COMBINED LOOK-LOCKER ARTERIAL SPIN LABELING (ASL) AND INTRINSIC R2* SUSCEPTIBILITY RESPONSE TO VASCULAR DISRUPTION IN A CLINICALLY RELEVANT LIVER METASTATIC MODEL OF COLORECTAL CARCINOMA

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Introduction
The main cause of mortality for patients with colorectal carcinoma (CRC) is metastatic dissemination of cancer cells to the liver. Surgical resection of metastases leads to a 5-year survival rate of ~40%, but is only possible in 10-20% of cases. Other treatment approaches are therefore necessary, either to 'de-bulk' tumour mass and allow resection with curative intent or to directly prolong long-term survival. One such treatment is the vascular disrupting agent (VDA) OXi4503, which increases survival in murine models of liver metastases through destruction of tumour vasculature and resultant central necrosis, albeit with a surviving rim of viable cells. A phase I clinical trial of OXi4503 in patients with liver metastases has recently been reported using R2* as a potential early biomarker of therapeutic efficacy, although the observed change in R2* was variable and the physiological mechanisms underpinning these changes difficult to interpret. Novel therapeutic approaches require effective non-invasive methods to assess response in patients and experimental models. Tumour perfusion (measured by arterial spin labelling [ASL]), which has recently been demonstrated in a preclinical liver metastatic model, may provide a further potential biomarker of efficacy of OXi4503. Objective: To acquire and compare measurements of R2* and perfusion in a preclinical orthotopic liver metastasis model of CRC before and after administration of OXi4503 and assess suitability to monitor tumour response.

Method
The colorectal carcinoma cell line SW1222 was grown in vitro by tissue culture techniques and prepared to a concentration of 1x10^7 cells/mL in serum free media. To establish liver metastases MF1 nu/nu mice (n=3) were injected intrasplenically with 100ul cell suspension, cells were allowed to wash through to the liver for 1 minute, and splenectomy performed. Tumour development was initially monitored by IVIS bioluminescence, and later with T2 weighted MRI. MRI was performed using a 9.4T Agilent VNMRS 20cm horizontal bore system with a 39mm birdcage coil and a warm air blower to maintain animal temperature. To assess perfusion of metastases respiratory gated (SA instruments, New York, USA) fast spin echo images were used to define a suitable imaging slice across the liver followed by a segmented FAIR Look-Locker ASL sequence with a single slice spoiled gradient readout. R2* values, as a reflection of presence of deoxyhaemoglobin, were assessed by a multi-gradient echo (MGE) image sequence covering the entire liver. A total of n=10 distinct metastases were evaluable. Both ASL and R2* were acquired at baseline and 90 minutes following i.v. dosing via remote line of 40mg/kg OXi4503 without movement of the animal between scans. For histological analysis tumours were excised at 24hr post OXi4503 when central tumour necrosis is expected. Perfusion and R2* maps were created using IDL and Amira 5.3.1 software, with median values tested for significance by paired t-test.

Results
Figure 1A shows significant (p<0.01) changes in median values for both ASL and R2* across the n=10 metastases 90 minutes after OXi4503 administration. 1B shows that central tumour necrosis has occurred within the metastases at 24 hours post dose. 1C shows an example of an imaging slice from which ASL and R2* have been calculated. Values of percentage change from baseline for the four metastases present are depicted, and show variable response in ASL and R2*. 1D shows a scatter plot of the change in these values across the n=10 metastases, with an R2* value of 0.03 (no correlation).

Discussion
We were able to detect acute changes in tumour pathophysiology caused by OXi4503 with both ASL and R2*, with a significant decrease in mean perfusion and increase in R2*. This is consistent with the mechanism of action of VDAs: cessation of blood flow leads to a reduction in tumour perfusion and an increase in paramagnetic deoxygenated haemoglobin. The central tumour necrosis at 24hr observed in H&E sections is expected to correlate with changes in R2* and perfusion values across the n=10 metastases, with an R2* value of 0.03 (no correlation).

References:

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