A Prospective Study of Endoscopic Ultrasound Shear Wave Elastography for Assessment of Liver Fibrosis

NCT05097963

6/1/2021

Study Title: A Prospective Study of Endoscopic Ultrasound Shear Wave Elastography for Assessment of Liver Fibrosis

Principal Investigator: Vinay Chandrasekhara, MD
Division of Gastroenterology and Hepatology
Department of Medicine
Mayo Clinic
[redacted] Rochester, MN 55905

Co-Investigator: [redacted]

Funding Sponsor: Investigator-Funded

Protocol Number: (IRBe) 21-003779
PLM MSR: 2021-304355-H01

Initial version: 6/1/2021 Version **(1.0)**
Revised:

Protocol Investigator Signature Page

STUDY TITLE: **A Prospective Study of Endoscopic Ultrasound Shear Wave Elastography for assessment of liver fibrosis**

PROTOCOL VERSION: 01/JUN/2021 Version (1.0)

STUDY CENTER:

(Print name of study center)

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the trial as described in the protocol and in accordance with applicable laws and regulations. In addition, when applicable, I agree to enlist sub- investigators who also agree to perform and conduct the trial as described in the protocol.

_____

Date

Principal/Coordinating Investigator (Print Name)

_____

Principal/Coordinating Investigator (Signature) **Date**

Table of Contents

LIST OF ABBREVIATIONS

EUS	Endoscopic Ultrasound
MRE	Magnetic Resonance Elastography
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOE	Schedule of Events
SOP	Standard Operating Procedure
E	Elastic Modulus
Vs	Shear wave velocity
VsN	Reliability Index
IQR/M	Interquartile Range/Median

Study Summary

Title	**A Prospective Study of Endoscopic Ultrasound Shear Wave Elastography for assessment of liver fibrosis**
Running Title	EUS shear wave elastography VS MRE
Title Acronym	EUS vs MRE
IRB Protocol Number	21-003779
Phase	Prospective comparative study
Methodology	Subjects who are eligible will undergo EUS for clinical indications. After completion of EUS, subjects will undergo subsequent MR Elastography if not already performed for clinical purposes. EUS Shear wave measurements will be studied to determine diagnostic accuracy when compared to MR Elastography.
Overall Study Duration	6 months Recruitment and Active study execution, 3 months analysis and 3 months publication. Total: 12 months
Subject Participation Duration	Up to 60 days screening prior to study procedure, and up to 60 days post procedure to follow-up MRE.
Objectives	To assess the diagnostic accuracy of EUS shear wave elastography in liver fibrosis staging in both normal subjects and subjects with advanced liver fibrosis/cirrhosis
Number of Subjects	Fifty (50)
Diagnosis and Main Inclusion Criteria	Subjects over 18 years of age who are scheduled to undergo endoscopic ultrasound procedure as part of clinical care.
Study Device	EUS shear wave elastography
Reference Imaging Modality	Magnetic resonance elastography (MRE)
Statistical Methodology	All continuous variables will be expressed as mean and standard deviation. Categorical variables will be expressed as percentages. Multivariate analysis will be performed.

1 Introduction

This document is a clinical research protocol relating to the prospective study on endoscopic ultrasound (EUS) shear wave elastography in assessment of liver fibrosis. The described study will be conducted in compliance with this protocol, applicable United States government regulations and Mayo Clinic policies and procedures.

1.1 Background

Shear wave elastography (SWE) uses shear waves to assess tissue elasticity in a non-invasive fashion. This technology has been incorporated into conventional trans-abdominal ultrasonography to evaluate for liver stiffness, especially in patients with suspected chronic liver disease. Endoscopic assessment of the liver is routinely performed during endoscopic ultrasound (EUS). Recent software package enhancements have allowed for the option of shear wave measurement during EUS procedures. To date, there is little to no literature on the performance of EUS SWE and its applicability in the assessment of liver fibrosis in the clinical setting. Therefore, we wish to determine the applicability of EUS SWE and evaluate its diagnostic accuracy compared to magnetic resonance imaging elastography, which is widely utilized to determine the presence of advanced fibrosis/cirrhosis in current clinical practice.

1.2 Investigational Device

EUS shear wave is available commercially, through a software package upgrade on the existing EUS machine. The Olympus Aloka Arietta 850 EUS processor and shear wave elastography software package are FDA-approved devices that have been purchased for clinical purposes and is being used in clinical practice. Shear wave measurements are obtained by the press of a button on the EUS machine to switch on the SWE software and measurements obtained.

1.3 Clinical Data to Date

Currently there is no available literature that systemically evaluates the performance of EUS shear wave elastography. Our study would provide the first prospective, comparative evaluation of EUS SWE with MR elastography, which is a widely adopted non-invasive imaging modality utilized for liver fibrosis assessment.

1.4 Study Rationale and Risk Analysis (Risks to Benefits Ratio)

1.4.1 Study Rationale

Patients with chronic liver disease who are suspected to have advanced fibrosis will often undergo endoscopy for a variety of reasons (e.g. variceal screening). If successful and reliable, EUS-SWE will enable us to provide single session, comprehensive assessment of the liver including fibrosis staging and screening for complications of advanced liver disease such as gastroesophageal screening and liver cancer. The perceived practical advantages include reduced number of appointments, thereby confers cost and time benefits for the patients. Furthermore, EUS obviates the need for shear waves to travel through abdominal wall and visceral adiposity, hence provides unobstructed views of the liver in which accurate measurements can be obtained. This is particularly beneficial in many patients with non-alcoholic fatty liver disease (NAFLD) associated with significant underlying obesity (e.g. BMI > 35), where other imaging modalities often under-performs due to BMI limitations.

1.4.2 Anticipated Risks

There would be no additional anticipated risks associated with EUS shear wave elastography. Patients will undergo EUS procedure as clinically indicated and therefore would be subjected to the standard procedural risks associated with performing EUS.

1.4.3 Potential Benefits

If successful and reliable, EUS-SWE will enable us to provide single session, comprehensive assessment of the liver including fibrosis staging and screening for complications of advanced liver disease such as gastroesophageal screening and liver cancer. The perceived practical advantages include reduced number of appointments, thereby confers cost and time benefits for the patients.

1.5 Anticipated Duration of the Clinical Investigation

The overall duration of the study is estimated to be six to twelve months. There will be no planned follow up at the completion of the MRE.

2 Study Objectives

2.1 Primary Objective

To evaluate the diagnostic performance of EUS shear wave elastography in the assessment of liver fibrosis compared to MR elastography.

2.2 Secondary Objective

1. Explore the predictive value of EUS shear wave elastography in prognosticating patients with chronic liver disease and its complications.

3 Study Design

3.1 General Design

This is a prospective, paired study. Study subjects who are scheduled to undergo EUS at Mayo Clinic will be identified through Epic. Chart review will be performed including review of prior imaging, medical history, and laboratory results as available in Epic to determine study eligibility. Subjects without history of chronic liver disease (screened by low FIB-4 score) and those with known advanced fibrosis/cirrhosis will be eligible for the study. Eligible study subjects will then be contacted either before, or at the time of their endoscopy procedure to discuss study participation. All subjects will then receive standard clinical care based on the indication for the EUS procedure. During the EUS procedure, study subjects with undergo shear wave measurements obtained in a non-invasive manner as part of the endosonographic evaluation of the liver. 10 measurements (including shear wave velocity (Vs), elastic modulus (E)) will be obtained for point SWE (pSWE). Measurements will be obtained from both left and right lobes of liver unless technically infeasible to do so. Study subjects will then undergo a paired MR elastography (same day or at later date) after completion of EUS and only if consistent and reliable shear wave measurements were obtained (e.g., VsN > 70%(reliability index of each measurement expressed in percentages), IQR/M (interquartile range/ Median) is <15% for Vs and <30% for E). Enrolled study subjects who had undergone a previous MRE (within 6 months of enrollment) would be eligible for the study, without the need to undergo further research MRE. After completion of MR elastography, the subjects will then continue through their routine clinical care and will not be followed up by research staff. The expected duration of subject participation is anticipated to begin at the time of study enrollment and terminate after completion of MR elastography. There will be no additional follow up.

3.2

Figure 1: Study Design

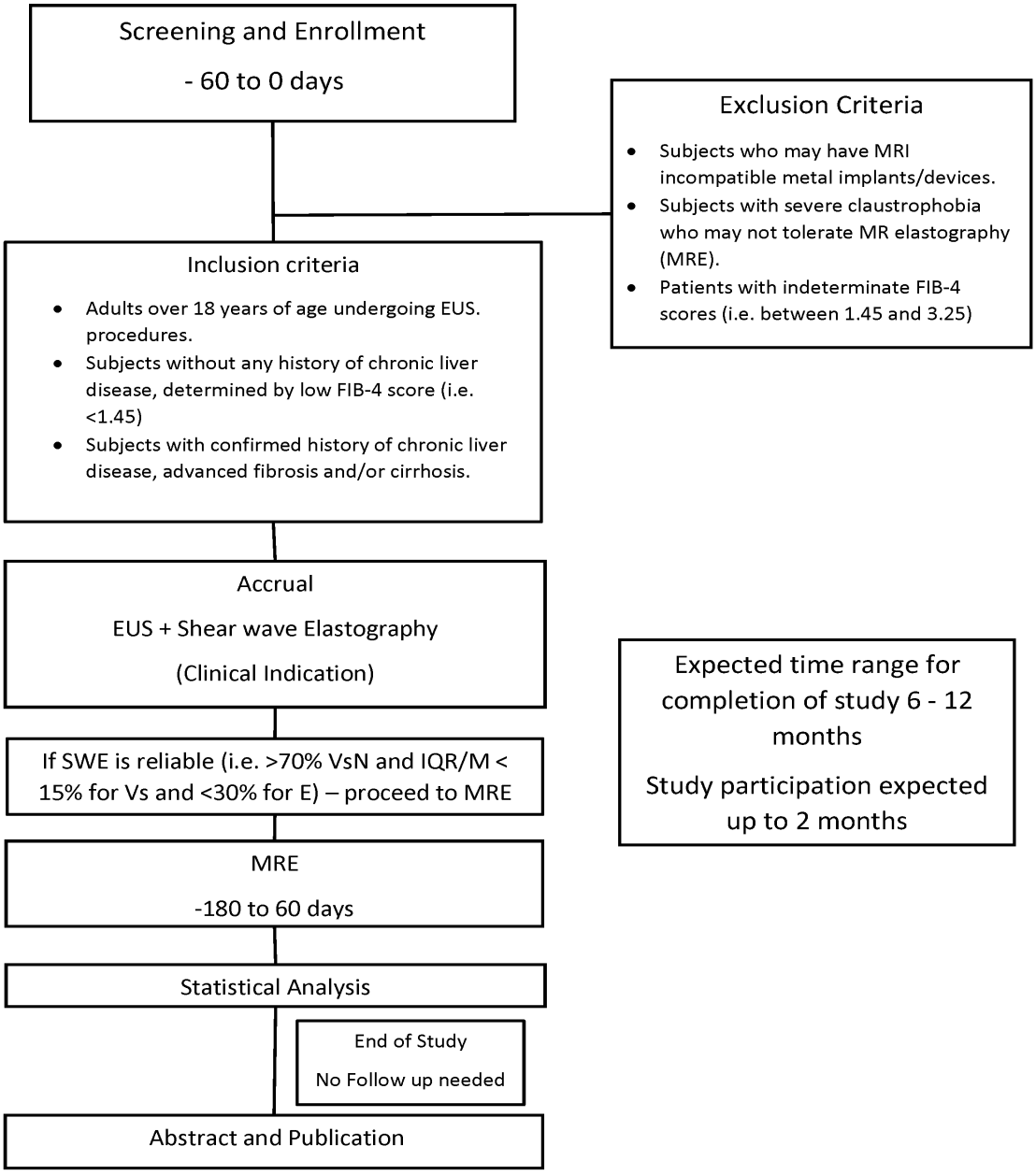

Table 1: Schedule of Events (SOE)

	Baseline Screening & Enrollment Visit 1 Days -180 to 0	**Accrual: Study Intervention Visit 2 Day 0**	**Follow up Visit 3 Days 0 to 60**
Inclusion/Exclusion	X		
EUS and Shear wave Elastography		X	
MRE	*X**		*X**

**MRE only required to be conducted once. Patients undergoing MRE for clinical purposes within the study timeframe can be recruited using the clinically performed MRE result.*

3.3 *Visit Descriptions*

3.3.1 Visit 1

Eligible study participants will be screened, approached and consented for the study. The screening and enrollment process may be performed remotely.

3.3.2 Visit 2

3.3.2.1 The participant will then undergo EUS procedure as clinically indicated. The shear wave measurements will be obtained during EUS. Study subjects will undergo MR elastography if no results within the previous 6 months are available. Subject participation is deemed complete at the end of MRE.

3.3.3 Follow-Up Analysis

Accuracy and efficacy of EUS shear wave elastography in assessing liver fibrosis when compared to MR elastography.

3.4 Primary Safety Endpoints

There are no specific primary safety endpoints pertaining to the study as EUS shear wave and MR elastography are non-invasive investigations. There is no investigational device involved in this study.

4 Subject Selection, Enrollment and Withdrawal

All patients who are undergoing EUS procedures may be eligible for the study. Patients with an established history of chronic liver disease with associated advanced fibrosis/cirrhosis will be of particular interest to the study.
It is anticipated that we will screen up to 250 subjects and enroll 50 subjects to the study.

4.1 Inclusion Criteria

1. Adults over 18 years of age who are undergoing EUS procedures.
2. Subjects with history of chronic liver disease, advanced fibrosis, or cirrhosis.
3. Subjects without any history of chronic liver disease.
4. Subjects able to give appropriate consent to the study.

4.2 Exclusion Criteria

1. Subjects who may have MRI-*incompatible* metal implants/devices.
2. Subjects with severe claustrophobia who may not tolerate MR elastography.
3. Subjects with unreliable EUS-SWE measurements.

4.3 Subject Recruitment, Enrollment and Screening

Potential subjects will be identified by the study team referencing the procedure and surgery calendars for upcoming procedures. If patients are scheduled for an EUS, they may be contacted by study staff prior to their procedure, to gauge interest.
Potential subjects may also be identified by physician referral. These patients would also be contacted prior to their procedure to gauge interest.
Outpatient subjects may be approached about the opportunity by phone, email, portal, or in-person to discuss the study details. Inpatients may be approached by phone or in their room as allowed by the charge nurse. An electronic or paper copy of the consent may be provided via these methods, prior to consent. to discuss and address any questions.

Recruitment will take place at the pre-procedural area prior to the procedure, or study team will reach out via email or phone to convey informed consent information which may include giving a copy of the consent form for review. Consenting and enrolment of patients on day of procedure will occur in a private room on the procedural floor prior to the procedure. These rooms house only one patient at a time and closing the door and blinds will eliminate the chance of individuals outside the room from hearing or witnessing the informed consent process. 30 minutes will be provided for discussion. Minimum 30 minutes will be provided between

discussion and decision allowing patients time to consider and talk with friends and/or family. Patients will have access to any glasses and/or hearing aids.

Investigators and/or study team will come to the potential subjects to explain the details of the study and obtain written informed consent and complete the questionnaires. These may also be collected digitally through Ptrax via Remote Consenting and either a video meeting or telephone meeting prior to signing the ICF. Subjects will have time ample time to learn about our study and decide if they want to enroll prior to consent.

The consent visit will occur through a video or phone consult with the subject and a witness if the subject is not able to physically sign consent. Once a time for the consent is agreed upon, the consent will be sent via email. The subject will be reminded not to sign the form prior to the consent appointment. The identity of the subject will be confirmed through the video or phone connection, as well as clinic number, name, and birthdate. A 30- minute consent appointment will be scheduled. Additional time can be added as needed. After the subjects' questions are answered and if the subject agrees, the form will be signed electronically.

Documentation of informed consent will involve the use of the Remote Electronic Consent technology. The subject may print or electronically save the form through DocuSign or from their patient portal or the subject may contact the study team to provide a copy of the form. Note: If the subject prefers not to use the Electronic Consent technology, the study team will provide a paper consent form for signature either in person or by mail.

4.4 Early Withdrawal of Subjects

4.4.1 When and how to Withdraw Subjects

The subjects will undergo EUS shear wave elastography and MRE in a sequential order, unless subjects had undergone previous MRE. If EUS shear wave measurements are unreliable (i.e., VsN < 70%). Then subjects will be withdrawn from the study and therefore will not proceed to undergo MRE, or to be included in the final analysis.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Withdrawn subjects will be recorded in the study record in order to calculate the withdrawal rate. There will be not further utilization of any subject related data.

5 Statistical Plan

5.1 Sample Size Determination

The hypothesis is at EUS-SWE is non-inferior to MRE at differentiating (“diagnosing”) cirrhosis vs those without fibrosis.

Using the pooled AUC above for MRE of 0.972, and data from our preliminary analysis that EUS-SWE had an AUC of 0.89., a sample size of 50 would give us 99% power and a sample size of 25 gives us 91% power. We anticipate screening up to 250 potential study participants.

5.2 Statistical Methods

Descriptive Statistics
Baseline values for demographic, clinical, and outcome will be tabulated for the study subjects. Continuous variables will be expresses as mean and standard deviation. Categorical variables will be expressed as percentages.

Analytical Statistics
The obtained shear wave measurements will be compared to MR elastography measurements to determine the AUC of EUS-SWE using MRE serving as the gold standard. Logistic regression will be used to generate ROC curves, and exploratory multivariable analyses using baseline differences in each group and other important clinical factors will be performed to identity confounders and interactions during the exploratory sensitivity analyses.

Handling of Missing Data
Subjects in which EUS shear wave measurements are unreliable (i.e., VsN < 70%) will not proceed to undergo MR elastography and will be excluded from the study, therefore will not be part of the statistical analysis. However, the subject will be recorded for the study to determine the rate of unreliable EUS shear wave measurements.

5.3 Subject Population(s) for Analysis

Subjects who have completed both EUS shear wave elastography and MR elastography will be included in the analysis.

6 Safety and Adverse Events

The EUS Shear wave elastography is being performed clinically and the safety and adverse events are not different from those inherent to the EUS procedure. Shear wave measurements typically require 5-10 minutes of procedural time.
There are no expected clinical adverse events for the study as the study intervention (MRE) is a non-invasive scan without any published safety concerns. Therefore, this study will not track any adverse events.

Definitions

Adverse Effect (Event)
Any untoward medical occurrence in a subject involved in clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study related treatment(s).

Life-threatening adverse effect: Any adverse effect that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the effect **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse effect: An adverse effect is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect.

Unanticipated adverse effect: Any adverse effect, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol or elsewhere in the current IDE application.

All inclusion and exclusion criteria are set out and there will be no protocol deviation.

7 Data Handling and Record Keeping

7.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study?
- Who will have access to that information and why?
- Who will use or disclose that information?
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

7.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification

as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

Data Management
All data points gathered for the study will remain confidential and only available to designated research personnel. The data will be managed using Excel Subject Tracking.

Data Security and Confidentiality

All collected data points and information will be securely stored in Mayo Clinic issued laptops, desktops or tablets with password encryption. Only study personnel will have access to the study data and information.

7.3 Records Retention

The study team will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The study team will retain the specified records and reports during the study and for the longer of the following.

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"[redacted]

   OR

2. A period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

8 Study Monitoring, Auditing, and Inspecting

8.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. Data safety monitoring plan (DSMP) will be completed after the first subject, then at 3 months and then annually if required. Delegated study staff will conduct the review. The review will be written up as reports and submitted to IRB for further review if required. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given

access to all the study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

8.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

9 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

10 Study Finances

10.1 Funding Source

This is an investigator-initiated and investigator-funded study.

11 Publication Plan

The results of the study will be written up and submitted to gastroenterology/endoscopy/hepatology journals for publication.

12 References

There is minimal available literature on this topic. We are performing a small pilot study with retrospective then prospectively collected EUS shear wave measurements. The preliminary results suggest that EUS shear wave carries good diagnostic accuracy in differentiating subjects with normal liver stiffness and those with advanced fibrosis/cirrhosis. The results will require full statistical analyses. However, our positive observation with the pilot study will form the basis of our current comparative study between EUS shear wave and MRE.