Improvement of Colorectal Liver Metastases Detection Sensitivity and Specificity by Hemodynamic Response Imaging Combined with a Machine Learning Approach

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Background & Aims Colorectal liver metastases (CRLM) are a major cause of death of colorectal carcinoma patients. Imaging plays a vital role for early tumor diagnosis. It is well known that, whereas a normal liver is predominantly supplied by the portal vein, in patients with overt CRLM, a higher proportion of liver blood flow is derived from the hepatic artery. Moreover, even small or occult CRLM may lead to subtle changes in liver blood flow. Therefore, perfusion imaging of the liver has been suggested to improve diagnosis sensitivity and specificity. Recently, we demonstrated the feasibility of *Hemodynamic Response Imaging (HRI),* an fMRI method combined with hypercapnia and hyperoxia[1], for monitoring changes in liver perfusion and hemodynamics during liver regeneration, fibrosis and acute bleeding without the need of contrast agent administration[2]. In the present study, we aim to develop a non-invasive strategy based on *HRI*, in order to improve CRLM detection sensitivity and specificity in a mouse model. Additionally, we aim to develop software, which is based on a machine-learning approach, for the interactive classification of suspected CRLM. This approach may facilitate earlier diagnosis, hence improving prognosis.

Methods ***Animals***: CB6F1 mice underwent splenic injection with CT-26 colon cancer cells to generate CRLM. Animals were monitored by MRI twice a week and were sacrificed at the end of the experiment and their livers were harvested for histology. ***MRI:*** Experiments were performed on a 4.7T Bruker Biospec spectrometer using a 3.5 cm bird cage coil. Hepatic volumetric assessment was acquired by serial coronal and axial T_1W SE images (TR/TE=250/18ms). Tumor assessment was done using T_2W fast SE images (TR/TE=2000/40ms). Changes in hepatic hemodynamics were evaluated from T_2*W GE (TR/TE=147/10ms) images acquired during breathing of air, air-CO_2 (5% CO_2), and carbogen (95% oxygen; 5% CO_2) as described[1]. Data analysis was performed using a home written IDL software and MATLAB® with SVM engine implemented with EMD (Earth Mover's Distance) based kernel. CO_2 and O_2 reactivity maps are given as the percentage of change in signal intensity (ΔS)[1].

Results Previously, we demonstrated the feasibility of *HRI* for monitoring changes in liver perfusion during CRLM development[3]. In this study, we compared the *HRI* sensitivity to the standard DCE-MRI perfusion imaging in the early-phase of tumor growth. *HRI* showed superior detectability of small lesions. In Fig. 1, we show an example of a suspected lesion in the T_2W image (Fig. 1A marked box; 1.2 mm in diameter). This suspected foci was not enhanced with Gd-DTPA (Fig. 1B-C). In contrast, in the *HRI* maps, the suspected CRLM were clearly highlighted (Fig. 1D-E). The enhanced sensitivity of *HRI* compared to DCE-MRI was demonstrated in additional 6 lesions.

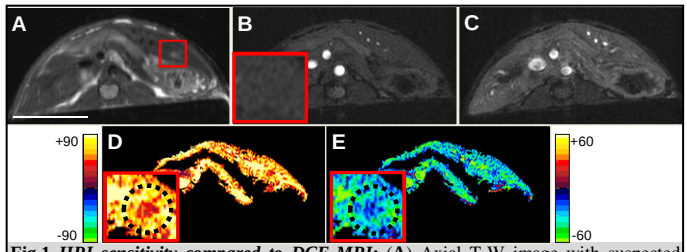

Fig.1 ***HRI sensitivity compared to DCE-MRI:*** (**A**) Axial T_2W image with suspected CRLM (red square); (**B,C**) The corresponding T_1W images obtained before (**B**) and 66 sec after (**C**) i.v. injection of Gd-DTPA; The suspected lesion was not enhanced with DCE-MRI (**B**, enlarged square), despite the injection success as the whole liver was enhanced (**C**). In the corresponding *HRI* maps (**D**-ΔSo_2 map; **E**-ΔSco_2 map), the suspected CRLM were clearly highlighted (**D,E** circles). Bar=1 cm in **A** and applies for all images;

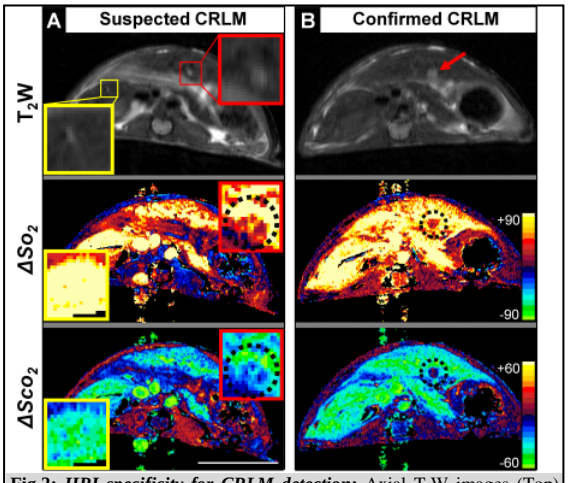

Fig.2; ***HRI specificity for CRLM detection:*** Axial T_2W images (Top) and maps of ΔSo_2 (Center) and ΔSco_2 (Bottom) of a representative mouse with suspected CRLM acquired 14 days following cell injection (**A**, enlarged squares,x3) and 4 days later (**B**). Only one suspected region (red square in **A**) was classified as CRLM by *HRI* and was later confirmed by standard MRI follow-up (**B**, red arrow and circles). Bar=1 cm;

Our next goal was to challenge the usage of *HRI* for the early detection of CRLM. In this model, CRLM were usually detected by using T_2W fast SE images, and the smallest suspected lesion visible was 1 mm in diameter. We analyzed T_2W images obtained at early time points (11-15 days after cell injection) and marked suspected points (see 2 examples in Fig. 2A, enlarged squares). The *HRI* method highlighted areas with "tumor-like" ΔS values (Fig. 2A red box) and others with "healthy-like" ΔS values (yellow box). As suggested by *HRI*, the region marked in red was later confirmed as CRLM in the advanced growth phase, while the region marked in yellow was confirmed as healthy liver (Fig. 2B). The isolation and analysis of areas with significant hemodynamical changes in the T_2W images, acquired in the early-phase of tumor development, was difficult, time consuming, and had tendency for intra-observer variation. Thus, in order to facilitate the differentiation between CRLM and healthy liver, we developed a software which is based on a machine-learning approach for the interactive classification of the suspected CRLM using the *HRI* and T_2W images. A set of suspected spots (n=44) were classified as either CRLM (n=30) or healthy liver (n=14), by using the *HRI* maps with the automatic classification. The classification performance of our method was 77% accuracy, 88% precision, and of 77% recall (true positive-23; false positive-3; false negative-7; true negative-11).

Conclusions We concluded that *HRI* has a higher sensitivity to subtle changes in liver blood flow induced by CRLM than the conventional DCE-MRI method, and that the machine-learning approach can provide a useful assistance to early and accurate detection of CRLM.

References: *[1]Barash,H;Gross,E;Matot,I;Edrei,Y;Tsarfaty,G;Spira,G;Vlodavsky,I;Galun,E;Abramovitch,R;Radiology 243(3),2007; [2]Barash,H;Gross,E; Edrei,Y; Spira,G;Vlodavsky,I;Galun,E;Matot,I;Abramovitch,R;Hepatology Oct;48(4),2008; [3]Edrei,Y;Galun,E;Gross,E;Pikarsky,E;Abramovitch,R; #1752, ISMRM[2006];*