Factors Affecting ADC Measures in Breast Cancer Patients

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Introduction and Aims: Breast Magnetic Resonance Imaging (MRI) is becoming more routinely used for lesion characterisation and assessment of response to neoadjuvant chemotherapy in breast cancer patients. The addition of diffusion weighted imaging (DWI) characteristics to standard morphological features and enhancement kinetics can improve lesion characterisation through improved specificity [1]. DWI reflects underlying water motility in the tissue of interest, and it is well established that in tumours the high cellularity leads to a reduction in diffusion. This can be quantitatively characterised by measuring the Apparent Diffusion Coefficient (ADC).

There is little data available within the literature as to the repeatability of such measurements and the effect of various extraneous factors on these quantitative values. Therefore it is imperative to characterise the various influences on these measures to ensure accurate, repeatable reporting of ADC so that it can be used in routine clinical practice. The aim of this work was to investigate the influence of scanner stability, scan-scan variability, intra- and inter- observer repeatability and the effect of measuring a whole tumour ADC compared with a minimum ADC value in order to fully characterise potential errors within the measurement.

Methods: To assess scanner stability, an ice-water phantom [2] was used and scanned weekly in each side of the breast coil using the standard clinical imaging sequence over the course of six weeks. ADC values were recorded and stability was assessed using the coefficient of variance (CoV) across all measurements. Scan-scan reproducibility was assessed in 10 healthy female volunteers (age range: 26-61; mean: 44.7 years) who were scanned twice on a 3.0T MRI scanner (Siemens Trio; Erlangen, Germany) using the standard DWI sequence (b=50, 800 s/mm^2, voxel size: 1.8×1.8×4 mm^2). Volunteers were scanned with a 4-week time interval between examinations to ensure each volunteer was scanned in the same phase of their menstrual cycle, since the latter can influence ADC measures [3]. Scan data was anonymised and the scans were analysed in random order. For analysis, the slice with the most homogeneous fibroglandular tissue was chosen by comparison with an axial T2 weighted scan. A region of interest (ROI) of around 40 pixels was placed within healthy fibroglandular tissue on the ADC map to obtain ADC values. Repeatability between examinations was then assessed using coefficient of reproducibility (CoR, units mm^2/s) and intraclass correlation coefficients (ICC).

Repeatability of measures within patient lesions was assessed using images from 46 patients with biopsy-proven cancer who had been imaged using our clinical protocol described above. Measurements of whole tumour ADC (ADC_{WT}) and lowest ADC (ADC_{min}) were assessed by manually drawing around the entire lesion, avoiding artefact and by interrogating the tumour using a 3mm^2 ROI to identify the lowest ADC respectively. Analysis was performed by a technical and a clinical observer twice, with a minimum of one week between analysis sessions. Repeatability of measurements was assessed using CoR and ICC.

Results: Scanner stability, as assessed using the phantom measurements, demonstrated excellent stability within the breast coil with an average ADC of 1.089×10^{-3} mm^2/s and a CoV of 6.6% (0.07×10^{-3} mm^2/s). Average measures over time from each individual side of the breast coil were $ADC_{LEFT}=1.096\times10^{-3}$ mm^2/s and $ADC_{RIGHT}=1.082\times10^{-3}$ mm^2/s and no significant differences were demonstrated between measures of ADC on either side.

Analysis of the healthy volunteer data demonstrated that there was a slight difference in ADC measures between the left and right breast, with average values of $ADC_{LEFT}=1.499\times10^{-3}$ mm^2/s and $ADC_{RIGHT}=1.473\times10^{-3}$ mm^2/s, however these were not found to be significantly different across all volunteers at both time-points (p=0.887; students t-test). When comparing the baseline and follow-up examinations, a CoR= 0.122×10^{-3} mm^2/s was calculated, with average ADC values of $ADC_{baseline}=1.503\times10^{-3}$ mm^2/s and $ADC_{follow\text{-}up}=1.544\times10^{-3}$ mm^2/s leading to an overall estimation of CoR of 8.0%. Intra class correlation coefficients were found to be good, at 0.811.

Table 1 summarises the intra-observer measurements for the whole tumour and worst case tumour ADC values for the technical and clinical observer. From these, it is clear that both technical and clinical observers demonstrated excellent repeatability. The average repeatability for the clinical observer was 17% for both measures, while for the technical observer was 11.1% for ADC_{WT} and 16.8% for ADC_{min}.

The inter-observer repeatability was ADC_{WT}, CoR= 0.302×10^{-3} mm^2/s (ICC=0.939; 30.0%) and ADC_{min}, CoR= 0.120×10^{-3} mm^2/s (ICC=0.872; 31.9%).

	ADC_{WT}		ADC_{min}	
	Technical	*Clinical*	*Technical*	*Clinical*
Mean	1.020	1.290	0.778	1.033
CoR	0.113	0.220	0.131	0.177
ICC	0.983	0.980	0.976	0.972

Table 1*- Summary of CoR and ICC measures for intra-observer measures of whole tumour and worst case tumour ADC values*

Discussion: Our phantom measurements were found to be within 1% of the ADC reported for water at 0°C (1.1×10^{-3} mm^2/s). Our repeatability measures suggest that scanner stability has minimal effect on the repeatability of measures of ADC. With just a contribution of 6%, this is found to be in line with the measured scan-scan variation as assessed within our healthy volunteer population.

The coefficient of repeatability for scan-scan variations within the volunteer population was measured to be on the order of 10%. This measure is likely to reflect uncertainty when placing an ROI within a region of healthy fibroglandular tissue, and therefore slight positional differences between analyses of each time-point scan. This may also reflect the fatty composition of some of the breasts included which could potentially have resulted in some partial volume effects on the ADC measurements. Absolute ADC values measured were variable, but this is likely due to the age range and breast characteristics of the volunteer population. All women were imaged in the same phase of their menstrual cycle at baseline and follow-up in order to negate any cyclic effects that have been previously noted [3].

The results from the patient study identify the whole tumour ADC to be most repeatable both for measurements made by the one observer, and between observers. While the intra-observer repeatability of ADC_{min} is still good, the higher variability is likely to be due to the use of such a small ROI and influences of tumour heterogeneity, observer perception and imaging artefacts. In order to assume a repeatable clinical protocol, measures of the averaged ADC across the whole tumour are likely to be more useful.

The biggest influence on the ADC measures was the inter-observer variability, with around 30% error on the average measured value for both ADC_{WT} and ADC_{min}, but slices were not matched for analysis between observers and had this step been performed, an increase in the repeatability is highly likely.

Conclusions: We conclude that measurements of ADC in patients are relatively unaffected by scanner stability or scan-scan variation, as both of these measures were found to contribute less than 10% variation on the measurement. Intra-observer repeatability was good with ICC values of greater than 0.9 for all whole tumour measures. Inter-observer variability was found to be the biggest factor influencing ADC measures with up to 30% error on the average measured value. This factor should therefore be considered in departments with multiple reporting radiologists and in research or follow-up studies and in research or follow-up studies performed in multiple centres.

References:

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