

# Influence of multiparametric tumour delineation methods on the median transfer constant ( $K^{trans}$ ) tumour values and their reproducibility

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**Introduction:** Dynamic contrast enhanced (DCE)-MRI is a recognised biomarker for assessment of anti-angiogenic therapies<sup>1</sup>. Diffusion-weighted MRI (DW-MRI) is being explored as a promising response biomarker because an increase in tumor apparent diffusion coefficient (ADC) correlates with cell death<sup>2</sup> and may discriminate between nonperfused but viable and nonperfused, nonviable (necrotic) tissues<sup>3</sup>. Therefore, a multiparametric protocol combining these two techniques, would potentially provide better characterisation of tumor response. However, amongst the challenges for implementing a combined protocol in clinical trials is the delineation of the tumor region of interest (ROI) across the different modalities. Employing the same ROI would allow a more accurate cross-correlation between functional MRI parameters and considerably reduce analysis time. In particular in the liver, where rim enhancement is a common feature of metastases, it is difficult to determine the edge of the tumor with regard to this rim. The extent of tumor within the rim as opposed to peritumoral desmoplastic reaction is not known<sup>4,5</sup>. Currently tumor delineation on DCE-MRI uses anatomical or early subtraction images<sup>6</sup>. This study explores the impact on median transfer constant ( $K^{trans}$ ) values of ROIs drawn on T1 weighted (T1w), early subtraction DCE-MRI and DW-MRI images (transferring ROIs to the DCE MRI in the latter case).

**Methods:** 11 lesions in 10 patients with metastatic disease referred for phase I trials were analysed using the ROIs defined on T1w, early subtraction and DW-MRI images. Each patient was scanned twice, prior to any treatment, 1-5 days apart. The location of the lesions was liver (8), adrenal (1), kidney (1) and lymph node (1). Patients were studied using an 1.5T Avanto (Siemens Medical Systems, Erlangen, Germany). The DWI measurements were performed using single-shot echo-planar MR imaging with a multiple-averaging technique, coronal oblique plane, respiratory triggered (TR/TE 2000/70, 128x128 matrix interpolated to 256/256). Isotropic ADCs were calculated in all patients using b values of 50, 100, 300, 600 and 900 s/mm<sup>2</sup>. The DCE-MRI studies were obtained using a T1-weighted 3D gradient-echo (GRE) sequence, volumetric interpolated breath-hold examination (VIBE, Siemens Medical Solutions), flip angle – 16° (5mm slices, 128x128 matrix interpolated to 256/256). Proton Density weighted images were acquired prior to the dynamic sequence to allow conversion of MR signal intensity to quantitative contrast agent concentrations. A standard dose of 0.1 mmol kg<sup>-1</sup> intravenous Gadolinium-DTPA contrast agent (MagnevistR, Bayer Schering Pharmaceuticals) was injected at 3 ml s<sup>-1</sup> followed by a 20 ml saline flush at 3 ml s<sup>-1</sup>. The same volume and slice thickness was chosen for the DWI and DCE sequences.

An experienced radiologist drew an ROI on 3 slices through each tumor for each slice as follows: on the pre-contrast T1 anatomical image (roi A), on the early DCE-MRI subtraction images, using as tumor border the inner contour of the enhancing lesion rim (roi B) and on the highest b value image (roi C). Pixel-by-pixel values of  $K^{trans}$  were then calculated for each ROI using Tofts methods and MRIW software (MRI Workbench, Institute of Cancer Research, London)<sup>7</sup>. For each lesion, the distribution of the  $K^{trans}$  pixel values was asymmetric, and median values were used to summarise the distribution. However, as distribution of the median values of all tumors conformed to a normal distribution, a Bland-Altman analysis was performed to test variability. To test the repeatability of the 3 types of ROIs, 33 (single central slice) out of the 198 ROIs were redrawn 3 – 5 days after the initial analysis.

**Results:** The reproducibility of the median  $K^{trans}$  cohort across the 3 analysis methods was similar with r being between 0.08-0.09 (Table 1). There was however a relatively large variability between the median  $K^{trans}$  in tumor as obtained using the differently defined ROIs (r value ranged from 0.03 to 0.05). ROIs delineated on T1 may incorporate adjacent vessels if these are close to the tumor (Fig.2) and may include perilesional oedema (Fig.3). The thickness and visibility of the rim enhancement of the liver lesions on the early subtraction was variable (Fig.3d) and there was a displacement (both cranio-caudal and axial) between the ROI generated on DW-MRI and that generated on DCE-MRI due to patient breathing in 7 patients.

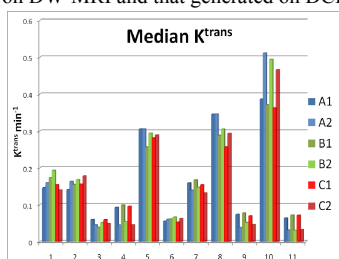


Fig.1

Distribution of the median K on the 2 baseline studies (1 and 2) using differently defined ROIs (A –blue, B–green, C–red).

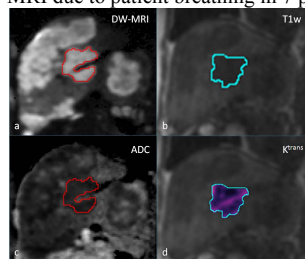


Fig.2

Tumor delineation on T1w images includes the intra-tumoral vessel which is excluded using DW-MRI

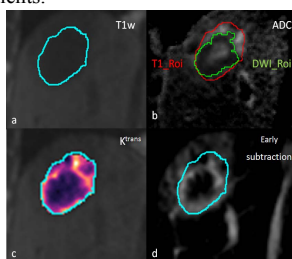


Fig.3

Tumor delineation on T1w images (larger ROI) includes peritumoral oedema.

	Roi A (T1w)	Roi B (early subtraction)	ROI A (DW-MRI)	ROI A vs ROI C	ROI A vs ROI B	ROI B vs ROI C
Median $K^{trans}$ (min <sup>-1</sup> )	0.18	0.18	0.17			
wCV	0.18	0.18	0.17	0.13	0.11	0.07
r	0.09	0.09	0.08	0.06	0.05	0.03
r as %	49.37	50.67	47.94	35.28	30.94	19.75
Repeatability (%)	11.6	16.75	9.23			

Table 1

Bland Altman variability across the median tumor  $K^{trans}$  (min<sup>-1</sup>) using differently defined ROIs

**Discussion and Conclusion:** The choice of tumor ROI delineation did not influence median  $K^{trans}$  reproducibility. However, the absolute  $K^{trans}$  values varied significantly between the three methods because of the extent to which the high vascularity tumor rim was included in the measurement. In the context of clinical trials it is crucial that the same method is employed across studies. As the treatment effect on the enhancing rim of the lesion is unknown, this warrants further evaluation separately. From our experience, both anatomical T1 and DW-MRI have advantages of a better ROI repeatability compared to early subtraction and should be used in preference. Using the ROI delineated on DW-MRI images allows a more accurate multiparametric correlation and reduces considerably the analysis time.

**References:** 1. Zweifel M et al. Eur J Nucl Med Mol Imaging 2010 2. Charles-Edwards EM et al, Cancer Imaging 2006 3. Berry LR et al, MRM 2008 4. Semelka RC et al, Radiology 2000. 5. Yu J-S et al AJR 2006. 6. Leach MO et al, Br J Cancer. 2005. 7. d'Arcy JA et al, Radiographics 2006.

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