Method for quantitation of dynamic MRI contrast agent uptake in colorectal liver metastases

H. van Laarhoven1, M. Rijpkema2, C. Punt3, T. Ruers3, J. Hendriks4, J. Barentsz2, A. Heerschap1
1Medical Oncology, UMC Nijmegen, Nijmegen, Netherlands, 2Radiology, UMC Nijmegen, Nijmegen, Netherlands, 3Surgery, UMC Nijmegen, Nijmegen, Netherlands, 4Epidemiology & Statistics, UMC Nijmegen, Nijmegen, Netherlands

Synopsis: For the prediction and follow up of therapy outcome in cancer treatment by dynamic contrast enhanced MRI (DCE-MRI), reproducibility of DCE-MRI should be determined. We investigated the reproducibility of DCE-MRI in ten patients with colorectal liver metastases. The use of an arterial input function (AIF) from pixels in the aorta was compared with the use of a vascular normalization function (VNF) from the spleen. The use of the VNF was superior to the AIF in terms of reproducibility and is therefore recommended when this DCE-MRI technique is used for prediction and monitoring of therapy outcome in colorectal liver metastases.

Introduction: Dynamic contrast enhanced MRI (DCE-MRI) is becoming increasingly widespread for the prediction and monitoring of treatment outcome. Therefore, assessment of the reproducibility of DCE-MRI is necessary. To be able to compare DCE-MRI data from different patients and from one patient at different times, normalization should be applied to minimize variations due to variable systemic blood flow. In this study we compare the reproducibility of DCE-MRI in colorectal liver metastasis using an arterial input function (AIF) from the aorta and a vascular normalization function (VNF) taken from the spleen.

Patients and methods: DCE-MRI was performed on a 1.5 T Siemens Vision MR system in 10 patients with colorectal liver metastasis. All patients gave written informed consent and the study was approved by the local ethical committee. 15 ml 0.5M Gadolinium-DTPA (Gd-DTPA, Magnevist®, Schering, Berlin, Germany) was administered intravenously in 6 seconds by a Spectris™ MR injection system (Medrad, Inc.). Using a T1-weighted fast low-angle shot (FLASH) sequence with a flip angle 90°, slice thickness 7 mm, 4 slices, matrix 160x256, FoV 263x350, acquisition time 90 s. A saturation band was used to reduce inflow artifacts in the aorta. The measurement protocol was repeated after minimally 24 hours and maximally four days. Slice positions were matched with the first session using the spine as a reference. Analysis of DCE-MRI data was adapted from Rijpkema et al. (1) We obtained the VNF from pixels in the spleen using an automated algorithm based on the concentration of Gd-DTPA (high in blood vessels) and time to bolus passage (short in arteries). Using a physiological pharmacokinetic model (2) the Gd-DTPA uptake rate $k_{ep}$ was calculated and the spatial distribution of $k_{ep}$ was represented in a map. A region of interest (ROI) was applied to this map in order to obtain single values of $k_{ep}$ for all tumor pixels. The geometric mean of the Gd-DTPA uptake rate of these pixels was calculated after log transformation and averaged over all slices containing tumor tissue, resulting in an average $k_{ep}$ value for the whole tumor. The same method of analysis was repeated for each patient using pixels from the aorta as AIF. One way analysis of variance was used to estimate the within patient standard deviation and the between patient standard deviation of the duplicate $k_{ep}$ values using a VNF from the spleen ($k_{ep,spleen}$) and an AIF from the aorta ($k_{ep,aorta}$). The dependent variable was $k_{ep,spleen}$ and $k_{ep,aorta}$, respectively, and the independent class variable was patient.(3) Data of both $k_{ep}$ measurements were visualized according to the method of Bland and Altman (4) and the appropriate coefficients of repeatability (i.e. twice the standard deviation of the differences between both values of $k_{ep}$ were calculated.

Results: A VNF was determined from pixels in the spleen for each patient (fig.1). An example is shown in fig. 1. In the second measurement of one patient only 5 pixels from the spleen were selected by the algorithm used to calculate the VNF. For each patient the difference in $k_{ep}$ between session 1 and 2 versus the mean $k_{ep}$ of session 1 and 2 is plotted in fig. 2. Within patient variance of $k_{ep,aorta}$ is more than two times larger than the within patient variance of $k_{ep,spleen}$ (table 1). The total variance of $k_{ep,spleen}$ consists to a larger extent of variations between patients than the total variance of $k_{ep,aorta}$, as is reflected in the values of R (85% vs 70%). The overall mean $k_{ep,spleen}$ of the two sessions for all patients was 0.031 s⁻¹ with a repeatability coefficient of 0.009 s⁻¹. For $k_{ep,aorta}$ the overall mean $k_{ep}$ of the two sessions for all patients was 0.028 s⁻¹ with a repeatability coefficient of 0.021 s⁻¹.

Discussion: A smaller within patient variance and a smaller repeatability coefficient was found for the method using the VNF than the AIF, probably due to flow- and pulsation artifacts in the aorta. Patient characteristics could be identified that would predict in which patients results would be compromised by these artifacts in the aorta. The repeatability coefficient of 0.009 s⁻¹ for the Gd-DTPA uptake rate $k_{ep,spleen}$ implies that for 95% of pairs of observations the absolute difference between two measurements on the same patient is expected to lie below this threshold. In view of the observed between patient standard deviation (0.018, table 1) the presented method for quantitation of contrast agent uptake in colorectal liver metastases may be of clinical value for the prediction and monitoring of treatment outcome. The presented repeatability coefficient compares well with the literature on reproducibility of $k_{ep}$ values in tumor tissue. For a set of various tumors Galbraith et al.(5) reported mean $k_{ep}$ values of 0.022 s⁻¹ and 0.023 s⁻¹ with repeatability coefficients of 0.015 s⁻¹ and 0.015 s⁻¹, respectively. The mean $k_{ep}$ value reported by Rijpkema et al.(1) is 0.030 s⁻¹ in brain, head and neck and prostate tumors using a cored geistered AIF per patient, with a repeatability coefficient of 0.006 s⁻¹. In comparison with the abdominal region DCE-MRI data from especially the brain and head and neck region will be less compromised by motion artifacts. Breath-hold perfusion and permeability mapping of hepatic malignancies with DCE-MRI has been described by Jackson et al. (6) which would allow detection of changes in mean values of $k_{ep}$ in the order of 15-20%. However, for this method a breath-hold of 41 seconds is required, which in our experience is difficult for patients to perform.

Conclusions: Determination of the Gd-DTPA uptake rate $k_{ep}$ using a vascular normalization function taken from pixels in the spleen can be performed with adequate reproducibility in patients with colorectal liver metastases. Reproducibility is better using a VNF from the spleen than an AIF from the aorta, probably due to less flow- and pulsation artifacts. The presented method enables reproducible acquisition and analysis of DCE-MRI data, which is a necessary prerequisite for prediction and monitoring of therapy outcome.

$$\begin{array}{l|c|c|c|c|c}
\text{within patient variance} & \text{between patient variance} & \text{mean } k_{ep}(s^{-1}) & R (\%) & \text{repeatability (s}^{-1}) \\
\hline
k_{ep,spleen} & 0.003 & 0.018 & 0.031 & 85 & 0.009 \\
k_{ep,aorta} & 0.008 & 0.017 & 0.028 & 70 & 0.021 \\
\end{array}$$

Table 1 Reproducibility of $k_{ep}$ using the VNF from the spleen and the AIF from the aorta. R = between patient variance divided by the total variance.


Fig. 1a Typical results of a VNF taken from pixels in the spleen and an arterial input function taken from pixels in the aorta. Fig. 1b: Difference in Gd-DTPA uptake rate $k_{ep}$ between measurement 1 and 2 versus average $k_{ep}$ of measurement 1 and 2 using the spleen to determine the VNF (1b) and the aorta to determine the AIF (1c).