Quantitative assessment of diffusion of contrast agent in liver metastases using dynamic contrast-enhanced MRI

G. Jia[1,2], J. T. Heverhagen[1,2], X. Yang[1,2], J. Liang[1,2], N. A. Mayr[1], M. V. Knopp[1,2]

[1]Department of Radiology, The Ohio State University, Columbus, Ohio, United States, [2]Wright Center of Innovation in Bioimaging, The Ohio State University, Columbus, Ohio, United States

Introduction

Both perfusion and diffusion contribute to MRI signal enhancement after intravenous injection of a nonspecific contrast agent. Perfusion contributes to the enhancement of pure vascular malformations or hypervascular lesions. Extravascular diffusion is the major factor in delayed MR signal enhancement in liver metastases with large extravascular diffusion space. And diffusion is generally considered a factor that can obscure lesions in both CT and MRI since metastases tend to disappear after slow infusion contrast medium or delayed scanning. Fast MRI techniques like dynamic contrast-enhanced MRI (DCE-MRI) can reduce the scan time to less than 1 s. The rapid acquisition minimizes motion artifacts that have plagued MRI studies of the abdomen, and facilitates dynamic studies to observe the perfusion and diffusion process of contrast agent in liver tumors. The lesion heterogeneity in liver metastases was assessed by an onion-peeling region of interest (ROI) analysis approach for DCE-MRI scans and the microcirculation characteristics were assessed by a two-compartment model, based on which a theoretical diffusion model was set up and the diffusion in liver metastases was quantitatively investigated.

Material and methods

Eight patients with liver metastases were imaged within a clinical trial. The patient population included 4 men and 4 women, with an average age of 1 years ± 11 (standard deviation) and weight of 74 kg ± 21. All patients underwent MR imaging twice (MR1 and MR2). The target lesion was selected with largest diameter larger than 30 mm. DCE-MRI was performed with the target lesion covered in an oblique-coronal plane by using a T1-weighted spoiled gradient echo sequence (SPGR) with saturation recovery preparation (TR/TE/α = 1000 ms/2.42 ms/16°; field of view = 500 x 500 mm^2; NEX = 1; 8 mm slice thickness with 2 mm gap between each slice; 4 slices per volume, acquisition time per volume: 5 s, 100 time points). A Gadolinium chelate 0.1 mmol/kg body weight was used with the injection to be initiated after the first 5 repetitions of dynamic sequence (Power injector rate: 2.0 ml/s).

The analysis on DCE-MRI data sets was composed of two parts: the selection of ROIs and the generation of the DCE-MRI parameters from the time-signal data of the ROIs. The target lesion ROI covering the whole tumor area was drawn in pre-enhanced dynamic images in the largest cross section of the tumor. A normal liver tissue ROI was drawn as a reference. Manual shift adjustment of the ROIs was completed when there was subject motion artifact during MR scanning. The whole tumor ROI was sub-segmented into several layer ROIs using an onion-peeling approach and the thickness of each layer ROI was about 4 mm (Fig. 1). The layer ROIs were labeled as layer-1, layer-2 … from peripheral to central region. The time-signal data of these ROIs obtained from DCE-MRI were analyzed, and the microcirculation characteristics were assessed by a two-compartment-model (the amplitude of contrast enhancement A, the exchange rate k_{ep} and the elimination factor k_{el}) by using an in-house developed software based on IDL (Interactive Data Language, v. 6.0, Research Systems, Boulder, CO). The difference of k_{el} between whole tumor ROI and normal liver tissue ROI were compared and the changes of k_{el} from outer layer to inner layer ROI in the tumor were investigated.

For the whole tumor ROI, the sum of the concentration gradient of contrast agent for all pixels within the ROI divided by the average concentration of contrast agent was defined as I_{cg}, a plot of which versus post-injection time gave a decaying exponential curve. The decay factor was proposed to be related to the effective diffusion coefficient D_{eff} by setting up a sphere model with impermeable surface. The difference of D_{eff} between the two studies was tested using a paired-samples t-test where there is no significant differences if $P > 0.05$.

Results

The elimination factor k_{el} was -0.003 min^{-1} ± 0.02 for the whole tumor ROI, which is very small, compared to 0.1 min^{-1} ± 0.02 for the normal liver tissue ROI. There was no substantial washout in the whole tumor ROI (Fig. 1), from which we can assume that there is no elimination of contrast agent from the tumor during the measured time frame for D_{eff} calculation. For the elimination factor of the layer ROIs, the basic trend was that k_{el} decreased gradually from positive value in the tumor margin to negative values in the lesion center, which is the so-called delayed-enhancement in the tumor center (Fig. 2). Thus we can assume the initial distribution of contrast agent in the tumor: the peripheral region contains a homogeneous concentration of contrast agent and the inner region does not contain any contrast agent.

Based on the above assumptions, we obtained the solution to the diffusion equation for a constant diffusion coefficient and the evolution of I_{cg} over time. The mono-exponential decay factor from I_{cg} was proportional to D_{eff} by a factor of S/a, where S is the area of the whole tumor ROI and a is a constant from the solution to the diffusion equation. The average value of D_{eff} was 0.24 mm^2/s ± 0.23 for MR1, 0.28 mm^2/s ± 0.26 for MR2. There was no significant difference between D_{eff} in two studies ($P = 0.31$).

Discussion and conclusion

The quantitative assessment of contrast enhancement patterns in inhomogeneous lesions such as liver metastases remains a challenge and is on the other hand of critical clinical importance to assess biologic effects of therapies. Based on our observations of many DCE-MRI studies, we proposed a theoretical model to describe the intralesion diffusion process and propose the use of a diffusion coefficient as an adjunctive quantitative parameter. The initial pilot assessment revealed a good intra-individual reproducibility. The findings suggest that the diffusion coefficient measurement appears to be a potentially reliable method to characterize tumor microcirculation. Furthermore, we believe that this parameter can help assess potentially the effectiveness of large molecular size therapeutics, when their transport through tumor extracellular matrix is impaired and thus limiting their therapeutic effectiveness. Since drug delivery to the tumor interstitium can be partly detected and predicted by the delivery of MR contrast agent; these findings may suggest a new method to screen tumors for potential resistance to macromolecule-based therapy. Moreover, as the diffusion of contrast agent is closely related to the tissue structure at the cellular level and cellular density, the method could be used as a sensitive technique for assessment of therapeutic drug efficacy.

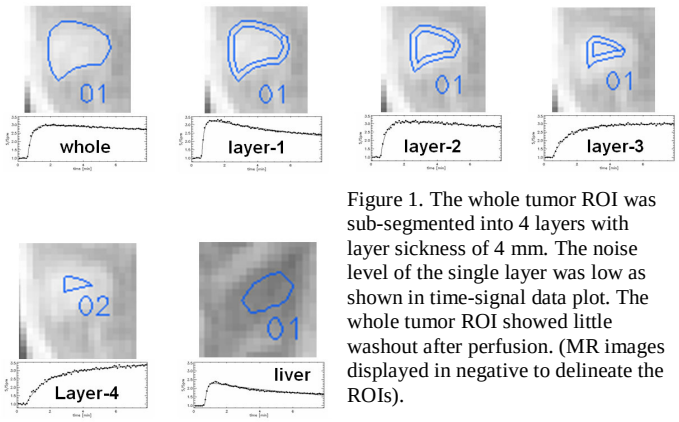

Figure 1. The whole tumor ROI was sub-segmented into 4 layers with layer sickness of 4 mm. The noise level of the single layer was low as shown in time-signal data plot. The whole tumor ROI showed little washout after perfusion. (MR images displayed in negative to delineate the ROIs).

References

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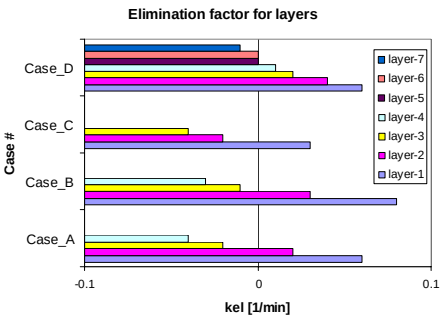

Figure 2. The bar plot of the elimination factor k_{el} from part of the studies. From outer layer (layer-1) to inner layer, the elimination factor gradually changed from positive (washout in time-signal data) to negative (delayed enhancement).