OMNISCAN (gadodiamide) a gadolinium-based contrast agent (GBCA) for diagnostic magnetic resonance imaging (MRI)

Medical Imaging Drugs Advisory Committee (MIDAC)

September 8, 2017

Introduction

Mark Hibberd, MD, PhD
Head of Global Medical Services and
Chief Medical Officer, Life Sciences
GE Healthcare

Substantial Data and Decades of Use Support Overall Safe Use of GBCAs and OMNISCAN

- US approval in 1993
- Currently approved in 107 countries with > 100 million doses administered
- Trace amounts of gadolinium (Gd) detected with all GBCAs
  - Adverse findings or clinical effects not causally linked
- More research needed
  - Initiated robust research program to address uncertainties
  - Committed to label changes to support appropriate use
- Different agents allow for choice to best fit patients' needs

Agenda

Introduction	**Mark Hibberd, MD, PhD** Head of Global Medical Services and Chief Medical Officer, Life Sciences GE Healthcare
Safety of GBCAs	**Robert McDonald, MD, PhD** Medical Scientist and Neuroradiologist Mayo Clinic at Rochester, Minnesota
Risk Mitigation	**Mark Hibberd, MD, PhD**

Safety of GBCAs

Robert McDonald, MD, PhD
Medical Scientist and Neuroradiologist
Mayo Clinic at Rochester, Minnesota

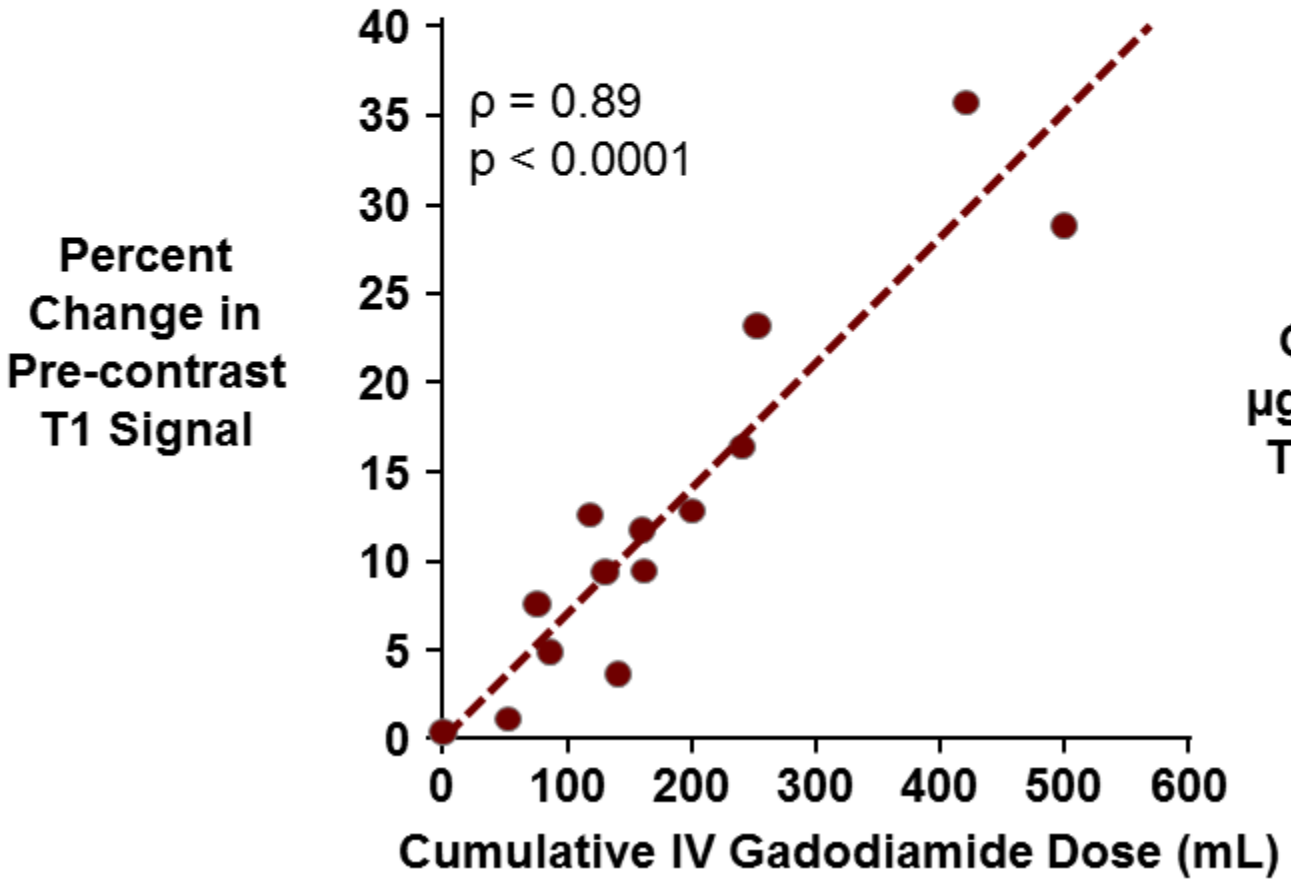
Financial Disclosures

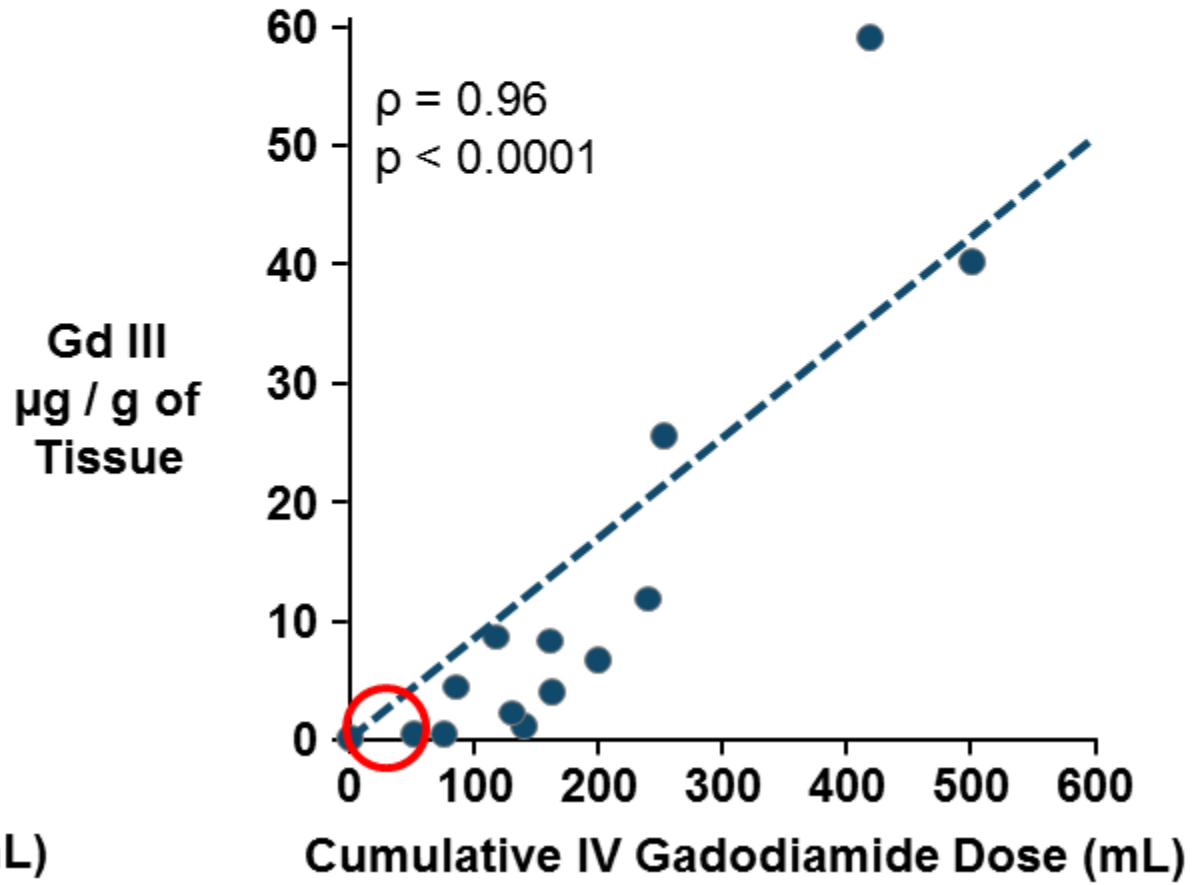
- Consultant to GE Healthcare
- Research funding from GE Healthcare and Bayer
- Previous consultant to Bracco and Guerbet
- No financial stake in companies or outcome of meeting

Spectrometry Shows Dose Dependent Gadolinium Retention in Brain

Dentate

$\rho_{MRI:ICP-MS} = 0.93, p<0.0001$



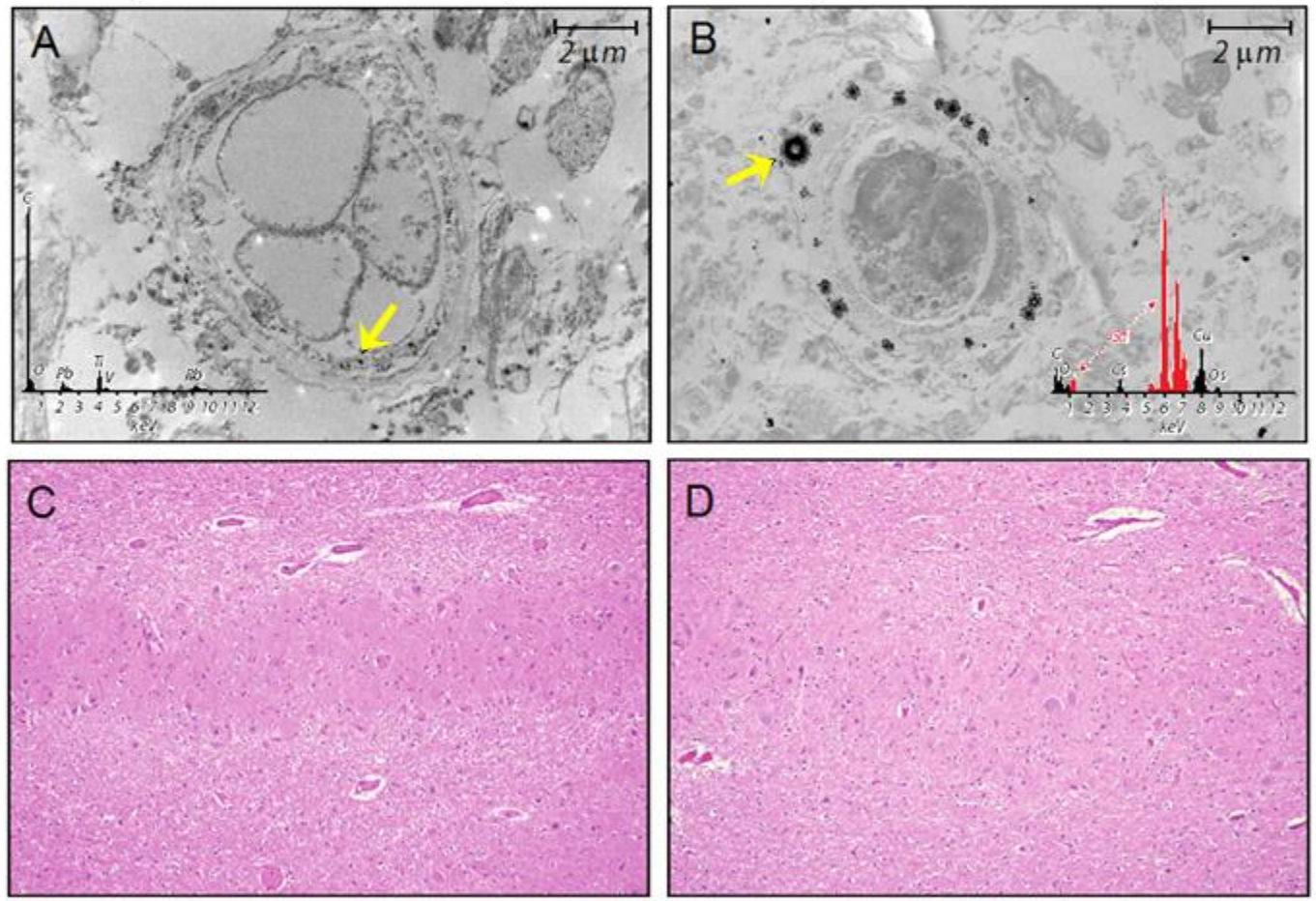


Adapted from McDonald et al. Radiology, 2015.

No Observed Histological Evidence of Injury to Neural Tissues

Control Patient
(0 doses of GBCA)

Gadolinium Exposed Patient
(29 GBCA doses)



Electron Microscopy

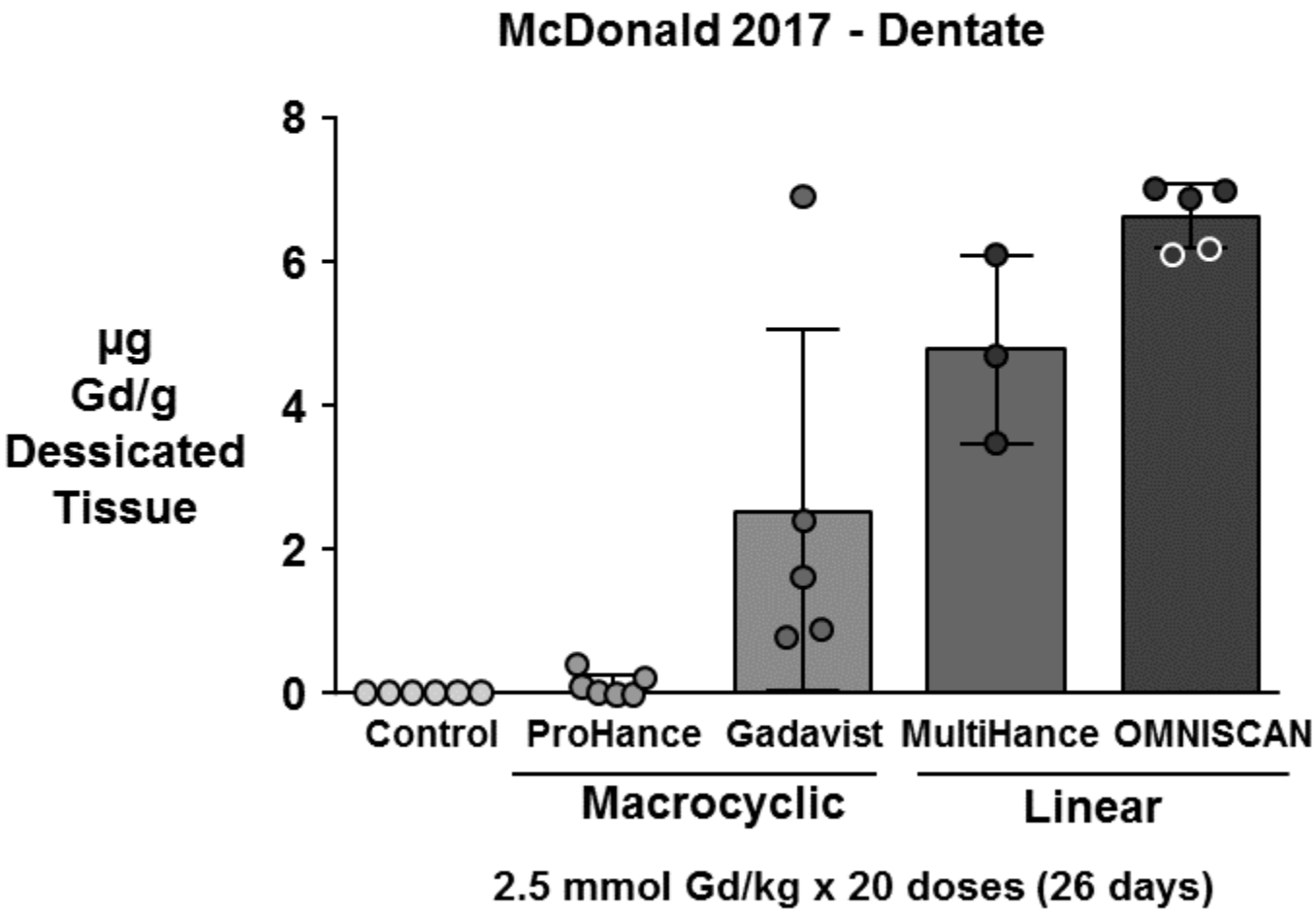
- Gd foci predominantly cluster within endothelial wall
- Gd not detected in control patients

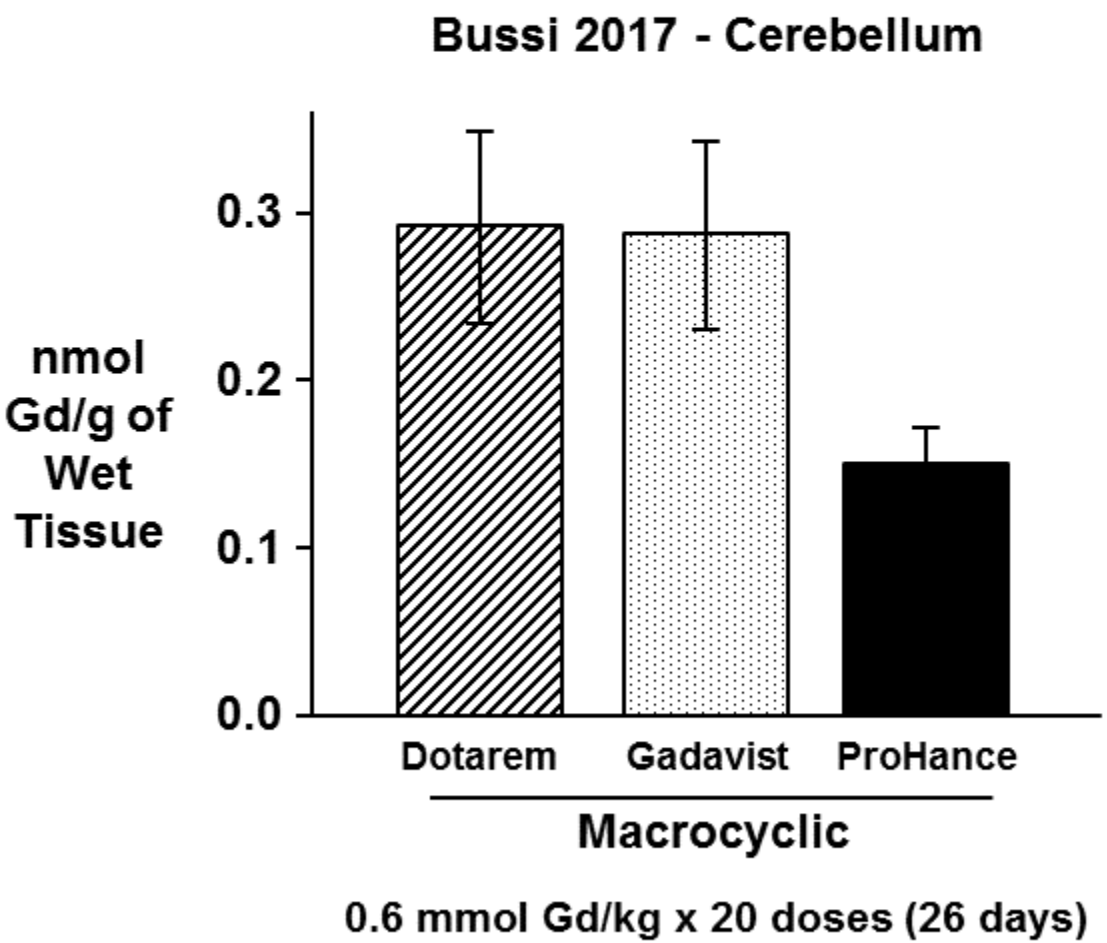
Light Microscopy

- No evidence of histopathological changes in Gd-exposed patients

Adapted from McDonald et al. Radiology, 2015.

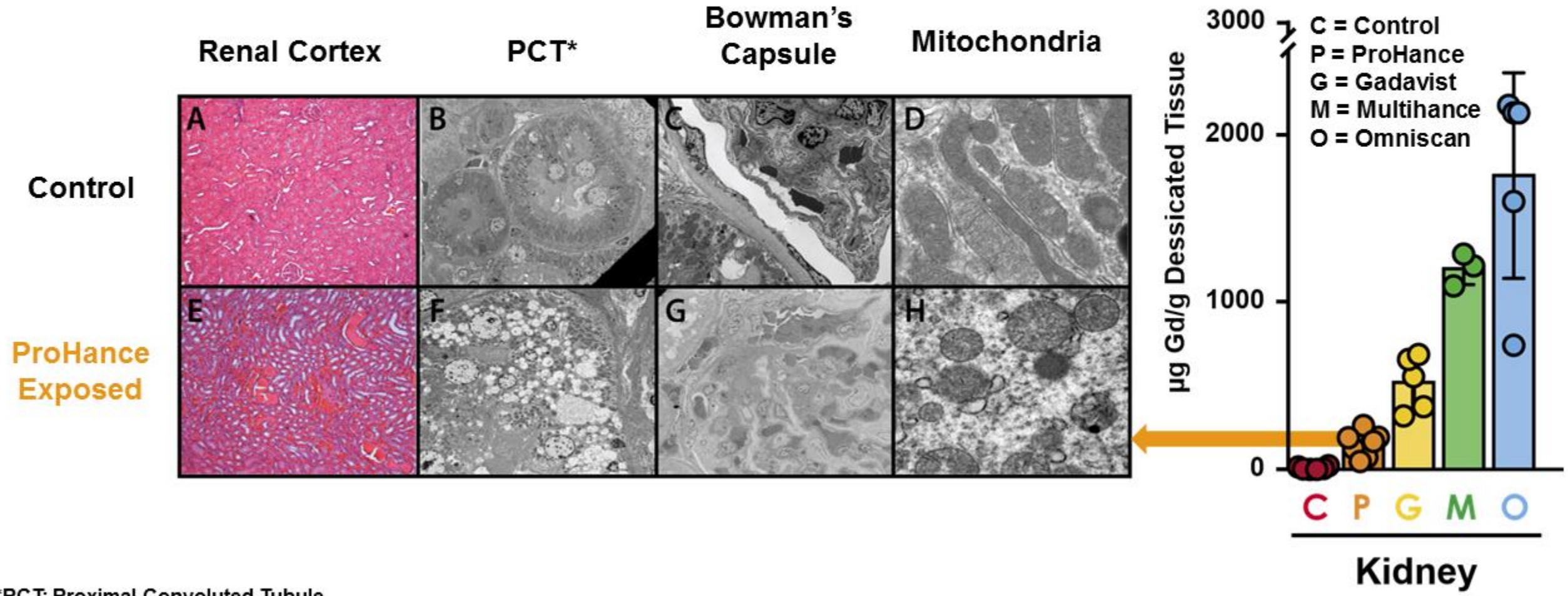
Nonclinical Evidence that Gadolinium Retention in Brain Occurs with Macrocyclic and Linear GBCAs





McDonald et al. Radiology, 2017. Bussi et al. JMRI, 2017.

Gadolinium Levels Not Predictive of Renal Toxicity



*PCT: Proximal Convoluted Tubule
McDonald et al. Radiology, 2017.

Studies Do Not Show Harm from Gadolinium Exposure in Brain

Study Type	Study	Number of Subjects Total / Exposed	Dose range	Observation time	Endpoint
Animal	Smith 2017	42 / 30	20 HED	Up to 6 months	Histopathology
	Marino, in prep	42 / 30	20 HED	Up to 1 year	Histopathology + EM
	McDonald 2017	25 / 19	80 HED	5 weeks	Histopathology + EM
	Lohrke 2017	50 / 40	80 HED	12 weeks	Histopathology + EM
Clinical	McDonald 2015	23 / 13	1 to 29 doses	Up to 9.7 years	Histopathology
	McDonald 2017 (peds)	6 / 3	4 to 9 doses	Up to 9 months	Histopathology
	Cao 2016	76 / 25	1 to 2 doses	1 month	Number of clinical issues post/post-Gd
	Welk 2016	246,557 / 99,739	97.5% <4 doses 2.5% ≥4 doses	Mean 4 years	Incidence of parkinsonism
	Mayo Aging Study	4261 / 1315	1 to 28 doses	Median 5.5 years	Neurological function

HED: Human Equivalent Dose

Welk 2016: No Significant Association Between Gadolinium Exposure and Risk of Parkinsonism

Primary Analysis (N=264,557)	Gd Naïve Control Population (N=146,818)	Exposed to Gd-enhanced MRIs	
		≥ 1 MRI (N=99,739)	≥ 4 MRIs (N=2,446)
Incidence of Parkinsonism	**1.16%**	**1.17%**	**0.70%**
Rate (95% CI)	**2.71** (2.59-2.84)	**3.17** (2.99-3.36)	**2.56** (1.54-4.02)
Adjusted HR: per Additional Dose (95% CI); p-value	**1.04** (0.98-1.09); p=0.18		
Unadjusted HR: per Additional Dose (95% CI); p-value	**1.08** (1.04-1.13); p<0.001		

Welk et al, JAMA. 2016.

Mayo Clinic Aging Study: Large, Ongoing, Prospective, Observational Study

- Endpoints
  - Cognitive and neurological assessments
- Retrospective analysis of OMNISCAN exposure
  - OMNISCAN exposed cohort (N=1,315)
    - Range: 1 to 28 doses (Mean: 3.0 doses)
    - 44% had 5 or more doses
  - Matched GBCA naive cohort (N=2,946)
- Observation time ~ 5 years

McDonald et al, in preparation, abstract accepted. RSNA, 2017.

Mayo Clinic Aging Study: OMNISCAN Exposure No Effect on Clinical Neurologic Outcomes

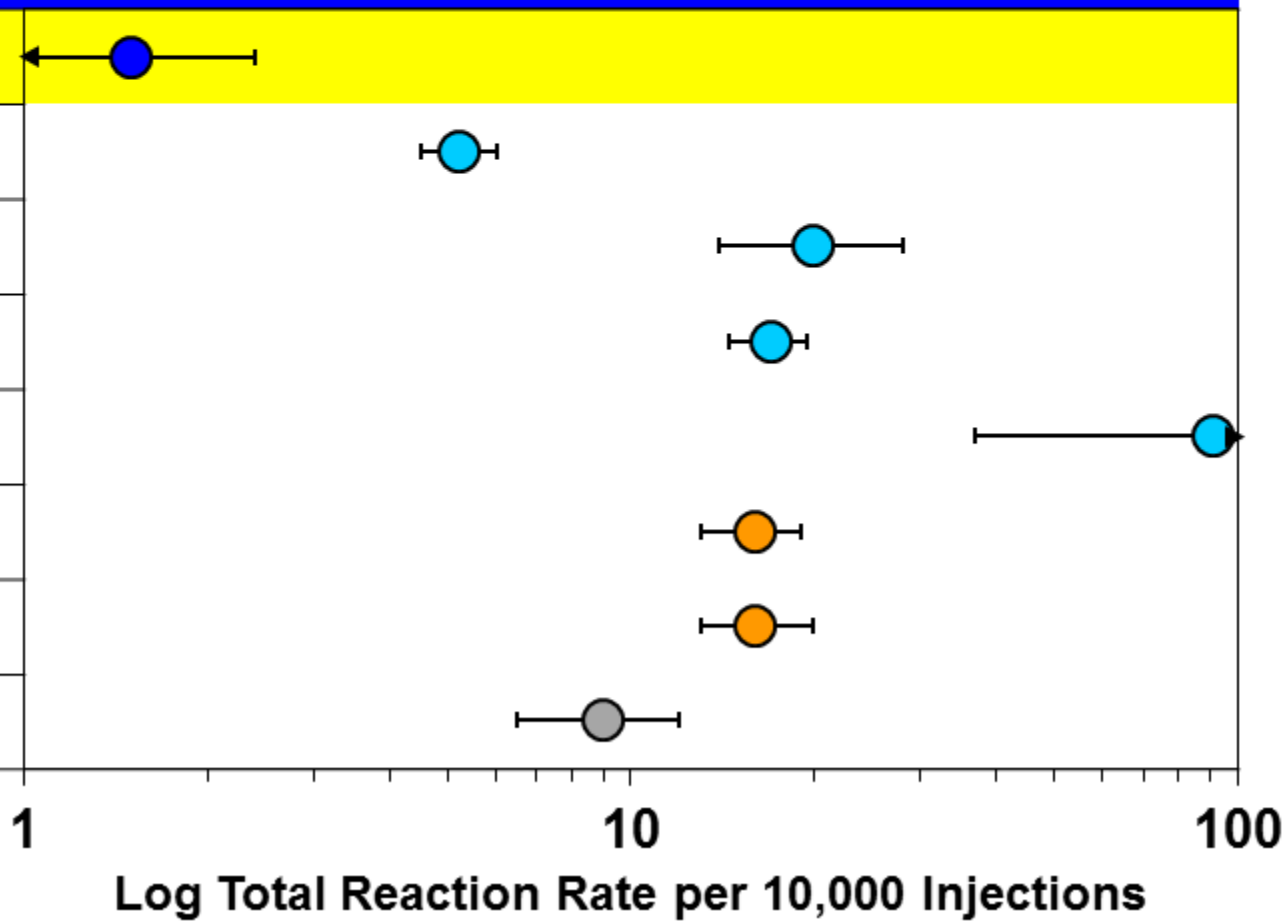
Neurologic Outcomes	Odds Ratio (95% CI)	p-value
Mini-mental status exam	0.95 (0.89-1.04)	.16
Memory Z score	1.04 (0.97-1.12)	.58
Language Z score	1.01 (0.98-1.05)	.96
Attention Z score	0.97 (0.92-1.02)	.79
Visual Z score	1.02 (0.98-1.05)	.80
UPDRS score	1.01 (0.96-1.07)	.22

No effect of exposure, nor any dose-response relationship observed

McDonald et al, in preparation, abstract accepted. RSNA, 2017.

OMNISCAN Associated with Significantly Lower Allergic Reaction Rate Across Entire GBCA Class

Subclass	Trade Name
Linear non-ionic	OMNISCAN
Linear ionic	Magnevist
Linear ionic	Eovist
Linear ionic	MultiHance
Linear ionic	Ablavar
Macrocyclic non-ionic	Gadavist
Macrocyclic non-ionic	ProHance
Macrocyclic ionic	Dotarem



Adapted from Behzadi et al. Radiology, 2017.

Lowest Hypersensitivity-Related Mortality Risk with Linear, Non-Ionic Agents

Subclass	Trade Name	Number Doses (Millions)	Events	Events per Million	Deaths	Deaths per Million
Linear non-ionic	OMNISCAN	13.5	63	4.7	2	0.15
Linear non-ionic	OptiMARK	5.4	45	8.3	1	0.19
Linear ionic	Magnevist	26	1616	62	25	0.97
Linear ionic	Eovist	-	14	-	0	-
Linear ionic	MultiHance	3.4	1097	322	9	2.7
Macrocyclic non-ionic	ProHance	2.8	139	49	2	0.70

Prince, et al. AJR, 2011.
Time Period 2004-2009; Excluding nephrogenic systemic fibrosis (NSF)

Summary

- Preclinical studies show no evidence of acute or chronic brain toxicity
- Further research required to address uncertainties
  - Chemical form, mechanism, biological activity, and potential clinical significance of retained gadolinium
- Hypersensitivity reactions significantly lower with OMNISCAN
- 300-400 million doses of GBCAs without systematic evidence of retention-related toxicity while helping millions of people

Risk Mitigation and Conclusion

Mark Hibberd, MD, PhD
Head of Global Medical Services and
Chief Medical Officer, Life Sciences
GE Healthcare

Risk Management Plan Overview

- Intensified monitoring of adverse reactions
  - Delayed, persistent events and all with potential relationship to Gd retention
  - Reviewed weekly by multidisciplinary Task Force and monthly by Safety Management Team
- Labeling changes
  - Up to date scientific evidence for Gd retention
  - Appropriate use and dosing
  - DHCP letter
- Clinical and nonclinical research program

Clinical Research Program to Address Uncertainties Related to Gadolinium Retention

Study	Completion	Study Focus
Data mining / epidemiologic study	Q1 2018	Persistent AEs involving neurological, musculoskeletal, skin and pain symptoms
Human brain autopsy	Q2 2018	Gd tissue morphology in linear and macrocyclic agents
GBCA neuro analysis	Q4 2017	Neurological function and cognitive impairment
Breast cancer study	Q4 2017 (protocol draft)	Neurological function following frequent GBCA exposure
Long-term effects study ALS-Gd64	Q2 2018	Potential long-term retention of Gd in bones

Nonclinical Program to Address Uncertainties Related to Gadolinium Retention

Study	Status	Study Focus
Clearance / tissue effects in rat brain	Complete	Long-term kinetics of Gd in rat brain and potential toxicity
Rat behavior	Q2 2018	Long-term presence of Gd in rat brain and potential effects on behavior and neurological function
Rat brain Gd localization	Q2 2018	Regional distribution and kinetics of Gd in the rat brain following GBCA (linear and macrocyclic)
Gd form methodology	Q3 2018	Exploration of methods to study chemical form
Electrophysiology rat brain ex vivo	Q3 2018	Investigation of functional effects on axonal and synaptic transmission ex vivo
Kinetics in multiple rat tissues - single dose	Q2 2018	Understand how Gd levels in multiple rat tissues change with time using the sensitive ICP-MS method

Scientific Evidence Supports Safe Use of OMNISCAN

- No causally-related AEs from long-term retention of low levels of Gd in linear and macrocyclic agents
- Committed to research and working with FDA, patient groups and all manufacturers to better understand unknowns
- All AEs should be considered
  - Lowest rate of acute hypersensitivity reactions with OMNISCAN

OMNISCAN (gadodiamide) a gadolinium-based contrast agent (GBCA) for diagnostic magnetic resonance imaging (MRI)

Medical Imaging Drugs Advisory Committee (MIDAC)

September 8, 2017