Multi-modality imaging in the prediction of response to systemic treatment in colorectal cancer: Preliminary results

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Introduction: Colorectal cancer is one of the most frequently occurring cancers and about half of the patients develop distant metastases, mainly in the liver. Early response monitoring is desirable as only a subset of patients receiving systemic treatment responds to this potentially toxic and expensive treatment. Dynamic contrast enhanced MRI (DCE-MRI) has been suggested to provide potential biomarkers to monitor early treatment response[1-3]. There is an increasing interest in diffusion weighted imaging (DWI) and magnetic susceptibility or T_2* MR imaging to replace or complement DCE-MRI [4], as this circumvents the need for contrast agent administration. The apparent diffusion coefficient (ADC) measured by DWI reflects membrane (cell) density and T_2* MR contrast arises from local inhomogeneities of the magnetic field mainly due to the tissue level of blood deoxyhemoglobin next to specific tissue characteristics. This level of deoxyhemoglobin is governed by blood volume, flow and tissue O_2 consumption. In a previous study a good reproducibility for DWI and T_2* was reported [5,6].

Aim: The aim of this study is to predict response to systemic treatment in patients with colorectal liver metastases using pre-treatment measurements of ADC and T_2*.

Methods: Up till now, 25 patients (mean age 62 years, range 29-75) starting palliative cytotoxic treatment, consisting of capecitabine, bevacizumab and in most patients (n=23) also oxaliplatin, for liver metastases of colorectal cancer have been included in this study. Before start of treatment CT and MR scans were performed on a Siemens hybrid PET/CT and a 1.5T MR system, respectively. After conventional T_1- and T_2-weighted MR imaging, DWI was performed in three orthogonal directions (TR=2000ms, TE=82ms, b-values: 50, 300, and 600 s/mm^2) using an EPI sequence. ADC-maps were calculated using Siemens Syngo (VB17) software. After DWI, T_2* imaging was performed using a FLASH 2D sequence. Every image slice was obtained with a TR of 225 ms and multiple TE values (4.76, 9.53, 14.29, 19.06, 23.82, 28.58, 33.35, 38.11, 42.88, 47.64, 52.40 ms). T_2* calculated maps were generated by fitting the data to a mono-exponential curve, using in-house built software. On the ADC- and T_2* calculated maps, 3D ROI's were drawn around each lesion and the voxel values were extracted. A maximum of 5 liver metastases per patient were analyzed. After 3 and 6 cycles of treatment a CT was performed. Patients were diagnosed with progression in case the maximal diameter of a lesion increased by more than 20% compared to lesion size before start of treatment, or after clinical progression.

Results: In total 79 lesions were analyzed. Three of the 25 patients had evident clinically progressive disease before the end of the third cycle. None of the other patients had clinical or radiological progressive disease after 3 cycles of therapy. There was no significant correlation (Pearson, r=-0.14, p=0.23) between the mean ADC and the mean T_2* value. Significant differences in ADC values on the pre-treatment scan were observed between the group of patients that were not progressive (N=18, mean ADC=1.25x10^{-3} mm^2/s), the group of patients that were progressive before or at the evaluation after the third cycle (unpaired t-test, N=3, mean ADC=1.02x10^{-3} mm^2/s, p=0.02) and the group of patients that were progressive before or at the evaluation after the sixth cycle (unpaired t-test, N=4, mean ADC=1.01x10^{-3} mm^2/s, p=0.01) (fig.1A). A significant correlation (Pearson, r=0.66, p=0.04) between the pre-treatment mean ADC values and the progression free survival (PSF) was also noted (fig.1B). Pre-treatment mean T_2* values were lower (N=17, mean T_2*=30.59ms) in the group of patients without progression compared to the patients with progressive disease before or at the evaluation after the third or sixth cycle, but this was not-significant (unpaired t-test, N=3, mean T_2*=38.65ms, p=0.12 and N=4, mean T_2*=37.48ms, p=0.13) (fig.1C).
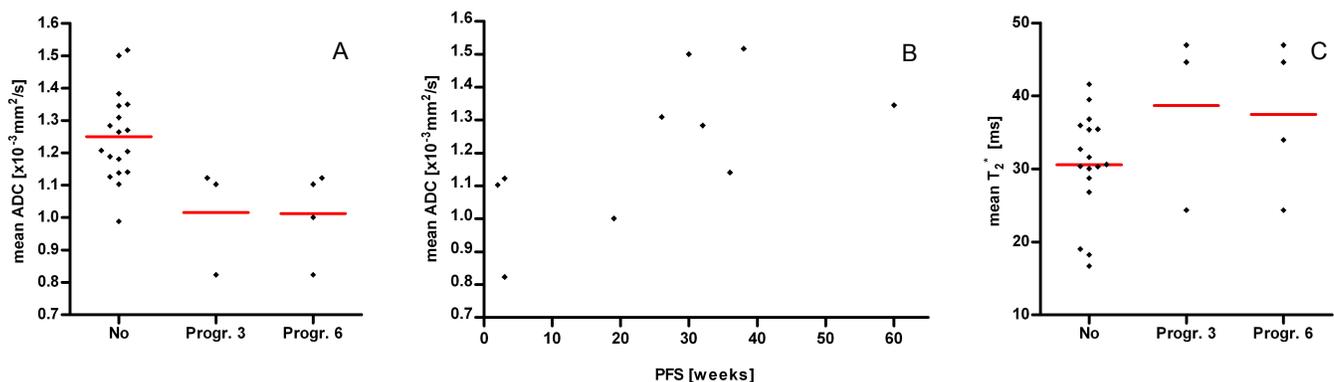

Figure 1: (A) and (C) indicate, respectively, the mean ADC and the mean T_2 values per patient of the pre-treatment scan of patients with no clinical or radiological progression, and with clinical or radiological progression before or at the evaluation after the 3rd and 6th cycle. (B) shows the mean ADC value per patient in relation to the progression free survival (PFS).*

Discussion and conclusion: These preliminary results indicate that high pre-treatment ADC values in tumor tissue predict good treatment outcome. Low pre-treatment T_2* values in tumor tissue may also predict good treatment outcome, but results are not significant yet. From the lesion by lesion analysis it also follows that the mean T_2* and the mean ADC are not significantly correlated. From a biological point of view, low ADC values reflect cell dense tissue and high T_2* values represent high oxygenation. Areas with dense tissue require a high level of oxygenation by blood, possibly explaining why high T_2* values in these areas are observed. Areas with low ADC values and high T_2* values might therefore be the more aggressive tumor areas. Thus, the combination of both parameters could provide an even better prediction of treatment outcome.

Contribution: *First and second listed authors contributed equally.* **References**: *[1] Cui Y. et al. Radiology 2008;248:894-900, [2] Padhani A.R. et al. Clin Radiol 2001; 56: 607-620, [3] van Laarhoven H.W. et al. J Magn Reson Imaging 2003;18:315-320. [4] Zweifel et al. ISMRM 2010, [5] ter Voert E.G.W. et al. ISMRM 2011, pn1064, [6] Heijmen L. et al. ISMRM 2011, pn1065.*