String capsule endoscopy for screening and surveillance of esophageal varices in patients with cirrhosis

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Abbreviations: EGD, esophagogastroduodenoscopy; SCE, string capsule endoscopy; NIEC, North Italian Endoscopy Club

Background: EGD is the gold standard for the screening and surveillance of esophageal varices. A less invasive, safer and sedationless alternative procedure is needed.

Objective: To assess the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) as well as the beyond the chance agreement (kappa index), of string capsule endoscopy (SCE) in the diagnosis of esophageal varices.

Methods: Cirrhotic patients underwent string capsule endoscopy (SCE) and EGD for screening and surveillance purposes. Varices were graded at EGD and SCE as small, medium and large. Descriptors at SCE were added as follows: PLUS, for the presence of red wale signs or, MINUS for their absence, irrespective of the estimated variceal size. Clinically significant varices were defined by their size (medium/large at either EGD or SCE) and/or, the PLUS descriptor irrespective of the estimated size at SCE. Sensitivity, specificity, PPV, NPV, accuracy and kappa index were calculated. Procedure time, procedure-related discomfort and patient's preference were documented.

Results: 100 patients (33 for screening and 67 for surveillance) were enrolled. The sensitivity and specificity of SCE for clinically significant varices when using the PLUS/MINUS descriptors were 82% and 90%, respectively with a PPV of 84% and NPV of 89% and a kappa of 0.73.

Conclusion: String capsule endoscopy had an acceptable sensitivity and specificity for the diagnosis of clinically significant esophageal varices but the lack of air insufflation still hampers its correlation with the grading used with EGD.

Introduction

The aim of screening and surveillance of esophageal varices in patients with cirrhosis is to identify those at increased risk for bleeding.¹ Bleeding from esophageal varices is the most common fatal complication of cirrhosis, a major cause of morbidity and, is associated with significant costs.^{2,3} The gold standard test to identify patients at risk for bleeding esophageal varices is esophagogastroduodenoscopy (EGD).¹ EGD however is not risk-free; it is mostly performed using moderate sedation increasing its risks by adding the effects of sedative drugs in the cirrhotic population and is also expensive because of its direct- and indirect-associated costs. Wireless capsule endoscopy, a non-invasive modality is an alternative for EGD. The major drawback of capsule endoscopy in the diagnosis of esophageal

varices is the lack of a validated grading system derived mainly from its inherent inability to use air insufflation to compare it with EGD. String capsule endoscopy (SCE), where a tethering device is attached to the video capsule, offers advantages over conventional capsule endoscopy in the esophagus such as the ability to: 1) be independent of esophageal transit time, 2) study the entire esophageal length multiple times, 3) eliminate the risk of capsule retention and, 4) reuse the device multiple times after high grade disinfection and/or sterilization. We have previously demonstrated the feasibility and safety of string capsule endoscopy in a group of 30 patients with known esophageal varices⁴. We present our experience with 100 additional consecutive patients with cirrhosis scheduled for undergoing screening and surveillance for esophageal varices (and thus unknown of their variceal status and without being part on any prior SCE study), to determine the sensitivity, specificity, positive- and negative-predictive values of SCE compared to the gold standard EGD.

Methods

Patients with clinically and/or biopsy-proven cirrhosis scheduled

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to undergo EGD for screening or surveillance purposes were asked to undergo SCE. The latter was performed for the most part on the same day and immediately preceding the EGD. This was an IRB-approved protocol. Patients signed an informed consent prior to SCE.

SCE was carried out by using the small bowel capsule endoscopy device (PillCam SB; Given Imaging Limited, Yoqneam, Israel) to which a tethering device consisting of a sleeve and strings was attached and swallowed with water in the sitting position, as described elsewhere.^{4,5} In short, upholstery threads were attached and tied up to a piece of plastic tubing that was then placed over the capsule without interfering with the front lens (**Fig. 1a, Fig. 1b**). This assembly is different from the original design (**Fig. 2a, Fig. 2b**) that wrapped 4 of the threads around the middle of the capsule, and then brought to the back of the capsule and tied up and did not use the plastic sleeve. At the completion of each procedure the entire device was retrieved from the patient's esophagus. The strings and sleeve were discarded, the capsule rinsed, manually cleansed with water and an enzymatic solution and placed in a 2% glutaraldehyde solution for 45 minutes for

high grade disinfection while a magnet turned the capsule's battery off. After disinfection, the capsule was thoroughly rinsed with water and alcohol and reused by applying a new set of strings/sleeve.

Each patient underwent evaluation of the discomfort associated with the procedure immediately after retrieving the capsule. This was performed in 5 different domains: difficulty for swallowing, throat discomfort associated with the strings, gagging triggered by the strings, discomfort associated with moving the capsule up/down and finally the discomfort associated with retrieving the capsule completely out. For patients undergoing surveillance (prior experience with EGD) they were asked about their preference between SCE and EGD immediately after SCE. Otherwise (patients undergoing EGD for the first time for screening purposes) they were contacted via telephone by a LPN at least 24 hours after the EGD.

The SCE grading system used in this study was based on 2 main parameters: 1) estimation of variceal size based on the occupancy of the radius of the endoscopic field as described by the North Italian Endoscopy Club (NIEC) for EGD⁶ (0=no varices; 1=small

Figure 1a and 1b: String Capsule Endoscopy Device: strings and sleeve in place

Figure 2a and 2b: Original string capsule endoscopy device (strings only; no sleeve)

Figure 3. Small varices with "red signs"

Figure 4. Small varices with "red signs"

Figure 5. Medium varices

Figure 6. Medium varices with "red signs"

Figure 7. Large varices

Figure 8. Large varices

and with an estimated size <1/3 of the radius; 2=medium, with an estimated size between 1/3 and 2/3 of the radius and, 3=large, with an estimated size >2/3 of the radius) and, 2) a PLUS/MINUS descriptor based on the SCE evaluator's assessment of whether red signs were present (PLUS) or absent (MINUS). These latter descriptors were independent of the evaluator's estimated size of varices (**Fig. 3-Fig. 8**). This grading system was then matched with the EGD findings and interventions taken by an experienced endoscopist performing the EGD and who was unaware of such descriptors. Grading of esophageal varices during EGD was based on the estimated variceal size using the NIEC system (0=no varices; I=small, II=medium and III=large). As a step further, varices were classified as clinically significant by size alone (grade 2-3 on SCE or, II-III on EGD) and/or the presence of a PLUS descriptor on any SCE-estimated size. An endoscopist (FCR) blinded to the EGD results assessed the video capsule recordings independently for presence/absence of varices and their grades. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) as well as accuracy were calculated. The beyond the chance agreement also known as the kappa (κ) index, between the SCE and the EGD (gold standard) grading scores was also calculated.^{7,8}

Results

A total of 100 patients with cirrhosis underwent both EGD and SCE. There were 99 men and 1 woman with a mean age of 55.9 years. Screening was the indication in 33 patients and surveillance in the remaining 67 patients. The etiology of cirrhosis was alcohol and chronic hepatitis C infection alone and/or in combination in 91 patients. The mean Child-Pugh score was 5.9 whereas the MELD score was 10.8 (**Table 1**).

The sensitivity and specificity of SCE for the presence of varices (of any size) was 84.1% and 72.2% when compared to EGD. The PPV, NPV and observed accuracy were 93.2%, 50.0% and 82%, respectively. The "kappa" index was 0.48. The sensitivity and specificity of SCE for the diagnosis of clinically significant esophageal varices was 82.1% and the specificity 90.2%. The PPV, NPV and observed accuracy were 84.2%, 88.7% and

87%, respectively. The "kappa" index was 0.73. These results are summarized in **Table 2**. There were 28 patients who had a PLUS descriptor (5 in screening, 23 in surveillance groups). Of these, 23 (82.1%) had a therapeutic intervention during and/or after the EGD without knowing the SCE readings.

We used a total of 4 capsules (21-24 studies/capsule) for the study. The tethering device remained in place in all cases, and no capsule was lost. The mean esophageal recording time (time elapsed from the moment the capsule entered into the esophagus for the first time to the moment it was out from the esophagus at the end of the procedure) was 281 seconds (4.7 minutes). The discomfort associated with the procedure is shown in **Table 3**.

When patients were asked regarding their preference between SCE and EGD if and when another endoscopy was needed, 71% indicated that they would prefer SCE over EGD. There were no differences among those preferring one method to the other in regards to age, etiology of cirrhosis or indication for the procedure (screening vs. surveillance). However, patients preferring EGD to SCE showed significantly more attempts to swallowing the device (25.9% vs. 6.8%; $p < 0.05$) defined as more than 1 attempt at placing the device in their mouth and, took longer to actually swallow it (65.9 ± 15.6 sec vs. 35.3 ± 3.5 sec; $p = 0.006$) defined as the interval elapsed between the first image of the esophagus and the first image of the mouth.

Discussion

Examination of the esophagus with wireless capsule endoscopy can be performed via esophageal capsule endoscopy (Pill Cam ESO) or, SCE. The main advantage of the latter is the ability of multiple passes across the esophagus and thus a better and detailed evaluation of any area of concern. The SCE device has been now used for the study of esophageal disorders including gastroesophageal reflux disease and screening of Barrett's esophagus,^{5,9-11} dysphagia¹² and, esophageal varices.^{4,13-16} We found in this study that SCE had a sensitivity of 84% and a specificity of 72% for the diagnosis of esophageal varices of any size when compared to the gold standard EGD. The sensitivity and specificity of SCE for clinically significant varices were 82%

Table 1. Demographic and Clinical characteristics

	Screening	Surveillance	Total
n	33	67	100
Mean age	55.2	56.7	55.9 years
Etiology			
ETOH	6	22	28
HCV	14	13	27
ETOH+HCV	10	26	36
NASH	2	1	3
HBV		2	2
HCV+HBV	1		1
Autoimmune		1	1
Cysticfibrosis		1	1
Cryptogenic		1	1
Mean MELD score	10	11.1	10.8
Mean Child-Pugh score	5.8	6.1	5.9

and 90% and a kappa index, of 0.73. Kappa values between 0.40 and 0.67 are considered of moderate to substantial agreement whereas values of 0.75 or higher are considered excellent.⁷

During EGD, esophageal varices are graded using air insufflation and avoiding assessment during peristalsis. Since no air insufflation is possible during wireless capsule endoscopy and due to its relatively weak illumination power, the best details are obtained when the capsule lens is close to the mucosa. Thus, any comparison between EGD and wireless capsule endoscopy regarding the variceal grade must be taken in the context of the above-mentioned limitations. To the present time there are no standardized/validated esophageal varices grading system for using with capsule endoscopy. In the published studies,^{4,13,14,16} the grading system used has been for the most part the same used for conventional EGD. Similar to the study by Lapalus et al.¹⁴ and in order to compensate for the lack of air insufflation, we took advantage of the potentially better identification of mucosal details ("red color signs") and incorporated it in the grading system. The PLUS/MINUS descriptors give the capsule endoscopist the ability of render an opinion as to whether treatment (either medical or endoscopic) may be needed and, classifying the varices as clinically significant avoiding thus missing an intervention in patients at higher risk for bleeding. The kappa index found when

using these descriptors was consistent with better than substantial and close to excellent agreement.

The two early studies reporting the utility of capsule endoscopy (PillCam ESO) in the diagnosis of esophageal varices although included relatively small number of patients, were encouraging since the concordance between capsule endoscopy and EGD was found to be 96.9%,¹³ and 84.2%¹⁴ and as with our study, the tolerability and patient's preference was in favor of capsule endoscopy when compared to the gold standard with or without sedation.¹⁴ A more recent multicenter study,¹⁵ involving 288 patients (195 for screening and 93 for surveillance) graded the variceal size as no varices, small and large varices based on whether or not they occupied <25% (small) or >25% (large) of the circumference of the capsule picture frame. The study reported an overall agreement for the detection of esophageal varices (85.8%) that was similar to the found in our study (82%). Likewise, sensitivity, specificity, positive- and negative predictive values, overall agreement and kappa values for medium/large varices were similar to those obtained for clinically significant varices in our study. The 78% sensitivity for detecting large varices using the estimated variceal size only in that study¹⁵ raised a major critique in the accompanying editorial¹⁷ for misdiagnosing patients with large varices. Although our sensitivity was slightly

Table 2. Sensitivity, specificity, positive- and negative- predictive values (PPV, NPV) and beyond chance agreement ("kappa index")

Presence versus Absence of Esophageal Varices				
	EGD Present	EGD Absent	Totals	
SCE Present	69	5	74	Sensitivity: 84.1%; PPV: 93.2%
SCE Absent	13	13	26	Specificity: 72.2%; NPV: 50%
Total	72	18	100	"kappa" index: 0.48
Clinically significant versus insignificant varices using the PLUS (+)/MINUS (-) option				
	EGD (II-III)	EGD (0-I)	Totals	
SCE (2-4 or any size with PLUS)	32	6	38	Sensitivity: 82.1%; PPV: 84.2%
SCE (0-I and with MINUS)	7	55	62	Specificity: 90.2%; NPV: 88.7%
Total	39	61	100	"kappa" index: 0.73

Table 3. Discomfort/difficulty scores associated with SCE

Score	0	1	2	3
Difficulty Swallowing (n)	37	38	20	4
Screening (n)	12	12	9	0
Surveillance (n)	25	26	11	4
Throat discomfort (n)	53	29	14	3
Screening (n)	21	8	4	0
Surveillance (n)	32	21	10	3
Gagging associated with strings (n)	52	26	15	6
Screening (n)	17	7	8	1
Surveillance (n)	35	19	7	5
Throat discomfort while moving string up/down (n)	56	30	10	3
Screening (n)	19	11	2	1
Surveillance (n)	37	19	8	2
Discomfort associated with pulling capsule out	33	36	25	5
Screening (n)	13	12	6	2
Surveillance (n)	20	24	19	3

Discomfort scores: 0 = no discomfort or difficulty; 1 = mild; 2 = moderate; 3 = severe

higher (82%) is still far from perfection. This drawback may be inherent to capsule endoscopy (due to lack of air insufflation), to a weakness of the gold standard itself (EGD) or, a combination of both. A significant variation in the agreement on the presence/absence and grading of esophageal varices using conventional EGD among a group of several endoscopists has been previously reported.¹⁸ Our study also compares favorably to a recent observational study where using a 25% lumen circumference for discriminating large/medium size varices by capsule endoscopy, was deemed unreliable with sensitivity, specificity, PPV and NPV of 23.5%, 88.2%, 66.7% and 53.6%, respectively.¹⁹

The steps to ensure a more accurate evaluation include: 1) once the capsule is swallowed, to let it pass across the esophago-gastric junction into the stomach; 2) to pull the capsule into the distal esophagus and slowly up into the upper esophagus (when felt against the resistance caused by the upper esophageal sphincter); 3) by swallowing small sips of water to repeat the process 3 times; 4) if the real time reader is used the area of interest can be assessed multiple times pulling and letting the capsule travel distally or, to remain in the area for a longer period of time. The real time reader allows cleaning the lens of any bubbles or secretions by allowing the patient to swallow water while maintaining the position of the capsule.

SCE in this study was well-tolerated and associated with no complications (capsule retention in particular). The most difficult parts of the study were swallowing and retrieving the device. The strings caused minimal or no discomfort at all in the majority and overall, it was well accepted over EGD. The a priori identification of patients who would prefer EGD to SCE seems to be possible since based on our results they have significantly more repeated attempts to swallow the device and take a significantly longer time to swallow it. The procedure time was short (less than 5 minutes) and thus rendering the procedure ideal for screening/surveillance programs. The introduction of real time capsule endoscopy however, will likely result in a significant decrease in procedure time.

The value of SCE also rests on the ability to study several (up

to 24 patients in this study) with the same small bowel capsule, rendering the device very likely to be cost-effective when used for large scale screening/surveillance programs²⁰ and in contrast to what has been currently described with conventional esophageal capsule endoscopy when used in the screening of Barrett's²¹⁻²² and esophageal varices.²³ The capsule device can be considered as a semi-critical device (Spaulding classification, widely accepted by the FDA) that is impermeable and has a smooth surface and as such, it could undergo high-grade disinfection. High-grade disinfection kills all vegetative organisms, mycobacteria, small or non lipid viruses, medium or lipid viruses, fungal spores and some but not all bacterial spores. Two important steps for the high grade disinfection include the manual (mechanical) cleaning of the device with enzymatic solutions (for eliminating biofilm) and the total immersion of the device in the high grade disinfecting solutions. 2% glutaraldehyde is one of such FDA-approved high-grade disinfectants that inactivate all microorganisms with the exception of high numbers of bacterial spores. In the US, guidelines recommend 20 min in 2% glutaraldehyde immersion that along with proper cleaning, completely eliminates HIV from endoscopes.²⁴⁻²⁹ Alternatively, since patients likely undergo repeated screening/surveillance procedures, the capsule can be used in the same patient (avoiding thus any potential for "cross contamination") on multiple occasions at different times. If the PillCam ESO however is used with the attached tethering device, given the short battery life and, if no reuse is intended, the strings could be cut once the diagnosis is established, and the device let pass through the GI tract as recommended when used without the tethering device. Preliminary experience in our unit indicates that a small caliber tube can be passed over the strings and used to both insufflate air and rinse with water at the endoscopist's demand (**Fig. 9**) and have a comparable mean to EGD to grade esophageal varices.

In conclusion, string capsule endoscopy had an acceptable sensitivity and specificity for the diagnosis of clinically significant esophageal varices. The grading system used with SCE although far from perfect (due to the lack of air insufflation) for screening and/or surveillance of esophageal varices, yielded significant agreement with EGD.

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Conflict of interest Statement

No conflict of interest by any of the authors listed,

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Figure 9. SCE over a small caliber feeding tube

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