DF/HCC NON-CLINICAL PROTOCOL TEMPLATE
Version Date: October 2, 2017

PROTOCOL TITLE:

The Value of Advanced MR Imaging
in Gynecological Tumors and Benign Uterine Fibroids

PRINCIPAL INVESTIGATOR:

Dr. Clare Tempany MB BAO BCh, FACR, FISMRM
Department of Radiology
Tel: 617-732-7858
ctempany@bwh.harvard.edu

VERSION NUMBER:

Version 1.0

DATE:

March 7, 2019

Table of Contents

1.0 Objectives*

Magnetic Resonance Fingerprinting (MRF) and Q-space Trajectory Imaging (QTI) are advanced new magnetic resonance imaging (MRI) sequences that provide rapid quantitative tumor metrics and enable visualization of the tumor microstructure, respectively. This would have substantial value in diagnostics and tumor characterization in cases such as insufficient biopsy specimens, MRI-guided treatment planning, and in evaluating treatment response and differentiating residual tumor from treatment related changes. Furthermore, quantitative metrics from MRF and QTI may provide prognostic or predictive biomarkers that guide the proper oncologic workup and treatment for the patient. We hypothesize that QTI provides deeper insight into the tissue microstructural environment and that quantitative metrics from QTI and MRF accurately characterize the gynecological malignancy in comparison with the tumor histology. Furthermore, we hypothesize that MRF and QTI provide prognostic information valuable to the patient and treating physician.

Primary Objective

- to investigate the feasibility of advanced MRI sequences in participants with gynecologic malignancy and in control participants with benign uterine fibroids by measures of image quality and by comparing the MRI parameters between different tumor entities and normal anatomic structures

Secondary Objectives

- to study the diagnostic value of MRF and QTI in characterizing the tumor by comparing the tumor parameters with normal structures, benign fibroids, and tumor histology
- to study the prognostic value of MRF and QTI by comparing tumor parameters with treatment effect and participant outcome

2.0 Background*

Uterine cervical, endometrial, and ovarian cancer are the most common gynecologic malignancies, with cervical cancer being worldwide the leading cause of cancer-related death in women. Conventional MRI is routinely used in gynecologic malignancies for its ability to depict the extent of disease at diagnosis providing guidance in staging and treatment planning [1–3]. Diffusion weighted imaging (DWI) and dynamic contrast enhanced MRI further improve tumor delineation and characterization and are often included into standard protocol [4]. Moreover, DWI has shown promise regarding histological grading and subtype differentiation within endometrial and cervical cancer, however, results are not fully consistent [2, 5].

MRF is a recently introduced approach in accelerating multiparametric quantitative MR imaging [6]. Quantitative MRI methods, as opposed to traditional visual assessment of images, provide objective parameters and would particularly be advantageous in oncology for diagnosis, treatment response assessment and follow-up to reduce subjectivity of image interpretation. Traditional quantitative MRI approaches, however, are relatively slow and provide only a single property at a time. In MRF, multiple tissue properties are acquired simultaneously by randomly varying the sequence parameters [7]. Pattern recognition is then used to compare each voxel's signal fingerprint with a dictionary of anticipated combinations of tissue properties, to identify the best match of a tissue property for that voxel. MRF enables simultaneous measurement of multiple tissue properties such as T1, T2, T2*, B0, proton density, and perfusion. MRF has mainly been employed in brain imaging [8]. Recently, the proof-of-principle for using MRF in abdominal imaging and prostate cancer, was reported [9, 10].

QTI is a framework for advanced diffusion MRI that enables imaging of the tissue microstructure on a sub-voxel level that is not possible with the traditional diffusion MRI [11, 12]. By using q-space trajectory encoding and a diffusion tensor distribution model, QTI improves the discrimination of diffusivity, shape, and orientation of diffusion microenvironments and therefore carries major potential for imaging the tumor microenvironment. The feasibility of QTI in brain MR imaging has been shown in pilot studies involving patients with schizophrenia and brain tumor [12–14]. Furthermore,

studies that investigate the role of QTI in unraveling the microstructure of both brain and prostate cancers are in progress at Brigham and Women's Hospital (BWH). Neither MRF nor QTI have previously been studied in gynecological malignancies.

3.0 Inclusion and Exclusion Criteria*

Patients with gynecological cancer who are referred to receive treatment at Brigham and Women's Hospital (BWH) and/or Dana-Farber Cancer Institute (DFCI), and who will undergo routine clinical standard of care pelvic MRI, are eligible to participate in the study. Subjects with benign uterine fibroids referred to routine pelvic MRI at BWH will serve as controls.

Inclusion Criteria

- Participants with suspected or histologically confirmed diagnosis of primary or recurrent gynecological cancer including uterine endometrial, cervical, vaginal, vulvar, ovarian, and smooth-muscle tumors undergoing routine clinical standard of care pelvic MRI
- Control subjects with benign fibroids undergoing routine clinical standard of care pelvic MRI
- Age ≥ 18 years
- ECOG performance status of ≤ 2, based on treating physician's discretion (Appendix A)
- Ability to understand and the willingness to sign a written informed consent document

Exclusion Criteria

- Contraindication to MRI identified by the MR procedure screening form, such as a pacemaker, aneurysm clip, inner ear implant, neurostimulator, or other MR non-compatible device or implant
- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac

arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

- Adults unable to consent
- Non-english speaking subjects
- Pregnant women
- Prisoners

4.0 Study-Wide Number of Subjects*

N/A

5.0 Study-Wide Recruitment Methods*

N/A

6.0 Multi-Site Research*

N/A

7.0 Study Timelines*

Participation in this research study requires 10–15 minutes additional scanning time to perform QTI or MRF along with the routine clinical standard of care pelvic MRI. No other procedures or extra hospital visits are required by the participants. Anticipated duration to enroll all study subjects is 1–2 years. The estimated date to complete this study (complete primary analyses) is 05/31/2021.

8.0 Study Endpoints*

Please see section 1.0 for primary and secondary study objectives.

9.0 Procedures Involved*

The eligibility of participants with gynecologic cancer will be evaluated by the treating gynecologic surgeon or oncologist during the routine standard of care practice at

BWH/DFCI. If a participant meets the inclusion criteria, she will be informed about the study both orally and in paper by handing out the informed consent form. If the subject is willing to participate in the study, her signature to the consent form is obtained by the treating physician at the end of the appointment. In case the participant requests time for reflection, the consent signature can be obtained just prior to MRI by the research coordinator.

The eligibility of control participants with benign fibroid(s) is evaluated by the treating interventional radiologist based on the referral and a phone call made to the participant to give information about the study (Phone Script in Appendix B). Upon eligibility, informed consent will be sent by email or mail. Signature to the consent form will be obtained by a research coordinator prior to the MRI scan.

If the subject is willing to participate in the study, the advanced MRI sequence (either QTI or MRF) will be run along with the routine standard of care MRI. If the subject wishes not to participate, only standard of care MRI sequences will be performed according to the routine protocol.

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC SOP REGIST-101. When required by REGIST-101, registration must occur prior to the initiation of protocol-specific procedures or assessments.

Routine clinical standard of care pelvic MRI will be performed using a clinical 3T MRI scanner at BWH. The advanced MRI sequence (MRF or QTI) will be supplementary and included along with the current clinical exam. No invasive procedures are needed for MRF or QTI. No extra hospital visit is required related to this study. The duration of routine clinical pelvic MR exam is approximately 30–45 minutes. Running MRF or QTI along with the routine clinical protocol will add this scanning time by approximately 10–15 minutes. There are no reported toxicities related to MRI itself when all the safety guidelines are being followed. No intravenous contrast agent is needed for the advanced MR

sequences (QTI and MRF). Scanning time will be increased with 10–15 minutes which may cause discomfort to participants due to laying on the scanning table for a longer period of time.

Follow-up data including treatment outcome, tumor histology, clinical variables, laboratory results, medical images, and survival data, will be collected from the participant's electronic medical records. For survival data, the duration of follow-up is up to 4 years after participation and the MRI scan with new MRI methods.

10.0 Data and Specimen Banking*

N/A

11.0 Data Management* and Confidentiality

11.1 Data analysis plan and statistical procedures

Primary endpoint of this study is to evaluate the feasibility of MRF and QTI in gynecological pelvic MRI. Feasibility will be assessed in two ways. First, the aspects of image quality such as artifacts, sharpness, and noise will be evaluated by two radiologists. Second, regions-of-interest (ROI) of the tumor and normal tissue (uterine normal endometrium, myometrium, cervical stroma, ovaries) will be recorded and ROI-based parameters from MRF (T1 and T2 relaxation values) and QTI (total mean kurtosis MK_T, microscopic anisotropy MK_A, isotropic heterogeneity MK_I, fractional anisotropy FA, microscopic fractional anisotropy μFA) will be compared between the tumor and normal tissue, and between different tumor histologies. One-way analysis of variance will be used to determine the statistical difference of each MRF and QTI value between the malignant tumors, benign fibroids, and normal tissue.

Secondary endpoint is to assess the predictive and prognostic value of MRF and QTI in gynecological malignancies. For this purpose, MRF and QTI parameters from gynecological malignancies will be compared with the treatment effect

assessed by clinical examination and/or cross-sectional follow-up imaging, and the participants' outcome by means of Kaplan-Meier method with log rank test, and Cox proportional-hazards model.

Variables that will be collected include the quantitative MRI parameters, demographic information (age, sex), clinical variables (diagnosis, tumor stage, histopathologic and molecular data, laboratory results, treatment, dates of diagnosis and treatments), follow-up images, and outcome data (recurrences, survival). An Excel database including MRI and clinical variables will be developed for the purposes of this study.

11.2 Power analysis

The sample size calculation is exploratory in nature since no protocols with MRF or QTI in gynecological imaging have been published. One prior publication reports the range of traditional T2 relaxation values in one patient with endometrial cancer [15]. Based on the average value of 78 ms T2 relaxation time in endometrial cancer, and on the assumption of 5% difference to other histologies and SD of 5 ms, the calculated targeted sample size is 27 patients per group with power set at 80% and type I error rate of 5% (www.sample-size.net/sample-size-means/).

11.3 Data safety and quality

To secure the data during storage, use, and transmission, only investigators with the required training and authorization of access will analyze the data. All the computers handling the data will be encrypted and password-protected. The principal investigator and the research group will be responsible for continuous monitoring of the data quality and data safety.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

N/A. This research proposal does not involve more than Minimal Risk to subjects.

13.0 Withdrawal of Subjects*

Participants will be removed from the study in case of a withdrawal of consent for data submission

14.0 Risks to Subjects*

There are no reported toxicities related to MRI itself when all the safety guidelines are being followed. No intravenous contrast agent is needed for MRF or QTI. Storing and use of data pose a minimal risk to the confidentiality and participant's privacy.

Potential risks, discomforts, and hazards related to MRI

- Anxiety, stress
- Claustrophobia
- Discomfort due to laying on the scanning table for a longer period of time (10–15 minutes)
- Rare but serious: Injury associated with foreign bodies and the MR magnet; this is most likely to occur should the institution fail to ask or should a participant fail to inform the site of contraindications to MR use (e.g. presence of metallic or surgical implant or metal pieces in the body)

15.0 Potential Benefits to Subjects*

There are no expected direct benefits to participants included in this pilot study.

16.0 Vulnerable Populations*

N/A

17.0 Community-Based Participatory Research*

N/A

18.0 Sharing of Results with Subjects*

Results will not be shared with participants.

19.0 Setting

Potential study subjects will be identified by the treating physician at BWH/DFCI. The following standard of care pelvic MRI will be scheduled into either one of the two clinical MRI scanners at BWH/DFCI that include the new sequence, QTI (3.0 Tesla Siemens Magnetom Prisma at Hale Building for Transformative Medicine) or MRF (3.0 Tesla Siemens Verio at BWH main building L1) upon the subject's interest in participating into the study.

20.0 Resources Available

The primary research team involves the principal investigator and co-investigators. Investigators include radiologists and computer scientists who are experts in the field of diagnostic MRI, technical aspects of new advanced MRI sequences, and MRI analysis. The investigators also include treating physicians in the field of gynecological surgery, radiation oncology, interventional and diagnostic radiology, who will ensure that participants eligible for this study are recruited in line with the study objectives. All study staff will have completed required training per DF/HCC SOP EDU-100: Training Requirements for Research Personnel, prior to starting on any research procedures associated with this protocol.

21.0 Prior Approvals

N/A

22.0 Recruitment Methods

Please see section 9.0 for recruitment methods.

23.0 Local Number of Subjects

Based on sample size calculation (see Section 11.2 Power Analysis), following number of participants will be included in this research study:

1. MRF for participants with gynecologic malignancy; n=27
2. MRF for participants with benign uterine fibroid; n=27
3. QTI for participants with gynecologic malignancy; n=27
4. QTI for participants with benign uterine fibroid; n=27

24.0 Provisions to Protect the Privacy Interests of Subjects

Personal health information (PHI) will only be used for research purposes and released solely to study staff listed on the protocol. The participant name and medical record number will be used to download images from PACS and to collect clinical information regarding treatment, pathology, and outcome from the medical record. All of these are obtainable only by using PHI which will be stored electronically on a password-protected encrypted computer. Participant's clinical information will be coded using a unique code number identifier. Access to the code key linking the hospital identification number will be limited to the study investigators. Any clinical data shared with collaborators (statistician) will be supplied with code number identifiers only, without PHI.

25.0 Compensation for Research-Related Injury

No compensation is available since this research does not involve more than Minimal Risk to subjects.

26.0 Economic Burden to Subjects

Participating in the study will not lead to additional costs to the subjects. The routine clinical standard of care pelvic MRI is covered by the participant or her insurance company as usual. Subjects will not be charged for including QTI or MRF to the routine protocol.

27.0 Consent Process

Informed Consent Process according to SOP# CON-100 will be followed. Please see section 9.0 for the detailed consent process.

28.0 Process to Document Consent in Writing

Informed Consent Process according to SOP# CON-100 will be followed.

29.0 Drugs or Devices

N/A

30.0 References

1. Freeman SJ, Aly AM, Kataoka MY, et al (2012) The revised FIGO staging system for uterine malignancies: implications for MR imaging. Radiographics 32:1805–27. https://doi.org/10.1148/rg.326125519
2. Nougaret S, Horta M, Sala E, et al (2018) Endometrial Cancer MRI staging: Updated Guidelines of the European Society of Urogenital Radiology. Eur Radiol. https://doi.org/10.1007/s00330-018-5515-y
3. Sadowski EA, Robbins JB, Rockall AG, Thomassin-Naggara I (2018) A systematic approach to adnexal masses discovered on ultrasound: the ADNEx MR scoring system. Abdom Radiol 43:679–695. https://doi.org/10.1007/s00261-017-1272-7
4. Park S Bin (2016) Functional MR imaging in gynecologic malignancies: current status and future perspectives. Abdom Radiol 41:2509–2523. https://doi.org/10.1007/s00261-016-0924-3
5. Dappa E, Elger T, Hasenburg A, et al (2017) The value of advanced MRI techniques in the assessment of cervical cancer: a review. Insights Imaging 8:471–481. https://doi.org/10.1007/s13244-017-0567-0
6. Ma D, Gulani V, Seiberlich N, et al (2013) Magnetic resonance fingerprinting. Nature 495:187–192. https://doi.org/10.1038/nature11971
7. Bipin Mehta B, Coppo S, Frances McGivney D, et al (2018) Magnetic resonance fingerprinting: a technical review. Magn Reson Med. https://doi.org/10.1002/mrm.27403

8. Panda A, Mehta BB, Coppo S, et al (2017) Magnetic resonance fingerprinting – An overview. Curr Opin Biomed Eng 3:56–66. https://doi.org/10.1016/j.cobme.2017.11.001
9. Chen Y, Jiang Y, Pahwa S, et al (2016) MR Fingerprinting for Rapid Quantitative Abdominal Imaging. Radiology 279:278–286. https://doi.org/10.1148/radiol.2016152037
10. Yu AC, Badve C, Ponsky LE, et al (2017) Development of a Combined MR Fingerprinting and Diffusion Examination for Prostate Cancer. Radiology 283:729–738. https://doi.org/10.1148/radiol.2017161599
11. Westin C-F, Szczepankiewicz F, Pasternak O, et al (2014) Measurement tensors in diffusion MRI: generalizing the concept of diffusion encoding. Med Image Comput Comput Assist Interv 17:209–16
12. Westin C-F, Knutsson H, Pasternak O, et al (2016) Q-space trajectory imaging for multidimensional diffusion MRI of the human brain. Neuroimage 135:345–362. https://doi.org/10.1016/j.neuroimage.2016.02.039
13. Szczepankiewicz F, van Westen D, Englund E, et al (2016) The link between diffusion MRI and tumor heterogeneity: Mapping cell eccentricity and density by diffusional variance decomposition (DIVIDE). Neuroimage 142:522–532. https://doi.org/10.1016/j.neuroimage.2016.07.038
14. Nilsson M, Englund E, Szczepankiewicz F, et al (2018) Imaging brain tumour microstructure. Neuroimage 182:232–250. https://doi.org/10.1016/j.neuroimage.2018.04.075
15. Ghosh A, Singh T, Bagga R, et al (2018) T2 relaxometry mapping in demonstrating layered uterine architecture: parameter optimization and utility in endometrial carcinoma and adenomyosis: a feasibility study. Br J Radiol 91:20170377. https://doi.org/10.1259/bjr.20170377