CASE WESTERN RESERVE UNIVERSITY | CASE COMPREHENSIVE CANCER CENTER

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

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Study Title: ***Role of Magnetic Resonance Fingerprinting and Quantitative MR Imaging in Assessment of Response to Neo-Adjuvant Chemotherapy in Breast Cancer***

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Statistician:

Support/Funding:

Study Site(s):
University Hospitals Health System

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Version date/#	Section #/page	Description of change (s)	Rationale for change
V1.4, 4/15/20	Section 11 Compensation	Patient stipend increase: visit 1 from $20 to $100 visit 2 from $20 to $150 visit 3 from $20/100 to $50/100	Increased enrollment
V1.5 5/21/2020		Visit 2: addition of anatomical imaging-no additional time	Anantomical images as reference for 3D MRF
09/01/2020	Section 3: Objective/Hypothesis Section 4: Recruitment Section 4.4.2 Study procedures	Addition of single pre-therapy scan for patients with low Mammaprint scores	Patients with low Mammaprint scores will not undergo chemotherapy, but will provide a useful genetic control group to compare with the existing cohort of breast cancer patients.
9/24/2020	Section 4.3 vulnerable populations	Rescinded previous attempt to include non-english speaking individuals	translated documents and translators not available

1. Introduction

There has been a growing trend towards using quantitative MRIs for early response assessment in oncology[1]. Methods already utilized clinically for measuring treatment response in breast cancer include 1) size criteria, 2) diffusion weighted imaging (DWI) with calculation of Apparent Diffusion Coefficient and 3) Contrast-enhanced dynamic contrast enhanced MRI (DCE-MRI)[2-4]. While these techniques assess various tumor properties such as volume, cellularity and perfusion, these techniques have their own individual limitations. For example, a change in size requires at least 2-3 cycles of chemotherapy to be measurable and have a predictive value[5]. Waiting till at least 2-3 cycles or mid-therapy to detect non-response implies that patients might be subjected to unnecessary cycles of ineffective treatment. Thus earlier measures of treatment response are essential. While DWI and DCE-MRI in combination have shown to be useful for early prediction of treatment response[6,7], DWI is hampered by low signal-noise-ratio in breast imaging and the measured ADC is highly dependent on MR system parameters and b-values used[8]. DCE-MRI requires administration of contrast and quantitative analysis of DCE-MRI is complex and time-consuming. Moreover, the results from DCE-MRI are affected by physiological factors, acquisition technique and post-processing pharmacokinetic modeling used for analysis[2,9,10].

On the other hand, T1 and T2 relaxation times represent intrinsic tissue properties in MRI. Relaxometry, i.e. measurement of T1 and T2 relaxation times can also provide objective and reproducible information about pathology. Older studies showed that relaxation times differed between healthy breast tissue and breast cancers[11,12] and could potentially be used to predict early response to chemotherapy[13-15]. However, relaxometry as a response assessment technique has not yet crossed the translational gap because it is technically difficult in breast and there is very limited evidence on breast relaxometry for response assessment. We developed a novel 3D Breast

Magnetic Resonance Fingerprinting (3D MRF) technique, which allows simultaneous estimation of both T1 and T2 relaxation times in a clinically feasible manner and in less than 6 minutes of scan time[16]. This is a volumetric acquisition technique that generates co-registered quantitative maps to characterize breast tumor and peritumoral and contralateral breast tissue.

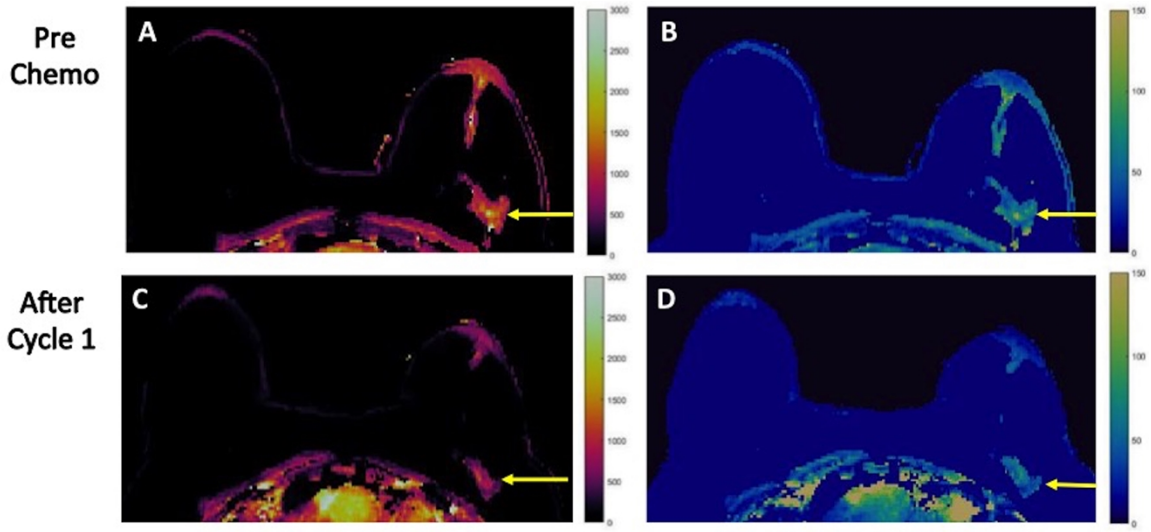
2. Preliminary Studies:

Our preliminary work on 3D breast MRF has shown that there are significant differences in T1 and T2 relaxation times between tumor and normal breast tissue[16, 17]. We scanned 12 women with biopsy proven breast cancer and the tumor T1 and T2 relaxation were longer compared to normal breast tissue (mean ± SD, Tumor T1: 1156 ± 200 ms, Normal breast T1: 846 ± 388 ms, Tumor T2: 72 ± 14 ms, Normal breast T2: 48 ± 12 ms, $p = 0.039$ for T1, $p < 0.001$ for T2). In addition, we performed a repeat 3D MRF scan after one cycle of chemotherapy in 7 patients and patients with decrease in tumor size showed significant decrease in tumor T1 and T2 relaxation times while non-responders showed only a negligible change in tumor T1 and T2 relaxation times[17] (Table 1). Figure 1 shows representative 3D breast MRF maps from one patient who was scanned before and after one cycle of chemotherapy. Thus we hypothesize that 3D MRF before, during and after chemotherapy can provide additional quantitative information about changes during treatment and may predict early response to chemotherapy.

Table 1: Pilot data showing greater % decrease in T1 and T2 relaxation times in patients showing treatment response after one cycle of chemotherapy compared to non-responders

Patient No	**Baseline tumor size (cm)**	**%Δ Size after one cycle of treatment**	**%Δ Tumor T1 after one cycle of treatment**	**%Δ Tumor T2 after one cycle of treatment**	**Response status by surgical pathology staging or RECIST criteria**
1	3.6	-25	**-43**	**- 20**	Responder (pCR)
2	3.0	-20	**-13**	**-22.5**	Responder (pCR)
3	2.0	-45	**-26**	**-27**	Partial Response (RECIST)
4	2.3	-39	**-23**	**-54**	Partial Response (RECIST)
5	3.6	-11	**3.6**	**-5**	Non-Responder (pT2N2)
6	3.3	58.00	**6**	**-2**	Progressive Disease (RECIST)
7	1.5	-13	**0**	**5**	Stable Disease (RECIST)

Figure 1: Representative T1 (A,C) and T2 (B,D) MRF color maps of tumor before and after one cycle of chemotherapy in a patient who was treatment responder. Pre-treatment T1 and T2 were 1087 ms and 60 ms respectively while post treatment T1 and T2 were 619 ms and 47 ms respectively



3. Objectives/ Hypothesis

- To assess the utility of quantitative MRI in assessment of response to neo-adjuvant chemotherapy in breast cancer

- MR Fingerprinting based relaxometry allows quantification of T1 and T2 relaxation times of tumor and normal breast tissue. Response to chemotherapy is associated with measurable changes in these properties and may be used to predict treatment response earlier than conventional MRI.

- We hypothesize that 3D MRF before, during and after chemotherapy can provide additional quantitative information about changes during treatment and may predict early response to chemotherapy.
- We hypothesize that MRF-based T1 and T2 maps will be significantly different for breast cancer patients with low and high MammaPrint scores before therapy. This will provide additional capability to differentiate low grade and high grade breast cancer and potentially eliminate the need for invasive biopsy.

4. Research Plan

4.1 Recruitment

Patients will be identified from clinical visits to UH Breast Surgery/Hematology-Oncology Clinics and Radiology and the MRI inpatient/outpatient schedules. Patients will be recruited for two different study cohorts:

1. Patients with biopsy proven cases of breast cancer who will undergo chemotherapy treatment. These subjects will receive 3 MRI scans: 1 before chemotherapy, Scan 2 one week to ten days after the first round of chemotherapy, Scan 3 after completion of chemotherapy.
2. The range of scores for MammaPrint is -1 to +1. Any score above 0 is considered low risk. Any patients who have scores 0.355 or above are considered Ultra Low Risk. Patients with biopsy proven cases of breast cancer who have had a low MammaPrint assessment will not be treated with chemotherapy prior to surgery as per clinical standard of care. These subjects will receive only one MRI scan before clinically indicated surgery and/or therapy.

We propose the following pathways for patient recruitment:

- for patients first seen at the Clinics, the treating physician (breast cancer surgeon/breast oncologist) will introduce the study and a flyer with key information about the study may be given to the patient. If the patient shows willingness to participate, the patient's MRN will be sent via UH email to the Radiology Research Coordinator for actual study consent on the day of the baseline diagnostic MRI at UHCMC.

- if the patient has already had a diagnostic scan elsewhere before visiting the Clinic and is still interested in participating in the study, they will be scheduled for a *research only* non-contrast MR Fingerprinting scan at UHCMC before starting chemotherapy.

- alternatively, for patients who are first scheduled for breast MRI at UHCMC Radiology department, consenting will be directly done on the day of MRI without a referral from the breast clinic.

We are requesting a HIPAA waiver to identify eligible patients before approaching them to participate in the study. To confirm study eligibility, we will access the Physician Portal to get information about the breast cancer diagnosis and pathology results.

Request for waiver of HIPAA authorization and waiver of consent: We are requesting a waiver of HIPAA authorization and waiver of consent for identifying and contacting patients in person and not a waiver of the consent for the research study as such. We intend to identify patients from physician portal, inpatient/outpatient MRI schedule and/or referred by treating physician for a clinically indicated breast MRI and contact them in person. There will be no improper use of or disclosure of PHI under this waiver. The investigator will take precautions to protect the subject's privacy and the confidentiality of the data pertaining to his/her participation in this research study. Only the research staff will access the PHI for above described purpose. The patient identifiers accessed under this waiver of HIPAA authorization will not be retained. The identifiers will be destroyed on the same day once the purpose of contacting the patients in person is complete. We assure that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule. We are requesting a waiver of HIPAA authorization for contacting the patients in person and not a waiver of informed consent process for the study itself. For this purpose, the waiver of HIPAA authorization and waiver of consent is necessary for recruitment. We will not be able to meet our recruitment goals without this waiver.

Inclusion and exclusion criteria will be assessed for each potential study patient, and written informed consent will be obtained by qualified study personnel in a private setting at UHCMC.

We will also obtain contact information of the patients to schedule them for follow-up scans for assessing tumor response. We hope to get at least one-two eligible patients per week and recruit patients over the first eighteen months. Since the chemotherapy regime takes about 4-6 months to complete followed by surgery, we hope to get the complete information for the last patient recruited within 2 years of initiating the study

4.2 Inclusion/Exclusion Criteria

	Inclusion Criteria:
1.	Biopsy proven cases of breast cancer
2.	Women ages 18 and over

	Exclusion Criteria
1.	Patients with *only* benign lesion
2.	Patients with *only* ductal carcinoma in situ (DCIS)
3.	Patients with recurrent/ residual breast cancer in same breast
4.	Pregnant women
5.	Lactating Women
6.	Patients with ferromagnetic or otherwise non-MRI compatible aneurysm clips.
7.	The presence of an implanted medical device that is not MRI-compatible, including, but not limited to: pacemaker, defibrillator
8.	Patients with contraindications for MRI due to embedded foreign metallic objects. Bullets, shrapnel, metalwork fragments, or other metallic material adds unnecessary risk to the patient.
9.	Known history of severe claustrophobia.
10.	Patients under the age of 18
11.	For patients with known history of allergic reaction to MR contrast material or abnormal kidney function (GFR < 40 mL/ min), a contrast enhanced exam will not be performed; however, a non-contrast exam may be performed in these patients.

4.3 Vulnerable Populations

Illiterate individuals may be enrolled by having a witness present at the time of consent. The consent form will be read to the participant and they will sign the consent by making their mark in the signature section. A witness will be present to confirm the consent process has taken place; the witness will sign the consent document. We will not actively recruit students and employees of UH and CWRU, however, they will not be excluded from participation. UH/CWRU students and employees who may consider participation will be informed that their decision to participate will in no way influence their job or status in any way and study results will not be reported to their supervisor. We will not actively recruit student or employee populations, but they will not be excluded if they otherwise meet enrollment criteria.

Prisoners and many other vulnerable populations will be excluded from this study; these populations will not provide any unique information to the study and will not benefit from participation.

4.4 Methods

4.4.1 Breast MRI:

This is a prospective, longitudinal study comprising of pre-treatment baseline scan, interim scan after one cycle of chemotherapy and end-of-chemoetherapy scans. The research sequence being evaluated is 3D MR Fingerprinting sequence. This is a painless technique that takes about 6 minutes to perform and does not have any risks or discomfort other than those associated with regular breast MRI. 3D MR Fingerprinting technique is also a non-contrast technique and generates quantitative information about MR-visible tumors without having to administer contrast. Since we propose to add 3D MR Fingerprinting sequence to regular clinical MRI scans ordered as part of standard of care, this would only add approximately 20 minutes to overall scan time. For patients who undergo research only 3D MR Fingerprinting scans, the entire scan time would be approximately 30 minutes, less than the time taken for regular clinical MRIs. All patients would be screened for MR Safety and Eligibility to eliminate any risks of undergoing MRI, For patients getting contrast (Gadavist®) for research purposes, the eGFR would be checked from patient records and contrast would only be administered to patients who have a documented eGFR > 40 ml/min/1.73 m^2 within the previous 3months.

4.4.2 Study procedures:

Radiology study personnel will obtain consent in the Radiology department prior to performing 3D MR Fingerprinting scans. Consent to participate will be obtained prior to performing any research scans:

Visit 1: 3D MR Fingerprinting images will be added to the clinical MRI scan before start of chemotherapy or before surgery for the MammaPrint cohort. The additional research images will take less than 20 minutes to acquire.

Visit 2: Patients receiving chemotherapy will be scheduled for a research only non-contrast 3D MR Fingerprinting and anatomical MRI scans 7- 10 days after the first cycle of chemotherapy. Acquisition of images will take approximately 30 minutes.

Visit 3: For patients receiving chemotherapy, if the treating physician orders a clinical MRI scan within 1 month of end of chemotherapy treatment, we will add a 3D MR Fingerprinting sequence to the clinical scan. The additional research images will take less than 20 minutes to acquire.

If the patient is not scheduled for a clinical scan within 1 month of end of chemotherapy treatment, we will contact the patient to schedule a research only 3D MR Fingerprinting scan. Breast cancer is hard to visualize on MRI post treatment, so we would like to administer IV gadolinium contrast for research purposes. Patients will be reconsented prior to the research only scan to determine whether or not they will receive IV contrast. If the patient declines

administration of contrast for the post treatment scan, we will perform a non-contrast scan. Acquisition of images will take 30-45 minutes.

Criteria for response assessment

Final surgicopathology results would be used for response assessment. Thus pathology reports with pT0N0 would be designated as pathological complete response while pT0 but with residual nodal deposits on pathology would be considered as primary tumor response for analysis purpose. Presence of any residual tumor on pathology would be considered as non-responder.

In the sub-group of patients who fail to undergo surgery at the end of treatment due to reasons beyond the control of study researchers, RECIST version 1.1 criteria would be considered as surrogate criteria for response (1). Thus no visible tumor and nodes at end of treatment scan will be considered complete response, >30% decrease in long-axis diameter (LAD) compared to baseline will be partial response, > 20% increase in LAD will be progressive disease while < 30% decrease/ > 20% increase in LAD will be considered stable disease.

All categories of response would be considered independently for analysis.

5. STUDY PARAMETERS/ DATA COLLECTION

Data may be extracted from UH patient medical records by UH research-credentialed (CREC/CITI-certified) or UH employees and recorded onto UH Radiology password-protected computers. Data will be collected and stored in REDCap or in a password protected folder on the secured UH s:drive in order to correlate image findings with patient progress/care. Data will include the following:

- Name
- MRN
- Age
- Email
- Phone number
- Date of last menstrual period
- Date of biopsy
- Biopsy results
- TNM status/cancer stage
- Pathology report with hormone receptor status
- MammaPrint score
- Chemotherapy schedule and treatment regime
- Date of surgery
- Type of surgery (mastectomy or breast conserving surgery)
- Final surgical pathology
- MRI images

6. STATISTICAL CONSIDERATIONS

1. From the 3D MR Fingerprinting maps, T1 and T2 relaxation times will be obtained for tumor, and peritumoral and normal breast tissue at all three scans.
2. From routine MRI scans, the tumor size and tumor ADC will be obtained.
3. Changes in all quantitative measurements will be compared between responders and non-responders based on final surgical pathology and the predictive value of 3D MR Fingerprinting as compared to existing techniques would be assessed using appropriate t-tests and logistic regression analysis.

Sample Size Calculation: Based on our pilot data, we expect a 25% change in T1 and T2 relaxation times in responders and less than 7% change in non-responders with an effect size of 18% (0.18). At a significance level of 0.05 and power of 80%, the expected sample size is 62. Based on our pilot data, we also expect an attrition and drop-out rate of 50%, and thus total number of subjects recruited will be 124.

7. POTENTIAL RISKS

7.1 Breast MRI

Certain metals are not safe to go into an MRI scanner. Prior to all MRI exams (standard clinical or research), stringent safety checklists will be used to determine if an MRI study can be performed on each patient. All patients will be receiving an MRI exam as part of the standard of care at baseline. This study will add several minutes to the duration of this baseline exam, but will not need any additional administration of contrast agents or drugs.

7.2 MRI Contrast Agent

If the referring physician schedules a standard-of-care MRI exam within 1 month of completion of chemotherapy, MRI contrast agent will not be administered for research purposes.

However, if the referring physician does not schedule a standard-of-care MRI exam within 1 month of completion of chemotherapy treatment (for visit 3), a research only exam will be performed. This exam will include administration of MRI contrast agent unless the subject declines contrast administration. If contrast is administered for research only purposes in this subset of patients, the following risks are present:

Potential risks of IV contrast agents are allergic reaction. Gadolinium-based contrast agents (dyes) may increase the risk of a rare but serious disease called nephrogenic systemic fibrosis in people with poor kidney function with drastically decreased glomerular filtration rate (GFR) below 30ml/min, Chronic kidney disease, CKD 4 and 5). To exclude the risk of Gadolinium induced nephropathy, we will exclude all patients with a GFR below 40 ml/min. This threshold is considerably higher than the current clinical threshold of GFR below 30.

Over 300 million doses of Gadolinium based contrast agents (GBCAs) have been administered since the introduction of these medications in the mid 1980s. The known and

proven adverse effects of these drugs are the possibility of allergic reactions (rare and idiosyncratic), and the development of the extremely rare disease Nephrogenic Systemic Fibrosis (NSF) with the administration of contrast agents in patients with severe renal dysfunction. NSF has been virtually eliminated upon not administering GBCAs in patients with end stage renal disease. Additional precautions such as minimizing use of GBCAs associated with NSF, and elimination of simultaneous administration of double/triple doses of agents, have also contributed. While all GBCAs are known to deposit in neural and other tissues, no harmful effect of this deposition has been documented[18].

7.3 Confidentiality

Finally, there is a risk of a breach of confidentiality. To lower this risk, information will be de-identified by a co-investigator trained in the protection of PHI (Protected Health Information). A unique study code will be assigned to every study subject. This code will be used instead of identifiable information to describe which study subject is which when cases are discussed among study personnel.

8. BENEFITS

There may be no direct health benefits for participation in this study. Participation in this study will help the investigators determine whether these MRI techniques are useful, and may provide benefit to patients undergoing MRI examinations in the future.

9. ALTERNATIVES TO PARTICIPATION

Patients may choose not to participate in this study and clinical care will not be affected.

10. COST TO RESEARCH PARTICIPANTS

The study will pay for all procedures that are directly associated with this research study. Procedures or drugs that are considered standard of care will be the responsibility of the patient and their insurance company.

11. COMPENSATION

Visit 1: Subjects will receive $100 for research scan
Visit 2: Subjects will receive $150 for non-contrast research scan
Visit 3: Subjects will receive $50 for non-contrast research scan or $100 for contrast research scan

9. ADVERSE EVENTS

An adverse event (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments. Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of

the subject. In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

Grades 1 are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

Grades 2 are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 4 are life threatening or disabling adverse events (e.g., complicated by acute, life threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grades 5 are fatal adverse event resulting in death.

9.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

1. Results in death.
2. Is a life-threatening adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as serious, UNLESS at least one of the following expectations is met:
4. The admission results in a hospital stay of less than 12 hours OR
5. The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
6. The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care. However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be

reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

7. Results in persistent or significant disability/incapacity. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
8. Is a congenital anomaly/birth defect.
9. Is an important medical event. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.2 Expectedness

Adverse Events can be Expected or Unexpected.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

9.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for AEs for 30 days after biopsy or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

1. Description of the event
2. Date of onset and resolution
3. Grade of adverse event
4. Action taken as a result of the event
5. Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for AE reporting.

Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

9.4 Reporting Procedure for Serious Adverse Event

Serious adverse events that occur beginning with the signing of the informed consent form, or within 30 days of the individual undergoing prostate biopsy must be reported to the University Hospitals Principal Investigator.

10. RECORDS/DATA TO BE KEPT

10.1 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

10.2 Written Informed consent

Provision of written informed consent will be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects will also be notified that they are free to discontinue from the study at any time. The subject will be given the opportunity to ask questions and allowed time to consider the information provided.

The consent will take place at the clinical practices of the listed co-investigators in a private location. The patients will be evaluated a second time for MR safety prior entering the magnet prior to each MRI examination.

The original, signed written Informed Consent Form will be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form will be given to the subject.

10.3 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

10.4 Accessing Electronic Medical Records for University Hospitals Health System

This study will access electronic medical records systems to obtain medical information for the subjects enrolled in this study. We seek a HIPAA waiver to identify eligible patients and check whether patients meet inclusion criteria before approaching them for the study (see Recruitment section 4.1).

In order to ensure patient safety, investigators and study personnel must have up-to-the minute health information for subjects enrolled to this study. Therefore, electronic medical records must be utilized to obtain medical information in a timely manner. The following electronic systems will be used: IDX program to access scheduling information; UH Physician Portal/EMR/AEMR to access lab results and physician notes; PCOSS LITE as necessary to locate archived medical records; COPATH to locate archived pathology records; PACS to access radiological imaging results; and MySecureCare (Sunrise Clinical Manager) to access some or all of the above information when this application is fully functional.

Access to these systems is required for the life of this research study. Information obtained from electronic systems will be copied into the research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to UH policy.

The PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login will obtain study data. The coordinator will be assessing EMR to obtain spontaneous adverse events. All study personnel involved in this research will adhere to the UH policies regarding confidentiality and Protected Health Information.

Patient MRI images will be de-identified to protect personal information and will only referred to by a unique number identifier.

Research MRI and MRF images may be reconstructed or analyzed in either an online or offline manner. If images are reconstructed online, it is possible to share these images with referring physicians or radiologists using the PACS database. If requested and available online, these images may be shared via PACS. However, there may be no direct benefit of sharing these research images.

10.5 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, case report forms, source documents, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations and the institution in which the study will be conducted, or for the period specified by the sponsor, whichever is longer. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

10.6 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

10.7 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

The group of investigators, including the principal investigator, and the research support staff will carry out the Data and Safety Monitoring Plan. Adverse events will not be submitted to an external Data and Safety Monitoring Board or Committee for assessment; instead, there will be an ongoing review of the aggregate data each month to ensure that the study can continue without undue risk to participants. Data will be reviewed to ensure that they are accurate, complete, and that data collection is in compliance with the protocol.

There will also be a continual assessment of the risks and benefits through the review of individual adverse events and other safety parameters as they occur throughout the study to determine whether individual participants can safely continue to participate. Serious adverse events, should any occur, will be reviewed within 48 hours of occurrence with a determination made for medically appropriate follow-up for the subject involved. Adverse event reporting will be strictly performed in compliance with IRB rules for reporting.

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