

**Accuracy of Magnetically Maneuvered Capsule
Endoscopy for Detection of Esophagogastric
Varices in Patients with Cirrhosis
(CENTERS study)**

Principal Investigator: Prof. Zhuan Liao

Protocol Version: V4.0

Date: 2021-06-15

Sponsored by:

Changhai Hospital, Naval Medical University

Statement of Confidentiality

The information contained in this document is privileged and confidential. Any distribution, copying, or disclosure is strictly prohibited unless required by regulations. Any individual who has access to the document shall be aware that the document is proprietary or confidential and shall not disclose the document without authorization.

Investigator Protocol Signature Page

I have read and understand the protocol and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will conduct the study according to the protocol and complete the study within the specified period of time. I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss these materials with them to ensure that they fully understand how to conduct the trial. I am aware that this protocol must be approved by the Ethics Committee. I agree to adhere strictly to the attached protocol.

Principal Investigator:

Signed: _____

Date: _____

Institution: _____

Abbreviations

AE	adverse events
BBS	black brown spots
CE	capsule endoscopy
CECR	capsule endoscopy completion rate
CI	confidential interval
CRF	case report form
CRS	cherry red spots
DSMB	data safety monitoring board
ds-MCE	detachable string magnetically maneuvered capsule endoscopy
EC	ethics committee
ECE	esophageal capsule endoscopy
eCRF	electronic case report form
EDC	electronic data capture
EGD	esophagogastroduodenoscopy
EGV	esophagogastric varices
ETT	esophageal transit time
EV	esophageal varices
FPI	first patient in
GCP	Good Clinical Practice
GET	gastric examination time
GOV	gastroesophageal varices
GTT	gastric transit time
GV	gastric varices
HRV	high-risk varices
IEC	independent ethics committee
LC	liver cirrhosis
LLT	lower level term
MCE	magnetically maneuvered capsule endoscopy
mITT	modified intent-to-treat
MLP	mosaic like pattern
NPV	negative predictive value
OC	observed cases
PHE	portal hypertensive enteropathy
PHG	portal hypertensive gastropathy
PHT	portal hypertension
PI	Principal Investigator
PPS	per protocol set
PPV	positive predictive value

PT	preferred term
RPL	red point lesions
SAE	serious adverse events
SAP	statistical analysis plan
SAS	safety analysis set
SBTT	small bowel transit time
SCE	string capsule endoscopy
SOC	primary system organ class
TRT	total recording time

Study Synopsis

Title of study	Accuracy of Magnetically Maneuvered <u>Capsule Endoscopy</u> for Detection of <u>Esophagogastric Varices</u> in Patients with Cirrhosis (CENTERS study)
Condition	Liver cirrhosis; esophagogastric varices
Sponsor	Changhai Hospital, Naval Medical University
Principal Investigator	Prof. Zhuan Liao Changhai Hospital, Naval Medical University, Shanghai, China
Study Type	Diagnostic accuracy study
Objectives	Using EGD as the reference standard, to estimate the diagnostic performance of the ds-MCE in identifying and grading esophagogastric varices in liver cirrhotic patients.
Interventions	Consenting patients with liver cirrhosis will be recruited to undergo ds-MCE first, followed by EGD within 48 hours. EGD is the reference standard against which ds-MCE is compared.
Primary endpoint	To estimate the diagnostic accuracy of ds-MCE in identifying EGV in patients with cirrhosis, using the detection by EGD as the reference.
Secondary endpoints	<ul style="list-style-type: none"> • To estimate the diagnostic accuracy of ds-MCE in identifying high-risk EV, using the detection by EGD as the reference. • To estimate the diagnostic accuracy of ds-MCE in identifying high-risk EGV, using the detection by EGD as the reference. • To estimate the diagnostic accuracy of ds-MCE in identifying EV, using the detection by EGD as the reference. • To estimate the diagnostic accuracy of ds-MCE in identifying large EV, using the detection by EGD as the reference. • To estimate the diagnostic accuracy of ds-MCE in identifying red signs of EV, using the detection by EGD as the reference. • To estimate the diagnostic accuracy of ds-MCE in identifying GV, using the detection by EGD as the reference. • To estimate the diagnostic accuracy of ds-MCE in identifying cardiofundal GV, using the detection by EGD as the reference. • To estimate the diagnostic accuracy of ds-MCE in identifying PHG, using the detection by EGD as the reference. • To assess the incidence of PHE in small bowel under ds-MCE. • To evaluate the examination time of ds-MCE and EGD procedures. • To assess the patient satisfaction score of the ds-MCE and

	<p>EGD procedures.</p> <ul style="list-style-type: none"> • Safety evaluation.
Key inclusion and exclusion criteria	<p><u>Key inclusion criteria:</u> Adult patients with clinically evident or biopsy-confirmed cirrhosis, aged 18 years or older.</p> <p><u>Key exclusion criteria:</u> has dysphagia, known Zenker's diverticulum, known or suspected gastrointestinal stenosis, pregnancy, active gastrointestinal bleeding, cardiac pacemaker or other implanted electromedical device, life-threatening conditions, plan to undergo magnetic resonance imaging examination before excretion of the MCE, current participation in another clinical study, refusal to give informed consent or any condition that precludes compliance with study.</p>
Number of subjects	591 patients will be required.
Trial duration	<p>First patient in to last patient out (months): January 2021 to January 2023</p> <p>Duration of the entire trial (months): 36 months</p> <p>Recruitment period (months): 24 months</p> <p>Subject participation duration: approximately two days</p>
Participating Centers	14 centers in China
ClinicalTrials.gov identifier	NCT03748563

Table of content

1 BACKGROUND INFORMATION AND RATIONALE	9
2 STUDY OBJECTIVES AND OUTCOME MEASURES	11
<i>2.1 Primary objective</i>	11
<i>2.2 Secondary objectives.....</i>	11
3 SUMMARY OF STUDY DESIGN	12
4 STUDY RISKS AND BENEFITS	14
<i>4.1 Known potential benefits.....</i>	14
<i>4.2 Potential risks.....</i>	14
<i>4.3 Risk/benefit ratio.....</i>	14
5 STUDY POPULATION.....	15
<i>5.1 Inclusion criteria</i>	15
<i>5.2 Exclusion criteria</i>	15
<i>5.3 Subject Identification and Enrollment.....</i>	15
<i>5.4 Withdrawal</i>	16
6 STUDY METHODOLOGY	17
<i>6.1 Baseline evaluation assessment.....</i>	17
<i>6.2 The ds-MCE and EGD examination procedures.....</i>	17
<i>6.3 Patient satisfaction assessment</i>	23
<i>6.4 Study follow-up</i>	23
<i>6.5 Outcome measures.....</i>	24
7 SAFETY CONSIDERATION	27
<i>7.1 Adverse Events (AE).....</i>	27
<i>7.2 Serious Adverse Events (SAE)</i>	27
<i>7.3 Follow-up of Adverse Events</i>	28
<i>7.4 Monitoring of safety risks</i>	28
8 DATA HANDLING AND RECORD KEEPING	28
<i>8.1 Data collection</i>	28
<i>8.2 Data management and quality.....</i>	29
<i>8.3 Confidentiality and Security.....</i>	29
<i>8.4 Record Retention and Archiving.....</i>	30
9 STATISTICAL CONSIDERATIONS	30
<i>9.1 Hypothesis</i>	30
<i>9.2 Sample size.....</i>	31
<i>9.3 Statistical Analysis Set.....</i>	31
<i>9.4 Statistical Analyses.....</i>	32

10 ETHICAL CONSIDERATIONS.....	35
<i>10.1 Statement of compliance</i>	<i>35</i>
<i>10.2 Subjects information and consent</i>	<i>35</i>
<i>10.3 Benefits and risks assessment</i>	<i>36</i>
<i>10.4 Compensation for injury</i>	<i>36</i>
11 MONITORING AND QUALITY ASSURANCE.....	36
12 PUBLIC DISCLOSURE AND PUBLICATION POLICY.....	37
13 STUDY ADMINISTRATION	38
<i>13.1 Study committees</i>	<i>38</i>
<i>13.2 Funding source</i>	<i>41</i>
<i>13.3 Study timetable.....</i>	<i>41</i>
14 REFERENCES	42

1 Background information and rationale

Portal hypertension (PHT) is the hemodynamic abnormality in patients with cirrhosis, which is associated with various pathological changes throughout the entire gastrointestinal tract, manifesting as esophagogastric varices (EGV), portal hypertensive gastropathy (PHG), and portal hypertensive enteropathy (PHE)¹⁻⁶. EGV is the major cause of morbidity and mortality due to the risk of variceal hemorrhage⁷. It has been estimated that at least two thirds of cirrhotic patients develop esophageal varices (EV) during their lifetime⁸. Gastric varices (GV) are seen in 15%–20% of cirrhotic patients with a high mortality rate and a greater propensity to rebleed⁴. Moreover, the presence of large EV and “red sign” on varices relate to an increased risk of bleeding, which needs prophylactic treatment with appropriate medical or endoscopic treatment⁹⁻¹¹. International practice guidelines recommended endoscopic screening and periodic surveillance for EGV and provide prophylactic treatment for high-risk varices (HRV) to prevent variceal bleeding^{1,12-15}.

Esophagogastroduodenoscopy (EGD) is recognized as the gold standard for detection of EGV in cirrhotic patients, allowing for direct mucosal visualization and therapeutic intervention. EGD is however an invasive procedure and there is potential for procedure-related complications, such as perforation and bleeding. Besides, conscious sedation is always required because the unpleasant procedure can't be well tolerated by cirrhotic patients, leading to increased cost, risk, and inconvenience for the patients¹⁶. These factors lead to a decrease of patient compliance as well as the effectiveness of the screening program. In this context, noninvasive approaches have been proposed to determine the presence of varices so as to circumvent the need for screening endoscopies^{1,17}. The combination of laboratory tests and radiological techniques showed encouraging results for excluding high-risk varices or varices needing treatment in approximately 20%-40% patients with compensated cirrhosis¹⁸⁻²². However, these techniques predict the presence, rather than confirming or grading, of varices. Besides, as recommended by guidelines, compensated patients with ongoing liver injury and decompensated patients still should undergo screening endoscopy and repeated surveillance endoscopies²³.

The capsule endoscopy (CE) system provides a noninvasive and relatively comfortable approach to visualize the GI tract, and the development of esophageal capsule

endoscopy (ECE) makes it possible to capture clear images of esophageal disease without the need for sedation^{24,25}. Several studies have confirmed its safety and tolerability in diagnosis of EV²⁶⁻³³. But the accuracy of ECE is not currently sufficient to replace EGD for the detection and grading for the esophageal varices, which mainly restricted by the inability to distend the distal esophagus, wash bubbles, active control of ECE or real-time visualization of key areas during esophageal examination^{26-28,31}. Furthermore, ECE has poor visualization of the stomach so that gastric varices and other clinically significant gastric lesions can't be detected²⁶⁻²⁸. Ramirez et al³⁴ developed string capsule endoscopy (SCE) in 2005, allowing controllable movement of the capsule in esophagus. Studies showed that SCE had an acceptable accuracy for the diagnosis of clinically significant esophageal varices, but the ability of SCE for grading EV was far from precise^{35,36}. The limitations still remained: (i) the string attachment procedure is complicated and time consuming; (ii) the lack of a validated grading system for differentiation between small and large gastroesophageal varices; (iii) observation of the stomach lesions including GV and PHG was not feasible.

To overcome these limitations, a new technique, so-called detachable string magnetically maneuvered capsule endoscopy (ds-MCE) (Ankon Technologies Co., Ltd, Wuhan, China) was developed. The ds-MCE system consists of two parts: the magnetically maneuvered capsule endoscopy (MCE) system and a transparent latex sleeve with a hollow string. The detachable latex hollow string is 120cm in length, with a thin latex sleeve at one end that can be attached to the CE and a thick latex sleeve at the other end that can be attached to the syringe. The capsule, which is partially enclosed within the sleeve, can be actively moved in the esophagus through the control of string. In this case, investigator can examine the entire esophageal mucosa several times under real time views. After completion of the esophageal examination, the capsule then could be detached from the string system through injecting air into the hollow string with the syringe. The magnetic capsule in the stomach can be accurately controlled through multidimensional rotation and adaptive matching of an external C-arm robot. Previous studies have demonstrated that the diagnostic accuracy of MCE for detecting gastric focal lesions is comparable with that of conventional EGD³⁷⁻⁴⁰. Two previous studies of ds-MCE confirmed it was a feasible, safe and well-tolerated method for completely viewing esophagus and stomach, without the need for sedation^{41,42}. Besides, the 8-10h battery life of the ds-MCE enables complete examination of the small bowel, which enables to provide a more comprehensive evaluation of

gastrointestinal changes^{43,44}.

This study intends to conduct a prospective, multicenter, diagnostic study to assess the diagnostic performance of ds-MCE in detecting and grading of EGV in patients with liver cirrhosis, using EGD as the reference.

2 Study objectives and outcome measures

2.1 Primary objective

- To estimate the diagnostic accuracy of ds-MCE in identifying EGV in patients with liver cirrhosis, using detection by EGD as the reference.

2.2 Secondary objectives

2.2.1 Key secondary objective

- To estimate the diagnostic accuracy of ds-MCE in identifying high-risk EV, using the detection by EGD as the reference.

2.2.2 Other secondary objectives

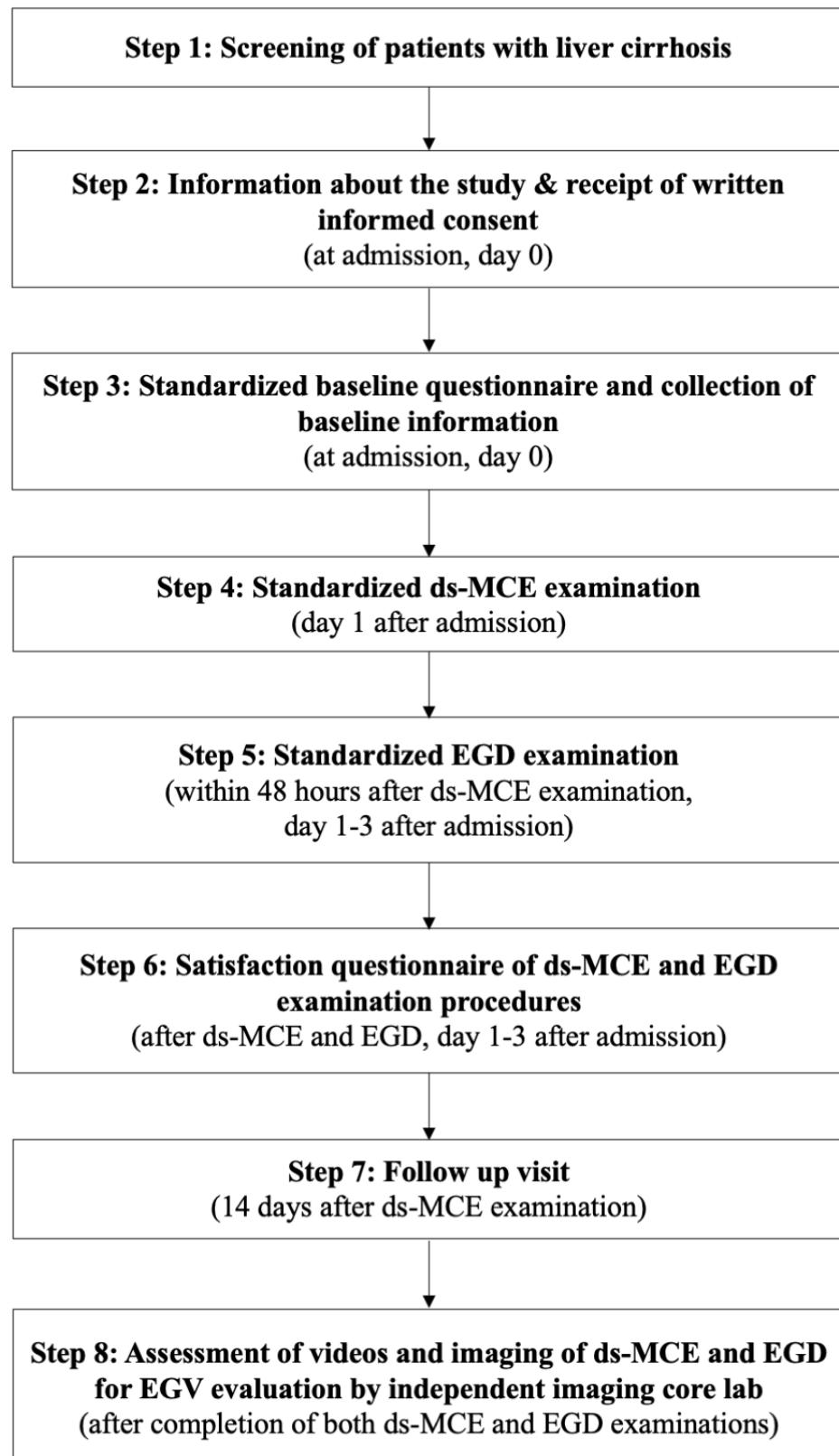
- To estimate the diagnostic accuracy of ds-MCE in identifying high-risk EGV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying EV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying large EV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying red signs of EV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying GV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying cardiofundal GV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying PHG, using the detection by EGD as the reference.
- To assess the incidence of PHE in small bowel under ds-MCE.
- To evaluate the examination time of ds-MCE and EGD procedures.

- To assess the patient satisfaction score of the ds-MCE and EGD procedures.
- Safety evaluation: to record the adverse events occurring during the study.

3 Summary of study design

This is a multicenter, prospective diagnostic accuracy study. Five hundred and ninety-one patients with liver cirrhosis will be recruited from 14 clinical centers. We will prospectively register appropriate candidates. After informed consent, eligible individuals will be enrolled, interviewed to obtain demographic and medical information, and asked to undergo ds-MCE and EGD examinations. EGD is the standard against which ds-MCE is compared, and it will be performed within 48 hours after ds-MCE examination. The duration of a participant's involvement is approximately two days. The primary outcome is the sensitivity and specificity of ds-MCE in identifying the presence of EGV in patients with cirrhosis, using detection by EGD as the reference. The diagnostic accuracy of ds-MCE in detection of high-risk EV, high-risk EGV, EV, large EV, red signs of EV, GV, cardiofundal GV and PHG compared with the EGD will also be assessed. The incidence of PHE in small bowel under ds-MCE, the examination time of ds-MCE and EGD procedures, patient satisfaction assessment and safety evaluation will also be determined. The study will run for approximately 3 years in recruiting centers.

Figure 1. Trial flow



4 Study risks and benefits

4.1 Known potential benefits

Knowledge gained from this study may benefit society by improving EGV and PHE screening and surveillance for cirrhotic patients in the future. Study participants may benefit directly from the study because they will be provided with a free ds-MCE examination and a free standard EGD examination that can fully evaluate the abnormalities in esophagus, stomach and small intestine.

4.2 Potential risks

- CE not being ejected outside the body within 2 weeks after initiation of the procedure indicates the stay of CE in the gastrointestinal tract. The incidence of this complication is reported to be around 1% in previous studies⁴⁵. This risk will be informed to each participant prior to study enrollment.
- As the CE be actively moved in the esophagus through the control of string, this may induce nausea in patients, and severe nausea probably lead to the variceal bleeding.
- When patients undergo the EGD examination, there is potential for procedure-related complications, such as perforation and bleeding.
- These risks will be small since careful procedure will be provided during ds-MCE and EGD examinations.

4.3 Risk/benefit ratio

Given the minimal risks associated with this study and the potential benefits to society and individuals, the benefits outweigh the risks. As for any clinical study, there is a possibility of unknown and unforeseen risk; that possibility is small for this study. If unforeseen risks are recognized during the study, then the sponsor, ethics committees, and participants will be provided with relevant information.

5 Study population

5.1 Inclusion criteria

Subjects meeting all of the following criteria are eligible for enrollment as study participants:

- Gender is not limited.
- Patients aged 18 years or older.
- Both inpatients and outpatients.
- Clinically evident or biopsy-proven liver cirrhosis.
- Able to provide informed consent.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for enrollment as study participants:

- Patients aged less than 18 years.
- Patients with dysphagia.
- Patients with Zenker's diverticulum.
- Suspected or known intestinal stenosis or other known risk factors for capsule retention.
- Pregnancy or suspected pregnancy.
- Patients with active gastrointestinal bleeding.
- Patients with cardiac pacemaker or other implanted electromedical devices which could interfere with magnetic resonance.
- Patients with life-threatening conditions.
- Patients plan to undergo magnetic resonance imaging examination before excretion of the MCE.
- Patients who are participating in or have participated in other clinical trials.
- Patients who refuse to give informed consent.
- Patients with any condition that precludes compliance with the study.

5.3 Subject identification and enrollment

Subjects will be prospectively enrolled from the inpatient wards and outpatient clinics at participating centers. Subjects who are candidates for enrollment into the study will

be evaluated for eligibility by the investigator or their nominee, e.g. a member of the research team or the participant's usual care team, to ensure that the inclusion and exclusion criteria have been satisfied and that the subject is eligible for participation in this clinical study. Once a subject is determined to be eligible by the clinical study site, the Investigator or designee will obtain informed consent from the subject, then assign a unique identification number, and enroll the subject in the electronic data capture (EDC) system. Once an identification number has been assigned, it cannot be reused. No subject may have any study procedures performed prior to study consent.

5.4 Withdrawal

Participants may withdraw voluntarily from study participation at any time. The investigator can decide to withdraw a subject from the study for any of the following reasons, but not limited to: non-adherence to the protocol requirements; subject no longer meets the protocol entrance criteria; urgent medical reasons; sponsor request (e.g., due to significant protocol deviations). The participants will be made aware that this will not affect their future care. At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a subject's withdrawal from the study is to be recorded in the case report form (CRF). All patients who cannot be analysed per protocol but have signed informed consent are called drop-outs. Patients who withdraw their participation or who are withdrawn by the principal investigator are also drop-outs and are labelled as withdrawals.

6 Study methodology

6.1 Baseline evaluation assessment

Subjects will be enrolled and consented by the investigator or their nominee. The baseline visit will occur prior to ds-MCE and EGD examinations. Demographic characteristics (age, sex, race, body weight, height and body mass index), etiology of liver diseases, patient's medical history (e.g. history of ascites, splenectomy, bleeding esophagogastric varices, TIPS insertion, endoscopic variceal therapy), indicative physical findings (e.g. vascular spiders, palmar erythema, and leg edema), laboratory testing results (e.g. complete blood count, liver function tests, coagulation test, prothrombin time and renal parameters), radiographic features of the upper abdomen (e.g. irregular liver contour, portal vein thrombosis, ascites, collateral vein, splenomegaly, and hepatocellular carcinoma), liver biopsy findings, previous endoscopic findings, Child-Pugh score, liver cirrhosis compensation status and comorbidities (e.g. diabetes, hypertension, coronary artery disease, arrhythmia, and asthma) will be documented.

6.2 The ds-MCE and EGD examination procedures

6.2.1 The ds-MCE system and examination procedure

6.2.1.1 The ds-MCE system

The ds-MCE system (Ankon Technologies Co., Ltd, Wuhan, China) mainly consists of two parts: the NaviCam magnetically maneuvered capsule endoscopy (MCE) system and a detachable latex hollow string attachment.

The MCE system consists of a guidance magnet robot, an endoscopic capsule, a capsule locator, a computer workstation with ESNavi software, and a data recorder (Fig. 2). The capsule has a size of 27×11.8 mm, weighs 4.8 g and has a permanent magnet inside its dome. Images are captured and recorded at 0.5-6 frames per second (fps) with a resolution of 480×480 pixels. The view angle of the capsule is 150°, and the view depth is 0 to 60 mm. The battery life of the capsule is more than 10 hours. The guidance magnet robot is a C-arm type robot, with two rotational and three translational degrees of freedom. The magnetic field generated by the magnetic robot can reach a maximum of 200mT and is adjustable. The computer workstation with ESNavi software is

designed for real-time viewing and controlling. The capsule locator is a device for activating the capsule and detecting whether it is inside the human body. The data recorder is used for receiving image data via wireless transmission from the capsule endoscope. There are two joysticks on the workstation desktop (Fig. 3). The left joystick controls capsule orientation in 2 rotational axes (horizontal and vertical directions), and the right one controls capsule location in 3 translational axes (forward/backward, up/down, left/right). The detachable latex hollow string is 120cm in length, with a thin latex sleeve at one end that can be attached to the capsule endoscopy and a thick latex sleeve at the other end that can be attached to the syringe (Fig. 4). The capsule, which is partially enclosed within the sleeve, can be actively moved in the esophagus through the control of string. After completion of the esophageal examination, the string can be separated from the capsule by injecting around 5mL of air using the syringe and removed from the mouth; the capsule then enters the stomach.



Figure 2. The NaviCam magnetically maneuvered capsule endoscopy (MCE) system. It consists of (A) a guidance magnet robot and computer workstation; (B) a magnetic capsule endoscope; (C) a capsule locator; (D) ESNavi software; (E) a data recorder.

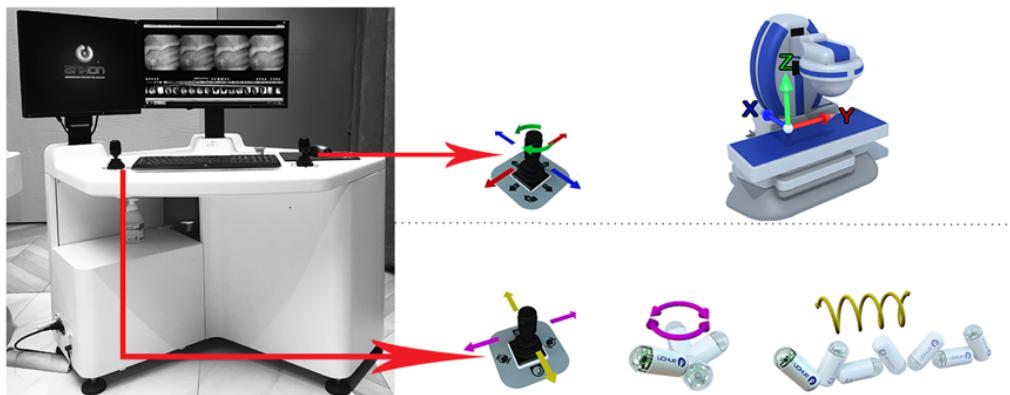


Figure 3. Two joysticks of the workstation. The left controls the capsule orientation in 2 rotational axes (horizontal and vertical directions), and the right controls the capsule location in 3 translational axes (forward/backward, up/down, left/right).

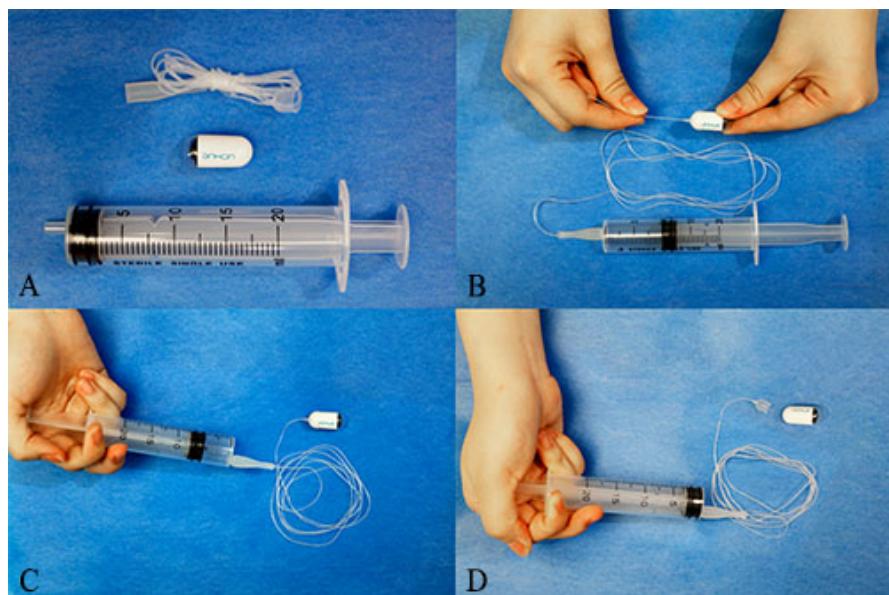


Figure 4. The procedure of ds-MCE. (A) the string system; (B) enclosing the capsule with the sleeve; (C) injecting air into the hollow string with the syringe; (D) the detachment of the capsule and the string system.

6.2.1.2 The ds-MCE examination procedure

The ds-MCE examination will be performed prior to EGD in all enrolled patients and be performed by a dedicated certified operator at each center with experience of >200 MCE operation cases and all operators had completed standardized training for ds-MCE examination before the enrollment.

(1) Gastric and Small Bowel Preparation Regimen

All enrolled patients will be instructed to maintain a clear liquid diet for the entire day

prior to the ds-MCE examination followed by a 12-h overnight fast. To improve the small bowel visualization, a purgative preparation (2L polyethylene glycol solution) or no purgative preparation will be used the night before the examination according to the patient's condition. Forty minutes before the examination, patients are asked to ingest 2.5g of dimethicone (Honghe Medicine, Zigong, China) as a defoaming agent and encouraged to walk freely to maximize contact with the gastric mucosa. Ten minutes before the examination, 100ml of water is ingested to initially flush the stomach cavity. Patients will then be encouraged to drink 500ml-1000ml water as tolerated just before swallowing the capsule to fill the stomach cavity for capsule navigation. Water ingestion will be repeated to optimize gastric distension during the examination. All the patients will be informed that clear fluids could be consumed 2 hours after capsule ingestion and solid food 4 hours after the capsule entering into the small bowel.

(2) Esophagus examination of ds-MCE

During esophageal examination, the capsule will be actively controlled by the latex hollow string. Before ingestion of the capsule, the CE is partially enclosed in the sleeve that could be detached from the string system through injecting air into the hollow string with the syringe (Fig. 4). Patient then swallows the capsule with water in a left lateral position, without sedation, and the capture rate of the capsule is set as 6 frames per second. Firstly, the CE will be allowed to travel down approximating the cardia, from where the string is slowly pulled up to inspect the esophagus under the guidance of real-time viewing. The process will be repeated for at least three passages up and down, during which participants will be instructed to drink water to distend the distal esophagus and wash bubbles for better observation. Target areas of interest could be observed repeatedly as the capsule travels down with swallowed water and be pulled up by attached string. After completing the esophageal examination, the string will be separated from the capsule through injecting 5 ml of air with the syringe, took out of the mouth and discarded, and the capsule will enter the stomach with additional water ingestion.

(3) Stomach examination of ds-MCE

During the gastric examination, the capsule will be actively controlled by external magnetic field. When the capsule entering the stomach, the capsule will be lifted away from the posterior wall, rotated, and advanced to the fundus and cardiac regions, and then to the gastric body, angulus, antrum, and pylorus. Of note, target areas of interest

could be observed repeatedly. If distension is insufficient, water ingestion will be repeated. Stomach examination procedures will be performed twice in each participant according to standardized protocol^{46,47}, and the mucosa of the gastric cardia, fundus, body, angulus and antrum will be fully recorded. Once the operator is satisfied that an adequate examination of stomach has been completed the capsule will be allowed to pass into the small bowel.

(4) Small bowel examination of ds-MCE

During the small bowel examination, the capsule moves passively under gastrointestinal peristalsis. After completion of the gastric examination, the operator then clicks the “small intestine mode” button under the “real-time view” interface. The capsule will be switched to “small intestine examination mode” with an adaptive capture rate of 0.5–6 fps. The capsule then moves passively under gastrointestinal peristalsis to further examine the small bowel. The patient will then be allowed to leave the hospital with the data recorder for further collection of images of the small intestine. Patients are allowed to drink clear water 2 hours after completing the gastric examination and a light meal 4 hours after completing the gastric examination. When the battery of capsule is exhausted or the capsule is discharged, the recording device and sensor array can be removed.

“Procedural success of ds-MCE” is defined as complete evaluation of the esophagus and stomach, irrespective of the completeness of small bowel evaluation. For patients who fail to complete esophageal and gastric evaluation under ds-MCE, the reason will be documented in the case report form in time.

(5) Collection of ds-MCE examination images

The patients will be instructed to return the data recorder after the capsule battery expired or the capsule is discharged. Then all images captured by the CE will be downloaded to the computer workstation by operator.

(6) Evaluation of ds-MCE examination

The coded videos of ds-MCE examinations will be assessed by an independent imaging core-lab blinded to the patient identification information. Two different independent gastroenterologists, who are experienced in MCE reporting and are blinded to the results of EGD examinations, will analyse the recorded ds-MCE images and videos. A consensus reading will be performed by a senior gastroenterologist experienced in ds-

MCE in case of discrepancies. They will be instructed to identify and grade the esophageal varices (EV) and gastric varices (GV) according to the ds-MCE grading system described in the “Study Outcomes Measurements” section, record the presence of portal hypertensive gastropathy (PHG) and portal hypertensive enteropathy (PHE). Besides, esophageal examination time (EET), gastric examination time (GET), gastric transit time (GTT), small bowel transit time (SBTT) and total recording time (TRT) of the ds-MCE will be recorded. Other focal lesions observed in the esophagus, stomach and small bowel will also be recorded. All the results will be documented on the designated CRF.

6.2.2 The EGD examination procedure

The EGD examinations will be performed by experienced endoscopists using peroral conventional standard forward-viewing upper gastrointestinal video endoscopes at each center, within 48 hours of ds-MCE procedure. The endoscopist will not be blinded to the patient’s prior medical history but will be blinded to the preceding ds-MCE results. All procedures are conducted either without sedation or with sedation, according to the standard procedure of the center and the preference of the patient. During the course of the endoscopy, a complete evaluation of the esophagus, stomach and duodenum will be carried out. Grading of esophageal varices (when present) will be performed by all endoscopists using a predefined protocol: after examination of the stomach, the gastric cavity is fully deflated; the EGD is then withdrawn into the esophagus, and the esophageal lumen will be fully inflated. At that point, esophageal varices and red color signs will then be evaluated. The esophageal varices will be graded as small (<5 mm) or large (≥ 5 mm) and, if in doubt, it will be measured against the open endoscopic biopsy forceps (5 mm). The video of entire EGD examination procedure and the captured pictures will be digitally recorded for each participant.

“Procedural success of EGD” is defined as complete evaluation of the stomach and esophagus, irrespective of the completeness of duodenal evaluation. For patients who fail to complete esophageal and gastric evaluation under EGD, the reason will be documented in the case report form in time.

The coded videos and captured pictures of EGD examinations will be assessed by an independent imaging core-lab blinded to the patient identification information. Another two different independent gastroenterologists, who are experienced in EGD and are

blinded to the results of ds-MCE examinations, will analyse the recorded EGD images and videos. A consensus reading will be performed by a senior gastroenterologist experienced in ds-MCE in case of discrepancies. They will be instructed to identify and grade the esophageal varices (EV) and gastric varices (GV) according to the EGD grading system described in the “Study Outcomes Measurements” section, record the presence of portal hypertensive gastropathy (PHG). Besides, examination time of the whole EGD procedure will be recorded through the video and images. Other focal lesions observed in the esophagus, stomach and small bowel will also be recorded. All the results will be documented on the designated CRF.

6.3 Patient satisfaction assessment

After completing the ds-MCE procedure or EGD procedure, patients will undergo a face-to-face interview at which they are asked to respond to the questions on the three-item questionnaire that addressed procedure satisfaction.

(1) Did you experience discomfort during the ds-MCE/EGD procedure?

4 = none; 3 = minor; 2 = mild; 1 = severe; 0 = intolerable

(2) Did you experience discomfort after the ds-MCE/EGD procedure?

4 = none; 3 = minor; 2 = mild; 1 = severe; 0 = intolerable

(3) How would you rate the entire ds-MCE/EGD examination procedure?

4 = very comfortable; 3 = comfortable; 2 = tolerable; 1 = uncomfortable; 0 = very uncomfortable

6.4 Study follow-up

Two weeks following the ds-MCE procedure, patients will be contacted to confirm excretion of the capsule and to verify that there are no changes in their wellbeing following participation in this study. If the patient has not observed capsule excretion within 2 weeks, an X-ray procedure will be performed to confirm the capsule exit if deemed necessary by the investigator. This study is designed to comply with the requirements of good clinical practices and the other regulatory requirements that govern clinical research in China. During the study, adverse event and serious adverse event surveillance and reporting will be conducted accordingly.

6.5 Outcome measures

6.5.1 Primary outcome

The primary outcome is the sensitivity and specificity of ds-MCE to identify EGV in patients with cirrhosis, using the detection by EGD as the reference.

6.5.2 Secondary outcomes

6.5.2.1 Key secondary outcome

- i. The sensitivity, specificity of ds-MCE in detection of high-risk EV, using the detection by EGD as the reference.

The high-risk EV is identified by either large EV or small EV with presence of red signs according to the Baveno VI consensus¹.

6.5.2.2 Other secondary outcomes

- ii. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy of ds-MCE in detection of high-risk EGV, using the detection by EGD as the reference.
High-risk EGV are defined as high-risk EV or any GV^{19,48}.
- iii. The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of EV, using the detection by EGD as the reference.
- iv. To investigate the optimal threshold of the proportion of ds-MCE esophageal luminal circumference occupied by the largest esophageal varix present in differentiating large EV from small or no EV, using the detection by EGD as the reference.
 - a) EV identified during EGD are classified based on the standard Baveno III consensus to differentiate between large EV (varix diameter $\geq 5\text{mm}$) and small EV (varix diameter $< 5\text{mm}$)⁴⁹.
 - b) As grading EV by endoscopy requires fully distention of the esophagus with air insufflation, which is lacking in CE, there has been no consensus on the standard classification of large EV under ds-MCE. In this study, we grade the EV under ds-MCE according to the proportion of the esophageal luminal circumference occupied by the largest esophageal varix present²⁶.
 - c) The Youden Index, defined as $[(\text{sensitivity} + \text{specificity}) - 1]$, will be calculated

to determine the optimal ds-MCE luminal circumference percentage threshold derived from the training cohort that resulted in the best combination of specificity and sensitivity for distinguishing large EV, using the results of EGD as the reference standard.

- v. The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of large EV, using the detection by EGD as the reference.
 - a) EV under EGD are classified into three grades: no, small or large, with the latter signifying a diameter ≥ 5 mm.
 - b) EV under ds-MCE are classified into three grades: no, small or large, with the latter signifying that the esophageal varix occupied more than the prespecified “optimal threshold” proportion of the capsule picture frame circumference.
- vi. The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of the red sign of EV, using the detection by EGD as the reference.
- vii. The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of gastric varices (GV), using the detection by EGD as the reference. GV are classified according to Sarin’s classification⁴. Gastric varices could be classified on the basis of its location in the stomach and its relationship with esophageal varices during ds-MCE procedure and EGD procedure. These are divided into two groups: gastroesophageal varices (GOV) and isolated gastric varices (IGV)^{4,46}. GOV1 are the extension of esophageal varices which across the cardia onto the lesser curve, and GOV2 extend onto the fundus. Isolated gastric varices (IGV) are vascular protrusions without direct connection to the esophageal varices. IGV1 are located in the fundus, while IGV2 are located elsewhere in the stomach, typically in the distal body and antrum.
- viii. The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of cardiofundal GV, using the detection by EGD as the reference. Cardiofundal gastric varices including GOV2 and IGV1 are at high risk of bleeding due to the unique vascular anatomy as opposed to lesser-curvature gastric varices (GOV1)⁵⁰.
- ix. The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of portal hypertensive gastropathy (PHG), using the detection by EGD as the reference.

The PHG is classified as four elementary gastric endoscopic signs proposed by the NIEC group: 1) mosaic like pattern (MLP); 2) red point lesions (RPL); 3) cherry

red spots (CRS); 4) black brown spots (BBS)^{3,51}.

- x. The incidence of PHE in small bowel under ds-MCE.

Endoscopic findings of PHE include mucosal inflammatory-like abnormalities, vascular lesions. In addition, mucosal inflammatory-like abnormalities and vascular lesions can lead to spontaneous bleeding⁵²⁻⁵⁴.

- xi. Examination time of ds-MCE and EGD procedures.

Examination time of ds-MCE include esophageal transit time (ETT), gastric examination time (GET), gastric transit time (GTT), small bowel transit time (SBTT), and total running time (TRT). ETT is defined as the time between the first esophageal image and the first gastric image. GET is defined as the time for examination of gastric primary anatomic landmarks twice. GTT is defined as the time between the first gastric image and the first duodenal image. SBTT is defined as the time between the first duodenal image and the first cecal image. TRT is defined as the time of the last picture taken by the capsule. Capsule endoscopy completion rate (CECR) is also recorded which defined as the proportion of the capsule that has a complete visualization of the entire small bowel⁴⁴. Examination time of EGD is defined as the duration from the endoscope entering to exiting from the esophagus.

- xii. Patient satisfaction score of ds-MCE and EGD procedures.

The patient satisfaction score assessment is based on the questionnaire of Section 6.3.

- xiii. Safety outcomes are based on adverse-event reporting.

All adverse events occurring during the study will be recorded.

7 Safety consideration

7.1 Adverse Events (AE)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to trial procedure. As far as possible, each AE should be evaluated to determine the severity grade (mild, moderate, severe); its relationship to the study procedure; its duration (start and end dates or if continuing at final exam); action taken (no action taken; hospitalization); whether it constitutes a serious adverse event (SAE). All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded and documented on the designated CRF.

7.2 Serious Adverse Events (SAE)

A Serious Adverse Event is any unfavorable event within the study timeframe fulfilling at least one of the following criteria:

- results in death;
- life-threatening (at the time of the event);
- inpatient hospitalization required or prolonged;
- event that results in persistent or significant disability/incapacity;
- medically important event or event that requires a medical or surgical intervention to prevent one of the above health implications.

Any other important medical event that did not result in any of the outcomes listed above due to interventions but could have been based upon appropriate medical judgment. An elective hospital admission will not be considered as a serious adverse event.

As far as possible, each SAE should be evaluated to determine the severity grade (mild, moderate, severe); its relationship to the study procedure; its duration (start and end dates or if continuing at final exam); action taken (no action taken; hospitalization).

Serious adverse events will be immediately, after coming to notice of the investigator, reported to the trial coordinator, who is 24/7 available. The investigator will report the following SAEs occurring in the study period to the sponsor without undue delay of obtaining knowledge of the events: death from any cause; esophagogastric variceal hemorrhage during ds-MCE examination; acute esophagogastric variceal hemorrhage

during EGD examination; acute esophagogastric variceal hemorrhage during ds-MCE examination. The investigator should report to the sponsor and ethics committee within 24 hours of SAEs. SAEs need to be documented additionally on a separate SAE form.

7.3 Follow-up of Adverse Events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study, the interventions required to treat it and the outcome. For a follow-up report, the investigator may be required to collect further information for a detailed description and a final evaluation of the case, including copies of hospital reports and other relevant documents.

SAEs need to be reported till the end of the study in China, as defined in the protocol.

7.4 Monitoring of safety risks

For the monitoring of safety risks and potential harms for the study participants caused by study procedure or study design, the sponsor and a Data Safety Monitoring Board (DSMB) will carefully review all (S)AEs. In case of any safety issue that might change the risk benefit balance unfavorable, the sponsor will take appropriate measures to guarantee the safety of the patients.

8 Data handling and record keeping

8.1 Data collection

Source documents provide evidence of participant involvement, consent and permit collection of the data acquired. Data from source documents will be entered onto study CRFs. When the CRFs are complete, they will be reviewed and signed by the investigator and returned to the sponsor or designees. All data from the original CRF will be entered into a web-based electronic data capture (EDC) system by local research personnel. It allows the documentation of study data in electronic case report forms (eCRF). Subject records are coded by a unique study number. The local investigators

will keep a list showing codes and names. The EDC system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. The technical support will be provided for the study centers during the study duration (administration of logins, roles and rights). The eCRF will be adapted due to changes in the study design, if necessary.

8.2 Data management and quality

The investigator is required to ensure that all CRFs are completed for every participant entered in the trial. When the data be entered in the EDC system, a comparison program will be run. Any out-of-range values and missing or inconsistent key variables will be reviewed, and any resulting queries will be resolved with the investigator and amended in the EDC system. All elements of data entry will be recorded in an electronic audit trail to allow all data changes in the database to be monitored and maintained in accordance with local regulations. At the end of the study, the entire database will be exported. The final data management process contains plausibility, consistency and range checks of the data. The missing data will be identified as well. If there are any queries, data clarification forms will be generated and will be sent to the respective study centers for clarification. The related data correction will be performed either direct in the eCRF by the study centers or with programmed scripts by the data management team. After all data management processes are completed, the cleaned data will be available for the statistical analysis. The final data can be delivered in a defined data format like SAS data file, including a data management report as well.

8.3 Confidentiality and Security

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor and their agents. This confidentiality includes documentation, investigation data, subjects' clinical information, and all other information generated during participation in the study. No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the sponsor and the subject. The study monitor or other authorized

representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigators, including but not limited to medical records (office, clinic, or hospital) of the subjects in this study. The clinical study site will permit access to such records.

Medical and research records should be maintained at each site in the strictest confidence. All study forms will be stored in locked secure locations and will not be available to personnel not associated with the study. Computerized data are accessible only by password. Electronic CRFs (eCRFs) will be identified by unique identification number only, to insure subject anonymity. No subject identifiers will be used in the presentation of data. The document linking the unique identification number to patients' name and medical record numbers will be kept in a locked document, will not be accessible to personnel not associated with the study.

8.4 Record Retention and Archiving

In compliance with the Good Clinical Practice (GCP) guidelines and regulations, the site investigators will maintain all records and documents regarding the conduct of the study. These will be retained for at least 3 years, or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility. Each site participating in this study will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law) clinical records for the purposes of clinical site monitoring, quality assurance reviews, audits, and evaluation of study safety and progress.

9 Statistical considerations

9.1 Hypothesis

The primary objective of this study is to evaluate the diagnostic performance of ds-MCE in detecting EGV by assessing its sensitivity and specificity, using EGD as the reference standard. The hypothesis is that both the sensitivity and specificity of ds-MCE

for detecting EGV will exceed 85% when compared to EGD. The target value of 85% is set based on literature review⁵⁵ and expert consensus from the steering committee.

H_{01} : Sensitivity $\leq 85\%$

H_{11} : Sensitivity $> 85\%$

H_{02} : Specificity $\leq 85\%$

H_{12} : Specificity $> 85\%$

9.2 Sample size

As a single-arm confirmatory diagnostic accuracy study, we primarily aimed to test whether both the sensitivity and the specificity of ds-MCE for detecting EGV would be $>85\%$. With estimated sensitivity of 90%, specificity of 94%, a two-sided alpha of 5%, power of 80%, EGV prevalence of 62%, and a dropout rate of 3%, 591 patients would be needed.

When considering the accuracy of ds-MCE for detecting high-risk EV (key secondary outcome), the validation cohort of approximately 200 patients would provide an estimation precision (CI width/2) of $<7\%$, with estimated sensitivity of 90% and specificity of 94%, using CENTERS luminal circumference percentage threshold derived from the training cohort, and high-risk EV prevalence of 40%.

9.3 Statistical Analysis Set

The analyses will be performed on modified intent-to-treat (mITT), per protocol set (PPS) and safety analysis set (SAS). Each analysis set will summarize the number of subjects and its percentage from subjects.

Efficacy set: The analysis of mITT is primary, and PPS is a sensitivity analysis of mITT.

The effectiveness analyses will be based on mITT population who go through procedures of ds-MCE and EGD modalities and can be evaluated for the results of EV and GV.

The effectiveness analyses will also be conducted on the PPS, which includes all

subjects in the mITT population who have no major protocol deviations (defined to be protocol violations that may have a significant impact on subject outcomes) and who do not meet any of the following criteria:

- Subject withdraws
- Capsule ingestion failure
- Esophageal or gastric examination failure under ds-MCE
- Esophageal or gastric examination failure under EGD
- System technical failure of ds-MCE or EGD

Safety Sets: The evaluation of safety parameters will be conducted on the SAS

Safety Analysis Set (SAS): actual data that has been inspected at least once and has safety indicators recorded. Security missing values do not need to be carried forward.

9.4 Statistical Analyses

9.4.1 The general principle

Descriptive statistics for continuous variables will include arithmetic mean (standard deviation) or median (interquartile ranges) as appropriate. Frequency and percentage will be calculated for categorical variables. Unless otherwise specified, for continuous variables, comparisons between groups will be assessed using the paired t test or Wilcoxon signed-rank test as appropriate. Categorical variables will be compared using the McNemar test as appropriate.

All statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 4.2.2 (R Foundation for Statistical Computing). Unless otherwise specified, all significance testing will be 2-tailed using $\alpha = 0.05$. Tests will be declared statistically significant if the calculated p-value is <0.05 .

9.4.2 Interim Analyses

No interim analysis is planned for this study.

9.4.3 Missing data

The primary analysis will be conducted on both mITT and PPS. For mITT analysis, the

observed cases (OC) for each visit will be used and the worst outcome carried forward (WOCF) method will be applied for the primary endpoint to impute missing data, unless otherwise specified.

No imputation for missing data will be performed for the secondary and safety outcomes analysis.

9.4.4 Multiple Comparisons

Since the primary outcome hypothesis testing based on the two primary endpoints should be met simultaneously, no multiplicity adjustment will be performed.

For the analysis of the secondary and safety outcomes, no adjustment for multiple comparisons will be made.

9.4.5 Demographics and Baseline Characteristics

All data recorded at baseline will be summarized using the methodology described in section 9.4.1. Summaries will be presented for the analysis set.

Summary tables (descriptive statistics and/or frequency tables) will be provided for all variables at different endpoints. For continuous variables, means and standard deviations will be presented, unless the variable has a skewed distribution, in which case medians, 25th and 75th percentiles will be presented. For categorical variables, the number and percentage of participants within each category will be presented. For each variable (continuous or categorical), the number of missing values will be reported.

9.4.6 Analysis for Primary Outcome

The primary outcome is the diagnostic accuracy of ds-MCE for discrimination of patients with EGV using sensitivity and specificity, along with the corresponding 95% CIs estimated using the Wilson's method. Sensitivity and specificity will be compared with 85% using one-sample exact test.

The accuracy, and positive and negative predictive values (PPV and NPV) will be calculated as other measures simultaneously, along with the corresponding 95% CIs estimated using the Wilson's method⁵⁶.

9.4.7 Analyses for Secondary Outcomes

The training cohort and validation cohort will be divided based on centers, in the order of the first patient in (FPI). Centers with earlier FPI date will be allocated to the training cohort (whose sample size should meet approximately 2/3 of the total sample size), and the remaining centers with later FPI date will be allocated to the validation cohort.

The Youden Index⁵⁷, defined as $[(\text{sensitivity} + \text{specificity}) - 1]$, will be calculated to determine the ds-MCE optimal luminal circumference percentage threshold derived from the training cohort that resulted in the best combination of specificity and sensitivity for distinguishing large EV, using the results of EGD as the reference standard. When the optimal threshold has decimals, its integer portion will be set as the modified optimal threshold for internal and external validation (for the ease of clinical application and ensuring sensitivity). Based on the training cohort, the modified optimal threshold is internally validated with bootstrap method, with 1000 replicates. The diagnostic accuracy of identifying large EV, high-risk EV and high-risk EGV will be assessed on the basis of the modified optimal threshold above in the validation cohort using sensitivity, specificity, PPV, NPV and accuracy, corresponding 95% CIs calculated using the Wilson's method.

The diagnostic accuracy of ds-MCE in detection of EV, red signs of EV, GV, PHG compared with the EGD will be assessed using sensitivity, specificity, PPV, NPV and accuracy, corresponding 95% CIs calculated using the Wilson's method.

Description and comparisons of other secondary outcomes of ds-MCE and EGD groups will be performed using the methodology described in section 9.4.1.

9.4.8 Subgroup analysis

To determine whether the accuracy is consistent across subgroups, the estimate of the between-group accuracy for EGV, high-risk EV based on the modified optimal threshold value, high-risk EGV based on the modified optimal threshold value will be estimated within each category of the following classification variables:

- Cirrhosis stage (compensated phase, decompensated phase);

- Indication for endoscopy (screening, surveillance).

9.4.9 Safety Analyses

All adverse events and serious adverse events will be listed.

10 Ethical considerations

10.1 Statement of compliance

The study will be conducted according to the principles of the Declaration of Helsinki. The study will be approved by the ethics committees of the participating hospitals. This study will be conducted in compliance with the protocol approved by the independent ethics committee (IEC) and according to GCP standards. No deviation from the protocol will be implemented without prior review and approval of the IEC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IEC as soon as possible. All investigators undertaking this work have undertaken the necessary GCP training.

10.2 Subjects information and consent

All patients that are included have to give written informed consent. They will be provided a consent form describing the study and providing sufficient information for them to make an informed decision about the participation in this study. This consent form will be submitted with the protocol for review and approval by the IEC. The investigators should adequately explain the details of the clinical trial, including known, foreseeable risks and possible adverse event, etc., to the subject or to the guardians of subjects without capacity for civil conduct or with limited capacity for civil conduct. The rights and welfare of potential subjects will be protected by emphasizing that neither their access to medical care nor the quality of their care will be adversely affected if they decline to participate in this study. After full and detailed explanation, the subjects or their guardians sign the name and date in the informed consent form, and the investigators also need to sign the name and date in the informed consent form.

10.3 Benefits and risks assessment

Knowledge gained from this study may benefit society by improving EGV and PHE screening and surveillance for cirrhotic patients in the future. Study participants may benefit directly from the study because they will be provided with a free ds-MCE procedure and a free standard EGD examination that can fully evaluate the upper gastrointestinal mucosa and small intestine mucosa. The main risk of ds-MCE is retention of the capsule behind a stricture, occurring in around 1% of patients with suspected small bowel disease^{45,47}. When patients undergo the EGD examination, there is potential for procedure-related complications, such as bleeding. These risks will be small since careful procedure will be provided in the study.

Given the minimal risks associated with this study and the potential benefits to society and individuals, the benefits outweigh the risks. As for any clinical study, there is a possibility of unknown and unforeseen risk; that possibility is small for this study. If unforeseen risks are recognized during the study, then the sponsor, ethics committees, and participants will be provided with relevant information.

10.4 Compensation for injury

Each participating center has purchased liability insurance. This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 1 year after the end of the study.

11 Monitoring and quality assurance

The principal investigator will ensure that all study personnel are appropriately trained, and applicable documentations are maintained on sites. The study investigators are responsible for conducting routine quality assurance and quality control activities to internal monitoring to ensure that, for this study:

- human subjects' rights and well-being are protected.
- data are accurate, complete, and verifiable from source documents.
- the study complies with the protocol/amendment(s), sponsor requirements, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

In addition, monitoring visits by a sponsor-designated professional or monitor will

occur at scheduled intervals prior to, during, and at study completion. The extent, nature and frequency of on-site visits will be based on enrolment rate, the quality of the documents provided by the site, consistency of follow-up of the patients according to this protocol. Monitoring visits may include, but are not limited to, review of regulatory files, CRFs, informed consent forms, protocol compliance and the integrity and consistency of EDC data entry. Study monitors will check and assess the progress of the trial, review trial data collected, conduct source document verification and identify any issues and address their resolution. This will be done in order to verify that the data are authentic, accurate, and complete, that safety and rights of subjects are being protected and that the trial is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions. The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of internal monitoring and in the event of auditing by the sponsor and inspection by regulatory authorities. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Direct access to these documents must be guaranteed by the investigators, who must provide support at all times for these activities.

12 Public disclosure and publication policy

The results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. Participants will not be identified in any publications. The presentation or publication of any or all data collected by participating investigators on patients is under the direct control of the study's steering committee. No individual participating investigator has the right to use this study's data to perform analyses or interpretations, or to make public presentations or seek publication of any or all of the data without the specific approval of the study's steering committee. Any presentation or publication related to this study should be circulated to participating investigators for review, comments and suggestions at least one weeks prior to submission of the manuscript to the presenting or publishing body. All publications

must give proper recognition to the funding source and should list all study participants (not necessarily as authors of the manuscript). The manuscript will be shared with the sponsor(s) one month before submission, but the sponsor(s) will have no influence on its contents.

Anonymous data can be requested from the study steering committee with a detailed description containing the aims and methods of the study for which the data are intended to be used. Data will be made available for this purpose at least 18 months after publication of the main report. Under the approval of the study steering committee, data may also be shared with non-commercial parties for scientific purposes, and with commercial parties for regulatory purposes.

These purposes should be specified in the informed consent form.

13 Study administration

13.1 Study committees

Steering Committee:

1. Chairman: Prof. Zhuan Liao, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;
2. Prof. Zhao-Shen Li, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;
3. Prof. Chang-Qing Yang, Department of Gastroenterology and Hepatology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China;
4. Prof. Xiu-Li Zuo, Department of Gastroenterology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China;
5. Prof. Shui-Xiang He, Department of Gastroenterology, the First Affiliated Hospital of Xi'an Jiaotong University. Xi'an, China.

Coordinating Center:

1. Dr. Xi Jiang, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;
2. Dr. Jun Pan, Department of Gastroenterology, Shanghai Hospital, Naval Medical

University, Shanghai, China.

Statistical Center:

1. Prof. Yan Hou, Department of Biostatistics, Peking University, Beijing, China.

Safety events committee:

1. Prof. Zhen Li, Department of Gastroenterology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China;
2. Dr. Xiao-Ou Qiu, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;
3. Dr. Shan Wu, Department of Endoscopy, Shanghai Jiao Tong University affiliated Sixth People's Hospital, Shanghai, China.

Core laboratory for EGD and ds-MCE imaging/video assessment

1. Esophagogastroduodenoscopy (EGD):

- 1) Prof. Wen-Bin Zou, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;
- 2) Prof. Tian Xia, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;
- 3) Prof. Xiao Liu, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;

2. Detachable string magnetically maneuvered capsule endoscopy (ds-MCE):

- 1) Prof. Yang-Yang Qian, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;
- 2) Dr. Chen He, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China;
- 3) Dr. Ting Zhang, Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China.

Enrolling Study Centers and Investigators:

1. Department of Gastroenterology, Shanghai Hospital, Naval Medical University, Shanghai, China: Zhuan Liao, M.D., Zhao-Shen Li, M.D., Xi Jiang, M.D., Jun Pan, M.D., Wei Zhou, M.D.
2. Department of Gastroenterology, Ruijin Hospital, Shanghai Jiao Tong University

School of Medicine, Shanghai, China: Duo-Wu Zou, M.D., Ye Chu, M.D., Chun-Hua Zhou, M.D., Wei Wu, M.D.

3. Department of Gastroenterology and Hepatology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China: Chang-Qing Yang, M.D., Qing Xu, M.D.
4. Department of Endoscopy, Shanghai Jiao Tong University affiliated Sixth People's Hospital, Shanghai, China: Xin-Jian Wan, M.D., Shan Wu, M.D.
5. Endoscopy Center, Department of Gastroenterology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China: Mei-Dong Xu, M.D., Ben-Song Duan, M.D., Tao Chen, M.D., Mao Li, M.D.
6. Department of Gastroenterology, Yangpu Hospital, Tongji University, Shanghai, China: Li Li, M.D., Jun-Zhi Cao, M.D.
7. Department of Gastroenterology, Zhujiang Hospital, Southern Medical University, Guangzhou, China: Hua Mao, M.D., Shao-Qin Jin, M.D.
8. Department of Gastroenterology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China: Xiu-Li Zuo, M.D., Zhen Li, M.D., Cheng Peng, M.D.
9. Department of Gastroenterology, The Third Xiangya Hospital, Central South University, Changsha, China: Xiao-Yan Wang, M.D., Ding-Hua Xiao, M.D., Shao-Jun Liu, M.D., Zhen-Yu Yang, M.D., Fen Wang, M.D.
10. Department of Gastroenterology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China: Shui-Xiang He, M.D., Huan-Huan Sun, M.D.
11. Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China: Jun Liu, M.D., Xiao-Ping Xie, M.D., Yu-Hu Song, M.D.
12. Department of Gastroenterology and Endoscopy, The fifth affiliated Zhuhai Hospital of Zunyi Medical University, Zhuhai, China: Chao-Hui He, M.D., Yang Yang, M.D., Yuan-Hong Xu, M.D.
13. Department of Gastroenterology, The First Afilliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China: Shuo Zhang, M.D., Hai-Biao Bao, M.D.,

Lu Zhang, M.D., Jin-Feng Dai, M.D.

14. Department of Gastroenterology, Shanghai Pudong New Area Gongli Hospital, Shanghai, China: Yi-Hai Shi, M.D., Li-Juan Hu, M.D.

Data Safety Monitoring Board:

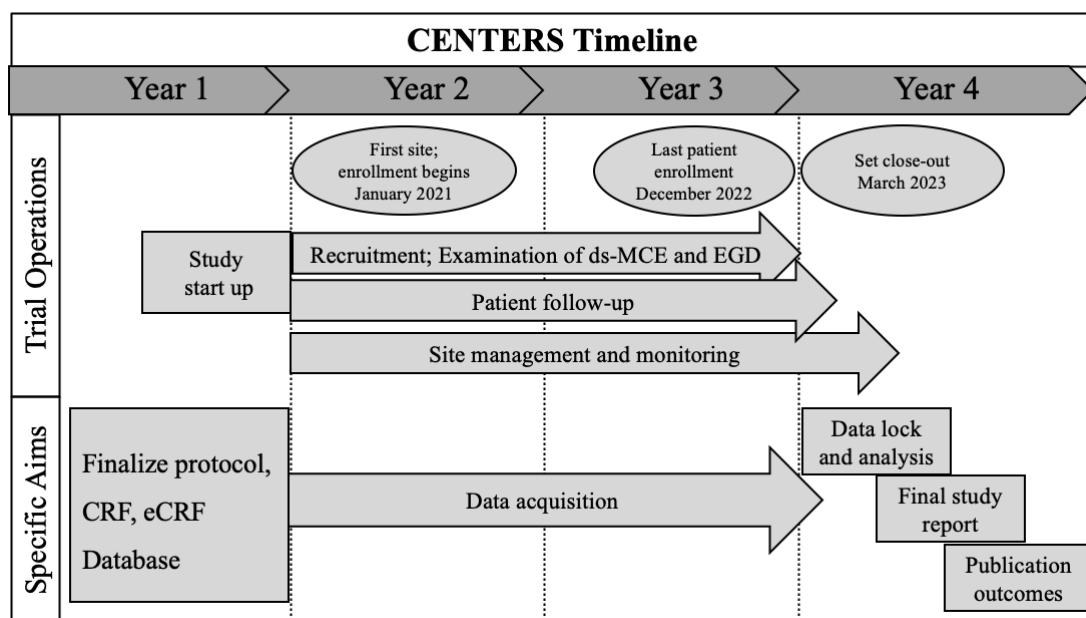
1. Prof. Liang Zhong, Department of Gastroenterology and Endoscopy, Huashan Hospital, Fudan University, Shanghai, China.
2. Prof. Feng Liu, Digestive Endoscopy Center, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China.
3. Prof. Cheng Wu, Department of Military Health Statistics, Naval Medical University, Shanghai, China.

13.2 Funding source

The CENTERS trial is funded by Shanghai Municipal Hospital Emerging Frontier Technology Joint Project (to Z. Liao, No. SHDC12019105); "Ten Thousand Plan"-National High Level Talents Special Support Plan (to Z. Liao).

13.3 Study timetable

The CENTERS timeline includes a 6-month start up period, followed by approximately 24 months of enrollment, approximately 6 months of close out and data analysis.



14 References

1. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;63:743-52.
2. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. *N Engl J Med* 1988;319:983-9.
3. Spina GP, Arcidiacono R, Bosch J, et al. Gastric endoscopic features in portal hypertension: final report of a consensus conference, Milan, Italy, September 19, 1992. *J Hepatol* 1994;21:461-7.
4. Sarin SK, Lahoti D, Saxena SP, et al. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992;16:1343-9.
5. Kodama M, Uto H, Numata M, et al. Endoscopic characterization of the small bowel in patients with portal hypertension evaluated by double balloon endoscopy. *J Gastroenterol* 2008;43:589-96.
6. Bresci G, Parisi G, Capria A. Clinical relevance of colonic lesions in cirrhotic patients with portal hypertension. *Endoscopy* 2006;38:830-5.
7. Wang FS, Fan JG, Zhang Z, et al. The global burden of liver disease: the major impact of China. *Hepatology* 2014;60:2099-108.
8. Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. *Gastroenterology* 2002;122:1620-30.
9. D'Amico G, De Franchis R, Cooperative Study G. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003;38:599-612.
10. de Franchis R, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis* 2001;5:645-63.
11. Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. *Hepatology* 2001;33:802-7.
12. de Franchis R, Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010;53:762-8.
13. Tripathi D, Stanley AJ, Hayes PC, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 2015;64:1680-704.
14. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Practice Guidelines Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of G. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007;46:922-38.
15. Tajiri T, Yoshida H, Obara K, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). *Dig Endosc* 2010;22:1-9.
16. Levy I, Gralnek IM. Complications of diagnostic colonoscopy, upper endoscopy, and enteroscopy. *Best Pract Res Clin Gastroenterol* 2016;30:705-18.
17. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology* 2017;66:1980-8.
18. Ding NS, Nguyen T, Iser DM, et al. Liver stiffness plus platelet count can be used to exclude high-risk oesophageal varices. *Liver Int* 2016;36:240-5.

19. Maurice JB, Brodkin E, Arnold F, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. *J Hepatol* 2016;65:899-905.
20. Perazzo H, Fernandes FF, Castro Filho EC, et al. Points to be considered when using transient elastography for diagnosis of portal hypertension according to the Baveno's VI consensus. *J Hepatol* 2015;63:1048-9.
21. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. *Gastroenterology* 2013;144:102-11 e1.
22. Qi X, Berzigotti A, Cardenas A, Sarin SK. Emerging non-invasive approaches for diagnosis and monitoring of portal hypertension. *Lancet Gastroenterol Hepatol* 2018;3:708-19.
23. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017;65:310-35.
24. Lapalus MG, Dumortier J, Fumex F, et al. Esophageal capsule endoscopy versus esophagogastroduodenoscopy for evaluating portal hypertension: a prospective comparative study of performance and tolerance. *Endoscopy* 2006;38:36-41.
25. Gralnek IM, Adler SN, Yassin K, et al. Detecting esophageal disease with second-generation capsule endoscopy: initial evaluation of the PillCam ESO 2. *Endoscopy* 2008;40:275-9.
26. de Franchis R, Eisen GM, Laine L, et al. Esophageal capsule endoscopy for screening and surveillance of esophageal varices in patients with portal hypertension. *Hepatology* 2008;47:1595-603.
27. Aoyama T, Oka S, Aikata H, et al. Is small-bowel capsule endoscopy effective for diagnosis of esophagogastric lesions related to portal hypertension? *J Gastroenterol Hepatol* 2014;29:511-6.
28. Lapalus MG, Ben Soussan E, Gaudric M, et al. Esophageal capsule endoscopy vs. EGD for the evaluation of portal hypertension: a French prospective multicenter comparative study. *Am J Gastroenterol* 2009;104:1112-8.
29. Chavalidhamrong D, Jensen DM, Singh B, et al. Capsule endoscopy is not as accurate as esophagogastroduodenoscopy in screening cirrhotic patients for varices. *Clin Gastroenterol Hepatol* 2012;10:254-8 e1.
30. Eisen GM, Eliakim R, Zaman A, et al. The accuracy of PillCam ESO capsule endoscopy versus conventional upper endoscopy for the diagnosis of esophageal varices: a prospective three-center pilot study. *Endoscopy* 2006;38:31-5.
31. Sacher-Huvelin S, Cales P, Bureau C, et al. Screening of esophageal varices by esophageal capsule endoscopy: results of a French multicenter prospective study. *Endoscopy* 2015;47:486-92.
32. Schreibman I, Meitz K, Kuselman AR, et al. Defining the threshold: new data on the ability of capsule endoscopy to discriminate the size of esophageal varices. *Dig Dis Sci* 2011;56:220-6.
33. Cardey J, Le Gall C, Michaud L, et al. Screening of esophageal varices in children using esophageal capsule endoscopy: a multicenter prospective study. *Endoscopy* 2019;51:10-7.
34. Ramirez FC, Shaukat MS, Young MA, et al. Feasibility and safety of string, wireless capsule endoscopy in the diagnosis of Barrett's esophagus. *Gastrointest Endosc* 2005;61:741-6.
35. Ramirez FC, Hakim S, Tharalson EM, et al. Feasibility and safety of string wireless capsule endoscopy in the diagnosis of esophageal varices. *Am J Gastroenterol* 2005;100:1065-71.
36. Stipho S, Tharalson E, Hakim S, et al. String capsule endoscopy for screening and surveillance of esophageal varices in patients with cirrhosis. *J Interv Gastroenterol* 2012;2:54-60.
37. Zou WB, Hou XH, Xin L, et al. Magnetic-controlled capsule endoscopy vs. gastroscopy for

gastric diseases: a two-center self-controlled comparative trial. *Endoscopy* 2015;47:525-8.

38. Liao Z, Hou X, Lin-Hu EQ, et al. Accuracy of Magnetically Controlled Capsule Endoscopy, Compared With Conventional Gastroscopy, in Detection of Gastric Diseases. *Clin Gastroenterol Hepatol* 2016;14:1266-73 e1.

39. Zhu SG, Qian YY, Tang XY, et al. Gastric preparation for magnetically controlled capsule endoscopy: A prospective, randomized single-blinded controlled trial. *Dig Liver Dis* 2018;50:42-7.

40. Ching H-L, Hale M, Sidhu R, et al. PTH-050 Robot magnet-controlled upper gi capsule endoscopy using the ankon navicam® system: first reported experience outside china. *Gut* 2017;66:A230-A.

41. Chen YZ, Pan J, Luo YY, et al. Detachable string magnetically controlled capsule endoscopy for complete viewing of the esophagus and stomach. *Endoscopy* 2019;51:360-4.

42. Song J, Bai T, Zhang L, et al. Better view by detachable string magnetically controlled capsule endoscopy for esophageal observation: a retrospective comparative study. *Dis Esophagus* 2020;33.

43. Jiang X, Qian YY, Liu X, et al. Impact of magnetic steering on gastric transit time of a capsule endoscopy (with video). *Gastrointest Endosc* 2018;88:746-54.

44. Luo YY, Pan J, Chen YZ, et al. Magnetic Steering of Capsule Endoscopy Improves Small Bowel Capsule Endoscopy Completion Rate. *Dig Dis Sci* 2019;64:1908-15.

45. Nemeth A, Wurm Johansson G, Nielsen J, et al. Capsule retention related to small bowel capsule endoscopy: a large European single-center 10-year clinical experience. *United European Gastroenterol J* 2017;5:677-86.

46. Jiang X, Pan J, Li ZS, Liao Z. Standardized examination procedure of magnetically controlled capsule endoscopy. *VideoGIE* 2019;4:239-43.

47. Wang YC, Pan J, Liu YW, et al. Adverse events of video capsule endoscopy over the past two decades: a systematic review and proportion meta-analysis. *BMC Gastroenterol* 2020;20:364.

48. Stafylidou M, Paschos P, Katsoula A, et al. Performance of Baveno VI and Expanded Baveno VI Criteria for Excluding High-Risk Varices in Patients With Chronic Liver Diseases: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2019;17:1744-55 e11.

49. de Franchis R. Updating consensus in portal hypertension: report of the Baveno III Consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol* 2000;33:846-52.

50. Henry Z, Patel K, Patton H, et al. AGA Clinical Practice Update on Management of Bleeding Gastric Varices: Expert Review. *Clin Gastroenterol Hepatol* 2021;19:1098-107 e1.

51. Primignani M, Carpinelli L, Preatoni P, et al. Natural history of portal hypertensive gastropathy in patients with liver cirrhosis. The New Italian Endoscopic Club for the study and treatment of esophageal varices (NIEC). *Gastroenterology* 2000;119:181-7.

52. De Palma GD, Rega M, Masone S, et al. Mucosal abnormalities of the small bowel in patients with cirrhosis and portal hypertension: a capsule endoscopy study. *Gastrointest Endosc* 2005;62:529-34.

53. Aoyama T, Oka S, Aikata H, et al. Major predictors of portal hypertensive enteropathy in patients with liver cirrhosis. *J Gastroenterol Hepatol* 2015;30:124-30.

54. Otani I, Oka S, Tanaka S, et al. Clinical significance of small-bowel villous edema in patients with liver cirrhosis: A capsule endoscopy study. *J Gastroenterol Hepatol* 2018;33:825-30.

55. Korevaar DA, Gopalakrishna G, Cohen JF, et al. Targeted test evaluation: a framework for designing diagnostic accuracy studies with clear study hypotheses. *Diagn Progn Res* 2019;3:22.

56. Wilson EB. Probable Inference, the Law of Succession and Statistical Inference. *Journal of the American Statistical Association* 1927;22:209-12.
57. Youden WJ. Youden WJIndex for rating diagnostic tests. *Cancer* 3(1): 32-35. *Cancer* 1950;3:32-5.