Quantified ^{19}F MR spectroscopy reveals heterogeneous capecitabine metabolism in human liver

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Introduction

Predicting the sensitivity of a specific tumour to chemotherapy in cancer patients would enable individualisation of therapy, which could avoid unnecessary toxicity in non-responding patients. ^{19}F MR spectroscopy can be used to monitor the metabolism of fluorinated drugs. It has been suggested that an increased half-life of the chemotherapeutical drug 5-fluorouracil (5FU) as measured by ^{19}F MRS correlates with patient response to 5FU therapy (1). Knowledge of the tissue content of 5FU and its metabolites may provide further possibilities for the prediction of response to therapy. In patients with advanced colorectal cancer, oral capecitabine has shown comparable activity to intravenous (iv) 5FU (2,3). It is used as an alternative to iv 5FU treatment with increasing frequency, due to its ease of administration and favourable toxicity profile. Capecitabine is preferentially metabolized to 5FU in tumors and liver involving conversion into 5'deoxy-5-fluorocytidine (5'DFCR), followed by conversion into 5'deoxy-5-fluorouridine (5'DFUR). 5FU is further metabolized via different biochemical pathways to cytotoxic metabolites and 5FU catabolites like α-fluoro-β-alanine (FBAL) and 5-fluoro-ureido-propionic acid (FUPA). Recently we have shown that capecitabine and its metabolites can be measured by means of ^{19}F MRS (4). The aim of this study was to develop a method for quantified localized detection of capecitabine and its metabolites in human liver by *in vivo* ^{19}F MRS at 3 Tesla.

Patients and Methods

MR measurements were performed on two patients taking oral capacitabine using a 3 T Siemens Trio MR system. A flexible circularly polarized coil was used consisting of a 16cm circular coil and a 2 x 14cm butterfly coil. The coil is tunable to both 123MHz and 116MHz and connected to a home build interface with less than 0.1dB difference at both frequencies. Patients gave written informed consent and the study was approved by the local ethical committee. For quantification, spatial proton density information was obtained using a 3d chemical shift imaging (CSI) method with a 100% hamming filter (FOV = 27cm. 10 x 10 x 10 matrix, true voxel size of 4 x 4 x 4 cm^3). A 45 degree BIR4 pulse was used for excitation with a TR of 1s, such that the data was hardly affected by T1 or T2 differences of water in healthy liver versus tumor tissue. Spatial and spectral FFT was performed and the resulting data was fitted automatically to single gaussian line shapes by the software platform of the MR system. The localised ^{19}F MRS measurement was obtained with the same spatial settings as the water reference measurement. An adiabatic half passage (tan-hyperbolic, 1.2ms) was used with the carrier frequency set to +5 ppm and the Tr was set to 500ms. Hamming weighted acquisition was applied with 12 averages of the centre k-lines, such that the total scan duration was 9 minutes. Another 3D CSI was obtained in the next 9 minutes with the carrier frequency of the 90 degree excitation pulse set to –19 ppm, a TR of 1s and 5 averages of the centre k-lines. Spectra from the voxel, which had highest sensitivity in liver (i.e. closest to coil conductor) and from the voxel, which had highest SNR, were analysed separately. The spectra were fitted to Gaussian line shapes. The integral of each metabolite peak was divided by the integral of the water peak from the corresponding voxel in the reference dataset. The results were corrected for saturation effects due to T1 relaxation [5]. Finally a theoretical sensitivity correction was applied based on ratio of the larmor constants and the number of nuclei per molecule and the differences in receiver gain were taken into account. The quantification method was validated using a 4 ml spherical phantom with 0.384 M of 5FU positioned at different locations with respect to the coil (i.e. one at the centre of the coil at a distance of 8cm from the coil, and one 2 cm from the upper left conductor of the coil). The method described for the patients was used with the difference that the carrier frequency of the ^{19}F excitation pulse was set to 0 ppm.

Results

The ^{19}F MRS results from a 3D CSI on a patient using a broadband, but non-adiabatic excitation pulse are shown in figure 1a-c. Although this patient had no metastasis visible on the MRI, a different spatial distribution of signal amplitudes from capacitabine versus FBAL can clearly be seen. From another patient ^{19}F MRS data was acquired using the adiabatic excitation pulse. In addition a water reference file with the same spatial settings had been acquired. Quantified results are shown in table I for the DFCR+DFUR and FBAL metabolites in two voxels from the liver.

Using the signals from the voxel of the 5FU phantom, and correcting for T1 saturation, receiver differences, Q-factor differences and Larmor constants, the calculated value for 5FU concentration was 0.352 M/kg_{water} and 0.380 M/kg_{water} for the two locations.

Table I	Absolute concentration [SD] $mMol/kg_{water}$	
	Voxel at maximum sensitivity	Voxel at maximum SNR
DFCR/DFUR	0.029 [0.015]	0.029 [0.015]
FBAL	0.06 [0.03]	0.59 [0.09]

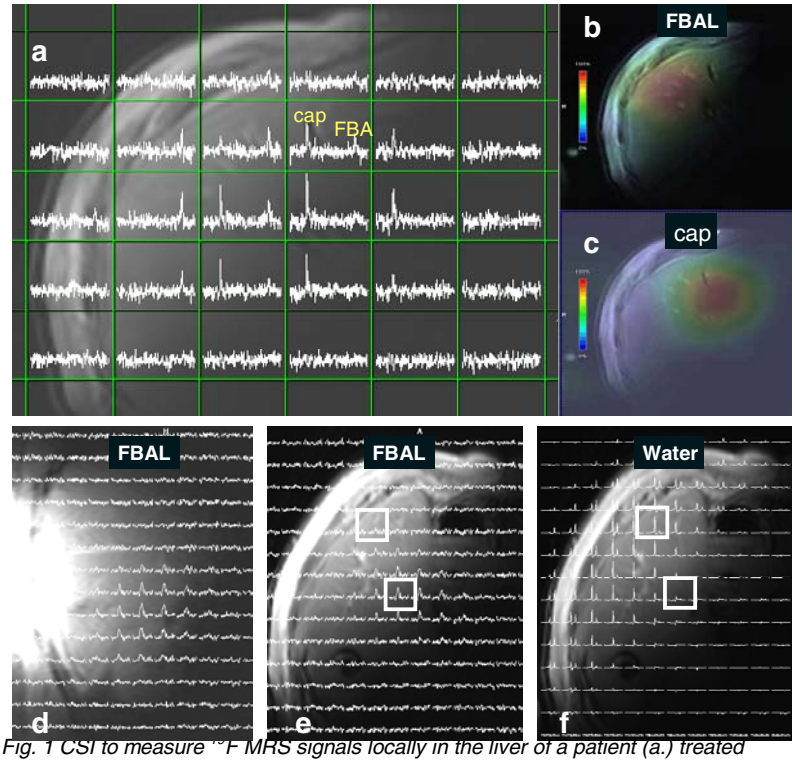

Fig. 1 CSI to measure ^{19}F MRS signals locally in the liver of a patient (a.) treated with oral capecitabine. b,c: color coded distribution of FBAL and capecitabine; coronal (d.) and transversal (e.) view of FBAL and water (f.) distribution in 2nd patient.

Discussion

In the CSI an inhomogeneous distribution of FBAL and capecitabine was observed in the liver, which underscores the relevance of quantifying the concentration of capecitabine and its metabolites. In contrast to results found in literature after bolus injection of 5FU, we found a non-homogeneous distribution of FBAL in liver in the second patient after capecitabine. Although the absolute concentration of FBAL in liver in our study is in the same order of magnitude as found by Li et al. [6], the local concentration within the same liver differs more than 9-fold, whereas the conventional MRI of the liver is homogeneous and shows no structural abnormalities. Hence, this non-homogeneous distribution of FBAL in liver after oral intake of capecitabine seems to reflect a fysiological non-homogeneous catabolism of 5FU in human liver after oral intake of capecitabine.

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