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An observational cohort study of patients with chronic liver disease undergoing variceal screening and surveillance using capsule endoscopy

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Competing interests

Prof McAlindon has received capsule endoscopy from Ankon Ltd. for use in clinical research trials. No other authors have conflicts of interests.

Contributorship

Profs McAlindon, Sidhu and Dr Harrison devised the study with Dr Neill. Miss Shivakumar, Drs Neill and McKenzie collated the patient data. Dr McKenzie and Miss Shivakumar analysed the data. Prof McAlindon wrote the first draft of the manuscript and all were involved in writing the final draft, addressing the reviewers comments and composing the draft being resubmitted. Prof McAlindon is the guarantor.

Objectives

Rapid transit risks inadequate oesophageal capsule endoscopy. Success rate, completion of examination, time taken to read the video and impact on management of a novel dual camera capsule capable of 35 frames per second were determined.

Methods

Patients referred for screening or surveillance of oesophagogastric varices who declined gastroscopy and throughout the COVID pandemic were examined by capsule endoscopy using the PillcamTM UGI capsule.

Results

Capsule endoscopy was performed on 207 patients (median (IQR) age 62 (±18), 53% male). The median reading time was 4 (± 2) minutes. Oesophageal views were complete in 205 (99%); no views were obtained in 2 (1%) patients. Cardiac views were complete in 197(86.5%), partial in 11(5.3%), and not seen in 17(8.21%). Fundal views were complete in 108 (52.2%), partial in 27 (13%), and not seen in 72 (34.8%). Oesophagogastric varices were detected in 58 (28%) patients, mostly (55 (94.2%)) oesophageal varices (38 (66%) grade 1). Overall, 23 (11.1%) patients required further management on the basis of capsule endoscopy findings and gastroscopy was avoided in 194 (94%) of patients. During a median follow up period of 24 months (± 19), 2 patients were successfully treated for variceal bleeding. Capsule retention required endoscopic retrieval in one patient (0.5%).

Conclusions

A dual camera capsule endoscope capturing 35 frames per second provided excellent oesophageal views, avoided gastroscopy in the majority of patients and effectively and safely guided management.

What is already known on this topic

A double camera capsule endoscope capturing 14 images per second high image capture rate has proven to be modestly successful in identifying oesophageal pathology.

What this study adds

A double camera capsule endoscope capturing 35 images per second provided extremely reliable oesophageal imaging, saved most patients with suspected oesophagogastric varices from having conventional endoscopy and guided management safely with excellent short term outcomes.

How this study might affect research, practice or policy

Clinical trials comparing conventional endoscopy with high frame capture rate, double camera capsule endoscopes are warranted.

Introduction

Capsule endoscopy is preferred to fibreoptic endoscopy by patients and does not incur the risks of intubation or sedation. [1] First developed to examine the small bowel, a high frame rate capsule with cameras at both ends was developed for use in the colon. [2] Meta-analyses of studies of a similar double ended capsule capturing 14 frames per second found a pooled sensitivity and specificity of 79.7% (95% CI, 73.1-85%) and 90.5% (95% CI, 84.1-94.4%), respectively, for the detection of large varices. [1] The final iteration, the Pillcam™ UGI (Medtronic Ltd., Minneapolis, USA) acquired 35 frames per second with cameras at both ends providing simultaneous antegrade and retrograde viewing. [3] This device has not been studied in clinical trials of patients with liver disease.

Oesophageal varices are present in 30% of patients at diagnosis of cirrhosis, with a first episode of bleeding occurring in 12% per annum, each episode carrying a 15-20% mortality rate. Targeted pharmacological or endoscopic therapy reduces the risk of bleeding and mortality by 50%. [1,4] However, compliance with screening programmes may be as little as 30%, partly due to clinician concern about safety of endoscopy in patients with significant co-morbidities [4] but probably also due to patient anxiety about an invasive test. [5]

During the COVID-19 pandemic, routine endoscopy was suspended to minimise the risks of spreading infection during aerosol-generating procedures. To mitigate the risks of bleeding from undetected and untreated varices, and as part of a nationwide initiative to explore alternatives, [6] patients with chronic liver disease were offered

screening and surveillance using Pillcam^{TM} UGI capsule endoscopy (Medtronic Ltd, Dublin, Ireland).

Aims

This study aimed to determine the success rate and completeness of oesophageal examination using the Pillcam^{TM} UGI, assess the time taken to read a video, document the prevalence and size of varices detected and determine the outcomes regarding impact on management and subsequent bleeding episodes.

Methods

Capsule endoscopy

Patients referred for variceal screening or surveillance in Sheffield Teaching Hospitals NHS Foundation Trust were offered Pillcam^{TM} UGI capsule endoscopy. This included all patients referred during the COVID-19 pandemic and some patients prior to this who refused to have fibreoptic oesophagogastroduodenosopy (OGD) based on Baveno VI criteria (platelet count $<150x10^9$/L or liver stiffness measurement ≥20kPa). [7] Patients with dysphagia and those at risk of gastrointestinal strictures (due to Crohn's disease, previous radiation therapy or long term use of non-steroidal anti-inflammatory drugs) were excluded. A data recorder featuring a live image monitor was connected to sensor leads attached to the patient's chest. [3] Patients drank one litre of water containing 80mg simethicone to cleanse and distend the stomach. The capsule was swallowed in the left lateral position (with the patient leaning on their elbow if necessary) with water sipped

through a straw. Once the stomach was identified on the monitor, the patient was asked to lie supine for two minutes followed by the right lateral position for a further two minutes before the equipment was removed and the data downloaded onto the computer system prior to video reading by a single expert gastroenterologist.

Capsule endoscopy video reading and reporting

Each video reading was timed. Views of the oesophagus, cardia and fundus were graded as complete, partial or none. Oesophageal and gastric varices were described and graded (0: no varices; 1: small straight varices; 2: enlarged, tortuous varices occupying less than one third of the lumen; 3: large, coil shaped varices occupying more than one third of the lumen) [8] and the presence of red wale signs and portal hypertensive gastropathy documented.

Outcomes

Outcomes were assessed retrospectively by reviewing patient records.

Statistical analysis

Statistical analysis was supported by the Statistics Clinic at Sheffield Teaching Hospitals Research Department. SPSS Statistics for Macintosh, Version 28.0 (IBM Corp, Armonk, New York, USA) was used to calculate descriptive statistics, mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for continuous data without normal distribution and number (N) and percentage for categorical variables. Data normality for the above was assessed through visual inspection of histograms created using SPSS statistics

for Macintosh and the Shapiro-Wilk test was applied to statistically evaluate the normality of continuous data. 95% confidence intervals were worked out for all estimated parameters using SPSS Statistics for Macintosh, Version 29.0 (IBM Corp, Armonk, New York, USA). Sensitivity, specificity, positive and negative predictive values were calculated and logistic regression carried out using SPSS Statistics for Macintosh Version 29.0 (IBM Corp, Armonk, New York, USA). This analysis was chosen because the outcome variables were binary (presence or absence of varices). The logistic regression model included predictor variables that were identified as potentially significant based on clinical relevance (fibroscan score and platelet count). Hosmer-Lemeshow goodness-of-fit test was used to assess the fit of the logistic regression model.

Ethics approval and data collection

Ethics approval was obtained from the University of Sheffield (registration number 051067). Investigators accessed databases containing personalised data on password protected computers in a locked office.

Results

Patients

Capsule endoscopy was performed on 207 patients (median (IQR) age 62 (±18), 53% male) between 2014 and 2023, 55 prior to, and 152 during, the COVID-19 pandemic and who were followed up for 24 months (± 19). Patients had metabolic

dysfunction-associated steatotic liver disease (n=74 (35.7%)), alcoholic liver disease (56 (27.1%)) and chronic viral hepatitis hepatitis (28 (13.5%)), the remainder having mixed alcoholic and metabolic-dysfunction associated steatotic liver disease, portal vein thrombosis, primary biliary cholangitis, biliary atresia, hereditary hemochromatosis, alpha-1 antitrypsin deficiency and mitochondrial depletion syndrome. Child-Pugh scores were A in 88.4%, B in 10.6%, C in 1.0% and 9.2% had decompensated advanced chronic liver disease.

Capsule endoscopy reading and reporting

The median (IQR) reading time was 4 minutes (±2 minutes). Median transit time was 7 seconds (±10 seconds). Complete views were obtained in the oesophagus in 205 (99%; 95% CI 97.7%-100%) patients, in the cardia in 197 (86.5%; 95%CI: 95% 81.9%-91.1%) and in the fundus in 108 (52.2%; 95% CI 45.4%-59.0%; figure 1).

Oesophageal or gastric varices were detected in 58 (28%; 95% CI 22.0%-34.0%) patients, 8 (3.9%; 95% CI 1.3%-6.5%) had red wale signs and 29 (14%; 95% CI 9.2%-18.8%) had portal hypertensive gastropathy. Most (55 (94.2%)) were oesophageal varices (38 (66%; 95% CI 53.8%-78.1%)) grade 1, 14 (24%; 95% CI: 13.7%-37.3%) grade 2 and 3 (5%; 95% CI 0%-11.4%) and gastric varices (all grade 1) were detected in 3 (5%; 95% CI 0.0%-10.6%) patients.

The Baveno VI criteria had a sensitivity, specificity, positive and negative predictive value of 93%, 81%, 94%, 80% respectively in predicting the presence of any varices.

Logistic regression analysis showed that a liver stiffness measurement by transient elastography of over 20kPa predicted the presence of varices (odds ratio 3.3; P= 0.007) but not thrombocytopaenia (platelets < $150x10^9$/L; P=0.9). The Hosmer-Lemeshow test indicated a good logistic regression model fit (P = 0.231).

Impact of capsule endoscopy on immediate management

Overall, 23 (11.1%; 95% CI 6.9%-15.4%) patients required further management on the basis of capsule endoscopy findings and OGD was avoided in 194 (94%; 95% CI 90.4%-97.0%) Of the 58 patients with varices, management was changed in 16 (28%; 95% CI 16.1%-39.1%) on the basis of the capsule endoscopy report (figure 2).

Of those who required OGD, grade 2 oesophageal varices were identified in 4 patients (2 patients each had grade 1 and 2 oesophageal varices, all with red wale signs, identified on capsule endoscopy) and were treated with β blockers and one had variceal band ligation for grade 3 oesophageal varices (capsule endoscopy had reported grade 2 oesophageal varices and grade 1 gastric varices). One patient had no treatment as grade 2 varices identified on capsule endoscopy were not confirmed at OGD (figure 3).

Of the 149 patients who had no varices, seven (5%; 95% CI 1.3-81%) had different pathologies requiring further management (an eighth patient with an oesophageal stricture required capsule retrieval). OGD was advised in five patients to assess polypoid lesions: in three, no lesion was seen; one patient declined and one did not tolerate OGD and had a further capsule study which showed a bleeding polyp and portal hypertensive gastropathy which was treated with β blockers. Acid suppression

therapy was prescribed for a patient with oesophagitis and anticoagulation in another with atrial fibrillation following the exclusion of varices.

Impact of investigation and treatment on longer term outcomes

There were 11 deaths during follow up. One patient died of hepatocellular carcinoma and five with end-stage cirrhosis and multiorgan failure, two of whom also had bleeding as pre-terminal events (one patient had oesophageal varices banded eight days earlier and the other best supportive care only). One patient each died of pancreatic cancer, biliary sepsis and respiratory failure. Details of the deaths of two patients were not retrievable.

Two patients (1.0% of the whole cohort; 3.4% of those with varices) were admitted with acute GI bleeding during the follow up period: capsule endoscopy had shown grade 1 varices without red wale signs in one patient who bled 12 months later from grade 2 varices with red spots. (figure 4) Another patient whose capsule endoscopy was normal presented four years later with bleeding due to grade 2 varices. Neither patient had other endoscopic investigations performed between the capsule endoscopy and the bleeding episode and both survived after variceal band ligation.

Complications

OGD was performed in one patient (0.5%) to retrieve a capsule retained proximal to a post-variceal banding stricture. There was a capsule endoscopy technical failure in one patient.

Discussion

Capsule endoscopy visualised the oesophagus in almost all patients, avoided the need for OGD in 94% as although 28% had oesophagogastric varices identified, most were small and a change in management was only needed in 11.1% of the whole cohort. The procedure was safe, with only one patient (0.5%) requiring capsule retrieval from proximal to a post-banding stricture and two patients requiring treatment for bleeding one and four years after their procedure.

Capsule endoscopy is much better tolerated than OGD, patients are more likely to comply and encourage others to do so. [9] It offers a useful alternative for patients who decline or are not fit for conventional endoscopy, obviates the need for clotting factors or fibrinolytics in patients with bleeding disorders who need investigation [10] and can be swallowed by children as young as four years old, avoiding the need for general anaesthesia. [11] Although using a different upper GI capsule, we previously found that the cost was twice that of OGD. [12] However, the analysis did not include the cost of training the practitioners and the cost differential is likely to improve as the technology becomes more widely used and competition is introduced into the market.

Systematic reviews and meta-analyses concluded that capsule endoscopy was not a reliable alternative to OGD. [1,13] However, the majority of the studies analysed used the PillCam ESO, which captured only four frames per second, although the only one investigating the PillCam ESO2, which images at 14 frames per second, did not demonstrate an obvious improvement. [14] As capsule oesophageal transit can

be as fast as 20cm per second, it is unsurprising that pathology might be missed. The median transit time of the UGI capsule (capturing 35 frames per second) of seven seconds equates to 235 oesophageal images, compared to 98 images if the PillCam ESO2 was used or 28 images using the PillCam ESO. Indeed, an observer-blinded study by Koslowsky et al. in 2006 showed that the PillCam ESO2 had a 100% sensitivity in the detection of oesophageal pathology compared to the PillCam ESO, which had a sensitivity of 82% (P<0.02). [15] This is consistent with our previous findings that the UGI capsule visualised the whole Z line in 92.5% of cases, [3] compared to at least 75% visualisation of the same in only 82% of patients using the PillCam ESO2. [16]

Recent studies using a detachable tether, or string, to slow transit of a swallowed capsule showed 97.6% concordance in the detection of oesophagogastric varices by OGD and string capsule endoscopy, with sensitivities and specificities of capsule endoscopy of 97.5% and 97.8% respectively. [17,18] However, the presence of the string may make swallowing more uncomfortable or difficult and even increase the risk of capsule inhalation. [19] The UGI capsule is no longer commercially available, but our experience supports the development of a device with a high frame capture rate to provide a comprehensive oesophageal examination without the need for a string to slow transit.

Although OGD is the accepted gold standard with which to compare capsule endoscopy, there is significant interobserver variation in the OGD grading of varices between endoscopists, Bendtsen et al., calculating a κ value of only 0.38 for the

agreement of the presence (grades 1-3) or absence (grade 0) of varices and 0.52 for the discrimination of small (grade 1) from medium and large (grades 2-3) varices. [20] This could be relevant in the discrepancies in variceal assessment between capsule endoscopy and OGD described in this series. Future studies would benefit from including a second OGD examination (perhaps using blinded reporting of OGD recordings) to determine the role of interobserver variation in identifying and grading pathology when studying comparisons with capsule endoscopy. Adopting this approach in a controlled trial comparing novel capsules with OGD as the gold standard would establish the diagnostic sensitivity, specificity, positive and negative predictive values and accuracy of the new technology and address the limitations of this observational cohort study.

The frequency of bleeding from small varices over two years is 5-18%, [1] somewhat higher than the 3.4% bleeding rate (6.8% if the two patients with bleeding as pre-terminal events are included) reported in this study. However, the presence of varices in only 28% of patients seems low compared to the reported rates of almost 30-50% in patients with new diagnoses of cirrhosis [1,4], suggesting that this might be a select, relatively low risk cohort. Even if so, it is clear that clinicians can offer capsule endoscopy as a safe and non-invasive option to the appropriate patients.

Grading of varices has not been validated for capsule endoscopy which, therefore, is not considered in Baveno consensus documents. [7] However, we used the Snady and Heinman grading system which does not rely on insufflation [8] and the recent multicentre studies showing that diagnostic sensitivity of string capsule endoscopy

approached that of OGD also assessed variceal size (large or small) alone. [17,18] Further studies are needed, but grading varices based on size may be a reasonable approach which circumvents the use of systems which assess response to insufflation.

The Baveno VII criteria suggest that patients with liver stiffness measurement of over 20kPa or those with a platelet count of less than $150x10^9$/L only need screening OGD if they are not suitable for treatment with β blockers [11], the recent guideline from the National Institute of Health and Care Excellence recommending a similar approach. [21] This means that fewer screening procedures will be needed than previously. Nonetheless, capsule endoscopy may be a useful alternative for patients who decline OGD pending further research into its potential role.

Although isolated fundal varices are rare, these might be missed in up to half the patients in whom fundal views were incomplete using this protocol, a limitation of this tool which may have been inappropriately denied OGD to some patients. However, magnetically controlled movement of the Navicam (AnX Robotica, Texas, USA) in the water-filled stomach visualised the fundus in 96% of cases, although being a single camera capsule acquiring six frames per second meant that oesophageal views were less reliable. [22] It seems likely that a combination of high frame rate and a double camera capsule which can be magnetically navigated around the stomach is achievable and could provide a comprehensive examination of the upper GI tract in the near future.

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Figure 1. Views of oesophagus, cardia and fundus described as complete, partial or not obtained.

Figure 2. Impact on management of capsule endoscopy showing patients who avoided (dotted boxes), were offered (boxes in bold) OGD and those whose management was changed without OGD (dashed boxes).

Figure 3. Grade 2 varix identified by capsule endoscopy (two left images): vein reported at OGD but not considered to be a varix (right image).

Figure 4. Patient with grade 1 varices identified on capsule endoscopy (upper images) who bled 12 months later and had band ligation of grade 2 varices (lower images).