Pictorial Review on Applications of Ferumoxytol in MR Imaging

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Disclosure

• Nothing to disclose
Image contrast in MRI: regional differences in T1 and T2 relaxation times
Intravenous contrast agents: alter image contrast and generate clinically useful information
Contrast agents are divided into two categories:

**Paramagnetic Compounds**

*eg: Gadolinium Based Contrast agents (GBCAs)*
- Reduce T1 relaxation → bright on T1w images
- Most commonly used contrast agent
- Complications: a) nephrogenic systemic fibrosis
  - b) deposition

**Super Paramagnetic Nanoparticles**

*eg: Iron oxide*
- Strong effect on T2 relaxation
- Ferumoxytol – Ultrasmall superparamagnetic iron oxide (USPIO)
- Initially approved as Fe replacement therapy in chronic kidney disease
Ferumoxytol molecule and its properties

Current applications

A. Inflammatory conditions
B. Oncologic imaging
C. Neurovascular and oncologic imaging
D. Vascular imaging
E. Lymphography

Future potential of Ferumoxytol as a contrast agent

Target audience: Radiologists
Structure & magnetic properties

- Particle size = 30 nm
- Molecular weight = 750 kDa

Pharmacokinetics

- Can be administered as a rapid bolus
- Has a prolonged intravascular residence time (12 hours) due to its size and carbohydrate coating. This makes it a promising agent for vascular and perfusion-weighted MRI
- Taken up by macrophages within the liver, spleen, bone marrow, and lymph nodes within 24-36 hours
- Slowly broken down by macrophages and taken up into the reticuloendothelial system
- Viable option for patients at risk for NSF
Ferumoxytol causes a strong decrease of T2 and T2* relaxation times and appears dark on T2/T2* W images (negative contrast agent).

Because of T1 shortening effects, long blood pool residence time, and clearance through the reticuloendothelial system, ferumoxytol can be used as a vascular and nodal metastasis contrast agent.

**Effect on T2* relaxation times**

- TE - 2.5 ms
- 5 ms
- 7.5 ms
- 10 ms
- 12.5 ms
- 15 ms

Ferrumoxytol

Greater T2* signal drop with Ferrumoxytol
Clinical applications
Ferumoxytol accumulates in tissue macrophages which can be used as a method of detecting tissue inflammation.

Inflammatory Conditions

**Type 1 Diabetes**
- Mouse model and human studies validate use for imaging pancreatic inflammation in recent onset type 1 DM

**Atherosclerotic Plaques**
- Assess inflammation/activity within atherosclerotic plaques

**Inflammatory Bowel Disease**
- Sensitive for detecting subtle inflammatory activity that is below the resolution of conventional MR

**Infarct related inflammation**
- Non-invasive monitoring of macrophage recruitment to ischemic brain lesions
Macrophage infiltrates in the inflamed islets demonstrate uptake of ferumoxytol in recent-onset Type1 DM

High-resolution maps of pancreatic inflammation in autoimmune diabetes should prove invaluable in assessing disease at initiation, progression and as an indicator of response to emerging therapies

Lower panel images demonstrate increased nanoparticle accumulation in diabetic patient.
**USPIO-enhanced MRI in Crohn’s Disease.** Ferumoxytol was infused 24 hours prior to imaging. T2* weighted imaging demonstrates areas of low signal in the cecum and ascending colon (blue arrows) without obvious abnormality on single shot fast spin echo and T1 weighted images (white arrows).
Inflammation within atherosclerotic plaques can be quantitatively assessed by measuring T2* value of these plaques following Ferumoxytol. These images are from a recent study which demonstrated higher plaque uptake in abdominal aorta in patients who received radiation therapy for pancreatic cancer.
Pancreatic Ductal Adenocarcinoma (PDAC): better tumor delineation

- Ferumoxytol-enhanced MRI has been shown to enhance primary tumor delineation with PDAC patients on chemotherapy.
- It has potential for achieving disease-free margin at the time of surgery, and thus improving the prognosis of PDAC.
- T2- (upper panel) and T2*- (lower panel) weighted images showing pathologically proven PDAC in the pancreatic head (asterisk).
- Tumor interface with the duodenal lumen (yellow dashed line), superior mesenteric vein (blue dashed line), and superior mesenteric artery (red dashed line) is also more clearly depicted on T2*-weighted images compared to the conventional T2 images.

Pancreatic Ductal Adenocarcinoma (PDAC): better tumor delineation

- The $T_2^*$ difference between the tumor and adjacent parenchyma is more pronounced in patients undergoing neoadjuvant chemotherapy.
- In a 55-year-old with PDAC in pancreatic head who underwent neoadjuvant therapy. Pseudofused images of $T_2^*$ maps over $T_1$-VIBE pre- and post-ferumoxytol (A) and (B) showing striking differences in the ferumoxytol uptake between the tumor and background (arrow).
- In a 62-year-old with PDAC in pancreatic head who did not undergo neoadjuvant therapy. Pseudofused images of $T_2^*$ maps over $T_1$-VIBE pre- and post-ferumoxytol (C and D) showing less distinct differences in ferumoxytol uptake (arrow).
Inflammation at the BBB is a fundamental component of CNS pathology in tumors as well as injury from trauma or multiple sclerosis. Ferumoxytol does not leak out of blood vessels in the early phase after injection and therefore is excellent for dynamic MR perfusion and angiography.

Can be used at early time points (seconds to minutes) to image vasculature by MR Angiography (MRA) without the rapid extravasation into CNS lesions that limit MRA with Gadolinium-based contrast.

Improves the visualization of tumor vasculature, CNS vascular malformations, tumor-associated inflammation, and relative cerebral blood volume (rCBV) measurements.

Tumefactive demyelinating lesions are large lesions accompanied by mass effect and abnormal enhancement, mimicking brain tumors. Definitive non-invasive diagnosis is not possible and can be given only by histopathologic confirmation. Ferumoxytol MRI is valuable in addressing this diagnostic dilemma.

Delayed T1 enhancement with ferumoxytol may help distinguish between meningioma and dural metastases.

Ferumoxytol MRI: Differential diagnosis in CNS neoplasms.
Ferumoxytol MRI in a patient with newly diagnosed primary central nervous system lymphoma.

**Dynamic imaging:** Cerebral blood volume (CBV) map calculated from dynamic susceptibility contrast perfusion with ferumoxytol shows mildly elevated relative CBV in the neoplasm (a).

**Blood pool imaging:** Susceptibility-weighted image shows curvilinear branching hypointensities compatible with abnormal tumor vasculature (b). Steady-state. CBV map with a high resolution shows increased blood volume (c).

**Delayed imaging:** Axial T1 magnetic resonance imaging (MRI) demonstrates a typical enhancement 24 hours after ferumoxytol administration (d). Axial T2 MRI shows marked hypointensity in the tumor 24 hours after ferumoxytol administration (e).

Reprinted with permission. *Current and potential imaging applications of ferumoxytol for magnetic resonance imaging.* Kidney Int. 2017 Jul;92(1):47-66
Ferumoxytol enables the measurement of blood volume using a **steady-state technique**, with **high spatial resolution** because rapid acquisition is not required.

Steady-state cerebral blood volume (CBV) maps reflect brain tumor malignancy by revealing hypervascular, highly perfused tumor regions and are in **agreement with GBCA-derived values**.

Steady-state cerebral blood volume (SS-CBV) maps using ferumoxytol offer higher spatial resolution and allow **better identification of hypervascular areas** for surgical targeting in glioblastoma patients.

Spatial resolution of CBV map by perfusion-weighted imaging with gadolinium (DSC-CBV) (left) and the SS ferumoxytol CBV map (right) using ferumoxytol. The scan on the right more clearly demonstrates a central hypervascular area in the right occipital hemisphere with the greatest vascularity, which is likely the most malignant portion of the tumor.
A 42-year-old male patient with glioblastoma. The T1-weighted postgadoteridol administration scan shows no-to-minimal enhancement. In contrast, a highly vascular area (arrows) is seen on high-resolution steady-state cerebral blood volume (CBV) maps obtained with ferumoxytol. Residual tumor with high CBV shows reduction following chemoradiotherapy (postsurgery scan), with a continued decrease 1 month following chemoradiotherapy, indicating a treatment response.
Ferumoxytol MRI: Differential diagnosis in CNS neoplasms

Ferumoxytol MRI may help distinguish between meningioma and dural metastases when used in addition to GBCA. While all dural metastases (yellow arrows) and high grade glioma (black arrows) strongly enhanced with ferumoxytol and GBCAs, meningioma showed poor to no enhancement with ferumoxytol (arrowheads).

Ferumoxytol Vascular Imaging: Body applications

- Ferumoxytol can be safely given as a short intravenous bolus for MR angiography (MRA) and dynamic MRI.
- It can be administered as a bolus injection, allowing both first-pass arterial and blood pool imaging.
- Ferumoxytol is increasingly reported as an alternative to gadolinium-based contrast agents for MRA, particularly for patients with renal failure.
- Macrophage-selective feature of ferumoxytol allows the identification of pathologic inflammation, which can be applied to vessel wall imaging.
- Contrast-enhanced MRI with iron oxide particles has been shown characteristic changes that correlate with iron accumulation within intraplaque macrophages.
As a blood pool contrast agent, Ferumoxytol provides a much longer temporal window for data acquisition than extracellular agents, allowing imaging to be performed repeatedly beginning as early as the arterial phase and continuing into later phases.
Vascular contrast enhancement

Another example showing T1 effects of Ferumoxytol. There is good contrast enhancement in the vessels and around a hematoma in the splenectomy bed.
Accurate lymph node staging at the time of initial diagnosis is an important and prognostic predictions for most tumors. Ferumoxytol can be used in assessing the spread of malignancy to the lymph nodes in patients with known abdominal and pelvic malignancies.

- **Reactive lymph nodes** have macrophages and demonstrate homogenous signal drop on delayed phase ferumoxytol MRI.

- Infiltration by metastatic process replaces normal macrophage rich parenchyma by tumor cells.

- The normal parts of nodes with uptake of USPIO in macrophages show a signal drop on the T2*-weighted sequence due to the effect of iron oxide; on the contrary, the **tumor deposit parts of nodes keep relatively high signals for lack of normal macrophages**.

- USPIO has been the most sensitive and specific non-invasive imaging modality in metastatic LN detection.
Pathologically proven 10 mm benign left inguinal lymph node in patient with penile cancer. A, axial T2-star gradient echo image shows hyperintense inguinal lymph node (arrow). B, 24 hours after administration of ferumoxtran-10 node (arrow) shows homogeneous decrease in signal intensity indicating benign etiology. These findings were confirmed at surgery.

Pathologically proven 11 mm malignant right inguinal lymph node in patient with penile cancer. A, Precontrast T2-star image shows hyperintense (arrow) right inguinal lymph node. B, 24 hours after ferumoxtran-10 injection there is no decrease in signal intensity indicating malignant infiltration which was proven by pathology.
Biopsy-proven benign right external iliac node. The lymph node cannot be completely characterized by conventional imaging. The size criteria used for differentiation of benign vs. malignant nodes is inaccurate.
Differentiate **benign vs malignant lymph nodes**: potential to improve lymph node staging

**Hyperintense left perirectal lymph node**

**Precontrast GRE**

**Biopsy**

**24 hrs with Ferumoxytol**

**HPE**

No signal change indicating malignant infiltration

CT-guided biopsy of the node

Architectural distortion due to malignant infiltration from prostate cancer

Lymphotrophic superparamagnetic nanoparticle-enhanced magnetic resonance imaging. (A) Axial T2-weighted image shows a left perirectal node. (B) Axial post-ultrasmall super paramagnetic iron oxide (USPIO) T2*-gradient-echo image shows hyperintense node (arrow), indicating lack of USPIO uptake within the node, (C) Metastasis was proven on computed tomography -guided lymph node biopsy.
Lymphotropic nanoparticle enhanced MRI allows for characterization of small size (diameter <10 mm) lymph nodes in pelvis.

A) Precontrast T2* image showed there were two small benign external iliac lymph nodes (arrows), with a big hilar (asterisk) in the larger one.

B) Both nodes showed homogeneous decrease of the signal.

C) Another round shape lymph node presented slightly high signal on Precontrast T2* image.

D) The signal of a involved part of the node (asterisk) decreased on postcontrast image, while the uninvolved part (hallow asterisk) kept the slightly high signal.
Future applications

- Novel magnetic cationic liposomes based treatments are being used for enhancing drug delivery in cancer treatment.
- MRI may be used to monitor drug delivery to the target.

Representative T2 * maps of tumors before and 24 h after injection; without and with magnetic guidance. Accumulation of magnetic cationic liposomes is evident through the color change of the tumors between pre- and post-images: from red (high T2 *) to yellow (low T2 *). Magnet placement is shown with dashed lines.
It has been shown that inflammatory cells and molecules in the tumor microenvironment influence different aspects of cancer progress, including the tumor cells' ability to metastasize.

As macrophages are one of the key mediators of inflammation, Ferumoxytol MRI may be used to detect/quantify tumor inflammation.

**Future applications**

Ferumoxytol MRI image (at 24 hours) in patient with pancreatic cancer demonstrates surrounding ferumoxytol uptake suggestive of inflammation. Similarly, there is uptake of ferumoxytol in urinary bladder mass.

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Ferumoxytol shows great potential for a number of applications and can be substituted as a blood pool contrast agent for ceMRI of both the arterial and venous systems in patients in whom GBCA administration is unsuitable.

Despite its advantages, some limitations to the use of ferumoxytol remain:

- Low rate of side effects but some **serious anaphylactic reactions have been reported**.
- **Dose and the corresponding pulse sequence should be adjusted** to avoid susceptibility artifacts.
- **Interfere with regular MRI image acquisition for up to 3 months** due to T1, T2, and T2* shortening effects.

Thank you  

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