Magnetization transfer imaging in a mouse model of orthotopic pancreatic cancer

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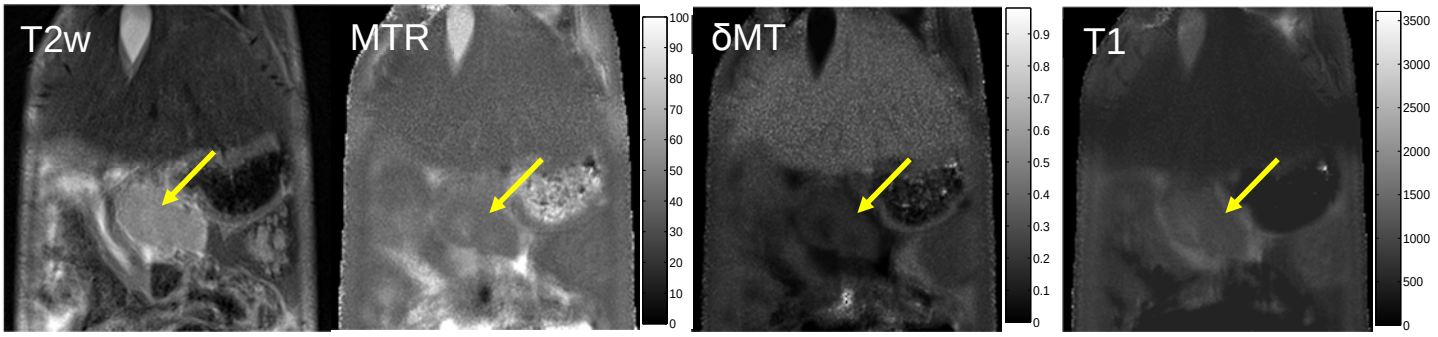
Target Audience: Physician or physicists who are interested in visualization and quantification of pancreatic carcinoma.

Purpose: Pancreatic ductal adenocarcinoma (PDAC) ranks fourth among the tumor related causes of death. Desmoplasia characterizes PDAC and is associated with proliferation of fibroblasts and secretion of collagen which strongly contribute to chemotherapy resistance. Therefore noninvasive characterization of tumor-associated stromal tissue is of great importance for a better understanding of differences in treatment response and for individually optimized therapy planning. Moreover, *in vivo* monitoring of fibrosis in mouse models of PDAC over time may contribute to a better understanding of tumor-stroma interactions. Recently an increase in the magnetization transfer (MT) ratio with increased fibrosis level has been reported in a mouse model using subcutaneous injection of the human PDAC cell lines BxPC3 and Capan-1 [1]. However this model only partly resembles the local tumor environment found in the pancreas. In this study, we inject BxPC3 and Capan-1 cells in the pancreas of nude mice in order to analyze desmoplasia in an orthotopic setting. Our goal was to evaluate the robustness of MT measurements in the abdomen and its potential for quantitative stroma characterization.

Material & Methods: Tumors were established by injecting BxPC3 and Capan-1 tumor cells into the pancreatic body of adult nude mice (n=5/5). At days 14 and 21 after inoculation mice were anesthetized with isoflurane (1.75%) and examined in a 7 T MR-System (ClinScan, Bruker BioSpin, Germany) using a 4-channel phased-array coil for signal reception. The MRI protocol consisted of four different measurements: (1) T2-weighted images were obtained by a BLADE-TSE sequence (TR/TE = 1785/30 ms, FOV = 32 × 32 mm², spatial resolution = 125 × 125 × 400 µm³, 30 slices, acquisition time = 2 min and 38 s); (2) proton density weighted images were acquired by a spoiled radial FLASH sequence (TR/TE = 95/2.02 ms, flip angle = 5°, FOV = 32 × 32 mm², 401 spokes, spatial resolution = 125 × 125 × 500 µm³, 6 slices and 32 averages). (3) The MT-weighting were achieved by adding a band selective RF pulse to the mentioned sequence (pulse duration = 10 ms, frequency offset = 1200 Hz and flip angle = 500°). The latter two datasets yielded maps of the MT ratio (**MTR**). (4) T1-weighted images were acquired by changing the flip angle of the proton density image to 30°. The MT saturation (**δMT**), that is the percentage of magnetization destroyed by a single MT pulse, was calculated from the MT-weighted signal by correcting for the signal amplitude and T1 as detailed in [2]. To evaluate the impact of respiratory motion, images were reconstructed either by including all acquired spokes or by using retrospective self-gating based on signal and phase changes in the k-space center. The latter resulted in images of six different respiration phases. ROIs of the tumor were selected on the map of proton density excluding cystic and possibly necrotic tissues identified on T2-weighted images. After the final MR measurement the animals were sacrificed and prepared for histology.



Results: A T2-weighted image and the corresponding maps of MTR, δMT and T1 of a mouse with pancreatic cancer are shown in the figure. The tumor was clearly distinguishable on all these images (yellow arrows). Quantitative ROI analyses (mean ± SD) are summarized in the table below. None of the parameters (MTR, δMT and T1) showed significant changes related to the different respiratory phases (ANOVA, p = 0.99). The BxPC3 tumors (known to be associated with extensive fibrosis) exhibited significantly higher δMT at day 14 compared to Capan-1 tumors (p = 0.01). Interestingly, δMT of Capan-1 tumors increased over time (p = 0.001) in contrast to BxPC3 which decreased. Consequently, at day 21 there were no differences in δMT between these two tumor types. Moreover, the T1 relaxation time of Capan-1 tumors decreased over time (p = 0.001). The mean of MTR was also higher in BxPC3 tumors but this difference was not significant. MTR and δMT revealed results with an apparent inverse relationship as indicated at day 21 whereby the MTR was significantly lower in Capan-1 compared to BxPC3 (p = 0.003). This is consistent with the dependency of T1 relaxation time on the product of the fraction of bound protons [4].

Tumor cells	Day	MTR/%	δMT	T1 (ms)
BxPC3	14	65 ± 6	0.17 ± 0.04	1336 ± 329
	21	66 ± 2	0.14 ± 0.02	1441 ± 121
Capan-1	14	60 ± 6	0.11 ± 0.01	1551 ± 274
	21	60 ± 2	0.15 ± 0.01	1055 ± 141

Discussion: Using a radial acquisition scheme respiratory motion did not significantly affect the quantitative analysis of orthotropic pancreatic cancer in this mouse model. Thus, averaging over different breathing phases could be used to further shorten the measurement time. The observed increase in δMT is well in line with the expected higher degree of desmoplasia in BxPC3 including the accumulation of collagen [1, 4]. Noteworthy, Capan-1 cells that give rise to a mucin-producing adenocarcinoma [5], exhibited a reduction of T1 over time, which may alter the validity of MTR.

Conclusion: To the best of our knowledge this is the first report of magnetization transfer imaging in an orthotropic model of pancreatic cancer. MT saturation, that corrects the MT-weighted signal for signal amplitude and T1 relaxation, appears to be a promising parameter for the quantification of tumor-associated fibrotic tissue. Ongoing studies involve the comparison of MRI with quantitative histological analyses.

References: [1] Li W et al. MRM 2012;68:1291-1297. [2] Helms G et al. MRM 2008;60:1396-1407. [3] Henkelman RM et al. NMR Biomed., 2001;14:57-64. [4] Farace P et al. Eur J Nucl Med Mol Imaging. 2009;36(4):616-623. [5] Kyriazis AP et al. Am J Pathol. 1982;106(2):250–260.