PROTOCOL TITLE: Validation of a Multi-Parametric Ultra-high Field MRI Protocol for Central Nervous System Malignancy

Principal Investigator: Max Wintermark, MD

Co-Investigators: Maria Gule, MD, Sujit Prabhu, MD, Jason Stafford, MD, Ho-Ling (Anthony) Liu, PhD, Ken Hwang, PhD, Mark Pagel, PhD, Jihong Wang, PhD and Jingfei Ma, PhD; Dawid Schellingerhout, MDMelissa Chen, MD, Frederick Lang, MD, Jeffrey Weinberg, MD, Ping Ho, PhD, Sherise Ferguson, MD, Jing Li, MD, PhD, Vinay Puduvalli, MD, Clifton Fuller, MD, Abdallah Mohamed, MD, John Slopis, MD, Chirag Patel, MD, Leomar Ballester, MD

Statistician: Roland Bassett, Jr. MS.

Outside collaborator:

*Steve H. Fung, MD (Medical Director, MRI Core & Assistant Clinical Member, Research Houston Methodist)

Robert Rostomily, MD (Neurosurgery, Houston Methodist)

****

This is an MD Anderson faculty written and supervised research activity. This project is funded by the Division of Diagnostic Imaging. Only MD Anderson patients will be recruited for enrollment in this study.

The primary research activity (MRI examination) in this study will take place at the Houston Methodist Research Institute.

*Steve H. Fung, MD, is the Medical Director of the MRI Core at the Houston Methodist Research Institute. He will supervise and monitor study activities at the HMRI.

1 OBJECTIVES

1.1 Primary Objectives

1.1.1. To estimate the contrast-to-noise ratio (CNR) for several imaging modalities in brain malignancy as compared with normal brain parenchyma separately by type of malignancy and treatment status. The methods to be studied include Quantitative MRI (T1 and T2 sequencing), Chemical Exchange Saturation Transfer (CEST) MRI, Multiple B-Value Diffusion Imaging (Adv Diff), and Multiple inversion time (TI) arterial spin labeling (ASL) perfusion imaging (Adv ASL).

1.2 Secondary Objective

1.2.1. To assess the conspicuity of each imaging modality to differentiate radiation necrosis from progressive disease.

1.3 Exploratory Objectives

1.3.1 To assess patient experience in the 7T MRI system compared to their most recent MRI examination.

1.3.2 Functional MRI (fMRI) - To assess the typical significance values seen for areas of maximal brain activity associated with each fMRI test.

1.3.3 To assess the geometric distortion of a radiation planning sequence on a ultra-high field (UHF) system.

2 BACKGROUND

This study is seeking to examine a group of advancing imaging techniques in patients with known or suspected brain malignancy to assess whether future clinical and research protocols may benefit from their utilization. These advanced imaging techniques, in a limited number of publications, have shown improvements at 7T over lower field strengths (detailed below). There have additionally been limited applications of these techniques on the Magnetom Terra Siemens 7T system (FDA approved for brain imaging in 2018 and available at the Houston Methodist Research Institute for The University of Texas MD Anderson Cancer Center faculty usage) and specifically related to brain cancer. This study seeks to validate these techniques on this specific system in a population of patients with known or suspected brain cancer.

The majority of all malignancies of the central nervous system can be categorized as either primary brain neoplasms (such as primary brain tumors) and metastatic disease (such as from breast cancer, lung cancer or melanoma). There has been growing recognition of the need for novel, effective therapies for brain malignancies. Vice President Joseph Biden in a January 15, 2016 roundtable at the Abramson Cancer Center stated a goal of catalyzing greater investment, coordination, and collaboration in cancer therapy including a specific focus on advances in the

treatment of glioblastoma. Currently validated treatments for glioblastoma and other central nervous system tumors are few in number and short on proven effectiveness. These treatments are also often toxic, threaten neurological function, and hamper the quality of remaining life. The Brain Tumor Center at the MD Anderson has defined their Glioblastoma Moon Shot goal as an aim for better, safer therapeutics along with quadrupling the five-year survival rate, from 10% to 40% over the next decade. [1]

Despite years of scientific work resulting in thousands of publications, there are limited advanced MR features that have enough validated evidence to support clinical implementation to assist in evaluating tumor response. Techniques including diffusion-weighted imaging (DWI), diffusion tensor imaging, perfusion MRI, and magnetic resonance spectroscopy (MRS) allow tumor assessment at the metabolic and physiologic level, but they have not yet been able to reliably identify tumor volumes or differentiate tumor recurrence from pseudoprogression and radiation necrosis. [2] [3] [4] [5] [6] A significant challenge in the field of MRI has been the ability to meaningfully compare findings across studies and institutions due to wide variability in the image acquisition, post-processing, analysis, and interpretation.

Ultra-high field (UHF) MRI shows promise to improve detection and characterization of brain tumors, preoperative planning for neurosurgical resection, and longitudinal monitoring of the effects of radiation and antibody-based therapies. Addition research revealed that the clinical advantages of 7T magnets, including higher signal-to-noise ratio, higher contrast-to-noise ratio, smaller voxels, and stronger susceptibility contrast, may increase lesion conspicuity, detection and characterization compared to lower field 1.5T and 3T. [7]

2.1 Primary brain tumors

Primary brain tumors are the most common primary brain tumor in the United States, and despite aggressive multimodal therapy with maximum safe resection, radiotherapy in combination with concurrent and adjuvant temozolomide, the median survival of the most aggressive form of primary brain tumor, glioblastoma, in clinical trial populations is **16 months**. There has been an unfortunate stagnation in the ability of non-invasive diagnostics to accurately differentiate between treatment response and failure. Even under optimal circumstances with the use of ‘state of the art' diagnostic and therapeutic interventions, less than 15% of patients will survive five years. [8] [9] [10] While the introduction of temozolomide into the first-line standard of care [11] achieved some survival improvement, nearly all patients relapse and treatment options for recurrent disease remain limited and largely ineffective.

The ability to measure the response to treatment is a critical component in evaluating the efficacy of new therapies. Unfortunately, current diagnostic neuroimaging paradigms fail to evaluate treatment response for glioblastoma reliably. The initial landmark imaging evaluation guidelines – the Macdonald criteria – were established in 1990 and was based solely on the assessment of contrast-enhancement as a surrogate for tumor size. Contrast-enhancement is non-specific and reflects the degree of extravasation of a contrast agent across a disrupted blood-brain: changes in contrast-enhancement may be attributable to real progression, imaging technique, treatment (surgery, radiation, or chemotherapy), steroids and parenchymal changes unrelated to the tumor (postsurgical changes, ischemia, seizures). Particularly with the use of multimodal therapy with radiation and temozolomide and new systemic therapies such as bevacizumab, new radiological

phenomena including pseudoprogression and pseudoresponse have added further complexity to assessing treatment response.

In the context of clinical trials, accurate response assessment is essential. Misclassification of patients may lead to premature discontinuation of an actually effective agent, thereby withholding a potentially active treatment from the patient or inappropriate continuation of an inactive treatment that may have associated toxicities. Moreover, such misclassification may confound the data obtained in such studies and may lead to false conclusions with regards to the efficacy (or safety) of an investigated drug. An effort to address this challenge to accurately evaluate brain tumor response resulted in the formation of the Response Assessment in Neuro-Oncology (RANO) working group. In 2010, this group published updated guidelines for response assessment of high-grade gliomas incorporating additional MRI and clinical considerations, which addressed the recognized and accepted limitations of the Macdonald Criteria. [12]

Advanced imaging techniques that provide added value in the evaluation of primary brain tumors include MRS for detection of a 2-HG peak which identifies patients at harboring an IDH1/2 gene mutation and thus can serve as a non-invasive diagnostic indicator of astrocytoma versus an oligodendroglioma. In a study of MRS at 7T, the ability of 2D L-COSY to unambiguously detect 2HG in addition to other neuro metabolites was demonstrated. [13] 7T MRS has also provided a better detection of major neuronal metabolites when there are overlapping peaks. This is a feat that is often challenging with technology at 3T and 1.5T imaging systems. [14]

2.2 Brain metastasis.

Brain metastases have been reported to occur in up to 30% of patients with cancer, and treatment options include supportive care, surgery, and radiotherapy. [15] The incidence of brain metastases is increasing, partly because of increase in the incidence of primary cancers and partly because improvements in treatment options have prolonged survival of patients with cancer, which increases the chance of primary tumors metastasizing. [16] There are very few chemotherapy options open to patients with brain metastases. Stereotactic radiosurgery (SRS) has become an increasingly important treatment option for the initial management of patients with brain metastases. Early and accurate detection of small metastases is associated with improved treatment success. [17] At present, gadolinium-enhanced MRI is considered to be the imaging technique of choice in patients suspected of brain metastases. [18]

Significant limitations to the utilization of gadolinium-enhanced MRI in the screening for brain metastasis is cost and the requirement of an intravenous injection of a contrast agent. [19] Some patients have claustrophobia requiring sedation. Additionally, underlying conditions, such as back pain, may make it hard for the patients to lie still for the duration of the MRI. Achieving standard-of-care MR imaging in these populations can be challenging. There is a vital clinical necessity for a safe and efficient screening imaging technology to offer patients as risk of brain metastases, who have contraindications to gadolinium as well as the ability to tolerate long examination times. [20]

A comparison of brain malignancy at 7T and 3T revealed that routine contrast doses at 7T provided higher lesion enhancement than the full dose at 3T, which indicates the possibility of

contrast dose reduction at 7T. This could provide particularly useful in pediatric and renal failure populations. (Noebauer-Huhmann, 2015)

This UHF work on patients with multiple sclerosis at 7T revealed the ability of the combination of MP2RAGE (magnetization prepared 2 rapid acquisition gradient echoes) and T2*-weighted imaging at 7T to improve detection of cortical lesions. This work suggests that similar techniques could be used to improve detection of small metastases, including those involving the cortical structures. [21]

2.3 Quantitative MRI

Intensity values on routine MR imaging are not defined in terms of any consistent scale since the signal is dependent on many hardware and patient-specific factors. Hence there is very little gained in measuring the “bright” or “dark” pixel values on an MR image, and the images must be interpreted subjectively. [22] This would be analogous to subjectively describing “hot” or “cold” spots on an infrared heat map image when the absolute temperature scale of the pixels is not known. This study proposes to use multi-parameter mapping to quantitatively measure the signal changes in the tissues to address these challenges. In MR imaging, hydrogen nuclei or "spins" are the sources of the signal. In the strong magnetic field of an MR scanner, these spins emit RF signals in response to transmitted RF pulses. Thus, contrast mechanisms in MR imaging are highly dependent on the hydrogen spin density or proton density (PD), as well as the longitudinal and transverse relaxation times (T1 and T2, respectively), which tend to vary between different tissues or fluids. However, measurement of relaxation times requires multiple acquisitions, and as a result, measurement or quantitation of these parameters can be excessively long for clinical MR exam.

Recent developments in rapid multi-parameter mapping techniques are possible due to advances in accelerated imaging and reconstruction techniques. [22, 23] These typically incorporate efficient pulse sequence designs and mathematical constraints to assess the desired information in each pixel. SyntheticMR developed the first clinically available method and released by GE Healthcare as "MAGIC" (MAGnetic resonance Image Compilation), which can achieve whole-brain quantitation in 5-6 minutes. [24] The SyntheticMR method assumes the process of T1 and T2 relaxation times to be monoexponential, whereas it may be multi-exponential for many tissues. However, a phantom study has revealed good accuracy and reproducibility for T1, T2, and PD measurements by the SyntheticMR method. These measured parameters can also be applied to an MR spin model produce images with almost any contrast weighting by virtually changing repetition time (TR), echo time (TE), and inversion time (TI). 1 Synthetic MRI is particularly useful when many different contrast settings (for example, T1 weighted imaging (WI), T2WI, proton density WI) are required. Synthetic MRI of the brain without the use of a contrast agent has been reported to produce images that although inferior in image quality the diagnostic power of the images was comparable to that of images obtained via conventional MRI sequences. [25] Therefore, if the diagnostic power of images obtained via synthetic MRI after administration of a contrast agent is also proved to be comparable to that of conventional MRI, synthetic MRI could be a useful means of screening for brain metastases, significantly reducing scan time and providing quantitative data. [26]

Multiple investigators have also demonstrated CEST imaging at UHF. These results indicate the potential utility of amide proton transfer (APT) at the high field as a noninvasive biomarker of white matter pathology, providing complementary information to other MRI methods in current clinical use. Also, contrary to results obtained at lower fields, APT imaging at 7T revealed significant contrast between white and gray matters, with a higher APT signal apparent within the white matter. These findings suggest that UHF CEST imaging would be sensitive to alternations in the APT signal related to both malignancies and treatment-related changes. [27]

2.4 Multiple B-Value Diffusion Imaging (Adv Diff)

Molecular diffusion is a stochastic process, and, as such, it may be described by probability distributions. The most basic of these is the probability of a molecule moving a given displacement over a given time interval. For pure, homogeneous liquids (e.g., a glass of water), this displacement probability distribution function is Gaussian, and the diffusion is referred to as Gaussian diffusion. In conventional MR imaging, diffusion of water molecules in the tissues has a tiny contribution to the MR signal. In diffusion MRI, powerful magnetic gradients with an echo-planar sequence are used. Thus, the measurement of the molecular diffusion of water has been possible for decades using MRI, and diffusion-weighted imaging (DWI) with MRI has been possible for greater than thirty years. [28]

A diffusion coefficient called apparent diffusion coefficient (ADC) value can be calculated within each image voxel, and ADC maps can be generated on a pixel-by-pixel basis. Because diffusion coefficients are high in fluids where diffusion is free, a low signal is observed on diffusion imaging at b = 1000 mm2/s (high signal on corresponding ADC maps). Normal CSF is an example of this. On the other hand, if the mobility of water molecules is restricted such as in ischemia (cytotoxic edema) high signal is observed on diffusion imaging at b = 1000 mm2/s (low signal on corresponding ADC maps). [29]

Diffusion-weighted imaging has been proposed as a set of tools to improve diagnostic accuracy and achieve a better understanding of the pathophysiology of brain cancer. A specialized form of DWI is *diffusion tensor imaging* (DTI) that provides information not only about the random displacement, or passive diffusion, of water molecules but also about fiber directionality and integrity. DTI can allow visualization of neuronal projections in the central nervous system and estimation of the neuronal changes in the white matter of healthy subjects and patients with various neurological diseases. [30]

Fractional anisotropy (FA) and mean diffusivity (MD) obtained from diffusion tensor imaging (DTI) has been used to assess the nature of brain metastasis and their response to treatment. However, FA and MD have limitations in accurately evaluating brain metastasis. New technologies, such as *diffusion kurtosis imaging* (DKI), can provide a more informative insight into the biology of tissue, including brain metastasis. [31] An advantage of DKI is that it is relatively simple to implement for human imaging on conventional MRI clinical scanners. DKI protocols differ from DTI protocols in requiring at least three b-values (as compared to 2 b-values for DTI) and at least 15 independent diffusion gradient directions (as compared to 6 for DTI). Typical protocols for brain have b-values of 0, 1000, 2000 s/mm2 with 30 diffusion

directions. The **apparent excess kurtosis coefficient** (AKC) is a dimensionless metric that quantifies the degree of deviation from Gaussian diffusion behavior. [32]

Defining the relationship between DKI and brain metastasis prior, during and following treatment can provide more abundant imaging to guide cancer diagnosis and treatment. [33] DKI has been used to measure the non-Gaussian nature of water diffusion, which can reveal a more complex microstructure in both normal and pathological tissues compared to DTI alone. Previous studies have demonstrated that there was a significant difference in mean kurtosis (MK) value between high- and low-grade astrocytomas. [34] However, to the best of our knowledge, no comparison of different diffusion imaging approaches for assessing brain metastasis has been performed.

Early work on DKI at UHF suggests that it is not only feasible but provides improvements over diffusion imaging at lower field strengths. Researchers have shown that with modern statistical approaches, including an autoregressive model for the inference that ultra-high field functional magnetic resonance imaging is successful. [35] Additional research has shown that UHF DKI is a viable option for imaging tissue change in MS lesions and normal-appearing WM. [36]

2.5 Chemical Exchange Saturation Transfer (CEST) MRI

Chemical exchange saturation transfer (CEST) is a promising new MRI contrast mechanism that has been used in studying the tumor microenvironment through the detection of mobile proteins and peptides. This technique relies on the labeling of endogenous populations of exchanging protons by a radiofrequency pulse at a specific frequency. These pools can transfer their magnetization to the unbound water (through the exchange), the extent of which constitutes the MRI image contrast, and by varying the radiofrequency pulse frequency, a spectrum is generated. In the absence of the CEST effect, this spectrum is generally considered to be symmetric; however, in its presence, the signal is attenuated at specific frequencies, resulting in chemical-specific negative peaks. Two CEST effects apparent in vivo are attributed to protons of mobile proteins: backbone amide signals with their base-catalyzed proton transfer (APT), and nuclear Overhauser enhancement (NOE) mediated aliphatic proton magnetization transfer (so-called exchange-relayed NOE. [45]

MRI based on the chemical exchange saturation transfer (CEST) effect from amine, amide, sulfhydryl, and hydroxyl protons associated with endogenous metabolites has been shown to provide imaging maps of metabolites in tissue noninvasively. [46] Amide proton transfer (APT) imaging has been developed, which detects amide protons of low concentration in endogenous proteins and peptides in tissue. [47] APT has shown promising results in differentiating radiation necrosis from tumor progression in primary brain tumors and necrosis models in rats. [48] APT has also been applied to human primary brain tumor patients to differentiate high-grade tumors from low-grade ones with encouraging results. [49]

Ten glioblastoma patients were studied in this paper which revealed both that CEST imaging was feasible at 7T and also that it appeared to provide superior information to CEST imaging performed at lower field strengths (including 3T). Signal and contrast gained in CEST imaging at

7T have provided new insights into the conceptualization of CEST imaging in brain tumors. Their work also suggests that previous CEST approaches might not have shown pure CEST effects, but rather water relaxation shine-through effects. Their insights help to improve understanding of the CEST effect changes in tumors and correlations on a cellular and molecular level. [45]

2.6 Multiple inversion time (TI) arterial spin labeling (ASL) "Adv ASL" perfusion imaging

Arterial spin labeling (ASL) is an MRI technique that can noninvasively and quantitatively determine cerebral blood flow (CBF) by magnetically labeling the arterial water spins with radiofrequency pulses. [50] This method takes advantage of the fact that water protons of the arterial blood in the feeding vasculature of the brain are magnetically labeled and used as an endogenous tracer. After a specific inversion time, the labeled blood arrives at the image plane in which the image is acquired. In clinical studies, it has been used to assess perfusion in neurodegenerative diseases, epilepsy, central nervous system neoplasms, and vascular malformations. [51] However, a disadvantage of ASL-MRI is that in patients with cerebrovascular disease, the quantification of CBF is hampered by the recruitment of additional blood flow through collateral pathways. [52] These alternative pathways of blood flow lead to delayed arrival of the labeled blood bolus to the brain. [53]

As most ASL-MRI techniques acquire the labeled images at a fixed time after the initial labeling of arterial blood, it is possible that the magnetic label may not have reached the imaging plane, leading to underestimation of CBF. Previous studies reported that tumor-brain blood flow ratios determined by arterial spin-labeling were markedly higher than those obtained with dynamic susceptibility-weighted contrast-enhanced MR imaging. [54] The underestimation of perfusion probably causes this in brain regions with long arterial transit times. The use of higher inversion times would overcome these limitations; however, this would conversely lead to a decrease in the SNR caused by the rapid decay of the ASL perfusion signal over time. Recently, ASL-MRI with the acquisition of a series of images at multiple delay times after the initial labeling has been introduced as a method to compensate for these issues and also demonstrated the ability to differentiate low-grade and high-grade astrocytomas. [55]

The inherently low contrast-to-noise ratio of ASL techniques is substantially improved when scanning at 7T, which allows data to be collected at higher spatial resolution. This work demonstrated the ability to quantify the perfusion of small cortical lesions in MS at 7 Tesla, demonstrating that an optimized ASL acquisition is sensitive to focal hemodynamic pathology. [56]

2.7 Protocol Particular Disease Description

Brain malignancy will be defined as suspected or pathologically proven space-occupying intra-axial lesion. Suspected (not pathologically proven) brain malignancy will require confirmed suspicion from a neurosurgery and neuroradiology collaborator.

3 ELIGIBILITY

3.1 Inclusion Criteria

Patients

- 13 years old and above.
- Written Informed consent must be obtained by the patient (age 13-17)'s parent or legally authorized representative (LAR)
- Patients must meet one set of inclusion criteria:
    - Newly identified and untreated primary brain tumor or metastasis of at least 5 mm or greater in size.
        - Suspected central nervous system neoplasms will require agreement from a study neuroradiologist and a study neurosurgeon, neuro-oncologist, or a radiation oncology that a lesion exists that is most likely either a primary brain tumor or a metastasis.
        - Patients with suspected brain metastasis must also have a history of solid organ malignancy.
    - History of primary brain tumor or metastasis treated with surgery, radiation, chemotherapy, or immunotherapy with new or increasing signal on MR imaging that is suspicious for progressive disease (treatment failure).
        - Suspected recurrent neoplasms will require agreement from a study neuroradiologist and a study neurosurgeon, radiation oncologist, or neuro-oncologist that lesion behavior is suspicious for recurrent disease.

Healthy Volunteers

- Volunteers without history of brain cancer.
- 13 years old and above.
- No pregnant subjects will be enrolled.
- No contraindications to MR exam(s) – healthy volunteers will use the same screening process utilized for MDACC patients.
- Written Informed consent must be obtained by the patient (age 13-17)'s parent or legally authorized representative (LAR)

3.2 Exclusion Criteria

Patients

- Contraindication to MR imaging.
- Absolute or relative contra-indication to 3T MRI due to metallic foreign bodies and devices and/or other conditions that are not MR safe, which include implants with unknown behavior in 3T MRI as well as:
    - electronically, magnetically, and mechanically activated implants
    - ferromagnetic or electronically operated active devices like automatic cardioverter defibrillators and cardiac pacemakers
    - metallic splinters in the eye
    - ferromagnetic hemostatic clips in the central nervous system (CNS) or body
    - cochlear implants

  - other pacemakers, e.g., for the carotid sinus
  - insulin pumps and nerve stimulators
  - non-MR safe lead wires
  - prosthetic heart valves (if dehiscence is suspected)
  - non-ferromagnetic stapedial implants
- pregnancy
- Claustrophobia that does not readily respond to oral medication
- Known allergy to gadolinium-based contrast agents.
- Renal failure as defined by a GFR less than 30 or the use of hemodialysis.
- Pregnant.
- Patients less than 13 years of age will be excluded.
- Interval treatment with radiation or surgery between the diagnostic MRI lesion identification and planned study MRI.
- Wards of the state

3.3 NUMBER OF PARTICIPANTS

One hundred (100) patients will be studied. Up to twenty (20) healthy volunteers will be studied for the purposes of MRI sequence optimization.

4 STUDY PLAN/DESIGN

4.1 Patient Enrollment:

Patients being evaluated for treatment of a suspected brain malignancy at MD Anderson Cancer Center will be screened for eligibility based on their screening diagnostic MRI scan and available clinical information. Once eligibility is confirmed, patients will be approached for protocol introduction and consenting and enrollment. Attempts will be made to scan patients in the 7T system within 30 days of an MRI scan performed at either 3T or 1.5T.

Up to twenty (20) healthy volunteers will be recruited through local advertisement for the purposes of MRI sequence optimization. Volunteers will be scanned in accordance with the UTMDACC Division of Diagnostic Imaging Policy # 3.00: Imaging of Healthy Volunteers for Quality Assurance/Improvement and Technical Development.

4.2 Procedure to Obtain Consent

The patients and volunteers will be approached in person or using IRB approved remote consent procedures by either the Diagnostic Imaging (DI) faculty or Research Staff, including research nurses and research coordinators for their approval before their procedure. For subjects' age 13-17 years old, a parental or LAR permission must be obtained and documented that the informed consent occurred prior to the study subject's entry into the study and prior to any study related procedures. During the consenting process, patients will be educated and consented for their

research participation in this study. All subjects and volunteers who meet eligibility and complete the informed consent process will be registered in UTMDACC CORe system.

4.3 Houston Methodist Research Institute (HMRI) Registration

If inclusion/exclusion criteria are met and patients agree to participate in the study, the research study team will then contact the Houston Methodist Research Institute (HMRI) to register the patient and schedule their research MRI scan. Patient information including patient name, date of birth, prior allergic reaction to gadolinium based contrast agents, prior surgical history (as it pertains to surgical implants which may be a contraindication to MR scanning) which will be provided to HMRI as part of the study procedure (Appendix A – MRI Safety Questionnaire) and Referral Questionnaire for MDACC (Appendix B).

A copy of the completed MRI safety questionnaire and Referral Questionnaire for MDACC will be stored in REDCap and only authorized members of research team from MD Anderson (MDA) & HMRI who signed the delegation of authority log will have access to the data.

Research patients and volunteers will be contacted by MDA DI research study staff and given instruction for their research MRI scan once it is scheduled at HMRI.

4.4 MR Scanning:

Patients:

The study MRI will be performed on a 7.0-T MRI system. All patients will undergo conventional anatomic MR imaging including 3D T1 pre and post-contrast weighted imaging, 3D T2 weighted imaging, 3D T1 SPACE post-contrast, dynamic contrast-enhanced perfusion imaging, magnetic resonance spectroscopic imaging, functional magnetic resonance imaging (speech and motor paradigm), as well as the study-specific sequences to include:

- Quantitative MRI
- CEST
- Adv Diff
- Adv ASL

The entire scan time is expected to be approximately sixty (60) minutes. Routine and study sequences obtained on the 7T system may be obtained with the system in parallel transmit (pTx) scanning mode. Scanning in pTx mode can lead to increases in specific absorption rate (SAR) compared to single transmit mode; however, system software controls and sequences in both modes adheres to non-significant risk standards as defined by both IEC 60601 and the

US Food & Drug Administration including specifically that the SAR for the head will be less than 3.2W/kg head.

Volunteers:

The study MRI will be performed on a 7.0-T MRI system. Volunteers will not get an IV line placed or receive contrast as per UTMDACC Division of Diagnostic Imaging Policy # 3.00: Imaging of Healthy Volunteers for Quality Assurance/Improvement and Technical Development.

Volunteers will undergo a selection of research sequences above for the purposes of sequence optimization and quality assurance. The volunteer scan time is expected to be approximately sixty (60) minutes. Routine and study sequences obtained on the 7T system may be obtained with the system in parallel transmit (pTx) scanning mode. Scanning in pTx mode can lead to increases in specific absorption rate (SAR) compared to single transmit mode; however, system software controls and sequences in both modes adheres to non-significant risk standards as defined by both IEC 60601 and the US Food & Drug Administration including specifically that the SAR for the head will be less than 3.2W/kg head.

4.5 Patient experience survey

Patients will be given a one-page survey regarding their experience in the 7T MRI system following their scan. For subjects' age 13-17 years old, Research study staff will review questionnaires for completeness and ask subjects with the presence of subject's parent or LAR to complete any missing responses.

4.5.1 [Appendix A]

4.6 Imaging Time Points

4.6.1 A single research imaging session will be planned for each patient. However, patients will still undergo follow-up imaging scans as part of their standard of care. These follow-up scans will serve as the basis for statistical analyses that consider treatment response or disease recurrence.

4.7 Conclusion of Study Participation:

4.7.1 Completion of planned study or volunteer scan.

4.7.2 Upon patient or volunteer request.

4.7.3 Death.

5 Image Analysis

5.1 Lesion size evaluation:

5.1.1 A patient must have a single intraaxial brain lesion of 5 mm or greater for study inclusion as measured on either T2-weighted or T1-post contrast weighted imaging.

5.1.2 Lesions will be measured on either axial T2 FLAIR weighted or T1 post-contrast imaging on a slice displaying the maximal lesion size using the longest diameter after appropriate magnification on the picture archiving and communicating system (PACS) monitors.

5.1.3 For patients with multiple lesions appropriate for study assessment, the five (5) largest lesions will be assessed.

5.2 Lesion CNR evaluation:

5.2.1 The largest circular ROI that fits within the lesion on axial T1 post-contrast imaging will be placed and will define the lesion ROI.

5.2.2 The ROI mean signal intensity will be recorded.

5.2.3 A mirror ROI will be placed in the contralateral normal-appearing white matter and used as the "background" mean signal intensity measurement.

5.2.4 An extracranial ROI without visible artifact will be used as the “noise” mean signal intensity measurement.

5.3 Quantitative MRI

5.3.1 The largest circular ROI that fits within the lesion on axial T1 post-contrast imaging will be placed and will define the lesion ROI.

5.3.2 The T1 and T2 tissue weighting that maximizes the ROI mean signal intensity will be identified.

5.3.3 A mirror ROI will be placed in the contralateral normal-appearing white matter and used as the "background" mean signal intensity measurement.

5.3.4 An extracranial ROI without visible artifact will be used as the mean “noise” signal intensity measurement.

5.4 CEST MRI

5.4.1 The largest circular ROI that fits within the lesion on axial T1 post-contrast imaging will be placed and will define the lesion ROI.

5.4.2 The mean signal intensity for a corresponding ROI location on the processed CEST data will be recorded.

5.4.3 A mirror ROI will be placed in the contralateral normal-appearing white matter on the processed CEST data will be used as the “background” mean signal intensity measurement.

5.4.4 An extracranial ROI without visible artifact will be used as the “noise” mean signal intensity measurement.

5.5 Multiple B Value Diffusion Imaging (Adv Diff)

5.5.1 The largest circular ROI that fits within the lesion on axial T1 post-contrast imaging will be placed and will define the lesion ROI.

5.5.2 The AKC for the lesion will be determined using B-values of 0, 1000, and 2000 mm2/s.

5.5.3 The ADC of the lesion will also be determined using B-values of 0 and 1000 mm2/s.

5.5.4 A mirror ROI will be placed in the contralateral normal-appearing white matter, and "background" AKC and ADC measurement will be measured.

5.6 Adv ASL

5.6.1 The largest circular ROI that fits within the lesion on axial T1 post-contrast imaging will be placed and will define the lesion ROI.

5.6.2 This ROI will be used to assess the cerebral blood flow (CBF) from the processed ASL data.

5.6.3 A mirror ROI will be placed in the contralateral normal-appearing white matter for assessment of the “background” CBF.

5.6.4 This ROI will be used to assess the bolus arrival time (BAT) from the processed ASL data.

5.7 Task-based fMRI

5.7.1 fMRI data will be analyzed using custom software, IClinfMRI.

5.7.2 The general linear model will be used to generate an activation t-value map for each task-based fMRI data. The model includes the convolution of the task paradigms with a canonical hemodynamic response function.

5.7.3 Significantly activated areas will be determined by thresholding the t-value map at corrected $P < .05$.

5.8 Resting-state fMRI

5.8.1 Resting-state datasets will be pre-processed through slice timing, motion correction, de-spiking, detrending, regressing out covariates (including six motion parameters and two averaged fluctuations over masks of white matter and cerebrospinal fluid), band-pass filtering of 0.01-0.08 Hz, and 4-mm FWHM smoothing.

5.8.2 Functional connectivity maps will be generated by using both seed-based analysis and independent component analysis.

5.8.3 For the seed-based analysis, seed locations will be determined by anatomical motor and language areas with the assistance of a regional homogeneity map.

5.8.4 For the independent component analysis, 30-50 independent components will be determined, and the relevant functional connectivity maps will be determined with template matching and inspection by neuroradiologists.

5.9 Radiation planning validation

5.9.1 A 3D T1 SPACE sequence will be obtained to validate the ability of UHF MRI to provide acceptable levels of geometric distortion for radiation therapy planning purposes.

5.9.2 The specific parameters of the sequence will be optimized to maximize contrast and minimize artifact and distortion.

5.9.3 The geometric distortion will be evaluated with a full-field geometric distortion phantom to assess the geometric accuracy of the SPACE sequence with its specific parameters.

5.9.4 For radiation therapy purposes, the geometric distortion of less than 1mm is desired for the typical head field of view and 2 mm is the targeted limit for the useable field of view

6 Patient Information Confidentiality Plan

6.1 Collection of Identifiers:

The patient identifiers that will be collected in this study consist of patient medical record numbers and dates. Electronic data will be kept securely at MD Anderson (password protected behind the institution firewall).

The study will be performed following institutional policies for the use of existing medical information for research. Confidentiality will be maintained throughout the study. No identifying information will be used in any publication from this study. Electronic study data will be stored on password-protected institution computers behind the institution firewall. Only the PI and collaborators who have completed Human Subject Protection Training (HSPT) will have access to the study data.

6.2 Training of personnel:

Only MDACC personnel designated by the PI who have completed HSPT training will have access to study records. These personnel will be fully trained to maintain patient health information confidentiality.

6.3 Data Storage:

Electronic study data will be kept on password-protected computers behind the institution firewall. Paper records (data forms, and unique identifiers, etc.) will be kept in a locked file cabinet with access granted only to study investigators and research staff.

6.4 Data Sharing:

Study will utilize REDCap to store and share data with study collaborators and research staff with HMRI. Only authorized members of research team from MDA & HMRI who signed the delegation of authority log will have access to the data in REDCap.

Study data will be collected and managed using the REDCap (Research Electronic Data Capture) system hosted at MD Anderson. REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Oncology Care & Research Information Systems. REDCap has undergone an annual Governance Risk & Compliance Assessment (since May 2014) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335.

Those having access to the data include the study PI and research team personnel at MDA & HMRI. Internal users are authenticated against MDACC's Active Directory system. External

users will be granted access to the study. The application is accessed through Secure Socket Layer (SSL). The linking of patient protected health information (PHI) will be removed from the data when it is exported from REDCap for final analysis. All dates for a given subject will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each subject will be shifted by a different randomly generated number.

The digital imaging data will be stored on secure servers held by HMRI. Access to these research images in the HMRI will be restricted to Dr. Steven Fung, Dr. Robert Rostomily or the authorized research personnel at HMRI who will oversee the release of research MRI images of this IRB protocol and shared with Dr. Max Wintermark, Principal Investigator of this IRB protocol: 2019-1032. Complete confidentiality will be maintained; the investigators will be responsible for the transmission, sharing and storage of research imaging data.

6.5 Final Disposition of study records:

After publication, any printed paper records will be placed into the Shred-it confidential waste bins for disposition. The study will be performed following current institutional standards for the use of existing medical information, banking the data, and identifiers for research. There will be no further use of the study data without prior review and approval by the IRB.

7 STATISTICAL CONSIDERATIONS

7.1 Definitions

7.1.1 Lesion "**treatment response**" will be defined by size and contrast to noise ratio (CNR). Treatment response will be assessed only in patients with treatment prior to enrollment.

7.1.1.1 Size – treatment response in a single lesion will be considered as a decrease in size of 30%. (see section 5.1)

7.1.1.2 CNR—treatment response will be considered as a decrease in T1 post-contrast CNR of at least 20%. (see section 5.2) by standard T1 post-contrast imaging.

7.1.1.3 Lesions that do not meet these criteria for treatment response will be considered treatment failure.

7.1.2 Disease **recurrence** will be determined by surgical pathology (if available) or at least three months of imaging follow-up. Disease recurrence will be assessed only in patients with treatment prior to enrollment. Imaging findings will be considered recurrent disease in a lesion if:

7.1.2.1 The lesion was initially considered to be a treatment responder.

7.1.2.2 The lesion showed a successive increase in the size of 25% from nadir or a single imaging time point increase of 40%. (see section 5.1)

7.1.2.3 Lesions that do not meet these criteria will be considered radiation necrosis.

7.2 Overview

Patients with untreated disease (new lesions) will be categorized as having brain metastasis, primary brain tumor, or non-tumor based upon the following:

1. Patients with well-defined intra-axial lesions seen in the setting of pathology-proven solid organ malignancy will be considered metastasis.
2. Patients without history of a primary malignancy and agreement on a likely diagnosis of primary brain tumor by both a neurosurgical and neuroradiology co-investigator will be considered primary brain tumor.
3. Patients that do not the above criteria will be categorized as having non-tumor.

Patients in categories 1 and 2 will be further classified as having received treatment and not having received treatment.

7.3 Sample Size

The healthy volunteers' data will only be used for fMRI sequence optimization, quality assurance and will not yield data for the study. The optimization scans on healthy volunteers will not affect the statistical results.

Patients will be divided into 5 groups as discussed above. It is assumed that 90% of patients enrolled will represent either brain metastasis or primary brain tumor, approximately half in each category. We also expect approximately half of each group to have received treatment. We thus expect to have approximately 20-25 patients in each of the first four groups (metastasis with and without treatment and primary brain tumor with and without treatment). The other 10% will be in group 5 and are assumed to be non-tumor mimics of malignancy (for example, stroke, demyelinating disease).

For the primary endpoints, the objective is to calculate the contrast-to-noise ratio (CNR) or equivalent parameter for each method for both primary brain tumors and metastases separately by whether the patient has received treatment. For each imaging modality, we will calculate the CNR separately in the largest lesion/metastasis per patient as well as in all study lesions (see 5.1.3). As an example, for CEST, under the assumption of only a single lesion per patient and an expected mean CEST CNR of 14.9 and corresponding standard deviation of 3.0, 20 patients in a group will give a 95% confidence interval between 13.6 and 16.2. [40] Similar calculations apply for the CNR for each of the other imaging modalities.

We may also combine groups for the purpose of analysis. Continuing the above example, with 45 patients in a group, and the same assumed mean and standard deviation, a 95% confidence interval around the CEST CNR will range from 14.0 to 15.8. Again, similar calculations apply for other imaging modalities.

7.4 Analysis Plan

Patients with metastasis are expected to have on average 2-3 detectable brain lesions each. Patients with primary brain tumors are expected to have a single lesion. All analyses will be performed on the largest lesion within patients, and some analyses will be repeated on a per-lesion basis.

The CNR for each imaging method will be determined and reported along with the corresponding 95% confidence interval. In secondary analyses, for the conspicuity endpoints, the T1 sequence by MRI will be considered the gold standard, and we will compare the conspicuity of each of the other methods to that of T1 sequencing by using McNemar's test. This analysis will first be performed in the largest lesion per patient, and then analyses will be repeated using all lesions.

If enough follow-up images are obtained (see section 4.5), we will compare the CNR in lesions that respond to treatment to those that do not by using a Wilcoxon rank-sum test. We will compare the CNR between baseline and follow-up within patient by using a Wilcoxon signed-rank test. Also, for those lesions that initially respond, some will subsequently grow in size after the initial response. Of these, some will be considered radiation necrosis and some progressive disease. The CNR will be compared between lesions with necrosis and those that are progressive disease using a Wilcoxon rank-sum test.

Exploratory aims will be analyzed with descriptive statistics. fMRI paradigms will be summarized by the group mean and standard deviation. Patient satisfaction will be reported on a five-point Likert scale and compared between the 7T scan and the most recent clinical scan by using a Wilcoxon rank-sum test.

8 PROTOCOL MONITORING PLAN

This is not a treatment study, and no adverse effects are anticipated related to contrast-enhanced MR imaging. There is a tiny risk of an allergic reaction to the gadolinium-based contrast agent for which the patient will go through regular Departmental screening.

The principal investigator is responsible for monitoring the study and the safety of patients who enroll in the study. Approval is required to share study data and images with individuals or entities specified in a data or material transfer agreement.

Reports will be provided to the IRB as per current institutional policies for the use of existing medical information for research. This study will be approved by the Institutional Review Board at MD Anderson and Houston Methodist Research Institute for the Protection of Human Subjects. Participants will be protected according to the processes outlined by the MD Anderson IRB.

Personal information will be protected by taking the following measures:

- All HIPAA identifiers including names and medical records will be kept in a confidential manner, stored behind the institutional firewall. Paper copy will be stored in locked file in the office of a study investigators and authorized research staff.
- Data will be shared with HMRI investigators and staff and only as required to fulfill this research goals and objectives.
- Study data will be stored into REDCap. Access will be granted to HMRI and MDA study investigators and research staff authorized by the PI.
- A study code number rather than the participants' real names will be used on the research transcribed documents. This code linking the participants' demographic information will be known only to the study staff and will be kept in a separate locked cabinet in the locked PI's office at MD Anderson.
- Study data will be stored permanently on a secure institutional computer behind the institutional firewall in the office of the PI.
- REDCap will be utilized to store study data, forms, questionnaires and research MRI images.
- Only the study investigators and authorized research study staff who signed the delegation of authority log will have access to the study data.
- Study data will be collected and managed using an UT MD Anderson Cancer Center – approved database. The investigators will be responsible for data processing, in accordance with the institution`s data management procedures.

9 REFERENCES

1. Glioblastoma. In: http://www.cancermoonshots.org/cancer-types glioblastoma. Accessed 13 Jul 2019

2. Hamstra DA, Galbán CJ, Meyer CR, et al (2008) Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival. Journal of Clinical Oncology 26:3387–3394. doi: 10.1200/JCO.2007.15.2363

3. Hu LS, Baxter LC, Pinnaduwage DS, et al (2010) Optimized Preload Leakage-Correction Methods to Improve the Diagnostic Accuracy of Dynamic Susceptibility-Weighted Contrast-Enhanced Perfusion MR Imaging in Posttreatment Gliomas. AJNR Am J Neuroradiol 31:40–48. doi: 10.3174/ajnr.A1787

4. Bobek-Billewicz B, Stasik-Pres G, Majchrzak H, Zarudzki L (2010) Differentiation between brain tumor recurrence and radiation injury using perfusion, diffusion-weighted imaging and MR spectroscopy. Folia Neuropathol 48:81–92.

5. Hygino da Cruz LC, Rodriguez I, Domingues RC, et al (2011) Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. AJNR Am J Neuroradiol 32:1978–1985. doi: 10.3174/ajnr.A2397

6. Vöglein J, Tüttenberg J, Weimer M, et al (2011) Treatment monitoring in gliomas: comparison of dynamic susceptibility-weighted contrast-enhanced and spectroscopic MRI techniques for identifying treatment failure. Invest Radiol 46:390–400. doi: 10.1097/RLI.0b013e31820e1511

7. Obusez EC, Lowe M, Oh S-H, et al (2018) 7T MR of intracranial pathology: Preliminary observations and comparisons to 3T and 1.5T. NeuroImage 168:459–476. doi: 10.1016/j.neuroimage.2016.11.030

8. Stupp R, Hegi ME, Mason WP, et al (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. The Lancet Oncology 10:459–466. doi: 10.1016/S1470-2045(09)70025-7

9. Ostrom QT, Gittleman H, Liao P, et al (2014) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. Neuro-oncology 16 Suppl 4:iv1–63. doi: 10.1093/neuonc/nou223

10. Ostrom QT, Gittleman H, Xu J, et al (2016) CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. Neuro-oncology 18:v1–v75. doi: 10.1093/neuonc/now207

11. Stupp R, Mason WP, van den Bent MJ, et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996. doi: 10.1056/NEJMoa043330

12. van den Bent MJ, Vogelbaum MA, Wen PY, et al (2009) End point assessment in gliomas: novel treatments limit usefulness of classical Macdonald's Criteria. Journal of Clinical Oncology 27:2905–2908. doi: 10.1200/JCO.2009.22.4998

13. Verma G, Mohan S, Nasrallah MP, et al (2016) Non-invasive detection of 2-hydroxyglutarate in IDH-mutated gliomas using two-dimensional localized correlation spectroscopy (2D L-COSY) at 7 Tesla. J Transl Med 14:274. doi: 10.1186/s12967-016-1035-1

14. Li Y, Lafontaine M, Chang S, Nelson SJ (2018) Comparison between Short and Long Echo Time Magnetic Resonance Spectroscopic Imaging at 3T and 7T for Evaluating Brain Metabolites in Patients with Glioma. ACS Chem Neurosci 9:130–137. doi: 10.1021/acschemneuro.7b00286

15. Patel AJ, Suki D, Hatiboglu MA, et al (2010) Factors influencing the risk of local recurrence after resection of a single brain metastasis. J Neurosurg 113:181–189. doi: 10.3171/2009.11.JNS09659

16. Kaye AH, Laws ER (2001) Brain Tumors. Gulf Professional Publishing

17. Mayr NA, Yuh WT, Muhonen MG, et al (1994) Cost-effectiveness of high-dose MR contrast studies in the evaluation of brain metastases. AJNR Am J Neuroradiol 15:1053–1061.

18. Barajas RF, Cha S (2012) Imaging diagnosis of brain metastasis. Prog Neurol Surg 25:55–73. doi: 10.1159/000331174

19. Smith TE, Steven A, Bagert BA (2019) Gadolinium Deposition in Neurology Clinical Practice. Ochsner J 19:17–25. doi: 10.31486/toj.18.0111

20. Caraiani C, Dong Y, Rudd AG, Dietrich CF (2018) Reasons for inadequate or incomplete imaging techniques. Med Ultrason 20:498–507. doi: 10.11152/mu-1736

21. Beck ES, Sati P, Sethi V, et al (2018) Improved Visualization of Cortical Lesions in Multiple Sclerosis Using 7T MP2RAGE. AJNR Am J Neuroradiol 39:459–466. doi: 10.3174/ajnr.A5534

22. Warntjes JBM, Leinhard OD, West J, Lundberg P (2008) Rapid magnetic resonance quantification on the brain: Optimization for clinical usage. Magn Reson Med 60:320–329. doi: 10.1002/mrm.21635

23. Kvernby S, Warntjes MJB, Haraldsson H, et al (2014) Simultaneous three-dimensional myocardial T1 and T2 mapping in one breath hold with 3D-QALAS. J Cardiovasc Magn Reson 16:102. doi: 10.1186/s12968-014-0102-0

24. Tanenbaum LN, Tsiouris AJ, Johnson AN, et al (2017) Synthetic MRI for Clinical Neuroimaging: Results of the Magnetic Resonance Image Compilation (MAGiC) Prospective, Multicenter, Multireader Trial. AJNR Am J Neuroradiol 38:1103–1110. doi: 10.3174/ajnr.A5227

25. Blystad I, Warntjes JBM, Smedby O, et al (2012) Synthetic MRI of the brain in a clinical setting. Acta Radiol 53:1158–1163. doi: 10.1258/ar.2012.120195

26. Hagiwara A, Hori M, Suzuki M, et al (2016) Contrast-enhanced synthetic MRI for the detection of brain metastases. Acta Radiol Open 5:2058460115626757. doi: 10.1177/2058460115626757

27. Dula AN, Asche EM, Landman BA, et al (2011) Development of chemical exchange saturation transfer at 7 T. Magn Reson Med 66:831–838. doi: 10.1002/mrm.22862

28. Moseley ME, Kucharczyk J, Mintorovitch J, et al (1990) Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. AJNR Am J Neuroradiol 11:423–429.

29. Sener RN (2001) Diffusion MRI: apparent diffusion coefficient (ADC) values in the normal brain and a classification of brain disorders based on ADC values. Computerized Medical Imaging and Graphics 25:299–326. doi: 10.1016/S0895-6111(00)00083-5

30. Taylor W (2003) Diffusion tensor imaging: background, potential, and utility in psychiatric research. Biological Psychiatry. doi: 10.1016/S0006-3223(03)00813-8

31. Wang X-C, Lei Y, Wang L, et al (2018) Diffusion Kurtosis Imaging Reflects Glial Fibrillary Acidic Protein (GFAP), Topo IIα, and O^6-Methylguanine-DNA Methyltransferase (MGMT) Expression in Astrocytomas. Med Sci Monit 24:8822–8830. doi: 10.12659/MSM.911631

32. Jensen JH, Helpern JA (2010) MRI quantification of non-Gaussian water diffusion by kurtosis analysis. NMR Biomed 23:698–710. doi: 10.1002/nbm.1518

33. Fujima N, Sakashita T, Homma A, et al (2018) Utility of a Hybrid IVIM-DKI Model to Predict the Development of Distant Metastasis in Head and Neck Squamous Cell Carcinoma Patients. Magn Reson Med Sci 17:21–27. doi: 10.2463/mrms.mp.2016-0136

34. Falk Delgado A, Nilsson M, van Westen D, Falk Delgado A (2018) Glioma Grade Discrimination with MR Diffusion Kurtosis Imaging: A Meta-Analysis of Diagnostic Accuracy. Radiology 287:119–127. doi: 10.1148/radiol.2017171315

35. Yang X, Holmes MJ, Newton AT, et al (2012) A Comparison of Distributional Considerations with Statistical Analysis of Resting State fMRI at 3T and 7T. Proc SPIE Int Soc Opt Eng 8314:831416. doi: 10.1117/12.911307

36. (2019) Characterizing Microstructural Tissue Properties in Multiple Sclerosis with Diffusion MRI at 7 T and 3 T: The Impact of the Experimental Design. Neuroscience 403:17–26. doi: 10.1016/j.neuroscience.2018.03.048

37. Fink JR, Muzi M, Peck M, Krohn KA (2015) Multimodality Brain Tumor Imaging: MR Imaging, PET, and PET/MR Imaging. J Nucl Med 56:1554–1561. doi: 10.2967/jnumed.113.131516

38. Boxerman JL, Ellingson BM, Jeyapalan S, et al (2017) Longitudinal DSC-MRI for Distinguishing Tumor Recurrence From Pseudoprogression in Patients With a High-grade Glioma. Am J Clin Oncol 40:228–234. doi: 10.1097/COC.0000000000000156

39. Chaskis C, Stadnik T, Michotte A, et al (2006) Prognostic value of perfusion-weighted imaging in brain glioma: a prospective study. Acta Neurochir 148:277–85– discussion 285. doi: 10.1007/s00701-005-0718-9

40. Barajas RF Jr, Chang JS, Segal MR, et al (2009) Differentiation of Recurrent Glioblastoma Multiforme from Radiation Necrosis after External Beam Radiation Therapy with Dynamic Susceptibility-weighted Contrast-enhanced Perfusion MR Imaging 1. Radiology 253:486–496. doi: 10.1148/radiol.2532090007

41. Boxerman JL, Zhang Z, Safriel Y, et al (2013) Early post-bevacizumab progression on contrast-enhanced MRI as a prognostic marker for overall survival in recurrent glioblastoma: results from the ACRIN 6677/RTOG 0625 Central Reader Study. Neuro-oncology 15:945–954. doi: 10.1093/neuonc/not049

42. Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM (1995) MR contrast due to intravascular magnetic susceptibility perturbations. Magn Reson Med 34:555–566.

43. Kiselev VG, Strecker R, Ziyeh S, et al (2005) Vessel size imaging in humans. Magn Reson Med 53:553–563. doi: 10.1002/mrm.20383

44. Kang H-Y, Xiao H-L, Chen J-H, et al (2016) Comparison of the Effect of Vessel Size Imaging and Cerebral Blood Volume Derived from Perfusion MR Imaging on Glioma Grading. AJNR Am J Neuroradiol 37:51–57. doi: 10.3174/ajnr.A4477

45. Zaiss M, Windschuh J, Paech D, et al (2015) Relaxation-compensated CEST-MRI of the human brain at 7T: Unbiased insight into NOE and amide signal changes in human glioblastoma. NeuroImage 112:180–188. doi: 10.1016/j.neuroimage.2015.02.040

46. Cai K, Singh A, Poptani H, et al (2015) CEST signal at 2ppm (CEST@2ppm) from Z-spectral fitting correlates with creatine distribution in brain tumor. NMR Biomed 28:1–8. doi: 10.1002/nbm.3216

47. Zhou J, Payen J-F, Wilson DA, et al (2003) Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. Nat Med 9:1085–1090. doi: 10.1038/nm907

48. Zhou J, Tryggestad E, Wen Z, et al (2011) Differentiation between glioma and radiation necrosis using molecular magnetic resonance imaging of endogenous proteins and peptides. Nat Med 17:130–134. doi: 10.1038/nm.2268

49. Togao O, Yoshiura T, Keupp J, et al (2014) Amide proton transfer imaging of adult diffuse gliomas: correlation with histopathological grades. Neuro-oncology 16:441–448. doi: 10.1093/neuonc/not158

50. Williams DS, Detre JA, Leigh JS, Koretsky AP (1992) Magnetic resonance imaging of perfusion using spin inversion of arterial water. Proc Natl Acad Sci USA 89:212–216. doi: 10.1073/pnas.89.1.212

51. Wolf RL, Detre JA (2007) Clinical Neuroimaging Using Arterial Spin-Labeled Perfusion Magnetic Resonance Imaging. Neurotherapeutics 4:346–359. doi: 10.1016/j.nurt.2007.04.005

52. Liebeskind DS (2003) Collateral Circulation. Stroke 34:2279–2284. doi: 10.1161/01.STR.0000086465.41263.06

53. Calamante F, Williams SR, van Bruggen N, et al (1996) A Model for Quantification of Perfusion in Pulsed Labelling Techniques. NMR Biomed 9:79–83. doi: 10.1002/(SICI)1099-1492(199604)9:2<79::AID-NBM399>3.0.CO;2-4

54. Warmuth C, Günther M, Zimmer C (2003) Quantification of Blood Flow in Brain Tumors: Comparison of Arterial Spin Labeling and Dynamic Susceptibility-weighted

Contrast-enhanced MR Imaging1. Radiology 228:523–532. doi: 10.1148/radiol.2282020409

55. Bokkers RP, Bremmer JP, van Berckel BN, et al (2009) Arterial Spin Labeling Perfusion MRI at Multiple Delay Times: A Correlative Study with H215O Positron Emission Tomography in Patients with Symptomatic Carotid Artery Occlusion:. Journal of Cerebral Blood Flow & Metabolism 30:222–229. doi: 10.1038/jcbfm.2009.204

56. Dury RJ, Falah Y, Gowland PA, et al (2019) Ultra-high-field arterial spin labelling MRI for non-contrast assessment of cortical lesion perfusion in multiple sclerosis. Eur Radiol 29:2027–2033. doi: 10.1007/s00330-018-5707-5

10 APPENDICES

Appendix A - MRI Safety Questionnaire)

Appendix B - Referral Questionnaire for MDACC

Appendix C - UTMDACC Division of Diagnostic Imaging Policy # 3.00: Imaging of Healthy Volunteers for Quality Assurance/Improvement and Technical Development.