Characterization of liver lesions in a mouse model of endocrine tumors using MRI

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Introduction

Endocrine tumors, with digestive localization, are tumors with variable forecast which are independent of their local and metastatic extensions. Animal models play a major role in cancer research. Many aspects of malignancy, including the formation and treatment of metastases, can be studied in animals. A murine model of the liver dissemination of the human enteropancreatic endocrine tumors has recently been developed [1]. The goal of this study was to assess the detection level and to quantify lesion volume as well as the transverse relaxation time parameters in the athymic nude mouse model. A follow-up was performed using a dedicated MRI protocol and an optimized synchronization strategy for high magnetic field strength.

Material and Methods

A group of 8 mice was followed 7, 12, 17 and 24 days after injection of tumoral cells. Average weight started at 22.4 ± 1.8 g at D7 and decreased down to 17.3 ± 1.6 g at last stage. At the ultimate stage, mice were sacrificed for histomorphometry analysis. The whole experimental protocol was approved by the Animal Care and Use Committees of the University Lyon 1. The cardiac and respiratory movements were detected using a home-made air pillow connected to a sensitive pressure sensor (Honeywell, Freeport, IL, USA) with a thin plastic tube. Pressure sensor was interfaced (connection and power supply) with an ECG Trigger Unit HSB-T (Rapid Biomedical, Würzburg, Germany), to use the adapted functionalities of this trigger unit (amplification, filtering, trigger level, trigger delay and trigger window). The experiments were performed *in vivo* at 7 T, on a Biospec system (Bruker, Ettlingen, Germany). For both RF emission and reception, a cylindrical volumetric coil with a 32 mm internal diameter (Rapid Biomedical) was used. A fat suppressed (FS) multiple spin-echo (SE) sequence, with three echoes (TE=20, 40, 60 ms) was used with the following parameters: 30 x 30 mm^2 FOV, 256 x 256 matrix, 36 slices, 0.5 mm slice thickness and 17 kHz receiver bandwidth. To avoid artifacts in the upper part of the liver due to heart motion, a dual cardiac-respiratory triggering based on the pressure sensor signal was used. Using this dual cardiac-respiratory triggering strategy, a unique trigger pulse is generated per heart beat during the allowed acquisition window (between the end of the expiration and the beginning of next inspiration). For each trigger pulse, a unique slice is selected. Using this method, all the slices are acquired over several respiratory cycles corresponding to an effective TR of about 6 sec [2]. A water tube placed bellow the mouse was used as an external reference for the segmentation procedure. The image analysis was performed using IDL (RSI, Boulder, CO, USA) programming language. A threshold was defined using a dual reference limit, based on the average signal intensity calculated in the background (I_{bg}) and a reference water tube (I_w). The threshold was set up to 30% of (I_w - I_{bg}). The hepatic lesion volume fraction (HLVF) was calculated for all mice between stages D12 and D24 for the three echo times. The HLVF was calculated as the volume of lesions divided by the total hepatic volume. The total liver volume was obtained by drawing manually on every single slice, a region of interest (ROI) corresponding to the liver region. The transversal relaxation time was obtained from multiple SE images acquired at the three echo times. The T2-maps were calculated for every pixel image by fitting a mono-exponential decay function to the data. The T2-values were averaged in the liver for each mouse, using the same ROI used for the HLVF.

Results

The unique pressure sensor used for both respiratory and cardiac triggering was sensitive enough to perform the dual cardiac and respiratory synchronization on all animals. The signal from the pressure sensor was uncorrupted by the eddy currents induced by RF pulses or by gradient commutations and was used without limitations regarding the sequences and RF pulse types, with a good reproducibility for *in vivo* experiments. Lesions appear as hyper intense nodules as compared with adjacent normal liver tissue. The first lesions were visualized and detected at stage D12. On the images with the shortest TE (20 ms) all the lesions appear hyper intense. For the longest TE (60 ms), fewer lesions are visible on images. The segmentation procedure, using a dual reference, enables the segmentation and the quantification of the HLVF. The threshold used provides good discrimination between parenchymal phase and lesion phase. The HLVF for the three echo times and all the stages were quantified with exception of stage D7 for which the lesions were not visible. As expected, the HLVF increases with stage: 6.78%, 23.13%, 37.95% at 20 ms; 0.12%, 2.63%, 16.46% at 40 ms; 0.01%, 0.56%, 7.81% at 60 ms. For each stage the HLVF decreases with TE. Significant HLVF differences were found between all stages and echo times. Mean transverse relaxation time T2-values measured for every stages are reported in Fig 2. From D12, the mean T2-values increase with stage with 25.8 ± 1.2 ms at D7, 25.5 ± 1.0 ms at D12, 28.2 ± 2.2 ms at D17 and 41.8 ± 4.1 ms at D24. All the differences between stages were statistically significant with the exception of stages D7 with D12. The reading of the histological sections depicting macro-cystic lesions confirmed the cystic nature of the lesions at final stage.

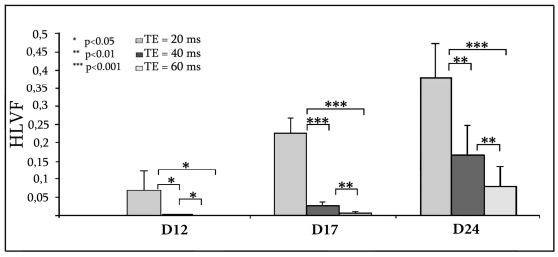

Fig. 1: HLVF quantified from D12 to D24 for each echo time and displayed as a function of stage.

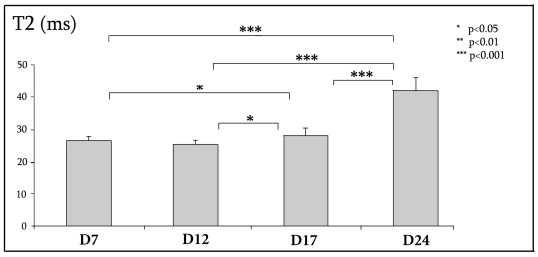

Fig. 2: Mean transverse relaxation time T2-values measured at all stages.

Conclusion

The level of lesion detection was assessed using a devoted protocol with a suitable synchronization strategy dedicated to high field MRI. Quantified parameters were used to follow and characterize the lesion's evolution. The described MR imaging protocol could be used with relevance in the evaluation of new therapeutics protocol for treatment of liver lesions in neuroendocrine tumors using mouse models.

References

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