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Comparative analysis of ferumoxytol and gadoteridol enhancement using T1- and T2-weighted MRI in neuroimaging

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Abstract

Purpose—Ferumoxytol, an ultrasmall superparamagnetic particle of iron oxide, was suggested as a potential alternative MRI contrast agent in patients with renal failure. We compared ferumoxytol to gadoteridol enhancement on T₁- and T₂-weighted MRI in CNS pathology to explore its diagnostic utility.

Materials & Methods—Data were collected from 3 IRB-approved HIPAA-compliant protocols in 70 adults who underwent alternate day post-gadoteridol and post-ferumoxytol MRI using identical parameters.

Two neuroradiologists measured lesion enhancing size and intensity on post-contrast T₁-weighted acquisitions in consensus. T₂-weighted images were evaluated for the presence of post-contrast hypointensity.

Mixed model repeated measures analysis of variance determined differences between T₁ – weighted enhancement size and intensity for individual protocols and group.

Results—Following exclusions, 49 MRI studies in 29 males and 20 females (mean age 51 years) were assessed. T₁-weighted estimated enhancing sizes were different between agents ($p = 0.0456$) as a group, however no differences were observed with untreated gliomas ($n=17$) on two protocols ($p = 1.0, 0.99$ respectively).

Differences in T₁-weighted enhancement intensity between agents were significant for the group ($p = 0.0006$) until interactions of protocol and agent were considered (non-significant).

T₂-weighted images were assessed for post-contrast hypointensity, observed in 26/51 (51%) of ferumoxytol and 0/51 (0%) of gadoteridol scans.

Conclusion—Ferumoxytol may be a useful MRI contrast agent in patients unable to receive gadolinium-based contrast agents (GBCA). Greater experience with a wider variety of pathology is necessary in order to understand differences in enhancement with ferumoxytol compared to GBCA given different mechanisms of action.

Introduction

Patients at high risk for nephrogenic systemic fibrosis (NSF) are unable to safely receive gadolinium-based contrast agents (GBCA). These patients have few or no practical alternatives for a diagnostic contrast-enhanced MRI. Although computed tomography (CT) is a useful screening test in neuroimaging, giving CT contrast in renally impaired patients can be very harmful unless patients are dialyzed. Dialysis is not a reasonable option in new onset renal failure. CT with or without contrast is generally inferior to MRI for most diagnostic neuroimaging, other to evaluate hemorrhage, calcifications, and mass effect.

Ferumoxytol, one of the ultrasmall superparamagnetic iron oxide nanoparticles (USPIO) agents, approved by the FDA in 2009 for use as an intravenous iron replacement therapy in renal failure patients, was recently proposed as a possible alternative contrast agent for MRI¹. Similar to other iron oxide nanoparticles, ferumoxytol is a promising MRI contrast agent, although its use in imaging remains off-label and investigational. In contrast to other USPIOs, ferumoxytol is less limited by anaphylactoid reactions during rapid IV bolus injection, making vascular studies such as MRA and perfusion imaging possible^{1,2}. Ferumoxytol provides excellent intravascular opacification at early time points and preliminary studies suggest that it may be superior to GBCA for MRA and perfusion¹⁻⁴.

A potential application of ferumoxytol outside of vascular imaging is that of diagnostic neuroimaging. Unlike GBCA, enhancement of intracranial pathology with ferumoxytol requires intracellular uptake by phagocytic WBCs such as macrophages, reactive astrocytes and activated microglia². This requires delayed scanning at later time points post-injection than with GBCA. Macrophages for example, are present within and around many types of neuropathology, including glial neoplasms⁵⁻⁷.

We compare ferumoxytol to gadoteridol enhancement on MRI using standard T₁- and T₂-weighted sequences in order to explore its possible diagnostic utility by assessing enhancement size and signal intensity in a series comprised mostly of glial tumors.

Materials and Methods

Data were collected from 3 different MR imaging protocols at a single institution: Glioblastoma multiforme (GBM) Protocol, Inflammation Protocol, and 3T vs 7T Protocol. Studies were performed in accordance with the ethical standards of the World Medical Association. Local IRB approval and informed consent for all subjects was obtained.

Criteria for inclusion in the GBM protocol were: subjects with known or suspected GBM (by histology and/or initial MRI) not previously treated with radiation and/or chemotherapy, measurable enhancing disease on MRI, age over 18 years, stable dexamethasone dose of up to 8 mg throughout study, life expectancy $\geq$ 6 months, and Karnofsky performance scale of 60% or greater.

Inflammation protocol inclusion criteria were: subjects with known or suspected multiple sclerosis, stroke, vascular lesions, and subjects with central nervous system (CNS) inflammatory lesions suspicious for neoplasm vs radiation induced inflammation, age over 18 years, Karnofsky performance scale of 50% or greater, and pretreatment MRI within 28 days of the study scan.

For the 3T-7T protocol, inclusion criteria were: a histologically confirmed primary malignant brain tumors or brain metastasis, radiographically measurable enhancing disease with standard MRI, no history of prior surgery, radiation therapy, or chemotherapy, age over

18 years, life expectancy > 2 weeks, and ECOG (Eastern Cooperative Oncology Group) performance status < 3.

All studies were performed on a 3T MRI scanner, except for two outside GBCA studies performed before admission and study enrollment. These were used for comparison to the ferumoxytol exams since a gadoteridol MRI could not be performed on protocol since policy at our institution precludes administration of GBCA in the setting of renal failure with estimated glomerular filtration rates (eGFR) below 30 mL/min. Only the 3T studies from the 3T vs 7T Protocol were reviewed to maintain uniformity of field strength.

Identical sequence parameters were used for the gadoteridol and ferumoxytol exams, with imaging performed using two or three sequential sessions within 24–48 hours of the prior. For the purposes of this study, only the routine pre- and post-contrast T1 and T2-weighted sequences were the focus of this study. Additional sequences were concurrently performed on these protocols, but not formally assessed. For subjects who participated on more than one protocol or who were imaged multiple times on a given protocol, only the first imaging session at the time of enrollment was reviewed, in order to avoid repeated measures within the same patient.

The following sequences were performed on day one: (standard pre- and post-gadoteridol, no ferumoxytol given on day one): Axial spin echo (SE) T1 pre-contrast, axial T1 magnetization-prepared rapid gradient echo (MP RAGE) pre-contrast, axial turbo SE (TSE) T2 post-contrast, axial SE T1 post-contrast, axial T1 MP RAGE post-contrast. Ferumoxytol was given on day 2 (no gadoteridol given) and the following sequences were obtained: axial TSE T2, axial SE T1, and axial T1 MP RAGE. Day 3 represented 24-hour delayed post-ferumoxytol imaging (no contrast agent was given on day 3), and included identical sequences to day 2. Parameters for the individual sequences are as follows:

1. Axial 2D TSE T2: voxel size 0.9x0.9x2mm, PAT:2, Slices:49, TR:9000, TE:93, Slice thickness: 2.0 mm, Flip angle: 140 deg, Time: 2:35
2. Axial 2D TSE T1: voxel size 0.9x0.9x2mm, PAT:2, Slices:36, TR:900, TE:10, Slice thickness: 2.0 mm, Flip angle 90 deg; Time: 4:15
3. Axial 3D turbo flash T1 MP RAGE: voxel size 0.9x0.9x1.0mm, PAT:0, Slices: 128, TR:2300, TE:3, TI:900 ms, Slice thickness 1.00 mm, Flip angle 12 deg; Time: 7:22

Gadoteridol dose was 0.1 mmol/kg, with imaging performed immediately following injection. Ferumoxytol dose was 2 mg/kg (GBM protocol), 4 mg/kg (3T vs 7T Protocol), or 510 mg (Inflammation Protocol), and given at the beginning of the second day of the study. Different doses were used on the various protocols in order to assess the optimal dose for MRA and perfusion that were not the primary focus of this review. Both contrast agents were administered by IV bolus followed by routine saline flush without complication.

Imaging Review

Two CAQ (certificate of added qualifications) certified neuroradiologists graded all examinations, with consensus review of conventional MR imaging sequences for pre- and post-contrast enhancement, comparing gadoteridol to ferumoxytol enhancement.

Two T₁ weighted sequences were obtained before and following each contrast agent administration and used for the size and intensity measurements: SE and MP-RAGE. Gadoteridol enhancement was measured on day one, and 24 hour ferumoxytol enhancement was measured on day three scans in order to estimate T₁-weighted lesion enhancement size for each contrast agent and sequence type. Given that immediate post ferumoxytol images

demonstrated little or no enhancement on T₁ - or T₂-weighted sequences, size and intensity measurements for day 2 were not included in the formal statistical analysis.

Enhancing lesion sizes on T₁ - weighted images were recorded by selecting the axial slice where the enhancing tumor appeared largest. Two roughly perpendicular linear measurements of the gadoteridol based enhancing tumor size were obtained by a single reviewer (with agreement by the second reviewer) on this single representative axial slice, rounded to the nearest mm for each of the T₁ -weighted sequences. The same slice was selected from the 24-hour delayed post-ferumoxytol scan, and measurements were obtained in the same way on corresponding T₁-weighted sequences, in order to closely parallel the gadoteridol-based measurements.

Enhancement intensity was scored 0–10 (0 = no enhancement to 10 = maximal enhancement similar to vessels) for T₁-weighted SE and MPRAGE respectively for the highest area(s) of signal intensity (compared to the same area(s) on each scan). For the two patients with no GBCA-enhanced exam on protocol, size and intensity measurements were based on a recent clinically obtained study that had GBCA.

TSE T₂-weighted images were assessed for the presence of new T₂ hypointensity on post-gadoteridol, immediate post ferumoxytol, and 24 hours post ferumoxytol administration compared to the pre-contrast TSE T₂-weighted images. No size or intensity measurements were obtained for comparative review, since this phenomenon is not routinely observed with GBCA.

Additional diagnostic data

All studies were correlated with clinical and treatment history and histologic data, when available. Routine demographic data were collected. Follow-up clinical imaging studies were reviewed, when pertinent to the study data.

Statistical Evaluation

A mixed model repeated measures analysis of variance (ANOVA) was used to determine differences between the volume and intensity of enhancement relative to SE and MPRAGE T₁ weighted sequences for each of the three protocols and the group as a whole.

Factors in the model include contrast agent (gadoteridol or ferumoxytol), sequence type (SE or MPRAGE), protocol (3T/7T, GBM, and Inflammation) and all possible interactions of these factors. The unstructured covariance structure was optimal based on comparisons to other covariance structures using Akaike's corrected information criteria. For significant factors and interactions, multiple comparisons were performed using least-squares means and Tukey-Kramer adjustments. All analyses were performed using SAS® Version 9.2 for Windows. A p value of < 0.05 was considered significant. The p values were adjusted for multiple comparisons (Tukey-Kramer adjustment), that takes into account the number of pair-wise comparisons).

Results

A total of 70 subjects from the 3 separate imaging protocols using ferumoxytol at our institution were collected over two years (2007–2009). From this group, 21/70 were excluded for lack of gadoteridol study for comparison (usually for renal failure), inability to complete the exam, lack of enhancing abnormality, and/or excessive motion precluding adequate study evaluation.

This left a total of 49 MRI studies in 29 males and 20 females (age range 19–74 years; mean age 51 years) that formed the basis of this comparison study. Six patients were evaluated on the GBM protocol (4 male, 2 female), 32 patients on the inflammation protocol (19 male, 13 female), and 11 patients on the 3T vs 7T protocol (6 male, 5 female).

Diagnoses

Neoplastic diagnoses included 17 GBM, 3 astroblastomas, 2 oligodendrogliomas, 2 astrocytomas, 2 metastatic melanomas, 2 post-transplant lymphoproliferative disorder (PTLD), one anaplastic ependymoma, one CNS lymphoma, and two additional histologically indeterminate gliomas. Vascular lesions included 2 subacute to chronic strokes, 2 cavernous malformations, 2 capillary telangiectasias. Patients enrolled on the inflammation protocol had the following diagnoses: 12 suspected treatment related necrosis or pseudoprogression (considered “inflammatory” lesions) vs residual/recurrent glioma, one case of CNS inflammation (suspected demyelination), and one presumed internal auditory canal schwannoma. CNS neoplasms were confirmed histologically except for the schwannoma. Characteristic imaging appearances and clinical history confirmed diagnosis in the remainder.

From the above 52 lesions in 49 patients, three were incidentally discovered lesions (one each of capillary telangiectasia, cavernous malformation, and intracanalicular schwannoma) that were not included in the formal measurements and statistical analysis.

Estimated enhancement size: Gadoteridol vs Ferumoxytol

We compared 24-hour ferumoxytol to gadoteridol *estimated enhancement* size on T₁-weighted SE and MPRAGE for each protocol (Table 1). Note that while glial neoplasms predominated across all protocols, the GBM and 3T-7T protocols reflect previously untreated neoplasms (Figure 1) while the inflammation protocol contained a variety of lesions that included CNS neoplasms previously treated with radiation and chemotherapy, suspected demyelination and vascular lesions (Figures 2–4).

When the entire group is taken into consideration, there were significant differences in estimated enhancing lesion size between contrast agents ($p = 0.0456$) and between sequences ($p = 0.0152$), but no significant interaction between contrast agent and sequence ($p = 0.0735$). These differences in size were entirely explained by differences on the inflammation protocol. If only untreated brain malignancies ($n=17$) were considered (GBM and 3T-7T Protocols), no significant differences in enhancement size were apparent.

Entirely discrepant enhancement patterns were observed with the two meningiomas (Figure 5) and an incidentally discovered schwannoma (this sub-centimeter size mass was not measured), where no intra-tumoral enhancement of these lesions was observed using ferumoxytol compared to gadoteridol.

Intensity of enhancement: Gadoteridol vs Ferumoxytol

For the entire group, there were statistically significant differences in enhancement intensity between the two contrast agents ($p = 0.0006$), but no difference between the sequences ($p = 0.8406$) and no interaction between the type of contrast agent and sequence ($p = 0.01010$).

An overview of the average enhancement intensity scores for each protocol and contrast agent is provided in Table 2. With respect to protocol by contrast agent interaction, there were no significant pair-wise differences when adjusted for multiple comparisons. We were thus unable to generate three-way significance p values (i.e. non-significant). This may reflect insufficient power or no difference.

T₂ Hypointensity with ferumoxytol

T₂ hypointensity was observed in 26/50 patients on 24 hour delayed ferumoxytol enhanced scans compared to pre-contrast imaging (FIGURE 2C). This was observed in one GBM, 21 inflammation, and four 3T vs 7T protocol patients. T₂ hypointensity was not observed on immediate post-ferumoxytol or gadoteridol scans (0/51; 0).

Discussion

Ferumoxytol may be a useful MRI contrast agent in patients unable to receive GBCA. Since its mechanism of action is different than GBCA, it is important to anticipate different patterns of pathologic enhancement with ferumoxytol. Ferumoxytol enhancement depends on the presence of macrophages and other phagocytic WBCs within pathology. Macrophages are commonly present within and around high-grade glial tumors and CNS lymphomas, explaining why high-grade gliomas are visible on ferumoxytol-enhanced MRI²⁻⁸.

A brief explanation of differences in mechanism of action is important for understanding how ferumoxytol enhancement differs from enhancement with conventional GBCA. GBCA are relatively small molecules (molecular weight 600 D, for gadoteridol) that enhance CNS pathology with a compromised BBB through extravascular, extracellular tissue enhancement. By contrast, ferumoxytol (molecular weight about 750,000 D) is over 1000 times larger, and is composed of an iron oxide core with a carbohydrate coating². Consequently ferumoxytol remains intravascular at early time points, when it is an excellent vascular imaging agent. At later time points (hours to days) ferumoxytol is taken up by phagocytic WBC, including macrophages and monocytes, reactive astrocytes, microglia, and dendritic cells in brain, where it acts as an intracellular agent². Since macrophages are present in a wide variety of intracranial pathology from glial tumors to lymphomas and many inflammatory disorders, ferumoxytol may be very useful for enhancing such conditions.

Lesional contrast enhancement on MRI is also affected by relaxivity, r_1 and r_2 , values that in turn affect T₁ and T₂ contrast. Relaxivity of ferumoxytol ($r_1 = 15$, $r_2 = 89 \text{ mM}^{-1} \text{ second}^{-1}$) is much higher than one of the commonly used GBCAs, gadoteridol ($r_1 = 4$, $r_2 = 6 \text{ mM}^{-1} \text{ second}^{-1}$). Although the current study used 3T MRI, 1.5T and other lower field strength scanners have shown better T₁ enhancement with USPIOs^{4,9}. T₂ hypointensity was only seen with ferumoxytol, and is presumed related to the significantly higher r_2 .

Peak ferumoxytol CNS lesion enhancement typically occurs around 24–28 hours, unlike GBCA where enhancement is immediate and transient⁴. Given its prolonged circulation in blood vessels and higher relaxivity, ferumoxytol may be a superior vascular imaging agent for MRA and PWI²⁻⁴. Ferumoxytol is recycled with the body's normal iron, stored in the reticuloendothelial system¹⁰. Since there is no renal clearance, ferumoxytol is safe in renal failure patients¹.

T₁-weighted enhancement with gadoteridol compared to ferumoxytol

The current preliminary study had a predominance of glial neoplasms. Untreated glial tumors (GBM and 3T-7T protocols) showed no differences in T₁-weighted enhancement size when comparing gadoteridol to ferumoxytol, while subjects on the inflammation protocol showed significantly lower overall enhancement sizes. The inflammation protocol also showed an interesting trend towards higher overall mean enhancement intensities with ferumoxytol compared to gadoteridol, while the reverse was true on the other protocols (consisting of untreated CNS neoplasms). The percentage of subjects demonstrating T₂ - weighted post-contrast hypointensity was also greatest on the inflammation protocol.

Although the pathologic heterogeneity within the inflammation protocol limits interpretation of these findings, the highest proportion of lesions included high-grade gliomas post radiochemotherapy. We suspect that patients responding to ongoing therapy may have greater inflammatory responses than non-responders that may be in part reflected in the patterns of ferumoxytol enhancement, and hope to further characterize this in future studies.

T₂ – weighted post-ferumoxytol hypointensity

A characteristic of ferumoxytol not seen with GBCA is T₂ hypointensity on 24 hour delayed SE T₂ imaging. This was seen in over 50% of patients in this study, and not observed with gadoteridol. This difference is explained by the much higher r₂ of ferumoxytol. T₂ hypo-enhancing areas post ferumoxytol may correlate to more active sites of inflammation or macrophage activity that could be used for targeting biopsies. Baseline pre-contrast T₂- in addition to T₁ -weighted images are thus required for correct study interpretation since ferumoxytol-induced signal changes occur with both T₁ - and T₂ – weighting.

A side effect of T₂ hypointensity in some cases is mitigated T₁ enhancement intensity from “R₂ shine through” especially for MP RAGE (FIGURE 2C). R₂ shine through effects may explain why significant differences in signal intensity were not observed with MP RAGE, since it is a gradient echo type sequence with greater sensitivity to susceptibility effects, compared to SE. By contrast, significant differences in size were observed between MP RAGE and SE.

Many studies of USPIOs particularly for MR lymphography outside of the CNS, have focused on T₂*-weighted (gradient echo) imaging. T₂*-weighted images were not formally reviewed for this study because most were degraded by susceptibility artifacts from blood products and other post-operative changes in a majority of brain tumor patients that limited interpretation of post-contrast lesional hypointensity. T₂*-weighted imaging could prove more sensitive for detecting post-ferumoxytol hypointensity in patients without such limitations, however.

Prolonged T₁ and T₂ shortening effects after ferumoxytol injection uncommonly can persist weeks to months after injection¹⁰. This may mimic subacute blood products, as was the case in one study patient who was imaged on the clinical service one month following a ferumoxytol study on protocol (FIGURE 3A,B).

Timing of imaging

Intensity and size of lesion enhancement is affected by the timing delay relative to injection. SPIOs and USPIOs are primarily taken up by macrophages and reactive astrocytes and microglia along the periphery of glial tumors^{2,4,11}. This may explain why ferumoxytol enhancement is usually less intense compared to gadoteridol. Enhancement in primary CNS tumors with ferumoxytol usually peaks around 24 to 28 hours, although enhancement persists even 72 hours later⁴. This delayed enhancement of ferumoxytol could be exploited to improve surgical resections with intraoperative MRI. This approach has been successfully used with other iron oxide nanoparticles⁸.

Benign pathology

Two meningiomas in our series demonstrated different ferumoxytol enhancement patterns compared to gadoteridol (FIGURE 4). Lack of macrophages explains the lack of intrinsic tumor enhancement with ferumoxytol. Both demonstrated peri-tumoral enhancement in adjacent brain using ferumoxytol that was not seen with gadoteridol, and potentially was related to radiation effect. A single suspected schwannoma, discovered incidentally, also demonstrated no convincing enhancement with ferumoxytol.

True “peri-tumoral” enhancement was not observed with other pathology, although two metastatic lesions showed additional peripheral enhancement than corresponding GBCA exams. Prior studies have also demonstrated that longer delays (>24 hours) after iron oxide nanoparticle administration show growing peripheral enhancement around glioma margins that reflects macrophage presence in the periphery of glial neoplasms^{4,7}.

Vascular pathology such as cavernous malformations and capillary telangiectasias may be very conspicuous with ferumoxytol due to strong intravascular blood pool effects and greater r_1 and r_2 values, although the degree of enhancement compared to GBCA could vary considerably. One small cavernoma showed greater intralesional ferumoxytol- than gadoteridol-based T_1 -weighted enhancement, however another low-flow vascular lesion, a mixed cavernous malformation and co-located capillary telangiectasia, showed less T_1 -weighted enhancement with ferumoxytol (FIGURE 5A–D). The appearance likely varies in relation to the degree of T_2 -weighted hypointensity.

Potential for other imaging applications

Other potential imaging applications include atherosclerotic plaque characterization with MRI. This has been developed using other iron oxide particles¹². An advantage of ferumoxytol compared to other iron oxide nanoparticles is that can be safely given by rapid IV bolus injection without anaphylactoid reactions. Ferumoxytol could provide high quality contrast-enhanced MRA with a single injection, with delayed imaging to exploit the macrophage-targeting characteristics of ferumoxytol for assessing unstable plaque.

MR lymphography could be more easily performed with ferumoxytol. MR lymphography using ferumoxtran-10 was shown to be a cost-effective strategy for detecting metastatic lymph nodes in prostate cancer in intermediate- and high-risk patients compared to CT followed by pelvic lymph node dissection or CT-guided biopsy¹³.

Kupffer cells take up iron oxide nanoparticles, and thus ferumoxytol could improve hepatic imaging. Prior research using other iron oxide nanoparticles has shown that moderately or poorly differentiated hepatocellular carcinomas can be distinguished from well-differentiated hepatocellular carcinomas and dysplastic nodules¹⁴.

Limitations

The most important limitation of our study is insufficient experience with common CNS pathology such as stroke, benign tumors, and infections, that limits generalization, however as experience grows, this will improve. Although ferumoxytol appears safe when given for iron replacement in chronic renal failure patients, multiple doses given for the purpose of imaging over short time periods could put a patient at risk for iron overload toxicity. Clearance of iron deposited in the brain with ferumoxytol over the long term is uncertain, with theoretical concerns regarding increased oxidative stress^{7,14–17}.

Another limitation of our study includes the variable doses of ferumoxytol given across the three protocols. This occurred in part to determine the optimal dosing for vascular imaging that was not the focus of the current study. Prior experience with ferumoxytol has suggested that imaging between 12–72 hours after administration is optimal for brain tumor visualization^{4,7}.

In conclusion, ferumoxytol may represent an alternative MRI contrast agent in patients unable to receive GBCA. Since ferumoxytol induces both T_1 - and T_2 -weighted signal changes, baseline pre-contrast T_1 - and T_2 -weighted sequences are important to review. Given different mechanisms of action, recognizing differences in enhancement will require greater experience with a wider variety of pathology.

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Figure 1A

Figure 1B

Figure 1C

Figure 1D

Figure 1.

Figure 1A. Axial SE T1-weighted image performed 24 hours post-ferumoxytol administration in a 59 year-old female with GBM shows moderate tumor enhancement. Note that the scan is reasonably diagnostic, despite differences in enhancement compared to the gadoteridol-enhanced scan in Figure 1B.

Figure 1B. Axial post-gadoteridol SE T1-weighted image (same patient as Figure 1A, 2 days prior) shows comparatively greater enhancement size and intensity.

Figure 1C. Axial MPRAGE image performed 24 hours after ferumoxytol administration shows modest enhancement (same patient and time point as Figure 1A).

Figure 1D. Axial gadoteridol-enhanced MPRAGE image (same patient as Figure 1C, 2 days prior) shows greater enhancement intensity compared to ferumoxytol-enhanced MPRAGE (compare to Figure 1C).

Figure 2A

Figure 2B

Figure 2C

Figure 2D

Figure 2.

Figure 2A. Axial SE T1-weighted 24-hour post ferumoxytol image shows moderately intense enhancement in this 19 year-old male who has undergone previous radiation and chemotherapy for GBM, with a clinical suspicion for pseudoprogression. Compare to the gadoteridol-enhanced scan (Figure 2B).

Figure 2B. Axial SE T1-weighted post-gadoteridol scan (same patient as Figure 2A, 2 days prior) shows relatively concordant enhancement size and intensity.

Figure 2C. MPRAGE 24 hour post-ferumoxytol scan (same patient in Figures 2A,B) shows mild enhancement intensity. Compare to greater enhancement intensity with gadoteridol (see Figures 2D).

Figure 2D. Axial post-gadoteridol MPRAGE (same patient as Figure 2C) shows more homogeneous enhancement and greater enhancement intensity.

Figure 3A

Figure 3B

Figure 3C

Figure 3D

Figure 3.

Figure 3A. Axial SE T1-weighted image performed for clinical reasons in a 63 year-old female with post-transplant lymphoproliferative disorder (GBCA not given due to renal transplant history; no contrast given in preceding 4 weeks). T1 shortening within the brainstem (arrow) was initially interpreted as hemorrhage until prior ferumoxytol scan (see Figures 3C,D) was reviewed. Concurrently obtained CT scan (not shown) showed no hyperdensity to suggest hemorrhage.

Figure 3B. Axial T2-weighted image (same patient as Figure 1A) shows corresponding T2 shortening (arrow) in the brainstem, also suggesting hemorrhage.

Figure 3C. MRI study obtained on protocol 4 weeks earlier shows larger T1 shortening (closed arrow) within the area of PTLD-involved brainstem related to ferumoxytol administration 24 hours earlier. Note mass effect on fourth ventricle (open arrow) that is absent on the later study in the same patient (Figures 3A,B).

Figure 3D. MRI study obtained on protocol 4 weeks earlier (same patient as figures 3A,B) also shows a ring of T2 shortening (white arrow) within the area of PTLD-involved brainstem related to ferumoxytol administration 24 hours earlier. Intense areas of macrophage uptake can show persisting ferumoxytol accumulation on MRI up to 3 months after administration. Note again greater mass effect on the fourth ventricle (black arrow) compared to the earlier study (Figures 3A,B). These findings were initially interpreted as hemorrhage until recognized as diminishing iron accumulation from prior ferumoxytol administration.

Figure 4A

Figure 4B

Figure 4C

Figure 4D

Figure 4E

Figure 4.

Figure 4A. Non-contrast SE T1-weighted image shows focal mixed signal intensity in the midbrain of this 31 year-old female referred for further work-up of “brainstem glioma”. Further imaging clarified this lesion as a mixed vascular anomaly of the brainstem, with a cavernous malformation (closed arrow) and co-located capillary telangiectasia (open arrow). Figure 4B. Axial post-gadoteridol SE T1-weighted image (same patient as Figure 5A) shows faint transparent- or brush-like enhancement without mass effect (open arrow), consistent with capillary telangiectasia. No significant enhancement was seen in the cavernous malformation, which was largely intrinsically T1 hyperintense (closed arrow).

Figure 4C. Twenty-four hour post ferumoxytol T1-weighted image (same patient as Figures 5A,B) shows unchanged appearance of the cavernous malformation (closed arrow). The capillary telangiectasia (open arrow) shows no appreciable enhancement.

Figure 4D. Non-contrast T2-weighted TSE image (same patient as Figures 5A-C) shows mixed signal intensity within the cavernous malformation (closed arrow) and intrinsic T2 hyperintensity within the capillary telangiectasia (open arrow).

Figure 4E. Axial T2-weighted TSE image obtained 24 hours post ferumoxytol (same patient as Figures 5A–D) shows new marked T2 hypointensity consistent with persisting intravascular contrast. Lack of enhancement within the capillary telangiectasia on T1-weighted SE imaging in Figure 3C might be explained by the presence of competing T2 hypointensity from “R2 shine-through”. When using ferumoxytol, baseline pre-contrast T2-weighted images are equally important to pre-contrast T1-weighted images for correct interpretation.

Figure 5A

Figure 5B **Figure 5.**

Figure 5A. Axial T1-weighted SE image 24 hours post ferumoxytol administration in a 50 year-old female with meningioma post radiation therapy shows no intrinsic tumor enhancement (open arrow). This is likely due to lack of macrophages and other phagocytic cells within the tumor. There is peri-tumoral enhancement related to ferumoxytol uptake within the adjacent brain that might reflect the presence of regional macrophages. Small blood vessels within the tumor did enhance with ferumoxytol due to intravascular effects (not shown).

Figure 5B. Axial T1-weighted SE image post gadoteridol administration shows typical meningioma enhancement (open arrow), but does not demonstrate the brain enhancement seen with ferumoxytol.

Table 1

Mean lesion estimated enhancement sizes are measured as the product of the bi-dimensional measurement, in centimeters squared (CM²) for gadoteridol and ferumoxytol on each protocol, with unadjusted 95% confidence intervals (CI) in parentheses. P values < 0.05 (highlighted) were considered significant.

	Gadolinium	Ferumoxytol	P value
GBM: SE (CM²)	15.00 (95% CI: 5.71–24.16)	14.94 (95% CI: 5.35–24.64)	1.0
GBM: MP RAGE (CM²)	15.13 (95% CI: 5.520–24.75)	14.66 (95% CI: 5.69–23.64)	1.0
Inflammation: SE (CM²)	13.28 (95% CI: 9.32–17.24)	10.94 (95% CI: 6.95–14.93)	0.0036
Inflammation: MP RAGE (CM²)	13.19 (95% CI: 9.25–17.13)	7.31 (95% CI: 3.49–11.14)	0.0001
3T-7T: SE (CM²)	8.64 (95% CI: 1.79–15.49)	7.86 (95% CI: 0.81–14.90)	0.9998
3T-7T: MP RAGE (CM²)	8.26 (95% CI: 1.79–15.49)	7.22 (95% CI: 0.51–13.93)	0.9925

Table 2

Average enhancement intensity of gadoteridol compared to ferumoxylol by protocol with corresponding unadjusted 95% confidence intervals (CI). Protocol by contrast agent interaction showed no significant pair-wise differences when adjusted for multiple comparisons, therefore p values were non-significant (ns).

	Gadoteridol	Ferumoxylol	P value
GBM: T1 SE	4.67 (95% CI: 3.22–6.11)	2.00 (95% CI: 0.74–3.26)	ns
GBM: MP RAGE	4.33 (95% CI: 2.72–5.95)	1.5 (95% CI: –0.46–3.46)	ns
Inflammation: T1 SE	3.38 (95% CI: 2.84–3.93)	3.90 (95% CI: 3.29–4.51)	ns
Inflammation: MP RAGE	3.92 (95% CI: 3.22–4.62)	4.78 (95% CI: 3.98–5.58)	ns
3T-7T: T1 SE	4.48 (95% CI: 3.44–5.52)	2.64 (95% CI: 1.72–3.56)	ns
3T-7T: MP RAGE	3.84 (95% CI: 2.70–4.98)	2.47 (95% CI: 1.22–3.72)	ns