Novel image contrast enables probing tissue microstructure: a potential future for improved patient management in oncology

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A growing body of literature in both pre-clinical studies and preliminary clinical studies has shown that time-dependent diffusion MR has the capability to characterize tumor structure at the microscopic level.[1-11] In gliomas, for example, time-dependent diffusion MR has shown image contrast sensitive to tumoral cellularity and cell size that supports differentiation between high grade gliomas (HGG) from low grade gliomas (LGG) in both animal models and patients.[5, 12] It has further shown to support detection of treatment-induced apoptosis in animal models. Developing these advanced techniques may improve non-invasive assessment of heterogenous lesion types for both pre-surgical and post-treatment oncological evaluation. Such technical advances may improve radiographical differentiation of tumor recurrence from pseudoprogression, one of the most challenging clinical problems.[8] The translation of such advanced MR techniques into clinical use to serve a broad population of patients is highly promising and impactful.

Background

Readers will recall that two key imaging parameters affect image contrasts in diffusion MR: diffusion time and diffusion weighting (i.e., b-value). By changing these parameters, the resulting image contrast can be weighted based on different tissue properties.

An emerging time-dependent diffusion MR technique to probe tissue microstructure leverages a gradient encoding waveform that is characterized with oscillating shapes—a technique known in the literature as Oscillating Gradient Spin Echo (OGSE) diffusion MR. In OGSE diffusion MR, the shortest achievable diffusion time is not limited by the gradient separation due to the refocusing radiofrequency pulse. By changing the oscillating frequency, which is inversely proportional to the diffusion time, there is more flexibility with the diffusion time. This diffusion time can be much shorter than the diffusion time achievable in pulsed gradient spin echo (PGSE) sequences—the current diffusion weighted imaging (DWI) technique in the clinic. With this shorter diffusion time, there is higher sensitivity to molecular movements of water in the restricted space with a small dimension, which allows the probing of tissue microstructure characteristics.

OGSE techniques have previously been implemented in ultra-high field, pre-clinical scanners equipped with high-performance gradients. These scanners allow OGSE to be applied with diffusion times of less than 10 ms, owing to their very high maximum gradient amplitudes of up to 100 G/cm, compared to 4-8 G/cm achievable in current clinical whole-body MR scanners. Recent innovations in gradient coils and gradient power electronic systems advance the development of human high-performance gradient MR scanners, achieving 20-50 G/cm. The hardware innovations largely facilitate the future translation of research findings from pre-clinical studies to human research, and ultimately clinical practice.

Besides the high-performance gradient, two key issues have been emphasized as challenges for clinical translation of OGSE diffusion MR: peripheral nerve stimulation (PNS) and power efficiency. Here, we discuss these challenges and how these are addressed by the

SIGNA™ MAGNUS 3.0T‡ system, a head-only high-performance gradient MR scanner by GE HealthCare.

High PNS threshold is essential to safely apply a high gradient amplitude and a high slew rate simultaneously in human subjects. The high-amplitude and fast-switching oscillating diffusion encoding gradient waveforms require a high PNS threshold to fully leverage the advantage of a high-performance gradient MR scanner. Gradient performance of 30-50 G/cm in a whole-body gradient coil cannot operate at the maximum slew rate of the scanner due to the relatively low PNS threshold. Innovative gradient coil designs, like the head-only gradient coil in the SIGNA MAGNUS system, have three to five times higher PNS threshold compared to whole-body MR gradient coils. Thus, the translation of OGSE diffusion MR to human studies largely benefits from head-only gradient coils and/or PNS-optimized coils.

Furthermore, the increased gradient performance necessary to achieve OGSE gradient waveforms is directly proportional to electrical and power requirements. These, in turn, are tied to the gradient coil size. The 18-20 cm gradient coil diameter of a typical animal scanner allows it to generate high gradient performance relatively efficiently in terms of electrical power. This is due to the relationship between gradient coil diameter, d, and required electrical power, W, such that:

$$W \sim \frac{1}{d^5}$$

The challenge lies in scaling up for human scans. When scaling the same gradient performance to that of a whole-body scanner, a 60 cm gradient coil would require 243 times the power, which is not a practical design consideration. SIGNA MAGNUS balances this constraint by delivering an asymmetric gradient coil with a 42 cm diameter, thus dramatically reducing the increase in required power and achieving a reasonable design output.

At GE HealthCare, OGSE diffusion MR has been implemented in a new application called ODEN‡‡ (Oscillating Diffusion Encoding). ODEN is very flexible in that the user can change diffusion times by selecting a broad range of OGSE frequencies to achieve short diffusion times while specifying a desired high b-value. Thus, different image contrasts that are sensitive and specific to different tissue microstructure can be formulated.

Expectations

Pre-clinical scanners have already demonstrated that ODEN has the ability to perform tissue microstructure characterization—where histopathology ground truths were comparable to MR-based measurements in terms of cell size and cellularity. These are very important imaging biomarkers for tumor grading and the evaluation of tumor aggressiveness, as well as prediction of therapy outcomes.

Based on this prior evidence, we started a preliminary patient study of ODEN in oncology, specifically gliomas, which is one of the most aggressive tumor types in the adult and pediatric human brain.

In oncology, a key challenge with conventional imaging is the ability to differentiate between recurrent tumor and non-tumoral lesions. For example, in post-treatment imaging of gliomas, it can

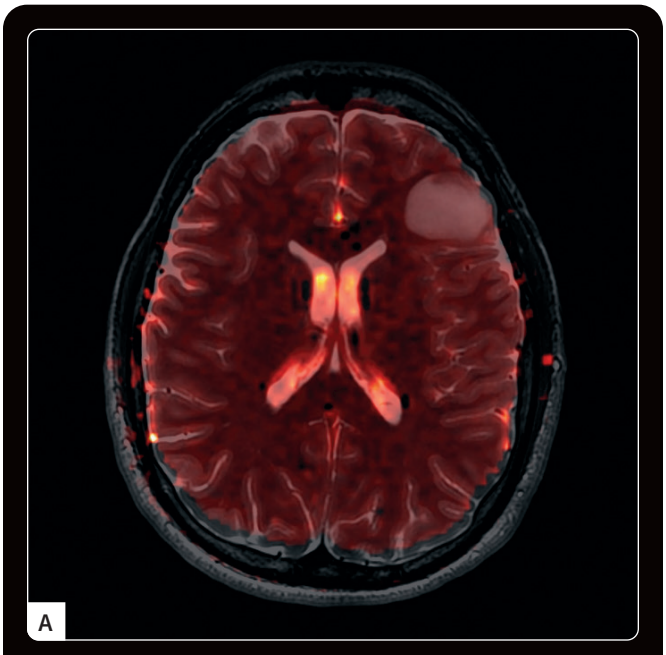

Figure 1. Time-dependent diffusivity (ODEN) data fused with T2 PROPELLER image in a patient with biopsy-confirmed WHO Grade II Astrocytoma. ODEN data represents the ratio of 100 Hz OGSE signal to PGSE signal.

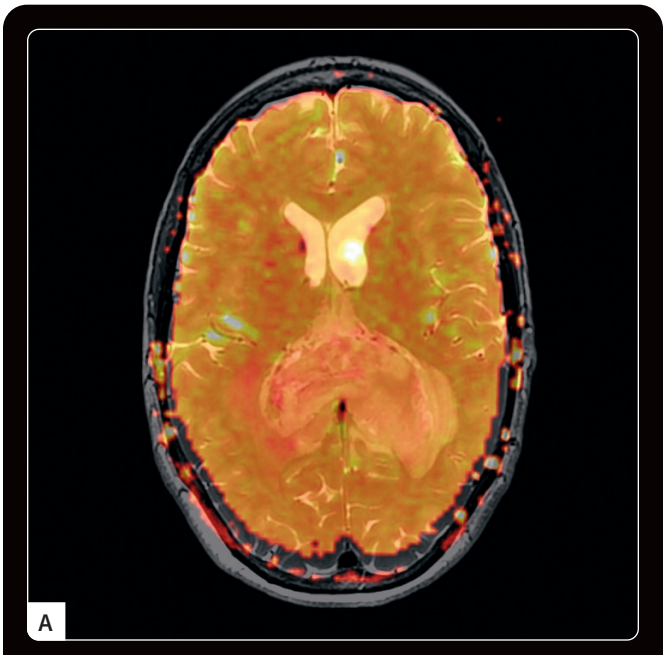

Figure 2. Time-dependent diffusivity (ODEN) data fused with T2 PROPELLER image in a patient with biopsy-confirmed WHO Grade IV Glioblastoma. ODEN data represents the ratio of 100 Hz OGSE signal to PGSE signal.

‡ SIGNA MAGNUS is 510(k) cleared with the US FDA. Not yet CE Marked. Not available for sale in all regions.
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be difficult for clinicians to determine tumor recurrence versus pseudoprogression using contrast-enhanced T1-weighted, T2 FLAIR or conventional DWI with the PGSE encoding. The image contrast and contrast enhancement can be very similar and the apparent diffusion coefficient (ADC) in DWI overlaps between the two patient cohorts. By adding ODEN/OGSE and providing an image contrast that reflects tissue cellularity and cell size observed in histopathology, we may be able to provide more information to clinicians to help them discern the difference between tumor recurrence and pseudoprogression. In an initial study, using ADC from OGSE and ADC from PGSE, we could correlate that iso-intensity areas were likely edema, while high hyperintensity regions were likely tumoral tissue.[8]

In our pilot studies, the new image contrast provided by ODEN was very well-received by clinicians for its potential ability to provide new diagnostic information. The impact of this new image contrast requires further validation in larger population studies that represent the heterogeneity of the disease. If successful, ODEN will play a significant role in radiological-oncological applications, including both the pre-treatment (for surgical planning) and post-treatment (treatment monitoring) workflows.

ODEN is brimming with potential. What has been studied in human OGSE diffusion MR is just the tip of the iceberg. Other exciting areas for translational studies of ODEN in the brain includes the evaluation of stroke and neurodegenerative diseases, where pre-clinical studies have shown promise, for example in evaluating demyelination. ODEN may also enable further study of the underlying biophysics of the human brain. For example, it may be possible to study small microstructures in the brain, along with the water exchange rate in different water pools in the brain. This may provide some unique imaging markers of disease status. In addition, ODEN can also be applied to body applications, especially in body oncology.

In conclusion, the potential clinical translation of ODEN/OGSE diffusion MR is now feasible thanks to MR system innovations. More importantly, it brings to bear novel image contrasts that increase diagnostic information to address clinically significant problems. Novel imaging technologies like ODEN, and the high-performance platforms that enable them, cannot be successfully translated to the clinic without an interdisciplinary team of physicists, engineers, radiologists, surgeons, pathologists, oncologists, bioscientists, computer scientists and more. Together, we can push the envelope of what is possible in novel imaging biomarker technology to improve patient outcomes and quality of life—that is our purpose and our true reward.

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