Parametric DCE-MRI HPI Maps - A Qualitative and Quantitative Analysis in Phase I Clinical Trial Patients with Liver Metastases

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Introduction: The liver has a unique dual vascular inflow derived from the hepatic artery and the portal vein. The relative contribution of the arterial versus portal inflow can be quantified by the hepatic perfusion index (HPI). Relative increase in arterial inflow results in elevated HPI, which was first observed in patients with liver metastases using radionuclide scintigraphy in the mid 1980s [1]. Since then, HPI measurements have been obtained by dynamic contrast enhanced CT [2,3,4], Doppler sonography [5] and more recently, dynamic contrast enhanced (DCE) MRI [6]. HPI measurements using MRI can potentially overcome limitations posed by other imaging techniques, such as poor spatial resolution in radionuclide studies, lack of reproducibility in Doppler HPI and radiation exposure using CT. HPI information may be displayed as pixel-by-pixel parametric maps, allowing both visualisation and quantification of regional vascular perturbations. However, the potential utility of parametric HPI maps for lesion identification and for monitoring treatment response in patients with metastatic liver disease is not established. The aim of this study was to qualitatively and quantitatively assess parametric HPI maps obtained using DCE-MRI in a group of Phase I anti-cancer clinical trial patients with metastatic liver disease.

Method: Eight patients with metastatic liver disease who were candidates to receive a novel anti-VEGF drug underwent DCE-MRI before commencing treatment. In three patients, a repeat MRI was performed 24 to 48 hours later at similar prandial states to allow assessment of reproducibility using Bland-Altman statistics. Dynamic contrast-enhanced (iv. Magnevist® 0.1 mmol/kg body weight) three-slice coronally acquired breath-hold MR imaging was performed using a combined PD and T1-weighted gradient-echo sequence (TR = 20/ 10.2 ms, TE = 4.7 ms, α =3°/35°, two acquisitions, 350 mm^2 field of view, 160 x 256 matrix, 8 mm slice thickness). Each dynamic measurement lasted 13s and was repeated 34 times. Images were acquired during 6s of breath-hold at expiration followed by 7s of free breathing. The images were registered using a technique based on navigator methodology [7]. All images were assessed by a radiologist with more than 10 years experience in body MRI. Regions of interest (ROI) were drawn encompassing the whole liver, the spleen and marker metastases using the T1 weighted images in each patient. The T1 signal intensity-time course curves of the ROIs were converted to gadolinium concentration-time course curves by the Hittmair method [8]. The HPI value for each pixel in the liver was calculated by dividing the arterial perfusion (A) by the sum of arterial and portal perfusion (P). The splenic peak was used to mark the end of the arterial phase. A and P were taken as the gradients of the gadolinium concentration-time course curve prior to and after the splenic peak respectively. Parametric HPI maps were generated using values calculated. The HPI maps were (a) qualitatively assessed by comparing with the dynamic T1-weighted MR images and (b) quantitatively assessed by recording the HPI of the whole liver and HPI of marker metastases in each patient.

Results:. ***(a) Qualitative analysis.*** 33 tumours were observed and in all cases, visual assessment showed marked increase in HPI around metastases (Figure 1). The area of increased HPI was noticeably larger than the area of peri-tumoral enhancement on the T1-weighted images in most cases. The centre of metastases showed a more variable appearance: 24/33 showed increased HPI but 9/33 showed decreased HPI within the centre of metastases. The black voids seen in the centre of some metastses may be due to poor perfusion. ***(b) Quantitative analysis.*** The mean whole liver HPI was 0.588±0.207. This is similar to values published in the literature [2]. There was good reproducibility (n = 9, 3 slices from 3 patients) with only 15.7% variation in the HPI value within 2 standard deviations of the mean difference between the two measurements. The mean HPI obtained from metastases was 0.725±0.155, which was significantly higher compared to whole liver HPI ($p < 0.05$, Mann-Whitney test). However, reproducibility analysis from ROIs drawn around metastases (n = 9) also showed good reproducibility in HPI calculation with 18.9% variation within 2 standard deviations of the mean difference.

Discussion: Qualitative analysis of HPI maps in patients with metastatic liver disease shows striking increase in relative arterial perfusion around hepatic metastases. However, the area of increased peritumoral HPI was frequently larger compared to the area of T1 peritumoral enhancement observed following gadolinium contrast administration. Rim enhancement around metastases has been ascribed to increased arterio-portal shunting [9] which may relate to increased angiogenesis, and the HPI map appears sensitive to such vascular perturbation. Parametric HPI maps are thus potentially useful for visualising smaller metastases. Quantitative measurements of whole liver and tumoral HPIs showed good reproducibility. Hence, there is potential for using such measurements for monitoring treatment response with the aim to detect early tumour regression.

Conclusion: On visual assessment of parametric HPI maps, hepatic metastases showed areas of increased peritumoral HPI larger than the area of rim enhancement observed on the T1-weighted gadolinium enhanced images, which can aid lesion detection. Quantitative HPI demonstrates good reproducibility and may be investigated as a potential marker for treatment response in clinical drug trials.

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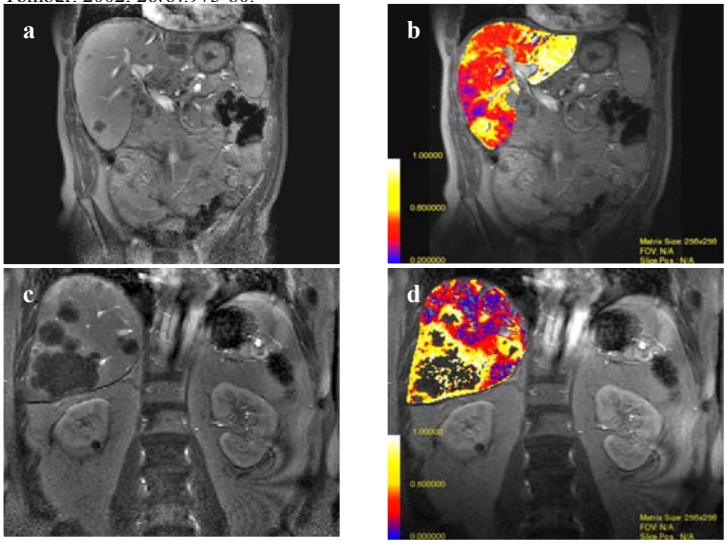

Figure 1: a & c) Dynamic T1-weighted images and b & d) the corresponding HPI maps of the liver in two patients. Several hypointense metastases are visible within the left and the right lobes of the livers with variable rim enhancement on the T1-weighted images. Increased HPI is seen around metastases on the HPI maps using a colour scale, where blue represented low HPI and white high HPI.

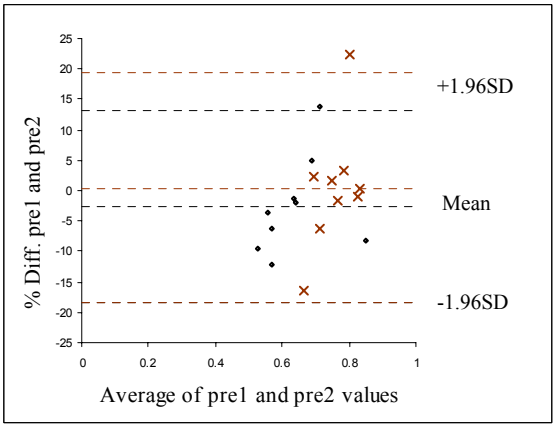

Figure 2: Bland-Altman reproducibility data of the HPI values (black = liver HPI, brown = lesion HPI). There was only 15.7% variation in the HPI value within 2 standard deviations of the mean difference between the two measurements for whole liver analysis. The variation was 18.9% for tumour ROIs.