# Qualitative and Quantitative Assessment of Breast Tumour Appearance in Diffusion-weighted Imaging and Correlation with Molecular Prognostic Factors

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INTRODUCTION: Breast tumours are heterogeneous, characterised by different behaviour, prognosis and response to therapy. Apart from traditional prognostic indicators such as age, axillary lymph node status, tumour size and grading, there are molecular prognostic factors which are usually assessed such as estrogen receptor (ER) and progesterone receptor (PgR) expression, overexpression of HER-2 and Ki-67 expression. Although diffusion weighted magnetic resonance imaging (DW-MRI) has shown potential in assessing breast tumours, there is only one study that has correlated the value of the apparent diffusion coefficient (ADC) with prognostic factors [1] and another study which assessed the intra- and interobserver variability in the calculation of breast tumour ADC values [2]. The aims of our study were to prospectively perform a qualitative analysis of diffusion weighted magnetic resonance imaging (DW-MRI) of breast tumours in order to identify semiotic characteristics common to breast tumours, to assess the interobserver variability in the calculation of ADC values, and to correlate the quantitative analysis of ADC with molecular prognostic factors of breast tumours.
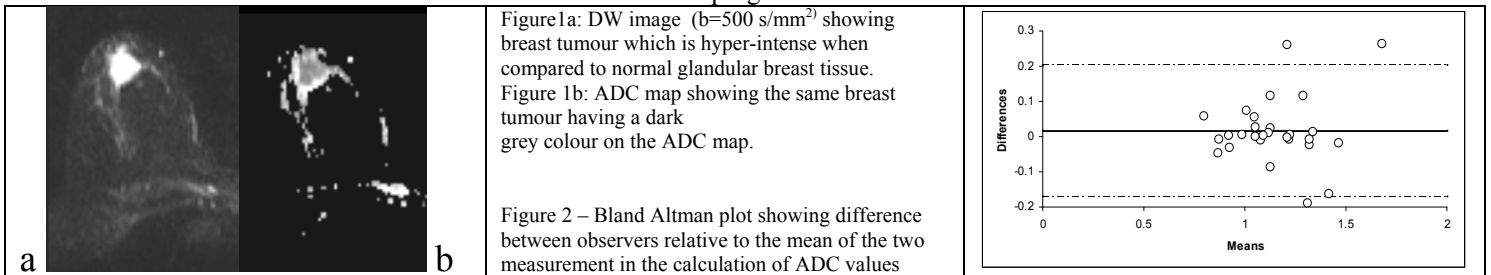
MATERIALS AND METHODS: The study was approved by our institutional ethics committee, and written informed consent was obtained from all participants before entry into study. Twenty-eight patients (28 F, mean age 48.8, range 28-81 years) with solid malignant breast tumours greater than 10mm diameter, who were candidates for surgery underwent conventional MR with an integrated DW-MRI acquisition. All exams were performed on a 1.5T scanner (Avanto, Siemens Medical Systems, Erlangen, Germany). The conventional imaging included T2 weighted Short-Tau Inversion Recovery (STIR), and dynamic T1 weighted Gradient Echo 3D sequences (one pre- and 7 post-administration of paramagnetic contrast agent). Diffusion weighted imaging the imaging parameters were: TE/TR 71/4800 ms, FOV/SLT/gap 307x200/5/1mm, IPAT=2, b-values: 0, 250, 500 and 1000s/mm$^2$.

Qualitative analysis consisted of categorizing the signal intensity of lesions in STIR and DW images (hyper-, iso- or hypo-intense relative to normal surrounding glandular breast tissue). For the apparent diffusion coefficient (ADC) maps the tumour was visually rated as having a high or low ADC (seen as light or dark grey respectively in the ADC maps). For quantitative analysis, a volume of interest mask was defined on the high b-value (b = 500, 1000s/mm$^2$) images in which the lesion was present and isolated from the surrounding breast tissue by manual thresholding using a general purpose image analysis software (ImageJ, NIH, USA). Mean, median and standard deviation of the ADC values in the tumour masks were then calculated using scripts written in-house (based on fsl tools, FMRIB, University of Oxford, England). The segmentation process was performed by two radiologists. The agreement between observers in the calculation of the ADC values was assessed using the Bland and Altman plot [3].

According to the final pathological result from the surgical specimen, the tumours were classified in 4 subtypes: (1) LUMINAL A (ER positive or PgR positive, HER-2 negative, Ki-67<14%), (2) LUMINAL B (ER positive or PgR positive, HER-2 negative, Ki-67≥14%), (3) HER-2 (Overexpression of HER-2), (4) Triple receptor negative (ER negative, PgR negative and HER-2 negative). Differences in the mean ADC values were assessed using analysis of variance (ANOVA) for the following categories: the four subtypes (LUMINAL A, LUMINAL B, HER-2, triple receptor negative), vascular invasion, grading, ER status (positive or negative), PgR status (positive or negative), HER-2 status (positive or negative), Ki67 status (<14% or >14%) and TNM staging. Spearman coefficient was used to assess the correlation between ADC values and continuous variables (age, percentage of ER, PgR, Ki-67).

RESULTS: 20 tumours were hypo- or iso-intense compared to normal surrounding glandular breast tissue on STIR images. The remaining 8 tumours were hyper-intense. All breast tumours appeared hyper-intense on DW images and correspondinglyhad low ADC values (figure 1). The mean ADC value over all tumours was 1.1 x 10$^{-3}$mm$^2$/sec. As illustrated in Figure 2, the mean of the difference between readers was 0.015 x 10$^{-3}$mm$^2$/sec and interobserver variability 20% (95% limits of confidence –0.17/+ 0.20 x 10$^{-3}$mm$^2$/sec). Higher mean ADC values were observed for the LUMINAL A subtype when compared to other subtypes (LUMINAL B, HER-2, triple negative), but this difference did not reach statistical significance. There was a marginally significant correlation (Spearman r=0.37, P<0.0533) between ADC value and percentage of PgR. No correlation with the other molecular prognostic markers was identified.

CONCLUSIONS: Hyper-intensity in DW images and dark grey on ADC maps (low ADC values) are semiotic characteristics common to breast tumours. Differences in defining the tumour margin likely contributed to the rather large inter-reader variability, an optimize the threshold selection to avoid this variability amy be possible. LUMINAL A subtype may be associated with higher mean ADC than other subtypes, and ADC was marginally correlated with percentage of PgR. A larger patient population is needed to draw definite conclusions on the correlation between DW-MRI and molecular prognostic factors.



a b

Figure1a: DW image (b=500 s/mm$^{2)}$ showing breast tumour which is hyper-intense when compared to normal glandular breast tissue.
Figure 1b: ADC map showing the same breast tumour having a dark grey colour on the ADC map.

Figure 2 – Bland Altman plot showing difference between observers relative to the mean of the two measurement in the calculation of ADC values

References: [1] Rubesova et al. J Magn Reson Imaging. 2006;24(2):319-24. [2] Kim et al. J Magn Reson Imaging. 2009;30(3):615-20. [3] Bland JM and Altman DG. Lancet 1986;1:307-10