Higher pre-treatment Apparent Diffusion Coefficient predicts poorer disease survival in patients with colorectal hepatic metastasis

H. H. Tam[1], D. J. Collins[2], G. Brown[1], I. Chau[3], D. Cunningham[3], M. O. Leach[2], and D-M. Koh[1]

[1]Department of Radiology, Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom, [2]CRUK-EPSRC Cancer Imaging Centre, Institute of Cancer Research, Sutton, Surrey, United Kingdom, [3]Department of Medical Oncology (Gastrointestinal), Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom

INTRODUCTION: Apparent diffusion coefficient (ADC), derived from diffusion weight magnetic resonance imaging (DW-MRI), provides information on microscopic movement of water molecules. In the brain, pre-treatment ADC value has been shown to predict tumour response [1] and survival times [2]. While studies have shown that high pre-treatment ADC value of colorectal liver metastases predicts for poor response to chemotherapy [3, 4], the relationship of pre-treatment ADC value and patient clinical outcome has not been previously examined in extracranial malignancies. Pre-treatment identification of patients at risk of poor clinical outcome and disease survival provides the opportunity to intensify treatment with the aim of maximizing treatment benefits and prolonging survival. The aim of this study is to explore the relationship between pre-treatment ADC value and survival times in patients with colorectal hepatic metastasis. Here, we report on the findings of an interim analysis of 69 out of 136 patients in our study cohort.

MATERIALS AND METHODS: We retrospectively identified 136 consecutive patients with suspected or confirmed colorectal liver metastases who underwent DW-MRI between 2006 and 2009 prior to initiating treatment. Imaging was performed on either a Philips Intera or a Siemens Avanto 1.5T MR systems using phased array body coil. Axial DW-MRI of the liver was performed using breath-hold single-shot echo-planar (EPI) imaging (TR/TE, 1,850/56; α, 90°; 7 mm thickness; NEX =1; FOV, 340 cm; 112 × 256 matrix; SENSE factor, 2) or free-breathing EPI DW-MRI (TR/TE, 2500/76; 6 mm thickness; NEX = 4; FOV, 340 cm; 112 × 256 matrix; GRAPPA/ SENSE factor = 2) Three b-values (0, 150 and 500 s/mm^2) were employed for breath-hold DW-MRI and six b-values (0, 50, 100, 250, 500, 750 s/mm2) for free-breathing DW-MRI. Image analysis was performed by two radiologists in consensus. In all patient, maps of ADC*total* (using all b-values) and perfusion insensitive ADC*high* (using b-values of 150 & 500 or 100 & 500 s/mm^2) were generated. Regions of interest (ROIs) were drawn on b=500 s/mm^2 images encompassing metastases and copied onto the ADC maps to record their values (**Fig. 1**). In each patient, the ADCs of up to three randomly selected metastases of different size (1-2 cm, >2 to5 cm and >5 cm) were recorded. The relevant clinical data of the patients were recorded: age at diagnosis, sex, date of diagnosis of metastasis, date of progression, date of death or last known contact, treatment (chemotherapy, surgery and/or radiofrequency ablation). Other prognostic indices were also recorded: site of primary tumour, haemoglobin level, white cell count (WCC), platelet count; serum alkaline phosphatase, lactate dehydrogenase and carcinoembryonic antigen (CEA) levels. Patients and metastases were classified as responding or non-responding based on conventional imaging at 12 weeks after treatment using size-based RECIST criteria. The progression free survival and overall survival (number of days from diagnosis of liver metastasis to date of progression, and to date of death, respectively) were calculated. The mean pre-treatment ADC*total*, ADC*high* and clinical parameters were compared between responders and non-responders by one-way ANOVA. Receiver operating characteristic (ROC) analysis was performed to identify threshold ADC value for distinguishing responding from non-responding metastases. Kaplan-Meier curves with log-rank test was used to compare survival curves (time to progression and time to death) in two groups of patient stratified by the threshold ADC value. Cox regressions were performed to assess the effect on survival times (progression free survival and overall survival) of the clinical/prognostic factors listed above and the threshold ADC value.

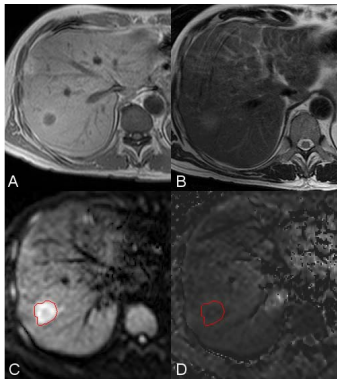

Fig 1. A liver metastatsis in a 57 year old male patient. **A.** T1-weight imaging. **B.** T2-weight imaging. **C.** ROI (red circle) drawn around the lesion on b500 image. **D.** The same ROI in C. copied onto ADC map.

RESULTS: 113 metastases in 69 patients (27 female, 42 males), mean age at diagnosis 63 years (range 27-85) have been analyzed so far. 67 patients received chemotherapy of which 32 also underwent hepatic resection or radiofrequency ablation, while 2 patients had no treatment. 39 patients were classified as responders. WCC (7.37 ± 0.24 vs 6.62 ± 0.22, F=4.65, p=0.033), CEA (113.07 ± 30.43 vs 25.51 ± 4.88, F=5.33, p=0.023), pre-treatment ADC*total* value (1.27 ± 0.05 vs 1.52 ± 0.10, F=5.34, p=0.024) and pre-treatment ADC*high* value (1.01 ± 0.05 vs 1.39 ± 0.13, F=8.58, p=0.005) differed significantly between responders and non-responders (one-way ANOVA). There was no significant difference in lesion size between the two groups. By ROC analysis, a threshold ADC*high* value of 1.12 x 10^{-3} s/mm^2 had 71% sensitivity and 63% specificity for identifying non-responding metastases. When applying this ADC threshold on a per patient basis, Kaplan-Meier analyses and log-rank tests did not show a significant difference in progression free survival times when the averaged mean ADC value of all lesions in each patient was used. However, when the highest mean ADC value in each patient was used, Kaplan-Meier estimates of 1 and 2 years progression free survival were significantly higher for the group with ADC*high* ≤1.12 x 10^{-3} s/mm^2 [61.9±8.7% and 27.5±9.4%] than ADC*high* >1.12 x 10^{-3} s/mm^2 [47±8.6% and 9±5.9%) (p = 0.024) (**Fig. 2a**). Median progression free survival was 476 days ± 65.9 days versus 284 ± 73.9 days respectively. Cox regression revealed hazard ratio for the higher ADC*high* group of 2.703 (95%CI=1.178 to 6.204, p=0.019) (**Fig. 2b**). We found no significant difference in the overall survival time (**Fig. 3a**) between the two groups by Kaplan-Meier analysis. However, by subgroup analysis of those who only received chemotherapy, an ADC*high* value > 1.12 x 10^{-3} s/mm^2 also predicted for poorer overall survival curves (p=0.041)(**Fig. 3b**).

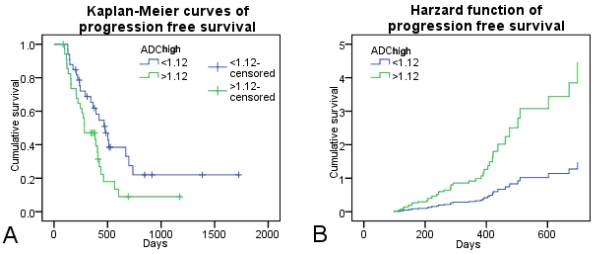

Fig 2A. Significant difference in progression free survival in the 2 groups stratified by ADC*high*=1.12 x 10^{-3} s/mm^2 (p=0.024). **B.** The group with higher ADC*high* values shows a hazard ratio of 2.7 (p=0.019).

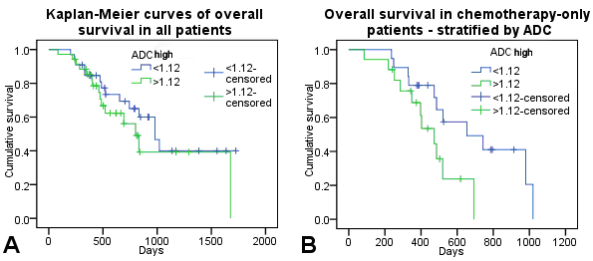

Fig 3A. Kaplan-Meier curves of overall survival of all patients where stratification by ADC*high* value of 1.12 x 10^{-3} s/mm^2 did not show significant difference. **B.** When chemotherapy-only patients are analysed as a subgroup, there was significant difference between the ADC groups (p=0.041).

CONCLUSIONS: Higher pre-treatment perfusion insensitive ADC*high* values predict for shorter time to disease progression and poorer overall survival in colorectal hepatic metastases. This study demonstrates the potential of DW-MRI as a biologically relevant response and prognostic biomarker.

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