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IVIM reveals increased blood perfusion of liver metastases after oral intake of Salovum®

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1. Purpose

Elevated interstitial fluid pressure (IFP) in tumours impairs perfusion, which hinders anti-cancer drugs and oxygen to reach tumour cells[1-3]. AF-16, a 16 amino acid long sequence from the amino terminal end of the endogenous protein Antisecretory Factor (AF), supresses IFP in animal models of solid tumours[4], and could improve drug delivery to tumour cells. Salovum®, a spray-dried egg yolk powder with high content of antisecretory peptides, should be tested on humans, but requires non-invasive tumour IFP/perfusion assessment methods. The IntraVoxel Incoherent Motion (IVIM) model applied to multi-b DWI enables determination of tissue diffusion (D), pseudo-diffusion (D) and voxel volume fraction of actively perfused capillaries (f)[5].*

The aim of this study was to investigate if f could be used to monitor changes induced by Salovum® in colorectal liver metastases in vivo.

2. Material and Methods

Previously untreated patients (n=6) with colorectal liver metastases were imaged before, and 24h after intake of 48g Salovum® dissolved in water, using IVIM-MRI (3T Philips, 16channel phased array receiver; Single-shot SEEPI (breath-hold); FOV covering liver, 3x3x5mm^3 voxels; TR/TE/NSA/SENSE=1900ms/50ms/2/2; 11 bvalues (0,10,20,30,40,50,75,100,200,300,400,500,600); acquisition time~10min.

MATLAB-based images processing comprised:

1) Inter-scan image registration (volume preserving free-form deformation[6])

2) Voxelwise fitting of D and A [eq.2] to $S(b_{200\text{-}600})$ (for b>200, [eq.1] reduces to [eq.2], assuming D<<D), followed by fitting f and D* [eq.1] to $S(b_{0\text{-}600})$ keeping D and A fixed*

3) Manual delineation of metastases (diameter>2cm) on DWI (b=600), transfer of ROIs to corresponding f-maps for calculation of median ROI f before and after Salovum® intake

4) Mann-Whitney U-test for statistical significance (α-level=0.05)

3. Results

Liver and metastases were well visualised on DWIs and f-maps (Fig.1).

Median f in metastatic tissue increased after intake of Salovum® in 5/6 patients and decreased in one patient (Tab.1).

4. Conclusion

The results show that the proposed IVIM method is a promising, non-invasive tool for studying Salovum® induced changes in liver metastases in vivo. The increase in f was statistically significant but small, suggesting that additional time-points after Salovum® intake, dose escalation and intra-tumour effect heterogeneity should be investigated. The increased perfusion fraction in the liver metastases may offer an important "window of opportunity" for improved transport of drugs to tumour cells.

References

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[2]*Milosevic,M.F.,et al.,Int J Radiat Oncol Biol Phys,1999*

[3]*Wiig, H.,et al.,Scand J Clin Lab Invest,1982*

[4]*Al-Olama, M.et al., Acta Oncol,2011*

[5]*Le Bihan, D.,et al.,Radiology,1988*

[6]*Rueckert, D.,et al., IEEE Trans Med Imaging,1999*

5. Mediafiles

Equations

$$S(b) = S_0\left((1-f)e^{-bD} + fe^{-b(D+D^*)}\right) = Ae^{-bD}\left(1 + \frac{f}{1-f}e^{-bD^*}\right) \quad [eq.1]$$

$$S(b) = Ae^{-bD}, where\ A = S_0(1-f) \quad [eq.2]$$

fig1.jpg

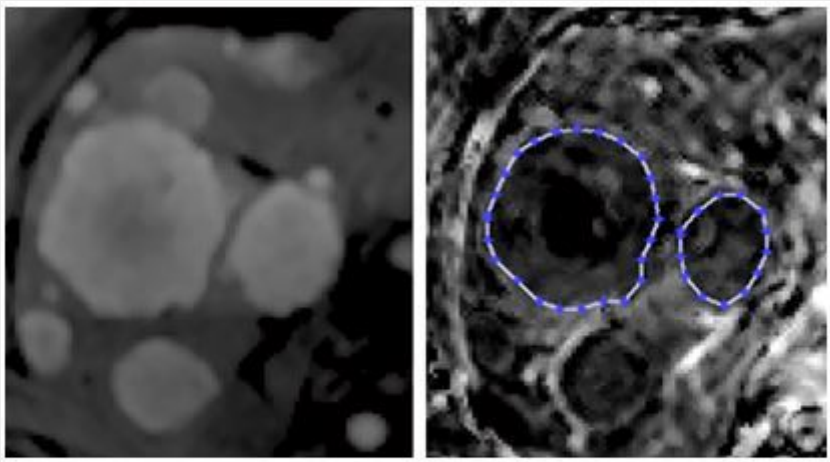

Figure 1. Left: Liver DWI (b=600) used to delineate all metastases (hyperintense regions) with a diameter > 2 cm. Right: Corresponding *f*-map where ROIs are superimposed and used to calculate median *f* of metastatic tissue.

tab1.jpg

Table 1. The median tumour perfusion fraction (*f*) increased in 5/6 patients (green), and decreased in 1 patient (red) after Salovum® intake. All changes were statistically significant with $p < 0.0001$

Median tumour f (%)		
	Before	After
Pat. 1	5.3	9.2
Pat. 2	3.7	4.4
Pat. 3	7.7	8.6
Pat. 4	5.5	6.2
Pat. 5	6.9	7.5
Pat. 6	9.2	5.6