

CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER: CASE 7314

STUDY TITLE: Feasibility and Clinical Application of Magnetic Resonance Fingerprinting

PRINCIPAL INVESTIGATORS: Deborah Rukin Gold, MD
Department of Pediatrics
University Hospitals Cleveland Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106
(216) 844-3691

CO- INVESTIGATORS: Mark Griswold, PhD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

Andrew Sloan, MD
Director, Brain Tumor & Neuro-Oncology Center
Vice Chair, Department of Neurological Surgery
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

Vikas Gulani, MD, PhD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

Chaitra Badve, MD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

Jeffrey Sunshine, MD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University

11100 Euclid Avenue
Cleveland, OH 44106

Barbara Bangert, MD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

Sara Dastmalchian, MD
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

Duncan Stearns, MD
Department of Pediatrics
Division of Hematology & Oncology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

Deborah Rukin Gold, MD
Department of Pediatrics
Division of Neurology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

Joshua Batesole
Department of Radiology
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Ave.
Cleveland, OH 44106

Krystal Tomei, MD
Department of Surgery
Division of Neurosurgery
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106

STATISTICIAN:

Jill Barnholtz-Sloan, PhD
Case Comprehensive Cancer Center
CWRU School of Medicine
2-525 Wolstein Research Bldg,
2103 Cornell Rd.
Cleveland, OH 44106

STATISTICIAN:

Mark Schluchter, PhD
Biostatistics Core Facility
Case Comprehensive Cancer Center
11100 Euclid Avenue
Cleveland, OH 44106
Tel: (216) 368-2651

CLINICAL FACILITY:

Seidman Cancer Center,
University Hospitals Case Medical Center

STUDY COORDINATOR:

Sally Muehle
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106-5065

RESEARCH NURSE:

Kelly Laschinger, CNP
University Hospitals Case Medical Center
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106-5065

Jordonna Fulop, RN
Department of Neurology
Case Comprehensive Cancer Center
Wolstein Research Bldg.
2103 Cornell Rd. Rm. 1200
Cleveland, OH 44106

Karen Devine, RN
Department of Neurology
Case Comprehensive Cancer Center
W.O. Walker Bldg., Floor 3, WG72
10524 Euclid Avenue
Cleveland, OH 44106

APPROVALS:

Protocol Review and Monitoring Committee: 10/31/14
UHCCM IRB: 2/2/2015

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Table of Acronyms

MRF	Magnetic Resonance Fingerprinting
DTI	Diffusion Tensor Imaging
MRI	Magnetic Resonance Imaging
OPG	Optic Pathway Glioma
NF1	Neurofibromatosis type 1

1.0 BACKGROUND AND RATIONALE

Although recent therapeutic advances have improved survival in pediatric neuro-oncology, surveillance of brain tumors remains problematic. In young children, imaging surveillance often requires sedation which exposes children to additional risk. In addition, the interpretation of traditional MR imaging involves the qualitative comparison of relative T1 and T2 signal intensity which can lead to uncertainty, misdiagnosis and additional surveillance imaging. New imaging techniques that decrease scan time and allow for quantitative measurement of MR parameters could minimize the need for sedation and improve diagnostic certainty in children with brain tumors.

Our group (Griswold lab, co-investigator) has pioneered a novel magnetic resonance technique that may be an important noninvasive biomarker for pediatric brain tumors.¹ Magnetic resonance fingerprinting (MRF) uses pseudo-randomized variation in acquisition parameters to generate a multi-parametric data signal that can be compared to signal patterns calculated from all possible combinations of parameters of interest. The closest match in signal patterns yields the parameters used to calculate the theoretical signal, in each voxel, and thus a map of all parameters of interest for that tissue. This process is analogous to matching fingerprints to a database where a match in fingerprint to one from a database yields a vast array of uncollected information (for example name, address, date of birth, etc.) stored in the database. MRF data can be used to reconstruct high resolution parameter maps in a fraction of the time required by traditional MRI (**Figure 1**). Significantly, these images are robust to movement artifact¹, making them an ideal choice in children with minimal or no sedation.

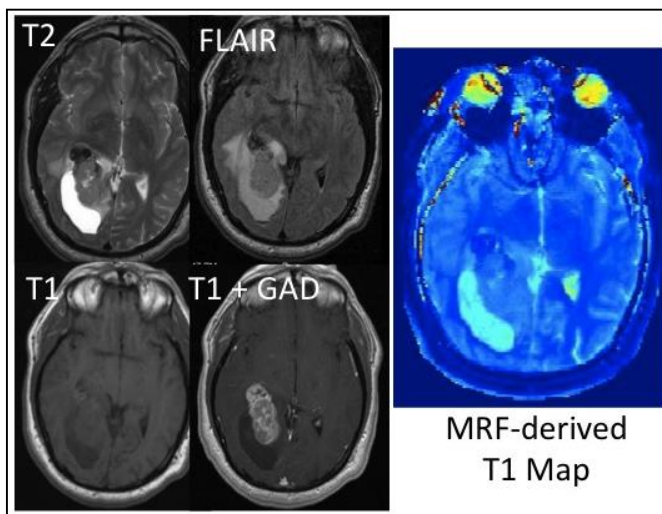


Figure 1: Traditional MRI sequences show a solid, centrally necrotic mass in medial right occipital lobe later shown to be metastatic adenocarcinoma. MRF-derived T1 map describes a similar lesion with greater extent of signal abnormality.

In addition, MRF may have unique clinical applications in pediatric and AYA brain tumors. While the interpretation of traditional MR sequences depends on the *qualitative* comparison of relative T1 and T2 signal intensity, MRF can rapidly *quantify* T1, T2, M0 and off-resonance signals to aid in tissue identification and delineation. Preliminary work from our group demonstrates that MRF can identify brain tumors and brain metastases from surrounding healthy tissue and differentiate these pathologies from one another, and has been useful in a series of brain tumors in suggesting a diagnosis prior to resection.

MRF is able to distinguish tumor from surrounding healthy tissue. In a series of fourteen subjects with pathologically defined intra-axial brain tumors (7 high grade gliomas, 4 low grade gliomas

and 3 metastases), mean T1 and T2 values derived from MRF were significantly different from contralateral white matter (1890 ± 170 ms and 219 ± 60 ms vs. 982 ± 77 ms and 77 ± 13 ms, $p=3.8 \times 10^{-7}$ and $p=2.4 \times 10^{-7}$, respectively, **Figure 2A**). While traditional MR sequences are limited in their quantitation of tumor involvement, *MRF has the potential to distinguish tumor grade and identify tumor infiltration more sensitively*. MRF quantitation of T2 values was significantly different between low grade and high grade gliomas ($p < 0.04$, **Figure 2B**). In addition, perilesional white matter T1 and T2 values were compared to contralateral white matter and lesional values. T1 and T2 values of perilesional white matter were less than those of lesional tissue, but more than contralateral white matter. The difference in T1 and T2 values between peritumoral white matter and contralateral white matter was statistically significant ($p < 0.0002$, $p < 0.0001$, respectively), suggesting that tumor infiltration or peritumoral edema may be easily quantified with this method.

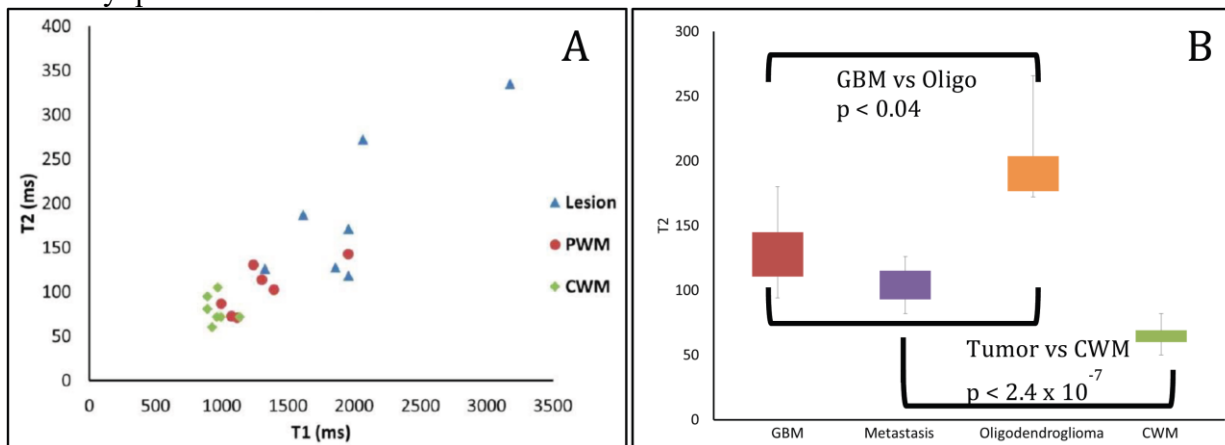


Figure 2: T1 and T2 values in adult intra-axial brain tumors, associated perilesional white matter (PWM) and contralateral white matter (CWM). (A) T1 and T2 values for lesional tissue and PWM are significantly different from contralateral white matter. (B) T2 values of low- (oligo) and high- (GBM) grade glioma are significantly different from each other and CWM.

Prior experience with MR relaxometry. MRF represents a novel technique to simultaneously acquire relaxation times (T1 and T2) as well as other MR parameters (such as M0 and off resonance) in a fast MR sequence. Unlike traditional methods of measuring T1 and T2 relaxation times, MRF is a fully quantitative method that is consistent across a range of instruments, personnel and scan dates. Prior studies have demonstrated the utility of T1 and T2 values in the diagnosis and surveillance of brain tumors. In vitro experiments on excised brain tissue have demonstrated that T1 and T2 relaxation times can distinguish tumor histology (astrocytoma, oligodendroglioma, meningioma, acoustic neuroma and metastasis) and grade of astrocytoma.² Subsequent in vivo experiments have shown that T2 relaxation time can differentiate glioma, meningioma and metastasis in human subjects,³ and may differentiate edema from invasive tumor.⁴ Combination of T1 and T2 relaxation times with other MR measured parameters has also been used to distinguish tumor (glioma and lymphoma) from edema, and distinguish tumor grade.⁵ In longitudinal experiments in human subjects with high grade glioma, T1 and T2 relaxation times have also been able to identify tumors that respond to anti-inflammatory therapies (steroids and bevacizumab) and correlate treatment effect with progression free and overall survival.^{6,7} Finally, the quantitative relaxometry has been used to identify lesions in multiple sclerosis, epilepsy and cerebrovascular infarct.⁸

This study will investigate the feasibility of using MRF in children, adolescents and young adults (AYA) with and without brain tumors, in subjects with and without neurofibromatosis type 1 (NF1). Further, it will explore potential applications of MRF signal quantification in pediatric and AYA brain tumors, including tissue characterization, determination of treatment effect and identification of occult tumor. To explore the feasibility and potential applications of MRF, this study will recruit up to 80 subjects but will stop once 10 evaluable subjects are achieved in each of six groups. Subjects will be recruited to the study according to the following criteria:

- a) 10 subjects with NF1-associated OPG
- b) 10 subjects with NF1 without brain tumor
- c) 10 subjects without NF1 and with low grade gliomas exposed to therapy
- d) 10 subjects without NF1 and with untreated low grade gliomas
- e) 10 subjects without NF1 and without brain tumor
- f) 10 subjects with brain tumors of assorted pathology

2.0 OBJECTIVES

2.1 Primary Objective

Specific Aim 1: Demonstrate the feasibility of MRF in children and AYA with and without brain tumors.

2.2 Secondary Objectives

Specific Aim 2: Characterize the MRF signature of low-grade gliomas

Specific Aim 3: Determine whether MRF can identify occult tumor in subjects with low-grade glioma.

Specific Aim 4: Determine whether MRF can identify treatment effects in low-grade gliomas.

Specific Aim 5: Explore whether common brain tumors can be differentiated by comparing pre-operative MRF signature with pathologic diagnosis.

3.0 PATIENT/SAMPLE SELECTION

We expect to approach up to 80 patients at Rainbow Babies & Children's Hospital (Rainbow) in order to enroll 10 evaluable subjects in each of 6 categories (see above). Sufficient statistical power would be achieved with 60 subjects. Recruitment will end once 10 evaluable subjects are accrued to each category or 80 subjects are recruited, whichever is first.

3.1 Inclusion Criteria

3.1.1 Age <35 years

3.1.2 Subjects undergoing MRI evaluation of the brain

3.1.3 NF1 status will be determined by clinical exam or genetic testing

3.1.4 NF1-associated OPG will be defined as radiographic evidence of glioma along the optic nerve, chiasm, tract or radiation in a child with NF1.

3.1.5 Untreated low grade gliomas will be imaging-defined gliomas that have not yet been exposed to radiation or systemic chemotherapy. Those exposed to therapy will have had radiation and/or systemic chemotherapy more than 1 month prior to scans.

3.2 Exclusion Criteria

3.2.1 History of mental retardation unrelated to brain tumor

3.2.2 Presence of a genetic disorder other than NF1 that effects cognition or is associated with MR imaging abnormalities (e.g. tuberous sclerosis)

3.2.3 History of cerebrovascular accident (stroke)

3.2.4 Birth weight below five pounds, premature birth prior to 36 weeks of gestation, or ischemic episode at birth

3.2.5 Major psychiatric diagnosis prior to neuro-oncological diagnosis

4.0 REGISTRATION PROCEDURES AND CONSENT

Participants will be recruited from the neurology, oncology and neurosurgery clinics. The oncology, neuro-oncology and neurocutaneous syndromes clinics have a focus on both pediatric as well as adolescent and young adult patients which includes patients up to 35 years of age. Healthy controls will be recruited from children and AYA undergoing brain MRI for other indications (new seizure, headache, etc) in which brain tumor may be a reasonable cause of symptoms. Study personnel including the study PI, co-investigators, and research nurses may consent eligible subjects. All subjects enrolled on study will be entered into a single secure database (OnCore) (please see section 8.1, below).

When appropriate, subjects ages 7-17 will be included in all discussions in order to obtain assent; they will be offered the opportunity sign the assent form. Assent will be waived for subjects under age 7, and parents/guardians will sign the consent form.

5.0 RESEARCH PLAN

This study will examine the feasibility of MRF in children and AYA and determine whether quantitative measures of T1 and T2 can be derived in subjects <35 years of age. Approximately 80 subjects will be evaluated and include subgroups where MRF may be of particular utility, including children and AYA subjects with brain tumors and subjects with NF1. Additional aims will investigate the utility of MRF in these groups.

SA1: Subjects undergoing MRI for other clinical indications will be included in the study. MRF will be included in the imaging sequences prior to contrast infusion (in those receiving contrast)

or at the end of the sequence (for those not receiving contrast) and will add approximately 10-15 additional minutes of scan time. Duration of MRF sequences will be recorded as a measure of feasibility. The ability to reliably extract values for T1 and T2 will also be assessed. Duration of scan and the proportion of evaluable scans will be described. Unevaluable scans will be those from which T1 and T2 values cannot be assessed. Scans may be unevaluable if no one is available to conduct the MRF sequence, the MRF sequence is temporarily unavailable on the scanner being used, or in the case of patient or clinician refusal.

Secondary aims will investigate the application of MRF to pediatric and AYA brain tumors.

SA2: Characterize the MRF signature of low-grade gliomas.

In order to define the multiparametric signature of low-grade gliomas, we will use MRF to measure T1, T2, M0 and off-resonance values of regions of interest within subjects with these tumors. In 20 subjects with NF1 (10 with NF1-OPG and 10 without), regions of interest within the optic nerve will be defined on T1 and T2 sequences and compared to analogous regions in NF1 subjects without OPG. Additional analyses will compare tumor involved optic chiasm, tracts and radiations with similar regions in NF1 subjects without OPG.

In 20 subjects without NF1 (10 with low-grade glioma and 10 without), regions of interest will be compared between tumor infiltrated regions and analogous areas from representative axial images through the brain. Tumor infiltrated regions of interest will be defined on traditional MR sequences by contrast enhancement or T2 abnormality if no enhancement is present. Unilateral tumors will also be compared to non-infiltrated tissue on the contralateral side.

To compare NF1 and non-NF1 low-grade gliomas, all four measured MRF parameters will be compared between 10 subjects with NF1-OPG and 10 subjects with low grade gliomas not associated with NF1. Regions of interest will be defined as above. A similar analysis will compare subjects without tumor in representative regions. If no significant difference is found between NF1 and non-NF1 MRF signatures, further analyses will combine these groups.

To distinguish NF1-OPG from spongiotic change from common radiographic mimics, the MRF signature of NF1-OPG will be compared to regions of NF1 spongiotic change. Spongiotic change will be defined as areas of T2 signal abnormality without contrast enhancement or mass effect, in NF1 subjects with and without OPG. Spongiotic change is common in children with NF1 and may appear in children unaffected by tumor, and so we reasonably expect at least 10 areas of spongiotic change to be defined outside the visual pathway.

In each analysis, all four measured parameters will be compared using Student's t-test and parameters with significant differences between tumor-involved and non-involved tissue will be used to define the OPG signature. Parameters with significant differences between tumoral and non-tumoral tissue will be used to define the tumor signature. Based on histograms of T1, T2, M0 and off-resonance parameters found in either group, cut-off values may be defined for measures that show a statistically significant difference between groups. Receiver operator curves may be constructed to identify maximum sensitivity and specificity of these measures to the presence of tumor. In an exploratory analysis, the effect of each quantitative MRF parameter on tissue type (tumor vs. healthy tissue) will be further evaluated using multiple logistic regression with an elastic net penalty, and this model will be used to define a multiparametric equation to define the probability of tumor presence based on the MRF signature.⁹

SA3: Determine whether MRF can identify occult tumor in subjects with low-grade glioma.

To investigate whether MRF is more sensitive than traditional MRI sequences to tumor involvement, we will use MRF to evaluate the optic radiations of children and AYA subjects with OPG who have already had DTI analysis. Data from our group suggests that tumor may affect white matter tracts (measured by DTI) that do not appear to be infiltrated on traditional MRI sequences.¹⁰ However, quantitative MRF measures may identify peri-tumoral areas that appear to have similar T1 and T2 signal to tumor regions. These areas may represent tumor infiltration or peri-tumoral edema that may damage white matter tracts and affect visual acuity.

To determine whether tumor identified by MRF correlates with white matter integrity, subjects with OPG who have been evaluated by DTI will undergo MRF. Optic radiations will be evaluated for evidence of tumor on MRF, defined by parameter limits that distinguish OPG from normal tissue determined in SA2 above. The proportion of voxels with a signature consistent with OPG will be compared to the FA of the optic radiations measured by DTI. Preliminary data demonstrate that approximately 80% of radiations with decreased white matter integrity (FA<0.51) have no evidence of tumor involvement on traditional MRI.¹⁰ A significant correlation between tumor involvement (defined by MRF) and white matter integrity may suggest that occult tumor was responsible for white matter tract damage.

To determine whether MRF abnormalities can predict tumor recurrence due to residual tumor, post-operative peritumoral areas in resected tumors will be examined. Scans performed in the immediate post-operative period (24-48 hours after surgery), will be used to acquire axial images of the region of interest. Peritumoral area will be defined as the area within 1cm of the resection cavity on the axial image. MRF signature will be measured in each voxel of these areas, and histograms of MRF parameters will be constructed in addition to a description of means or medians, as appropriate. In a further exploratory analysis, the MRF signature in each voxel will be converted into a probability of occult tumor (a heat map), using the multiparametric cut-off values derived in SA2. Histogram of probabilities will be examined for skewness and kurtosis. To evaluate test characteristics of MRF, a receiver-operator curve (ROC) will be created varying the probability cut-off of occult tumor to predict tumor recurrence.

SA4: Determine whether MRF can identify treatment effects in low-grade gliomas.

To determine the effect of treatment on low-grade gliomas, we will follow serial MRF scans in children and AYA subjects with low-grade gliomas that do and do not require treatment. In subjects that do not require treatment, serial MRF scans will be conducted along with surveillance imaging over the course of one year. In subjects that require treatment with radiation or chemotherapy, MRF signature of tumor tissue will be compared in pre- and post-therapy scans, performed approximately 3 months apart in accordance with their surveillance imaging schedule. Change in MRF signature between serial evaluations will be compared in treatment exposed and non-exposed groups.

Student's paired t-test or non-parametric Wilcoxon signed rank test will be used to compare each MRF parameter to determine statistically significant differences. Radiation and chemotherapy will also be considered in separate analyses as these therapies likely have varied effects on tissue

microstructure. Significant differences in pre- and post-therapy MRF signatures will define cut-off values demonstrating likely treatment effect.

SA 5: Explore whether common brain tumors can be differentiated by comparing pre-operative MRF signature with pathologic diagnosis.

In this exploratory aim, pre-operative MRF signature of low-grade gliomas and tumors of assorted pathology will be compared to post-operative pathologic diagnosis to determine the multiparametric signature that best defines tumor pathology. This aim remains exploratory and methods of analysis depend on the number of different pathologies investigated. Histograms may be constructed to determine cut-off values that best define each pathology.

6.0 STUDY PARAMETERS

6.1 Study Calendar

Parameters	Baseline	Surveillance Imaging (within 1 yr)	Further Observation (within 5 yrs)
<u>All Subjects</u>			
Age (years)	X		
Gender	X		
NF1 status	X		
MRI evaluation	X	X	
MRF evaluation	X	X	
Duration of MRF scan	X	X	
Treatment history	X	X	X
Ophthalmology exam ¹	X	X	
Post-Therapy MRF ²		X	
Pathology report ³		X	X

- 1 Ophthalmology exams will be recorded for subjects with OPG
- 2 For those requiring therapy. Post-surgical MRF will occur 24-48 hours after surgery with clinical scan. Post-chemotherapy or post-radiation MRF will occur at next surveillance imaging approximately 3 months from therapy.
- 3 For those who have a surgical biopsy or resection.

6.2 Case Ascertainment: Potential subjects will be identified from active patient lists and upcoming clinic appointments with the Divisions of Pediatric Oncology, Pediatric Neurology, and NeuroSurgery. Potential subjects who are scheduled for a scan prior to their next appointment will be contacted by telephone (see telephone script).

6.3 Data Elements and Sources

6.3.1 Chart review: A review of the medical chart will provide demographic information (date of birth, gender, NF1 status), ophthalmology records (visual acuity, visual field testing, optic disc evaluation), and pathologic diagnosis. Subsequent reviews determine any new treatments or pathology.

6.3.2 Imaging data: DTI, MRI and MRF imaging will be acquired from the PACS system for post-processing. DTI is currently standard of care for children with brain tumors and will not require additional sedated time.

7.0 SAMPLE SIZE and POWER CALCULATIONS

SA1: To determine whether MRF is feasible in subjects with and without brain tumors, we will record duration of MRF sequences in subjects' baseline scan and subsequent MRF scans over the course of one year. A separate analysis will investigate children <18 years old. Image quality and the ability to adequately extract T1 and T2 signal parameters will also be evaluated. Data will be evaluated descriptively both among all subjects, and among subpopulations (healthy control subjects, subjects with tumor, and subjects with NF1).

In this descriptive aim, we will measure the time required for MRF and the proportion of potential MRF scans that are evaluable. We will consider MRF feasible if scans are completed in less than 15 minutes and that greater than 75% are evaluable.

SA2: We hypothesize that MRF will distinguish brain tumor from matching healthy tissue.

Assuming a standard deviation of 170ms for T1 values for tumor and normal tissue (found in preliminary studies), 20 subjects (10 with tumors and 10 without) would be able to detect a difference of 225ms in T1 with 80% power and alpha of 0.05 using a two-sided T test. If MRF signature is found to be unaffected by NF1 status, combined groups would yield 40 subjects (20 with low-grade glioma and 20 without), which would be able to detect a difference of 155ms in T1 with 80% power and alpha of 0.05 using a two-sided T test. A difference of 908ms was found in T1 between tumor and contralateral white matter in preliminary data. Because T2, M0 and off-resonance values will be interrogated in addition to T1, we expect to have increased power to find a distinct tumor signature.

SA3: We hypothesize that MRF signature will be able to distinguish occult low-grade glioma.

We will compare fractional anisotropy (measured by DTI) in the optic radiations with MRF signature in correlate with OPG. With an alpha of 0.05, 10 subjects would provide 80% power to identify a correlation of 0.71 or greater between T1 or T2 and fractional anisotropy on a one-sided test, which would provide a clinically meaningful result.

We will create a receiver-operator curve comparing the likelihood of occult tumor with tumor recurrence. Six tumor recurrences among 20 subjects with NF1 or non-NF1 low-grade glioma (30% relapse rate) would achieve 80% power to detect an area under the ROC ≥ 0.83 compared to the null hypothesis area of 0.5 with an alpha of 0.05. Secondary analysis will also analyze whether peak tumor probability, rather than mean probability, is predictive of tumor recurrence. To explore

whether MRF can predict the site of recurrence, heat maps derived in **SA3** will be qualitatively compared to sites of recurrence.

SA4: We hypothesize that MRF signature will be able to distinguish treatment effects in low-grade gliomas.

The effect of treatment on low-grade gliomas has not yet been interrogated by MRF and standard deviations of T1 and T2 parameters are still unknown. Using standard deviations of high-grade gliomas as conservative estimates of T2 standard deviation in low-grade glioma (standard deviation of 60ms) and assuming a correlation of 0.5 between paired time points, a difference in T2 of 60ms could be detected with 80% power and an alpha of 0.05 when 10 low-grade gliomas are compared serially using a two-sided t test. As in **SA2**, we expect to have greater than estimated power because we will be comparing multiple parameters (T1, T2, M0 and off-resonance) to define the change in MRF signature over time.

SA5: We hypothesize that MRF signature will be able to distinguish common tumor pathologies.

This remains an exploratory aim that will provide preliminary data for future investigations. For each pathology, histograms of MRF parameters will be created and mean MRF parameter values will be described. Power will be inadequate for statistical comparison in this aim. However, this data will provide essential information for future work defining the MRF signature of multiple pathologies.

8.0 RECORDS/DATA TO BE KEPT

8.1 Data Collection and Management

Non-imaging data (demographics, pathology, ophthalmology, medical history) will be maintained on a secure, password-protected database (OnCore). Only those persons selected to perform data entry will have access to secure databases. Data will be reviewed for face validity and completeness before being accepted into the database. Raw images will be coded with a unique identification number to protect PHI. The master key will be kept in OnCore. Data from this study will also be sent to an outside institution for review by Peter de Blank, MD.

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management at Rainbow. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the Oncore Administrator at oncore-registration@case.edu.

8.2 Regulatory and Ethical Considerations

8.2.1 Risk Assessment

Subjects enrolling on study will be exposed to risks of privacy regarding protected health information. Diffusion Tensor Imaging is now standard of care at Rainbow and will not provide any additional sedated time for study subjects. MRF will be performed during the clinical MRI scans and will require approximately 10-15 additional minutes of scan time. Risk to privacy will be minimized by password protection of the database, and use of coded identifiers for raw imaging data. We consider these potential risks to be a minor increase over minimal risk in subjects undergoing sedation and no more than minimal risk in subjects who do not need sedation.

8.2.2 Potential Benefits of Study Participation

MRF provides additional data parameter maps that may be useful in identifying and interpreting pathology. Preliminary data (section 1.0) demonstrates that MRF has been able to differentiate tumor and normal tissue, and may help identify tumor type and location. MRF parameter maps may help radiologists refine the differential diagnosis of abnormal tissue and may contribute to patient care. The proposed study may also generate generalizable and important knowledge about the feasibility of MRF in children and AYA subjects, as well as determine whether MRF is more sensitive to occult tumor invasion than traditional MRI. Since all subjects recruited for this study will undergo clinical MRI for potential pathologic diagnosis, we consider this a potential benefit to subjects.

8.2.3 Risk-Benefit Assessment

This study involves a minor increase over minimal risk to subjects undergoing sedation or anesthesia, and presents the potential for benefit for all subjects. This study represents no more than minimal risk in subject who do not require sedation. This study will develop new knowledge about the feasibility and utility of MRF and has the additional potential to develop a new-non-invasive method to better evaluate residual tumor burden in children and AYA subjects with brain tumors.

8.3 Safety Management

8.3.1 Clinical Adverse Events

Unanticipated problems involving risks to subjects and others will be monitored throughout the study by the PI.

8.3.2 Adverse Event Reporting

Adverse events (AEs) will be graded according to the categorization below:

Grade 1 (MILD): Sign or symptom is noticeable, but does not interfere with normal daily activities.

Grade 2 (MODERATE): Sign or symptom interferes with normal daily activities.

Grade 3 (SEVERE): Sign or symptom is incapacitating, with inability to perform daily activities.

Grade 4 (LIFE-THREATENING): Sign or symptom poses immediate risk of death to this patient.

Serious adverse events (SAEs) will be grade 3 or 4 AE or any AE requiring hospitalization.

SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others happen during the course of this study (including SAEs) these will be entered into the local database and transferred to the OnCore database (if necessary). Unanticipated problems will be reported to the IRB according to current IRB guidelines. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format entered into the OnCore database and submitted to the IRB at the time of continuing review per current IRB guidelines.

8.3.3 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the current Case Comprehensive Cancer Center Data and Safety Monitoring Plan, in accordance with NCI regulations. The Data and Safety Toxicity Committee will review all serious adverse events and toxicity reports as well as protocol deviations.

9.0 FINANCIAL CONSIDERATIONS

There will be no cost to subjects for the additional experimental tests (MRF) on this study. Subjects and their insurance providers will be responsible for the payment of procedures that are considered standard of care, including doctor visits, MRIs (including DTI, which is part of the standard clinical MRI), medications and all other medical care.

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