testing methodology. In case of multivariate logistic regression, the bias of collinearity between features was evaluated using variance inflation factor (VIF) and the corresponding threshold was set at 3.

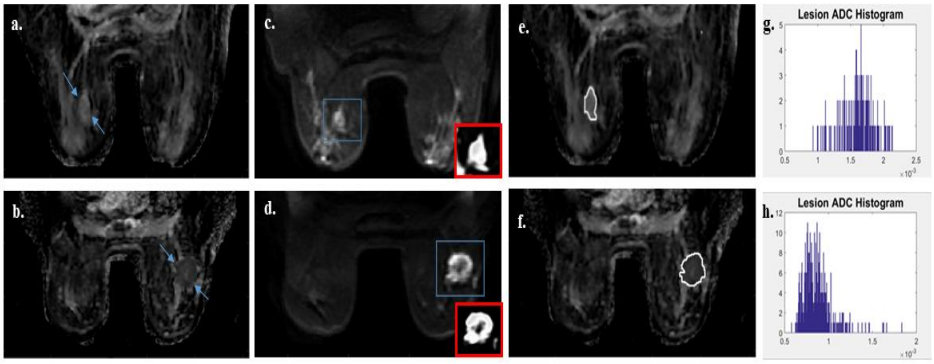

Fig.1 Benign (upper row) and malignant (lower row)breast lesion; ADC map with blue arrows indicating the lesion site (a, b); lesion ROI (blue outline) containing the lesion on high b-value diffusion weighted image (c, d)and corresponding FCM membership map (red outline);Lesion contour (white outline) on ADC map (e, f) provided by edge-based segmentation of FCM map; Lesion ADC histogram (g, h).

2 Results

Table 1 summarizes classification performance of individual texture features and of feature combinations .Among 1st order texture features, 25th Percentile achieved the highest classification performance (Az=0.943±0.029), while among individual 2nd order texture features, Entropy achieved the highest classification performance (Az=0.738±0.057).The highest classification performance (Az=0.965±0.024) was achieved by the selected fused feature subset [25thPercentile (1st order) and Entropy(2nd order)] suggesting the diagnostic significance of accurately quantifying lesion heterogeneity by second-order texture coupled to ADC histogram analysis.

Table 1. Discriminating ability of individual and selected ADC texture feature subset

1st order ADC features	Az ± SE	2nd order ADC features	Az ± SE
Mean	0.924 ±0.037	AngularSecondMoment	0.737±0.057
Standard Deviation	0.559 ±0.065	Contrast	0.647 ±0.062
Skewness	0.748 ±0.056	Correlation	0.550 ±0.066
Kurtosis	0.551±0.065	SumOfSquares	0.612 ±0.064
Entropy	0.821 ±0.064	InverseDifferenceMoment	0.524 ±0.067
Minimum	0.888 ±0.037	SumAverage	0.709 ±0.059
Maximum	0.831 ±0.052	SumVariance	0.605 ±0.066
25th Percentile	0.943 ±0.029	SumEntropy	0.691 ±0.061
50th Percentile	0.926 ±0.053	Entropy	0.738 ±0.057
75th Percentile	0.920 ±0.038	Difference Variance	0.556 ±0.066
Range	0.623 ±0.063	Difference Entropy	0.568 ±0.065
25th Percentile(1st order) + Entropy(2nd order)		0.965±0.024	

3 Discussion and Conclusion

Previously reported studies have demonstrated the ability of histogram ADC features in differentiating malignant from benign breast lesions[1-4]. As histogram ADC features provide a coarse quantification of lesion heterogeneity, 2nd order TA has emerged to extract high-throughput localized description of lesion spatial ADC heterogeneity (tumor phenotype). Results of the current study demonstrated that incorporating 1st and 2nd order ADC texture features into a multivariable diagnostic model in breast DW- MRI improves diagnostic accuracy. These findings agree with previously multiparametric MRI reported studies demonstrating that quantitative information captured by 1st and 2nd order TA is highly correlated to prediction of clinical diagnosis [5,6]. Limitations of the current study account for small patient cohort and empirically selected parameters of semi-automated segmentation, limiting standardization and validation procedures. Future steps will be focused on validating image registration and segmentation steps on an augmented dataset an on exploiting additional feature selection and classification schemes. The approach of combining 1st and 2nd order

ADC texture features is promising, especially in improving diagnostic accuracy, while dealing with cases of non-typical breast cancer morphologies. Towards this direction, a combined DCE and ADC texture analysis approach is currently under investigation.

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Conflict of Interest Declaration
Authors declare that there is no conflict of interest for the publication of this work.

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