Predicting Response to Chemotherapy: The Value of Pre-treatment Quantitative Diffusion-weighted MR Imaging in Colorectal Hepatic Metastases

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Introduction: Liver metastasis is an adverse prognostic factor in patients with colorectal cancer. Neoadjuvant chemotherapy in patients with advanced metastatic liver disease may render disease operable and thus improves patient survival [1]. Using diffusion-weighted MR imaging (DWI) with different gradient factors (*b* values) allows quantitative estimates of apparent diffusion coefficient (ADC), 'true' diffusion coefficient (TADC) and perfusion fraction (PF) of metastases to be derived [2]. Liver metastases have been shown to demonstrate higher ADC and TADC values but lower PF compared with normal liver [2-4]. However, it is unclear if the pre-treatment assessment of ADC, TADC and PF can help to predict response to chemotherapy and how these quantitative indices change with treatment.

Purpose: To determine if there is any significant difference in the pre-treatment apparent diffusion coefficient (ADC), 'true' diffusion coefficient (TADC) and perfusion fraction (PF) of colorectal hepatic metastases between responders and non-responders to chemotherapy, and to evaluate how these indices change following chemotherapy.

Materials and Methods: 10 patients (7 males and 3 females, mean age = 70 years) with 20 potentially operable hepatic metastases (mean size = 23 mm) arising from colorectal carcinoma were prospectively evaluated. MR imaging was performed on a 1.5T system (Intera, Philips Medical System, Best, Netherlands) using a SENSE phased-array body coil before and at 12 weeks following first-line chemotherapy (Capecitebine and Oxaloplatin) treatment. At each visit, DWI of the entire liver was performed axially using breath-hold single-shot echo-planar imaging. 12 sections were acquired during each 20 seconds breath-hold (TR = 1850 ms, TE =56 ms, gradient strength = 30 mT/s, 7 mm section thickness, slice gap = 1 mm, single acquisition, 340 cm FOV, Matrix = 112 x 256, SENSE factor = 2) and examination of the entire liver was completed in two breath-holds. Diffusion gradients with three b values (0, 150 and 500 sec/mm^2) were applied along the phase encoding (P), frequency encoding (M) and section-select (S) directions. The second *b* value of 150 sec/mm^2 was chosen because it has been shown to null capillary flow [5]. A median filter was applied to the DWI images, which were used to generate the quantitative ADC maps (using the *b* = 0, 150 and 500 sec/mm^2 images), the TADC maps (using only the *b* = 150 and 500 sec/mm^2 images) and PF maps. The maps were assessed by an experienced radiologist using an IDL-based software and in each patient; identical regions of interest encompassing metastases (n = 20) were placed on the ADC, TADC and PF maps to record their values. Regions of interest were also placed randomly within normal appearing liver (n = 38), taking care to avoid large vessels, to record values of ADC, TADC and PF. Responders were defined using RECIST criteria (at least 30% reduction in the maximum tumor diameter) The pre-treatment ADC, TADC and PF of responders versus non-responders were compared using the Mann-Whitney Test. We also compared the ADC, TADC and PF of metastases and normal appearing liver before and after chemotherapy.

Results: Seven patients with 15 metastasis responded to chemotherapy. Three patients with five lesions were non-responders. All metastases were histologically confirmed at surgery. There was no significant difference in the age, sex and mean size of metastasis between the two groups ($p > 0.05$, Mann-Whitney test). Metastases that showed response to chemotherapy had a significantly lower pre-treatment TADC ($p = 0.005$) and a trend towards higher PF values ($p = 0.08$) compared with non-responders (Table 1). The box-plots of the pre-treatment ADC and TADC value of responders and non-responders (Figure 1) showed that lesions with a TADC value > 1.60 x 10^{-3} mm^2/sec did not respond to chemotherapy. Following treatment with chemotherapy, there was a trend towards a rise in the TADC of metastasis ($p = 0.08$), although this did not reached statistical significance (Table 2). No significant change was noted in the ADC, TADC and PF of metastases in non-responders and in normal hepatic parenchyma ($p > 0.05$, Wilcoxon and t-Test)

Discussion: Our observations in this small group of patients suggest that the pre-treatment TADC of liver metastases can identify patients who are less likely to respond to chemotherapy. Identification of non-responders to first-line chemotherapy may help to refine current treatment strategies. Metastases that responded to chemotherapy had a lower TADC values suggesting that these are more cellular. Responders also had a trend towards higher perfusion fractions, which we postulate may result in better drug delivery. Following chemotherapy, there was trend towards a rise in the TADC of metastasis, in keeping with a reduction in the tumor cellularity or an increase in the extra-cellular space. However, analysis by regions of interest may not fully describe the heterogeneous change within metastases, and the change may be masked by cellular restabilization after treatment. We are currently validating these observations with a larger prospective study.

Conclusions: High pre-treatment TADC of colorectal metastases appears to predict poor response to chemotherapy, which may help to individualise therapy in the future. Following chemotherapy treatment, there was a trend towards a rise in the TADC within metastases in responders.

References: [1] Adam R et al., Ann Surgery 2004; 240:655-657 [2] Yamada I et al., Radiology1999; 210:617-623. [3] Taouli B et al., Radiology 2003; 226:71-78. [4] Koh DM et al., ISMRM 2004. [5] Le Bihan D et al., JMRI 1991; 1:7-28

Acknowledgements: This work was supported by Cancer Research UK (C1060/A808/G7643). We would like to thank Dr. Jan de Becker and Mr. Alun Jones, Philips Medical System, Best, for their help and support. Thanks also to Mr. Nariman Karanjia, Prof. David Cunningham and Dr. Gina Brown for their support of the study.

Table 1. Pre-treatment Mean ADC, TADC and PF of metastases in responders and non-responders. (* p-values obtained using Mann-Whitney Test)

	Responders (n=15)	Non-responders (n=5)	
Mean ADC (mm^2/sec)	1.78 x 10^{-3}	2.68 x 10^{-3}	P = 0.14*
Mean TDC (mm^2/sec)	1.21 x 10^{-3}	2.20 x 10^{-3}	P = 0.005*
Mean PF (%)	28.7	15.7	P = 0.08*

Table 2. Mean ADC, TADC and PF of metastases in responders before and after chemotherapy. (*p-values obtained using Wilcoxon-test)

	Before	After	
Mean ADC (mm^2/sec)	1.76 x 10^{-3}	1.93 x 10^{-3}	P = 0.23*
Mean TDC (mm^2/sec)	1.21 x 10^{-3}	1.50 x 10^{-3}	P = 0.08*
Mean PF (%)	28.7	22.1	P = 0.25*

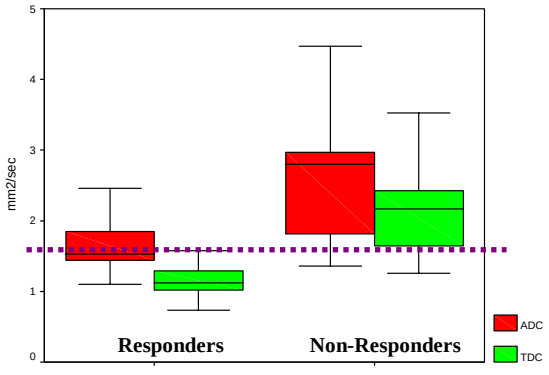

Figure 1. Box-plots of the pre-treatment ADC (red) and TADC (green) of metastases in responders and non-responders. Metastases showing a TADC value of more than 1.60 x 10^{-3} mm^2/sec (dotted line) did not respond to chemotherapy