Contrast-Enhanced MRI: validating the truth

This article summarizes the proceedings of the recent symposium on Contrast-Enhanced MRI sponsored by Bracco Imaging at the recent ECR 2020 virtual meeting. Chaired by Prof. L. Marti-Bonmati, the symposium featured presentations by three renowned experts who discussed 1) the status of gadolinium retention in 2020; 2) how daily clinical practice has been changed and 3) how and when Artificial Intelligence imight mpact MRI.

Gadolinium retention in 2020 — what we know, what we don't know and what we may never know

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The aim of Dr. Spinazzi's talk was to summarize the available scientific evidence regarding gadolinium (Gd) retention following exposure to Gadolinium-Based Contrast Agents (GBCAs) and to discuss if and how ongoing or future research may fill some of the gaps in the current knowledge base

Gd retention in brain and body tissues following single and multiple exposure to GBCAs has been investigated in animals and humans. It is indisputable that chemical forms containing Gd are retained in brain and body tissues after administration of all GBCAs, even if in trace amounts, as determined by the most reliable and relevant studies which directly measured tissue Gd concentrations using inductively coupled plasma mass spectrometry (ICP-MS), an elemental analysis technology capable of detecting most of the periodic table of elements at nanogram levels per liter.. [*McDonald et al. Radiology 2018; 289: 517-534*]

As far as Gd retention in the brain is concerned, both experimental animal studies and post-mortem studies in humans showed that the intravenous administration of the macrocyclic GBCA ProHance is associated with the lowest levels of Gd concentrations, often at the limit of quantitation by ICP-MS, and lower than those measured after administration of the other macrocyclic GBCAs. [*McDonald et al., Radiology 2017; 285: 536; Bussi et al. J Magn Reson Imaging 2018; 47:746; Jost et al., Radiology 2019: 290:340; Bussi et al., Pediatr Radiol 2019 49: 1110; Murata et al., Invest Radiol 2016; 51: 447; Murata et al., Magn Reson Imaging 2016; 34: 1359*]. Animal studies also showed that all the macrocyclic GBCAs, Dotarem and Gadovist included, caused significantly lower levels of Gd retention compared with the linear GBCAs. [*Robert P et al. Invest Radiol 2015; 50: 473; Robert P et al. Invest Radiol 2016; 51:73; Lohrke et al. Invest Radiol 2017; 52: 324; Frenzel et al., Invest Radiol 2017; 52: 396; McDonald R et al, Radiology 2017; 285: 536; Smith AP et al. Radiology 2017; 282; Jost G et al. Radiology 2019; 290: 340]*. However, preliminary data from post-mortem, tissue-sample studies in man do not show a clear demarcation between Gd levels retained after exposure to the macrocyclic agent Gadovist and those following the administration of linear GBCAs. [*Murata et al., Invest Radiol 2016; 51: 447; Murata et al., Magn Reson Imaging 2016; 34: 1359*] Among the linear GBCAs, Omniscan was shown to be associated with the highest brain Gd levels, whereas the lowest Gd levels were observed following administration of MultiHance.

It is commonly believed that the greater the number of exposures to GBCAs, the greater the amount of Gd retained. However, the correlation between extent of exposure and levels of retained Gd has been observed only for Omniscan [*McDonald et al., Radiology 2015; 275: 772-8*] and there are currently few data available to support this theory for all GBCAs.

What is not yet known are the exact chemical forms in which Gd is retained in tissues. ICP-MS is totally unsuitable for speciation purposes as it is a destructive technique that atomizes

Brand name	Chemical name	Structure
Magnevist®	gadopentetate (Gd-DTPA)	linear ionic
MultiHance®	gadobenate (Gd-BOPTA)	linear ionic
Omniscan™	gadodiamide (Gd-DTPA-BMA)	linear nonionic
Dotarem® Clariscan™	gadoterate (Gd-DOTA)	macrocyclic ionic
ProHance®	gadoteridol (Gd-HP-DO3A)	macrocyclic nonionic
Gadavist®	gadobutrol (Gd-BT-DO3A)	macrocyclic nonionic
Eovist® (USA) Primovist®	gadoxetate (Gd-EOB-DTPA)	linear ionic

Brand name, chemical name and structure category of Gadolinium- Based Contrast Agents (GBCAs). It should be noted that there is a difference in the regulatory status of GBCAS between USA and Europe. Linear GBCAs have been withdrawn from the European market, except for gadoxetate and gadobenate which can continue to be used for liver scans. In addition, gadopentetate can continue to be given intra-articularly for joint scans.

the sample and creates atomic and small polyatomic ions, which are then detected. Knowledge of the exact chemical forms in which Gd is retained would be important to assess their biological activity and toxicity, to predict whether they will be ultimately cleared from tissues and eliminated, and the possibility of chelation therapy to remove them from the body. However, this goal might not be achievable as highly sensitive speciation has to separate Gd forms from tissue, requiring tight and possibly too challenging control of a number of variables.

Certainly, there is no "free Gd" in tissues since any Gd dissociated from the chelate immediately forms simple salts (e.g., phosphates or carbonates), insoluble or matrixed entities (eg, hydroxyapatite), or is bound into macromolecular forms. Indeed, use of the term "free Gd" is both inappropriate and misleading since Gd ions cannot exist in a free form in biological systems; the toxicity of free Gd ions is irrelevant while assessing any possible effects of Gd retention in human tissues. [*McDonald et al. Radiology 2018; 289: 517-534*]

The overriding concern today centers on whether retained Gd affects the function of human biological processes or is associated with short- or long-term adverse clinical effects or outcomes. A particularly important concern is whether vulnerable populations such as children, renally impaired subjects or those requiring multiple GBCA administrations, are at greater risk of experiencing adverse health effects. The potential impact of retained Gd is different for brain and extracerebral tissues. Whereas retained Gd in the brain might potentially adversely affect cognitive or motor skills, retained Gd in body tissues might be associated with systemic adverse health effects (e.g. Nephrogenic Systemic Fibrosis, NSF).

Neurotoxicity from retained Gd.

Studies in adult and juvenile animals administered high GBCA doses for weeks did not show any neurological disorders, behavioral abnormalities, physiological dysfunctions, or any other signs of nervous system toxicity. Also, no short- or long-term gross histologic changes have ever been observed in brain tissues, and electron microscopic examination always reveals a regular tissue architecture within the neurons, glial cells, and focally typical cerebellar structure (granular and Purkinje cells), with no ultrastructural abnormalities. [*Robert P et al. Invest Radiol 2015; 50: 473-80; Robert P et al. Invest Radiol 2016; 51:73-82; Lohrke et al. Invest Radiol 2017; 52: 324-33; Frenzel et al., Invest Radiol 2017; 52: 396; McDonald R et al, Radiology 2017; 285: 536-45; Smith AP et al. Radiology 2017; 282:743-51; Bussi S et al. J Magn Reson Imaging. 2018; 47: 746-52; Bussi S et al. Regul Toxicol Pharmacol 2018; 92:268-77; Jost G et al. Radiology 2019; 290: 340-8*]. There has only been one animal study in which prenatal exposure of pregnant BALB/c mice to intravenous gadoterate meglumine or gadodiamide was associated with abnormal behavior and decreased muscle strength in the offspring. [*Khairinisa et al. Invest Radiol 2018; 53: 110-118*]

The United States Food and Drug Administration has requested all the Marketing Authorization Holders to carry out new studies of their GBCAs in pregnant mice to confirm or exclude any possible effect of fetal exposure on brain development. Preliminary results of our studies with MultiHance and ProHance seem to exclude any effect on brain structure and function following prenatal exposure to these GBCAs.

Post-mortem, tissue-sample studies in humans previously exposed to one or more doses of GBCAs could not see gross histologic changes of ultrastructural abnormalities in brain tissues that could be clearly ascribed to the presence of retained Gd, nor statistically significant differences in the number of glial cells and neurons that would suggest reactive changes. [*McDonald et al., Radiology 2015; 275: 772-8; Murata et al., Invest Radiol 2016; 51: 447-53; Murata et al., Magn Reson Imaging 2016; 34: 1359-65; McDonald et al. 2017; 285: 546-554; McDonald et al., JAMA Pediatr 2017; 171: 705-7*]. A large population study excluded an association between exposure to GBCAs, Gd retention in the globi pallidi and development of parkinsonism. [*Welk et al., JAMA 2016; 316: 96-8*]. An analysis of data from a large prospective cohort study (The Mayo Clinic Study of Aging) was recently carried out in a subset of 4261 patients older than 70 years of age (2946 controls and 1315 patients exposed to gadodiamide (742 receiving 4 doses or fewer, and 573 more than 5 doses) with a median follow-up of 5.6 years. Periodic monitoring of cognitive function and motor skills was carried out. It was found that exposure to gadodiamide was not associated with excess cognitive decline or altered motor performance compared to controls. [*Personal communication of Dr. Robert McDonald to the European Authorities and US Food and Drug Administration*]. In another study, 74 patients with remitting-relapsing multiple sclerosis, who had been exposed multiple times to GBCAs and followed up for 3.6 years, did not show changes in the expanded disability status scale associated with development of T1 hyperintensity in the dentate nucleus, taken as indirect sign of Gd deposition. [*Cocozza S et al. Neuroradiology 2019; 61:155-62*]

In summary, the available evidence seems to confirm that brain Gd retention is not associated with harmful effects and potential interaction with neurological disease processes. However, there is need for more evidence to detect or exclude long-term effects of possible Gd neurotoxicity in pediatric patients, in patients who had been exposed to GBCAs 5 times or more in their lifetime, or in patients followed up for more than six years since first exposure to these agents.

To address these latter two points, the FDA has mandated that all US manufacturers of GBCAs carry out a further, prospective study. This study will be a prospective, three - arm clinical study involving neurologically normal adult patients who need multiple contrast enhanced examinations. Patients in the first arm will receive five or more injections of macrocyclic contrast agent while patients in the second arm will receive five or more injections of linear contrast agent. Matched patients in the control arm will not receive contrast agent and will have no history of having received any contrast agent. The patients will be monitored by neurocognitive and motor skills testing as well as by clinical imaging examination. Assays for Gd and other analytes will be carried out in blood and urine.

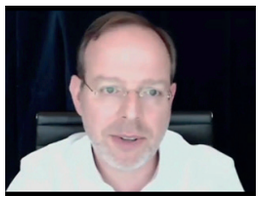
CONCLUSIONS

- Exposure to GBCAs is associated with Gd retention in brain and other tissues (skin, bone, kidney)
- Gd retention is observed in every patient exposed to linear or macrocyclic GBCAs, even after single administration.
- Retained Gd levels depend on the individual GBCA, the interval

between administrations, individual organs, and possibly the cumulative dose of GBCA.
• The chemical form (speciation) of retained Gd is still unknown, as well as how it may change over time in the different tissues.
• NSF is the only adverse event known to be associated with exposure to certain linear GBCAs in a specific patient population, namely patients with severe renal insufficiency.
• So far, apart from NSF, Gd retention has not been associated with any damage of involved tissues nor adverse health effects.
• The US FDA is addressing the most relevant knowledge gaps and is asking companies to perform specific animal and clinical studies.

GBCA use in 2020 - how has daily practice been affected?

Prof. Tim Leiner



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Prof Leiner's presentation covered three areas :
• A general overview of MR contrast agents
• Safety considerations — a 2020 update
• New developments

GENERAL OVERVIEW OF CURRENT GBCAs

Noting in passing that there were many publications describing non-gadolinium-based agents, Prof Leiner focussed his overview only on commercially available GBCAs. From the point of view of chemical structure these exist in three different chemical categories, the simple linear, the substituted linear and the macrocyclic. All of these agents have a similar half-life of 1-2 hours in serum. The intravascular half-life is also similar and all agents are in principle eliminated through the kidneys (with the substituted linear agents also being eliminated through the bile).

The GBCA field has been struck by two tsunami-like shocks:
• The first was Nephrogenic Systemic Fibrosis (NSF) originally described in 2006, which ultimately led to the contraindication of the simple linear GBCAs (Magnevist, Omniscan, OptiMARK) in patients with severe renal impairment.
•The second tsunami has been Gd retention. Although it has long been known that Gd is retained in bone after GBCA administration, the demonstration in 2014 of hyperintensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images possibly suggestive of Gd retention, ultimately led to the suspension of the simple linear GBCAs. for clinical use in Europe. Conversely, the substituted linear agents MultiHance and Primovist are available for liver indications only.

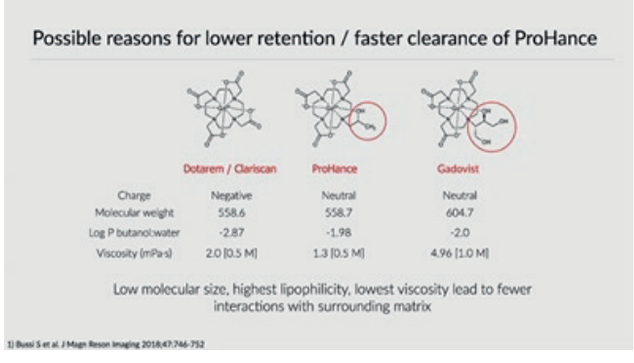
Relaxivity.
The various GBCAs have different relaxivities. However, the minimal differences in relaxivity among the macrocyclic agents do not translate into differences in the detectability of disease nor in clinical decision-making. Several studies comparing ProHance, Dotarem and Gadovist have failed to find any differences in either diagnostic efficacy or safety suggesting that these agents are essentially interchangeable for routine clinical use,

"... it is important never to deny a patient a CE-MRI examination that is clinically indicated. CE-MRI provides greater diagnostic information than alternative techniques across a wide range of indications..."

SAFETY CONSIDERATIONS IN 2020

The two most relevant sources of current information on GBCA safety are the American College of Radiology manual on Contrast Media and the ESUR guide on Contrast Agents. These publications are regularly updated and contain the most recent guidance on NSF and gadolinium retention.
Before addressing the impact of NSF and Gd retention on current clinical practice, Prof. Leiner emphasized that it is important never to deny a patient a CE-MRI examination that is clinically indicated. CE-MRI provides greater diagnostic information than alternative techniques across a wide range of indications and GBCAs are much safer than iodinated agents used in CT in patients with poor renal function.

As regards safety, there are essentially three areas of concern: Acute reactions, NSF and Gd Retention.
Acute reactions Prof. Leiner didn't elaborate on the issue of acute reactions to GBCAs; the incidence of acute reactions is very low.
NSF. Essentially NSF is no longer an issue. Based on the ACR 2020 guidelines, the GBCAs with the lowest risk for NSF are MultiHance, ProHance, Gadovist and Dotarem (classified as group II agents). A recent meta-analysis of these agents in patients with stage 4 or 5 Chronic Kidney (*Woolen et al. Risk of Nephrogenic Systemic Fibrosis in Patients With Stage 4 or 5 Chronic Kidney Disease Receiving a Group II Gadolinium-Based Contrast Agent: A Systematic Review and Meta-analysis JAMA Intern Med . 2020; 180: 223*) revealed no cases of NSF with any of these agents among 4931 patients included in the study. The conclusion was that "*the harm of withholding group II agents in CKD 4 and 5 may outweigh the risk of NSF*"



Even very slight differences in molecular properties are sufficient to markedly affect GBCA elimination behavior

Prof Leiner agrees with this statement; in his practice in Utrecht, patients with poor renal function and for whom MRI is indicated are given macrocyclic agents.

Gd Retention

Further to Dr. Spinazzi noting that there is no association between Gd retention and any clinical adverse effects Prof Leiner highlighted three studies, namely *McDonald et al, Comparison of Gadolinium Concentrations within Multiple Rat Organs after Intravenous Administration of Linear versus Macrocyclic Gadolinium Chelates. Radiology. 2017; 285: 536*); *Bussi et al. Differences in gadolinium retention after repeated injections of macrocyclic MR contrast agents to rats J Magn Reson Imaging. 2018;47: 746*; *Jost et al. Long-term Excretion of Gadolinium-based Contrast Agents: Linear versus Macrocyclic Agents in an Experimental Rat Model Radiology. 2019; 290: 340*). that show that ProHance is cleared more rapidly than other GBCAs, leading to lower levels of retained Gd in the first weeks and months after administration compared to that seen with other macrocyclic GBCAs. The reasons for this are not known precisely but likely reflect differences in molecular structure, ionicity and viscosity, with ProHance having physico-chemical properties that favor more rapid elimination. This was confirmed by a report which indicated that even very slight differences in molecular properties are sufficient to markedly affect GBCA elimination behavior (*Aime S. Differences in Molecular Structure Markedly Affect GBCA Elimination Behavior. Radiology. 2019; 291: 267*).

NEW DEVELOPMENTS

Advances in MR hardware and pulse sequences

Over the last 10 -15 years there have been several significant advances in MRI, such as a migration to higher field strengths, new pulse sequences, contrast mechanisms, and quantitative image mapping techniques. However probably even more important than these significant developments is that of faster image acquisition which has been made possible by parallel imaging and compressed sensing. A review of the recent innovations in MRI is given in a recent paper (*Börnert & Norris. A half-century of innovation in technology-preparing MRI for the 21st century. Br J Radiol. 2020;93(1111):20200113*). The net result of these innovations is that very low doses of contrast can now be used satisfactorily. For example in MR angiography a half of the usual single dose for 1 FOV is now considered as standard (0.05 mmol/kg) Even in peripheral vascular imaging which typically used to involve double or triple doses, ultra low-doses, e.g. 9 mL ProHance – 0.05 mmol/kg are increasingly commonplace.

Artificial Intelligence

AI is a vital, powerful and interesting innovation. As a general observation prior to Dr. Kuhn's presentation, Prof. Leiner pointed out that the potential of AI is not just limited to image reconstruction and image quality but can also be applied in fields such as indication and patient scheduling, the acquisition process itself, segmentation and quantification, classification reporting and even the establishment of possible prognoses.

TAKE-HOME POINTS

- Clinically indicated CE-MRI examinations should never be withheld.
- There are no validated alternatives for GBCAs.
- NSF is essentially an issue of the past and no harmful effects have yet been associated with Gd retention.
- Hardware advances are facilitating the trend towards lower dose imaging.
- Developments in AI will have significant impact in many aspects of the whole MRI examination process.

Beyond 2020: How and when will Artificial Intelligence impact MRI?

Dr. Matthew J. Kuhn

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Acknowledging that there are literally dozens of AI-based applications available that can increase the benefit of contrast-enhanced MRI, Dr. Kuhn's talk focussed on two particular AI tools which address Gd retention concerns:

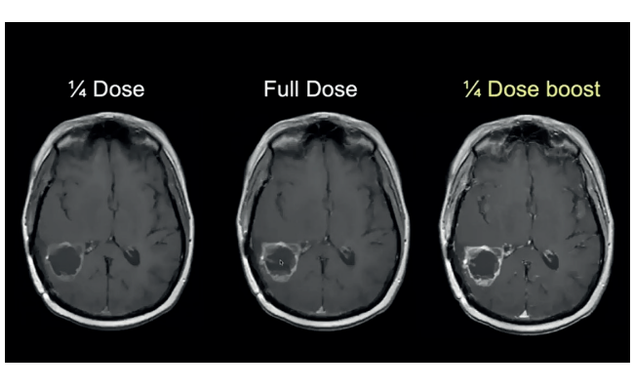
- A gadolinium dose management tool which allows synthetic image enhancement and so enables reduction of the Gd dose.
- Quantitative enhancement analysis which is an AI tool comparing the clinical efficacy of different GBCAs.

Gadolinium Dose Management — Synthetic Enhancement.

This software allows the use of low-dose gadolinium to create images which can then be processed by AI algorithms to result in images whose quality is equivalent to those of full-dose, double or even triple dose images. The technology behind this apparently magical performance is the use of genetic algorithms covering: proprietary registration; intensity normalization; bias field correction; scaling and significant region detection.

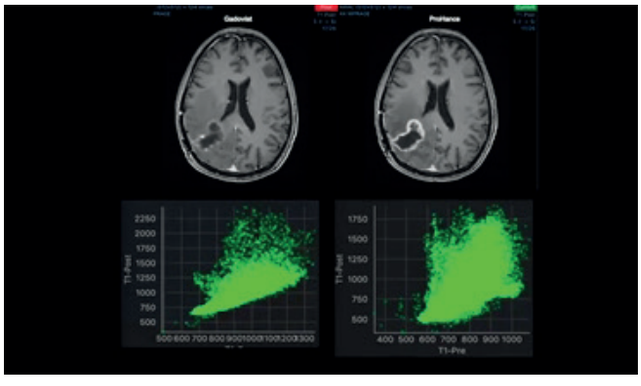
In practice, the degree of enhancement is easily controlled by the reader though use of a simple slider.

The reliability and robustness of synthetic enhancement software means that one quarter dose gadolinium may soon be considered a new standard. Lesions enhance as well or better than full dose GBCA, with acceptable background noise and artifact level. In time, even 1/10th dose may be adequate for synthetic enhancement, but this will require changes in pulse sequences and pre-processing design modifications. As always the increased signal strength from a higher field strength magnet and higher relaxivity



Through use of a simple slider control the enhancement of the image can be increased. Above is a glioblastoma case: the right panel shows that, after synthetic enhancement of a quarter dose image, (left panel)the image quality is equivalent to or better than that obtained with a full dose (central panel).

of the GBCA are beneficial to the synthetic enhancement process. By enabling reductions in gadolinium dosage, synthetic enhancement has particular clinical applications in vulnerable populations, such as pregnant women, pediatrics, women with BRCA gene mutations requiring annual breast MRI examinations and in patients with renal insufficiency. Synthetic enhancement is also extremely valuable in cases where background noise is less important, such as intra-operative MRI, in cases of multiple sclerosis (MS) and in extra-axial tumor follow-up. In intra-operative MRI, multiple administrations of low-dose gadolinium can show the amount of residual and enhancing brain tumor as the operation proceeds, allowing for optimal resection of the tumor and sparing of normal tissue. Contrast enhancing MS plaques are surrogates of biological activity and have a strong influence on treatment selection. The location of the plaques is already known from T2 and FLAIR images and increased noise from uninvolved parts of the brain is therefore unimportant. Extra-axial tumors, such as schwannomas do not actually require full-dose contrast since they do not involve the blood-brain barrier. Despite this, such tumors are often followed up for years using standard GBCA doses so the cumulative life-time gadolinium dose can be quite large. The synthetic enhancement AI tool allowing 1/10th gadolinium dose could significantly reduce the lifetime dose.

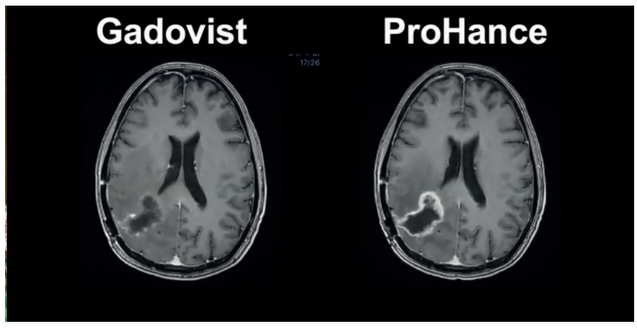


The Quantitative Enhancement Analysis software allows comparion of the clinical efficacy of GBCAs

Quantitative Enhancement Analysis — GBCA Comparison studies.

AI-derived algorithms can also assist in assessing which GBCA results in the lowest retention of Gd and if there are any losses in clinical efficacy resulting from the choice of a lower-retention agent. Quantitative enhancement analysis is one such AI derived algorithm which provides comprehensive, authoritative, quantitative and 100% reproducible outputs on the comparison of macrocyclic GBCAs. As mentioned earlier, in 2017, McDonald and colleagues showed in a rat model that there was less Gd retention when macrocyclic chelates were administered than with linear chelates (*McDonald et al, Comparison of Gadolinium Concentrations within Multiple Rat Organs after Intravenous Administration of Linear versus Macrocyclic Gadolinium Chelates. Radiology. 2017; 285: 536*). The article went on to show that ProHance had the lowest retention among the macrocyclics, a finding confirmed by Bussi *et al.* in studies published in 2018 and 2020 that compared all three macrocyclic agents (*Bussi S et al. Differences in gadolinium retention after repeated injections of macrocyclic MR contrast agents to rats J Magn Reson Imaging. 2018;47: 746; Bussi S, Coppo A, Celeste R, et al. Macrocyclic MR contrast agents: evaluation of multiple-organ gadolinium retention in healthy rats. Insights Imaging. 2020; 11:11.)*

The level of retained Gd was lower in the brains, kidneys and other organs after cumulative administration of ProHance than after similar cumulative administrations of Gadovist and Dotarem. The efficacy of these three GBCAs is essentially similar. In the TRUTH study published in 2015 (*Maravilla et al. Are there differences between macrocyclic gadolinium contrast agents for brain tumor imaging? Results of a multicenter intraindividual crossover comparison of gadobutrol with gadoteridol (the TRUTH study) Am. J Neuroradiol. 2015; 36: 14*), Maravilla *et al.* showed specifically that ProHance and Gadovist have equivalent diagnostic performance despite the 2-fold higher concentration of Gadovist. However, the findings were based on subjective reader analysis and the subjective placing of regions-of-interest for quantitative analysis. Evaluation of 32 patients with glioma from the TRUTH study using Quantitative Enhancement Analysis confirmed the equivalence of these two GBCAs in terms of diagnostic accuracy. The software measured the enhancement in each voxel of the tumor in a fully objective manner and automatically rated the degree of enhancement on a scale of 0 -1.0 per voxel and the change in enhancement from the unenhanced image to the post-enhanced image on a scale of -1.0 to +1.0 A region of interest volume was semi-automatically created for the volumes in the tumor. Color-coded change maps were generated showing increases in enhancements in yellow and decreased enhancements in purple. A scatter chart was created for each GBCA with the x-axis showing the unenhanced image and the y-axis the post-enhanced image. Each of the post-enhanced voxels was assigned an enhancement value; collectively this was multiplied by the number of voxels in the tumor to create an enhancement volume. In the majority of cases there was no statistically significant difference in enhancement characteristics between the standard concentration of ProHance and the double concentration of Gadovist.



In the analysis of images of glioblastoma patients particpating in the TRUTH trial, ProHance was confirmed to be non-inferior to Gadovist in the assessment of glioblastomas despite the differences in Gd retention, concentration, relaxivity, molecular weight and viscosity.

The conclusion of the study was that there was no statistically difference in the evaluation of glioblastomas when using equivalent doses of gadoteridol or gadobutrol, i.e. ProHance was confirmed to be non-inferior to Gadovist in the assessment of glioblastomas despite the differences in retention, concentration, relaxivity, molecular weight and viscosity.