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NCI Comprehensive Cancer Center
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STUDY TITLE: Assessment of Novel MRI Quantification Free Breathing Technique in Evaluation of Liver Lesions

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Amendment History

Protocol Version 2.3 Summary of Changes 01Aug/2017	
Section 1.0 Background and Rationale	No differentiation between patients receiving biopsies vs. those with benign lesions because we will not always be able to determine this prior to the liver intervention procedure. Patients are rather categorized based on recruitment procedure i.e. those that are scheduled for an intervention vs. those undergoing MRI. Indication that the research DCE liver MRI will take less than 10 minutes.
Section 3.0 Patient Sample/Selection	No differentiation between patients receiving biopsies vs. those with benign lesions because we will not always be able to determine this prior to the liver intervention procedure. Patients are rather categorized based on recruitment procedure i.e. those that are scheduled for an intervention vs. those undergoing MRI.
Section 5.0 Research Plan	During personnel training, certain sections of the protocol were found to be repetitive or confusing. These edits are administrative and do not change the study. The language has been streamlined to remove repetition and for better readability. Inclusion criteria and recruitment procedures were updated to remove differentiation between biopsy patients and benign patients.
Section 9.0 Data Safety Monitoring Plan	Addition of the following statement: *Very small amounts of MRI contrast agents deposit in certain tissues of the body including regions of the brain, in patients who have received multiple doses of these agents. No known harm has been associated with the deposition, before or since the description of this deposition in 2014. More than 300 million doses of gadolinium contrast have been given in humans since their first use.*
Section 10.0 References	References updated to include publication in support of the gadolinium deposition statement (section 9.0)

1.0 BACKGROUND AND RATIONALE

SUMMARY: *The primary objective of this study is to develop and validate simultaneous free-breathing 4D fat and water quantification and quantitative dynamic contrast enhanced perfusion in the liver. Secondary aims include developing and validating free breathing quantification of relaxation parameters T1 and T2, and developing and validating a minimal breath-hold (< 8 s) high quality diffusion exam using highly accelerated steady state diffusion imaging sequences. Investigators aim to scan 170 subjects who are scheduled for liver intervention or MRI exam of the liver. The study is greater than minimal risk.*

MR abdominal imaging made up 7% of the 30.2 million MRI examinations performed in the US in 2010, and liver MR is the most common abdominal exam [1]. MRI is extremely important in liver evaluation, where the capabilities to produce multiple and exquisite soft-tissue contrast and readily available multiphasic imaging without radiation risks have been leveraged to make it the technique of choice for lesion characterization. However, liver MR exams are complex, riddled with failures due to motion artifacts, and poor or variable lesion characterization due to small size, motion, and radiologist uncertainty in interpretation.

Almost every acquisition during an MR liver exam requires a breath-hold to limit motion artifacts. However, it is known that sicker patients provide shorter breath-holds [8]. Thus even with current fast imaging sequences, long breath-holds are difficult for patients, and result in non-diagnostic examinations. The direct cost of these exams, the missed diagnoses, the lost patient and physician time, the delays in treatment and inability to treat diseases properly means that the real dollar cost of motion in body MRI is immeasurable.

The second major set of problems with liver MRI is that of obtaining uniformly high quality exams and lesion characterization. Abdominal MRI is notoriously dependent on the quality of technologists because when motion or image quality issues arise, there are a myriad of adjustable parameters that require years of experience to master. The resulting images can be complicated by technical factors such as motion during the exam or simply small lesion size, differences in acquisition parameters and timings between exams, and difficulties in aligning the lesions on different kinds of contrast mechanisms. In the hands of experts, MRI liver characterization is often exquisite and definite, but in the hands of a majority of practicing radiologists, it is far from ideal.

These problems lead to frustration for both referring and interpreting physicians, and more importantly to biopsy of lesions for definitive diagnosis. If liver imaging could be converted to an ultra-fast examination performed at high spatial and temporal resolution, and at the same time provide quantitative information so that image characterization could be objective, the effect on clinical care could be significant. This would eliminate technically compromised exams, improve certainty in diagnosis, diminish the need for repeat or follow-up imaging, and most tantalizingly, potentially decrease the need for invasive tissue diagnosis.

We have developed techniques that we hope can turn the present standard liver examination into a high resolution exam that requires almost no breath-holds, and yet provides quantitative measures of all contrast mechanisms presently employed in the clinical standard examination. The research DCE liver MRI scan time will be less than 10 minutes, completely removing the

technologist competence and patient cooperativeness pieces from the factors that affect exam quality. **Preliminary data:** The novel free-breathing high spatiotemporal resolution DCE liver MRI using non-Cartesian parallel imaging technique for quantitative perfusion mapping was performed on a Siemens 3T Skyra scanner with six subjects, including four healthy volunteers and two patients. A stack-of-spirals trajectory was under sampled in plane with a reduction factor of 6, and reconstructed using through-time non-Cartesian GRAPPA. High-resolution 3D images were acquired with a true temporal resolution of 1.6~1.9 seconds, while the subjects were breathing freely. A dual-input single-compartment model was established to retrieve liver perfusion parameters from DCE-MRI data, which were co-registered using an algorithm designed to reduce the effects of dynamic contrast changes on registration performance.

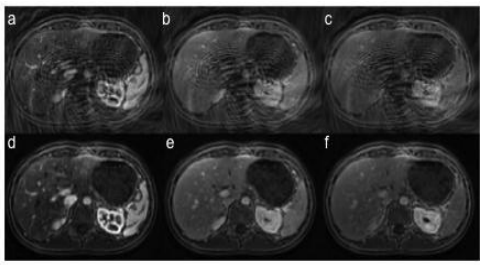


Figure 1

Results: Figure 1 shows representative under sampled and reconstructed images acquired from a normal subject at the arterial phase (~20 sec after contrast injection), portal phase (~70 sec) and equilibrium phase (~180 sec). With the automatic edge detection method, about 20-25% of the volumes from each subject were automatically detected by the algorithm to originate from the same position in the respiratory cycle, and thus pre-registered. After registering the remaining frames to the nearest "pre-registered" neighbor, almost no detectable solid organ motion remained. Figure 2 shows representative time courses of contrast concentration from the aorta, portal vein, and hepatic parenchyma (single voxel), and the model fit to the parenchymal time-course from a healthy subject. The time course from the liver voxel, same as before registration is also plotted as a comparison. The model fit after registration yielded an arterial fraction (AF), distribution volume (DV) and mean transit time (MTT) of 18.8%, 24.2%, and 4.6 s, respectively, while the same quantities prior to registration were 13.5%, 35.2%, and 10.6 s, respectively. The perfusion parameters after registration are all in good agreement with published literature for CT and MR (3,4,14).

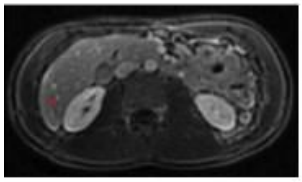
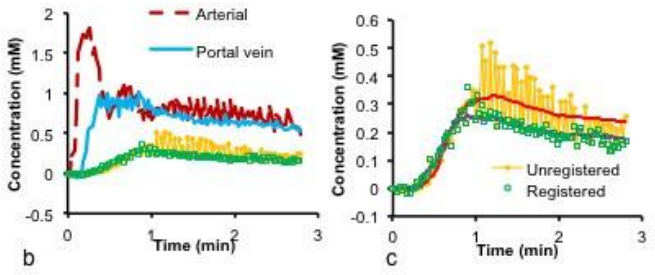


Figure 2 a



Two patients were scanned (both with previous traditional scanning) with the developed technique as representative clinical examples. Patient 1 had biopsy proven metastatic breast adenocarcinoma, and Patient 2 had a biopsy proven sclerosing hemangioma that had demonstrated atypical imaging characteristics on traditional imaging. Perfusion modeling for patient 1 is shown in Fig. 3. AF, DV, and MTT were 67.5%; 40.4%; and 99.8 s, respectively, for the lesion in Patient 1, all clearly different from surrounding parenchyma in the parametric maps.

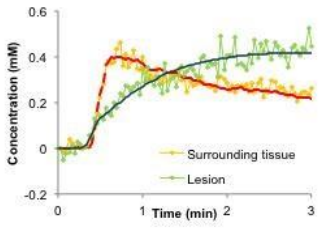
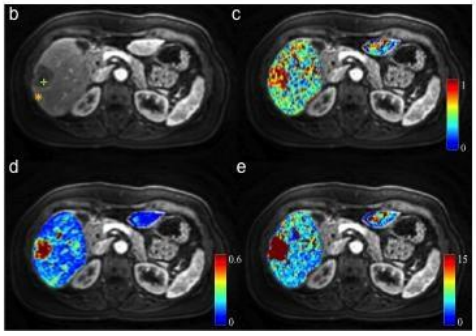


Figure 3 a



Similarly in Patient 2, the AF, DV and MTT were 99.4%, 21.0%, and 27.6 s, respectively, again different from surrounding tissue, and demonstrating nearly 100% arterial fraction as expected from hemangioma.

2.0 OBJECTIVES

We hypothesize that a quantitative and near free-breathing MRI approach will lead to improved tissue characterization, resulting in fewer ambiguous readings and thus fewer biopsies. As each component of the proposed methodology has been experimentally validated in our preliminary work, the next appropriate step would be to evaluate the clinical feasibility of the exam. **Our goal is to test the ability of our developed quantitative MRI techniques to provide high quality images of the liver and to differentiate liver lesions from one another in a timeframe shorter than a current clinical exam.**

3.0 PATIENT/SAMPLE SELECTION

We aim to scan at least 170 patients who are scheduled for liver intervention or MRI exam of the liver using the new quantitative protocol, assess the discrimination accuracy of binary classifiers in predicting lesion type, and compare the diagnostic accuracy of the new protocol to the clinical standard.

4.0 REGISTRATION PROCEDURES

If applicable, all patients enrolled on study will be entered into the Oncore database. If samples are being collected, a sample count will be entered into the database.

5.0 RESEARCH PLAN

Our abdominal imaging group performs at least 150-200 MRIs for liver lesions every year. A vast majority of these lesions are HCC or metastatic disease (approximately 40% each), a small number are cholangiocarcinoma (at most 10%) and an additional 10% are benign lesions such as adenomas, hemangiomas, or focal nodular hyperplasia (FNH). Most patients also undergo biopsies to establish diagnosis. For our analysis we will obtain a quantitative dataset of 170 focal liver lesions in which the biopsy or clinical "truth" is known.

Inclusion Criteria:

All patients scheduled for a MRI exam of the liver will be eligible to participate in this study.

1. Patients with known liver lesion
2. Male or female patients, age 18 to 100 years.
3. No contraindications to getting contrast enhanced MRI examinations.
4. GFR $\geq$ 40.

The study population may include illiterate persons and UH/Case employees if they meet other inclusion criteria. The consent process for these potential participants will be conducted according to IRB guidelines.

Exclusion Criteria:

1. Patients with ferromagnetic or otherwise non-MRI compatible aneurysm clips.
2. The presence of an implanted pacemaker or implanted defibrillator device

3. 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.
4. Pregnancy. Regular clinical practice already excludes pregnant patients from gadolinium contrast due to unknown effects on the fetus. The current clinical practice will be applied - patients will be verbally screened and asked if they think they could be pregnant. If the answer is yes, then the patient will be excluded from the study. If the patient is uncertain about the pregnancy status, she will be given an option to undergo a pregnancy test or not participate in the study altogether. Patients who self-report that they are not pregnant will be allowed to participate in the study. This procedure is based on current department policy guidelines.
5. Implanted medical device not described above that is not MRI-compatible;
6. Known history of claustrophobia;
7. Known history of allergic reaction to MR contrast material;
8. Late stage renal failure with estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m2 based on patient's serum creatinine due to the significantly increased risk of nephrogenic systemic fibrosis (NSF). ('Past' 3 months timeframe will be used to calculate the eGRF).
9. Minors will be excluded.
10. Prisoners and members of other vulnerable populations will be excluded from this study. The subject selection population will not regularly include prisoners and other vulnerable population members as these populations will not provide any additional unique information to or uniquely benefit from the study. Non-english speaking population will be excluded from the study due to lack of sufficient resources to pay for translator and interpreter services.

Recruitment procedures:
There will be two methods of recruitment. The first method is via referral of patients from the intervention radiology clinic. Secondly, we have a waiver of HIPAA authorization and waiver of consent to identify and contact patients from the out-patient schedule.

The abdominal imaging section runs an intervention radiology clinic where patients with liver lesions are evaluated in order to plan and conduct the liver intervention procedure. All of the physicians at this intervention radiology clinic are co-investigators on the current IRB protocol and have physician-patient relationship with these clinic patients. Upon referral, a member of the research team will approach these patients in person during their pre-procedure evaluation visit and give them an option to participate in the research study. During this visit, the patients will be given information about the research study procedure. The patient will be conveyed the information regarding potential direct and indirect benefits, and risks and discomforts associated with the study. The patients will also be informed that there are no financial charges to them or their insurance for this research scan and that they will receive an amount of $100 as compensation for participation in the study. All communication with the patient will be conducted in a private area. All of the patient questions regarding the research study will be answered satisfactorily. If the patients wish to participate in the study, they will be consented on the same day (pre-procedure evaluation visit to the clinic) and will be scheduled for research MRI scan before the day of their intervention procedure. The patients will be offered a copy of the signed consent form to take home with them to discuss with their friends and family if they wish to. Only if the patient consents to participate in the research study during the first meeting

and agrees to come in for research MRI in the future, then the study personnel will communicate with the patients by phone to confirm the appointment for research MRI and answer any questions the patient may have at this point. The referring physician/ primary care team will provide the diagnosis to the patients. The research team personnel will not provide any diagnosis to the patient.

We have a waiver of HIPAA authorization and waiver of consent to identify and contact patients from the outpatient MRI schedule.

Request for waiver of HIPAA authorization and waiver of consent*: 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. We are requesting a waiver of HIPAA authorization and waiver of consent for contacting the patients in person and not the waiver of the consent for the research study as such. We intend to identify patients on outpatient MRI schedule for a clinically indicated liver MRI and contact them in person. The will be no improper use of or disclosure of PHI under this waiver. 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. The patients with benign lesions are typically not biopsied. It is imperative to include a cohort of such patients in the study to increase the diversity of study population and demonstrate the robustness of the new imaging technique. We will use the MRI schedule to identify potentially eligible subjects who are undergoing liver scans. 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, because there is no other way we can contact the patients with benign lesions scheduled for clinical MRI.*

With the waiver of HIPAA authorization and waiver of consent, we will be able to use the MRI schedule to identify subjects who are undergoing liver scans on a given day. On the day of the scheduled clinical MRI exam we will approach the patient in person and give them brief information regarding the research study. The patient will be given information regarding potential direct and indirect benefits, and risks and discomforts associated with the study. The patients will be informed that there are no financial charges to them or their insurance for this research scan and that they will receive an amount of $100 as compensation for participation in the study. We will ask the patient if he/she is interested in participating in the research MRI. We will request permission from the patient if he/she is willing to be contacted by phone for scheduling a research MRI scan in the future. We will explain it clearly to the patient that he/she will be contacted for participation only if he/she is deemed eligible to participate in the study after discussion with his/her referring physician/primary care team. Thus, the consent for contacting the patients for future participation in research MRI study will be obtained from the patients on the day of their scheduled clinical MRI when the research team member can meet the patient in person. The subjects will not be approached at their doctor's visit. The patients will be

offered a copy of the informed consent form for the actual research MRI to take home with them to study and discuss with family/friends, if desired. All the communication and conversation with the patient will be conducted in a private area. For the research personnel to contact the patient in a manner that is suitable for them, we will ask the patient to provide their contact information (including phone number and/or email address). We will also ask the patients to specify which mode of communication is suitable for them and what time slot of the day is most acceptable if they choose to be contacted by phone. Only if the patient consents to be contacted for research MRI in the future, then the study personnel will communicate with the eligible patients by phone to schedule the study and answer any questions the patient may have at this point

If the patient has signed the consent to contact, we will call or email depending upon their preference to schedule the research scan. We will also ensure that the primary care team/ referring physician provides the diagnosis to the patients prior to being contacted by the research team for scheduling the research study in the following manner. If the patient consents to be contacted, about 3-5 days after the clinical MRI is done a member of the research team will communicate with the clinical care team member by phone or encrypted UH email and find out if the patient has received diagnosis for his liver problem from them. If the answer is no, we will repeat this process in another 3-5 days. If the answer is affirmative, then we will communicate with the patient by phone to schedule a research MRI study at his/her convenience.

The research MRI consent form will be signed on the day the patient comes in for the research study, unless the patient decides not to participate. The consent procedure for the research study will be again conducted in a private area. All the patient's questions will be answered satisfactorily. A copy of the signed informed consent will be offered to the patient for his/her record. The study population may include illiterate persons and UH/Case employees if they meet other inclusion criteria. The consent process for these potential participants will be conducted according to IRB guidelines. For illiterate individuals who may consider study participation, the consent form will be read out to the participant and the process will be documented in the research file. The participant will sign the consent form by making their mark in the signature section of the consent document in order to document their understanding. A witness will be present to confirm that the consent process has taken place. Both the witness and the person obtaining informed consent will sign and date the consent document. The UH/Case employees who may consider study participation will be informed that their participation in a study, or refusal to do so, will in no way influence their employment, or subsequent recommendations and that their job, promotion, salary, or status in any way depends on participation in research studies. Also they will be informed that refusal to participate will have no influence on recommendations or job status.
In total, 170 subjects who meet inclusion criteria and who are willing to consent to participation in the study will be recruited.

6.0 STUDY PARAMETERS

MRI of liver using the proposed research technique will be performed on all study subjects. The imaging data will be utilized as a study parameter. This imaging data will be compared with clinical standard imaging and biopsy results of the patient.

7.0 CORRELATIVE STUDIES (if applicable)

N/A

8.0 STATISTICAL CONSIDERATIONS

Ten-fold cross-validation will be used to assess the discrimination accuracy of binary classifiers predicting HCC vs. benign lesions, metastases vs. benign lesions, or metastases vs. HCC [69]. We hypothesize that each classifier will predict non-benign lesions with accuracy (ROC curve area) of at least 80%. With 40 abnormal and 80 benign cases, a one-sided test at a significance level 0.05 testing the null hypothesis that the area under the ROC curve is an uninteresting level of 0.65 vs. the alternative that it is greater than 0.65 will achieve 91% power when the ROC curve area is 0.80 for the new classifier. For a binary classifier discriminating metastases vs. HCC, with 40 cases per group, the power is 84% to test that the area greater than 0.65, when the true ROC area is 0.80 (SAS macro ROCPOWER, http://www.bio.ri.ccf.org/doc/rocpower_help.txt).

In a second step, the diagnostic accuracy of the quantitative protocol will be compared to the standard clinical exam. In each of the cases described above, the three radiologists will be asked to arrive at the most likely diagnosis, by consensus. The quantitative techniques will be similarly used to predict the most likely diagnosis for each lesion. Agreement between the quantitatively predicted "most likely diagnosis" and the actual diagnosis (categorized as HCC, other metastases, cholangiocarcinoma or benign/other) will be estimated and com-pared to the agreement between the clinical MRI-based diagnosis and true diagnosis using a McNemar test for correlated proportions. With the a sample size of 170, a difference in agreement proportions of 0.75 vs. 0.87 can be detected with 80% power with a two-sided 0.05 significance level test. Funding for Statistical Analysis: Dr. Schluchter with perform the statistical analysis and the grant funding listed for this project covers his time.

9.0 RECORDS/DATA TO BE KEPT

Records that will be kept by the investigators on each subject in the study include age and gender, clinical assessment, type of liver disease, co-morbidities, imaging as a part of standard of care, laboratory results, medications, allergies, MRI technical parameters (TR, TE, Matrix size, Coil used, flip angle, temporal resolution, slice thickness, FOV, number of slices, parallel imaging acceleration factor, total image acquisition time, total number of images), T1, T2, diffusion parameters, as well as perfusion data. These are primarily MR technical data recorded at the time of acquisition. The remainder of the information will be gathered from PACS, IDX and EMR.

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. In order to minimize the risk of loss of confidentiality, all records related to the study data will be kept in locked cabinets. The imaging data will be de-identified and stored and a linking sheet will be created. Access to study information and documents will be restricted to research personnel. A password system will be used to control access to all information stored on a secured computer. All reports, forms, or articles related to this study will be prepared such that no individual patient can be identified. No data that can be linked to the subject will be entered into a network computer that could allow access to confidential information. All data entered into the computer will be coded and personal

identifiers will be removed. The master list will be stored off-line and will be available only to the principal investigator or his designee(s). The data will be stored until three years after last publication of the results, at which time they will be destroyed/deleted.

Data Safety Monitoring Plan:
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.

Risks to patients in this study include all those risks currently associated with standard contrast enhanced MRI. These include discomfort involved with being required to lie still in a small space; and possibly risks that are unknown at this time. These risks are all considered rare (likely occurring in fewer than 10 of every 100 patients). Patients with severe renal dysfunction (GFR<30) are at risk of nephrogenic systemic fibrosis (NSF). Due to this risk, patients with GFR below 40 will be excluded from the study. This threshold is considerably higher than the current clinical threshold of GFR below 30. Very small amounts of MRI contrast agents deposit in certain tissues of the body including regions of the brain, in patients who have received multiple doses of these agents. No known harm has been associated with the deposition, before or since the description of this deposition in 2014. More than 300 million doses of gadolinium contrast have been given in humans since their first use.[71].

Identification of subjects with severe renal dysfunction**:** The subjects with severe renal function will be identified as follows. The subjects in both sets will undergo a clinical MRI study for evaluation of liver lesion before being recruited in the research study. As a result, they will be evaluated for the status of their renal function before the clinical MRI scan. The research team will access their renal parameters after acquiring consent for study participation in the 'biopsy set' and consent to contact in the 'benign lesion set'. Although an eGFR cut off of 30 mL/min/1.73 m2 is used for clinical MRI, patients with eGFR below 40 mL/min/1.73 m2 will not be included in the study for additional safety. Additionally, before undergoing research MRI, every participant will fill up the standard clinical MRI safety screening sheet which asks the patient about any current or previous renal problems.

The risks expected from participation in this study are minimal and usually are not serious. However, any subject who experiences problems from participating in this study will be provided all appropriate medical care. All patients will be otherwise followed according to standard of care. 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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