Received:
4 April 2016

Revised:
30 September 2016

Accepted:
5 October 2016

<https://doi.org/10.1259/bjr.20160304>

Cite this article as:

Bougias H, Ghiatas A, Priovolos D, Veliou K, Christou A. Whole-lesion apparent diffusion coefficient (ADC) metrics as a marker of breast tumour characterization—comparison between ADC value and ADC entropy. *Br J Radiol* 2016; **89**: 20160304.

FULL PAPER

Whole-lesion apparent diffusion coefficient (ADC) metrics as a marker of breast tumour characterization—comparison between ADC value and ADC entropy

¹HARALAMBOS BOUGIAS, ²ABRAHAM GHIATAS, MD, PhD, ²DIMITRIOS PRIOVOLOS, ³KONSTANTIA VELIOU, MD and ⁴ALEXANDRA CHRISTOU, MD

¹Department of Medical Imaging University Hospital of Ioannina, Ioannina, Greece

²Department of Medical Imaging IASO Maternity Hospital, Athens, Greece

³Department of Medical Imaging Chatzikosta General Hospital of Ioannina, Ioannina, Greece

⁴Department of Medical Imaging, Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Doncaster, UK

Address correspondence to: Dr Alexandra Christou

E-mail: alexandrachristou@gmail.com

Objective: To prospectively assess the role of whole-lesion apparent diffusion coefficient (ADC) metrics in the characterization of breast tumours by comparing ADC value with ADC entropy.

Methods: 49 patients with 53 breast lesions underwent phased-array breast coil 1.5-T MRI. Two radiologists experienced in breast MRI, blinded to the final diagnosis, reviewed the ADC maps and placed a volume of interest on all slices including each lesion on the ADC map to obtain whole-lesion mean ADC value and ADC entropy. The mean ADC value and ADC entropy in benign and malignant lesions were compared by the Mann–Whitney *U*-test. Receiver-operating characteristic analysis was performed to assess the sensitivity and specificity of the two variables in the characterization of the breast lesions.

Results: The benign ($n=19$) and malignant lesions ($n=34$) had mean diameters of 20.8 mm (10.1–31.5 mm) and 26.4 mm (10.5–42.3 mm), respectively. The mean ADC value of the malignant lesions was significantly lower than that of the benign ones (0.87×10^{-3} vs $1.49 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$; $p < 0.0001$). Malignant ADC entropy

was higher than benign entropy, without reaching levels of statistical significance (5.4 vs 5.0; $p = 0.064$). At a mean ADC cut-off value of $1.16 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, the sensitivity and specificity for diagnosing malignancy became optimal (97.1% and 93.7, respectively) with an area under the curve (AUC) of 0.975. With regard to ADC entropy, the sensitivity and specificity at a cut-off of 5.18 were 67.6 and 68.7%, respectively, with an AUC of 0.664.

Conclusion: Whole-lesion mean ADC could be a helpful index in the characterization of suspicious breast lesions, with higher sensitivity and specificity than ADC entropy.

Advances in knowledge: Two separate parameters of the whole-lesion histogram were compared for their diagnostic accuracy in characterizing breast lesions. Mean ADC was found to be able to characterize breast lesions, whereas entropy proved to be unable to differentiate benign from malignant breast lesions. It is, however, likely that entropy may distinguish these two groups if a larger cohort were used, or the fact that this may be influenced by the molecular subtypes of breast cancers included.

INTRODUCTION

The evaluation of the conventional MRI of the breast is based on the combined analysis of the morphology and the enhancement kinetics of the lesions. With this method, information about tumour physics, vascularity and vascular permeability is obtained.¹ The method provides high sensitivity for breast cancer, but the specificity is moderate. Previous results showed that dynamic contrast-enhanced (DCE) MRI has a 98% sensitivity and 76% specificity.² Overlapping in morphologic characteristics and kinetic features between benign and malignant lesions can result in misclassifications.

In an attempt to increase the diagnostic efficacy—mainly the specificity—of breast MRI, evaluation of the role of diffusion-weighted imaging (DWI) has already been investigated in a number of previous reports and suggested that the specificity of MRI has been improved to 89% with the combination of DCE-MRI and DWI, without significant decrease in sensitivity.¹

DWI can also be evaluated in a quantitative fashion, which is most typically achieved by computing apparent diffusion coefficient (ADC) values. ADC is a measure of the magnitude of water molecule diffusion.³

Entropy is a texture-based statistical measure of the variation in the histogram distribution of a given metric and represents the predictability of the intensity of the metric within the tissue. Thus, entropy reflects textural variation and increases with greater macroscopic heterogeneity.³ Higher entropy indicates the presence of a large number of voxels with different values in an unpredictable distribution and is believed to represent greater macroscopic structural heterogeneity of the tissue, suggesting a higher probability for malignancy. ADC entropy has been shown to be of value in the characterization of liver fibrosis, multiple sclerosis and adrenal masses.^{3–6}

This study aimed to investigate the significance of these two parameters of the histogram, the whole-lesion (multislice) mean ADC value and the ADC entropy in the characterization of the breast lesions, by evaluating their sensitivity and specificity and comparing their diagnostic efficacy.

METHODS AND MATERIALS

Subjects

We prospectively reviewed 49 females with 53 breast lesions with a mean age of 54 years (37–71 years). DWI was applied as a part of our standard breast MRI protocol together with DCE-MRI in all cases. The main referral indications were: pre-operative local staging of the tumour and clarification of suspicious findings on conventional imaging (mammography, ultrasound). Informed consent was

obtained. The research was initially approved by our institution and the director of the institution breast imaging department.

Imaging protocol

All patients were examined with a 1.5-T MR unit (Magnetom Avanto; Siemens Healthcare, Erlangen, Germany) equipped with a four-channel dedicated breast coil. Whenever appropriate, we performed the examination during the second week of the menstrual cycle for the pre-menopausal females. Patients were placed in prone position.

The conventional imaging protocol included an axial fat-suppressed T_2 weighted turbo spin-echo sequence [repetition time (TR)/echo time (TE): 4000/97 ms; matrix: 320×320 pixels; slice thickness: 4 mm], a three-dimensional T_1 weighted non-fat-suppressed sequence (TR/TE: 8.6/4.6 ms; matrix: 320×320 pixels; slice thickness: 1.5 mm) and a T_1 weighted fat-suppressed DCE sequence with one pre-contrast and six post-contrast acquisitions in the axial plane (dynamic scan duration: 1 min, slice thickness: 1.5 mm).

The Diffusion-weighted images were obtained as part of our protocol following the T_1 and T_2 weighted images and before the DCE sequences. A two-dimensional spin-echo echoplanar imaging sequence (TR/TE: 5800/97 ms; matrix: 192×192 pixels; signal average: 5; slice thickness: 4 mm; distance factor: 0%;

Figure 1. A 51-year-old female with a lesion in the right breast: (a) an axial three-dimensional (3D) T_1 weighted fat-saturated image with gadolinium is displaying the contrast-enhanced lesion. (b) An axial 3D T_1 weighted image is showing the lesion as a hypointense area. (c) A diffusion-weighted image with a b -value of 1300 s mm^{-2} is revealing increased signal intensity throughout the mass. (d) The apparent diffusion coefficient (ADC) map is showing a nearly homogeneous low mean ADC value within the mass. Whole-lesion analysis yielded a whole-lesion ADC mean value of $0.89 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. This low ADC mean value was suggestive of malignancy, which was also proven histopathologically, despite the relatively high lesion entropy (ADC entropy = 4.4).

acquisition voxel size: $1.7 \times 1.7 \times 4$ mm; band width: 1370 Hz/pixel; spectral attenuated inversion recovery fat suppression) was acquired in the axial plane. Diffusion gradients in three orthogonal directions with b -values of 0, 400, 800 and 1300 s mm^{-2} were applied. The ADC maps were created automatically by the system using the b -values 0 and 1300 s mm^{-2} in a mono-exponential fit according to the formula:

$$S(b)/S_0 = \exp(-b \times \text{ADC}),$$

where $S(b)$ is the signal magnitude with diffusion weighting b , S_0 is the signal magnitude with no diffusion weighting and b is the b -value.⁷

Imaging analysis

All breast MR images were evaluated and interpreted on a workstation by two radiologists with 15 and 4 years' experience, respectively (AG and AC).

The operators were blinded to the final diagnosis (histology). Subtracted and T_2 weighted images were primarily used to

morphologically describe and identify the suspicious lesions found on conventional imaging (mammography, ultrasound).

DCE breast MRI was used to visualize the initial enhancement of the invasive breast cancers and ductal carcinoma *in situ* and generally to characterize the enhancing structures, based on their enhancing features and their associated kinetic curves according to the Breast Imaging-Reporting and Data System lexicon.

DW images were coregistered to b_0 image for motion correction and then, the ADC maps were calculated. The radiologists reviewed the images using an in-house processing routine that allows the placement of three-dimensional volumes of interest (VOIs) incorporating voxels across multiple slices on the high b -value images where the suspicious lesion was best visualized and then, the VOIs were copied to ADC images (Figure 1). The axial high b -value and the ADC maps were viewed concurrently in a single session for each case. The whole-lesion ADC mean value and ADC entropy were then calculated from the histogram of ADC values. Entropy was computed as:

Figure 2. A 51-year-old female with a lesion in the right breast: histogram of the whole lesion is showing a large portion of pixels with low apparent diffusion coefficient values (invasive ductal carcinoma).

$$\sum (-\pi)/\log(\pi)$$

where π represents the frequency of ADC values in the VOI (*i.e.* the number of corresponding voxels normalized to the total number of lesion voxels).³

Images with susceptibility artefacts were excluded, as well as cases with lesion sizes <8 mm (*i.e.* twice the image slice thickness of 4 mm), as this is the minimum appropriate size to perform multislice processing. Biopsy of the suspicious breast lesions was performed after the MRI in all cases included in this study. Cases acquired after MRI biopsies were excluded from the study, owing to potential changes in the structure and the heterogeneity of the tumours.

Statistical analysis

Whole-lesion mean ADC value and ADC entropy between benign and malignant lesions were compared by the Mann–Whitney *U*-test (level of significance set at 0.05). Receiver-operating characteristic analysis was used to determine the most effective cut-off values of mean ADC and ADC entropy for the differentiation between benign and malignant pathologies. All analyses were performed by the use of MedCalc® v. 15.0 software (MedCalc Software, Ostend, Belgium).

RESULTS

Malignancy was diagnosed in 34 cases through the course of histological verification. Surgery was performed according to the pathological results. The remaining 19 lesions were categorized as benign; the majority (17 cases) underwent histological evaluation, while 2 of them did not comprise tissue sampling, but instead were followed up and found to remain stable for a time period exceeding 2 years. The malignant lesions were mainly invasive ductal carcinomas (19), invasive lobular carcinomas (13) and ductal carcinoma *in situ* (2) and the benign lesions

were mainly fibroadenomas (9), fibrocystic changes and sclerosis adenosis with no atypia (6) and papillomas with no atypia (2).

The mean size of the benign lesions was 20.8 mm (range 10.1–31.5 mm) and the mean size of the malignant lesions was 26.4 mm (range 10.5–42.3 mm).

Examples of malignant and benign breast lesions, whole-lesion ADC measurement and the corresponding histograms are illustrated in Figures 1–4.

The whole-lesion mean ADC value of malignant lesions was found to be significantly lower than that of the benign lesions (0.89×10^{-3} vs $1.49 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, respectively; $p < 0.0001$) (Figure 5).

Malignant ADC entropy was higher than benign entropy, approaching levels of statistical significance (5.4 vs 5.0, respectively; $p = 0.064$) (Figure 6) (Table 1).

Receiver-operating characteristic analysis revealed a whole-lesion mean ADC cut-off value of $1.16 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ as the best predictor of malignancy (area under the curve = 0.975). For the ADC entropy, the optimal cut-off was 5.18 (area under the curve = 0.664), but still its diagnostic efficacy was less than that of whole-lesion mean ADC (Figure 7) (Table 2).

DISCUSSION

Breast MRI is a well-established adjunct technique to mammography and ultrasound for the evaluation of breast lesions. It is widely used in a variety of clinical settings, such as local staging in patients recently diagnosed with breast cancer and as a screening tool for high-risk females.^{8–13} DCE breast MRI is the most proposed imaging method, with a high sensitivity ranging between 89 and 100%. However, its suboptimal specificity (reportedly around 75%) imposes a significant setback, particularly in

Figure 3. A 59-year-old female with a lesion in the right breast: (a) an axial T_2 weighted fat-saturated image is displaying a high-signal intensity lesion. (b) A diffusion-weighted image with a b -value of 1300 s mm^{-2} is revealing increased signal intensity throughout the mass. (c) The apparent diffusion coefficient (ADC) map is showing a nearly homogeneous high ADC value within the mass. (d) A subtracted image is displaying the contrast-enhanced lesion. This high ADC mean value was suggestive of benignity, which was also proven histopathologically, despite the relatively high lesion entropy (ADC entropy = 6.4).

Figure 4. A 59-year-old female with a lesion in the right breast: histogram of the whole lesion is showing relatively large apparent diffusion coefficient values comparing with the malignant case (fibroadenoma).

patients referred for evaluation of inconclusive findings on clinical examination and conventional breast imaging.^{14,15}

DWI provides a non-contrast mechanism in MRI and has a high sensitivity in the detection of changes in the microscopic cellular local biologic environment.^{1,16–20} Its effectiveness stems from the inverse correlation between the tumour cellularity and the ADC metrics. Nonetheless, overlapping ADC mean values between malignant and benign breast lesions have been described. This may be partly due to the selection of the b -value, which can influence the concomitant effect of perfusion and emphasize the contribution of multicomponent model influences.

While numerous studies have assessed the correlation between ADC mean value and tumour cellularity, the differentiation between benign and malignant lesions using this parameter is still challenging.^{21–26} This may be attributable to breast tumour heterogeneity, with the most aggressive part being located anywhere within the tumour volume, whereas ADC is traditionally measured as the average value within a region of interest just a single-slice thick.

However, imaging studies in other tissues have demonstrated the importance of measuring ADC using a whole-lesion

volume-based approach; apart from providing a more complete representation of the entire tumour, this also facilitates the computation of more advanced metrics that reflect overall lesion texture and heterogeneity.^{1,3} Thus, it is widely recognized that the whole-lesion analysis method, which contains all voxels from all sections covering the entire tumour, may better reveal intratumoral heterogeneity and improve clinical evaluation compared with focusing on a limited tumour area, such as the largest cross-sectional area.^{27–29}

In recent years, medical imaging of spatial tumour heterogeneity has drawn significant attention owing to its non-invasive nature and the potential to assess the lesion in its entirety, as compared with local tissue sampling through the course of a biopsy. Many mathematical models have been developed and employed to analyze tumour heterogeneity; whole-lesion histogram analysis is one of the most popular methods.^{30,31} The development of post-processing platforms has made histogram analysis easier and less time-consuming. The method holds a great potential, even though there are still many challenges to be addressed until its role in tumour characterization is established in everyday practice.²⁶

Figure 5. A boxplot showing mean apparent diffusion coefficient (ADC) for benign and malignant breast mass lesions.

In our study, we compared two different histogram parameters: the whole-lesion ADC mean value and the whole-lesion entropy of certain breast abnormalities.

Our results regarding whole-lesion (multislice) mean ADC value suggest that it is able to characterize breast lesions. This study showed high sensitivity comparable with single-slice ADC value sensitivities published in the literature.^{32–34} However, we achieved a specificity exceeding 93%. Although comparison of single-slice with multislice whole-lesion ADC results was not the purpose of this study, the high specificity may suggest that a volumetric analysis of each

lesion, instead of the single section-based measurement, may better depict the morphologic heterogeneity of breast lesions, which is mainly attributable to the fact that multislice whole-lesion ADC calculation eliminates the source of single-slice sampling errors deriving from tumour heterogeneity.²⁶ However, a further study comparing single-slice with multislice whole-lesion ADC should be performed providing accurate results.

It is, however, important to point out the parameter of lesion size. There were too few pixels/ADC values to get meaningful histogram (statistical) metrics from considering that our voxel

Figure 6. A boxplot showing apparent diffusion coefficient (ADC) entropy for benign and malignant breast mass lesions.

Table 1. Mean ADC and mean ADC entropy histogram parameters

Lesion type	ADC ($\text{mm}^2 \text{s}^{-1}$)	ADC entropy
Benign lesions ($n = 19$)	1.49×10^{-3} ($0.97\text{--}2.07 \times 10^{-3}$) ^a	5.0 (4.1–6.5) ^a
Malignant lesions ($n = 34$)	0.89×10^{-3} ($0.52\text{--}1.38 \times 10^{-3}$) ^a	5.4 (4.4–7.1) ^a
<i>p</i> -value (Mann–Whitney <i>U</i> -test)	<0.0001	0.064

ADC, apparent diffusion coefficient.

^aMean value (range).

size is $1.7 \times 1.7 \times 4$ mm. So the lesions we studied were at least double the size of our voxel size in order to have enough pixels for the histogram analysis.

Entropy is a texture-based statistical measure of the variation in the histogram distribution of a given ADC metric and represents the predictability of the intensity of the metric within the tissue. High-entropy images contain a large number of voxels with different values, each of which are more or less equally prevalent. Malignant pathologies tend to affect a tissue heterogeneously and are expected to result in less predictable intensity characteristics within the tissue and thus higher entropy.^{4,6} Entropy equals 0 if all values are the same and increases as the data distribution becomes more irregular.²⁶

The malignant tumours in our population displayed a tendency for higher entropies as compared with the benign ones, although a considerable degree of overlap between the two types of lesions precluded statistical significance. This is mainly the reason why the diagnostic accuracy of ADC entropy was found to be substantially inferior to that of the whole-lesion mean ADC value. The relatively smaller size of breast lesions, as compared with that of adnexal tumours or tumours in other organs, may in part hold a possible explanation, since the degree of malignant tissue

heterogeneity can increase with increasing lesion dimensions.³ However, although in our study, the mean size of the malignant lesions was higher than that of the benign ones, which suggests that the entropy should be higher, this did not show statistical significance in the differentiation of the lesions; in contrary, the overlap between the benign and the malignant lesions was surprisingly wide.

It is also important to point out the factor of heterogeneity of the malignant lesions in our popularity. The malignant lesions were mainly luminal cancers with only one triple-negative case; thus, the less heterogeneous molecular types of the tumours in our study might also be a possible reason why entropy did not reach statistical significance between malignant and benign lesions. It is known that triple-negative carcinomas are usually larger in size and more defined and necrotic tumours than luminal cancers, often with a pronounced peripheral rim enhancement which is restricted on DWI and frequently with a less restricted central component which reflects central necrosis/fluid within the tumour.^{35,36} Entropy is an indicator of tumour heterogeneity and most of the cancers included in our study might have been relatively less heterogeneous, more often seen in conventional cancers but not in triple-negative cancers.

Suo et al²⁶ (JMIR) (April 2016) recently showed in their study that entropy in malignant lesions is higher than the entropy in benign masses with statistical significance ($p = 0.001$). However, the DWI sequence was performed with a higher *b*-value of 600 s mm^{-2} , whereas in our study, the higher *b*-value was 1300 s mm^{-2} . The difference in the applied high *b*-values is possibly the main reason for the difference in our results and the overlap we found in entropy between benign and malignant breast lesions, as in higher *b*-values (e.g. 1300), the heterogeneity of the masses is less obvious. Another possible reason may be the limited number of our cases (54) comparing with 101 in the Sue et al study.

Figure 7. Receiver-operating characteristic analysis of the results for whole-lesion mean apparent diffusion coefficient (ADC) value and whole-lesion ADC entropy: the criterion for whole-lesion mean ADC value is $1.16 \times 10^{-3} \text{ mm}^2 \text{s}^{-1}$ with sensitivity 97.1% and specificity 93.7%. The criterion for whole-lesion ADC entropy is 5.18 with sensitivity 67.6% and specificity 68.7%.

Table 2. Comparison of mean ADC and mean ADC entropy ROC curves in differentiation of benign and malignant breast lesions

ROC analysis parameters	ADC ($\text{mm}^2 \text{s}^{-1}$)	ADC entropy
Cut-off value	1.16×10^{-3}	5.18
Sensitivity	0.971	0.676
Specificity	0.937	0.687
AUC	0.975	0.664

ADC, apparent diffusion coefficient; AUC, area under the curve.

Finally, as mentioned in our protocol, the b -values we used for this study were 0 and 1300 s mm^{-2} , based on the mathematics involved in the equation $S(b)/S_0 = \exp(-b \times \text{ADC})$, where S is the signal intensity after application of the diffusion gradient and S_0 is the signal intensity on the diffusion image acquired at $b = 0 \text{ s mm}^{-2}$. Although many articles in the radiology literature have used multiple b -values to calculate ADC maps, there have been prior published articles opposing the use of multiple b -values for creating ADC maps when using monoexponential models in DWI, suggesting that using more b -values may not change the resulting ADC maps at all or actually decrease the quality of the ADC maps.^{37–41}

The limitations of this study mainly pertain to the limited number of cases and the issues regarding measuring entropy (a statistical histogram measure) on limited number of values. As explained earlier, all the lesions we analyzed were at least 8 mm in order to get meaningful histogram (statistical) metrics from our voxel size ($1.7 \times 1.7 \times 4 \text{ mm}$). Another limitation is the possible relative low heterogeneity of the malignant lesions and the lack of histological verification in a small portion of the benign lesions.

In conclusion, the whole-lesion mean ADC value is a useful MRI index derived from the histogram and could play an

important role in the differentiation between the benign and the malignant breast tumours, with excellent specificity rates higher than those of the single-slice ADC value published in the literature and excellent sensitivity rates consistent with that of the single-slice ADC value published in the literature. On the other hand, the diagnostic accuracy of the ADC entropy in the differentiation of the benign and the malignant breast lesions seems to be inferior that of the whole-lesion mean ADC value although it has already been shown to play an important role in the lesions differentiation in many other organs. However, further studies on a larger scale and with different molecular subtypes of breast cancers to increase the heterogeneity are required to investigate more meticulously the diagnostic value of these two breast MRI diffusion parameters.

ACKNOWLEDGMENTS

We would like to thank Dr Spyridon Tsiouris, MD, for his valuable help in the preparation and editing of the article.

CONFLICTS OF INTEREST

No conflict of interest, financial or otherwise is declared in the data acquisition or preparation of this paper.

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