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Title: Magnetic resonance elastography to characterize and predict response following doxorubicin drug-eluting beads transarterial chemoembolization in patients with hepatocellular carcinoma

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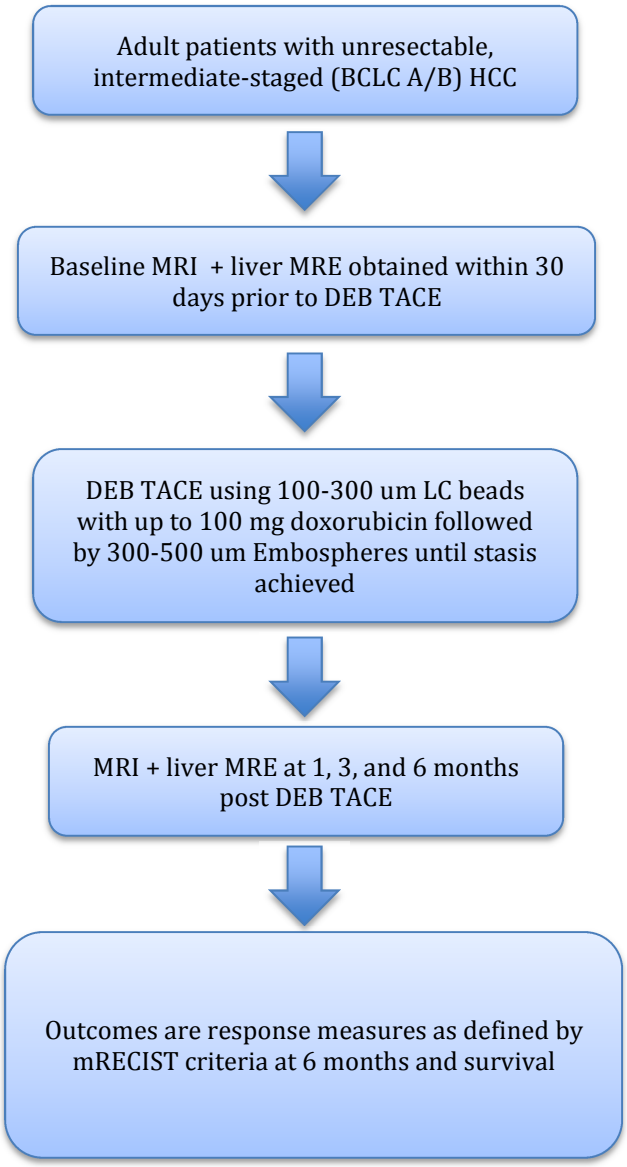
Magnetic resonance elastography to characterize and predict response following doxorubicin drug-eluting beads transarterial chemoembolization in patients with hepatocellular carcinoma

1.0 PROTOCOL SUMMARY AND/OR SCHEMA:



BACKGROUND AND SIGNIFICANCE

Patients with intermediate and advanced-staged hepatocellular carcinoma (HCC) are confronted with significant morbidity and mortality. Doxorubicin drug-eluting beads transarterial chemoembolization (DEB TACE) has emerged as an important therapeutic option for patients with unresectable disease. DEB TACE allows for controlled chemotherapeutic release in order to maximize local ischemia and tumor necrosis with possibly lower systemic drug concentrations and side effect profile than conventional TACE. However, an obstacle to improving patient care is the current inability to assess and reliably predict response in order to effectively provide a personalized treatment plan and allow for timely adaptive therapy. Recent evidence supports that liver stiffness correlates to liver fibrosis and is an independent risk factor for HCC development. In search of a predictive imaging biomarker, this proposal aims to utilize magnetic resonance elastography (MRE) to characterize tumor shear stiffness and predict the treatment response to DEB TACE.

Building upon previous work in MRE, we propose to characterize index liver tumors in patients with HCC by MRE before and following DEB TACE therapy. Shear stiffness estimates by MRE will be compared to conventional MR size and enhancement criteria within 30 5 days before and 1, 3, and 6 months 7 days following DEB TACE. The ability of changes in tumor stiffness by MRE at 1 month relative to baseline to predict the therapeutic outcome as determined by mRECIST criteria at 6 months will be evaluated. Indeed, the improved characterization of HCC tumors and early prediction of outcomes following DEB TACE by MRE may provide a personalized treatment strategy for patients with HCC and allow adaptive therapy to ultimately improve survival. The risks of the trial are minimal and include the addition of MRE to the standard of care MRI examinations obtained before and following DEB TACE therapy.

OBJECTIVES

1. Primary Objective

   Determine the ability of change in HCC average tumor shear stiffness, as measured by MRE obtained in patients 1 month following DEB TACE relative to baseline, to predict the mRECIST therapeutic response at 6 months post procedure.

2. Secondary Objectives

   Determine the ability of the MRE-derived tumor stiffness measurements at baseline to predict the 6-month mRECIST therapeutic response post DEB TACE.

   Determine the ability of change in MRE-derived tumor stiffness measurements at one month post DEB TACE relative to baseline to predict survival.

   Evaluate the inter-reader variability in average shear stiffness measurements by MRE of index HCC tumors obtained within 30 days prior to DEB TACE.

   Compare the percent change in HCC tumor stiffness by MRE following DEB TACE from the baseline estimates to those percent changes in conventional MR tumor size and mRECIST at similar time points in responders versus nonresponders.

   Compare the ability of changes in MRE-derived average tumor stiffness at 1 month post DEB TACE relative to baseline to predict the 6 month therapeutic response by mRECIST criteria to the predictive ability of DWI at the same time point.

   Measure the difference in average shear stiffness as measured by MRE following DEB TACE of the adjacent, non-tumorous liver parenchyma relative to baseline.

ELIGIBILITY

Adult individuals over 18 years with history of unresectsble, intermediate-staged HCC by European Association for the Study of Liver (EASL) criteria with preserved liver function and deemed suitable for DEB TACE therapy.

STUDY DESIGN

The overarching goal of this imaging protocol is to evaluate tumor shear stiffness by MRE as an additional parameter for monitoring HCC, independent of traditional MRI size and enhancement criteria, to guide therapeutic decisions. Those adult patients with intermediate-staged, unresectable HCC

determined to be treated by DEB TACE by our multidisciplinary tumor board will be considered for inclusion in this study. Written informed consent will be obtained from all patients prior to study inclusion. Standard liver mass protocol MRI with the addition of MRE will be obtained on study participants within 30 5 days of DEB TACE treatment. Transcatheter DEB TACE therapy will be performed according to standard protocol with infusion of LC beads impregnanted with doxorubicin. Standard of care MRI examinations will be obtained with the addition of MRE at 1, 3, and 6 months 7 days following DEB TACE therapy as coordinated with the patient's routine clinic visits. Tumor size, enhancement characteristics, and average shear stiffness will be measured at the acquired time points prior to and following DEB TACE for selected index lesions as well as the adjacent, non-tumorous liver parenchyma. The predictive power of changes in shear stiffness relative to baseline will be determined by utilizing the one month post DEB TACE MRE to predict the 6 month therapeutic outcome by mRECIST criteria.

REQUIRED SAMPLE SIZE

Given an estimated 60% response rate for DEB TACE in the literature (7-13), 30 subjects will give us 80% power to detect an area under the ROC curve (AUC) of 0.78 (vs. 0.50) at a 0.05 significance level.

2.0 BACKGROUND AND RATIONALE:

Hepatocelluar carcinoma

Hepatocellular carcinoma (HCC), the most common primary malignancy of the liver, is the fifth most prevalent cancer and the third most common cause of cancer-related mortality worldwide (1). Further, the incidence of HCC has increased three-fold in the United States from 1975 to 2005 (2). Since greater than 70% of patients present with intermediate or advanced disease, curative approaches including resection, transplantation or local ablation are only possible in a small minority of cases (3, 4). Additionally, the three-year recurrence rate following surgical resection can be as high as 70% (4). Therefore, systemic and hepatic-directed therapies remain the only option for the vast majority of patients (5). Given the poor outcomes for these patients, early evaluation of the therapeutic efficacy of a systemic or locoregional therapy continues to be paramount to guide a patient's personalized treatment plan and provide optimal care.

Transarterial chemoembolization

Hepatic-directed therapy has emerged as first-line treatment for many patients with intermediate-staged HCC. Transarterial chemoembolization (TACE) is indicated in patients with intermediate-staged, unresectable HCC with large-multifocal disease and no vascular invasion or extrahepatic spread (6). Conventional TACE incorporates hepatic arterial delivery of chemotherapy (doxorubicin, cisplatin, and mitomycin C) to liver tumors with embolic agents (6). Taking advantage of the liver's dual blood supply, the predominantly arterial fed HCC tumors become bathed in high concentrations of chemotherapy following intra-arterial delivery; whereas, the normal liver parenchyma is greatly spared as its supply arises mainly from the portal vein. TACE achieves partial responses in up to 62% of HCC patients with delayed tumor progression and vascular invasion (7-13). More recently, the use of doxorubicin drug-eluting beads transarterial chemoembolization (DEB TACE) (14-18) and ^{90}Yttrium microsphere radioembolization (19-22) have indicated long-term disease control and 5-year survival similar to that of conventional TACE with possibly a lower side effect profile (17, 18, 23). DEB TACE allows for controlled chemotherapeutic release in order to maximize local ischemia and tumor necrosis with lower systemic doxorubicin concentrations in comparison to conventional TACE (14-17, 23). The timing and necessity of repeated TACE procedures are not standardized in practice. Originally, conventional TACE protocol was repeated every 2 months for four cycles. Takayasu et al recently revealed this standard protocol may be less effective and more deleterious than repeating TACE as necessary (24). Therefore, treatment efficacy should be evaluated thoroughly after TACE therapy to determine the necessity for future TACE. Noninvasive techniques that can effectively predict an early therapeutic response may have a significant impact on personalized treatment planning.

Methods to monitor tumor response

Despite progress in the treatment of HCC, some patients fail to respond to hepatic-directed therapy due to tumor heterogeneity and the aggressive nature of their disease. The radiographic tumor response is essential to assess treatment and survival; however, tumor size assessments alone are limited by poor reproducibility. Current efforts have been aimed at noninvasive, diagnostic approaches to evaluate the therapeutic response, including tumor volume and density (25). Indeed, standard response evaluation criteria in solid tumors (RECIST) and world health organization (WHO) criteria are insensitive for disease response, since size reduction by imaging may be delayed or minimal despite effective therapy (5, 26-28). Response criteria that account for tumor necrosis and viable tumor, such as the European Association for the Study of Liver (EASL) and modified RECIST (mRECIST), better predict survival following treatment but do not account for tumor physiology (5, 28). A non-invasive functional imaging biomarker that can identify these changes may thus have potential to better characterize liver tumors, stratify treatment options, assess treatment response, and predict patient outcomes to treatment. Therefore, by the early prediction of outcomes, a patient's personalized treatment plan may be augmented to include other or additional hepatic-directed therapies.

Magnetic Resonance Elastography

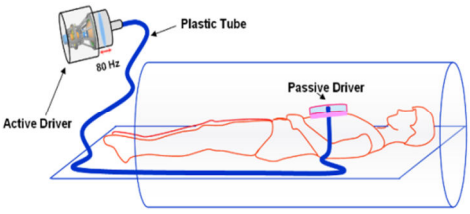


Figure 1. Non-invasive AMRE Driver Introduces Waves. Waves are generated from an active driver placed outside the scan room. The waves propagate through the air within a hollow plastic tube. A passive driver (a drum with thin diaphragm) is placed on the abdomen. Sound waves are non-invasively transmitted through the abdomen into the liver.

Assessment of the early response of HCC to local-regional therapy is critical in determining the success of therapy and guide future treatment options. New functional and molecular magnetic resonance (MR) imaging techniques have emerged as surrogate markers of tumor response that may be applicable to patients with HCC. Magnetic resonance elastography (MRE) is a novel imaging technique that images the tissue response to externally-generated acoustic waves in order to obtain the intrinsic mechanical shear stiffness of the tissue (29-38) (**Figure 1**). MRE is advantageous to ultrasound elastography in that it does not require an acoustic window, is operator independent, suitable in obese patients, and the entire liver, rather than a small volume, can be evaluated (39). Increases in viscoelastic parameters by MRE have been observed in chronic liver disease corresponding to liver fibrosis (40-45). Additionally, initial experience evaluating hepatocellular carcinomas by MRE demonstrated significantly increased absolute shear modulus and loss modulus compared to benign liver tumors (46). Most recently, liver stiffness by MRE has been identified as an independent risk factor for HCC development suggesting its potential role in HCC surveillance in select populations (47, 48). The resultant tumor necrosis following TACE may theoretically soften the tumor, or change its viscoelastic properties, over time. Therefore, MRE may represent a novel technique to characterize, follow, and predict the tumor response to hepatic-directed therapy in patients with HCC as well as the impact of treatment on residual liver integrity. Similar to how MRE-derived liver stiffness values may predict HCC development, tumor stiffness as measured by MRE may predict tumor response to therapy and reflect tumor aggressiveness.

Our experimental plan employs extending our current research on the use of MRE to evaluating HCC in patients before and following DEB TACE. The investigators have extensive prior experience in MRE (29, 34, 49-59) and have developed relevant technologies specifically toward the proposed objectives (49, 52).

Development of rapid MRE sequences to obtain stiffness maps. Ideally MRE sequences should acquire multiple MRE parameters (multiple offsets of wave motion, multiple encoding directions of the wave displacements) within a single breathhold. However, for liver MRE application, it is required to encode only through plane component of displacement. The breathhold time using standard MRE sequence (MREs) requires 18 sec, which might become difficult for some patients to hold their breath. Therefore, we have developed a rapid MRE sequence (MREr) that acquires data in a 9 sec breathhold (Figure 2). This rapid sequence was validated against a standard sequence for liver application demonstrating a strong correlation in stiffness measurements obtained using both techniques (60). Furthermore, this sequence was used to estimate stiffness of the aortic wall which was validated against pulse wave velocity (49). This sequence will be utilized to rapidly obtain liver stiffness measurements, particularly of hepatic tumors as proposed below, and decrease the risk of motion artifact during acquisition.

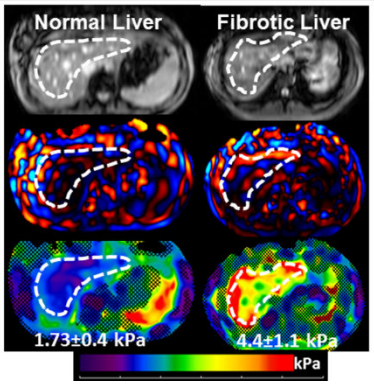


Figure 2: MRE performed on a normal liver and fibrotic liver showing differences in stiffness estimates. White lines show ROI's drawn to obtain mean stiffness values.

3.0 STUDY OBJECTIVES:

3.1 Primary Objective:

Determine the ability of change in HCC average tumor shear stiffness, as measured by MRE, obtained in patients 1 month following DEB TACE relative to baseline to predict the mRECIST therapeutic response at 6 months post procedure.

3.2 Secondary Objectives:

a. Determine the ability of the MRE-derived tumor stiffness measurements at baseline to predict the 6-month mRECIST therapeutic response post DEB TACE.
b. Determine the ability of changes in MRE-derived tumor stiffness measurements at one month post DEB TACE relative to baseline to predict survival.
c. Evaluate the inter-reader variability in average shear stiffness measurements by MRE of index HCC tumors obtained within 30 days prior to DEB TACE.
d. Compare the percent change in HCC tumor stiffness by MRE following DEB TACE from the baseline estimates to those percent changes in conventional MR tumor size at similar time points in responders versus nonresponders.
e. Compare the percent change in HCC tumor stiffness by MRE following DEB TACE from the baseline estimates to those changes in mRECIST at similar time points in responders versus nonresponders.
f. Compare the ability of changes in MRE-derived average tumor stiffness at 1 month post DEB TACE relative to baseline to predict the 6 month therapeutic response by mRECIST criteria to the predictive ability of DWI at the same time point.
g. Measure the difference in average shear stiffness as measured by MRE following DEB TACE of the adjacent, non-tumorous liver parenchyma relative to baseline.

4.0 ELIGIBILITY CRITERIA:

Prior to enrollment, patients will be presented to the HCC multidisciplinary tumor board for evaluation of eligibility. Patients entering the study must meet the following inclusion criteria:

4.1 Inclusion Criteria:

Patients aged ≥ 18 years with HCC unsuitable for resection or percutaneous ablation, (Barcelona Clinic Liver Cancer [BCLC] A/B, without portal invasion or extrahepatic spread)
Confirmed diagnosis of HCC by EASL
No previous chemotherapy, radiotherapy, or transarterial embolization
Deemed suitable to receive DEB TACE on the basis of ability to undergo angiography, and appropriate lab values (18),
Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and preserved liver function (Child-Pugh Class A or B).

4.2 Exclusion Criteria:

Contraindications to MR imaging, doxorubicin therapy or angiography
History of other primary tumor
Advanced liver disease (bilirubin >3 mg/dl, AST or ALT >250 U/l) or tumor disease (extrahepatic spread, vascular invasion, or diffuse disease >50% liver involvement)
Women who are pregnant or breast-feeding

5.0 RESEARCH DESIGN AND METHODS

5.1 Study Design:

Overview
The overarching goal of this imaging protocol is to evaluate tumor shear stiffness by MRE as an additional parameter for monitoring HCC, independent of traditional MRI size and enhancement criteria, to guide therapeutic decisions. This prospective study will utilize MRE to determine the ability of change in HCC tumor average shear stiffness measurements at one month post DEB TACE from baseline to predict the therapeutic response as determined by mRECIST criteria at six months following DEB TACE.

Design
Liver MR will be prospectively performed on patients with known HCC. Patients will be evaluated by the PI and/or Co-Investigators and selected based upon routine CT or MR at Ohio State University Wexner Medical Center (OSUMC) by EASL criteria. All HCC patients are discussed at our multidisciplinary tumor board and those patients determined to be treated by DEB TACE will be considered for inclusion in this study. Written informed consent will be obtained from all patients prior to study inclusion. All adult patients (> 18 years) who meet study inclusion criteria, including both men and women, will be eligible to participate. In accordance with the NIH policy on the inclusion of Women and Minorities in Research Involving Human Subjects, there is no *a priori* preference for the selection of subjects based on gender or ethnic origin based on the study hypotheses. Standard liver mass protocol MRI will be obtained on study participants within 30 5 days of DEB TACE treatment. Standard liver MRI includes unenhanced and gadolinium-based contrast enhanced images as well as diffusion-weighted images (further described in 5.10). Additionally, liver MRE will also be performed at that time as described in 5.10.

According to standard protocol, transcatheter DEB TACE therapy will be performed via a femoral artery approach and will include super selective catheterization of the tumor's feeding artery with infusion of a solution of 100-300 um LC beads (Biocompatible, Farnham, Surrey, UK) impregnated with 50 mg doxorubicin in each vial. Treatment endpoint is defined as complete administration (two vials of DEB for a total 100 mg doxorubicin) or five-beat stasis is achieved. If persistent antegrade flow is noted after the drug eluting beads have been used, then embolization will be continued using 100-300 and/or 300-500 μm microspheres (Embospheres; Biosphere Medical) until stasis is achieved (5, 67). Patients are admitted following the procedure with expected discharge the day following. As routine at our institution, patients are followed in our dedicated TACE clinic with clinic visits prior to procedure and 1 week, 1 month, and every 3 months to follow as necessary after TACE.

Following DEB TACE treatment, the response over time of hepatic index lesions in patients with HCC to DEB TACE will be evaluated. Standard liver MRI with MRE will be performed at 1 month 7 days, 3 months 7 days, and 6 months 7 days post treatment on the same 1.5 T whole-body MR unit, as coordinated with routine follow-up clinic visits. Tumor size and stiffness estimates will be measured at each time point. Up to 2 index lesions will be selected per subject based upon size greater than 2 cm and location entirely confined to the DEB TACE treatment zone as determined by post DEB TACE coned beam CT. Selected index lesions and adjacent, non-tumorous liver parenchyma will be evaluated at each time point.

Assessment of Therapeutic Response: Response rates will be assessed using mRECIST guidelines (68-70) by two independent radiologists on the selected index lesions. mRECIST criteria at 6 months after initial DEB TACE will be the primary end point (69-72). According to mRECIST guidelines (Appendix A), tumor response is classified by the percent decrease in the tumor's longest arterially enhancing diameter with response classified as either complete response (CR), partial response (PR), disease progression (PD) and stable disease (SD).

Patients will then be categorized as responders (CR+PR) or nonresponders (PD+SD) based on the 6 month MRI.

Table 1	mRECIST
Complete Response (CR)	Disappearance of any intratumoral arterial enhancement in all target lesions (up to two measurable liver lesions)
Partial Response (PR)	At least a 30% decrease in the sum of unidimensional diameters of viable (enhancement in the arterial phase) target lesions
Stable Response (SR)	Any cases that do not quantify for either partial response or progressive disease
Progressive Disease (PD)	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions
Responders = Complete response (CR) + Partial Response (PR)	
Nonresponders = Progressive disease (PD) + Stable disease (SD)	

Predictive Ability: The therapeutic outcome will be determined from the MRI obtained 6 month post DEB TACE as described above using mRECIST criteria. The estimated tumor stiffness and lesion diameter of the enhancing region will be analyzed independently by two radiologists. The predictive power of changes in shear stiffness relative to baseline will be determined by utilizing the one month post DEB TACE MRE to predict the 6 month therapeutic outcome by mRECIST criteria (primary objective) and survival (secondary outcome).

5.2 Reference Standard:

As described above, the reference standard for evaluation of therapeutic response following DEB TACE in patients with HCC is mRECIST criteria on standard liver MRI at 6 months post DEB TACE. This method utilizes both size criteria as well as enhancement characteristics to determine tumor response. Other response criteria, including RECIST and WHO, are insensitive for disease response, since they rely on tumor size reduction by imaging which may be delayed or minimal despite effective therapy. mRECIST response criteria account for tumor necrosis and viable tumor in addition to size measurements, and, therefore better predict survival following treatment. Ideally, a non-invasive imaging biomarker would be able to predict a tumor's response either prior to therapy or shortly thereafter in order to stratify treatment options and develop a patient's personalized treatment plan to include other or additional hepatic-directed therapies.

5.3 Study Calendar/Schedule:

Time line	Within 30 days 5 days	Time 0[1]	+ 1 Month 1 week	+ 3 Months 1 week	+ 6 Months 1 week	Continued Follow-up
Clinic visit	**x**		**x**	**x**	**x**	**X**
CBC	**x**		**x**	**x**	**x**	**X**
PT, INR, PTT	**x**		**x**	**x**	**x**	**X**
BUN, Cr	**x**		**x**	**x**	**x**	**X**
Albumin, total protein, total bilirubin	**x**		**x**	**x**	**x**	**X**
LDH, Alk phosphatase, ALT, AST, AFP	**x**		**X**	**x**	**x**	**X**
MRI	**x**		**x**	**x**	**x**	**X**
MRE	**x**		**X**	**x**	**x**	
TACE-DEB		**x**				
ECOG assessment	**x**		**X**	**x**	**x**	**X**
Vital signs checked	**x**		**X**	**x**	**x**	**X**

[1]Time 0 is the day DEB TACE is performed.

Within 4 weeks 5 days **prior to Time 0**
Patients will be seen in clinic within 4 weeks prior to initiating therapy. Patients will have vital signs (weight, blood pressure, temperature, and heart rate), CBC, chemistry profile with liver function tests, coagulation studies, and ECOG assessment. Patients will have multiphasic liver MRI with MRE prior to starting therapy.

Time 0 + 1 month 1 week
As standard of care, patients are routinely evaluated in clinic at one month following DEB TACE therapy. At this clinic visit, study patients will have vital signs (weight, blood pressure, temperature, and heart rate), CBC, chemistry profile with liver function tests, coagulation studies, ECOG assessment as well as MRI with MRE obtained. Patient's routinely receive a multiphasic liver MRI at this time point post procedure as standard of care to monitor disease response.

Time 0 + 3 months 1 week
As standard of care, patients are routinely evaluated in clinic at three months following DEB TACE therapy. At this clinic visit, study patients will have vital signs (weight, blood pressure, temperature, and heart rate), CBC, chemistry profile with liver function tests, coagulation studies, ECOG assessment as well as MRI with MRE obtained. Patient's routinely receive a multiphasic liver MRI at this time point post procedure as standard of care to monitor disease response.

Time 0 + 6 months 1 week
As standard of care, patients are routinely evaluated in clinic at six months following DEB TACE therapy. At this clinic visit, study patients will have vital signs (weight, blood pressure, temperature, and heart rate), CBC, chemistry profile with liver function tests, coagulation studies, ECOG assessment as well as MRI with MRE obtained. Patient's routinely receive a multiphasic liver MRI at this time point post procedure as standard of care to monitor disease response.

Continued Follow-up
Patients are continued to be assessed in multidisciplinary clinic, either by the interventional radiologist or surgical oncologist, in TACE clinic every three months to follow DEB TACE. These clinic visits include obtaining vital signs (weight, blood pressure, temperature, and heart rate) as well as routine laboratory values, including CBC, chemistry profile with liver function tests, coagulation studies. ECOG assessment as well as routine multiphasic liver MRI is also obtained as standard of care to monitor disease response.

End of Study
Primary study end point is therapeutic response as determined by mRECIST criteria based upon the MRI obtained 6 months post DEB TACE. A secondary objective is to evaluate the ability of MRE-derived tumor stiffness estimates to predict patient survival. As average survival for patients with intermediate-staged HCC is 12 to 24 months, we expect two years beyond the end of study to be sufficient for data collection. At the end of the study, patients will be surveyed to obtain survival data.

If the patient experiences progression of disease in the liver by mRECIST, further treatment per standard of care will be initiated as determined appropriate by the institutional multidisciplinary tumor board.

5.4 Pre-Registration Procedures (Visit 1):

Those patients with newly diagnosed HCC presenting for evaluation by a hepatobiliary surgeon, hepatologist, or interventional radiologist at OSUMC will be considered for study enrollment. We

will make every effort to include women and minorities. Patients will be recruited from these medical and surgical oncology clinics based on their eligibility criteria. These clinics, including the TACE clinic which sees all potential DEB TACE patients prior to therapy, are located in the Martha Morehouse Outpatient Center at OSUMC. The physician will perform the initial determination of eligibility when he/she sees patients in clinic. The physician will inform potentially eligible subjects about the study and ask them if they would be willing to meet with the study coordinator. The study coordinator will attend the physician's clinic and, during the clinic, meet briefly with willing subjects. This brief meeting will represent Visit 1, the pre-registration visit. At this visit, the study coordinator will outline the research protocol, give the subject an informational flyer, an MRI screening safety questionnaire, and a consent form. The study coordinator will record the subject's preferred contact information; and schedule the subject for a registration visit. This registration visit will coincide with the MRI and will be obtained approximately 30 5 days prior to the DEB TACE treatment procedure. There will be no financial compensation for patients enrolling on this protocol.

5.5 Registration Visit and MRI/MRE (Visit 2):

Day: -30 5 days

At this visit, the study coordinator will explain in detail the study to the patient and will review the informed consent with the patient. Patients will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits the patient may incur. The MRI screening questionnaire and consent form will be reviewed. With the subject's verbal permission, eligibility criteria will be rechecked. If the eligibility criteria are met, the subject will be asked by the PI or Co-I to sign informed consent and the subject will be registered for the study. The research coordinator will record demographic data (gender, date of birth, self-reported ethnicity, and self-reported racial group) as well as clinical and laboratory data related to the eligibility criteria (liver and renal function laboratory tests). The coordinator will then transport the patient to the OSUMC Martha Morehouse Imaging Center to be registered for the standard of care multi-phase MRI examination to include liver MRE. The coordinator will also review with the subject the pre-MRI instructions. The MRI and MRE protocols are described in detail below (5.10). This registration visit and MRI will be obtained within 30 5 days of the procedure and is per standard of care. Vital signs (weight, blood pressure, temperature, heart rate) will be assessed at the patient's routine clinic visit.

Prior to the MRI/MRE, the MRI research technologist will meet the research coordinator and subject and review the pre-MRI questionnaire as well as confirm consent. A urine pregnancy test will be obtained if the woman is of child-bearing potential. The MRI/MRE examination will be performed (5.10) and the study PI or study investigator will monitor each MR examination. Subjects will be observed for adverse events until the subjects leave the MR facility. Adverse events will be recorded on an adverse event form.

As routine for HCC patients being evaluated for DEB TACE therapy, patients will have a CBC, PT, INR, PTT, electrolytes, BUN/creatinine, liver function tests (albumin, total protein,total bilirubin, conjugated bilirubin, LDH, alkaline phosphatase, ALT, and AST) and AFP obtained within four weeks of the procedure.

5.6 DEB TACE Intervention (Visit 3):

Day 0: Chemoembolization procedure (DEB TACE)

DEB TACE will be performed per standard protocol at OSUMC.

On the day of the procedure, patients will take only clear liquids after midnight and nothing by mouth within 6 hours of the procedure. The morning of the procedure an IV will be started, and they will receive an anti-emetic and a pre-procedure antibiotic (cephazolin, 1 gram IV or, for those who have had a bilioenteric anastomosis, sphincterotomy, or any other reason to lack an

intact, functional sphincter of Oddi, Piperacillin/Tazobactam, 4.5 grams IV. Patients who are allergic to those medications will receive Clindamycin 900 mg and Gentamicin 1.5 mg/kg IV). Patients with a creatinine >1.5 will receive 1 liter intravenous normal saline prior to starting the procedure and will continue at 150 ml/hr during and following the procedure. Those who are allergic to contrast will be pre-medicated with prednisone. These patients receive 50 mg of prednisone by mouth every 6 hours for a total of 3 doses, beginning 13 hours before the procedure, thus administered at -13 hours, -6 hours, and -1 hour. In addition, 50 mg of diphenhydramine hydrochloride is given by mouth 1 hour before the procedure.

Baseline angiography including celiac and superior mesenteric angiography will be performed to delineate arterial anatomy and blood supply to the tumor.

Solitary HCC/Unilobar Disease

In the case of a solitary or low volume tumor in one lobe of liver, selective embolization may be performed. If a single vessel supplies the tumor then an attempt will be made to administer the entire 2 vial dose of LC Bead into that vessel. If stasis occurs before the entire dose is delivered, the amount administered is recorded, and the remainder is discarded. If there is continued antegrade flow after the LC Bead has been used, embolization will be continued using 100-300 and/or 300-500 micron particle embolic until stasis occurs.

Multifocal/Bilobar HCC

In the case of multifocal bilobar disease, either the right or left hepatic territory will be treated at the first session. This will be performed by placing the angiographic catheter selectively into either the right or left hepatic artery, and embolizing to stasis. 2 vials of 100-300 micron LC Beads will be prepared with up to 100 mg Doxorubicin (50mg/vial). The goal will be to administer all vials when possible, and if persistent antegrade flow is noted after the drug eluting beads have been used, then embolization will be continued using 100-300 micron and/or 300-500 micron particle embolic until stasis occurs.

Stasis is defined as the absence of antegrade flow within a vessel, such that even slow administration of contrast material results in reflux, or retrograde flow for 5 cardiac beats after the injection of contrast.

Following embolization, a coned beam CT will be obtained to confirm embolization of the target lesions. After the procedure, patients are monitored in the Post Anesthesia Care Unit for 3-5 hours. Patients are then transferred to the floor where they receive 24 hours of IV hydration as well as continued monitoring. Once patients are afebrile, are taking adequate nutrition by mouth, and have their pain controlled by oral analgesics, they are discharged home.

5.7 General Concomitant Medication and Supportive Care Guidelines:

The dedicated TACE clinic nurse practitioner coordinates patient follow-up for all patients after DEB TACE procedures. He/she will schedule subjects, as routine following DEB TACE, to return to TACE clinic at 1 week as well as 1 month, 3 months, 6 months, and every three months to follow as necessary dependent upon treatment response. The 1 month, 3 month, and 6 month clinic visits are coordinated with standard of care multi-phase liver MRI studies to monitor treatment response. The nurse practitioner and/or interventional radiologist will perform a history and physical examination at these routine clinic visits. As routine for HCC patients following DEB TACE therapy, patients will have a CBC, PT, INR, PTT, electrolytes, BUN/creatinine, liver function tests (albumin, total protein,total bilirubin, conjugated bilirubin, LDH, alkaline phosphatase, ALT, and AST) and AFP obtained at these scheduled clinic visits.

5.8 Post-Therapy Visits and MRI/MRE (Visits 4-6):

The research coordinator will meet the subject at the routine TACE clinic visit following DEB TACE therapy, either one month, three months, or six months following treatment. The research coordinator will then transport the research participant to the OSUMC Martha Morehouse Imaging Center. The MRI research technologist will meet the research coordinator and subject at each of these visits (1 month, 3 months, and 6 months 7 days post DEB TACE) upon arrival at the MR facility and confirm consent as well as re-review the MR safety screening questionnaire and obtain a urine pregnancy test (if subject is a woman of child bearing potential). The MRI/MRE examination will be performed as described (5.10). The PI or study investigator will again monitor each MR examination and observe the subjects for adverse events until the subjects leave the imaging center department. Adverse events will be recorded on an adverse event form.

5.9 Criteria for Removal from Study:

Registered subjects will be withdrawn from the study if any of the following conditions are met:

Baseline research MRI/MRE is not performed prior to DEB TACE procedure.
eGFR <30 on blood sample drawn after registration
Subject has a positive urine pregnancy test after registration
Subject withdraws his/her consent
Exclusion criteria are discovered after registration but prior to MRI.

5.10 Image Acquisition, Archiving, and Interpretation:

MRI/MRE Imaging: All imaging will be performed in the same 1.5-Tesla MRI scanner (Avanto, Siemens, Erlangen, Germany) either before or following DEB TACE treatment per the schedule described above. Routine clinical liver protocol includes: 1) unenhanced, transverse fat-suppressed and non fat-suppressed T2-weighted fast spin echo images, in- and opposed-phase T1-weighted gradient recalled echo (GRE) images, and diffusion-weighted images, 2) GRE T1-weighted transverse images of the liver during the arterial, portal venous, and delayed phases after bolus injection of 0.1 mmol/kg gadolinium-based contrast. ***MRE:*** T1-weighted scout images will be obtained in an axial plane covering the liver. 60Hz mechanical waves will then be introduced into the liver by a pneumatic driver system (29, 49-51, 60) as shown in **Figure 1**. Four MRE phase offsets (i.e. the MRI acquisition is performed with multiple offsets of the phase of the externally applied wave to obtain images of the wave propagation over time) and 16.67ms duration (60 Hz) motion encoding gradients will be applied in the z direction to measure the through-plane motion for all the slices as described previously (60). Other imaging parameters include TE:21.1ms, TR: 25ms, Flip angle: 30^{o}, acquisition matrix: 256x64, and GRAPPA acceleration factor of 2. The pneumatic driver used in this study is FDA-approved and generates the vibrational energy significantly below the criteria set by European Union (64).

Index Lesion Selection: For reproducibility and repeatability evaluation, up to two index liver lesions will be selected with diameters greater than 2 cm for each subject from the baseline MRI/MRE prior to DEB TACE therapy. Smaller, cystic or necrotic lesions as well as those close to the diaphragm will be excluded, similar to prior studies (46, 61). For purposes of index lesion selection for monitoring changes following DEB TACE, up to 2 index lesions will be selected per subject based upon size greater than 2 cm and location entirely confined to the DEB TACE treatment zone as determined by post DEB TACE coned beam CT. The estimated tumor stiffness and arterially enhancing index diameters will be analyzed independently by two radiologists at each time point as described below.

Imaging Analysis: Images will be automatically registered by implementing cross correlation techniques for subject motion during scans and evaluated by two independent radiologists. Electronic calipers will be used to measure the maximum diameter of the lesion in the axial dimension on subtracted portal venous phase images. Regions of interest (ROI) will also be routinely drawn to encompass adjacent, non-tumorous liver parenchyma, avoiding vascular

structures to represent the adjacent, non-tumorous liver parenchyma. For ADC calculations, ROIs will be drawn over a lesion at the level of the maximum diameter of the lesion, as seen on DWI at b values of 500 and 1,000 s/mm^2. Cysts and necrotic areas will not be included in the ROIs. Signal intensities will be measured three times, and the average intensity will be calculated for each lesion as described previously (62, 63, 73). All ADC values will be expressed as mean (SD) in square millimeters per second.

MRE Analysis: MRE wave images will be analyzed by applying multi modal direct inversion algorithm (38) using MRE Lab (Mayo Clinic, Rochester MN). The stiffness map contains regions showing 95% confidence intervals (un-hatched regions) to obtain the mean stiffness values (**Figure 2**). Effective stiffness values will be calculated for the index lesions and the adjacent, non-tumorous liver parenchyma, including measurements for the model-free viscoelastic parameters (complex shear modulus and storage and loss moduli) as described previously (46).

Imaging Time Points and Analysis: All patients will receive a baseline MR within 1 month of the DEB TACE procedure as well as follow-up MR imaging at 1, 3, and 6 months 7 days post DEB TACE on the same 1.5 T whole-body MR unit, as coordinated with routine follow-up clinic visits. Tumor size and stiffness estimates will be measured of selected index lesions, as described above, at each time point pre- and post- DEB TACE. The investigator will measure each index lesion in the same manner as at baseline. Up to 2 index lesions will be selected per subject based upon size greater than 2 cm and location entirely confined to the DEB TACE treatment zone as determined by post DEB TACE coned beam CT. The estimated tumor stiffness and arterially enhancing index diameters will be analyzed independently by two radiologists for calculation of intra-reader variability on the baseline MRE-derived stiffness estimates. Adjacent, non-tumorous liver parenchyma will also be evaluated as above at each time point.

6.0 STATISTICAL CONSIDERATIONS:

6.1 Study Design and Endpoints:

The research team will evaluate the predictive ability of change in average tumor stiffness measurements by MRE at one month post DEB TACE relative to baseline to predict the therapeutic response determined by mRECIST criteria at 6 months post procedure. The primary endpoint is therapeutic response at 6 months post TACE by mRECIST criteria. The secondary endpoints are survival, changes in index lesion size and DWI on follow-up MR imaging.

6.2 Objectives and Analysis Plans:

The null hypothesis is that MRE-derived average tumor shear stiffness at 1 month post DEB TACE does not correlate with the therapeutic response at 6 months following the procedure as determined mRECIST criteria.

Predictive Ability: The therapeutic outcome will be determined from the MRI obtained 6 months post DEB TACE using mRECIST criteria. The predictive power of shear stiffness pre- and 1 month post DEB TACE and change from baseline to 1 month post will then be evaluated relative to the 6-month post DEB TACE therapeutic response by calculating the area under the receiver operating characteristic curve (AUC). The ability for tumor shear stiffness as measured by MRE to predict therapeutic response at 6 months post DEB TACE will also be compared to that of ADC at similar time points.

Intra- and and inter-observer variability: The clinical validation will include a reproducibility study and the protocol will be assessed according to its technical feasibility, reproducibility of measurements, and comparison to similar parameter values (41-45). Agreement in measurements taken from different tumors from the same patient at the same time point will be

assessed with the Bland-Altman plot. Reader variability will be assessed by acquiring MRE data twice, by two different readers, and evaluating intra- and inter-observer variability in ROI positioning of resultant viscoelastic values.

Changes in parameters following DEB TACE: Regression analysis will be used to study changes in lesion size over time following DEB TACE and tumor stiffness as derived by MRE between responders and nonresponders. The percent change in MRE-derived tumor stiffness of index lesions will be evaluated against the percent change in index lesion size for responders and for nonresponders at each time point post DEB TACE. Similarly, the percent change in MRE-derived tumor stiffness of index lesions will be evaluated against the change in mRECIST for responders and for nonresponders at similar time points following DEB TACE. Change in mean apparent diffusion coefficient (ADC), a quantitative parameter of DWI, will also be obtained for comparison for each time point relative to baseline which has recently been shown promising in assessing early response following TACE (62, 63).

Wilcoxon signed-rank test will determine if patient characteristic differences (i.e. age, degree of non-tumorous liver fibrosis, gender, etiology of cirrhosis if present, and subject-reported race) between responders and nonresponders are significant. Further, stiffness values between the two groups (responders and nonresponders) will be compared at each time point using a Mann-Whitney U-statistic, which is equivalent to testing whether the AUC is greater than 0.5. Additionally, changes in average MRE-derived stiffness measurements of the adjacent, non-tumorous liver parenchyma relative to baseline will be evaluated to reflect any chemotherapeutic effect over time.

Baseline MRI/MRE Measurements: Statistical evaluation will be performed on MRE-derived average tumor stiffness measurements for up to two index lesions per liver with comparisons made between individuals on the baseline MRI/MRE for responders versus nonresponders. The difference in stiffness estimates of the index lesions and the adjacent liver parenchyma will be calculated for responders and nonresponders. The measured parameters between the index lesions and normal liver parenchyma can be compared in the same patient within the same slice improving reliability.

6.3 Sample Size Considerations:

Given an estimated 60% response rate for DEB TACE in the literature (7-13), 30 subjects will give us 80% power to detect an area under the ROC curve (AUC) of 0.78 (vs. 0.50) at a 0.05 significance level. At OSUMC, we perform approximately 100 first time DEB TACE procedures for newly diagnosed HCC patients per year. Therefore, recruiting 30 patients for this study will be achievable within 18 to 24 months from study initiation.

6.4 Stratification Factors:

This is a cohort study. There will be no randomization or stratification of subjects.

6.5 Study Monitoring, Interim Analysis, and Early Stopping Rules:

Because this is a small study with minimal risk, the PI will monitor the study for accrual and AEs. Every three months, the research coordinator will generate a summary report on accrual and participant demographics.

7.0 ADVERSE EVENTS: SAFETY ISSUES

7.1 Definition of Adverse Events and Potential Risks

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is an injury or illness that:

Causes death
Is life threatening, even if temporary in nature
Results in permanent impairment of a bodily function or permanent damage to a body structure
Necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to body structure
An increased level of care (e.g. unscheduled admissions, transfer from a routine inpatient bed to an intensive care unit, etc).

Events meeting the criteria for an SAE require notification of the sponsor and the reviewing IRB within the specified timeframe identified in 7.4.1.1.

7.3 Adverse Events Characteristics

7.3.1 Grading of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

7.3.2 Definition of Expected/Unexpected (Anticipated/Unanticipated) Adverse Events

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

the current known adverse events listed in the Agent Information Section of this protocol;
the drug package insert;
the current Investigator's Brochure

7.3.3 Attribution of Adverse Events

Attribution of the AE:

Definite – The AE is clearly related to the study intervention.
Probable – The AE is likely related to the study intervention.
Possible – The AE may be related to the study intervention.
Unlikely – The AE is doubtfully related to the study intervention.
Unrelated – The AE is clearly not related to the study intervention.

7.4 Adverse Event Reporting

7.4.1 When and How to Report Adverse Events

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.

7.4.1.1 Expedited Adverse Event Reporting

Expedited Reporting

The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

The IRB must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others”

The following events should be reported:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.

5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

7.4.1.2 Protocol-specific Expedited Adverse Event Reporting Exclusions

No protocol-specific expedited adverse event reporting exclusions for this protocol.

7.4.1.3 Routine Adverse Event Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.0 ETHICAL CONSIDERATINS (INCLUDING INFORMED CONSENT):

8.1 Protection of Patient Rights:

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to OSU IRB guidelines. The PI or Co-Is will monitor all MR examinations and report any major, unexpected events. The study will protect the rights of all human subjects and an informed consent will clearly define the risks, benefits, toxicities and side effects of the trial, as listed below.

MRE:
Patients will be screened prior to the MRI to ensure no contraindications for MRI (such as pacemakers). Trained technologists will perform the studies and trained medical personnel will be present in the event of unexpected outcome. Medical equipment, i.e. crash cart, will be present immediately outside of the MR scanner suite in the case of an emergency. The MR imaging suite is located in a multidisciplinary outpatient center with access to medical care if necessary.

MRE does not require gadolinium-based contrast; however, as part of the standard of care MRI obtained prior to and following DEB TACE therapy, gadolinium-based contrast is routinely administered. There are no additional risks to the patient beyond those involved in the patient's routine, standard of care MRI. During MRE, patients will experience the external pressure generated by the pneumatic driver lying on the patient's abdomen. This pneumatic drive is approved by the FDA, routinely used for liver MRE, and generates the vibrational energy significantly below the criteria set by European Union (64).

Blood Drawing: The blood samples collected are routine and standard of care for monitoring patients prior to and following DEB TACE therapy for HCC. No additional laboratory tests will be obtained as part of this study.

OSU's Privacy Office may allow the use and disclosure of protected heatlh information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

8.2 Confidentiality:

Subjects will be assigned unique study identifiers. The link to subject identity will be securely stored and separately from personal health information. MR images will be generated using only the subject's study ID and date of birth. We will not identify data collected during the subject's participation in this study with personal identifying information.

Data collected during this study will be kept either in a locked file cabinet or a password-protected database. All study data will be kept confidential. No publication or written reports will link subject data with a name or any individual protected health information.

8.3 Inclusion of Women and Minorities:

The racial, gender, and ethnic characteristics of the proposed subjects reflect the demographics of the patient population of the surrounding area. However, extra efforts will be made to recruit women and minorities. It is the policy of OSU that all research involving human subjects be conducted in compliance with policy concerning inclusion of minorities and women in research. Children will be excluded from the study. No exclusion criteria shall be based on race, ethnicity, or gender.

HCC affects both sexes and all ethnicities. Therefore, subjects will be recruited from clinic without regard to sex/gender or racial/ethnic group. The population sample selected for this study will be representative of the population sample followed at the surgical oncology and hepatology clinics.

8.4 Audit and Monitoring:

This study uses a longitudinal, multi-point interaction with the research subjects with low risk to the participants. Subjects will be monitored for adverse events and side-effects during the follow-up clinical appointments with the physician. In the unlikely occurrence of an adverse event considered to be related to the study protocol, this event will be reported to the OSU IRB and R & D service. If subjects are judged to be experiencing an adverse event from the study and are clinically stable, they will be referred back to their primary care physician for further evaluation and follow-up. If the subject is considered to be clinically unstable, the subject will be referred to the closest emergency room. A monthly meeting will be held with the PI, co-PIs and study coordinators to review and ensure the integrity of the collected data.

9.0 DATA MANAGEMENT; ADMINISTRATIVE ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

Data and Safety Monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular disease group meetings (at least monthly) and the discussion will be documented in the minutes.

The principal investigator (PI) of the trial will review responses of the trial where applicable at these disease group meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with the sponsors, to determine if the trial should be terminated before completion.

Serious adverse events and responses will also be reviewed by the OSUCCC –James Data and Safety Monitoring Committee (DSMC). All reportable serious adverse events will also be reported to the Institutional Review Board (IRB) of record as per the policies of the IRB.

10.0 REFERENCES:

1. Rampone B, Schiavone B, Martino A, et al. Current management strategy of hepatocellular carcinoma. *World J Gastroenterol* 2009; 15:3210-3216.
2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; 27:1485-1491.
3. Hung H. Treatment modalities for hepatocellular carcinoma. *Curr Cancer Drug Targets* 2005; 5:131-138.
4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011; 61:69-90.
5. Prajapati HJ, Spivey JR, Hanish SI, et al. mRECIST and EASL responses at early time point by contrast-enhanced dynamic MRI predict survival in patients with unresectable hepatocellular carcinoma (HCC) treated by doxorubicin drug-eluting beads transarterial chemoembolization (DEB TACE). *Annals of Oncology* 2013; 24:965-973.
6. Livraghi T, Makisalo H, Line PD. Treatment options in hepatocellular carcinoma today. *Scand J Surg* 2011; 100:22-29.
7. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma—a randomized controlled trial. *Gastroenterology* 1988; 94:453–456.
8. Group d'Etude et de Traitment du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995; 332:1256–1261.
9. Raoul JL, Guyader D, Bretagne JF et al. Prospective randomized trial of chemoembolization versus intra-arterial injection of 131-labeled iodized oil in the treatment of hepatocellular carcinoma. *Hepatology* 1997; 26:1156–1161.
10. Bruix J, Llovet JM, Castells A et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized controlled trial in a single institution. *Hepatology* 1998; 27:1578–1583.
11. Pelletier G, Ducreux M, Gay F et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. *J Hepatol* 1998; 29:129–134.
12. Lo CM, Ngan H, Tso WK et al. Randomized controlled trial of transarterial lipiodol

chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; 35:1164–1171.
13. Llovet JM, Real MI, Montana X et al. Arterial embolization or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. *Lancet* 2002; 359:1734–1739.
14. Malagari K, Alexopoulou E, Chatzimichail K, et al. Transcatheter chemoembolization in the treatment of HCC in patients not eligible for curative treatments: midterm results of doxorubicin-loaded DC bead. *Abdom Imaging* 2008; 33:512-519.
15. Lewis AL, Taylor RR, Hall B, et al. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. *J Vasc Interv Radiol* 2006; 17:1335-1343.
16. Lewis Al, Gonzalez MV, Lloyd AW, et al. DC Bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. *J Vasc Interv Radiol* 2006; 17:335-342.
17. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug-eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007; 46:474-481.
18. Lammer J, Malagari K, Vogl TJ, et al. Prospective randomized study of doxorubicin-eluting bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V Study. *Cardiovasc Intervent Radiol* 2010; 33:41-52.
19. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol* 2008; 31(3):271-9.
20. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y radioembolization for metastatic neuroendocrine liver tumors. *Ann Surg* 2008; 247(6):1029-35.
21. Sato KT, Lewandowski RJ, Mulcahy MF, et al. Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres – safety, efficacy, and survival. *Radiology* 2008; 247(2):507-15.
22. Memom K, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for neuroendocrine liver metastases: safety, imaging, and long-term outcomes. *Int J Radiat Oncol Biol Phys* 2012; 83(3):887-94.
23. Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. *AJR* 2011; 197:W562-W570.
24. Takayasu K. Transarterial chemoembolization for hepatocellular carcinoma over three decades: current progresses and perspectives.
25. Benjamin RS, Choi H, Macapiniac HA, et al. We should desist using RECIST, at least in GIST. *J Clin Oncol* 2007; 25:1760-1764.
26. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359:378-390.
27. Gillmore R, Stuart S, Kirkwood A, et al. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular carcinoma patients treated with transarterial chemoembolization. *J Hepatol* 2011; 55:1309-1316.
28. Forner A, Ayuso C, Varela M, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer* 2009; 115:616-623.
29. Kolipaka A, Woodrum D, Araoz PA, Ehman R. MR Elastography of the in vivo abdominal aorta: a feasibility study for comparing aortic stiffness between hypertensives and normotensives. *J Mag Res Imaging* 2012; 35:582-586.
30. Yin M, Talwalkar JA, Glaser KJ, et al. Assessment of hepatic fibrosis with magnetic resonance

elastography. Clin Gastroenterol Hepatol 2007; 5:1207-1213.
31. Muthupillai R, Lomas DJ, Rossman PJ, Greenleaf JF, Manduca A, et al. Magnetic resonance elastography by direct visualization of propagating acoustic strain waves. Science 1995; 269:1854-1857.
32. Sack I, Beierbach B, Hamhaber U, Klatt D, Braun J. Non-invasive measurement of brain viscoelasticity using magnetic resonance elastography. *NMR Biomed* 2008; 21:265-271.
33. Sinkus R, Siegmann K, Xydeas T, Tanier M, Claussen C, et al. MR elastography of breast lesions: understanding the solid/liquid duality can improve the specificity of contrast-enhanced MR mammography. *Magn Reson Med* 2007; 58:1135-1144.
34. Kolipaka A, Araoz PA, McGee KP, Manduca, Ehman RL. Magnetic resonance elastography as a method for the assessment of effective myocardial stiffness throughout the cardiac cycle. *Magn Reson Med* 2010; 64:862-870.
35. Dresner MA, Rose GH, Rossman PJ, Muthupillai R, Manduca A, et al. Magnetic resonance elastography of skeletal muscle. *J Magn Reson Imaging* 2001; 13:269-276.
36. Woodrum DA, Romano AJ, Lerman A, et al. Vascular wall elasticity measurement by magnetic resonance imaging. *Magn Reson Med* 2006; 56:593-600.
37. Manduca A, Lake DS, Kruse SA, Ehman RL. Spatio-temporal directional filtering for improved inversion of MR elastography images. *Med Image Anal* 2003; 7:465-473.
38. Manduca A, Oliphant TE, Dresner MA, et al. Magnetic resonance elastography: non-invasive mapping of tissue elasticity. *Med Image Anal* 2001; 5:237-254.
39. Faria S, Ganesan K, Mwangi I, et al. MR imaging of liver fibrosis: current state of the art. *RadioGraphics* 2009; 29:1615-1635.
40. Asbach P, Klatt D, Schlosser B, et al. Viscoelasticity-based staging of hepatic fibrosis with multifrequency MR elastography. *Radiology* 2010; 257:80-86.
41. Yin M, Talwalkar JA, Glaser KJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. *Clin Gastroenterol Hepatol* 2007; 5:e1202.
42. Rouviere O, Yin M, Dresner MA, et al. MR elastography of the liver: preliminary results. *Radiology* 2006; 240:440-448.
43. Motosugi U, Ichikawa T, Sou H, et al. Magnetic resonance elastography of the liver: preliminary results and estimation of interrater reliability. *Jpn J Radiol* 2010; 28:623-627.
44. Huwart L, Sempoux C, Salameh N, et al. Liver fibrosis: noninvasive assessment with MR elastography versus aspartate aminotransferase-to-platelet ratio index. *Radiology* 2007; 245:458-466.
45. Klatt D, Asbach P, Rump J, et al. In vivo determination of hepatic stiffness using steady state free precession magnetic resonance elastography. *Invest Radiol* 2006; 41:841-848.
46. Garteiser P, Doblas S, Daire J-L, Wagner M, et al. MR elastography of liver tumours: value of viscoelastic properties of tumour characterization. *Eur Radiol* 2012; 22:2169-2177.
47. Motosugi U, Ichikawa T, Koshiishi T, et al. Liver stiffness measured by magnetic resonance elastography as a risk factor for hepatocellular carcinoma: a preliminary case-control study. *Eur Radiol* 2013; 23:156-162.
48. Anaparthy R, Yin M, Talwalkar JA, et al. Liver stiffness measurement by magnetic resonance elastography is not associated with developing hepatocellular carcinoma in subjects with compensated cirrhosis. *Ailment Pharmacol Ther* 2011; 34(1):83-91.
49. Damughatla, A.R., et al., Quantification of Aortic Stiffness Using MR Elastography and its Comparison to MRI-Based Pulse Wave Velocity*. J Magn Reson Imaging*, 2013: p. *In Press.*
50. Damughatla, A., et al. Quantification of Aortic Stiffness Using MR Elastography and its Comparison to Pulse Wave Velocity: Early Validation. . in *Proceedings ISMRM.* 2013. Salt Lake City, Utah USA.

51. Kolipaka, A., et al., MR elastography of the in vivo abdominal aorta: a feasibility study for comparing aortic stiffness between hypertensives and normotensives. *J Magn Reson Imaging*, 2012. 35(3): p. 582-6.
52. Kenyhercz WE, Damughatla AR, Dowell, JD, Raterman B, Wassenaar, White, RD, Kolipaka, A. Quantification of aortic stiffness in abdominal aortic aneurysms using MR elastography: initial feasibility. *Proceedings ISMRM* 2014.
53. Kolipaka A, McGee KP, Araoz PA, et al. MR elastography as a method for the assessment of myocardial stiffness: comparison with an established pressure-volume model in a left ventricular model of the heart. *Magn Reson Med* 2009; 62:135-140.
54. Kolipaka A, Aggarwal SR, McGee KP, Anavekar N, Manduca A, Ehman RL, Araoz PA. Magnetic resonance elastography as a method to estimate myocardial contractility. *J Magn Reson Imaging* 2012; 36(1):120-7.
55. Mariappan YK, Kolipaka A, Manduca A, Hubmayr RD, Ehman RL, et al. Magnetic resonance elastography of the lung parenchyma in an in situ porcine model with a noninvasive mechanical driver: correlation of shear stiffness with trans-respiratory system pressures. *Magn Reson Med* 2012; 67(1):210-17.
56. Kolipaka A, McGee KP, Manduca A, Anavekar N, Ehman RL, et al. *J Magn Reson Imaging* 2011; 33(5):1224-28.
57. Litwiller DV, Lee SJ, Kolipaka A, Mariappan YK, Glaser KJ, et al. MR elastography of the ex vivo bovine globe. *J Magn Reson Imaging*. 2010; 32(1):44-51.
58. Kolipaka A, McGee KP, Manduca A, Romano AJ, Glaser KJ, et al. Magnetic resonance elastography: inversions in bounded media. *Magn Reson Med* 2009; 62(6):1533-42.
59. Kolipaka A, McGee KP, Araoz PA, Glaser KJ, Manduca A, et al. Evaluation of a rapid, multiphase MRE sequence in a heart-stimulating phantom. *Magn Reson Med* 2009; 62(3):691-98.
60. Mazumder, R., et al. *Rapid Acquisition Technique for MR Elastography of the Liver*. in *Proceedings RSNA.* 2012. Chicago, USA.
61. Li Z, Bonekamp S, Halappa VG, Corona-Villalobos CP, et al. Islet cell liver metastases: assessment of volumetric early response with functional MR imaging after transarterial chemoembolization. *Radiology* 2012; 264(1):97-109.
62. Windischberger C, Robinson S, Rauscher A, Barth M, et al. Robust field map generation using a triple-echoacquisition. *J Magn Reson Imaging* 2004; 20:730-34.
63. Kamel IR, Liapi E, Reyes DK, Zahurak M, Bluemke DA, et al. Unresectable hepatocellular carcinoma: serial early vascular and cellular changes after transarterial chemoembolization as detected with MR imaging. *Radiology* 2009; 250(2):466-73.
64. Ehman, E.C., et al., *Vibration safety limits for magnetic resonance elastography.* Phys Med Biol, 2008. 53(4): p. 925-35.
65. Xue, H., et al., *Motion correction for myocardial T1 mapping using image registration with synthetic image estimation.* Magn Reson Med, 2012. 67(6): p. 1644-55.
66. Murphy MC, Huston J 3rd, Jack CR, Jr, Glaser KJ, et al. Decreased brain stiffness in Alzheimer's disease determined by magnetic resonance elastography. *J Magn Imaging* 2011; 34(3):494-98.
67. Kamel IR, Liapi E, Reyes DK, Zahurak M, Bluemke DA, et al. Unresectable hepatocellular carcinoma: serial early vascular and cellular changes after transarterial chemoembolization as detected with MR imaging. *Radiology* 2009; 250(2):466-73.
68. Koh D-M, Scurr E, Collins D, Kanber B, Norman A, et al. Predicting response of colorectal hepatic metastasis: value of pretreatment apparent diffusion coefficients. *AJR* 2009; 188:1001-08.
69. Bruix J, Sala M, Llovet, et al. Chemoembolization for hepatocellular carcinoma.

Gastroenterology 2004; 127(5):S179-S188.
70. Therasse P, Arbuck SG, Eisenhauer EA, et al. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst*. 2000; 92(3):205-16.
71. Forner A, Ayuso C, Varela M, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer* 2009; 115(3):616-23.
72. Bruix J, Sherman M, Llovet JM, et al. EASL Panel of Experts on HCC: European Association for the Study of the Liver. Clinical management of hepatocellular carcinoma: conclusions of the Barcelona-2000 EASL conference. *J Hepatol* 2001; 35(3):421-30.
73. Muhi A, Ichikawa T, Motosugi U, Sano K, Fatima Z, et al. Diffusion-weighted imaging of hepatocellular carcinoma for predicting early recurrence and survival after hepatectomy. *Hepatol Int* 2013; 7:662-668.

11.0 APPENDICES

11.1 Glossary of Terms

11.2 Case Report Forms

11.3 Informed Consent Document