Structural spectroscopic analysis of tumor vasculature before and after contrast agent administration to mice

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BACKGROUND Tumour vasculature is important in the delivery of nutrients and drugs. It is used as a target for some types of therapy and may be modulated as a secondary effect of other cancer treatments. Modeling the uptake of MR contrast agents is widely used to evaluate tumour blood vessels, both before and after treatment. Anti-vascular drugs such as combretastatin-A4 phosphate are sometimes reported to have a large effect on the central regions of tumours while sparing the tumour rim. However, systematic image analysis approaches (either on MRI or autoradiography data) have not consistently demonstrated this effect (1,2). Two features likely to be an advantage in analyzing such data are (i) an automated approach, describing vascular parameters throughout the tumour and (ii) quantitative information about the dimensions of blood vessels and inter-vessel gaps. Structural Spectroscopy™ has been proposed as a technique for characterizing anatomical structures using magnetic resonance data. Data is acquired from rectangular prisms located in the anatomical region and orientation of interest using a novel pulse sequence. The resulting one-dimensional signal profiles are then analyzed using customized signal processing algorithms to determine the spacing and/or size distribution of the anatomical elements of interest.

AIMS The aim of this study was to estimate the dimensions of vascular features in animal tumour models using a combination of structural spectroscopy analysis and gadolinium-based MR contrast agents.

METHODS *In vivo* measurements either before or after gadoteridol (0.1mmol/kg, ProHance, Bracco Imaging) were carried out on cdi nu/nu mice (n=5) implanted on the flank with HT29 human colon carcinoma cells. Measurements were taken 14-21 days after inoculation when the tumours were ~10mm in diameter. Mice had their tail vein cannulated and were restrained within a 33mm ^{1}H quadrature volume coil (Rapid Biomedical GmbH) in a Varian 7T horizontal bore MR system. Mice were anaesthetized with isofluorane/oxygen inhalation and kept warm using a warm air feedback system. Respiration rate was monitored. Scout images were acquired and slices selected to include tumour. A one dimensional spin-echo pulse sequence was used to obtain spectroscopic data along the length of a 13x1x1 mm prism, as shown in Fig.1 a and b. Images were collected before and 10 min after contrast agent injection. Parameters included TR = 500 ms, TE = 18 ms, prism dimensions 1x1x13 mm, gradient strength 6.5-8.7 G/cm, 1.6 ms sinc pulses, spectral width 100kHz, 512 data points, 512 averages. The distribution of spatial dimensions in the 1D spectra was determined using fineSA software (Osteotronix Ltd, Swansea, UK). These are shown as structural frequency plots in Fig 1 c and d.

Results Pre contrast (left plot) showed no apparent structure. However, at 10-14 min post-contrast (right plot) fine structure was revealed at ~12 and 15/mm. For comparison, the noise level (red traces) is shown from regions outside the animal.

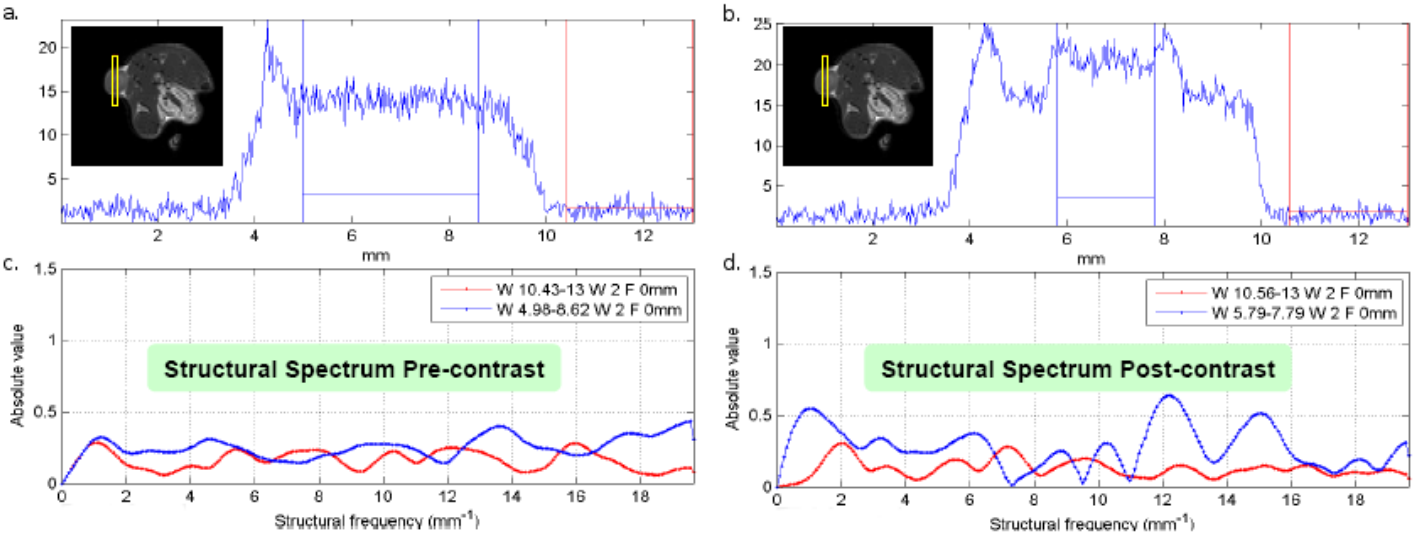

Fig1. Structural spectroscopy in HT29 tumour (a,c) before and (b,d) after injection of gadoteridol (0.1 mmol kg^{-1}).

CONCLUSIONS There was a clear difference in the intensity of structural features seen in HT29 tumours grown in mice after injection of contrast agent (gadoteridol) compared to those before contrast. This is consistent with the highlighting of signals inside and adjacent to perfused tumour blood vessels, the features having spatial dimensions of 50-100 microns. Future studies are planned to evaluate response to treatment and at a range of times after contrast agent injection.

REFERENCES 1. Prise-VE et al., Int J Oncol. 2002 21:717-726. 2. Galbraith-SM et al., J Clin Oncol. 2003 21:2831-2842.