Dynamic contrast-enhanced MRI parameters monitor and predict outcome of targeted radionuclide therapy in patients with neuroendocrine tumour liver metastases

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Introduction: Assessment of treatment response in neuroendocrine liver metastases using conventional imaging criteria is unreliable because lesions can be slow to regress despite clinical benefits. Dynamic contrast-enhanced (DCE-) MRI is a technique that enables non-invasive interrogation of the tissue microvascular environment. In this study, DCE-MRI was performed in patients with neuroendocrine tumour liver metastases (NETLM) before and after treatment with a targeted radionuclide therapy. Pharmacokinetic parameters derived using the dual-input single compartment model, as well as model-free parameters, were assessed.

Materials and methods: 12 patients with NETLM and initially elevated serum chromogranin A level underwent DCE-MRI studies before and 3 months after treatment with ^{90}Y-DOTATOC. Imaging was performed on Siemens Avanto 1.5T using a phased array body coil and a 3D FFE sequence. Coronal dynamic images were acquired in pairs during breath-holds on expiration with 5s gap between successive breath-holds. 40 volumes were acquired over a 4 minute period. Gd-DTPA was injected at the start of the third breath-hold (iv. Magnevist® 0.1mmol/kg body weight). The imaging parameters were TR/TE = 3.28/1.10 ms, FA = 18°, 12×5 mm partitions, NSA = 1, iPAT = 2, FOV = 350 mm^2, 256×256 matrix. The dynamic scan was preceded by a single scan with the same parameters except with FA = 2° and NSA = 3 to allow conversion of dynamic signal intensities to gadolinium concentration. Data analysis was performed using in-house software, MRIW [1]. Dynamic images were registered using a simple rigid body algorithm. Separate regions-of-interest (ROIs) encompassing the tumour and whole liver were drawn in the three central partitions. DCE-MRI parameters were evaluated on a voxel-by-voxel basis within the ROI. Model-free parameters evaluated were initial area under the gadolinium curve at 60s (IAUGC60), pre-contrast/native T_1 [2] and enhancing fraction. The latter was defined to be the number of voxels with IAUGC60 > 2.5 mMol.s relative to the total number of voxels in the ROI. The threshold was chosen using IAUGC60 values of fatty tissues as reference. A dual-input single compartment model validated by Materne et al was used in the compartmental analysis [3]. Tissue contrast agent concentration is described by the following expression: $c_t(t) = [\gamma c_A(t) + (1-\gamma)c_V(t-t_p)]\otimes F.\exp(-(t-\tau_0)F/DV)$, where $c_A(t)$ and $c_V(t)$ are the arterial and portal-venous curves, F, DV and γ are total hepatic pefusion, distribution volume and the ratio of arterial to total hepatic perfusions, respectively. τ_0 and t_p are the onset and portal delay times, respectively. A population-averaged arterial curve based on that published in the literature and a study-specific portal-venous curve estimated using a dispersion model were used in the analysis [4,5,6]. Arterial and portal-venous perfusions and mean transit time are calculated using the following expressions respectively: $F_a = \gamma.F$, $F_p = (1-\gamma).F$ and MTT = DV.60/F. The number of fitted voxels relative to the total number of voxels in the ROI was also evaluated. As lesion size measurements are known to be suboptimal for response assessment, we defined responders by biochemistry as those showing >50% reduction in the nadir Chromogranin A level after treatment. For both tumour and whole liver ROIs, pre-treatment median parameter values were compared between responders and non-responders using a Mann-Whitney U test. Pre- and post-treatment median parameter values were compared using a Wilcoxon signed ranks test for both responders and non-responders. P-values less than 0.05 were taken to be significant.

Results: The numbers of responders and non-responders were seven and five, respectively. For comparisons of pre-treatment median parameter values between responders and non-responders, the whole liver distribution volume and IAUGC60 and tumour distribution volume were found to be significantly different between the two groups (figure 1). All three parameters were significantly lower in the responders compared with the non-responders. For comparions between pre- and post-treamtent parameter values in the responding group, the whole liver distribution volume was found to significantly increase after treatment. The relative number of fitted voxels and the enhancing fraction in tumour ROIs were found to decrease significantly after treatment (figure 2). Parametric maps of IAUGC60 in a tumour of an example patient before *(top)* and after *(bottom)* treatment are shown in figure 3. Corresponding histograms show a shift towards lower IAUGC60 after treatment which resultsin a decrease in the enhancing fraction. Interestingly, the native T_1 of the liver significantly increased after treatment (figure 4) in the non-responders. There was no significant change in the T_1 of liver among the responders. **Discussion:** It was found that non-responders have significantly higher baseline distribution volume and IAUGC60 compared with responders. These observations may suggest that non-responders had more advanced disease prior to treatment, hence, less responsive to targeted radionuclide therapy. DCE-MRI parameters before and after treatment with ^{90}Y-DOTATOC showed that the distribution volume in the whole liver significantly increased after treatment among the responders. This may reflect treatment induced tumour lysis resulting in an increase in leakage space, which occurs in both the measurable disease, as well as micrometastases which are beyond the resolution of our imaging technique to confidently detect. In tumours, the number of fitted voxels and the enhancing fraction decreased after treatment. This is likely to reflect the effects of radiation-induced cell death, leading to non-enhancement of the treated tumour tissue. In non-responders, only the native T_1 of the whole liver was found to significantly increase after treatment. Metastases and necrosis are associated with longer T_1 values compared with normal liver tissues. The observed small increase in native whole liver T_1 in non-responders may indicate worsening of disease. **Conclusions:** Both model free (IAUGC, tumour enhancing franction EF) and model dependent (distribution volume) parameters provide potential biomarkers for response assessment and disease prognostication in patients with NETLM.treated using ^{90}Y-DOTATOC . Non responders were characterized by higher pre-treatment IAUGC and distribution volumes. The whole liver distribution volume significantly increased and tumour enhancing fraction significantly decreased after therapy in responders. The value of DCE-MRI in neuroendocrine liver metastases warrants further investigation and other analysis methods which account for spatial heterogeneity in the ROIs should be investigated. **References:** [1] d'Arcy JA et al. Radiographics 2006, 26, 621-632, [2] Wang HZ et al. MRM 1987, 5, 399-416, [3] Materne R et al. MRM 2002, 47, 135-142 [4] Parker GJM et al. MRM 2006, 56, 993-1000, [5] Orton MR et al. PMB 2008, 53, 1225-1239 [6] Orton MR et al. In proc ISMRM 2009, 3615 **Acknowledgements:** We acknowledge the support received from the CRUK and EPSRC Cancer Imaging Centre in association with the MRC and Department of Health (England) grant C1060/A10334, also NHS funding to the NIHR Biomedical Research Centre.

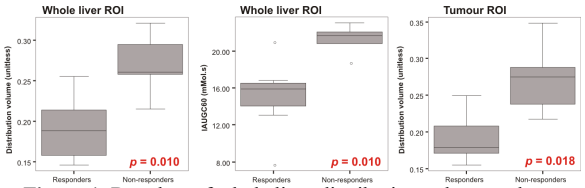

Figure 1: Boxplots of whole liver distribution volume and IAUGC60 and tumour distribution volume at baseline for responders and non-responders (L→R). At baseline, these parameters were found to be significantly lower in responders compared with non-responders (p≤0.01, Mann-Whitney U test).

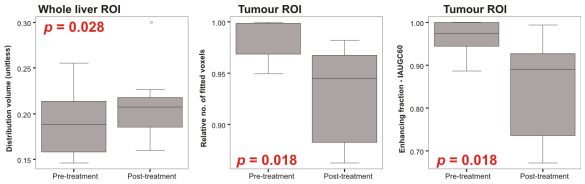

Figure 2: Boxplots of whole liver distribution volume, tumour relative number of fitted voxels and enhancing fraction at pre- and post-treatment for the responders (L→R). These parameters were found to be significantly different after treatment (p<0.05, Wilcoxon signed ranks test).

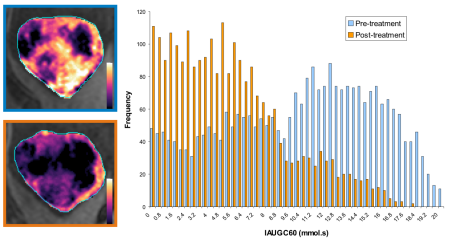

Figure 3: Parametric maps of IAUGC60 in a tumour of an example patient before *(top)* and after *(bottom)* treatment. Both maps are scaled from 0.0 to 20.0 mmol.s. Corresponding histograms show a shift towards lower IAUGC60 after treatment which resultsin a decrease in the enhancing fraction.

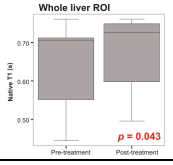

Figure 4: Boxplot of whole liver native T_1 for non-responders. This parameter was found to have a significant increase in this cohort after treatment (p<0.05, Wilcoxon signed ranks test).