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REVIEW

Pictorial review on abdominal applications of ferumoxytol in MR imaging

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Abstract

Though gadolinium-based contrast agents are the most widely used contrast media in MR for clinical use, problems with nephrogenic systemic fibrosis and tissue deposition render their safety debatable, at least in a selected patient population. Ferumoxytol has the potential to be used as an alternate contrast medium for various clinical applications across multiple organs. It has prolonged intravascular signal and delayed intracellular macrophage uptake which are unique properties compared to gadolinium-based agents. This pictorial review aims to review the current and potential clinical applications of ferumoxytol as a contrast agent in abdominal MR imaging.

Keywords Magnetic resonance imaging · Ferumoxytol · USPIO · Contrast media

Introduction

Image contrast in MR mainly results from regional differences in T1 and T2 relaxation times. Intravenous contrast agents are used to enhance image contrast and generate clinically useful information. MR contrast agents are divided into two categories: (1) paramagnetic compounds like gadolinium-based contrast agents (GBCAs), which mainly reduce the longitudinal (T1) relaxation resulting in a brighter signal on T1W images; and (2) superparamagnetic nanoparticles (SPMNPs) such as iron oxides, which have a strong effect on the transversal (T2) relaxation properties. In patients with GFR < 30 ml/min per 1.73 m^2, the GBCAs have safety issues as there is a concern for developing nephrogenic systemic fibrosis (NSF). The risk of NSF is considered lower for group II agents which are classified as "sufficiently low or possibly non-existent risk of NSF" but the risk still seems to exist. Also, the recent research has shown neural deposition of linear GBCA independent of renal function and the long-term implications of such deposition remain indeterminate [1, 2]. Superparamagnetic iron oxide (SPIO) nanoparticles are a unique yet alternate MR contrast agents that are categorized according to size (small: 50–180 nm, Ultrasmall: 10–50 nm, and very small < 10 nm) [3]. Ferumoxytol is an ultrasmall superparamagnetic iron oxide agent which is FDA-approved for intravenous iron-replacement therapy [4]. As an off-label use, it also serves as an alternative MR contrast agent and is safe in patients with compromised renal function. As a contrast agent, ferumoxytol has been investigated for imaging various inflammatory conditions and malignancies in different organs [5, 6]. In this pictorial essay, we review the current and potential clinical applications of ferumoxytol as a contrast agent in abdominal MR imaging.

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Ferumoxytol molecule: pharmacokinetics and magnetic properties

Ferumoxytol (Feraheme®, AMAG Pharmaceuticals, Waltham, MA, USA) is available as a 17-ml vial with 510 mg of elemental iron. Compositionally, the preparation consists of an iron oxide core with a carbohydrate coating [6].

Safety

Six studies ($n = 10{,}425$) that evaluated its adverse effects secondary to its use as a therapeutic agent report mild-to-moderate events with gastrointestinal complaints as most common [7–12]. Other side effects include headache, muscle spasms, and cough. Serious events were hypotension and anaphylactic reactions that can be fatal [13]. Ferumoxytol is contraindicated in patients with iron overload (normal total iron binding capacity: 45–66 µmol/l) and known hypersensitivity to its components.

Pharmacokinetics

Ferumoxytol was administered as a rapid bolus of 510 mg (1–7 mg/kg) over 17 s initially, but it has been lowered to a slow infusion of 510-mg-diluted ferumoxytol over 15 min, as suggested by the FDA [6]. Its 'large' size and carbohydrate coating prevent mast cell degranulation after administration. This allows for a prolonged intravascular time (dose-dependent plasma half-life 14–21 h) making ferumoxytol a promising agent for vascular and perfusion imaging [5, 6] (Table 1). Within 24–36 h, it is taken up by macrophages within the liver, spleen, bone marrow, and lymph nodes making it a suitable agent for imaging inflammatory and malignant disease processes (Fig. 1). Due to the extended blood pool phase and delayed intracellular uptake, intravascular enhancement from ferumoxytol may be seen until 3 days after administration allowing for extended image acquisitions which is not possible with GBCAs which rapidly equilibrate with the interstitial spaces and are excreted by kidneys [14, 15]. Later, the carbohydrate envelope is enzymatically cleaved and excreted by kidneys and/or gut, while the core enters the normal iron metabolism pathway [5]. Studies have also shown that delayed clearance results

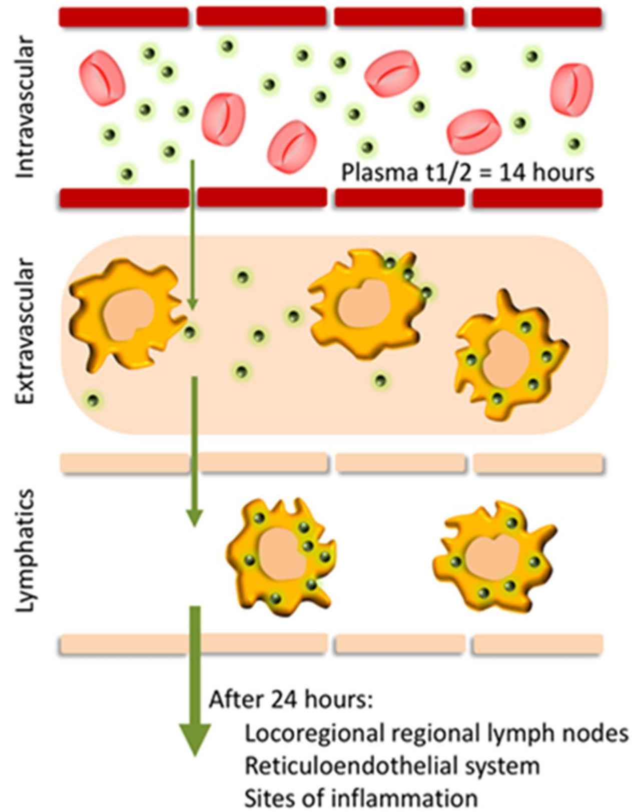

Fig. 1 Pharmacokinetics of ferumoxytol. After intravenous injection, ferumoxytol demonstrates a dynamic arterial and venous phase with prolonged blood pool stay. It then extravasates into the interstitium and is finally taken up by the mononuclear phagocytic system

Table 1 Comparison between ferumoxytol and gadolinium-based contrast agent

Parameter	Ferumoxytol	Gadolinium-based contrast agent[a]
Particle size	30 nm	0.357 nm
Distribution	Dynamic phase, blood pool phase, delayed phase in extra- and intra-cellular phases	Dynamic phase, extracellular phase
Half-life (plasma)	14 h	1.6 h
Dose injected	1–7 mg/kg	0.1 mmol/kg
Excretion	Accumulates body's iron stores, used for hemopoiesis	Renal
Major adverse events	Hypersensitivity including anaphylaxis	Potential nephrogenic systemic fibrosis, gadolinium retention

[a]Features of gadolinium diethylenetriamine penta-acetic acid are presented

in persistently reduced signal intensities in liver, spleen, and bone marrow that may last for several months [16, 17].

Magnetic properties

Though iron by itself is ferromagnetic, iron oxide (ferumoxytol) is supermagnetic due to greater magnetic dipole moment than iron alone [3]. Like GBCA, ferumoxytol has high longitudinal (R1) relaxivity. This implies T1 shortening with both contrast agents and hyperintense signal on T1 W images (Fig. 2).

In contrast, compared to GBCA, ferumoxytol has considerably higher transverse relaxivity and thus has applications in susceptibility-weighted T2- and T2*- weighted MR where enhancement with ferumoxytol appears hypointense (negative contrast agent) (Fig. 3).

The ratio of R1 and R2 relaxivity is inversely influenced by magnetic field strength [18]. Therefore, at clinically relevant field strengths of 1.5T and 3T ferumoxytol shows higher R1 (T1 W signal) at 1.5T. However, similar R2 and

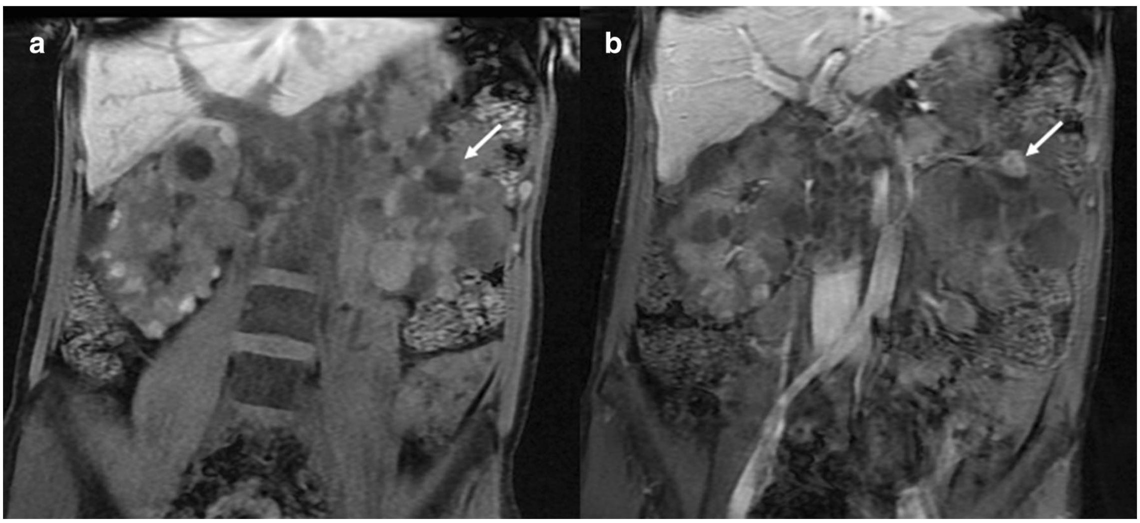

Fig. 2 Patient with VHL. Post-contrast coronal T1-weighted VIBE (volumetric interpolated breath-hold sequence) image (**b**) which was acquired after injection of ferumoxytol demonstrates a T1 hyperintense enhancing lesion near superior pole of left kidney. The lesion appeared hypointense on pre-contrast image (**a**). This is an example of the T1 shortening effects of ferumoxytol

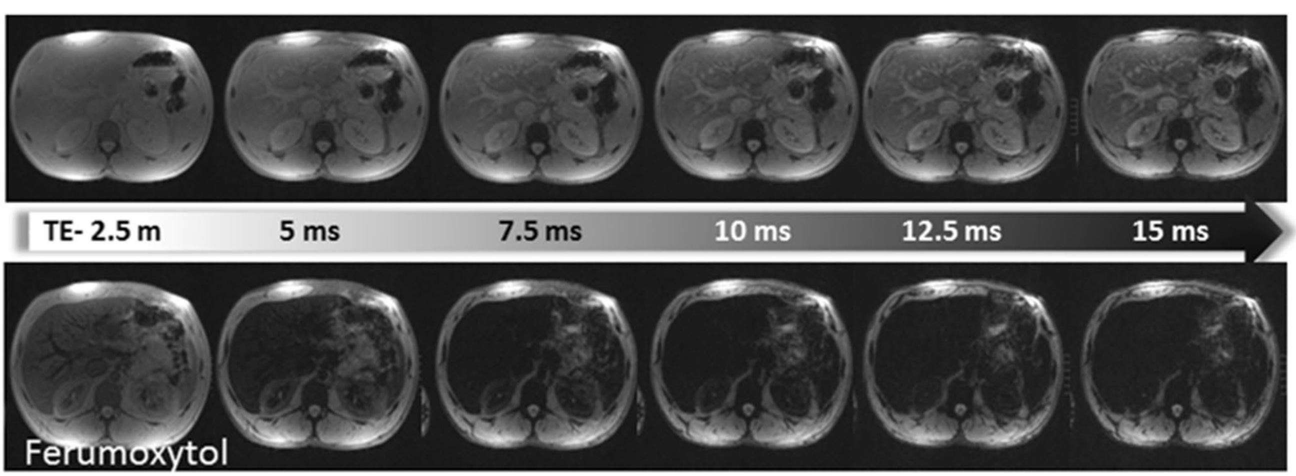

Fig. 3 Effect of ferumoxytol on T2* relaxation times. Top and lower panels show sequential T2*-weighted gradient echo images at increasing time to echo (TE), before (top panel) and 48 h (lower panel) after administration of ferumoxytol, respectively. The top panel demonstrates relatively slower decay of signal within liver and spleen compared to lower panel. The susceptibility effect of iron after ferumoxytol administration results in a faster signal decay which is the basis of detection of ferumoxytol uptake in the target organ/tissues

R2* have been shown at 1.5 and 3T for ferumoxytol in an in-vitro set up since it is maximally saturated at much lower field strengths [19].

Abdominal imaging applications

USPIOs have been shown to have a clinical potential because of their magnetic susceptibility which produces loss of signal on T2- and T2*-weighted sequences [3]. The applications can be broadly divided in three categories including inflammatory, oncologic, and vascular.

Inflammatory conditions

Ferumoxytol accumulates in tissue macrophages which can be used as a method of detecting tissue inflammation in blood vessels, solid abdominal organs, and potentially in the bowel loops.

Type 1 diabetes

Ferumoxytol MRI is an emerging method for imaging the pancreatic inflammation in patients with underlying type 1 diabetes. The infiltration of the islet cells by macrophages has been implicated in the pathogenesis of type 1 diabetes mellitus [20]. Mouse model and human studies have validated the ferumoxytol MRI for detecting pancreatic inflammation in recent onset type 1 DM [21–24]. The inflamed islets demonstrate uptake of ferumoxytol, and the heterogeneity of ferumoxytol uptake on high-resolution maps and drop in global parenchymal signal (ΔR2* Metric) following ferumoxytol uptake help to distinguish patients with T1DM from normal subjects (Fig. 4) [22]. This technique has several potential applications including aiding in difficult diagnoses (e.g., type 1B diabetes or individuals with latent autoimmune diabetes of the adult), identifying individuals at highest risk of converting from cryptic insulitis to overt diabetes, and helping to monitor

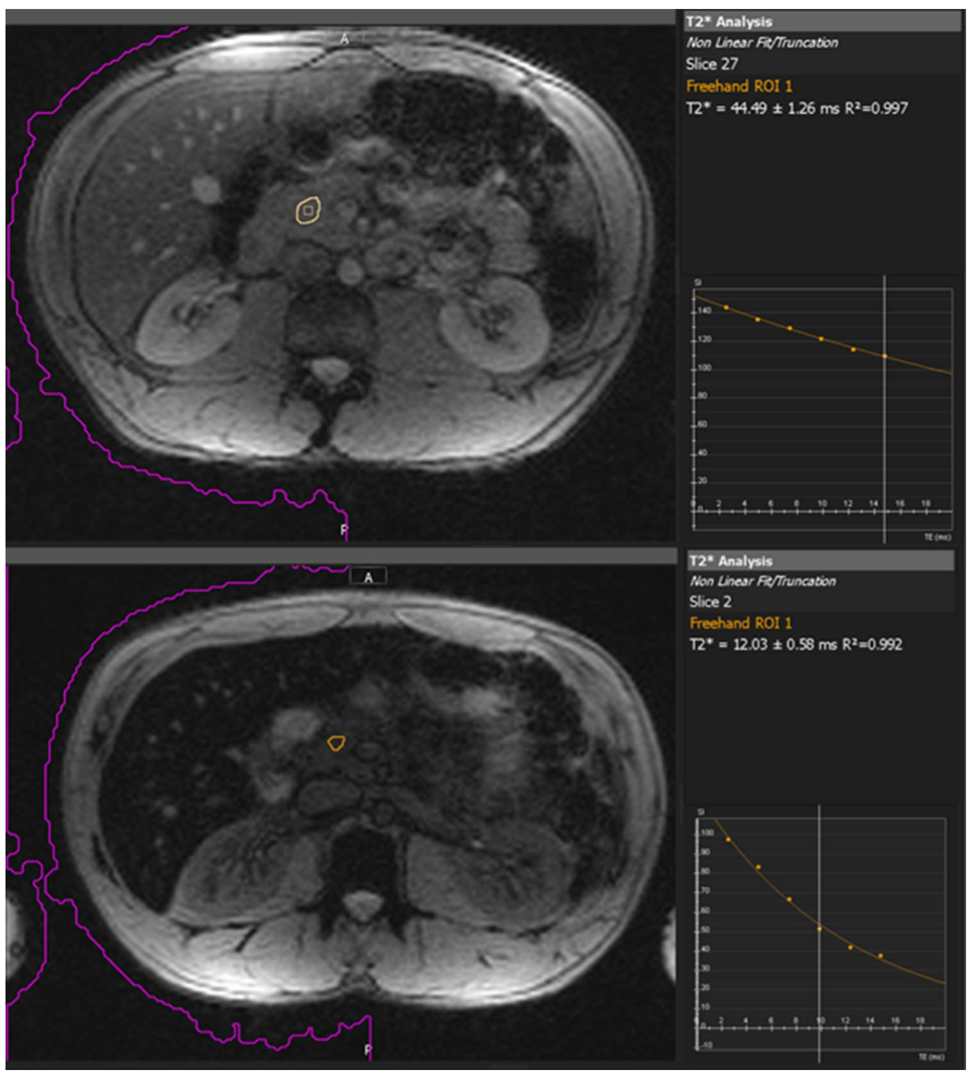

Fig. 4 Pancreatic nanoparticle accumulation and decreased T2* values in patients with T1DM. Regions of interest (ROIs) placed within the pancreatic head on pre-administration (top panel) and after 48 h of ferumoxytol administration (lower panel): ferumoxytol MRI in a patient with recently diagnosed T1D demonstrate drop in signal (darker appearance of pancreas) and decrease in T2* values (from 44.5 to 12 ms) after administration of ferumoxytol

patients' early responses to immunomodulatory interventions [22].

Inflammatory bowel disease

The hallmark of active inflammatory bowel disease is a pronounced infiltration into the lamina propria of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells) and adaptive immune cells (B cells and T cells). Ferumoxytol MR imaging signal characteristics within the bowel in IBD has been anecdotally reported [25]. Patients with Crohn's disease (CD) often suffer from iron deficiency anemia secondary to decreased GI uptake in a setting of inflammation [26]. These patients may require administration of parenteral iron [26, 27] and ferumoxytol is one of the agents that can be used [28]. Ferumoxytol has recently been approved by the FDA for intravenous administration to patients with iron deficiency anemia. Several recent phase III clinical trials have proven the safety and efficacy of ferumoxytol compared to conventional agent iron sucrose [27–29]. It means that ferumoxytol can not only act as a therapeutic agent in a subset of patients with IBD but also can provide an additional means of studying the mucosal disease activity in patients with CD (Fig. 5) [30]. There is limited preliminary evidence showing that T2* MR imaging-based techniques may be useful for the in-vivo tracking of macrophages in mice with IBD [31]. Our preliminary unpublished work also suggests that delayed macrophage phase imaging could prove to be useful in detecting and quantifying the inflammatory activity of IBD (Fig. 5). Ferumoxytol also offers potential advantages over gadolinium-based contrast agents for imaging patients with chronic renal insufficiency. Administration of ferumoxytol is safe in adult and pediatric patients with chronic renal insufficiency without any known links to nephrotoxicity or adverse reactions specific to underlying renal insufficiency (such as nephrogenic systemic fibrosis). Additionally, hemodialysis is not required after its administration.

Oncologic applications

Primary tumor applications

Inflammatory cell infiltration of tumors contributes to tumor invasion, growth, metastasis, and patient outcomes. Tumor infiltration by macrophages is generally associated with neo-angiogenesis and negative outcomes, whereas dendritic cell (DC) infiltration is typically associated with a positive clinical outcome in association with their ability to present tumor antigens and induce Ag-specific T cell responses [32]. Tumors in the abdomen including pancreatic ductal adenocarcinoma, rectal adenocarcinoma, and hepatic metastasis have been known to have an inflammatory infiltration [33, 34]. Ferumoxytol-enhanced MRI has been shown to enhance primary tumor delineation with PDAC patients on chemotherapy [35]. It has potential in pre-surgical planning for achieving disease-free margin at the time of surgery thus improving the prognosis of PDAC (Fig. 6).

Lymph node imaging

Accurate lymph node staging at the time of initial diagnosis is an important prognostic predictor for most tumors. Currently, the detection of positive lymph nodes is based mainly on size and uptake of nuclear imaging markers in some cases. The size criteria are insensitive for detection of small positive lymph nodes, similarly nuclear imaging studies such as PET/PET-CT are also not sensitive for detecting

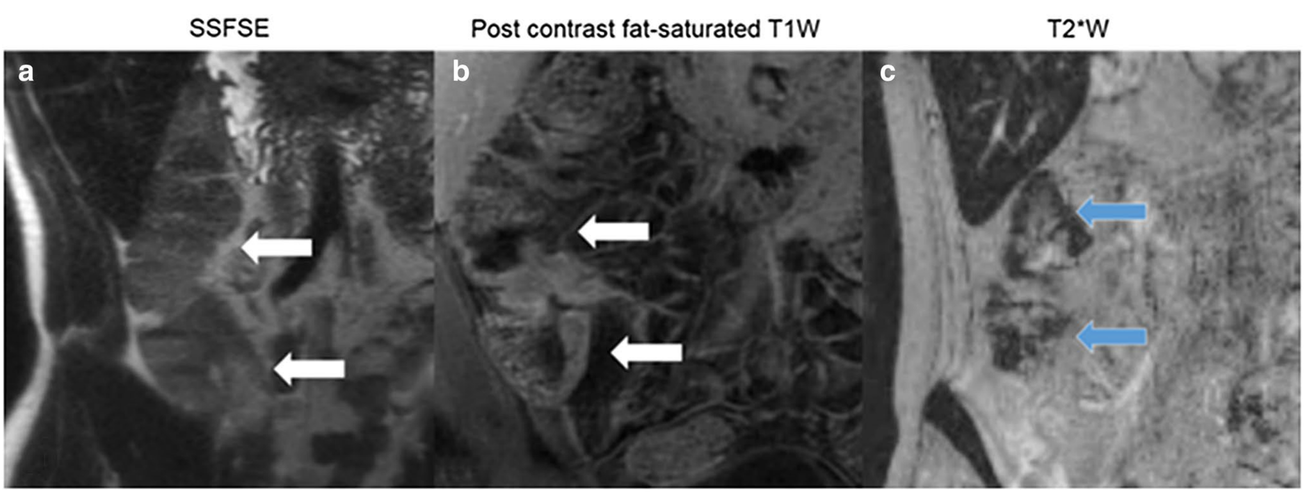

Fig. 5 Ferumoxytol was infused 24 h prior to imaging. T2*-weighted imaging demonstrates areas of low signal in the cecum and ascending colon (**c**; blue arrows). There is corresponding wall thickening (**a**, **b**) and contrast enhancement on T1-weighted image (**b**; white arrows)

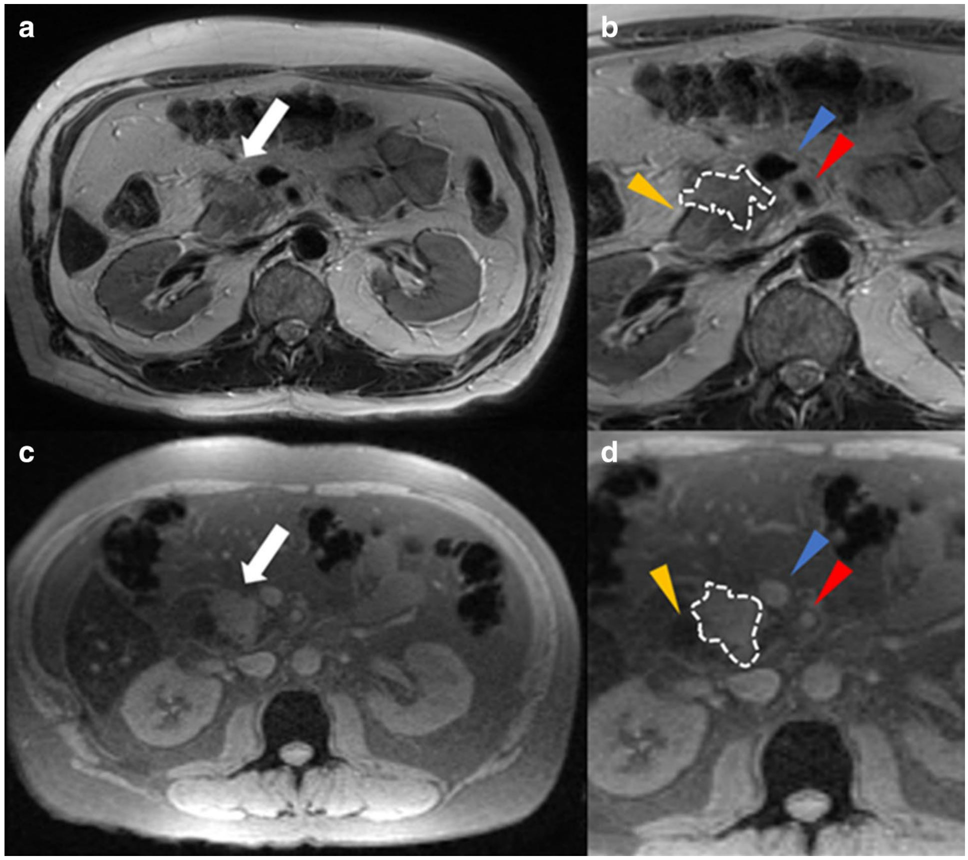

Fig. 6 USPIO-enhanced MRI in pancreatic cancer. T2-weighted (**a**, **b**) and post-ferumoxytol T2*-weighted image (**c**, **d**) in a 55-year-old male with painless jaundice. Improved delineation of the tumor (arrow) in the pancreatic head is seen with ferumoxytol. The tumor is resectable with no involvement of the duodenum (yellow arrowhead), superior mesenteric artery (red arrowhead), or vein (blue arrowhead)

metastatic lymph nodes smaller than 1 cm [36]. 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 distributed diffusely within the nodal parenchyma and demonstrate homogenous signal drop on delayed phase ferumoxytol MRI (Fig. 7). Infiltration by metastatic process replaces normal macrophage-rich parenchyma by tumor cells. After IV administration, USPIOs are taken up by macrophages within the reticuloendothelial system (RES), showing accumulation within the liver, spleen, bone marrow, and lymph nodes within 24–36 h [37–40]. This macrophage-dependent accumulation within the RES has been exploited to more accurately characterize both primary malignancies and metastatic disease within lymph nodes (Fig. 8). The normal parts of nodes with uptake of USPIO in macrophages show a signal drop on the T2*-weighted sequence because of iron oxide; on the contrary, the tumor deposit parts of nodes

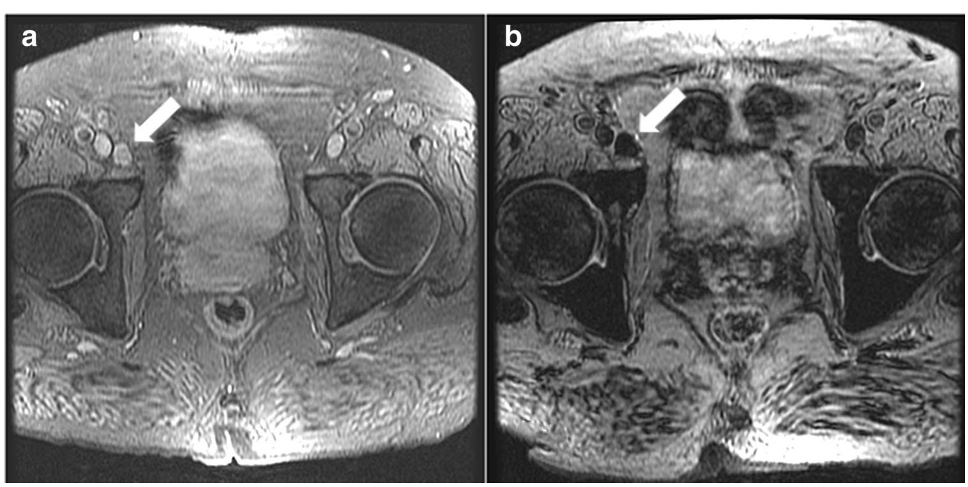

Fig. 7 Lymphotropic nanoparticle enhanced MRI allows for the characterization of small size (diameter < 10 mm) lymph nodes in the pelvis. Pre **a** and 24 h post **b** ferumoxytol T2*-weighted in a 55-year-old male with prostate cancer. The suspicious prominent right external iliac lymph node shows a homogeneous decrease in T2* signal uptake post ferumoxytol administration suggestive of benignity. This was subsequently proven as benign by pathology

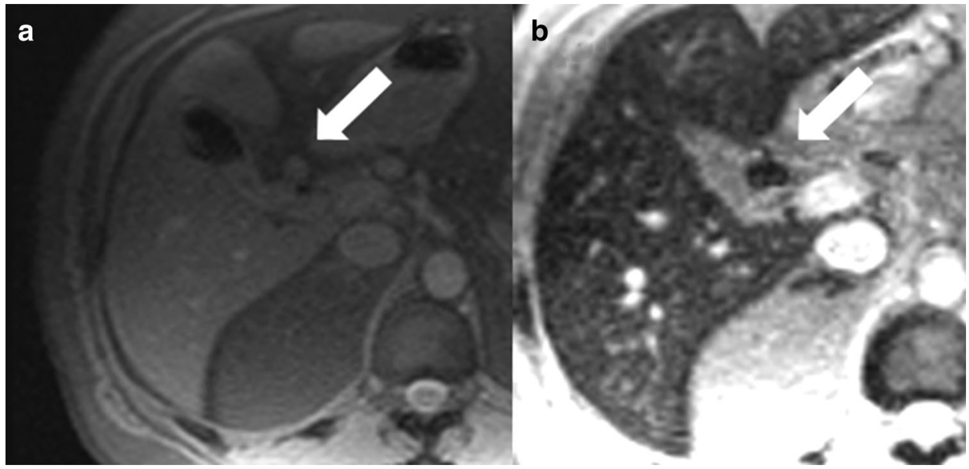

Fig. 8 Malignant lymph node with USPIO-enhanced MRI. Pre **a** and 48 h post **b** ferumoxytol T2*-weighted in a patient with pancreatic adenocarcinoma shows heterogeneous uptake of ferumoxytol of periportal lymph node suggestive of metastatic involvement. Surgical pathology confirmed malignant involvement of the lymph node

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 [41–43]. USPIO MRI has been used for prostate and penile cancer for detection of metastatic lymph nodes [41–43]. However, this technique may not detect metastatic nodes at an early stage [44]. There are also studies that show that lymphatic administration of USPIO results in maximum tissue concentration of injected contrast material within the lymph nodes and hence may be more sensitive detection of abnormal lymph nodes compared to intravenous route [45].

Vascular imaging: body applications of ferumoxytol MRI

The applications can be classified into two groups including blood pool applications and macrophage specific/plaque imaging application

Blood pool application for vascular contrast enhancement

Ferumoxytol is an attractive alternative to standard gadolinium-based MRI contrast agents that carry potential risks if given to patients with renal failure. Recent study has shown that ferumoxytol-enhanced MRI is a safe alternative to CTA in patients with renal failure for evaluating the aortic root and peripheral vascular access for pre-procedural imaging in cardiac interventional procedures like transcatheter aortic valve replacement (TAVR) [46].

As per FDA recommendation, ferumoxytol must be administered as a slow infusion which limits its utility for dynamic multiphase MRI. But given a long intravascular half-life, it can still provide diagnostic quality high CNR images for MR angiography even with slow infusion. But as it would not provide a dynamic information, venous contamination will be a challenge in visualizing small arteries. In cases where dynamic information is vital and the clinical scenario is life-threatening which outweighs the risk of anaphylaxis, ferumoxytol can be given as a short intravenous bolus for MR angiography (MRA) and dynamic MRI [47]. Also due to an extended plateau of an increased vascular signal, much longer imaging acquisitions are possible, allowing for higher SNR, improved performance of navigated MRI sequences, venous imaging, and the option for repeat imaging without the need for additional contrast material (Figs. 9, 10, 11). Ferumoxytol MRI can also serve as an alternative imaging modality in patients with poor renal function in the setting of suspected vascular injury (Fig. 12). However, hemodynamic stability and urgency for potential treatment should be weighted before accepting these patients for MR imaging.

Atherosclerotic plaque imaging

Plaque rupture, the most common cause of myocardial infarction, accounts for approximately 70% of all sudden deaths. The thin cap fibroatheroma is recognized as the plaque type that is most likely to rupture. It is identified histologically by a large necrotic core, a thin overlying fibrous cap, and macrophage and T-lymphocyte infiltration [48]. The degree of macrophage infiltration correlates well with lesion progression. Inflammation within atherosclerotic plaques can be quantitatively assessed by measuring T2* value of these plaques following ferumoxytol administration due to macrophage infiltrates in the inflamed plaques. Macrophage-selective feature of ferumoxytol allows the identification of inflammation, which can be applied to vessel wall imaging. Contrast-enhanced MRI with iron oxide particles has shown characteristic changes that correlate with iron accumulation within intraplaque macrophages. Recent study has shown USPIO-enhanced MRI is able to identify the inflammation within the aortic wall in patients with abdominal aortic aneurysms. This cellular inflammation can predict further growth of aneurysm and clinical outcome. This can also help with

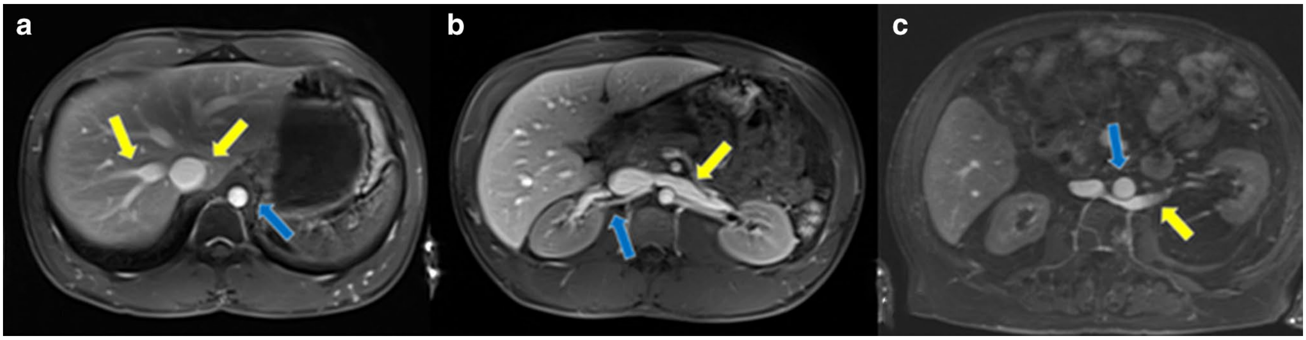

Fig. 9 USPIO-enhanced MRI in vascular imaging. Sequential axial T1-weighted fat-saturated post-ferumoxytol images during intravascular phase acquired 2 h of intravenous administration. The prolonged intravascular phase allows for a longer temporal window for data acquisition and depiction of both arterial and venous anatomies during the acquisition at a single time point. Images delineate excellent homogenous opacification of arterial (aorta, renal arteries: blue arrows) and venous anatomy (IVC, hepatic vein and renal veins: yellow arrows). Since ferumoxytol has not yet leaked into the interstitial/extravascular spaces, the concentration of contrast agent remains high in the blood pool of both arterial and venous compartments resulting in excellent contrast-to-noise ratio

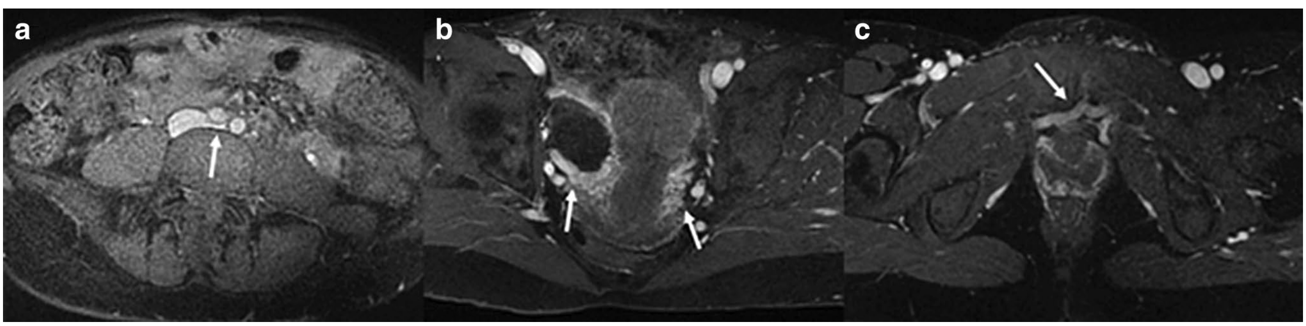

Fig. 10 May–Thurner syndrome (MTS): The left iliac vein may be compressed by the right iliac artery, which increases the risk of deep vein thrombosis (DVT) in the left extremity. Post-ferumoxytol T1 W VIBE image **a** demonstrates the > 50% reduction in the diameter of left iliac vein which is referred as May–Thurner anatomy which in the presence of physiologic features of flow diversion in the form of adnexal (**b**) and retropubic (**c**) collateral constitutes MTS

finding the patients that can benefit from anti-inflammatory therapy to reduce the disease progression [47, 49]. Our recent work demonstrated that even in the absence of visible atherosclerotic plaques, aortic wall may show a variable degree of ferumoxytol uptake after radiation exposure. As radiation exposure is known to cause atherosclerosis, this finding may be a manifestation of early atherosclerosis preceding visible plaque formation [50].

Future directions

Adrenal imaging

A variety of chronic iron-overload disorders such as hemochromatosis, hemosiderosis, and thalassemia show iron deposition within organs of the endocrine system, particularly the pancreas and, to a lesser extent, the adrenals [51, 52]. The imaging behavior of the normal adrenals on ferumoxytol-enhanced T2*-weighted MR and acute iron deposition within the adrenals after IV USPIO administration has been studied [53]. The SNR in both adrenals decreased significantly on ferumoxytol-enhanced, T2*-weighted MRI when compared with the pancreas and skeletal muscle [53] (Fig. 13). Thus, the data show acute ferumoxytol deposition within the adrenals 48 h after IV administration in a fashion similar to tissues of the RES [53]. This observation could provide a new tool, not requiring ionizing radiation, for the detection and characterization of adrenal abnormalities. For example, if ferumoxytol localizes in the adrenal medulla, ferumoxytol-enhanced MRI might be useful in the early structural diagnosis of adrenal medullary hyperplasia and the early detection of small pheochromocytomas in multiple endocrine neoplasia-2 syndromes.

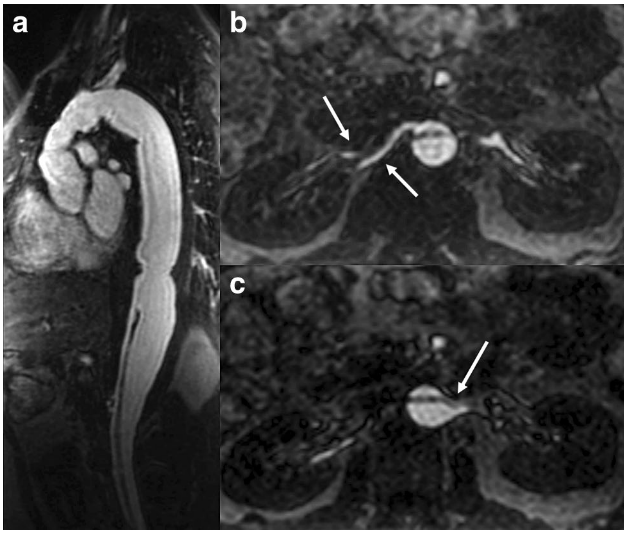

Fig. 11 A 64-year-old male with history of recent repair of aortic dissection and acute kidney injury. Dynamic MR angiography performed by injecting 4 mg/kg (10 cc) bolus injected at 1.5 cc/s after 6 times dilution with saline. It resulted in high CNR within the aorta (**a**), and small arteries (**b**, **c**) are comparable to standard gadolinium MRA. **b**. **c** demonstrate good visualization of small renal arterial branches without venous contamination. Extension of dissection flap to the left renal artery can also be visualized (**c**; arrow)

Monitoring and guiding targeted therapy

Novel magnetic cationic liposome-based treatments are being used for enhancing drug delivery in cancer treatment. There is a chance that ferumoxytol-enhanced MRI may be used for monitoring drug delivery to the target. With the use of magnet placement near the deliver target coupled with ferumoxytol-labeled liposomal chemotherapeutic agents, Gultepe et al. have shown enhanced drug delivery within the soft tissue sarcoma [54].

Tumor inflammation

As discussed earlier, the inflammatory cells and molecules in the tumor microenvironment influence different aspects of cancer progression, 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 [55].

Limitations

Only major adverse reaction to ferumoxytol is the risk of allergic reactions including anaphylaxis (0.02 to 0.2% incidence) [6, 56, 57]. Based on the reports of adverse allergic reactions, in 2015, the FDA recommended ferumoxytol to include the addition of a boxed warning, highlighting potential fatal and serious hypersensitivity reactions, including anaphylaxis [6, 56]. FDA also recommended a decrease in the administration rate from a 510-mg bolus over 17 s to a slow infusion of 510-mg-diluted ferumoxytol over 15 min which may help in reducing the number of adverse reactions [58]. In summary, the hypersensitivity reactions may occur but the incidence of serious ferumoxytol-related hypersensitivity is very low, and new FDA guidelines aim to further improve patient safety [6]. Besides known hypersensitivity or iron metabolic disorders, there is no absolute

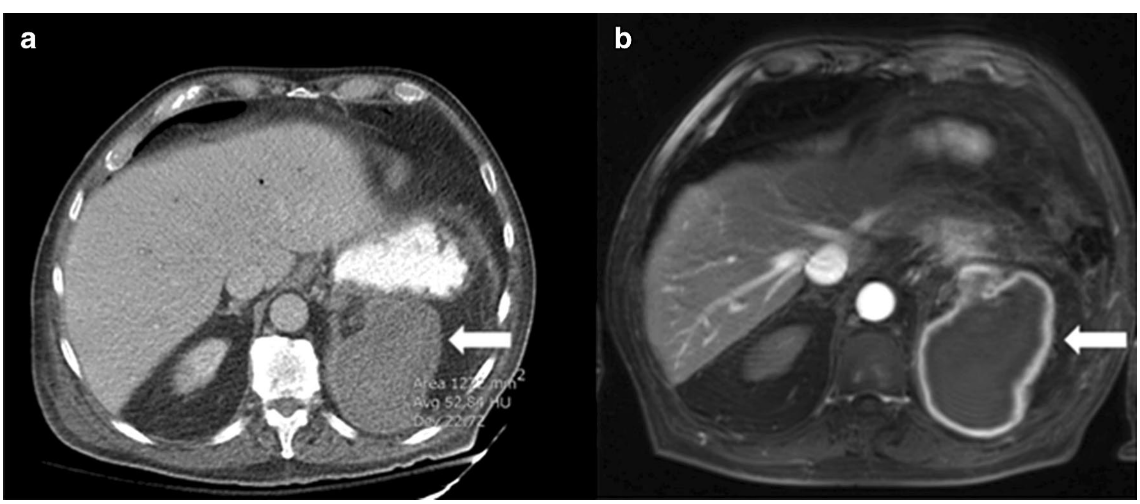

Fig. 12 USPIO-enhanced MRI in lesion assessment. Post-contrast CT image **a** shows a hyperattenuating (52HU) lesion (arrows) in the splenectomy bed. This patient was clinically stable but active bleeding needed to be ruled out. Due to decreasing GFR, the patient could not receive iodinated contrast and ferumoxytol-enhanced MRI was performed. T1-weighted post-ferumoxytol image **b** in intravascular phase shows only peripheral rim enhancement due to secondary inflammation but without any internal contrast pooling from active extravasation

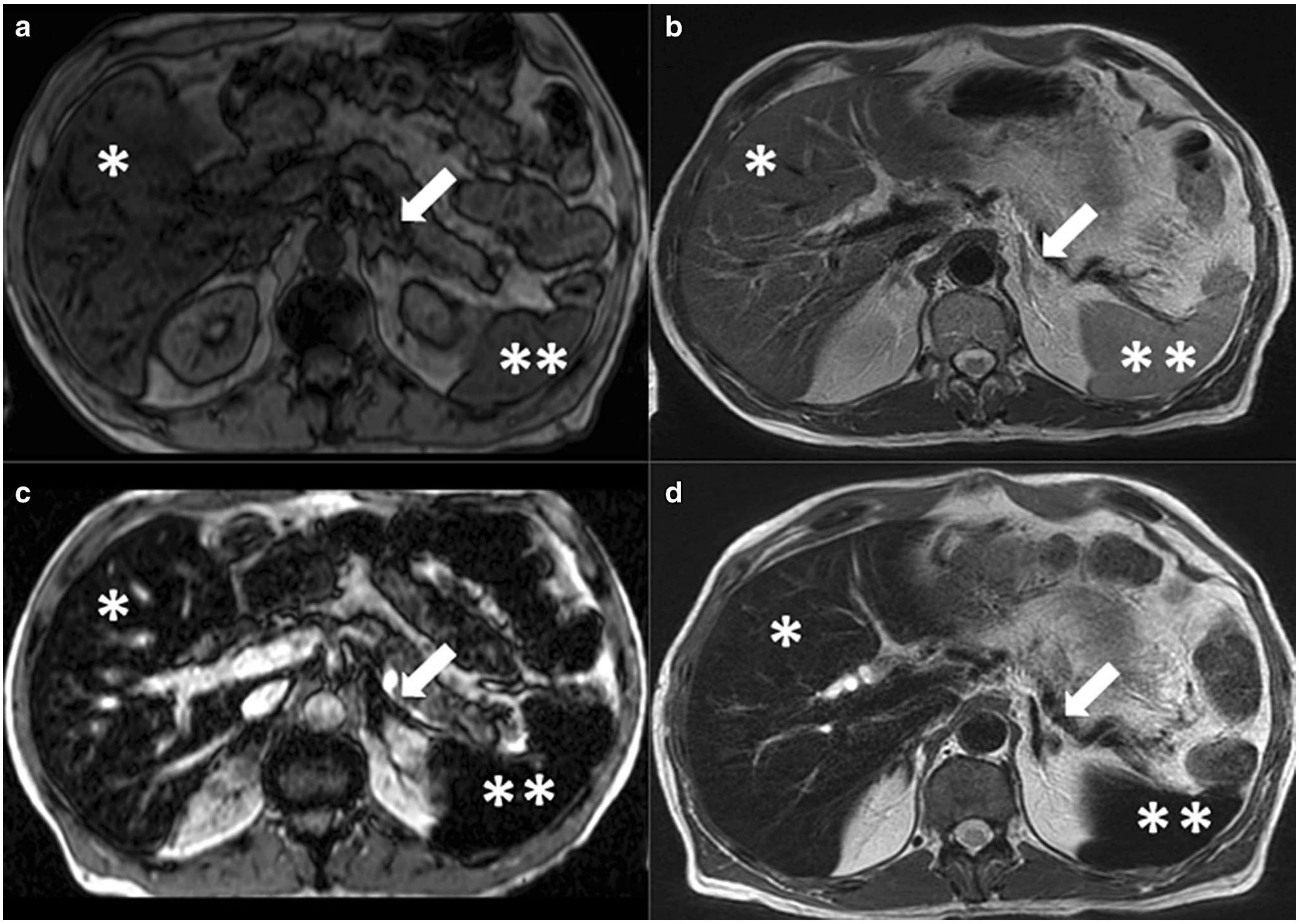

Fig. 13 Retained enhancement with USPIO-enhanced MRI. Pre (**a**, **b**) and 48 h post (**c**, **d**) ferumoxytol T2*-weighted (**a**, **c**) and BLADE (**b**, **d**) sequences reveal continued normal drop in signal intensity of normal liver (*), adrenal (arrow), and spleen (**)

contraindication for ferumoxytol in MRI, and importantly, it is safe in patients with renal impairment.

Vascular visualization improves early after administration, whereas late enhancement visualizes parenchymal-intracellular enhancement, which may require an additional visit, posing a logistical limitation with MRI scheduling. A signal change in the brain may persist from a few days to a week. Uptake in the liver, spleen, and bone marrow may alter MRI signal for months; therefore, radiologists must be aware of any prior history of i.v. iron oxide use [6].

Conclusion

Ferumoxytol MRI is emerging as an alternative MRI contrast agent in situations where GBCAs need to be avoided. In addition, by virtue of uptake by macrophages it has potential applications in detecting and monitoring inflammatory conditions such as type 1 diabetes and neoplastic conditions such as lymph node metastasis. Because of a prolonged intravascular phase, it is an excellent agent for vascular imaging. It also has various potential applications in inflammatory bowel disease, plaque imaging, and adrenal imaging. Other upcoming applications include monitoring targeted drug delivery and understanding tumor inflammation.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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