Dynamic contrast enhanced imaging with high temporal resolution for semiquantitative perfusion assessment of experimental liver tumors in rats at 9.4 T

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Authors: P. Fries, D. Morr, A. Müller, A. Massmann, G. K. Schneider, R. Seidel, A. Bücker; Homburg/DE
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Purpose

MRI at ultrahigh field strength beyond 3 Tesla has gained more and more importance for preclinical animal studies. Especially in tumor models MRI allows for non-invasive assessment of tumor development and the influence of different therapies on tumor growth in longitudinal studies.

However, the sensitivity of MR images to motion artifacts is a major issue particularly in studies of the abdominal organs. Thus, animal cancer studies are preferably performed in models with tumor localization in the brain or the subcutaneous soft tissue (1-4). Nevertheless, there are animal models of hepatic malignancies available (5-7), but MRI evaluation of these pathologies in small rodents remains challenging (8).

In addition, the very fast circulation time in small rodents represents a problem especially in the context of dynamic contrast enhanced MR examinations using extracellular Gadolinium agents.

One possibility to overcome the afore mentioned issues is the acquisition of fast respiratory gated FLASH sequences.

The aim of this study was to analyze the feasibility to assess differences in first-pass perfusion of liver tissue, hepatic metastases, renal cortex and erector spinae muscle using a respiratory self-gated FLASH (RSG-FLASH) sequences with high temporal resolution in rats at 9.4 Tesla.
Methods and Materials

Study population:

Ten female WAG-Rij rats (Charles River Laboratories, Sulzfeld, Germany) with a mean weight ± SD of 155 ± 15 g.

Anaesthesia:

The surgical procedures and MRI examinations were performed under general anesthesia, which was initiated in an induction chamber using a mixture of 4% isoflurane and 96% oxygen. During surgery and MRI acquisition, anesthesia was maintained with an animal nose mask supplying a mixture of 1.5 - 2% isoflurane and 98 - 98.5% oxygen at a flow rate of 1.5 l/min.

Implantation of colon cancer cells:

After a midline incision and luxation of the left hepatic lobe out of the abdominal cavity, a colon cancer cell suspension containing $5 \times 10^5$ tumor cells (CC531, CLS; Cell Lines Service and Tumor-Cellbank, Heidelberg, Germany) was injected into the left hepatic lobe.

MR Imaging:

14 days after tumor implantation, all animals were examined in a horizontal bore 9.4 Tesla MRI animal scanner (Bruker BioSpin 94/20, Ettlingen, Germany) using a 16-channel volume coil. The MR system was run with ParaVision 5.1 including the IntraGate® software for sequence acquisition and reconstruction. The animals were positioned prone in a dedicated animal cradle. Details of the sequence parameters are given in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Flip Angle</th>
<th>No. of averages</th>
<th>FOV (mm²)</th>
<th>Matrix Pixel size (µm²)</th>
<th>Slice thickness</th>
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</thead>
<tbody>
<tr>
<td>T2 RARE</td>
<td>917</td>
<td>27</td>
<td>90°</td>
<td>3</td>
<td>50x50</td>
<td>256x256 195x195</td>
<td>1 mm</td>
</tr>
<tr>
<td>T1 FLASH</td>
<td>45</td>
<td>2.5</td>
<td>45°</td>
<td>5</td>
<td>50x50</td>
<td>256x256 195x195</td>
<td>1 mm</td>
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<tr>
<td>RSG FLASH</td>
<td>57</td>
<td>18</td>
<td>10°</td>
<td>5</td>
<td>46x46</td>
<td>92x92 500x500</td>
<td>1 mm</td>
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</table>
Table 1: Performed MRI sequences

To localize the tumor within the left hepatic lobe, we acquired T2-weighted and T1-weighted sequences in axial slice orientation.

For the assessment of first-pass perfusion we acquired a single slice respiratory self-gated T1-weighted FLASH sequence covering the area of the tumor. The sequence acquisition was expedited mainly by reducing matrix and field of view.

Six seconds after initiation of the sequence we injected a contrast agent bolus (0.1 mmol/kg body weight Gd-DOTA) through a previously inserted tail vein catheter. The total acquisition time of this sequence was 90 sec. 45 images were retrospectively reconstructed from the acquired raw data resulting in a temporal resolution of 2 s/image.

After the first pass perfusion study we additionally acquired contrast enhanced high-resolution T1-weighted FLASH sequences.

Assessment of Signal-to-Noise Ratio (SNR):

Signal intensities were measured based on region-of-interest (ROI) analysis within normal liver tissue, the hypovascularized tumor center, the renal cortex and the erector spinae muscles using open-source image evaluation software (OsiriX, Pixmeo, Bernex, Switzerland).

The first two unenhanced images of the RSG-FLASH sequence were subtracted and the standard deviation of the measured signal intensity for the given ROI was considered the noise.

SNR values for the different anatomical localizations were calculated for all time points as given below (9):
\[
\text{SNR}_t = \frac{SI_t \cdot \sqrt{2}}{SD_{\text{subtract}}}
\]

**Fig. 1:** Equation for calculation of signal-to-noise ratio (SNR) for a given time point \(t\). SI: signal intensity as assessed by ROI measurement. SD: standard deviation of the signal intensity for the corresponding ROI in the subtracted data set.

**References:** Clinic of Diagnostic and Interventional Radiology, Saarland University Hospital - Homburg/DE

We calculated the area under the curve (AUC) of the SNR evolution over time for the different tissues. Statistical analysis included an ANOVA with Bonferroni multi-comparison (\(p<0.05\)).

**Histology:**

All animals were sacrificed following the MRI examinations, and the livers were harvested for histopathological evaluation.
Results

The histological evaluation of the liver specimen confirmed the presence of hepatic metastases in all examined animals. Peritoneal or extrahepatic metastases were not detected.

![Image of liver specimen showing colon cancer cells infiltrating liver parenchyma](image)

**Fig. 2:** Hematoxylin and eosin staining of a liver specimen demonstrating the homogeneous infiltration of liver parenchyma (left side) with colon cancer cells (right side), the black arrows indicate the tumor border.

**References:** Clinic of Diagnostic and Interventional Radiology, Saarland University Hospital - Homburg/DE

Axial T2-weighted sequences demonstrate the hepatic metastasis with homogeneous high signal intensity within the left liver lobe (arrow).
**Fig. 3:** Axial T2-weighted RARE sequence demonstrating the hepatic metastasis within the left liver lobe (arrow). The arrowhead points to the right kidney.

**References:** Clinic of Diagnostic and Interventional Radiology, Saarland University Hospital - Homburg/DE

The reconstructed movie from the first pass perfusion study demonstrates a strong enhancement of the abdominal organs especially the renal cortex (arrow head) while the metastasis in comparison shows hypovascularization (arrow).
Fig. 4: Reconstructed images of the RSG-FLASH sequence for the assessment of first pass perfusion at different times (a: unenhanced, b: early after contrast injection, c. late after contrast injection). The arrow indicates the hepatic metastasis, the arrowhead points to the right kidney.

References: Clinic of Diagnostic and Interventional Radiology, Saarland University Hospital - Homburg/DE
Fig. 5: Reconstructed movie of the RSG-FLASH sequence demonstrating the first-pass of the injected contrast agent bolus (0.1 mmol / kg BW Gd-DOTA) through the abdominal organs. The temporal resolution is 2 seconds per image.

References: Clinic of Diagnostic and Interventional Radiology, Saarland University Hospital - Homburg/DE

AUC was significantly lower for the tumor (mean +/- SD: 6290 +/- 2082) and muscle (5765 +/- 2082) as compared to normal liver parenchyma (8895 +/- 2636) and the renal cortex (8901 +/- 3240; p=0.0004). No significant differences were assessed between AUC of the renal cortex and normal liver parenchyma as well as between tumor and muscle.
Area under the curve (AUC) for SNR evolution over time for different tissues.

<table>
<thead>
<tr>
<th></th>
<th>liver</th>
<th>tumor</th>
<th>renal cortex</th>
<th>muscle</th>
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<tr>
<td>mean</td>
<td>8895</td>
<td>6290</td>
<td>8901</td>
<td>5765</td>
</tr>
<tr>
<td>SD</td>
<td>2639</td>
<td>2082</td>
<td>3240</td>
<td>2082</td>
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Fig. 6: Graphs demonstrate the SNR evolution relative to time (in seconds) for the different analyzed tissues in the first-pass perfusion study.

References: Clinic of Diagnostic and Interventional Radiology, Saarland University Hospital - Homburg/DE
T1-weighted FLASH sequence acquired before (left) and after the contrast enhanced first pass perfusion study (right) demonstrate the enhancement of the hepatic metastasis (arrow) and the right kidney (arrowhead).

Fig. 7: High resolution unenhanced (left) and contrast enhanced (right) T1w images demonstrating the contrast agent uptake of the hepatic metastasis (arrow) and the renal parenchyma (arrowhead).

References: Clinic of Diagnostic and Interventional Radiology, Saarland University Hospital - Homburg/DE
Conclusion

RSG-FLASH sequences with high temporal resolution can be used to quantify differences in the first-pass of contrast agent in different abdominal organs in small animal studies. In particular, this imaging approach permits detection of differences in perfusion of hepatic metastases and normal liver parenchyma. Potentially, it could be used to evaluate treatment-related changes of tumor perfusion in preclinical cancer studies.

Nevertheless, the demonstrated approach only leads to a semi-quantitative analysis. One major draw back of this sequence is the rather high signal intensity of the great vessels on both unenhanced and contrast enhanced T1-weighted images (mainly based on dephasing effects of stationary tissue and inflow of unsaturated spins in the vessels).

This inhibits assessment of accurate input function for the contrast agent bolus arrival in the aorta. Thus, quantification of contrast agent concentration for different anatomical localizations and subsequently regional quantitative assessment of tissue perfusion cannot be performed using this approach.

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References


Personal Information

Dr. Peter Fries, MD, Clinic of Diagnostic and Interventional Radiology, Saarland University Medical Center, Homburg, Germany

Denise Morr, Clinic of Diagnostic and Interventional Radiology, Saarland University Medical Center, Homburg, Germany

Dr. Andreas Müller, PhD, Clinic of Diagnostic and Interventional Radiology, Saarland University Medical Center, Homburg, Germany

Dr. Alexander Maßmann, MD, Clinic of Diagnostic and Interventional Radiology, Saarland University Medical Center, Homburg, Germany

Prof. Dr. Dr. Günther Schneider, MD, PhD, Clinic of Diagnostic and Interventional Radiology, Saarland University Medical Center, Homburg, Germany

Dr. Roland Seidel, MD, Clinic of Diagnostic and Interventional Radiology, Saarland University Medical Center, Homburg, Germany

Prof. Dr. med. Arno Bücker, MD, M. Sc., Clinic of Diagnostic and Interventional Radiology, Saarland University Medical Center, Homburg, Germany