Relation between 19F MR spectroscopy of 5-FU, dynamic Gadolinium-DTPA uptake and response to treatment in colorectal liver metastases

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Introduction

Only in a minority of patients with colorectal cancer chemotherapy is effective. Therefore, early selection of patients who could benefit from chemotherapy is desirable. It has been suggested that an increased half life, so called tumor trapping, of the chemotherapeutical drug 5-fluorouracil (5FU) as measured by ^{19}F MR spectroscopy (^{19}F MRS) correlates with patient response to 5FU therapy (1). Among other factors, properties of tumor vasculature, which can be assessed by means of dynamic contrast enhanced MRI (DCE-MRI), may be important for the tumor trapping of 5FU, since delivery of this agent to the tumor occurs via blood vessels. The aim of this study was to investigate the relationship between 5FU metabolism in liver metastases of colorectal cancer measured by ^{19}F MRS, dynamic Gadolinium-DTPA (Gd-DTPA) contrast uptake measured by DCE-MRI and response to 5FU treatment.

Patients and Methods

MR measurements were performed on a 1.5 T Siemens Vision MR system in 21 patients with colorectal liver metastases on the first day of treatment with 5FU. Patients gave written informed consent and the study was approved by the local ethical committee. 5FU (425 mg/m^2) was administered as a bolus injection within 3 minutes. For ^{19}F MRS a flexible circular polarized coil was used consisting of a 16cm circular coil and a 2 x 14cm butterfly coil, placed across the liver region. In all patients either a 8 x 8 x 8 CSI (TR 470ms, voxel size 4x4x4 cm) was used or an optimized technique (2) using spherical k-space sampling with Hamming weighted averaging to obtain optimum SNR in CSI (TR 450 ms, true voxel size 4x4x4 cm). The first ^{19}F MRS measurement was started at the same time when the 5FU bolus was injected. Acquisitions took place during a period of 40 minutes with a time resolution of 4 minutes. Data were inspected visually and analysed quantitatively using jMRUI. T1 and T2 weighted images were used for determination of the locations of the CSI voxels (in tumor or in healthy liver tissue). Quantitative changes in resonances of 5FU and α-fluoro-β-alanine (FBAL), the major MR visible 5FU catabolite, were fitted to a mono-exponential equation.

DCE-MRI was performed immediately after the last ^{19}F MRS measurement, using the body coil. 15 ml 0.5M Gadolinium-DTPA (Gd-DTPA, Magnevist®, Schering, Berlin, Germany) was administered intravenously in 6 s by a Spectris^{TM} MR injection system (Medrad, Inc.). Using a T1-weighted fast low-angle shot (FLASH) sequence with a time resolution of 2 s Gd-DTPA uptake in the tumor and the bolus passage in vessels in the spleen was monitored (TR 50 ms, TE 4.4 ms, flip angle 90°, slice thickness 7 mm, 4 slices, matrix 160x256, FoV 263x350, acquisition time 90 s). DCE-MRI data were analyzed as described previously (3). Using a physiological pharmacokinetic model the rate constant k_{ep} (s^{-1}) and the transfer constant K^{trans} (a.u. s^{-1}) were calculated for the same tumor of which ^{19}F MRS data were acquired. To assess response we measured the largest tumor diameter of the liver metastasis before and after 2 months of treatment. In case of multiple liver metastases the diameters of up to five metastases were measured and summed to compare the sum of those diameters before and after treatment, according to the RECIST criteria.

Results and Discussion

In 16 out of 21 patients ^{19}F MRS signals were detectable (fig. 1). Patients in whom no ^{19}F MRS signal was detected were all measured with the 8x8x8 non-optimized CSI technique, which underscores the relevance of the optimized technique. 5FU was detected in the tumor in 7 out of 16 patients, in the liver in 8 patients; FBAL was detected in voxels located in the tumor in 8 patients, in voxels located in the liver in 13 patients. Half life of 5FU decay ranged from 3.37-14.24 min in the tumor and 3.20-12.80 min in the liver. Time to 50% of maximum FBAL resonance amplitude ranged from 3.49-85.77 min in the tumor and 1.07-145.8 min in the liver. In some patients a relatively large standard error of the mean was obtained for the fitted time constants, probably due to the relatively low signal-to-noise-ratio in the spectra, although the influence of biological variation cannot be excluded. A significant positive correlation was found between the time to 50% of maximum FBAL resonance amplitude in the liver and in the tumor (fig. 2a). As FBAL is assumed to be produced in liver tissue, this correlation may be expected if it enters the tumor subsequently via the blood circulation. A significant negative correlation was found between the half life of 5FU in the tumor and the extravascular extracellular volume v_e (fig 2b). Possibly, in tumors with a larger v_e relatively less cancer cells are present that can trap 5FU, explaining the shorter half life of 5FU in these tumors. No significant correlations were found between half life of 5FU, the time to 50% of maximum FBAL resonance amplitude and k_{ep} or K^{trans}. Therefore, if k_{ep} and K^{trans} are interpreted in terms of tumor blood flow and the PS product (*P*ermeability and the total *S*urface area of perfused capillaries) tumor trapping of 5FU and production of FBAL may not dependent on tumor blood flow, vascular permeability or vascular surface area. No correlation was found between the qualitative and quantitative analysis of ^{19}F MRS measurements and tumor response.

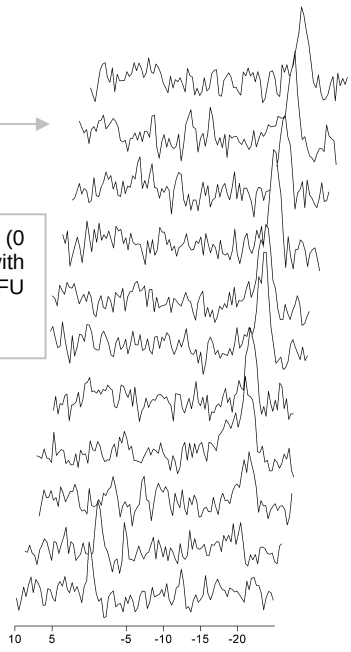
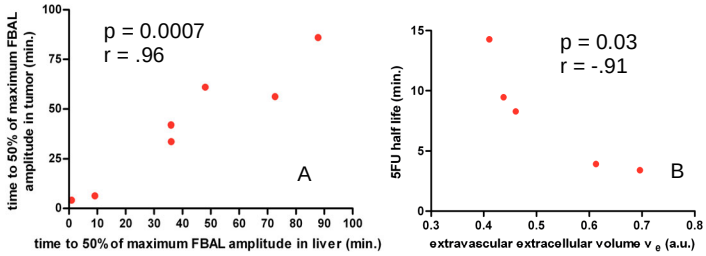


Fig. 1 ^{19}F MR spectra showing 5FU (0 ppm) and FBAL (-19 ppm) acquired with optimized CSI after start of injection of 5FU in the liver metastases.

Literature

1. Presant CA et al., Lancet, 343, 1184, 1994.
2. Klomp et al, MRM 2003:203.
3. Van Laarhoven et al., JMRI 2003: 315.

Fig. 2A Relation between time to 50% of maximum FBAL signal in liver and tumor. Fig. 2B Relation between extravascular extracelluar volume v_e and 5FU half life.



Acknowledgement

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