Published in final edited form as:

Magn Reson Med. 2018 July ; 80(1): 224–230. doi:10.1002/mrm.27028.

Quantitative comparison of delayed ferumoxytol T1 enhancement with immediate gadoteridol enhancement in high grade gliomas

Andrea Horvath¹, Csanad G. Varallyay^{1,2}, Daniel Schwartz^{1,3}, Gerda B. Toth¹, Joao P Netto^{1,2}, Ramon Barajas^{2,3}, Peter Varallyay⁴, Laszlo Szidonya¹, Jenny Firkins¹, Emily Youngers¹, Rongwei Fu⁵, Prakash Ambady¹, Peter Bogner⁶, and Edward A. Neuwelt^{1,7,8}

¹Dept. of Neurology, Oregon Health and Science University, Portland, OR, USA

²Dept. of Radiology, Oregon Health and Science University, Portland, OR, USA

³Advanced Imaging Research Center, Oregon Health and Science University, Portland, OR, USA

⁴National Institute of Clinical Neurosciences, Budapest, Hungary

⁵School of Public Health, Oregon Health and Science University, Portland, OR, USA

⁶University of Pécs, Department of Radiology, Pécs, Hungary

⁷Dept. of Neurosurgery, Oregon Health & Science University, Portland, OR, USA

⁸Portland Veterans Affairs Medical Center, Portland, OR, USA

Abstract

Purpose—Delayed ferumoxytol enhancement on T1-weighted images appears visually similar to gadoteridol enhancement. The purpose of this study was to quantitatively compare ferumoxytol T1 enhancement to gadoteridol enhancement with an objective, semiautomated method.

Methods—206 sets of post-gadoteridol and 24 hours post-ferumoxytol T1-weighted scans from 58 high grade glioma patients were analyzed (9 pre-chemoradiation, 111 <90 days post-chemoradiation, 21 >90 days post-chemoradiation, 65 post-bevacizumab scans). Enhancement volumes and signal intensities normalized to normal appearing tissue proximal to enhancement were calculated with a semiautomated method. Enhancement cube root volumes (D) and signal intensities (SI) were compared between the two contrast agents, and relative difference of D and SI were compared in different treatment groups with multivariate analysis. Within patient differences in D and SI before and after treatment with bevacizumab or steroid were assessed in 26 patients in each treatment group.

Results—When compared to gadoteridol, ferumoxytol D was 13.83% smaller and SI was 7.24% lower ($p < 0.0001$). The relative differences in D and SI between the two contrast agents were not significantly different between treatment groups ($p > 0.05$). Relative difference in D and SI did not change significantly in response to bevacizumab ($p = 0.5234$ and $p = 0.2442$, respectively) or to steroid ($p = 0.3774$, $p = 0.0741$) in the within patient comparison.

Conclusion—The correlation between the two contrast agents' enhancement size and signal intensity and their similar behavior in response to therapy suggest that ferumoxytol can be used for revealing enhancement in high grade glioma patients.

Keywords

ferumoxytol; gadoteridol; delayed enhancement; glioblastoma; alternative contrast agent; USPIO

Introduction

There is a current paucity of literature regarding the equivalence of enhancement for gadolinium-based contrast agents (GBCA) and non-GBCAs. Gadolinium enhanced magnetic resonance imaging (MRI) is the standard of care for imaging various central nervous system pathologies. Over 10 million doses of GBCA are administered annually in the United States (1). Concerns regarding gadolinium safety (nephrogenic systemic fibrosis or gadolinium deposition in basal ganglia, of which the clinical significance of the latter is still unknown) (2–6) draw attention to the need for alternatives such as manganese- and iron-based contrast agents (7–9).

Ferumoxytol is an ultrasmall superparamagnetic iron oxide nanoparticle that has been approved by FDA for iron replacement therapy. Previous studies have shown its utility as an MRI contrast agent when used off-label (10). While GBCAs leak into the brain parenchyma in areas where the blood brain barrier is not intact several seconds after administration, ferumoxytol predominately remains intravascular for hours due to its high molecular weight, enabling excellent vascular visualization. Parenchymal enhancement peaks about 24 hours after administration (11). Delayed phase ferumoxytol enhancement is manifested by T1 shortening on spin echo MRI, making its appearance similar to GBCA enhancement. However, it is still unknown how delayed ferumoxytol enhancement differs from standard of care in visualizing central nervous system pathologies and monitoring changes related to disease.

The goals of this study were to (1) quantitatively compare ferumoxytol and gadoteridol T1 enhancement magnitude and size with an objective, semiautomatic method in a large study population, and (2) to examine whether ferumoxytol enhancement changes similarly to gadoteridol enhancement in response to specific treatment regimens.

Methods

Subjects

Between September 2009 and April 2015, 138 brain tumor patients were scanned prospectively in our institutional review board approved, HIPAA-compliant protocol (<https://clinicaltrials.gov/ct2/show/NCT00103038>). All subjects gave informed consent.

Inclusion criteria for this analysis included post-surgical, histologically-proved high grade gliomas (World Health Organization classification grade III and IV), with both ferumoxytol and gadoteridol scans available. Initially, 221 sets of MR scans (221 post-gadoteridol, and 221 post-ferumoxytol) of 61 patients met the inclusion criteria, but 15 sets of scans were

excluded due to unsatisfactory image quality. Therefore, a total of 58 patients (37 males, 21 females, mean age $\pm$ SD 51.32 ± 13.25 years, 40 glioblastoma, 1 gliosarcoma, 6 anaplastic astrocytoma, 9 anaplastic oligodendroglioma, 2 anaplastic oligoastrocytoma) with 206 sets of MR scans from up to 6 available visits remained in the study. MR visits were stratified based on treatment received before each scan (pre-chemoradiation: 8 scans; within 90 days post-chemoradiation: 111 scans; greater than 90 days from chemoradiation: 21 scans; post-bevacizumab (Avastin, Genentech, South San Francisco, CA, USA): 64 scans). Steroid administration prior to scan was also recorded (yes or no).

Magnetic Resonance Imaging

All MRI scans were performed on a 3 Tesla (T) clinical scanner (TIM Trio, Siemens, Erlangen Germany) using a 12 channel receive only head coil. Pre-contrast, post-gadoteridol and 24 hour post-ferumoxytol T1-weighted scans were acquired using the same spin echo sequence with the following parameters: TR/TE: 900/11 ms, flip angle 90° , field of view 180×240 mm, matrix 192×256 , 44 axial slices, slice thickness 2 mm with no gap. Ferumoxytol was given in a 4mg/kg dose. Ferumoxytol was diluted 1:1 with saline, resulting in 15mg/ml concentration. Gadoteridol was administered using the 0.1 mmol/kg standard dose. Ferumoxytol was injected after performing post-gadoteridol scans, and delayed ferumoxytol scans were obtained approximately 24 hours after administration (mean $\pm$ SD: 23.10 ± 2.51 hours).

Image analysis

Image analysis was performed by two experts (D.S. and A.H.) with 12 and 6 years, and a radiologist (C.V.) with 10 years of experience in image processing. Post-gadoteridol and post-ferumoxytol images were co-registered to pre-contrast scans (6 degrees-of-freedom linear fit, correlation ratio cost function and trilinear interpolation) using FMRIB Software Library's (FSL) Linear Image Registration Tool (FLIRT) (12). Enhancing tumors were segmented using a semiautomated method. First, the same manually drawn region of interest (ROI) was applied on pre-contrast, post-gadoteridol, and post-ferumoxytol scans in FSL (13). The ROI was drawn to cover all voxels that visually appeared to be enhancing for either coregistered contrast enhanced scan in all slices, and also included normal appearing white and grey matter proximal to the enhancing volume (Figure 1A, B and D).

The final mask denoting contrast enhancement was the intersection of three independently derived binary masks, $A \cap B \cap C$, such that:

$$A_i = \text{CON}_i > \overline{\text{CON}_i \subseteq Q} + 0.5 * \sigma_i \subseteq Q$$

and

$$B_i \subseteq Q$$

and

$$C_i = \frac{CON_i}{NONCON_i} > \frac{\overline{CON_{i \subseteq Q}} + 0.5 * \sigma_{i \subseteq Q}}{NONCON_{i \subseteq Q}}$$

where i is a voxel, CON is a contrast enhanced T_1 -weighted volume, $NONCON$ is a non-contrast enhanced T_1 -weighted volume, Q is the manually drawn mask, $\sigma_{i \subseteq Q}$ is the standard deviation of a contrast enhanced image within the manually drawn mask, and where $\subseteq$ denotes the proper subset.

Put simply, in order for a voxel to be included in the final mask representing contrast enhancement, a) it must have an contrast-enhanced intensity value that is larger than the sum of the mean contrast-enhanced intensity value and half of the standard deviation of the values within the manually drawn mask, b) it must be a member of the manually drawn mask, and c) the value of the quotient of contrast-enhanced and non-contrast-enhanced must be larger than the quotient of the sum of the mean contrast-enhanced intensity value and half of the standard deviation of the values within the manually drawn mask and the mean non-contrast-enhanced intensity value within the manually drawn mask.

The standard deviation term in criteria 1 and 3 serves to adjust the threshold value (greater than the mean intensity) for manually drawn regions that contain more heterogeneous tissue samples. Since the order of tissue intensity on contrast-enhanced T_1 -weighted imaging generally follows [enhancement > white matter > gray matter > cerebrospinal fluid], any inclusion of tissue that is not enhancement will adjust the mean tissue intensity value downwards inside the manual mask. However, just as the mean value is adjusted downwards with the inclusion of non-enhancing tissue, the variance in the sample is adjusted upwards, and so a modest correction using half of the standard deviation of the intensity values in the sample serves to make the threshold more conservative with respect to contrast enhanced values relative to non-contrast enhanced volumes.

Enhancement volumes were calculated for both contrast agents by multiplying the voxel counts in each mask by the voxel volume. As the distribution of absolute volumes of enhancement for both gadolinium and ferumoxytol was very positively skewed (many relatively small volumes and relatively fewer larger volumes), the cube root was taken for all volume measurements (referred to hereafter as “D”) in order to more accurately represent a normal distribution for the purpose of statistical testing.

Enhancement signal intensities were normalized to the signal intensity value of non-enhancing voxels inside the manual ROI (the relative complement of the final mask in Q , i.e. $Q \setminus [A \cap B \cap C]$); normalized signal intensity values are referred to as “SI”.

Statistical analysis

The primary outcomes were enhancement volumes and signal intensity. To satisfy the assumption of normal distribution, the cube root of volumes (D) was used in all analyses. Due to the lack of uniformity in lesion sizes among subjects, relative differences (not

absolute differences) in D (i.e. $\frac{D_{Fe}}{D_{Gd}} - 1$, and SI ($\frac{SI_{Fe}}{SI_{Gd}} - 1$) for consistency) were used to reduce possible impact of lesion size on the results (for example, a large lesion may lead to a large difference between gadoteridol and ferumoxytol because the lesion size is larger, instead of due to the relative differential enhancement between gadoteridol and ferumoxytol).

Pearson's correlation was used to assess the relationship between ferumoxytol and gadoteridol enhancement cube root volumes (D_{Fe} and D_{Gd}) and signal intensities (SI_{Fe} and SI_{Gd}). Overall comparison of ferumoxytol and gadoteridol enhancement was made in a random effects model while accounting for correlation among the repeated measures with the same patient.

A linear mixed effect model was used to compare relative difference of D_{Fe} and D_{Gd} and relative difference of SI_{Fe} and SI_{Gd} among different treatment groups while accounting for repeated measures and adjusting for potential confounding variables (time to scan after ferumoxytol injection, previous radiation, steroid treatment, age at visit and gender).

Additionally, within-subject relative difference of D_{Fe} and D_{Gd} and of SI_{Fe} and SI_{Gd} were compared in patients before and after bevacizumab (n=26), and in patients before and after steroid (n=26) with a linear mixed effect model. A p value less than 0.05 was considered statistically significant in all analyses. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA.).

Results

Figure 2. illustrates specific cases where ferumoxytol and gadoteridol enhancement are similar (2A-C) or different (2D-L) from each other.

After running the segmentation algorithm, no voxels met the criteria of enhancement in 13 scans. Therefore, statistical analysis was performed on 193 cases (pre-chemoradiation: 8 scans; within 90 days post-chemoradiation: 107 scans; greater than 90 days from chemoradiation: 15 scans; post-bevacizumab: 63 scans.)

Overall comparison of contrast enhancement

There was a strong correlation in enhancement cube root volumes ($r=0.7979$, $p<0.0001$) and in signal intensities ($r=0.5362$, $p<0.0001$) between the two contrast agents (Figure 3).

Overall, cube root of enhancement volumes were 3.00 mm or 13.83% lower with ferumoxytol than with gadoteridol ($p<0.0001$) (Figure 4A, Table 1). Enhancement signal intensity was 7.24% lower with ferumoxytol than with gadoteridol ($p<0.0001$) (Figure 4B, Table 1).

Comparison of enhancement among treatment groups

The relative differences of D and SI between contrast agents were not statistically significantly different among the four different treatment groups after adjusting for patient characteristics (D, $p=0.7905$ and SI, $p=0.3725$) (Figure 4 C-D, Table 1).

Within-subject comparison of enhancement

Relative difference between contrast agents did not change significantly in response to bevacizumab (cube root volume: before bevacizumab vs. after bevacizumab 3.6%, $p=0.5234$; signal intensity: before bevacizumab vs. after bevacizumab -1.5%, $p=0.2442$, Figure 4 E-F, Table 1).

Similarly, results for within-subject assessment in response to steroid were not significantly different for cube root volumes (before vs. after steroid, 5.28%, $p=0.3774$), or signal intensity (before vs. after steroid, 2.9%, $p=0.0741$, Figure 4 G-H, Table 1).

Discussion

The apparent visual similarity between gadoteridol and delayed ferumoxytol T1 enhancement (14) raises the question whether ferumoxytol could be a feasible option for diagnosing central nervous system pathologies. The use of ferumoxytol as an alternative contrast agent in the future is predicated upon a complete understanding of how ferumoxytol enhancement behaves and how it differs from standard of care gadoteridol enhancement. Therefore, this study aimed to compare ferumoxytol and gadoteridol T1 enhancement in a standardized, unbiased, quantitative way in a large number of scans. For the overall cohort, ferumoxytol enhancement size was smaller and signal intensity was lower with the current imaging settings compared to those of gadoteridol. When stratified by treatment groups, the difference between contrast agents was not significant, although the sample size was smaller in this analysis. The longitudinal aspect of the study revealed unchanged relative differences between contrast agents in response to bevacizumab and steroid, i.e. when gadoteridol enhancement changed, ferumoxytol enhancement followed it.

In order to interpret the clinical significance of these results appropriately, it is important to understand what factors affect contrast enhancement. Enhancement size and signal intensity depend on the pathology, the relaxivity of the contrast agent, B_0 field strength, the sequence parameters, the injected contrast agent dose, the timing of the scan after contrast agent administration and the difference in enhancement mechanism between contrast agents (10,11,15). In this study, the two contrast agents were compared in the same pathologies on 3T field strength using the same sequence parameters. The rest of the listed factors were different between contrast agents. Specifically, longitudinal relaxivity of Feridex, an agent similar to ferumoxytol, is lower ($2.7 \text{ mM}^{-1}\text{s}^{-1}$) than that of gadoteridol ($3.7 \text{ mM}^{-1}\text{s}^{-1}$) in plasma at 37°C on 3T (15) which results in a lower signal intensity on a T1 scan performed with the same sequence parameters (longitudinal relaxivity of ferumoxytol at 3T is currently unavailable). On the other hand, at lower field strength (1.5T), longitudinal relaxivity of ferumoxytol ($15.1 \text{ mM}^{-1}\text{s}^{-1}$) is favorable compared to gadoteridol ($6.0 \text{ mM}^{-1}\text{s}^{-1}$) (16). In our experience, by increasing ferumoxytol dose, enhancement signal intensity normalized to

white matter increases, and relative difference in signal intensities between ferumoxytol and gadoteridol T1 enhancement becomes smaller (unpublished data).

Enhancement dynamics of ferumoxytol and gadoteridol are different due in part to their different molecular sizes (30 nm vs. 1 nm median displacement size, respectively) (10,17). Specifically, gadoteridol has a 0.2 hour distribution and 1.6 hours elimination half-life with peak enhancement in the brain parenchyma appearing 10 minutes after injection (18). On the other hand, plasma elimination half-life of ferumoxytol is 14.7 hours with enhancement in the parenchyma peaking 24 hours post administration (19). Ferumoxytol enhancement size increases over time even 70 hours after injection, while signal intensity peaks between 24 and 48 hours after injection (11). In addition, while gadoteridol is extracellular after extravasation, ferumoxytol can be present both intra- and extracellularly (20).

Based on this information, differences in enhancement size and signal intensity in this study may have originated from inequivalent timing or dosing of ferumoxytol compared to gadoteridol. Using a higher ferumoxytol dose at lower field strength and adjusting the timing of the scan after injection might alter delayed ferumoxytol enhancement size and signal intensity. Determining the optimal dose and timing for delayed ferumoxytol scan is out of the scope of this study, although results were linearly adjusted for time between injection and delayed ferumoxytol scan in the statistical analysis. Instead, this study compared delayed enhancement to standard of care post-contrast images with a commonly used ferumoxytol dose and the typical 24h post-injection scan timing. The difference in enhancement mechanism between gadoteridol and ferumoxytol suggests that changes in blood brain barrier permeability (i.e. after treatment with bevacizumab or steroid) would affect enhancement with the two contrast agents differently. Despite this, the relative differences between contrast agents were not significantly different before and after treatment. One possibility for this null finding is that, given enough time post-injection, both contrast agents will extravasate if the BBB is disrupted. If ferumoxytol enhancement immediately post-injection were being assessed in this report, instead of approximately 24 hours after administration, we would expect a larger differential effect of bevacizumab or steroids on the resultant T1 enhancement of GBCA relative to ferumoxytol. It is important to note that in this investigation, both GBCA and delayed ferumoxytol enhancement volumes decreased after the commencement of bevacizumab treatment.

These results are similar to the findings of Hamilton et al. (14) and Dosa et al. (21) who also measured slightly decreased enhancement size and signal intensity with ferumoxytol compared to gadoteridol. However, these studies included patients with various pathologies (i.e. the patient group was inhomogeneous), the ROIs were defined manually, and different ferumoxytol doses were used. In the study by Hamilton et al. lesion size was measured on one axial slice. In the present study, a greater number of cases were evaluated, volumetry was performed, and only high grade glioma patients were included, which resulted in a more homogeneous patient group. Our method was semiautomated in order to decrease subjectivity. Furthermore, the longitudinal aspect of our study enabled follow up of contrast enhancement changes over time in the same patient.

An important clinical question is whether it has a clinical impact if ferumoxytol enhancement size and signal intensity are slightly different of that of GBCA, and what degree of difference between contrast agents are acceptable in the clinical setting. If there is only a slight difference in enhancement size and signal intensity between contrast agents, and the clinical question is tumor location and morphology, this difference might not affect the actual clinical diagnosis. However, if the question is whether a lesion has grown or a disease has progressed, it is important to use the same contrast agent for follow up that was used as baseline in order to be able to precisely differentiate progression from stable disease.

In contrast, unique properties of an additional contrast agent can provide an added value to standard of care. Specifically, ferumoxytol provides improved vascular visualization on T2*-weighted scans (11), and can be used to obtain high resolution cerebral blood volume maps for more accurate neurosurgical targeting (22). Due to its greater transverse relaxivity, ferumoxytol shows delayed hypointense susceptibility on T2-weighted scans in the brain parenchyma in patients with increased blood brain barrier permeability. Hypointense T2-weighted signal is generally not available in the time frame of minutes to hours after GBCA administration due to the rapid washout phase of the smaller agent relative to ferumoxytol (14). The occasional mismatch in T1 enhancement pattern between gadoteridol and ferumoxytol might provide additional information on tumor pathology and is currently being investigated. Ferumoxytol is a feasible alternative MR contrast agent in renally compromised patients. Iron is an essential element in the body and the iron core of ferumoxytol incorporates into natural iron stores, therefore, the concern of toxicity due to deposition is low in people without iron storage diseases (23–26).

A limitation of this study is that, relative to the overall comparison, the smaller sample sizes for between treatment comparisons and within patient comparisons in response to bevacizumab or steroid limits the power to detect a meaningful difference. Another limitation is that in the within patient comparison, the time between the pre- and post-treatment scans was different in every patient; however, the comparison of ferumoxytol and gadoteridol was performed within the same study visit. In addition, since this is a clinical study, patients may have received other therapies besides steroid and bevacizumab that could have affected the results of the within patient comparison.

In conclusion, objectively comparing delayed ferumoxytol enhancement to current standard of care and assessing the ability of ferumoxytol to detect and monitor changes related to diseases are important steps towards developing ferumoxytol as an additional MR imaging agent. The correlation between the two contrast agents' enhancement size and signal intensity and their similar behavior in response to therapy is promising; however, the clinical impact of timing and dosing of ferumoxytol for delayed imaging needs to be further assessed.

Acknowledgments

This work was supported by a VA Merit Review Grant, National Institutes of Health grants CA19911, NS53468, CA137488, and CA137488-15S1, and a National Cancer Institute SAIC-Frederick Subcontract 26XS293. Funding also provided by the Walter S. and Lucienne Driskill Foundation. CV supported by NIBIB grant 1R25EB016671.

References

1. Zhou Z, Lu ZR. Gadolinium-based contrast agents for magnetic resonance cancer imaging. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2013; 5(1):1–18. [PubMed: 23047730]
2. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant. 2006; 21(4):1104–1108. [PubMed: 16431890]
3. Grobner T, Prischl FC. Gadolinium and nephrogenic systemic fibrosis. Kidney Int. 2007; 72(3):260–264. [PubMed: 17507905]
4. Kanda T, Fukusato T, Matsuda M, Toyoda K, Oba H, Kotoku J, Haruyama T, Kitajima K, Furui S. Gadolinium-based Contrast Agent Accumulates in the Brain Even in Subjects without Severe Renal Dysfunction: Evaluation of Autopsy Brain Specimens with Inductively Coupled Plasma Mass Spectroscopy. Radiology. 2015; 142690
5. Kanda T, Osawa M, Oba H, Toyoda K, Kotoku J, Haruyama T, Takeshita K, Furui S. High Signal Intensity in Dentate Nucleus on Unenhanced T1-weighted MR Images: Association with Linear versus Macrocyclic Gadolinium Chelate Administration. Radiology. 2015; 140364
6. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology. 2015; 150025
7. Gale EM, Atanasova IP, Blasi F, Ay I, Caravan P. A Manganese Alternative to Gadolinium for MRI Contrast. J Am Chem Soc. 2015; 137(49):15548–15557. [PubMed: 26588204]
8. Finn JP, Nguyen KL, Hu P. Ferumoxytol vs. Gadolinium agents for contrast-enhanced MRI: Thoughts on evolving indications, risks, and benefits. Journal of magnetic resonance imaging : JMIR. 2017
9. Toth GB, Varallyay CG, Horvath A, Bashir MR, Choyke PL, Daldrup-Link HE, Dosa E, Finn JP, Gahramanov S, Harisinghani M, Macdougall I, Neuwelt A, Vasanaawala SS, Ambady P, Barajas R, Cetas JS, Ciporen J, DeLoughery TJ, Doolittle ND, Fu R, Grinstead J, Guimaraes AR, Hamilton BE, Li X, McConnell HL, Muldoon LL, Nesbit G, Netto JP, Petterson D, Rooney WD, Schwartz D, Szidonya L, Neuwelt EA. Current and potential imaging applications of ferumoxytol for magnetic resonance imaging. Kidney Int. 2017
10. Weinstein JS, Varallyay CG, Dosa E, Gahramanov S, Hamilton B, Rooney WD, Muldoon LL, Neuwelt EA. Superparamagnetic iron oxide nanoparticles: diagnostic magnetic resonance imaging and potential therapeutic applications in neurooncology and central nervous system inflammatory pathologies, a review. J Cereb Blood Flow Metab. 2010; 30(1):15–35. [PubMed: 19756021]
11. Neuwelt EA, Varallyay CG, Manninger S, Solymosi D, Haluska M, Hunt MA, Nesbit G, Stevens A, Jerosch-Herold M, Jacobs PM, Hoffman JM. The potential of ferumoxytol nanoparticle magnetic resonance imaging, perfusion, and angiography in central nervous system malignancy: a pilot study. Neurosurgery. 2007; 60(4):601–611. discussion 611–602. [PubMed: 17415196]
12. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage. 2002; 17(2):825–841. [PubMed: 12377157]
13. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. Fsl. NeuroImage. 2012; 62(2):782–790. [PubMed: 21979382]
14. Hamilton BE, Nesbit GM, Dosa E, Gahramanov S, Rooney B, Nesbit EG, Raines J, Neuwelt EA. Comparative analysis of ferumoxytol and gadoteridol enhancement using T1- and T2-weighted MRI in neuroimaging. AJR Am J Roentgenol. 2011; 197(4):981–988. [PubMed: 21940589]
15. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann HJ. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. Investigative radiology. 2005; 40(11):715–724. [PubMed: 16230904]
16. Reeder SB, Smith MR, Hernando D. Mathematical optimization of contrast concentration for T1-weighted spoiled gradient echo imaging. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine. 2016; 75(4):1556–1564.

17. Corot C, Robert P, Idee JM, Port M. Recent advances in iron oxide nanocrystal technology for medical imaging. *Adv Drug Deliv Rev.* 2006; 58(14):1471–1504. [PubMed: 17116343]
18. McLachlan SJ, Eaton S, De Simone DN. Pharmacokinetic behavior of gadoteridol injection. *Investigative radiology.* 1992; 27(Suppl 1):S12–15.
19. Landry R, Jacobs PM, Davis R, Shenouda M, Bolton WK. Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *American journal of nephrology.* 2005; 25(4):400–410. [PubMed: 16088081]
20. McConnell HL, Schwartz DL, Richardson BE, Woltjer RL, Muldoon LL, Neuwelt EA. Ferumoxytol nanoparticle uptake in brain during acute neuroinflammation is cell-specific. *Nanomedicine: Nanotechnology, Biology and Medicine.*
21. Dósa E, Guillaume DJ, Haluska M, Lacy CA, Hamilton BE, Njus JM, Rooney WD, Kraemer DF, Muldoon LL, Neuwelt EA. Magnetic resonance imaging of intracranial tumors: intra-patient comparison of gadoteridol and ferumoxytol. *Neuro Oncol.* 2011; 13(2):251–260. [PubMed: 21163809]
22. Varallyay CG, Nesbit E, Fu R, Gahramanov S, Moloney B, Earl E, Muldoon LL, Li X, Rooney WD, Neuwelt EA. High-resolution steady-state cerebral blood volume maps in patients with central nervous system neoplasms using ferumoxytol, a superparamagnetic iron oxide nanoparticle. *J Cereb Blood Flow Metab.* 2013; 33(5):780–786. [PubMed: 23486297]
23. Muehe AM, Feng D, von Eyben R, Luna-Fineman S, Link MP, Muthig T, Huddleston AE, Neuwelt EA, Daldrup-Link HE. Safety Report of Ferumoxytol for Magnetic Resonance Imaging in Children and Young Adults. *Investigative radiology.* 2016; 51(4):221–227. [PubMed: 26656202]
24. Neuwelt EA, Hamilton BE, Varallyay CG, Rooney WR, Edelman RD, Jacobs PM, Watnick SG. Ultrasmall superparamagnetic iron oxides (USPIOs): a future alternative magnetic resonance (MR) contrast agent for patients at risk for nephrogenic systemic fibrosis (NSF)? *Kidney Int.* 2009; 75(5):465–474. [PubMed: 18843256]
25. Varallyay CG, Toth GB, Fu R, Netto JP, Firkins J, Ambady P, Neuwelt EA. What Does the Boxed Warning Tell Us? Safe Practice of Using Ferumoxytol as an MRI Contrast Agent. *AJNR American journal of neuroradiology.* 2017; 38(7):1297–1302. [PubMed: 28495944]
26. Vasanawala SS, Nguyen KL, Hope MD, Bridges MD, Hope TA, Reeder SB, Bashir MR. Safety and technique of ferumoxytol administration for MRI. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine.* 2016; 75(5):2107–2111.

Figure 1. Image analysis. The same region of interest (ROI, red line) was defined on co-registered pre-contrast (A), post-gadoteridol (B) and post-ferumoxytol (D) T1-weighted images. (C) and (E) show the resulting ferumoxytol and gadoteridol enhancement masks respectively after automated segmentation.

Figure 2.

Ferumoxytol and gadoteridol enhancement in specific cases. C, F, I and L illustrate overlay of ferumoxytol and gadoteridol enhancement. Green: gadoteridol only, magenta: ferumoxytol only, blue: overlapping gadoteridol and ferumoxytol enhancement.

A–C: Case 1. 57 year old male with grade IV glioblastoma post-bevacizumab. Ferumoxytol enhancement (A) appears similar to gadoteridol enhancement (B).

D–F: Case 2. 48 year old female with grade IV glioblastoma within 90 days of chemoradiation. Ferumoxytol enhancement (D) is larger than gadoteridol enhancement (E).

G–I: Case 3. 59 year old male with grade III anaplastic oligodendroglioma, post-bevacizumab. Ferumoxytol enhancement (G) is less pronounced than gadoteridol enhancement (H).

J–L: Case 4. 45 year old male with grade IV glioblastoma within 90 days of-chemoradiation. Ferumoxytol accumulates inside necrotic cavity (J), while gadoteridol shows ring enhancement (K).

Correlation of cube root volumes (D) **Correlation of signal intensities**

Figure 3. Scatterplots showing strong correlation between gadoteridol and ferumoxytol enhancement cube root volumes (A) and signal intensities (B).

Figure 4.

Bar graphs illustrating enhancement cube root volumes (A, C, E, G) and signal intensities (B, D, F, H) with ferumoxytol and gadoteridol in all MR scans (A-B), in different treatment groups (C-D), in the same patients (N=26) before and after bevacizumab (E-F) and in the same patients (N=26) before and after steroid (G-H). Gad: gadoteridol. Fe: Ferumoxytol. Pre-CRT: prior to chemoradiation, post-CRT: within 90 days post-chemoradiation, post-CRT

>90 days: greater than 90 days from chemoradiation, bevacizumab: post-bevacizumab. Error bars indicate standard error of mean.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Relative differences in D and SI between contrast agents and treatment groups.

	Cube root volume (D)		Signal intensity (SI)	
	relative difference $\pm$ SE	p	relative difference $\pm$ SE	p
All cases (Fe vs. Gd)	-13.83% $\pm$1.8	<0.0001	-7.24% $\pm$0.5	<0.0001
Differences in relative differences between Fe and Gd				
Among treatment groups		0.7905		0.3725
pre-CRT vs. <90 days post-CRT	0.4% $\pm$ 5.3	0.9381	2.4% $\pm$ 2.8	0.3877
>90 days post-CRT vs. <90 days post-CRT	2.7% $\pm$ 5.9	0.6484	1.1% $\pm$ 1.7	0.5240
post-bevacizumab vs. <90 days post-CRT	-3.1% $\pm$ 3.7	0.4094	1.9% $\pm$ 1.1	0.0926
Before vs after bevacizumab, within patient	3.61% $\pm$ 5.6	0.5234	-1.53% $\pm$ 1.3	0.2442
Before vs after steroid, within patient	5.28% $\pm$ 5.9	0.3774	2.87% $\pm$ 1.5	0.0741

^a Relative difference in cube root volumes was calculated with formula $\frac{D_{Fe}}{D_{Gd}} - 1$ while relative difference in signal intensity was calculated with

formula $\frac{SI_{Fe}}{SI_{Gd}} - 1$.

^b Statistically significant results are indicated in bold.

Fe: ferumoxytol, Gd: gadoteridol, SE: standard error of mean, CRT: chemoradiation