Vascular Characterization of Murine Brain Tumors by Gd-DTPA and USPIO contrast-enhanced MRI

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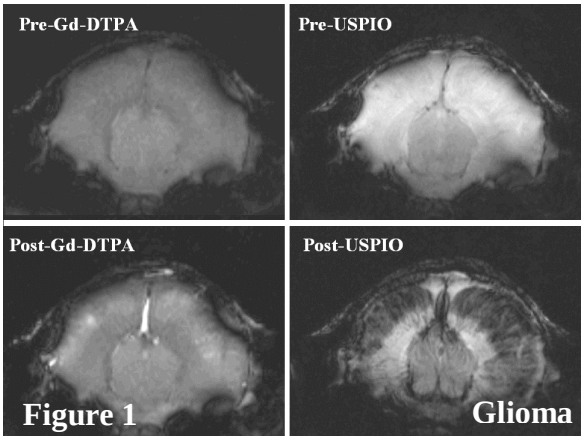
Introduction

MRI, in combination with administration of ultrasmall superparamagnetic particles of iron oxide (USPIO), has proven useful in the characterization of the tumor vasculature (1,2). In particular, measurements of the enhancement in the transverse relaxation rates ΔR2 and ΔR2* provide an index proportional to the blood volume of the microvasculature and macrovasculature, respectively. In this study, ΔR2 and ΔR2* were measured in murine brain tumors in order to characterize the tumor vasculature of three different cell lines. In addition, dynamic contrast-enhanced MRI with Gd-DTPA was performed on the same tumors to assess blood brain barrier leakage.

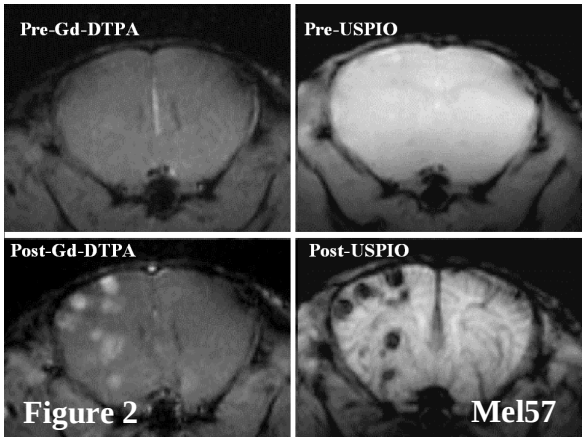


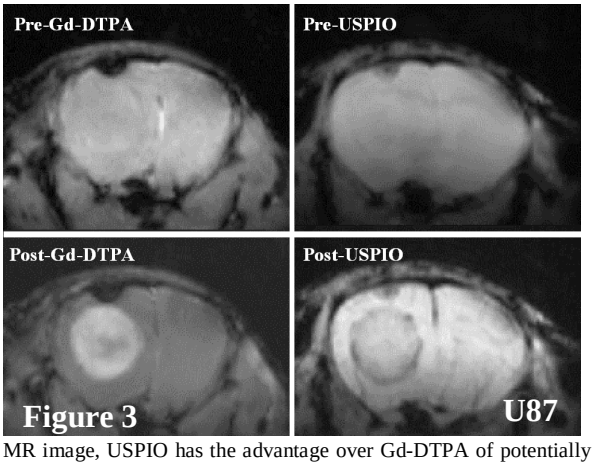
Materials and Methods

MRI experiments were performed on a 7T MR-spectrometer using a 12-mm-diameter surface RF coil. A total of 11 mice were imaged. Three different cell lines were investigated (Mel57, VEGF-165-A-isoform: n=4; glioma: n=3; U87: n=4; cells were injected into the carotid artery or intracranially). Multislice gradient-echo (TR/TE=1500/7ms, voxel-size=136x136x1000μm) and spin-echo (TR/TE=2000/9ms) imaging was performed prior to and following administration of a USPIO blood-pool agent (Sinerem, Guerbet, France; 170 μg Fe/mouse). For each tumor, pixel-by-pixel ΔR2 and ΔR2* maps were generated and the average values in lesions were calculated. The protocol of the Gd-DTPA contrast-enhanced MRI consisted of T1-weighted multislice gradient echo images with TR/TE = 400/6 ms. The other imaging parameters were as in the USPIO protocol. The images were acquired before and 1, 2, 10 and 20 min after injection of Gd-DTPA (Magnevist ®, Schering, Germany) at a dose of 0.2 mmol/kg.

Results

Pre-contrast images showed little or no contrast between tumor and healthy brain tissue for all three cell lines (Figure 1, 2 and 3). Following USPIO administration, tumor were easily identified. Tumors from the three cell lines displayed three distinctive vascular patterns. Glioma (the two banana-shaped structures in the right and left regions of the brain, Figure 1, bottom right corner) showed an infiltrative growth pattern with high values of ΔR2 and ΔR2* throughout the tumor (ΔR2 = 17 ± 5 Hz and ΔR2* = 153 ± 36 Hz). The Mel57 metastases, on the other hand, appeared as black spots and showed an expansive growth pattern, with very high values of ΔR2 and ΔR2* (ΔR2 = 40 ± 13 Hz and ΔR2* = 284 ± 89 Hz). The U87 tumors were characterized by a ring-like structure (ΔR2* = 17 ± 6 Hz, in the core; ΔR2* = 54 ± 15 Hz, in the rim). The values of ΔR2 and ΔR2* were also measured in healthy brain regions (Cortex: ΔR2 = 5 ± 2 Hz and ΔR2* = 21 ± 9 Hz; Caudate putamen: ΔR2 = 9 ± 3 Hz and ΔR2* = 36 ± 10 Hz). Following Gd-DTPA administration, the glioma showed a small signal intensity enhancement, while both Mel57 and U87 tumors displayed a substantial increase in the signal intensity (Figure 1, 2 and 3, respectively, bottom left corners).





Discussion and Conclusions

In this study, a dual-contrast MR imaging method (with Gd-DTPA and USPIO) was employed for tumor vasculature characterization. The ability to non-invasivily assess tumor vasculature plays a major role in tumor detection and, more in general, in investigating tumor physiology. Tumor growth might results in an abnormal local vascular volume and (in brain tumors) in blood brain barrier leakage. The dual-contrast MR imaging method provides complementary infomation on both these aspects. Steady-state measurements of USPIO-induced ΔR_2 and ΔR_2* provide a robust assessment of relative blood volume; vessel leakage, on the other hand, can be readily assessed by dynamic contrast-enhanced MRI with Gd-DTPA. The Mel 57 and U87 tumors were characterized by a substantial vessel leakage; they also presented a blood volume higher than brain healthy tissue. A high blood volume, accompanied only by a modest blood brain barrier leakage, was observed in the glioma. Thus, in the glioma, USPIO measurements resulted in better tumor detection. Tumor detection with conventional Gd-DTPA contrast-enhanced MRI relies only on the leakage of the blood brain barrier; moreover, even when the blood-brain barrier is leaky, Gd-DTPA diffuses rapidly out of the vessels into the local interstitium, precluding accurate estimation of tumor edges. Since tumor (and edge) detection rely on factors which include i) the signal intensity contrast between the lesion and healthy tissue and ii) the spatial resolution of the MR image, USPIO has the advantage over Gd-DTPA of potentially improving both i) and ii). In fact, USPIO provides a high sensitivity to alterations in local tissue blood volume, by generating a high signal contrast, in T2* weighted images, between regions in tissue with different blood volume. At 7 Tesla, the USPIO R2 relaxivity is ~ 100 mM^{-1} s^{-1}, that is, ~20 times greater than that of Gd-DTPA. Further, since USPIO stays intravascular for a prolonged period of time, it is possible then to acquire images with a spatial resolution higher than that of Gd enhanced MRI.

References

[1] Dennie J et al., Magn Reson Med 40:793-999, 1998 **[2]** Le Duc G et al., Magn Reson Med 42:754-761, 1999