



## Imaging Applications of Ferumoxytol for MRI: Focusing on the Vasculature and Inflammation

Edward Neuwelt

ISMRM  
April 23, 2017

## Disclosure

OHSU, Portland Veterans Affairs Medical Center (PVAMC) and the Department of Veterans Affairs have a significant financial interest in Fennec, a company that may have a commercial interest in the results of this research and technology. Dr. Neuwelt, inventor of technology licensed to Fennec, has divested himself of all potential earnings. These potential conflicts of interest were reviewed and managed by the OHSU Integrity Program Oversight Council and the OHSU and PVAMC Conflict of Interest in Research Committees.

## Disclosure

The ferumoxytol studies were entirely funded by Veterans Administration, Driskill Foundation, and NIH research grants, with the ferumoxytol USPIO nanoparticles donated by AMAG pharmaceuticals.

OHSU has received a sponsored research agreement from AMAG to conduct clinical trials of MRI with ferumoxytol. None of the authors have financial interest in this agent or in its developer AMAG.

**High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material<sup>1</sup>**

**Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging<sup>1</sup>**

**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<sup>1</sup>**

- Gadolinium may deposit in the dentate nucleus and globus pallidus
- New alternative contrast agents should be tested

### Dose-Dependent Neurotoxicity (Seizures) Due to Deposition of Gadolinium-based Contrast Agents in the Central Nervous System

From

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*Radiology*: Volume 277: Number 3—December 2015 • [radiology.rsna.org](http://radiology.rsna.org)

## Overview

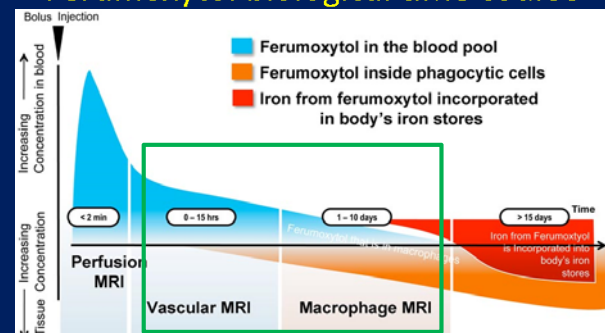
- ◊ What is ferumoxytol?
- ◊ Imaging of the vasculature
  - ◊ CNS
  - ◊ T2\*
  - ◊ Steady state cerebral blood volume maps
- ◊ Outside the CNS
- ◊ Imaging of inflammation
  - ◊ CNS
  - ◊ Outside the CNS
- ◊ Is it safe?
  - ◊ Summary

## What is Ferumoxytol?

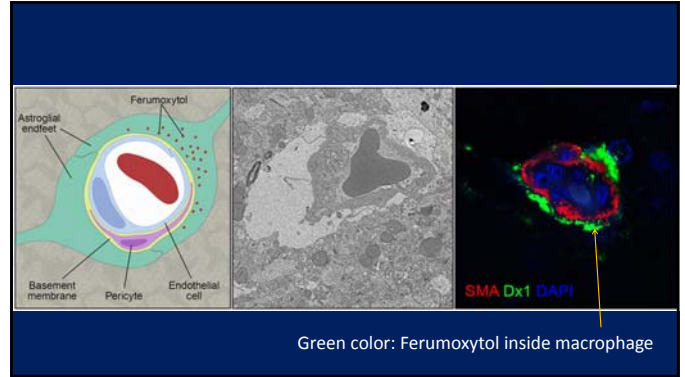
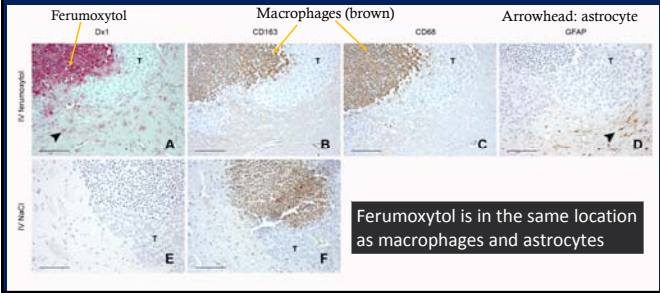
- FDA approved for iron replacement
- Used off label for MRI
- Safe in patients with impaired renal function



## Ferumoxytol biological time course



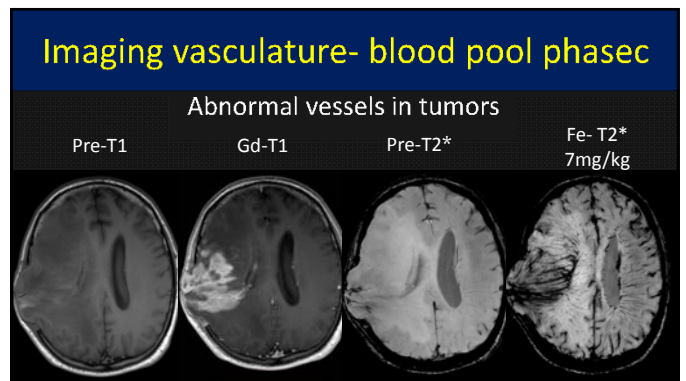
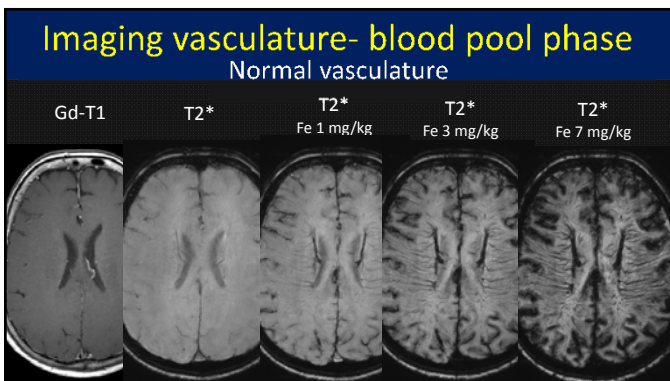
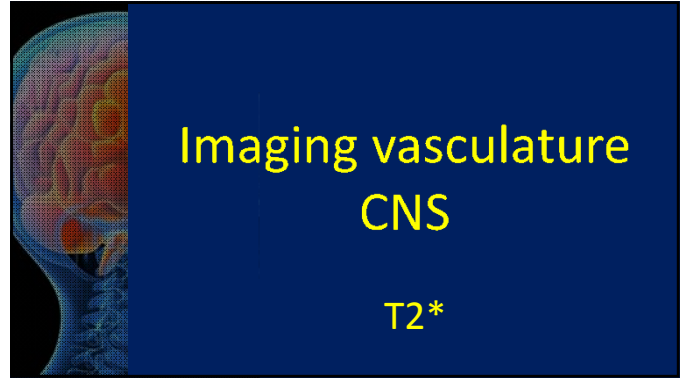
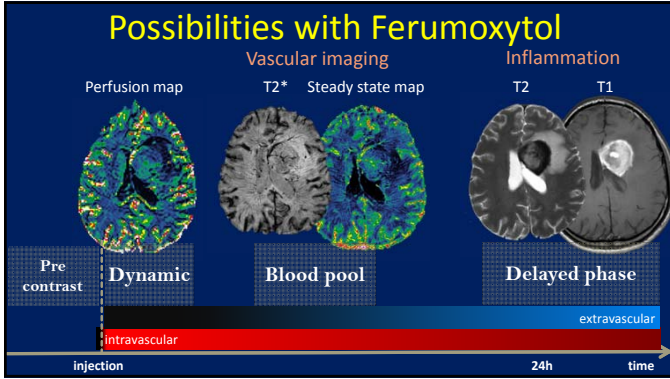
Immunostaining demonstrates that ferumoxytol traffics from system circulation to reactive CNS lesions

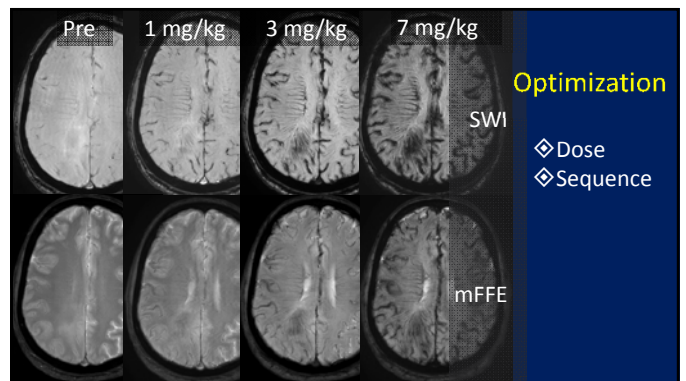
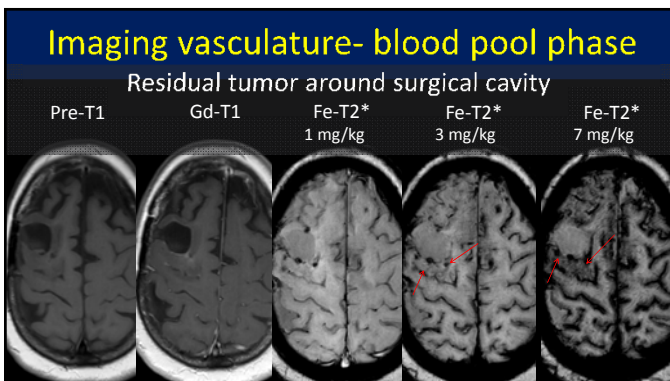
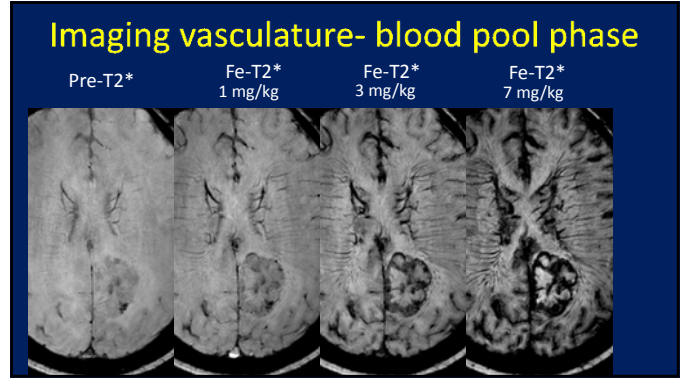
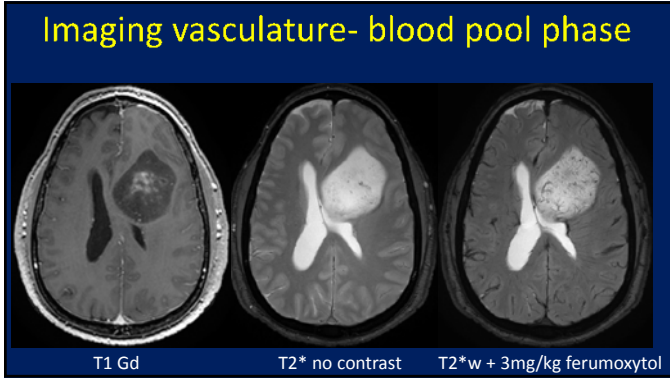


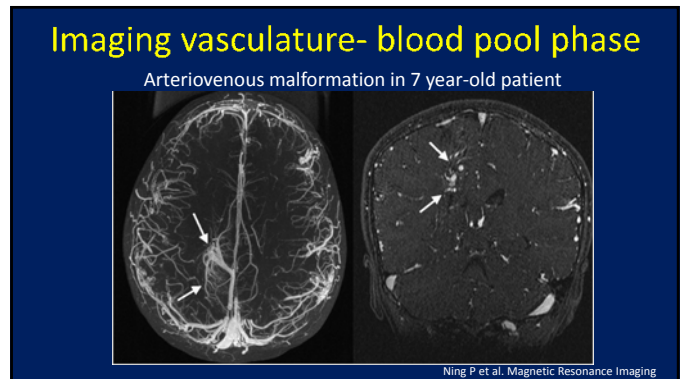
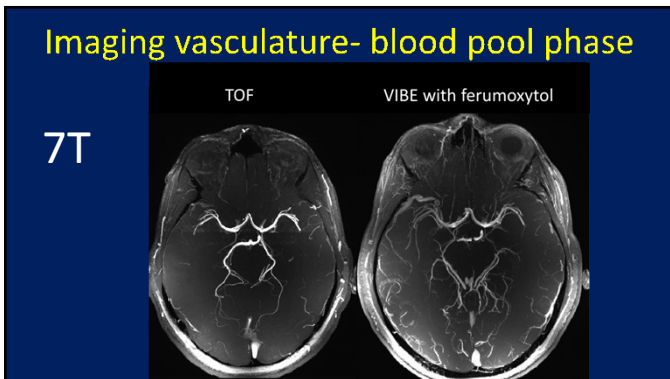
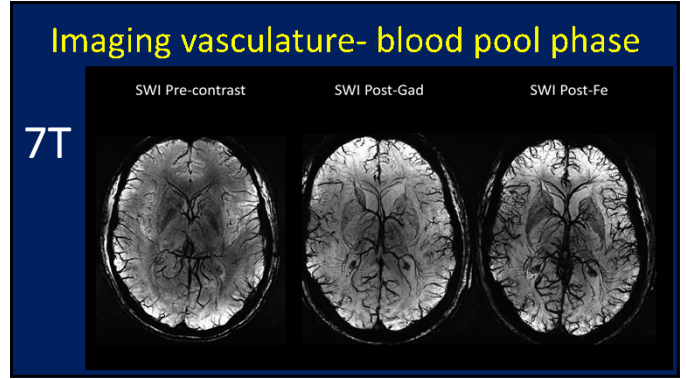
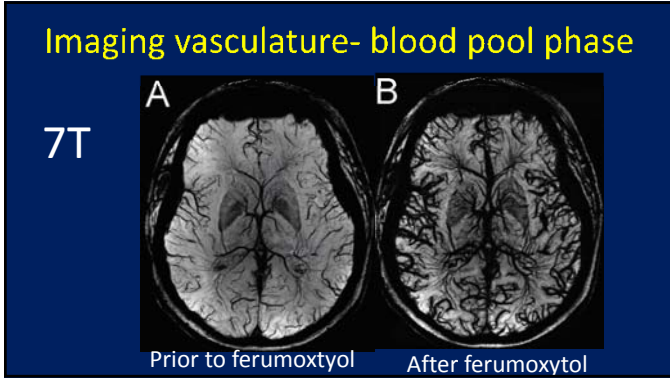
### Gadolinium vs Ferumoxytol

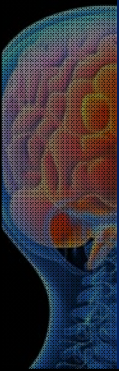
	GBCA	Ferumoxytol
Molecular size	1 nm	30 nm
Plasma half life	0.2 hour	15 hours
Location	brain parenchyma	blood pool --> brain parenchyma
Elimination	kidney	extra- and intracellular reticuloendothelial system

### Gadolinium vs Ferumoxytol










# Imaging vasculature CNS

## Steady state blood volume imaging

### Dynamic vs. Steady State CBV

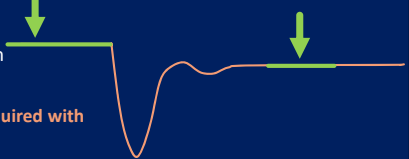
**Dynamic**

- TEMPORAL > spatial resolution



**Steady state**

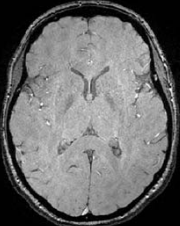
- very high spatial resolution



Steady state CBV is easily acquired with ferumoxytol

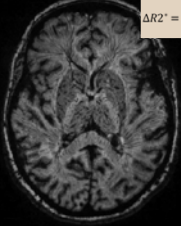
### Calculation of steady state blood volume maps

IV. injection of ferumoxytol

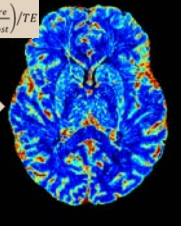


3D T2\*w image  
unenhanced

3D T2\*w image  
post ferumoxytol



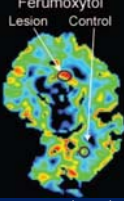
$\Delta R2^*$  map calculation  
after co-registration

$$\Delta R2^* = \ln \left( \frac{SI_{pre}}{SI_{post}} \right) / TE$$


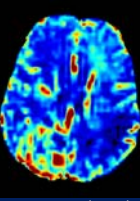
Steady State CBV map

Varallyay et al. J Cereb Blood Flow Metab. 2013 May;33(5):780-6.

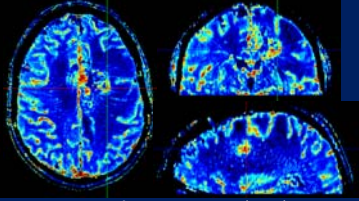
### Evolution of blood volume mapping 2013



CBV map (2005)



CBV map (2009)

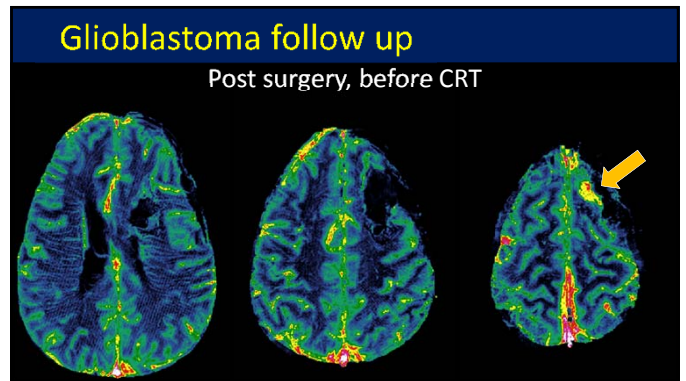
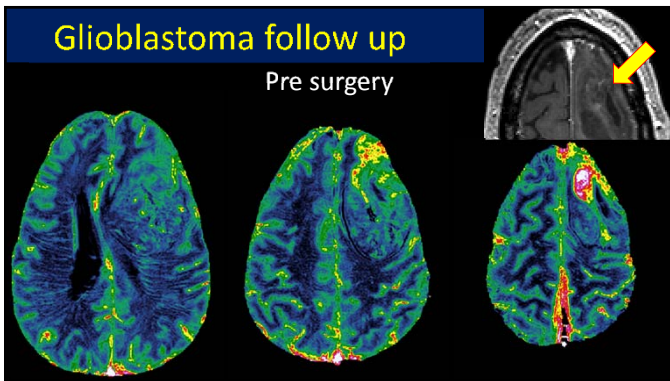
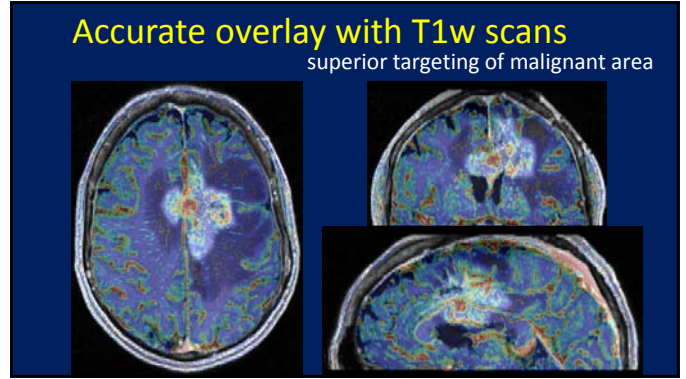
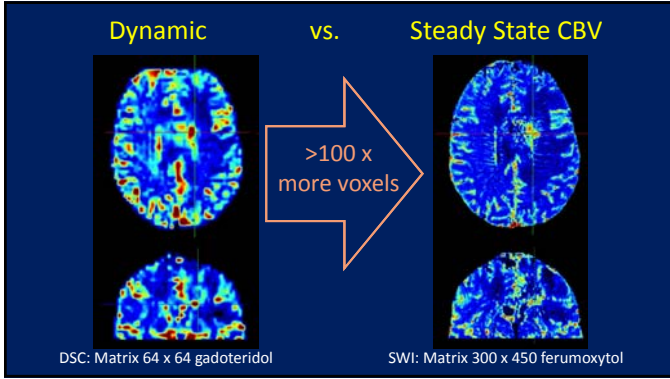


Steady State CBV map (2013)

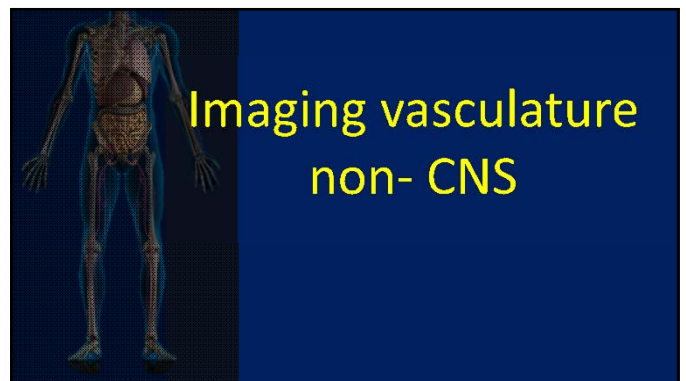
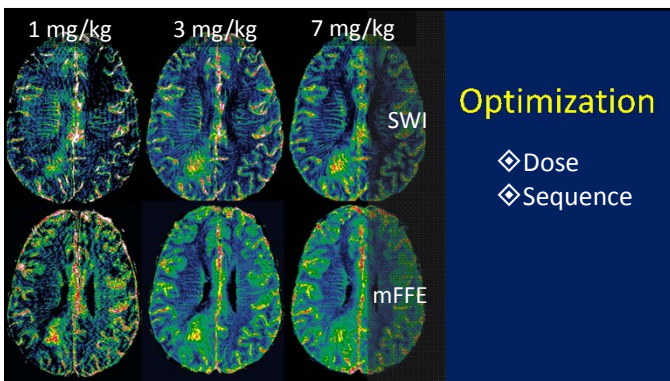
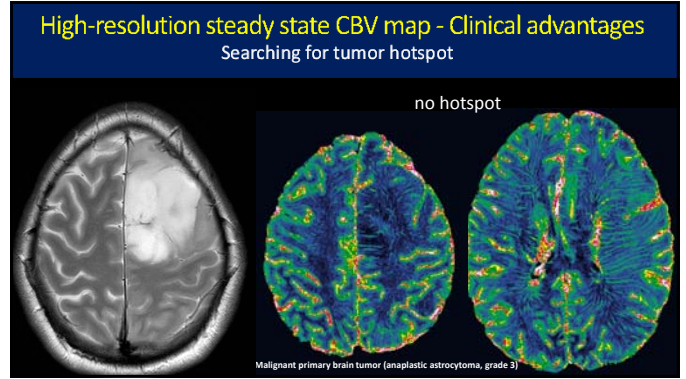
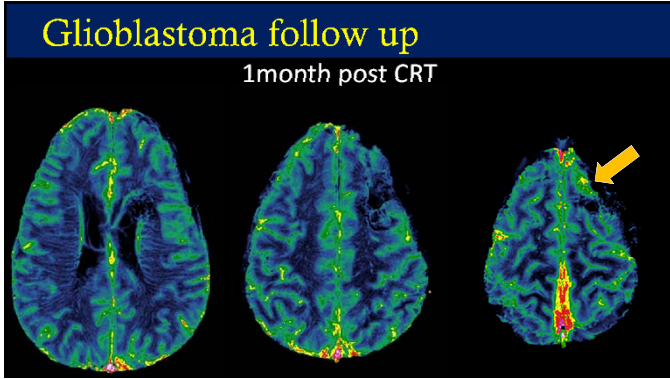
Advantages:

- high resolution
- 3D
- lack of echo spacing distortion
- possibly quantitative – remains intravascular

Csanad G Varallyay et al. J Cereb Blood Flow Metab. 2013 May; 33(5): 780-786.







**First pass vs. steady state MR Angiography and Venography**

**First pass MR angiography**

- Limited by breath held duration
- Motion artifact
- Bolus needed

**Steady state MR angiography**

- Long imaging window
- Higher resolution
- Fewer motion artifacts
- Improved signal-to-noise ratio
- Highly reproducible
- No bolus needed

**MRA/MRV with Ferumoxytol**

thin MIP

T = 25 secs    T = 2 min 30secs    T = 60 mins

Aortic dissection

First pass    Steady state

False lumen

Posterior view

JP Finn et al. 2016

**MRA/MRV with Ferumoxytol**

**Venous thrombosis**

CT venography  
Poorer vascular definition

Steady state MRA/MRV

detailed vascular anatomy

dilated left gonadal vein and pelvic varices

VS

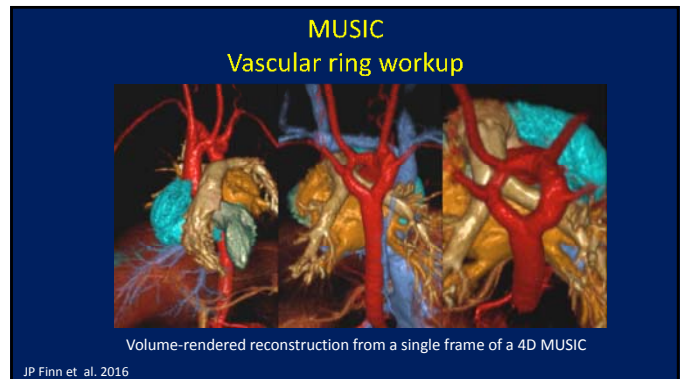
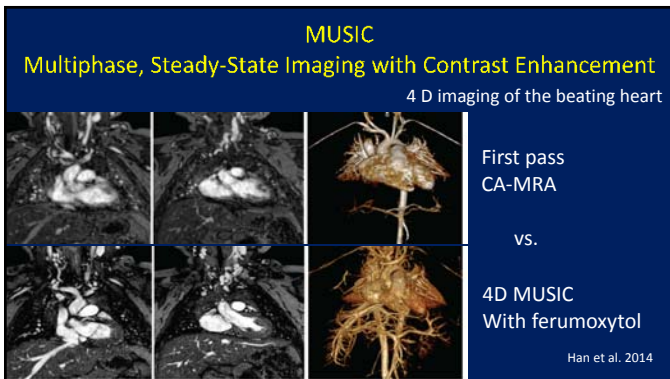
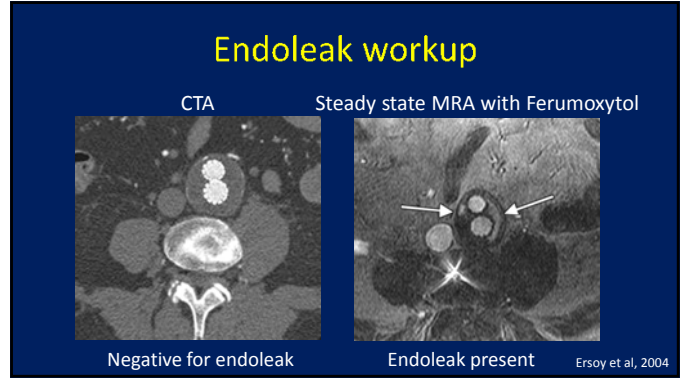
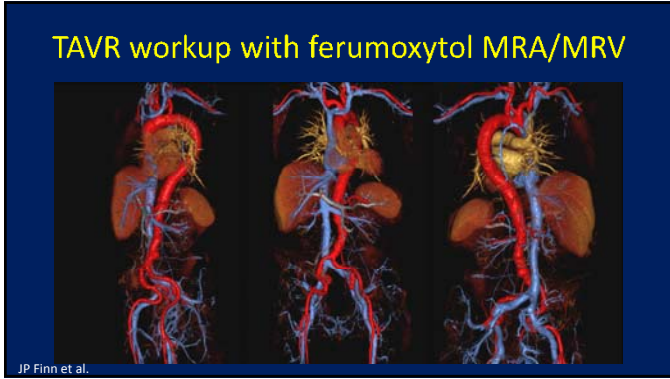
JP Finn et al. 2016

**MRA/MRV with Ferumoxytol**

**Inferior vena cava occlusion**

Detailed vascular anatomy with steady state MRA/MRV

JP Finn et al.



## MUSIC - Kawasaki disease



JP Finn et al. 2016

## Clinical utility of ferumoxytol MRA and MRV

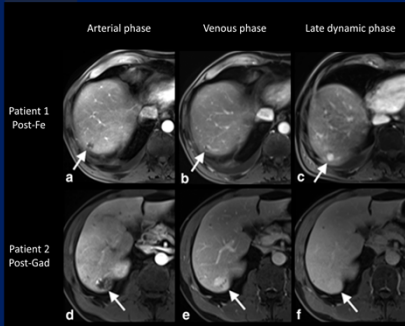
### Vascular

- ◊ Vascular integrity
- ◊ Vascular mapping for venous access
- ◊ Stenosis assessment
- ◊ Organ transplant workup
- ◊ Assess the status of renal transplant
- ◊ Pre-fistula assessment
- ◊ Detecting endoleaks
- ◊ Vascular malformations
- ◊ Endoleak followup
- ◊ Dissection flow analysis
- ◊ Aneurism, coarctation anatomy

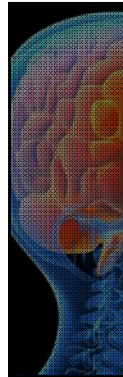
### Cardiac

- ❖ Congenital heart disease

## Imaging vasculature- Liver hemangioma



## Imaging inflammation CNS



### 62 year old female with suspected glioblastoma

Most malignant, most common primary brain tumor in adults, median survival ~15 months

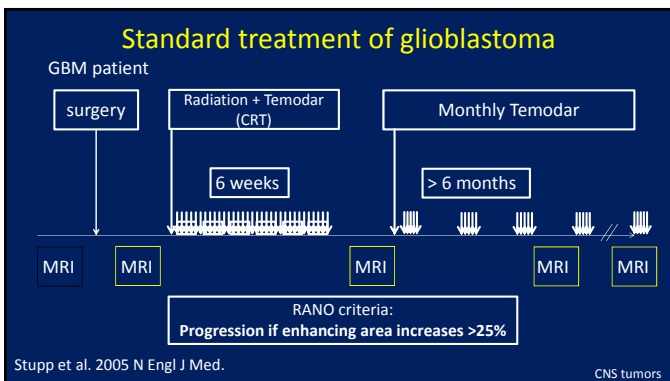
T1 T1+Gd T2

Gd CNS tumors

### Pathology confirmed glioblastoma

T1 T1+Gd T2

CNS tumors



post surgery 1 month post CRT 2 months post CRT 4 months post CRT 15 months post CRT

T1

T2

**Pseudoprogression**  
**A significant cancer problem**

CBV

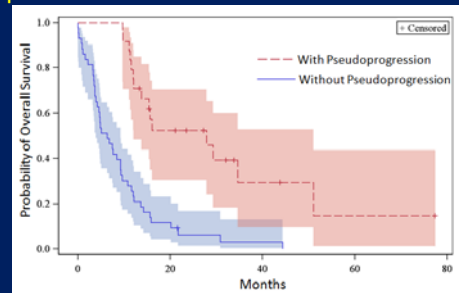
CNS tumors

## Treatment response assessment

- ◇ **True tumor progression - neovascularization**
  - ◇ Discontinue current treatment
  - ◇ New chemotherapy
  - ◇ Repeated surgery
  - ◇ Symptomatic therapy (steroids, Avastin)
- ◇ **Pseudoprogression (10-30%) - inflammation**
  - ◇ Continue current therapy (Temodar)
  - ◇ Treat symptoms (steroids, Avastin)
- Correct differential diagnosis is very important!
- Perfusion MRI with Ferumoxytol enables correct diagnosis

## Diagnosis of pseudoprogression in GBM patients can predict better outcome

2014

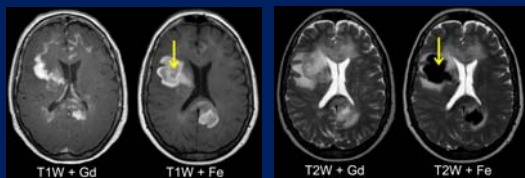


Seymur Gahramanov et al. CNS Oncol. (2014) 3(6)

CNS tumors

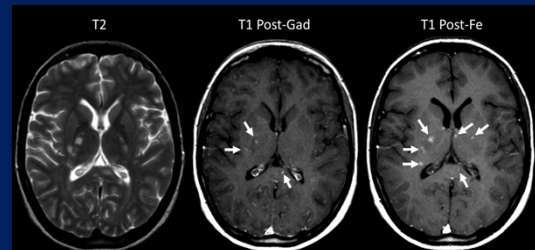
## Imaging inflammation

### PCNSL



## Imaging inflammation – multiple sclerosis

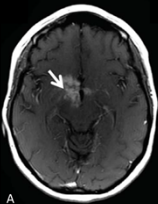
Mismatch between gadolinium- and USPIO-enhanced images



Tourdias et al.

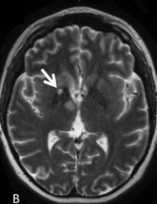
### Imaging inflammation

T1 Post-Gad



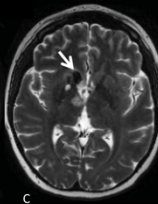
A

T2 Pre-contrast



B

T2 24 hours Post-Fe

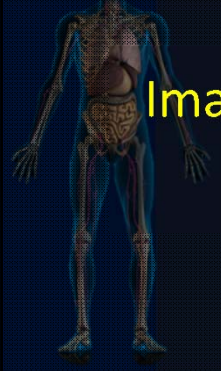


C

Biopsy from gad enhancing lesion:  
gliosis

New biopsy from Fe uptake:  
Demyelinating disease

## Imaging inflammation non- CNS




### Imaging inflammation

- Rheumatological diseases
- Acute and chronic inflammatory kidney disease
- Diabetic foot, osteomyelitis
- Crohn's disease activity


A Neuwelt et al. JMRI, 2016

### Osteomyelitis

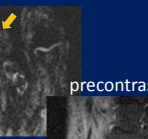
precontrast  
STIR T2



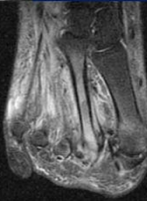
Fe STIR T2



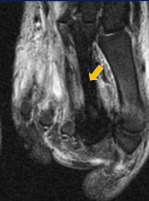
FeT2\*



precontrast STIR T2



Fe STIR T2



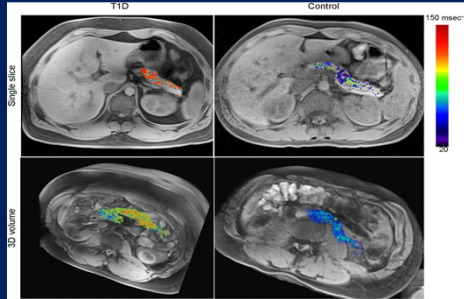
Inflammation is visible with ferumoxytol

Neuwelt et al.

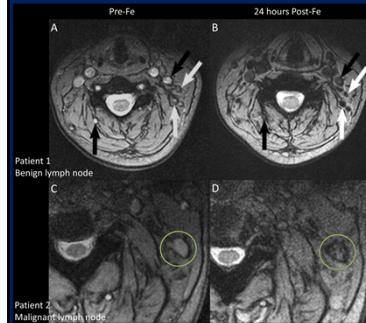
### Pancreatic inflammation

Increased pancreatic nanoparticle accumulation in patients with Type-1 diabetes

Gaglio et al. 2015



### Lymph node imaging with ferumoxytol

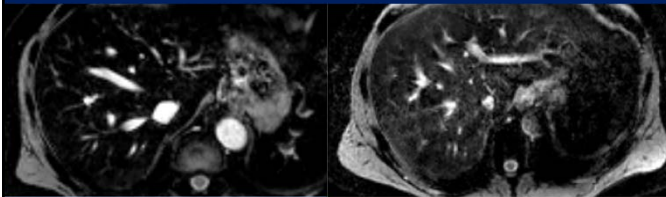


Hamilton et al.

### Imaging inflammation - hepatitis

Healthy control

NASH



Ferumoxytol

### Imaging inflammation - cardiovascular

Delayed phase- T1 and T2 enhancement

**T1 enhancement**

- ◆ Plaque analysis
- ◆ Vessel wall visualization
- ◆ Infectious disease follow up

**T2 enhancement**

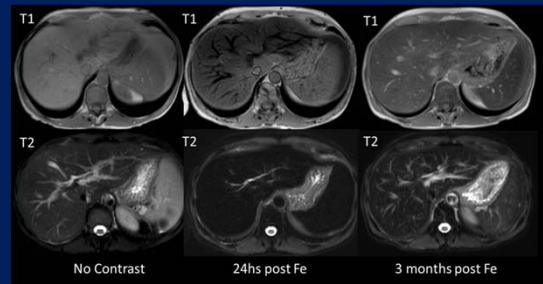
- ◆ Myocardial infarction



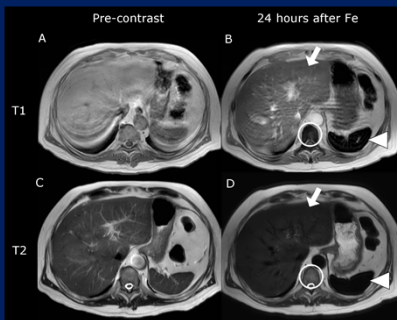
## Imaging inflammation with ferumoxytol other possibilities

- Mononuclear phagocytic system dysfunction measurements in liver
- Graft dysfunction and rejection after transplantation

## Prolonged signal in spleen and liver after ferumoxytol



## Prolonged signal in spleen and liver after ferumoxytol



Is it safe?

## How to administer ferumoxytol?

### IV bolus or slow injection?

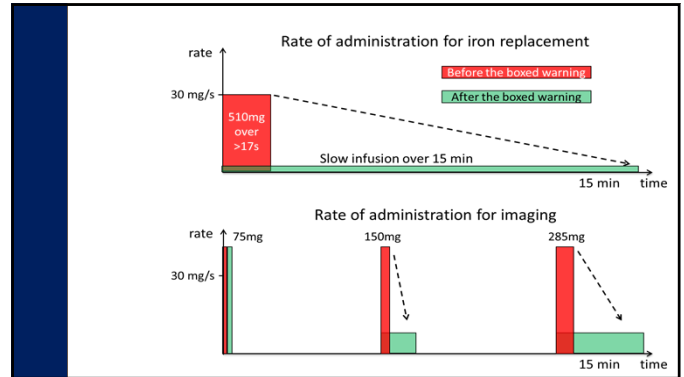
- ◆ Prior label allowed bolus injection of 510mg within 17 seconds. (very rapid injection)

### Post marketing safety data

- ◆ 1.3 million administrations total
  - ◆ 79 severe hypersensitivity reactions (0.006%)
  - ◆ 18 of which were fatal (0.0014%)

### Boxed warning and label changes in March 2015

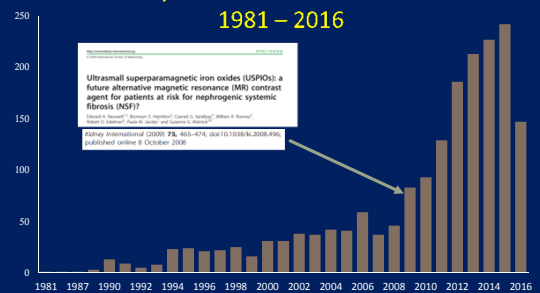
The FDA recommends slow infusion of 510mg ferumoxytol (diluted in 50-200 mL) over 15 minutes when used for iron replacement



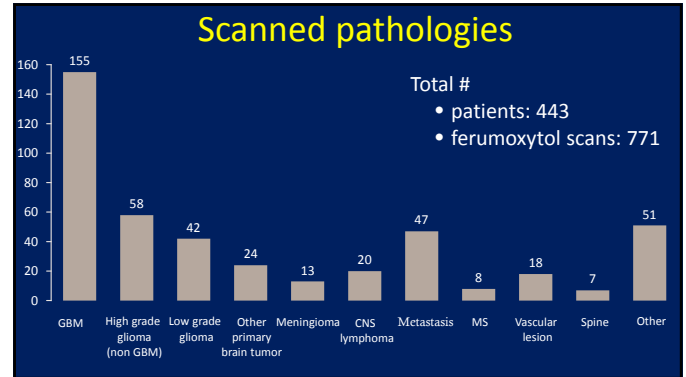
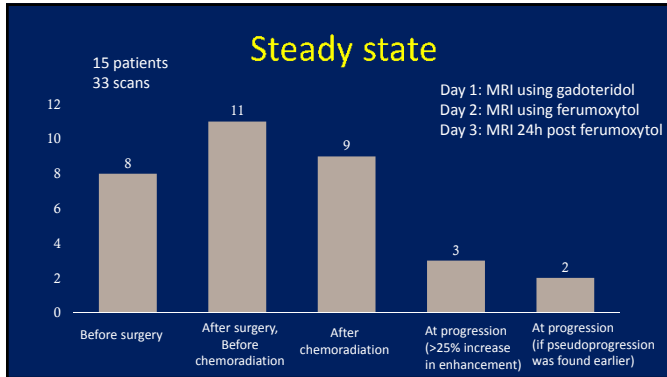
## Safety data of Ferumoxytol at OHSU in CNS imaging

- ◆ 671 ferumoxytol infusions in 331 patients
  - ◆ 4mg/kg or 510mg total dose,
  - ◆ all bolus injections, 1:1 diluted, 3ml/s
- ◆ No severe hypersensitivity reactions within 1 day
- ◆ Non severe reactions associated with ferumoxytol:
  - ◆ Hypertension 2.38%
  - ◆ Nausea 1.34%
  - ◆ Headache 1.04%
  - ◆ Diarrhea 0.89%
  - ◆ Back Pain 0.75%
  - ◆ Vomiting 0.60%

## Ferumoxytol and Cancer Publications 1981 – 2016



From a PubMed search "ferumoxytol" and "cancer"



### Summary

Potential clinical value of ferumoxytol in brain MRI

- ◇ Alternative to gadolinium
  - ◇ For patients with kidney disease
  - ◇ If gadolinium deposition is a concern
- ◇ Supplements gadolinium
  - ◇ To answer specific questions
    - ◇ neuroinflammation
- ◇ Unique intravascular applications
  - ◇ Abnormal vascularity
  - ◇ High resolution blood volume maps

### Take home message

Gadolinium enhanced brain MRI is standard of care, and **additional ferumoxytol may help** to answer specific questions, by improved assessment of **vasculature and inflammation**.

## Blood Brain Barrier Team

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Hossein Mousavi, M.D.

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Rochelle Fu, Ph.D.  
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Emily Youngers



Thank-you  
for your attention!

