Modelling diffusion-weighted MRI data from primary and metastatic ovarian tumours

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TARGET AUDIENCE: Physicists and clinicians using Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) in oncology.

BACKGROUND: An increase in Apparent Diffusion Coefficient (ADC) measured over the entire disease burden has been shown to be indicative of response to chemotherapy in patients with advanced ovarian cancer. [1] However, the decay of the DW-MRI signal with increasing diffusion-weighting (b-value) is not completely described by a mono-exponential function and may be better described by a multi-exponential function. [2] More advanced models potentially provide a better description of the data, which would enable more detailed investigation of differences between tumour sites.

PURPOSE: To assess goodness-of-fit and repeatability of mono-exponential, stretched exponential and bi-exponential models of DW-MRI data in primary and metastatic ovarian cancer.

METHODS: *Study protocol:* 31 patients with high-grade ovarian cancer (primary n = 17, relapsed n = 14) with at least one lesion larger than 2 cm recruited from 2 institutions as part of an ongoing prospective multi-centre clinical trial (DISCOVAR, CCR3694) were studied. Patients with primary disease were scanned twice before starting chemotherapy while those with relapsed disease were scanned only once. All patients had a scan after three cycles of platinum-based chemotherapy. *Imaging protocol:* Hyoscine butylbromide (20 mg) i.m. was administered before scanning to reduce image artefacts due to peristalsis. T_1-weighted and T_2-weighted images were acquired in order to provide anatomical information. After stacked DW sequences covering the abdomen and pelvis, an additional DW sequence with 10 diffusion-weightings between 0 and 900 s mm^{-2} was acquired for comprehensive analysis of non-mono-exponential models at a single station as time constraints prevented full volume coverage. The imaging volume for this sequence was positioned on the largest lesion on the baseline examination and copied to the same position on subsequent examinations. The protocol for this sequence was as follows: Siemens MAGNETOM Avanto (scanner 1) or GE Discovery 1.5 T MR scanner (scanner 2); anterior body matrix and posterior spine matrix (scanner 1) or 32 channel body array (scanner 2); axial; free breathing; single shot EPI; NSA = 4; FOV (read) = 380 mm; FOV (phase) = 88 %; acquired matrix (read) = 128; reconstructed matrix (read) = 256; acquired pixel size = 3 mm x 3 mm; parallel imaging reduction factor = 2; PE direction = AP; TR = 8000 ms; TE = 75 ms (scanner 1) or 81 ms (scanner 2); SPAIR fat suppression (scanner 1) or water-selective excitation (scanner 2); three-scan trace (scanner 1) or ALL (scanner 2); double spin-echo; b = 0, 50, 100, 150, 200, 250, 300, 500, 700, 900 s mm^{-2}; receive bandwidth 1776 Hz/pixel (scanner 1) or 1953 Hz/pixel (scanner 2); 26 slices; slice thickness = 6 mm. *Analysis:* Regions of Interest (ROIs) were drawn by region growing on computed DW images (b = 1000 s mm^{-2}) using in-house software. [3] ROIs were drawn on every slice on which the lesion appeared. Mono-exponential [$S(b) = S_0\exp(-bADC)$], stretched exponential [$S(b) = S_0\exp(-[bDDC]^{\alpha})$] and bi-exponential [$S(b) = S_0(f\exp(-bD^*) + (1-f)\exp(-bD))$] models were fitted to all 10 b-values for every pixel in the lesions using least-squares fits (Matlab 2014, MathWorks Inc., Natick, MA). When fitting the bi-exponential curves, starting values of D, f and D* were determined from a least-squares fit of a mono-exponential curve to the signal at the highest five b-values and another mono-exponential curve fitted to the remaining signal at the lower b-values; these starting values were used for the least-squares fit of the bi-exponential curve to the data at all 10 b-values. The goodness-of-fit of the three models were compared using the Akaike Information Criterion (AIC), which imposes a penalty for additional parameters in the model. [4] The preferred model for each lesion was defined as the model preferred by the largest number of pixels. The repeatability of estimates of ADC, DDC, α, D, f and D* were assessed using pairs of pre-treatment measurements from 22 lesions from patients with primary disease using the method of Bland and Altman. In order to reduce the sensitivity to outlier values, the median value of each fitted parameter from all pixels in the lesion was used for analysis of repeatability. Bland-Altman plots of untransformed data showed a relationship between the differences in the repeated measurements and their means that was improved by using the natural logarithm of the data. The Coefficient of Variation (CV) of the log-transformed data was used to describe the repeatability of the fitted parameters ($CV = \sqrt{[\exp(\Sigma d^2/2N)-1]}$, where Σd^2 is the sum of squared differences between pairs of measurements and N is the number of lesions).

RESULTS: Thirty-nine lesions were evaluated prior to treatment (9 ovarian, 11 omental and 16 peritoneal lesions and 3 lymph nodes). Additionally, 31 lesions imaged after 3 cycles of treatment (7 ovarian, 8 omental and 14 peritoneal lesions and 2 lymph nodes) were included in the statistical evaluation to assess goodness-of-fit of the model post-treatment. Tumours showed high signal intensities on diffusion-weighted images (Figure 1). CVs of ADC, DDC, α, D, f and D* are shown in Table 1. The bi-exponential model was unsuitable in these data owing to poor repeatability. After excluding the bi-exponential model, analysis using AIC showed that the stretched exponential model provided the better fit to the majority of pixels in 64 % of lesions in pre-treatment data and 65 % of lesions in post-treatment data. When separated by tumour site (ovarian, omental, peritoneal, lymph node), the stretched exponential model provided the better fit to the majority of pixels in the largest number of lesions in all sites.

DISCUSSION: The stretched exponential model provides a better characterisation of DW-MRI data from primary and metastatic ovarian cancer than a mono- or bi-exponential model. The preference for the stretched exponential model held true for lesions from different sites (ovarian, omental and peritoneal lesions and lymph nodes) regardless of whether or not treatment had been given. The repeatability of the stretched exponential model is good, which is a key consideration when applying advanced models that provide a better description of the experimental data because their utility in the investigation of treatment effects or inter-lesion heterogeneity may be undermined if they have poor repeatability.

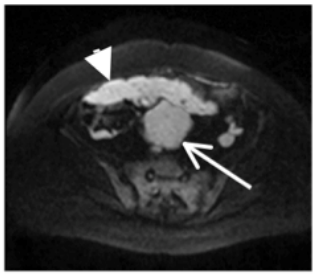

Figure 1: DW image (b = 900 s mm^{-2}) showing an ovarian lesion (narrow arrow) and an omental lesion (wide arrow).

Model	Parameter	Coefficient of Variation (%)
Mono-exponential	ADC	3.1
Stretched exponential	DDC	4.3
	α	7.0
Bi-exponential	D	13.2
	f	44.0
	D*	165.1

Table 1: Coefficients of variation of fitted parameters.

CONCLUSION: Of the three models considered here, the stretched exponential model provides the optimal fit to DW-MRI data from ovarian, omental and peritoneal lesions and lymph nodes in pre-treatment and post-treatment measurements with good repeatability.

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