THE UNIVERSITY OF TEXAS
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Protocol Page

Validation Study of Magnetic Resonance Elastography and 2-Point Dixon MR Imaging Techniques in Diffuse Liver Disease
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Background

Hepatic fibrosis refers to the interstitial or extracellular matrix accumulation or "scaring" after either acute or chronic liver injury. Vast majority of patients worldwide are associated with chronic hepatitis due to hepatitis B and C virus infection, steatohepatitis associated with chronic alcoholic use, and non-alcoholic steatohepatitis due to obesity, diabetes mellitus, and drugs. However, hepatic fibrosis can occur virtually from any acute or chronic liver disease that presents with hepatobiliary inflammation, which undergoes the steps of steatosis fibrosis, and cirrhosis [1, 2]. Liver cirrhosis, the end-stage of progressive fibrosis, is a major cause of morbidity and mortality in America.

In oncologic patients, there are several predisposing factors to hepatic inflammation that can lead to fibrosis: A few among these are chemotherapeutic agents, such as irinotecan or oxaliplatin, multiple transfusions in patients with hematologic malignancy, graft-versus host disease and hepatic veno-occlusive disease following bone marrow transplantation. The neoadjuvant chemotherapy with irinotecan or oxaliplatin is known as a predisposing factor to hepatic steatosis or steatohepatitis, which could affect the post-surgical morbidity negatively in those who are undergoing the hepatic resection [3-5]. Multiple transfusion induced hepatic hemosiderosis is a known risk factor for hepatic fibrosis. Certain tumors such as metastasis from breast cancer often heal with surrounding fibrosis of the liver tissue. Detection of recurrence can be challenging within the fibrotic liver using conventional cross-sectional images.

Typically, fibrosis requires years or decades to become clinically apparent but it can develop in months in children with biliary atresia, drug induced liver disease, or viral hepatitis associated with immunosuppression.

The parenchymal liver disease can be evaluated non-invasively using conventional CT, MR imaging, and ultrasound (US), primarily on the basis of morphological changes. However, once morphological change is recognizable by these imaging techniques, the liver disease is often advanced to the irreversible stage of cirrhosis with the concomitant risk of debilitating or possibly life-threatening complications.

While there is mounting evidence of reversibility of fibrosis and even of cirrhosis [2], diagnosis of reversible liver injury is still challenging. Efforts have been made to identify patients with chronic fibrosis while the disease is still amenable to therapy with the goal of preventing progression to cirrhosis, to decrease morbidity and mortality, and to improve the quality of life.

Traditionally, the biopsy has been the gold standard to detect and grade the hepatic steatosis and fibrosis. The biopsy, however, is an invasive procedure, associated with complications and is prone to the sampling error that can mislead the clinical outcome. A technique that can detect and grade the liver damage and can evaluate the entire liver non-invasively will be highly beneficial, especially in early and potentially reversible stages of liver disease.

Recently, stiffness-weighted magnetic resonance imaging (SW-MRI) technique, magnetic resonance elastography (MRE), and a fast dual-echo 2-point Dixon (2PD) MR imaging technique, have been shown promising results in detecting and grading the hepatic fibrosis [6, 7] and hepatic steatosis [8, 9], respectively. The value of MRE and 2PD MR imaging in liver damage prior to development of fibrosis is unknown.

This study is to validate MRE technique developed at Mayo Clinic (Rochester, MN) and modified 2PD technique using the new post-processing phase correction algorithm developed at M D. Anderson Cancer Center in oncologic and non-oncologic patients.

1. Magnetic Resonance Elastography (MRE)

The changes in MR voxel complex phase are proportional to the wavefront position, which is in turn affected by the elastic properties of the tissue within the voxel. By examining the patterns of wavefront propagation using MR magnetic field gradient waveforms synchronized with the wavefront generator, tissue elastic properties can be discerned. MRE is a modified phase-contrast MR imaging sequence to image propagating shear waves in tissue [10, 11]. The stiffness of the soft tissue can be estimated from the measured wave.

A research team at Mayo Clinic has recently introduced a simple, relatively fast, and quantitative phase-contrast based MR imaging technique to measure the degree of tissue stiffness in vivo and vitro [11]. The technique has been shown to be useful to measure the stiffness between the healthy and pathological muschels in patients with stroke and poliomyelitis [12]. In their recent feasibility study of chronic liver disease with 12 healthy volunteers and 12 patients, a clear separation of degree of stiffness (measured in kPa) has been shown between the normal and fibrotic liver tissue with histopathology [6].

2. Fast dual-echo 2-Point Dixon (2PD) MR Imaging Technique

Several imaging techniques, such as computed tomography (CT) [13, 14] or ultrasound (US) [15], have been suggested to measure the fat fraction in the liver or abdomen indirectly with a limited sensitivity. Magnetic resonance imaging (MRI), an imaging technique based on the water (proton) and fat content in the body, has been suggested using various different techniques, such as, fast spin-echo (FSE) T2 [16], chemical-shift gradient-echo (GRE) [17, 18], and 2D or 3D Dixon [19, 20] techniques.

Chemical shift fat saturation or conventional in- and out-of-phase GRE techniques are not capable to measure the hepatic fat directly and the magnetic field heterogeneity may lead to an inaccurate fat measurement. The conventional 2PD technique also suffers from the field heterogeneity but, unlike the in-phase and out-of-phase techniques, the field heterogeneity effect could be removed during the post processing. We have recently developed an efficient post-processing phase correction algorithm to correct this field heterogeneity of the conventional 2PD technique [21], of which accuracy has been validated in a phantom study [21]. We have also shown that this new efficient phase correction algorithm combined with the fast dual echo 2PD technique allowed to obtain the high quality water-only and fat-only images of an entire abdomen within a single-breath hold and to quantitate hepatic fat in 10 oncologic patients [9].

2.0 Objectives

The purpose of the study is to validate the MRE and 2PD MRI technique using the new post-processing phase correction algorithm in evaluating chronic liver disease, specifically the hepatic inflammation, steatosis, steatohepatitis, hepatic fibrosis and cirrhosis in patients with biopsy proven or clinically suspected hepatic steatosis and/or fibrosis.

Primary goals:

1. To assess the association between the degree of stiffness as measured by MRE in kPa and histopatholigical grades of fibrosis and steatohepatitis

2. To assess the association between the % fat fraction (FF) measured from 2PD MRI and histopathological grade of hepatosteatosis and steatohepatitis.

Secondary goal:
To evaluate the roles of MRE and 2PD MRI in predicting the steatohepatitis and hepatic inflammation.

3.0 Patient Eligibility

The study will have 2 groups of patients with a total of 30 patients each.

A total of 30 patients (Group 1) with biopsy proven or clinically suspected advanced parenchymal liver disease (fatty liver, fibrosis, and cirrhosis) will be recruited from VA Medical Center in Houston. An additional 30 patients (Group 2) will be recruited among those who are registered at MDACC and who are suspected to have hepatic damage, hepatic steatosis, hepatitis, hepatic fibrosis or cirrhosis clinically or radiographically. The number of accrual in Group 2 will be adjusted as needed upon completion of data analysis for the first 30 patients.

The patients recruited at MDACC will be approached by either the Diagnostic Imaging faculty or Research Staff, including research nurses and research coordinators for their consent prior to their procedure. During the consenting process patients will be educated and consented for their research participation in this study.

Inclusion criteria:
Group 1

1. Biopsy proven or clinically suspected advanced parenchymal liver disease
2. Core biopsies performed within 1-month* of MRI/MRE
3. No treatment affecting the status of liver between MRI/MRE and post-imaging biopsy
4. Signed consent

*The interval between the biopsy and MRI/MRE is allowed for up to 8 weeks if the liver condition is thought to be stable during this time per a collaborating hepatologist.

Group 2

1. Clinically or radiographically suspected liver damage, hepatic steatosis, hepatitis, hepatic fibrosis or cirrhosis
2. Surgical or core biopsy scheduled within 4 weeks* of MRI/MRE
3. Signed consent

*The interval between the biopsy and MRI/MRE is allowed for up to 8 weeks if the liver condition is thought to be stable during this time per the primary physician.

Exclusion criteria:

1. Claustrophobia
2. Contraindications for MRI
3. Unable to hold a breath
4. Ascites or other clinical or radiographical signs of portal hypertension

4.0 Study Plan

1. Scheme

Group 1:

Enroll ----------> MRI/MRE <----------> *Core Biopsy (up to 3 sites)
within 1 week within 1 month

* The "biopsy" is diagnostic purpose required for their clinical care.

Group 2:

Enroll ----------> MRI/MRE <----------> Surgical or *Core biopsy
within 1week within 1 month

* The "biopsy" is a diagnostic purpose required for their clinical care.

2. Imaging plans
All MRIs will be performed at a 1.5T HD system (GE Health Care, Milwaukee, Wis.) at MDACC. MRE and 2PD MRI will be performed prior to administration of intravenous contrast for the routine MRI, if applicable.

2.1. MRE
Once the patient is on the examination table, a pneumatic driver will be placed over the upper abdomen (transcostal approach) to generate acoustic mechanical waves to the liver. Operating frequency of driver will be set at approximately 60 Hz. MR elastography gradient-echo (GRE) sequence will be obtained using a body coil and the following parameters: TR//TE 150 msec/Minimal Full, flip angle 30 deg, field of view 34-38 cm, matrix 256x64, thickness 10 mm. One pair of 1.76 G/cm (1.76*10 -4T/cm) motion-encoding gradients will be synchronized to the passive pneumatic driver. Wave images will be obtained at 4 phase offsets. The acquisition of each offset (10sec) will be obtained during a single breath hold.
Once the images are acquired, the data will be automatically post processed to generate a stiffness map.

*The pneumatic driver for the study was developed at Mayo Clinic (Rochester, MN) and has not been FDA-approved. There is currently no federal regulation mandating maximum occupational vibrational exposure in the US. However, The typical vibrational displacement from the driver used for this study is well-below the values that would be permitted by European Union (EU) whole body standard [21]. The risk of the driver has been determined to be "minimal (non-significant risk)" to human tissue by IRB at Mayo Clinic (Appendices D, E, F). The procedure will be performed under the supervision of a trained scientist and a radiologist.

2.2. Dual-echo 2PD MRI

Dual-echo 2PD MRI will be obtained in conjunction with the routine MRI of abdomen (if applicable) prior to administration of the intravenous contrast. The imaging parameters for a dual echo 2PD MRI include: TR 150 msec, TE 2.2 msec for out-of-phase and T2 4.7 msec for in-phase, flip angle 85 deg, slice thickness/gap 5-7/0-2 mm, matrix size 256x192, and the total scan time 20 seconds (a single breath-hold).

Once the images were obtained, a water-only (WO) and a fat-only (FO) images were generated for each slice automatically using the new post processing phase correction algorithm to correct the field heterogeneity [22].

3. Imaging analysis
3.1 MRE

Overall quality of images will be evaluated based on the 1) line profile along the direction of wave propagation from each wave images, and 2) wavelength obtained by using a direct peak-to-peak measurement. The quality will be graded using a 5-point grading system: 1 being barely visible wave and 5 being the best.

The shear stiffness will be measured in kPa from the representative areas, up to 3 sites per patient.

3.2. 2PD MR images

The signal intensity (SI) will be measured on both fat (SI_f) and water (SI_w) images from the same area of region of interest. Then, % fat fraction (FF) will be calculated as $SI_f / (SI_f + SI_w)$ from FO and WO MR images.

4. Histopathological analysis
In Group I, core biopsies (at least 1.5 cm size) will be performed from up to 3 sites that are correlated with the representative areas for steatosis and fibrosis from MRE. The biopsy materials (slides) will be checked out by our collaborator at VAMC and will be hand-carried to our pathologist collaborator at MDACC for the study specific review. In group 2, surgical biopsies will be performed in the same manner.

The biopsy specimens will be evaluated and scored for hepatic steatosis, hepatic steatohepatitis, and fibrosis, based on the multiple histopathological features: 1) % of hepatocytes with macrovesicular steatosis (none, <5%, 5-33%, 33-66%, >66%) , 2) location of macrovesicular steatosis (periportal, centrilobular, azonal, panacinar), 3) microvesicular steatosis (absent, present), 4) lobular neutrophilic and lymphocytic inflammation (per 200x field), 5) ballooning degeneration (score 0-1 = none, few, many), 6) acidophilic bodies (absent, present), and 7) Mallory's hyaline (absent, present), and 8) fibrosis (none, perisinusoidal, mild and moderate portal, mild and moderate periportal, bridging, cirrhosis) [23].

4.1. Hepatic steatosis will be graded using 4 point grading system; 0 being no steatosis, 1 being <30%, 2 being ≥30 - <60%, and 3 being ≥ 60%.

4.2. Hepatic steatohepatitis will be scored using 9 point grading system based on the sum of steatosis score (0 being <5%, 1 being 5-33%, 2 being >33-66%, 3 being >66%), lobular inflammation (score 1-3), and ballooning (score 0-2) [22].

4.3. Hepatic fibrosis will be graded using 5 point grading system, 0 being none, 1 being sinusoidal, 2 being mild to moderate portal, 3 being mild to moderate periportal, 4 being septal).

4.4. Histopathological analysis will also be performed specifically for the underlying disease by the collaborating hepatic pathologist: e.g. in patients with hepatic iron overload the iron amount will be graded none, mild, moderate, and severe and in patients with GVHD the degree of bile duct injury and ductopenia will be evaluated.

5. The study will be terminated if we run into any unresolvable technical issues in data acquisition or unacceptable image quality to preclude the adequate analysis during the first 5 patient procedures.

5.0 Stastical Analysis

1. Design
This is a pilot study designed to evaluate MRE and 2PD as alternatives to liver biopsy in evaluating fibrosis, steatohepatitis, and hepatosteatosis in patients with liver disease. There are two groups of patients in the study: patients in Group 1 will have advanced liver disease, while Group 2 will be for patients who undergo hepatectomy or core biopsy. We expect to enroll 30 patients into each group for a total of 60 patients.The number of accrual in Group 2 will be recalculated as needed upon completion of data analysis for the first 30 patients.

2. Analyses
For the first primary objective, the association between degrees of stiffness measured by MRE in kPa and histopathological grades of fibrosis and steatohepatitis will be assessed using Pearson correlation.

For the second primary objective, the association between % fat fraction measured by 2PD MR images and histopathological grade of hepatosteatosis and steatohepatitis will be assessed using Pearson correlation.

Because the above analyses assume that the fibrosis, steatohepatitis and steatosis grades are continuous variables, analyses will be repeated using rank correlation methods. In addition, as a secondary statistical analysis, we will perform ordinal regression analyses to evaluate the individual ability of MRE kPA and 2PD MRI %FF measurements and combination of both as covariates to predict grades of fibrosis, hepatosteatosis, and steatohepatitis for these patient populations.

3. Sample Size and Power

With 30 patients in each group, for each of the four correlations above, there will be 90% power to detect a correlation of at least 55% between the kPa or the %FF and the histopathological grade, assuming a two-sided alpha=0.05 level test for a non-zero correlation.

Although there are four separate primary comparisons being performed simultaneously, no correction will be made for the multiplicity of testing due to the pilot nature of the study. Each of the two primary objectives (two comparisons each) will have a Type I error rate (alpha level) of no more than 10%.1. Degree of stiffness measured from MRE in kPa will be correlated with histopathological grades of fibrosis and steatohepatitis.

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