MRI-guided targeting of magnetic nanoparticles in an orthotopic 9L gliosarcoma brain tumor model

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Introduction

Magnetic targeting using iron oxide based nanoparticles coated with biocompatible polymers is a promising strategy for achieving localized drug delivery to tumor tissue. Several studies have demonstrated the feasibility of magnetic targeting in rodents bearing subcutaneous tumors (1). Typically, the particles were administered into afferent vasculature supplying the tumor, and the particle accumulation within the tumor tissue was enhanced by an external magnetic field. This strategy has been applied to brain tumors targeting with administration of the nanoparticles via carotid artery while the animal head is positioned within an electromagnet (2). However, the electromagnets typically used for this purpose generate a relatively uniform field density over a broad region, potentially compromising the targeting specificity and leading to nanoparticle aggregation at the injection site. We hypothesized that a magnetic field with a sharper gradient and smaller region of action can be used to overcome these problems. In order to insure nanoparticle accumulation at the target site it is instrumental to maximize the magnetic field density and gradient at the tumor location. The purpose of this study was to investigate the utility of MRI as a tool for precise positioning of the tumor lesion within the applied magnetic field to maximize targeting specificity.

Methods

Brain baseline scans of orthotopic 9L tumor bearing rats were acquired using T2-weighted fast spin echo sequence. Longitudinal and lateral location of the tumor relative to the middle of the eye and the midline of the head, respectively, was calculated using the acquired images. Animal heads were positioned either in between the poles of an electromagnet (0.4T, Fig. 1:A1) or on top of a small permanent magnet (0.15T, Fig.1: B1). In the latter case, animal heads were marked with MRI-derived tumor coordinates to allow precise positioning on the magnet. Magnetic nanoparticles of 100 nm hydrodynamic diameter, composed of iron oxide core and starch shell, were injected at a dose of 12mgFe/kg via surgically implanted intracarotid catheter. GE weighted MRI scans of the animal brains were acquired before the nanoparticle injection and immediately after magnetic targeting to visualize nanoparticle localization. Nanoparticle concentrations in excised tumor tissues were also quantified by ESR.

Results and Discussion

A typical subset of MRI images presented in Figure 1 reveals nanoparticle localization within the animal head obtained with two different configurations of an external magnetic field. Due to strong enhancement of proton spin-spin (T2/T2*) relaxation, iron oxide nanoparticles manifest themselves as hypointense regions on the GE images. With an electromagnet configuration, a strong magnetic interaction seems to be taking place at the injection site causing aggregation (Fig. 1:A4) and dramatically reducing tumor exposure to the nanoparticles. In contrast, there is no observed deposition of the particles at the injection site with the small magnet (Fig. 1:B4). Moreover, due to the accurate MRI-guided positioning of the animal with respect to the magnetic field gradient, the nanoparticles are specifically localized within the tumor lesion. Quantitative determination of magnetic nanoparticles in excised tumors has further revealed a 3-fold increase in nanoparticle accumulation achieved with the small magnet (Mean±SE: 21±7 nmolFe/g tissue) compared to the electromagnet (Mean±SE: 7±4 nmolFe/g tissue).

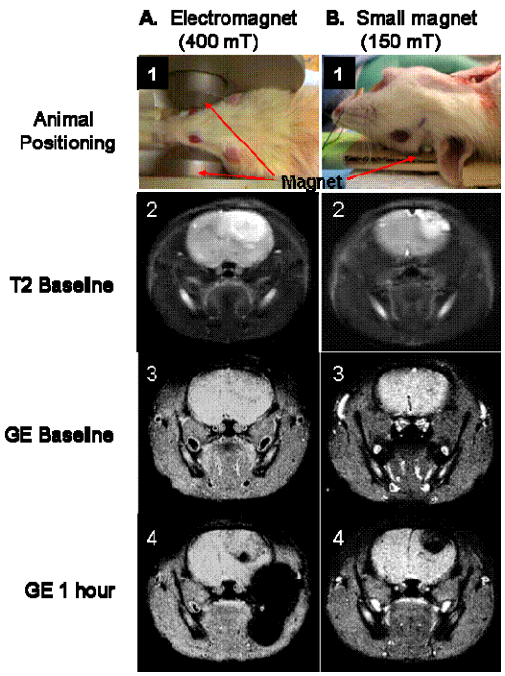

Figure 1: Representative subsets of MRI images revealing nanoparticle localization after magnetic targeting.

Conclusions

MRI-guided alignment of the gliosarcoma lesion with a short-range magnetic field has resulted in improved accumulation of magnetic nanoparticles within the tumor and minimized non-specific deposition of the nanoparticles at the injection site. Therefore, MRI-guidance techniques in conjunction with sharper magnetic field gradients warrant further investigation for enhancement of magnetic targeting.

References

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