19F MRSI of capecitabine in the liver using broadband TxRx antennas and dual-frequency excitation pulses at 7T

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Purpose: To investigate the feasibility of 19F MRSI at 7T for the monitoring of orally administered chemotherapy in the human body.

Introduction: Intravenously injected chemotherapeutic drugs containing fluorine (19F) can be detected with MR spectroscopy[1] to determine the metabolic rates and the bio-distribution, which are related to the treatment efficacy and toxicity[2]. To reduce side-effects for patients a treatment paradigm shift from intravenous injection to orally administered drugs (capecitabine) has been effectuated, which increases the difficulty for chemotherapy metabolism monitoring with previously developed MR protocols due to the absence of high concentration fluorine bolus. In this work we investigate the potential for orally administered chemotherapy monitoring with a high field 7T system equipped with a broadband eight channel radiative antenna. The 1H signals were used to optimize B1 shimming and signal combination to maximize the 19F MRSI sensitivity. To overcome the limits in B1+ required to excite the high spectral range of the 19F spins (~25ppm), multi-band excitation pulses were implemented.

Methods: *Patients:* Two patients with metastases in the liver were scanned at a 7T system (Philips, Best, The Netherlands) after local ethical approval and written informed consent. The scans were planned 10 hours (patient 1) and 1 hour (patient 2) after capecitabine intake.
TxRx Antenna: An eight channel radiative antenna (MRcoils, Drunen, The Netherlands) was used for patient scanning by placing four elements at the top and four at the bottom of the patient (fig 1,2). Phantom measurements were used to validate that the phase and amplitude weighting to obtain maximum B1+ and B1- fields from the combined elements are similar for 1H and 19F (at 280MHz and 298MHz)[3].
Acquisition: B_0 and B_1 shimming was performed at the 1H frequency before switching to the 19F frequency. Non-localized pulse-acquire spectroscopy scans were performed in 3.5 minutes per scan with TR/TE=100/0.28ms, NSA=2048, FA=40^0, 512 samples and 8000Hz sampling rate. First, the excitation frequency was shifted between +5 and -18ppm to excite the capecitabine or FBAL frequency (fig 3). 3D MR spectroscopic imaging (MRSI) data was acquired in 10.7min for 19F (NSA=16) and in 40 sec for 1H (NSA=1). Other acquisition parameters included 8x8x8 voxels of 40x40x40 mm, TR/TE=100/0.66ms, 512 samples, 8000Hz sampling rate. The 1H spectra were used for phase correction of the 19F data before combining the separate coil elements.
Dual-frequency pulses: A dual-frequency rf pulse was designed for a maximum B1 of 6µT using the SLR algorithm in Matpulse[4] to obtain an excitation pulse that can simultaneously excite the region from +3 to +8 ppm and -15 to -21 ppm (fig 4a-b).

Figure 1: 8 channel TxRx radiative Antennas used in this study. From left to right: Single antenna, all 8 channels and the positioning on the patient.

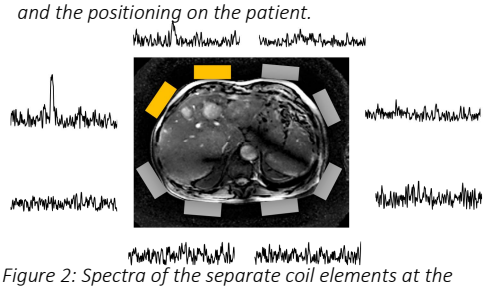

Figure 2: Spectra of the separate coil elements at the capecitabine frequency. Coil elements with clear 19F signal are highlighted.

Results: The coils placed close to the liver detected 19F peaks at the capecitabine (fig 2,3) and FBAL frequency (fig 3). To detect both resonances simultaneously the dual-frequency pulse was experimentally measured by changing the f0 frequency and plotting the magnitude value of the FID (fig 4c). The excitation profile was similar to the simulated profile (fig 4b) despite strong T_1 saturation (ca. 33% signal). An *in vivo* spectrum (f0=-6.5ppm) detected both the capecitabine and FBAL resonances (fig 4d). The MRSI data of the two patients showed clear differences related to the capecitabine ingestion time (fig 5). At 1h after ingestion the capecitabine peak was still detectable, while after 10h the breakdown products were clearly detected.

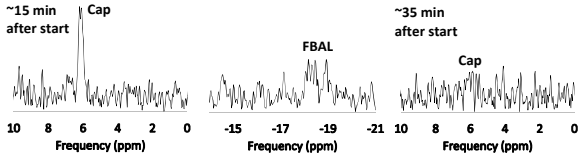

Figure 3: MRS of the 1h after drug intake from the highlighted coil elements in fig 2. MRS acquired at the Cap (left), FBAL (middle) and the Cap frequency at the end of the scan are shown (right).

Discussion: This work has demonstrated that it is feasible to detect capecitabine and FBAL in patients at 7T using radiative antennas and dual-frequency rf pulses. This paves the way to non-invasively study chemotherapy distribution and its chemical conversion in patients.

References: 1. Klomp et al, Magn. Res. Med.,50 p303-308 (2003), 2. Presant et al, 343 p1184-1187, Lancet (1994), 3.Andreychenko et al., Proc 20th ISMRM, Melbourne (2012), 4. Matson, Magn. Reson. Imag., 12 p1205-1224 (1994)

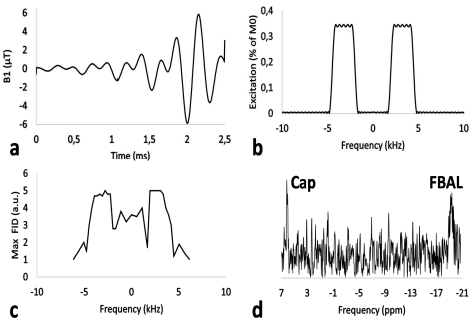

Figure 4: Dual-frequency pulse (a), excitation profile (b) and the measured profile (c) were used to acquire data in vivo ca 1.25h after drug intake (d).

Time after drug intake:

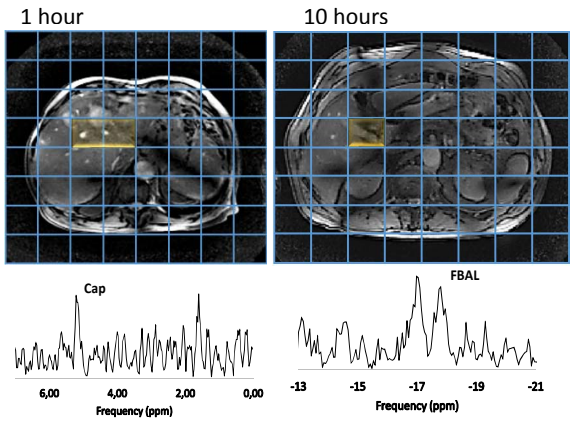

Figure 5: MRSI results of the two patients measured 1h and 10h after drug intake. The displayed spectra originate from the highlighted voxels in the MRSI grid.