Evaluation of HCC Response to Systemic Therapy With Quantitative MRI
PI: Dr. Bachir Taouli
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	Protocol Name:	Evaluation of HCC Response to Systemic Therapy with Quantitative MRI
	Principal Investigator:	Bachir Taouli, MD
	Primary Contact Name/Contact Info:	Maxwell Segall maxwell.segall@mssm.edu 212-824-8476
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PROTOCOL TEMPLATE INSTRUCTIONS HRP-503

- *These instructions accompany the MSSM "Template Protocol" document and are intended to assist you in developing a human research protocol.*
- *Using the MSSM "Template Protocol" document, prepare a document with the following sections.*
- *Note that, depending on the nature of your research, certain questions, directions, or entire sections below may not be applicable. Provide information if and when applicable, and in cases where an entire section is not applicable, indicate this by marking the section "N/A". Do not delete any sections.*
- ***For any items below that are already described in the sponsor's protocol, the investigator's protocol, the grant application, or other source documents, you may simply reference the title and page numbers of these documents in the sections below, rather than cutting and pasting into this document. Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

The incidence of hepatocellular carcinoma (HCC) has recently increased in the United States. Although imaging plays a major role in HCC screening and staging, the possibility of predicting HCC tumor grade, aggressiveness, angiogenesis and hypoxia with imaging are unmet needs. In addition, new antiangiogenic drugs now available to treat advanced HCC necessitate the use of new imaging criteria beyond size. In this proposal, we would like to develop and validate quantitative MRI and PET/MRI methods as markers of histopathologic features of HCC, and to predict and assess early response of HCC to systemic therapy with sorafenib. We also would like to develop quality control tools to improve the quality and decrease variability of quantitative MRI and PET/MRI metrics. These techniques combined could represent non invasive correlates of histologic findings in HCC, could enable individualized therapy, and provide prognosis in patients with HCC.

1) Objectives

a) Test and validate a quantitative multiparametric scoring system combining measurements of MR diffusion, perfusion, stiffness and hypoxia against histopathologic measures of tumor grade, cellularity, aggressiveness, angiogenesis, hypoxia and microvascular invasion in HCC.

b) Assess the role of combined FDG-PET and MRI for assessment of HCC tumor characteristics in a pilot study in a small subset of patients with HCC.

c) Compare the diagnostic performance of MRI to ultrasound elastography (ARFI: Acoustic Radiation Force Impulse) to measure liver and HCC stiffness.

d) Correlate advanced imaging findings with gene expression profiles measured in resected or biopsy tumor samples.
e) Assess the predictive value of multiparametric MRI in patients with advanced HCC treated with systemic therapy and/or Yttrium 90 radioembolization.

Hypothesis: There is a negative correlation between diffusion metrics (D: true diffusion coefficient and ADC) and tumor grade/cellularity and aggressiveness; a positive correlation between PF (perfusion fraction) measured with IVIM, arterial fraction (ART) measured with DCE-MRI and each of MVD (microvessel density) and VEGF expression; and a positive correlation between ΔR2* (measured with BOLD) and each of MVD and HIF 1-α (hypoxia inducible factor 1-alpha) expression.

Hypothesis: FDG-PET parameters correlate with HCC tumor grade, and may add information to MRI metrics.

Hypothesis: There is a correlation between quantitative MRI and PET and certain gene expression profiles in tumors.

Hypothesis: Quantitative MR parameters may enable prediction and assessment of response to systemic therapy and/or Y90 radioembolization.

2) Background

The incidence of hepatocellular carcinoma (HCC) has recently increased in the US mostly due to an increase in chronic hepatitis C infection. Angiogenesis is critical for the growth and metastatic progression of HCC, and involves different molecular pathways including VEGF (vascular endothelial growth factor) which is released following a hypoxic stimulus, inducing hyperpermeability of tumor vessels. The arterial vascular profile of HCC has provided the basis for the use of transarterial chemoembolization (TACE) as an effective therapy to cause tumor necrosis. Imaging plays an essential role in HCC screening, diagnosis and staging. However, the assessment of HCC tumor grade and aggressiveness, and the prediction of response of HCC to TACE using imaging criteria are not established. With the development of new antiangiogenic drugs recently approved in advanced human HCC, such as sorafenib, imaging methods to predict and assess therapeutic response beyond changes in size become critical. It has been recently suggested that assessing the degree of residual tumor enhancement on dynamic CT or MRI using modified RECIST (mRECIST) criteria in HCC treated with TACE or systemic therapy is more appropriate than the use of conventional RECIST criteria (which are based on size only).
Recently, functional MRI methods have shown promising results for evaluation of tumor cellularity and grade, angiogenesis and hypoxia. Apparent diffusion coefficient (ADC) measured with diffusion-weighted imaging (DWI) has been correlated with tumor cellularity in brain, prostate and breast tumors and with HCC tumor grade, and has been used for assessment of response of HCC to TACE. BOLD (blood oxygen level dependent) MRI experiments have demonstrated a decrease in R2* after oxygen or

carbogen challenge, thus providing a simple noninvasive tool to evaluate hypoxic tumors such as HCC. Dynamic contrast-enhanced MRI (DCE-MRI) has been correlated with tumor microvessel density (MVD) and VEGF expression and has been used to follow antiangiogenic treatments in liver metastases. Our recent data suggest that tumor ADC correlates with HCC grade and can be used to predict HCC response to TACE; and that tumor perfusion (measured with DCE-MRI) and oxygen uptake (measured with BOLD) are promising non invasive markers of HCC angiogenesis and hypoxia. In addition, recent work by other investigators and our group showed the possibility of separating diffusion and perfusion in the liver using the IVIM (intravoxel incoherent motion) model. Despite these promising results, data correlating DWI (without or with IVIM), DCE-MRI and BOLD with histopathology in human HCC remain extremely limited. Moreover, validated imaging methods to predict and assess early HCC response to new targeted agents such as sorafenib are lacking.

Intratumoral hypoxia has been shown to correlate with tumor invasiveness, progression, metastasis and radioresistance. Given that HCC is a hypervascular tumor, anti-angiogenic therapy offers a promising approach, and potent experimental antiangiogenic drugs such as angiostatin, endostatin, vasostatin and TNP-470 are effective in treating experimental models of HCC. Sorafenib (Nexavar, Bayer HealthCare–Onyx Pharmaceuticals) is an oral multikinase inhibitor with anti-angiogenic, pro-apoptotic and Raf kinase inhibitory activity, which has shown small increase in survival in the SHARP trial compared to placebo, and is currently FDA approved for use in advanced human HCC.

There is also recent interest in immunotherapy drugs in HCC, with a trial of nivolumab (Opdivo) opening soon at Mount Sinai. Yttrium 90 radioembolization is emerging as an efficient locoregional therapy in HCC, and is now often performed at Mount Sinai.

ADC measured with DWI has been shown to correlate negatively with tumor cellularity in brain, breast and prostate tumors. Recent data suggest a correlation between tumor ADC and HCC grade. ADC is also increasingly applied to evaluate tumor response to local or systemic therapy in liver tumors. Pre-clinical and clinical studies have shown that effective tumor treatment results in a rise in tumor ADC, which can occur prior to any measurable change in tumor size. Following the increase in ADC with treatment, the ADC will subsequently fall, related to tumor repopulation, fibrosis or tissue remodeling and decreased perfusion. There are several reports on the use of ADC to evaluate HCC response to chemo- or radioembolization. These studies demonstrated measurable differences before and after treatment. There is very limited published data on the use of DWI after treatment of HCC with sorafenib, and no data on the use of DWI for predicting response of HCC to therapy.

BOLD MRI can detect oxygenation changes secondary to changes in blood flow and deoxyhemoglobin in tumors. Deoxyhemoglobin acts as an endogenous paramagnetic MRI contrast agent by reducing apparent transverse relaxation time (R2*, in sec^{-1}) of neighboring tissues. BOLD MRI technique detects these relative changes in R2*. In various murine cancer models, significant changes in tumor R2* were demonstrated when altering concentrations of O_2 administration. Rhee et al demonstrated an increase in R2* values after HCC embolization in rabbits.

DCE-MRI has been used to study tumor pathophysiology and to follow antiangiogenic treatments. With the proposed concept of perfusion “normalization” with antiangiogenic therapy, a decrease in perfusion and blood volume is expected in tumors, however data on DCE-MRI in HCC treated with systemic

therapy is extremely limited. A recent perfusion CT paper showed that high pre-treatment MTT (mean transit time) and Ktrans were predictive of better response of HCC to bevacizumab and chemotherapy. MRE can be implemented on a standard MR system by installing a device for generating mechanical vibration in the liver under MR scanner control, a special MRE pulse sequence, and processing software to generate the diagnostic MRE images (elastograms). Several studies have demonstrated that MRE is an accurate method for diagnosing liver fibrosis, with liver stiffness increasing systematically with fibrosis stage. There is limited data on the use of MRE in focal liver lesions. This study showed that HCC and cholangiocarcinoma had significantly greater stiffness than fibrotic liver, benign tumors, and normal liver parenchyma.
FDG-PET has been used to probe HCC tumor grade, with increased uptake demonstrated in patients with high-grade HCC (102, 103). A correlation between FDG uptake and the number, size and stage of tumors as well as portal vein invasion has been demonstrated (104-108), suggesting that FDG-PET can identify more aggressive HCC tumor phenotypes. It is now possible to combine functional information from MRI and PET by using a whole body hybrid PET-MRI system (109, 110), which may maximize information on tumor aggressiveness, which may be in turn used for individualizing therapy (111). In this regard, PET-MRI systems may be instrumental for risk stratifying patients, and could be used as a preoperative tool for estimating the post-surgical risk of HCC tumor recurrence

The validation of new imaging criteria for prediction and assessment of early response to systemic therapy or to locoregional therapy with radioembolization will enable individualized therapy, such as patients not benefiting from these therapies may be proposed alternate therapies currently being developed.

3) Setting of the Human Research

The study will be conducted at the outpatient Radiology practice located in the Faculty Practice Associates (FPA) building or in the Center for Science and Medicine in the Hess Tower at Mount Sinai Medical Center. 1.5T and/or 3T FDA approved MRI systems (Siemens or GE) and/or a 3T mMR (hybrid PET/MR, Siemens) and ARFI ultrasound (Acuson S3000, Siemens) will be used for the study purpose.

4) Resources Available to Conduct the Human Research

Our MR research group has been actively investigating cutting edge MRI techniques for evaluation of focal and diffuse liver diseases. There is a large recruitment of patients with HCC at the Tisch Cancer Institute located at Mount Sinai School of Medicine (MSSM), and the Mount Sinai Medical Center (MSMC). Recruitment sources are from the Surgical Oncology group who performs approximately 100 resections for HCC annually, the Liver Transplant group (who performs approximately 100 adult liver transplants a year, including 40 for HCC), and the Hepatology group. The liver cancer program at Mount Sinai is structured as a multidisciplinary group including hepatologists, surgeons, oncologists, pathologists, radiologists, molecular biologists and epidemiologists. For this proposal, we expect to recruit 141 subjects over a 5-year period, including patients who will undergo liver resection referred

from Surgical Oncology group, and patients with unresectable HCC referred from Hepatology and Oncology services.
All personnel assisting with the research study are adequately informed about the protocol and their related duties and functions. The PI is an active member of the liver cancer program at Mount Sinai and has an open dialogue with all experts involved. Many members of the current research team already worked together in related projects and have experience and qualifications to conduct this research. All personnel supporting the project are trained according to IRB requirements. Their CVs/Biosketches to prove qualification are attached with this submission.

5) Study Design

a) Recruitment Methods

Subjects with HCC will be identified and recruited for the study by their treating physicians at Surgical Oncology, Liver Transplant and Hepatology. The selection will be recommended by the physicians, who are familiar with their patient's history. The referring physicians will be considered significant contributors to the project.

The treating physician will be providing potentially eligible subjects with study information in form of a flyer and the consent form of the study. Subjects can take the information home and can think about the study and potential participation. The subject will be given the opportunity to contact the Research Coordinator to discuss the study details and to answer all questions about it. Also the Research Coordinator will be on hand to speak with a potential participant after they met with their treating physician.

For all referred interested subjects the Research Coordinator will review their medical records to check for their eligibility according to the inclusion/exclusion criteria and contraindications for MRI. We ensure by reviewing data from medical records that the subject population being asked to participate would be eligible to do so and that their safety during the study would not be at risk. A waiver of authorization to release PHI for research purposes has been requested.

Healthy volunteers will be recruited for the study by word-to-mouth recommendation and later on by MSSM broadcast emails. The study specific announcement will then be submitted to the IRB. Interested volunteers are asked to contact the Research Coordinator, who will check for contraindications in a dialogue with the potential subject.

b) Inclusion and Exclusion Criteria

Inclusion criteria
Study group

1. Patients diagnosed with HCC, who will undergo resection or transplantation within 6 months, as part of routine clinical care and patients diagnosed with unresectable HCC.

2. Patients with unresectable HCC undergoing systemic therapy based on clinical indication or approved drug trial; and/or undergoing clinically indicated Y90 radioembolization.
3. 18 years of age and older.
4. Patient is able to give informed consent for this study.

Control group

1. Healthy volunteers 18 years of age and older.
2. Subject is able to give informed consent for this study.

Exclusion criteria

1. Age less than 18 years.
2. Unable or unwilling to give informed consent.
3. Contra-indications to MRI and/or PET/MRI
    a. Electrical implants such as cardiac pacemakers or perfusion pumps
    b. Ferromagnetic implants such as aneurysm clips, surgical clips, prostheses, artificial hearts, valves with steel parts, metal fragments, shrapnel, tattoos near the eye, or steel implants
    c. Ferromagnetic objects such as jewelry or metal clips in clothing
    d. Pregnant subjects
    e. Pre-existing medical conditions including a likelihood of developing seizures or claustrophobic reactions.

Patients with GFR <30 will not undergo DCE-MRI with Gadolinium contrast. For patients with GFR < 30, we will still consider enrolling patients for a non-contrast MR protocol, including non-contrast sequences (DWI, BOLD and MRE). Patients with severe COPD will not undergo oxygen-enhanced sequences, due to risk of respiratory decompensation. Patients with uncontrolled diabetes will not undergo the PET/MRI study. Uncontrolled Diabetes" will be defined by high blood levels of glucose observed over 200 mg/dl secondary to untreated diabetes or to incompletely treated diabetes.

As with all patients referred for MRI and PET/MRI, each patient is screened for possible contraindications with a routine questionnaire.

c) Number of Subjects

150

d) Study Timelines

Duration of the study is 3 Years.

All subjects will undergo 1 to 2 MRI exams and ARFI.

We would like to ask a subset of 23 additional patients out of 150 if they are willing to undergo a PET/MRI study and ARFI.

We propose to assess response of therapy in a subset of 30 patients with unresectable HCC. These patients will be selected when they undergo treatment with systemic therapy such as sorafenib

(indicated clinically) or immunotherapy (using nivolumab) and/or radioembolization (indicated clinically). These patients will be imaged before treatment and 2-4 weeks after initiating therapy. Imaging will involve MRI only.

The total examination time per visit including the setup and routine MRI/ARFI/PET/MRI will be approximately 60-90 minutes.

e) Endpoints

- *Tumor response:* defined as the % of tumor necrosis diagnosed on image subtraction on subsequent routine clinically indicated MRI performed 3-6 months after initiating therapy.
- *Time to tumor progression:* defined as the time from initiating therapy to disease progression according to mRECIST criteria as diagnosed on follow-up routine contrast-enhanced MRI. Progression will be defined as an increase of at least 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded since initiation of therapy.
- *Overall survival:* defined as the time from initiating therapy to death.

f) Procedures Involved in the Human Research

All subjects will undergo 1 to 2 MRI exams and ARFI. During each visit, we will obtain the following MR parameters (DWI, BOLD, MRE and DCE-MRI). Patients referred for MR evaluation of the abdomen will receive all conventional MRI necessary to address the referral indication in addition to DWI, DCE-MRI, BOLD and MRE.

23 patients will be asked to undergo a single PET/MRI and ARFI study. These patients will not be asked to come back for a second PET/MRI study.

We will perform an independent prospective study in up to 30 additional patients with advanced HCC treated with sorafenib or nivolumab and/or Y90 to assess the role of pre-treatment and early changes in quantitative MR parameters for predicting tumor response, time to tumor progression and overall survival.

Diffusion-weighted MRI (DWI) will be performed using multiple single shot Echo Planar Imaging (EPI) or segmented EPI acquisitions or non EPI sequences with selected varied parameters and gradients. Diffusion parameters will be calculated (ADC: apparent diffusion coefficient, D: true diffusion coefficient, PF: perfusion fraction).
BOLD MRI: Before contrast injection, we will use a breath-hold multiecho T2* sequence covering the whole liver under room air and after 20 min. of administration of pure O2 (10 L/min) and/or carbogen (95% oxygen and 5% carbon dioxide) through a facial mask or a cannula.
MR Elastography: Will be performed before contrast injection. The subject/patient will be asked to perform multiple breath-holds during the image acquisition.
DCE-MRI will be performed prior and after intravenous administration of Gadolinium chelates using a 2D or 3D fast T1-weighted sequence. An FDA approved gadolinium contrast agent will be administered. These include extra-cellular agents such as Gd-BOPTA (Multihance), a liver specific

agent such as Gd-EOB-DTPA (Eovist), and a blood-pool agent (gadofovesettrisodium, Ablavar). As the contrast is circulating through the body the patient will be imaged for approximately 5 minutes after contrast injection. The patient will hold his/her breath for as long as possible.
Routine MR sequences including T1 in and out-of-phase and T2 weighted-imaging will be obtained in all cases.
FGD-PET/MRI : The PET/MRI exam should last approximately 60 minutes and will include FDG-PET, DWI, BOLD with room air and then oxygen, DCE-MRI and routine MR sequences while the patients is lying in the same machine. After the injection of 10-15 mCi of F-18 FDG (0.14 mCi/kg; approximately 5-7 mSv radiation dose), the PET images will be obtained with the patient's arms raised to cover between the orbitomeatal line and the proximal third of the femurs. The study length will not be increased by the addition of PET images, as the image acquisition of PET and MR images is simultaneous.

Research Radiation Exposure

Test	**mSv/test**	**# per year**	**Total mSv/year**
PET MRI (10 mCi FDG)	**7.0**	**1**	**7.0**
Total Exposure			***7.0 mSv***

MRI Diffusion-weighted, DCE-MRI, BOLD, MRE and PET images will be evaluated for:

1. Optimal choice of operator-selected sequence parameters
2. Image quality (resolution, signal-to-noise, artifacts, etc,)
3. Suitability for routine use

The total examination time including the setup and routine MRI, ARFI with or without PET will be approximately 60-90 minutes. A physician will be present for all studies.
During the entire MR procedure (both standard and investigational), the investigator or his team will remain in contact with the patient via an intercom system. A squeeze bulb or closed circuit video camera may also be used.

ARFI (Acoustic Radiation Force Impulse, Siemens): ARFI is a new ultrasound machine. Patients will undergo and ultrasound examination of liver with special device called ARFI, for which they will be asked to lie on an examining table, and asked to raise their shirt of clothing above the stomach area. A gel will be applied over the skin, and a probe (a small medical instrument) will be placed on the skin in between the ribs. The ARFI device stays outside of the body the entire time. Measuring the liver stiffness takes about 10-20 minutes and will be done for research purposes. The patients will undergo an ARFI during the first visit with and MRI and during their second visit with an MRI or PET/MRI.

If a subject had a liver biopsy, liver surgery or transplantation as part of their routine clinical care, the pathologic specimen will be analyzed with special histological techniques (using special stains with microscopic evaluation), and final results will be compared with MRI,ARFI and PET/MRI results in order to validate our techniques.

Gene expression profiles: in patients who undergo liver biopsy, resection of transplantation, we will perform gene expression profiling of tumor samples and liver parenchyma.

Additional test: we would like to perform ex-vivo MRI of liver surgical samples in 20 patients. Exvivo MRI involves scanning of samples on the clinical MRI system for assessment of viscoelastic properties (MRE) and other parameters such as T1, T2 and diffusion. This will help us understand the relationship between invivo and exvivo quantification in the tumor and surrounding liver. The samples will be returned undamaged to Pathology department.

g) Specimen Banking

N/A

h) Data Management and Confidentiality

All research data will be stored separately from direct identifiers (e.g. name, address, DOB, MRN, SSN) that can link the data to a person's identity. Research data files will be stored using a unique "code" instead. The "linking code file" will be maintained separately.
The file that links the code to the person's identity (direct identifiers) will be maintained electronically and in an encrypted file on a departmental network drive with restricted access to the study team.

All research data files will be stored electronically in encrypted files. Access to the data files will be through restricted view set up by Radiology IT and password protected.
The data will be stored for a minimum of 7 years.

i) Provisions to Monitor the Data to Ensure the Safety of Subjects

MSSM Principal Monitor:

Last Name: Taouli
First Name: Bachir
Academic Title: MD
Department: Radiology
Mailing Address: Department of Radiology, One Gustave L. Levy Place, Box 1234
New York, 10029 NY
Phone: 212-824-8453
Fax: 212-241-4234
E-mail: bachir.taouli@mountsinai.org

The principal investigator is Professor of Radiology and Medicine and he is the monitoring entity for the minimum DSMP. The principle investigator will be present for the studies and will be informed about any issue, adverse event/unanticipated problem or subject complaint directly as available. Adverse events and all subject complaints will be observed and recorded by the study team and routinely evaluated for reporting by the Principle Investigator. The discretion of the principle investigator will guide the need to

report these problems immediately or more frequently, at least annually. Although unlikely, any unanticipated event that is related to the study and suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized will be reported to the PPHS according to established policy.

During the entire MR/PET-MR procedure (both standard and investigational), the investigator or his team will remain in contact with the patient via an intercom system. A squeeze bulb or closed circuit video camera may also be used. The probability of adverse effects is low and no serious adverse effects are expected as we have procedures in place to minimize the risk of serious adverse events.

The Principal Investigator is responsible for subject enrollment, data collection, and accurate documentation and reporting of clinical study information. In addition, the Principal Investigator is responsible for ensuring that the study is conducted in compliance with the study protocol and all the requirements of the MSSM PPHS. The Principle Investigator will assure that data integrity will be maintained during its collection, storage and analysis. Loss of data containing identifiable information will be reported to the PPHS within 10 working/14 calendar days.

j) Withdrawal of Subjects

Subjects may withdraw at any time from the study with no penalty. This will not affect their ability to receive medical care. If a subject withdraws from the study, they must contact the PI in writing. The subject's data may still be used after they have withdrawn authorization.

The study doctor, the sponsor or the institution may stop the subject's involvement in this study at any time without his/her consent. This may be because the study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in the subject's best interest, or for any other reason. If specimens or data have been stored as part of the study, they too can be destroyed without the subject's consent.

6) Risks to Subjects

Approximately two percent (2%) of participants experience some side effects with the use of gadolinium; however, they are mostly mild (nausea, headache, hives, temporary low blood pressure).

Risks Associated With Intravenous Catheter Placement:

Likely:

- Minor discomfort;
- Pain in the injection site.

Less Likely:

- Bleeding;
- Infection;
- Bruising.

Risks Associated With MRI:

- Anxiety/stress;
- Claustrophobia;
- Discomfort.

Because of the powerful magnetic force of the MRI scanner, a subject may not be able to participate in the study if he/she has:

- Metallic or other surgical implants (for example: pacemaker, heart valves, aneurysm clips, metal plates or pins and some orthopedic prostheses);
- Metal pieces in your eye(s) or other body part(s); or
- Difficulty lying still or inability to lie on your back.

Risks Associated with Gadolinium

Less likely
- Headaches;
- Nausea.

Less likely, but serious
- Allergic reaction.

Very rare, but serious
- Nephrogenic systemic fibrosis (NSF)/NephrogenicFibrosingDermopathy (NFD). NSF is a condition associated with the gadolinium contrast agent when there is severe kidney disease. Symptoms include tightening or scarring of the skin and organ failure. In some cases, it can be deadly. NSF has not been seen in patients with normal working kidneys or mild problems in kidney function.

Risks Associated With PET-MRI:

The radiation exposure from the PET injection used in this study is considered small and is not likely to adversely affect the subjects. We do not expect any side effects at all either during or after the scan. Subjects who receive a FDG injection as part of the study should not be the primary caregivers for small children or be in close prolonged physical proximity to women of childbearing age who might or are pregnant, for up to 10 hours after imaging.

Subjects will be exposed to some radiation from the PET. Radiation is measured in units called millisieverts(mSv). Below is a table showing the radiation exposure from each test involved in the study:

Test	Exposure
One PET MRI test	7mSv
One MRI	No radiation exposure at all from MRI

The maximum amount of radiation a subject would receive for research purposes from any combination of tests in this study is 7mSv per year.

Participants who have PET MRI will receive 7 mSv of radiation exposure from the radiotracer (FDG.) This is greater than average annual background and artificial exposure received yearly by people living in the USA (6.2 mSv), and is greater than the US NRC's recommended annual limit for additional exposure to the General Public of 1 mSv. It is however less than the NRC recommended yearly occupational exposure limit of 50 mSv.

The investigators will always seek to keep exposure As Low As Reasonably Achievable, by chosing procedures with the lowest exposure possible while achieving study goals.

The investigators understand that any radiation exposure resulting from this study is in addition to exposure that the participants may receive from the test and procedures outside of the study. The study team will instruct participants to let them know about any such tests.

Reproductive Risk

If a subject is pregnant or nursing or plans to become pregnant during the course of the study, he/she cannot take part in this research study. We do not know the effects on the fetus, breastfeeding baby, or mother-to-be, and this study may cause harm. A subject should not become pregnant or breastfeed, while on this study.

All procedures will be explained thoroughly to each subject before they are scanned.
The subject will be given an option to listen to music during the scan to help calm their fears and lessen the noise of the MRI scanner. All subjects will be given a call button to push if they need to speak to the technician if they feel anxious.

The loss of confidentiality or privacy is possible but all scans will be deidentified and all names, DOB and all other similar data will be removed using only a code which will be kept in a separate secure location. Every attempt will be made that confidentiality or /privacy will be maintained.

7) Provisions for Research Related Harm/Injury

In the event of harm or injury resulting from a subject's participation in this study, the facilities at Mount Sinai Hospital and professional attention together with appropriate medical treatment will be made available to the subject at his/her expense. Financial compensation from Mount Sinai will not be provided. This applies to patients and healthy volunteers likewise.

Physicians and nurses at Radiology Associates are available during all studies and other experts depending on the harm or injury may be consulted if required.

8) Potential Benefits to Subjects

The subjects may not receive any direct benefit from participation in this research study. Others may not benefit either.

9) Provisions to Protect the Privacy Interests of Subjects

All research data will be stored separately from direct identifiers (e.g. name, address, DOB, MRN, SSN) that can link the data to a person's identity. Research data files will be stored using a unique "code" instead. The "linking code file" will be maintained separately.
The file that links the code to the person's identity (direct identifiers) will be maintained electronically and in an encrypted file on a departmental network drive with restricted access to the study team.
All research data files will be stored electronically in encrypted files. Access to the data files will be through restricted view set up by Radiology IT and password protected.

Every effort will be made by the study team to keep all the information in this study strictly private, including subjects' personal information, from the time participants are identified for recruitment until they complete study participation. This includes communication when scheduling appointments, leaving phone messages and follow-up contact. Records of participation, progress and images taken while on the study will be kept secure at Mount Sinai.

All efforts will be made to make the subjects feel at ease with the research situations. They will have the opportunity to ask questions and will have ample time to review and think about any questions, examinations and procedures in the study. Research procedures will be explained in simple, clear, concise language. Members of the research team will be appropriately able to approach prospective participants about the study because the potential subjects may be eligible for enrollment, their physicians have referred them for potential enrollment, and the research team is knowledgeable about study guidelines and protocol.

10) Economic Impact on Subjects

The subject will incur no extra costs, the scans that are part of the standard of care will be submitted to their insurance and other scan time or scans that are part of the study will be paid for by the study sponsor.

11) Payments to Subjects

Subjects will receive $40 per visit for time and travel.

12) Consent Process

Subjects will be given the consent form by their physician to read and take home to think about and then call the research team to make an appointment if they would like to be part of the study. They will be given the opportunity to review the consent document at home, discuss it with whomever they like, think about the information that has been presented to them and be able to make an informed decision, without being concerned or be in any kind of anxiety provoking situation as to whether they wish to participate. Patients being called by the Research Coordinator will be given the opportunity to ask any questions or mention any concerns about the study and to call back with their decision whether they wish to be part of the study or not, or to ask further questions. They will be given time to think about the information that

has been presented to them over the phone and they will be offered to receive the consent form by mail or email prior to a decision whether to take part or not.
All patients will be consented in Radiology Department before they undergo the examination after they have been given time to review and consider being part of the study.

Consent will be obtained by only the members of the study team who have been trained properly and not by referring physicians who are not part of the study team. The subject will be provided with a copy of the signed consent form.

The consent document will be available in English, Spanish and simplified Chinese language. The study team will be following SOP HRP 090 Informed Consent Process for research through the entire consent process. If the subject cannot speak English, services of a translator fluent in both, English and Spanish or English and Chinese will be obtained for any conversation with the subject. The translated consent forms will be IRB approved prior to enrolling non-English speaking subjects.

13) Process to Document Consent in Writing

In order to document consent in writing the standard PPHS consent template will be used.

14) Vulnerable Populations

Economically or socially disadvantaged persons are eligible for the study if the Principal investigator believes that they will be good candidate. The study will be carefully explained and discussed with the patient. Any questions that the patient has will be explained thoroughly to both, the satisfaction of the principle investigator as well as the patient. We do not wish to enroll any person who is does not fully understand what is involved in this study, nor do we wish to improperly influence any participant.
In order to protect the rights and welfare of subjects, we will **not** preferentially enroll vulnerable subjects.
In order to protect the rights and welfare of subjects, we will provide information to the subjects that they can fully understand, and similarly write the consent document in a simple manner and language that someone with sixth grade language could comprehend.
Pregnant subjects are excluded from participation in this study because of the possible effect of gadolinum to the fetus.

Include	*Exclude*	*Vulnerable Population Type*
	x	*Adults unable to consent*
	x	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	x	*Wards of the State (e.g. foster children)*
	x	*Pregnant women*

	x	*Prisoners*

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

During the participation the subject will have access to any study information that is part of their medical record. The investigator is not required to release research information to the subject that is not part of the medical record. Results of the MRI, ARFI and PET/MRI exam will be accessible in the Mount Sinai electronic medical record. The results of the genetic profile analyses, MRI, ARFI or PET/MRI will not be given to the patient. MR, ARFI metrics or PET/MRI metrics will be part of their research record. This will include any incidental findings.

18) External IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

The drugs that are used in the protocol are just the contrast agents. They will be stored within the Department of Radiology.

Mount Sinai	**FORM HRP-213:** Modification of Approved Human Research		
Protocol Name:	**Evaluation of HCC Response to Systemic Therapy with Quantitative MRI**		
Principal Investigator:	**Bachir Taouli, MD**	**Phone: 212-824-8453**	**Email: bachir.taouli@mountsinai.org**
Primary Contact Name:	**Maxwell Segall**	**Phone: 212-824-8476**	**Email: maxwell.segall@mssm.edu**
Revised Date:	**5/11/18**		
Study Numbers:	**IF: IF2178980 HS: 12-01018 GCO: 12-0214**		

A. Most Common Institutional Approvals Required Prior to Modifying Research

1. GCO: If this modification includes a change in the PI or co-Investigators, or a change in funding.
2. FCOI: Any additions in research personnel must be made to the current IF# and any potential conflict of interest must be evaluated.
3. Dept/Div: Any addition of research personnel require Dept/Div Chair signature (the Dept/Div Chair of the added personnel) on HRP-211.
4. IDS: If this modification changes information contained in Appendix B, revised IDS forms need to be submitted to the IDS along with the revised Appendix B for IDS approval and signature.
5. RSC: Any changes to appendix D require review by the RSC.

B. Summarize the modification or attach a summary:

1. Summarize the modification request (what is changing?):

1) Changing the title from "Evaluation of HCC Response to Systemic Therapy with Quantitative MRI" to "Radiogenomics of Hepatocellular Carcinoma Using Quantitative MRI". Linking the current GCO number, 12-0124, with the newly approved GCO number, 17-0269.

2) We've added radiomics features (based on same MRI acquisition) to the protocol. The wording changes/ammendments are as follows:

a) On page 1 under brief summary of research

b) On page 1 under objections, objective b now states that we wish to "Correlate mpMRI and radiomics features with gene expression profiles measured in resected or biopsy tumor samples.

c) On page 2 under background, the first two paragraphs have modified to include data and background information that supports/reflects our aim to demonstrate that "mpMRI can address the challenges of predicting response to therapy by evaluating tumor heterogeneity and surrogating invasive tissue-based genomic molecular characterization."

3) On page 4 under Resources Available to Conduct the Human Research, we have added pathologists, radiologists, molecular biologists, and epidemiologists to the list of multidisciplinary specialties that are involved in the liver cancer program here at Mount Sinai and from whom we can draw upon for both recuritment and general research assistance.

4) On page 5 under study timelines, we have changed the study duration from 3 to 5 years.

5) On page 5 under study timelines, we have removed ARFI ultrasound from the exams patients will undergo. PET/MRI has been removed from the protocol as well.

6) On page 5 under study timelines, we state that we "propose to assess response of therapy in a subset of 30 patients with unresectable HCC. These patients will be selected when they undergo

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treatment with systemic therapy such as immunotherapy (such as but not limited to nivolumab). These patients will be imaged before treatment and 4-8 weeks after initiating therapy. Imaging will involve MRI only."
7) On page 6 under endpoints, we have added the use of iRECIST criteria to the protocol.
8) On page 6 under procedures involved in the human research, we have added that "Up to 15 patients will be asked to undergo a repeat MRI exam to measure repeatability of MRI metrics, including radiomics features. In addition, for patients treated with immunotherapy, we will perform baseline pre-treatment MRI as well as a repeat post-treatment MRI 4-8 weeks after initiation of therapy."
9) On page 6 under procedures involved in human research, we have added a statement that we would like to perform "an independent prospective study in 30 additional patients with advanced HCC treated with immunotherapy (eg, nivolumab) to assess the role of pre-treatment and early changes in quantitative MR parameters for predicting tumor response, time to tumor progression and overall survival."
10) On page 7 under procedures involved in human research, we have added that we will perform "histogram quantification and image texture quantification (Haralick features) on DWI, BOLD, DCE-MRI and T1-weighted imaging."

2. **Provide the justification (reasons) for the change:**

1) The change in title is to reflect a new, pending NIH grant that has already been approved by the grants and contracts office.
2) The addition of radiomics features is paramount to proving that there is a correlation between quantitative mpMRI and certain gene expression profiles in tumors, including expression of immune check-points, with a new aim being the correlation of mpMRI and radiomics findings with gene expression profiles measured in resected or biopsy tumor samples.
3) These additional disciplines demonstrate that ours is a lab suited and well-equipped to conduct a study of this scope.
4) The additional time would allow for further patient enrollment and data analysis.
5) ARFI and PET/MRI will no longer be performed.
6) We want to validate the use of mpMRi for prediction of tumor response to immunotherapy for patients with unresectable HCC.
7) iRECIST along with mRECIST criteria will be used to determine time of tumor progression.
8) A repeat MRI is necessary to demonstrate the inter-reliability of these exams.

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9) See justification number 6.
10) Extraction of additional features potentially improves the characterization of tumor tissue using quantitative mpMRI.

3. **Explain if this modification changes the consent document or information that may affect subjects' willingness to continue to participate in the research?**

The consent document has been changed to remain consistent with the ammendments to the protocol. The primary changes comprise the removal of PET/MRI and ARFI ultrasound. Fewer exams might compel patients to more readily participate.

4. **Explain the proposed plan to re-consent subjects or to provide them with the new information, or explain why the PI believes this is not necessary. Include a brief summary of the status of current subjects, including the number of subjects in each study phase (on study drug, in follow-up, no more study interaction, phone interviews, etc.):**

84 patients have been enrolled, none of whom are currently awaiting follow-up. There would be no need to re-consent patients, as these changes would in no way affect patients who have already completed participation.

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C. Other Documents

Update the Investigator Protocol if affected by the modifications, and provide 1 copy of the following documents if affected by the modification, **with the changes underlined, highlighted, or otherwise clearly marked**:

- FORM: HRP-211- Application for Human Research, including as applicable:
  - Appendix A: External Site Approvals
  - Appendix B: Drugs/Biologics
  - Appendix C: Devices
  - Any addition of personnel from a new Dept/Div must be signed off on by the newly involved Dept/Div Chair
- Evidence of qualifications of the key personnel related to their role in this research (biosketch, resume, CV, other description)
- Protocol Template *(If this is the activation of a previously approved protocol at a new site or sites that will be overseen by a principal investigator who will take separate and full responsibility for that site or those sites, include only site-specific information.)*
- Grant application
- Complete sponsor protocol (including DHHS-approved protocols such as an NIH-sponsored multi-site study or Cooperative Group Clinical Trial protocol)
- HIPAA forms
- Data collection instruments (questionnaires, etc.; do not submit case report forms)
- All written material to be provided to or meant to be seen or heard by subjects, including:
  - Evaluation instruments and surveys
  - Advertisements (printed, audio, and video)
  - Recruitment materials and scripts
  - Consent documents
- If consent will not be documented in writing, a script of information to be provided orally to subjects
- DHHS-approved sample consent document (e.g., sample consent from NIH-sponsored Cooperative Group Clinical Trial)
- Current investigator brochure for each investigational drug
- Current package insert for each marketed drug
- Current product information for each medical device being evaluated for safety or effectiveness.
  - If the research is conducted or funded by the Department of Energy, a completed "Checklist for IRBs to Use in Verifying that HS Research Protocols are In Compliance with DOE Requirements"

D. Principal Investigator Acknowledgement	
I agree to conduct this Human Research in accordance with applicable regulations and the organization's policies and procedures.	
Principal Investigator signature	Date
	*5/11/18*