Dual Energy CT as a Noninvasive Method to Screen for Gastroesophageal Varices

Study Protocol & Statistical Analysis Plan

NCT03910413

Date of Last Protocol Approval
02/22/2023

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Original Protocol: 4/01/2019

1. STUDY DESIGN / SUMMARY:

Cirrhosis leads to portal hypertension and development of gastroesophageal varices, which are the most common cause for bleeding in cirrhosis and a major cause of death. The American Association for the Study of Liver Disease (AASLD) recommends screening endoscopy every 2 years to evaluate for gastroesophageal varices, and annual surveillance for those with small varices on endoscopy. Unfortunately, endoscopy is costly, requires sedation, is poorly tolerated, is subject to high inter-observer variability, and is associated with risks that include bleeding, esophageal injury and aspiration. Noninvasive methods for evaluation of gastroesophageal varices are needed. CT is noninvasive, rapid, less expensive than endoscopy, requires no sedation, provides a quantitative measure of the size of the varices, and allows for assessment of para-esophageal varices, varices in other body locations, ascites, other signs of portal hypertension, patency of liver vasculature, and detection, diagnosis and staging of hepatocellular carcinoma. Single-Energy CT (SECT) has relatively high accuracy in prospective studies for detection of any and large varices but is associated with suboptimal contrast opacification of gastroesophageal varices. Dual-Energy CT with the GE scanners with GSI Xtream (DECT) improves the contrast-to-noise ratio by 60% compared to SECT and is currently standard of care at UAB for evaluation of cirrhosis. The primary objective of this study is to determine the accuracy of DECT for detecting any varices and high-risk varices. We hypothesize that the accuracy (AUROC) of DECT will be >0.90 and >0.95 for detecting any and high-risk varices in a prospective pilot study (N=50) that uses endoscopy as the reference standard. This will be a single-center pilot observational prospective IRB-approved study. We will enroll 50 adult patients presenting to UAB Endoscopy for surveillance endoscopy to detect and grade gastroesophageal varices.

2. BACKGROUND AND RATIONALLE

Cirrhosis leads to portal hypertension and development of gastroesophageal varices, which are the most common cause for bleeding in cirrhosis and a major cause of death. Bleeding varices have a 6-week mortality of 15%-25%.[1,2] About 50% of patients with cirrhosis have varices, and 30% have large varices (>5 mm) that are high risk for bleeding.[3]

The American Association for the Study of Liver Disease (AASLD) recommends screening endoscopy every 2 years to evaluate for varices, and annual surveillance for those with small varices on endoscopy.[4] Patients at a high risk of bleeding with large varices, small varices and red wale signs (an endoscopic finding), or small varices and decompensated cirrhosis proceed to treatment such as prophylactic band ligation and beta blockers.[5,6,7] Conversely, patients with no varices or small varices (≤5 mm) continue surveillance efforts by endoscopy to monitor for development of large varices.[3,7,8] Unfortunately, endoscopy is costly, requires sedation, is poorly tolerated, is subject to high inter-observer

variability, cannot detect other signs or portal hypertension or para-esophageal varices that are at risk for future bleeding events, and is associated with risks that include bleeding, esophageal injury and aspiration.[9] Many of these factors contribute to poor patient compliance with AASLD recommendations.

Noninvasive methods for detecting, grading, and risk stratification of esophageal varices are needed. Imaging tests such as ultrasound elastography to measure liver stiffness have been proposed as a method to predict the presence of varices but have insufficient accuracy to eliminate the need for endoscopy.[10] An ideal biomarker to screen for esophageal varices would be part of the routine standard of care of patients with cirrhosis, noninvasive, rapid, less expense than endoscopy, highly accurate, highly reproducible, and would require no sedation, provide a quantitative measure of the size of the varices, provide a mechanisms to assess the risk of future bleeding, allow for an assessment for other signs of portal hypertension, and provide other benefits to the patient (e.g. detect ascites and HCC and assess liver vasculature).

Computed tomography (CT) is standard of care to screen for HCC. CT is noninvasive, rapid, less expensive than endoscopy, requires no sedation, provides a quantitative measure of the size of the varices, and allows for assessment of para-esophageal varices, varices in other body locations, ascites, other signs of portal hypertension, patency of liver vasculature, and detection, diagnosis and staging of HCC. Conventional Single-Energy CT (SECT) has relatively high accuracy in prospective studies for detection of any and large varices and has higher inter-observer agreement than endoscopy (kappa 0.56 vs. 0.36, respectively).[11] Major deficiencies in SECT include relatively suboptimal contrast opacification of gastroesophageal varices, inconsistent accuracy that is dependent upon SECT image acquisition technique, and suboptimal stratification of the risk of bleeding (e.g. inability to detect red wale sign) compared to endoscopy.

Dual-Energy CT (DECT) improves the contrast-to-noise ratio by 60% compared to SECT. DECT also improves visualization by taking advantage of the markedly increased attenuation of iodine at photon energy levels just above the iodine K edge (33 keV). Using material decomposition techniques, DECT can map the concentration of iodine on a voxel by voxel basis which, combined with higher contrast to noise resolution on these same type of images, improves the conspicuity of enhancing structures. DECT is routinely used at the University of Alabama at Birmingham (UAB) to screen for HCC in cirrhotic patients.

While DECT has been shown to improve image quality and portal venography compared to SECT, the accuracy of DECT for screening for varices has not been reported.

3. OBJECTIVES

3.1 Primary Objective

To determine the accuracy of dual energy CT for detecting any varices and high-risk varices in patients with cirrhosis presenting for upper gastrointestinal endoscopy.

3.2 Secondary Objectives

3.2.1 To assess inter-observer agreement for the detection of any varices and high-risk varices on dual energy CT.

3.2.2 To compare the accuracy of grade of varices on CT to grade of varices on endoscopy for predicting gastroesophageal variceal bleeding at 2 years.

3.2.3 To develop and compare the accuracy of multivariate statistical models designed to predict 2-year risk of bleeding gastroesophageal varices, both without and with dual energy CT findings.

3.2.4 To predict 2-year liver-related events using the variceal grade on DECT, LSN score and MELD score.

4. PARTICIPANT SELECTION

This will be a single-center pilot observational prospective IRB-approved study. We will enroll 50 adult patients presenting to UAB Endoscopy for surveillance endoscopy to detect and grade gastroesophageal varices and follow up with patients for at least 2 years. These patients will present to the Highlands Gastroenterology Endoscopy Center or to the Kirklin Clinic Gastroenterology Endoscopy Center and will be seen by sub-investigator Omar Massoud MD, a hepatologist and gastroenterologist. Approximately 8 to 10 patients per week are expected to meet final inclusion criteria, and we anticipate that we will approach 100 patients about study participation to accomplish 50 recruited patients over 9 months.

4.1 Inclusion Criteria

Adult patients with cirrhosis presenting to UAB Endoscopy for surveillance endoscopy to detect and grade gastroesophageal varices

4.2 Exclusion Criteria

4.2.1 Inability to provide written informed consent

4.2.2 History of bleeding gastroesophageal varices, variceal intervention or portosystemic shunt

4.2.3 Prior liver transplant

4.2.4 History of malignancy

4.2.5 Severe chronic kidney disease with estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2

4.2.6 Presence of acute kidney injury

4.2.7 Prior iodinated contrast allergy

4.2.8 Patient weight >300 lbs

4.2.9 Multiphasic liver CT within 3 months of upper endoscopy

4.2.10 Pregnancy

4.3 Inclusion of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in this trial. The trial is open the accrual of women and men.

5. RECRUITMENT AND SCREENING

5.1 Recruitment Process

Patients presenting to the Highlands Gastroenterology Endoscopy Center or to the Kirklin Clinic Gastroenterology Endoscopy Center will initially be approached by the hepatologist (Omar Massoud MD, sub-investigator who routinely performs surveillance endoscopy procedures) to ask if the patient would be interested in the study. If the patient is interested, the study coordinator will meet with the patient prior to endoscopy, answer questions, review the inclusion/exclusion criteria, and obtain informed consent. The study coordinator will review the labs, order any missing research study labs, and schedule the DECT exam. The patients will be directed to our outpatient facilities at Leeds or

Gardendale, as both centers have a *Dual Energy GE Revolution CT with GSI Xtream* (DECT). After imaging, the patient will be given a $75 incentive for their time, and the patient will be discharged. Patients will provide consent for a follow up interview to evaluate for liver-related events, particularly bleeding varices. The study coordinator will arrange the interview and record all data in a secure web-based REDCap research database.

5.2 Screening Process

The study coordinator will screen the endoscopy schedule daily to look for potentially eligible patients. The study coordinator will inform the gastroenterologist of potentially eligible patients.

6. PROTOCOL PROCEDURES, METHODS, AND DURATION (LAYMAN'S DESCRIPTION)

After confirmation of patient eligibility, the study coordinator will obtain written informed consent. The informed consent process may take up to 45 minutes. The study coordinator will review the labs, order any missing research study labs to calculate the FIB-4 index and MELD score, and schedule the DECT exam at a time that is convenient for the patient but within 2 weeks of the endoscopy. Women of childbearing potential will receive either a blood draw or urine pregnancy test to make sure they are not pregnant. Baseline clinical and laboratory data will be gathered by the study coordinator and entered into a REDCap database.

The patient will undergo the upper gastrointestinal (GI) endoscopy procedure and recovery per standard of care. The endoscopy results (e.g. grade of esophageal varices) will be entered into the REDCap database. After the post-endoscopy procedure recovery period and prior to discharge, the study coordinator will complete a questionnaire with the patient to capture the patient's experience and document any complications related to the upper GI endoscopy. The questionnaire will take 15 minutes to complete. The questionnaire data will be entered into the REDCap database. The patient will be provided with the date and time of the scheduled DECT study, which may be on the same day as the endoscopy or within 2 weeks from endoscopy. The patients will be scheduled for DECT at Leeds or Gardendale, as both Imaging Centers have a *Dual Energy GE Revolution CT with GSI Xtream*, which is needed for this study. The patient will be discharged per standard of care, and the questionnaire data will be entered into the REDCap database by the study coordinator.

One the day of the DECT imaging, the patient will have nothing by mouth to eat or drink for 4 hours prior to the DECT exam. The patient will check in at the imaging center for their scheduled DECT exam. An intravenous line will be placed by the technologist, and the patient will undergo DECT imaging with intravenous iodinated contrast. CT imaging will be obtained in the late arterial phase using bolus tracking and in the portal venous phase using a dual energy CT approach. In order to reduce radiation dose, the noncontrast and delayed phases (present in a routine 4-phase liver CT) will not be obtained. The time from check in to completion of the imaging study is expected to be 45 minutes. After imaging, the study coordinator will complete a questionnaire with the patient to capture the patient's experience and document any complications related to the CT imaging procedure. The questionnaire will take 15 minutes to complete. The patient will be given a $75 gift card incentive for their time, and the patient will be discharged. The questionnaire data will be entered into the REDCap database.

The patients will be contacted by phone by the study coordinator at 1- and 2-years post endoscopy to capture information on complications of cirrhosis, particularly bleeding episodes and treatment of high-risk gastroesophageal varices. The phone interview is expected to take 15 minutes to complete. If the patient has a visit to the hepatologist, the interview may alternatively be conducted at that time per patient preference. The electronic medical records will also be searched for complication of cirrhosis and bleeding episodes. The study coordinator will conduct the interviews and record all data in a REDCap database. The patients will be discharged from the study after the 2 year follow up interview.

7. RISKS

7.1 Breach of Confidentiality – There is an unlikely potential risk of a breach of confidentiality.

7.2 Intravenous (IV) Catheter Placement - Participants may experience pain, bruising or bleeding at the IV catheter site. There is a very small risk for developing an infection.

7.3 Contrast Injection – Patients will receive FDA-approved iodinated contrast (dye) through an IV-line during the dual energy CT scan. The contrast is essential for improving visualization of varices. There is a small risk of IV-line infiltration. Immediately following injection, patients may feel a mild warm feeling that will go away in a few seconds. Uncommon side effects include physiologic reactions and allergic-like reactions such as abnormal heart rate, nausea, dry mouth, itching, hives, cough, or shortness of breath. Very rarely, people can experience life-threatening allergic reactions to iodinated contrast. The CT contrast dye can rarely cause kidney injury in patients who already have severe kidney disease.

7.4 Radiation – Study participants will be exposed to radiation from the DECT imaging. There is an extremely low risk that the radiation may cause cancer or other radiation effects years after the study. Exposure to the radiation through this study is not part of routine healthcare.

7.5 Risk of an Unexpected Imaging Finding – There is a risk that an unexpected imaging finding could be detected. In many cases, these are of benefit to the patient, such as detection of a unexpected cancer. In some cases, the unexpected finding may be indeterminate, such as a renal mass that is not clearly benign or malignant. Indeterminate findings may need additional workup that will not be covered as a part of this study.

8. PRECAUTIONS / MINIMIZATION OF RISKS

Participants will be monitored by study personnel for risks—physical, psychological, social, economic, and/or legal—that participants may encounter during their participation in this study or as a result of DECT imaging and data collection required in this protocol.

8.1 Breach of Confidentiality – The research team is experienced and will utilize best practices to avoid a breach of confidentiality. The risk of confidentially will be minimized by collecting only the data that is required by the study, labeling all data forms and samples with a coded identifier, and maintaining all study records in locked files or password-protected computer files.

8.2 Intravenous (IV) Catheter Placement - The radiology technologists are experienced with IV-line placement and will utilize best practices to minimize pain and avoid bruising, bleeding, and infection.

8.3 Contrast Injection – A power injector will be used to assist with detecting IV-line infiltration. The radiology technologists are trained to manage physiologic and allergic-like reactions, and there is a physician available for more severe reactions. Kidney function will be tested in all participants through a blood draw prior to the receiving the contrast. Patients who have had a prior allergic reaction or have severe kidney disease cannot participate in this study. All patients will be monitored for reactions during this study.

8.4 Radiation – The total radiation exposure is expected to be 16 mSv, equivalent to about 2.6 years of exposure to natural background radiation. Background radiation is radiation normally received from sources such as cosmic rays and natural radioactivity in building materials and the ground. Exposure to the radiation through this study is not part of routine healthcare. The

amount of radiation exposure has been minimized by the research doctors. For example, a normal liver CT for evaluation of cirrhosis includes 4 different scans of the liver, but this research scan only include 2 scans of the liver and therefore half the amount of radiation.

8.5 Risk of an Unexpected Imaging Finding – All of the research DECT liver CTs will be interpreted by a radiologist, a physician with expertise in CT imaging. A formal report will be placed permanently in the electronic medical records. Clinically significant unexpected imaging findings will be communicated by phone with the gastroenterologist, per standard of care at UAB.

9. BENEFITS

The dual energy CT scan will be interpreted by a radiologist, a physician with expertise in CT imaging. A formal report will be placed permanently in the electronic medical records. It is possible that the radiologist may detect liver cancer or another important but unexpected finding. Clinically significant unexpected imaging findings will be communicated by phone with the gastroenterologist per standard of care at UAB. The gastroenterologist will discuss these findings with the participants.

10. ALTERNATIVES

This is not a treatment study. The alternative is to not participate in this study.

11. DATA AND IMAGE ANALYSIS

11.1 Clinical Evaluation:

Baseline clinical and laboratory data (**Table 1)** will be gathered by the study coordinator and entered into a password-restricted and secure web-based REDCap database. Data from the post-endoscopy and post-DECT questionnaires will be entered into the REDCap database.

Table 2. Relevant Clinical and Laboratory Data

- **Demographics**: age, gender, race, ethnicity, body mass index
- **Comorbidities**: Charlson comorbidity index
- **Cirrhosis etiology**: AH, HBV, HCV, NAFLD, cryptogenic, autoimmune, and other
- **Baseline cirrhosis substage:** compensated without varices, compensated with varices, and decompensated
- **Baseline serum labs:** total bili, AST, ALT, albumin, INR, platelets, creatinine, calculated MELD and FIB-4 scores
- **Study procedure date:** date of endoscopy and DECT
- **Procedure complications:** From DECT or endoscopy
- **2-year follow up to track liver-related events:** ascites, hepatic encephalopathy, bleeding varices, intervention for varices, TIPS, liver transplant, HCC, or death

11.2 Endoscopy Evaluation:

All patients will undergo standard of care upper gastrointestinal endoscopy in The Kirklin Clinic or Highlands Hospital endoscopy suites for surveillance of gastroesophageal varices. The endoscopists will report the grade of esophageal varices: grade 0 = none, grade 1 = small (≤5 mm), and grade 2 = large (>5 mm). The endoscopists will also record the presence or absence of a red wale or red spot sign, presence or absence of gastric varices, presence or absence of signs of portal gastropathy, presence or absence of gastritis, duodenitis, or a gastric or duodenal ulcer, and presence or absence of active bleeding (and location if present). The hepatologist will also be contacted to confirm the substage of cirrhosis, which includes the information from the surveillance endoscopy.

11.3 Image Evaluation:

11.3.1 DECT Image Acquisition:

Study participants will undergo DECT imaging of the liver in the late arterial and in the portal venous phases. The late arterial phase will be performed with bolus tracking and occur 20 seconds after triggering. The portal venous phase will also be performed with bolus tracking and occur 40 seconds after triggering. Both phases will utilize our standard-of-care DECT image acquisition protocol. Imaging will be performed per standard of care, with the patient in the supine position with arms above the head. No oral contrast will be administered. Noncontrast and delayed phase imaging will not be performed to reduce the radiation dose.

11.3.2 DECT Image Evaluation:

The DECT images will be interpreted according to our standard of care with a dictated report by a board-certified abdominal radiologist. The radiologist interpreting the study will be asked to interpret the study using a structured reporting template that includes the grade of esophageal varices, presence or absence of other varices, presence or absence and stage of HCC, severity of ascites, and patency of liver vasculature. The structured report template is currently in use by multiple abdominal faculty and can be easily acquired by any abdominal radiologist at UAB through Powerscribe, our routine dictation reporting system.

Each DECT study will be de-identified per standard technique using OsiriX. A coded identifier will be applied to each image, and the images will be stored on OsiriX and on a secure password-restricted Server Message Block (SMB), a virtual hard drive established for Radiology Clinical Research that has restricted access to defined users. Study personnel will use the Liver Surface Nodularity (LSN) Software to measure the LSN score on all patients, while remaining blinded to the clinical data. Dr. Smith or Dr. Morgan will review all of the exported images and confirm a satisfactory measurement for each patient, with revising of measurements that are not satisfactory.

11.3.3 Inter-observer Analysis:

After all patients are recruited (N=50), a designated co-investigator will set up reading session for the other radiology co-investigators (N=4 radiology residents and N=4 radiology faculty). A training video will be prepared and used to instruct the readers on how to view the images, conduct the reading sessions, and record the data in a REDCap.

Each reader will interpret the images independently in timed reading sessions, while blinded to clinical data. The most important data point will be the grade of esophageal varices, though readers will also evaluate for presence or absence of other varices, presence or absence and stage of HCC, severity of ascites, and patency of liver vasculature.

12. 2-YEAR FOLLOW UP:

The primary purpose of screening for gastroesophageal varices is to prevent future variceal bleeding and the associated high mortality. Detection of bleeding events is therefore a critical component of the study. The patients will be contacted by phone by the study coordinator at 1- and 2-years post endoscopy to capture information on complications of cirrhosis, particularly bleeding episodes and treatment of high-risk gastroesophageal varices. If the patient has a visit to the hepatologist, the interview may alternatively be conducted at that time per patient preference. The electronic medical records will also be searched for complication of cirrhosis and bleeding episodes. The study coordinator will conduct the interviews and record all data in a REDCap database. The patients will be discharged from the study after the 2 year follow up interview.

13. STATISTICAL CONSIDERATION:

13.1 Sample size justification

Yufeng Li PhD (co-investigator and biostatistician) will conduct and supervise all statistical analyses. This is a prospective study to determine the accuracy of dual energy CT for detecting any varices and high-risk varices in patients with cirrhosis presenting for upper gastrointestinal endoscopy. The endpoint of the primary objective is accuracy which is determined by the Area Under the Curve (AUC) using Recursive Operating Characteristics (ROC) analysis (AUROC). Based on published studies [1,2,3] in patients with detected gastroesophageal varices, we will observe 32%, 32%, and 36% with no, small, and large varices, respectively. In order to test the hypothesis*:* the accuracy (AUROC) of DECT will be >0.90 for detecting any and high-risk varices in a prospective pilot study that uses endoscopy as the reference standard, we plan to enroll 50 patients such that we will have 16/50, 16/50, and 18/50 with no, small, and large varices. This size of the study will have >95% power to detect any varices, e.g. (16+18)/50 small and large varices with AUC >=0.90 comparing to null hypotheses of AUC=0.5 (not detect any) using a one-sided z-test at a significance level of 0.05 controlled false positive rates at 1%.

13.2 Statistical analysis plan

Patient and imaging characteristics will be summarized and compared using appropriate summary statistics, e.g. mean and standard deviation for continuous variables, frequency and percentage for categorical variables, and extensive exploratory data analysis and data visualizations will be utilized to assess diagnostics, identify outliers, and validate assumptions.

Receiver operating characteristic (ROC) analysis will be used in Aim1 to estimate the accuracy of DECT for differentiating no varices from any varices and for differentiating no and small varices from large varices in Aim 1. Sensitivity, specificity, accuracy, and AUC along with their two-sided 95% CI will be presented separately. The grade of varices (0, 1, 2) on DECT will be correlated with the grade of varices on endoscopy (0, 1, 2) using weighted Kappa coefficient for categorical data (Aim 2.2).

The MIXED effect model will be used in Aim 2.1 to estimate the ICC for the inter-observer agreement for the detection of any varices and high-risk varices on dual energy CT. Reader experience and subject will be the two random effects in the model used for interobserver variability. The intraclass correlation coefficient (ICC) will be defined as the ratio between subject variance and the sum of variances for subject, reader experience and error term. ICC values will be characterized as very poor (0 to <0.20), poor (0.20 to <0.40), moderate (0.40 to <0.60), good (0.60 to <0.80), and very good (0.80 to 1.00).

Time to development of bleeding varices (or hepatic event) will be modeled in Aim 2.3 using Cox proportional hazards models with clustered sandwich estimators to account for within and between cluster correlations. Cause specific proportional subhazards analysis while accounting for competing risks (e.g. gastroesophageal banding) and adjusting for covariates will be utilized to assess the association between endoscopic findings and DECT findings and time to developing individual vs. any hepatic complications.

A combination of variceal grade on DECT, LSN score and MELD score will have equal or greater accuracy for predicting 2-year liver-related events than a combination of endoscopic findings and MELD score. This analysis will be exploratory in Aim 2.4, but a trend may be evident and justify further investigation. Competing risks analysis will be used to assess the association of variceal grade on DECT, LSN score and MELD scores with development of liver-related events, with specific attention to 2-year variceal bleeding events. Cumulative Incidence Function (CIF) will be used to estimate the marginal probability of a liver-related event as a function of its cause-specific probability and overall survival probability.

All analysis will be carried out using SAS v 9.4.