Title: Diagnosis of Barrett's esophagus and Esophageal Varices using a Magnetically Assisted Capsule Endoscopy system

Authorship: Sabina Beg[1,2], Tim Card[1,2,3], Samantha Warburton[1,2], Imdadur Rahman[4], Emilie Wilkes[1,2], Jonathan White[1,2], Krish Ragunath[1,2]

Affiliations:

[1] NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, United Kingdom

[2]Nottingham Digestive Diseases Centre, The University of Nottingham, Nottingham, UK

[3] Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom

[4] University Hospital Southampton NHS trust, Southampton, UK.

Correspondence author: Professor Krish Ragunath, Nottingham Digestive Disease Centre, Queens Medical Centre campus, Nottingham University Hospitals NHS Trust, Derby Road, NG7 2UH, United Kingdom. K.Ragunath@nottingham.ac.uk

Specific author contributions:

SB: Designed study, performed MACE procedures, collected and analysed data.

TC: Participated in intra-observer readings, designed and over saw study.

SW: Participated in study design, patient recruitment and coordination.

IR: Participated in intra-observer readings and study design.

JW: Participated in intra-observer readings and performed endoscopic procedures.

EW: Participated in intra-observer readings and performed endoscopic procedures.

KR: Participated in intra-observer readings, designed and oversaw study.

All authors reviewed the final manuscript

Financial support: None. Potential competing interests: None.

Keywords: capsule endoscopy, Barrett's esophagus, Esophageal Varices

Abstract

Background

Magnetically Assisted Capsule Endoscopy (MACE) potentially offers a comfortable, patient friendly and community-based alternative to gastroscopy (EGD). This pilot study aims to explore whether this approach can be used to accurately diagnose Barrett's oesophagus and esophageal varices.

Methods

The MiroCam Navi capsule system was used to examine the upper gastrointestinal tract in patients due to undergo a clinically indicated EGD. A total of 50 participants were enrolled, of which 34 had known pathology, 17 Barrett's Esophagus (BE), 17 Esophageal Varices (EV), with 16 controls. Patients underwent the MACE procedure, with the operator blinded to the indication and any previous endoscopic diagnoses. The subsequent EGD was performed by an endoscopist blinded to the MACE findings. Diagnostic yield, comfort and patient preference between the two modalities were compared.

Results

Participants had a mean age of 61 years old, a M: F of 2.1:1, a mean BMI of 29.5, with an average chest measurement of 105.3cms. 47 patients undertook both procedures, 3 patients were unable to swallow the capsule. With the use of the magnet, it was possible to hold the capsule within the esophagus for a mean duration of 190 secs and up to a maximum of 634

secs. A correct real-time MACE diagnosis was made in 11/15 patients with EV (sensitivity 73.3% (44.9- 92.2%) and specificity 100% (89.1- 100%) and 15/16 patients with BE (sensitivity 93.8% (69.8- 99.8%) and a specificity of 100% (88.8- 100%). MACE was considered more comfortable than conventional endoscopy ($p<0.0001$) with a mean score of 9.2 with MACE compared to 6.7 with EGD, when assessed on a 10-point scale. No MACE or EGD related adverse events occurred.

Conclusion

This pilot study demonstrates that MACE is both safe and well tolerated by patients. Accuracy for the diagnosis of BE was high and may therefore have a role in screening for this condition.

Introduction

Esophago-Gastro-Duodenoscopy (EGD) has become the 'Gold Standard' investigation of the Upper Gastro Intestinal (UGI) tract, allowing for direct mucosal inspection and where required therapeutic intervention. This is not without drawbacks, endoscopy is often regarded poorly amongst patients, with this test perceived as both invasive and uncomfortable (1,2). This diagnostic modality is resource intensive, requiring the use of a staffed and equipped endoscopy unit, as well as recovery facilities to enable the use of sedation. Growing demand and increasing strain on endoscopy departments, means that the development of a technique which takes procedures outside of the endoscopy department is an attractive proposition (3).

Capsule endoscopy offers a comfortable and minimally invasive alternative to conventional endoscopy (4,5). The use of this technology beyond the small bowel is emerging (6). Examination of the UGI tract has thus far been limited by the rapid transit through the esophagus and the passive, undirected passage through the capacious stomach. With the use of a magnet within the capsule casing and an external magnet to manipulate movement, it is possible to overcome some of these obstacles to enable complete examination of the UGI tract.

The MiroCam Navi, Magnetically Assisted Capsule Endoscopy (MACE) system (Intromedic, Soeul, South Korea) consists of a magnetic capsule which is steered using an external hand-held magnet, allowing for portability (Figure 1). To date experimental studies have demonstrated non-inferiority compared to EGD in identifying markers within an ex-vivo porcine stomach as well as demonstrating visualization of the major UGI landmarks within healthy volunteers (7,8). In this study we aim to determine the accuracy of MACE in the

diagnosis of esophageal lesions. Secondary outcomes included patient comfort and preference, transit time and visualization of UGI landmarks.

Methods

Study design

This was a prospective single blinded, diagnostic cohort study, performed at Nottingham University Hospital, following approval from the local Research and Innovation department (Ref: 16GA006). All procedures were performed between July 2016 and September 2017. Approval to conduct this study was obtained from the East Midlands Research Ethics Committee (Ref: 16/EM/0089) and prospectively registered on clinicaltrails.gov (Ref: NCT02852161).

Sample size calculation

To date studies concerning the use of MACE have focused on proof of concept, with limited information on diagnostic accuracy for lesions in the UGI tract. Accurate power calculations are therefore not possible at this time. This study has been designed as a feasibility study, which will then inform power calculations for future trials.

For an observed sensitivity of 100%, a minimum of 17 patients were required in order to be able obtain confidence intervals that exclude a sensitivity below 80%. We therefore aimed to recruit 17 patients undergoing EGD for Barrett's Esophagus surveillance (BE), 17 for Esophageal Varices surveillance (EV) and to ensure a realistic diagnostic assessment, 16 controls without known esophageal lesions who were scheduled to undergo a clinically

indicated EGD. Based on available imaging modalities a sensitivity of more that 80% for the detection of eith BE or EV would suggest that MACE may have a role in diagnosis.

Patient selection

Patients who were scheduled to undergo an EGD as part of the surveillance of known BE or EV were invited to participate in this study as cases. Those undergoing a clinically indicated EGD for the investigation of UGI symptoms were invited to participate as controls. Patients who satisfied the eligibility criteria were approached by the study coordinator, with the MACE operator blinded to the indication for the endoscopy or any previous results. Patients who had an implanted electronic or magnetic devices, were unable or unwilling to swallow the capsule or those with known dysphagia or obstructive bowel pathology were excluded from participation. Written informed consent was obtained from all participants.

Interventions

Both diagnostic tests were undertaken on the same day, by two independent operators blinded to the findings of the other modality. The MACE procedure was performed first, to avoid any artefact caused by scope trauma or biopsy acquisition during the EGD.

Magnetically-assisted capsule endoscopy (MACE)

The procedures were performed by a single endoscopist (SB) with experience in both the MACE procedure as well as conventional UGI endoscopy. As per standard pre-endoscopy preparation, patients underwent a 6-hour fast. Upon attendance for their procedure participants were instructed to consume approximately 1 litre of a solution consisting of water with six drops of simethicone (Infacol, Teva UK Ltd). Sensing pads were placed across

the chest to enable the transmission of images from the capsule. Once lying supine, with the head raised at a 10-degree angle, the patient was instructed to place the capsule in the mouth, and then to swallow the tablet alongside water sipped through a straw. This reclined position was adopted to optimise the capsule transit time through the esophagus. The hand-held magnet was held above the sternum in order to catch the capsule within the esophagus. Real time images were viewed using a tablet equipped with proprietary MiroCam software. Changes in patient posture and placement of the handheld magnet were used to manipulate the capsule in order to enable examination of the esophagus and stomach, as described in previous studies (7). The capsule was held in the esophagus for as long as possible, successful oesophageal capture was defined as a transit time greater than 30 seconds, double the median transit of a non- magnetic capsule swallowed whilst recumbent (REF). Once adequate images of the had been obtained of the upper GI tract or the maximum examination time of 20 minutes had been reached, the capsule was released in the region of the pylorus and allowed to pass into the small bowel. Any abnormalities detected during the real time examination were documented on a Clinical Record Form (CRF) contemporaneously. The quality of views obtained at each of the major land marks was assessed by the operator using a 5-point scale (where 0 denotes the landmark was not visualised and 4 denotes complete views obtained (Appendix 1). A period of at least one hour was given between undergoing the MACE and EGD, in order to allow the intra-gastric volume of water to reach its resting volume of 35mls (9). The capsule sensing device was removed following completion of both the MACE and EGD procedures, with the capsule left to passively transit through the GI tract. As such recordings of the capsule reaching the caecum were not obtained. Where the patient had not visually identified excretion of the capsule by two weeks post procedure an xray was performed to exclude retention.

Esophago-Gastro-Duodenoscopy (EGD)

EGDs were performed by experienced endoscopists, certified for independent practice. These practitioners were aware of any findings from previous endoscopies and the indication for the procedure, but not the findings of the prior MACE procedure. The EGDs were performed using standard techniques, with no biopsies or interventions specifically performed as part of this study. Patients had the option of pharyngeal anaesthesia or intravenous sedation, with the requirement for post procedure recovery determined by this choice. Findings were ascertained by the performing endoscopist at the time of the procedure and documented on a CRF. The quality of views obtained at each of the major land marks was assessed by the operator.

Questionnaires

A series of patient comfort and anxiety questionnaires were completed throughout the course of this intervention. These were carried out prior to any intervention, following the MACE procedure, following the EGD and finally two weeks following participation. Patients were provided with a prepaid addressed envelope in order to return the two-week questionnaire. Where questionnaires were not returned, the study coordinator contacted the patient by phone as a reminder within three weeks. The questionnaires included a visual analogue scale to assess overall procedure tolerability (0- 10 scale, where 10 denotes the best possible experience), with separate scores recorded for specific symptoms, including gagging, choking or pain incurred.

Image review and inter-observer agreement

Recordings of both the MACE and EGD procedures were taken with patient permission. Anonymised endoscopic images were reviewed without clinical information by five endoscopists, to establish whether diagnoses could be accurately determined post procedure. The real time diagnosis made at EGD was considered to be the gold standard for comparison. Video clips were edited to include the esophageal images only, with any interventions or enhanced imaging techniques (such as the use of Narrow Band Imaging) performed during the EGD edited out to render the images comparable with those obtained during the MACE procedure.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism, Version 7 and Stata Version 15. A p-value of less than 0.05 was considered statistically significant. Normally distributed data were compared using paired t-tests, while non-normally distributed data were compared using Wilcoxon signed rank test. We examined the ralationships of esophageal transit time to factors which might influence it via spearman's rank correlation for continuous variables and Kruskal Wallis test for non-continuous variables. Proportions were compared using Chi Squared test. Sensitivity and specificity of diagnoses made by MACE were calculated based on EGD diagnosis being the gold standard. The intra-observer agreement in the recorded EGD and MACE images was determined using method of (Fleiss, Levin, and Paik 2003,p 615) to asses kappa for more than two ratings, with a constant number of raters as applied in Stata.

Results

Baseline characteristics

50 patients were recruited into the study, of which 47 (94%) completed the MACE procedure and 50 (100%) completed the EGD. As per the recruitment criteria these were composed of patients with endoscopically diagnosed BE (17), EV (17) and patients with neither BE or EV (16). In those with EV endoscopy graded these as large in 100% of cases, whilst in those with BE the average Barrett's segment legnth was 3 cms (2-5), with 22 patients diagnosed with a hiatus hernia. The recruitment process and baseline characteristics of the study cohort are summarised below (Table 1 and Figure 2).

Table 1. The baseline characteristics of study participants

Data presented as number (%) or mean (+/- SD) or median (IQR)

Characteristic		Number or mean (range)
Gender distribution	Male	34
	Female	16
Age (years)		60.5 (39-83)
Body Mass Index		29.5
Dimensions (cms)	Chest	104 (86-127)
	Waist	105 (63- 133)
	Hip	103 (92- 141)
Indication for procedure	Variceal surveillance	17
	Variceal screening	1
	Barrett's surveillance	18*
	Gastro-Intestinal bleeding	3
	Dyspepsia / pain	7
	UGI surveillance	4
Number of previous of EGDs (for any indication)		2.5 (0 - 12)

*One patient who was recruited in the Barrett's group did not have Barrett's on EGD and was therefore moved to the control group for the purpose of analysis.

Feasibility

All 50 patients were able to undertake the EGD. It was however noted that 45% opted to have sedation, with a median dose of 3mg of midazolam and 50mg of pethidine administered. Of the 50 patients recruited, three patients were unable to undertake the MACE procedure. In all cases this was due to being unable to swallow the capsule whilst supine, despite having no known swallowing disorders. All three managed to tolerate their EGD with the use of sedation in tw of these patients.

Tolerance and patient preference

The MACE procedure rated more favourably than EGD for all comfort related domains. The mean VAS associated with MACE was 9.4, compared to 6.6 with EGD ($P<0.0001$). This trend persisted even when the use of sedation prior to EGD was taken in to account (Table 2). Further, MACE was considered more comfortable for each of the specific symptoms recorded, gagging, choking and discomfort. Participants who completed the two-week questionnaire (37 of 47 participants) preferred to undergo the MACE procedure, should they require a further procedure (73% vs 0%).

Table 2. Comfort and tolerability of procedures

Expressed as median and Interquartile Range or Mean and Standard Deviation

		MACE	EGD	P Value
Specific symptoms	Gagging/retching	10 (IQR 4.0-10)	4 (IQR 1.0- 6.2)	0.0001
	Choking	10 (IQR 10-10)	6 (IQR 0.8-10)	<0.0001
	Discomfort	10 (IQR 10-10)	5 (IQR 1.0-7.0)	<0.0001
Visual Analogue Scale	All patients (n=50)	9.2 (SD +/-1.6)	6.7 (SD +/- 2.6)	<0.0001
	Sedated cohort (n=33)	9.4 (SD +/- 1.1)	6.6 (SD +/- 2.6)	<0.0001
	Unsedated Cohort (n=17)	8.7 (SD +/- 2.3)	7.0 (SD +/- 2.3)	0.0183
Preference	Preferred procedure at 2 weeks	27/37	0/37	

Capsule manipulation within the esophagus

Of the 47 patients who successfully swallowed the capsule, the esophagus was visualised in all cases. Control of the capsule was variable, with a mean esophageal transit time of 190secs, (range: 5secs- 634secs). The capsule was held within the esophagus for 30 seconds or more in 68% (n=32). It was not possible to identify any operator or patient factors which influenced esophageal transit time (Table 3). There was a non-significant trend towards increased transit

time in association with increased operator experience as the study progressed, R=0.13 (CI -0.17- 0.41) p=0.39.

Table 3. Regression model examining factors with the potential to influence esopahegal transit time

		Observations	**Rank sum**	**P-Value**
Gender	Male	31	791.50	
	Female	16	336.50	0.29
Condition	Barrett's	16	369.50	
	Varices	15	364.00	
	Controls	16	394.50	0.95
	Correlation coefficient	**P- Value**		
Age	-0.09	0.55		
BMI	-0.09	0.55		
Chest Circumference	-0.13	0.40		
Case order	0.13	0.39		

Capsule manipulation within the stomach

Complete visualisation of the stomach was attempted through a combination of position changes and use of the hand-held magnet. As demonstrated in previous studies, the fundus remains a potential blind spot during the MACE procedure, with EGD quality of views significantly superior (Table 4). This study was not powered to calculate the ability to detect

gastric pathology, however 2 lesions seen on EGD were not seen on MACE, whilst 1 lesion was missed by EGD.

Table 4. The quality of endoscopic view at the major landmarks

		MACE	EGD	P Value	95% Confidence Interval
Visualization Proportion with poor views (score <3)	Esophagus	3/47	0/50	P = 0.0803	-2.18 - 16.65
	z- line	8/47	0/50	P = 0.0013	7.75 - 32.38
	Fundus	12/47	0/50	P = 0.0001	13.41 - 40.01
	Body	5/47	0/50	P = 0.0165	1.58 - 23.04
	Antrum	3/47	0/50	P = 0.0803	-2.18 - 16.65

Capsule manipulation into the duodenum

The magnet could not be used to transfer the capsule from the stomach into the duodenum. When the MACE examination was complete, the capsule was placed within close proximity of the pylorus, but it was not possible to overcome pyloric contractions in order traverse the pylorus. For logistical reasons the sensing equipment had to be removed early in 4 cases, the capsule was left to transit through the small bowel, but was not observed to transit in to the duodenum during the shorter recording. Amongst the 43 cases where the duodenum was entered during recording, a mean gastric transit time of 35 mins (range: 2 mins- 2 hours 17 mins) was observed. This is consistent with a previous study, where it was concluded that the MACE system could not be used to reduce the gastric transit time, reporting an average passage of 35.5 minutes (10). Active small bowel bleeding was diagnosed on capsule following the MACE in one patient, which was beyond the extent of the EGD.

Accuracy in detection of esophageal lesions

With the use of MACE, it was possible to make a correct real-time diagnosis in 15 of the 16 cases of Barrett's Esophagus, with no false positives. Where Esophageal Varices were present, MACE was able to diagnose these in 11 out of the 15 cases, with no false positives. Esophageal lesions other than Barrett's or Varices, were seen in 3 cases. This included one inlet patch and esophagitis (table 5). All these lesions were seen in both imaging modalities.

Table 5. Accuracy in detection of esophageal lesions		
	Sensitivity	**Specificity**
Detection of Barrett's	93.8% (69.8- 99.8%)	100% (88.8- 100%)
Detection of Varices	86.7% (59.5- 98.3%)	100% (89.1- 100%)
Detection of esophageal lesions	90.3% (74.3- 97.7%)	100% (79.4- 100%)

Intra-observer variability

We examined intraobserver variability by the post procedural review of the videos of both the EGD and MACE. These were reviewed by 5 endoscopists, all of whom are certified to be independent in UGI endoscopy but had no specific training in the interpretation of UGI capsule endoscopy. The Kappa values for each condition using either modality is summarised in Table 6.

Table 6. Interobserver variability in diagnosis of post procedural review of MACE and EGD images.

	MACE			**EGD**		
	Kappa	**SE**	**P value**	**Kappa**	**SE**	**P value**
Barretts Esophagus	0.67	0.08	0.00	0.72	0.08	0.00
Esophageal Varices	0.46	0.08	0.00	0.39	0.08	0.00
Controls	-0.01	0.5	0.51	0.37	0.08	0.00

Discussion

Principle findings

The results from this study suggest that MACE is both technically feasible and safe. Accuracy in the diagnosis of esophageal lesions as compared with EGD was reasonable. Patients reported high levels of comfort, preferring this investigative modality over EGD. No procedure related adverse events were encountered.

There was a difference in technical success of -6% (94% with MACE versus 100% with EGD). This initial experience compares with published data suggesting a technical success of esophageal intubation of 99% with EGD (with the use sedation if required) (11), 96- 99% with unsedated trans-nasal endoscopy (12,13), 93.9% using the cytosponge (14) and 98% and with a dedicated esophageal capsule (15).

Once swallowed, it was possible to control the capsule within the esophagus, as demonstrated by the median and mean esophageal transit time of 163 and 190 secs respectively. This compares favourably with a previous study of a non-magnetic esophageal specific capsule, which demonstrated an average esophageal transit time of 14 secs (95% CI 4 to 86 secs) when ingested in a supine position, or of just 3 secs (95% CI 3 to 8secs) when the patients were standing at the time of ingestion (15). It not clear as to why there was a wide range in oesophageal transit time with the MACE system. We attempted to elucidate whether factors such as operator experience or patient characteristics were influential, however failed to reveal a significant trend. The shorter transit is likely as a result of propagatory oesophageal forces overcoming the forces between the magnetic attraction between hand held magnet and capsule, the former which can reach >180mm/hg.

Despite in some cases a rapid transit through the esophagus, the GEJ was visualised in 100% and the z-line in 91.5%. It is possible that this could be improved further with modifications in capsule design, with the esophageal capsule offered by PillCam ESO3 (Medtronic, Minnesotta USA) taking up to 35 images per second. Were this modification to be applied, this could result in an average of 5130 additional esophageal images acquired per patient in our study cohort.

Patient comfort scores demonstrated a preference of MACE over EGD. This remained the case even where sedation was given prior to performing the EGD. This corroborates previous studies, where capsule visualisation has been used as an alternative where patients have declined flexible endoscopy (5). However, its is appreciated that MACE was not performed on all comers and as such those more likely to have higher anxiety levels or report discomfort may have been selected out in the recruitment process. From this study design it is not possible to ascertain whether improved comfort would result in greater uptake rates.

In this pilot study, we were able to demonstrate a reasonable accuracy for the detection of esophageal lesions, although at present insufficient to replace conventional endoscopy for diagnosis. Our data compares to previous studies using either a string-capsule or the dedicated esophageal capsule, which report an accuracy in the diagnosis of EV of 86% (range: 77%- 96%) (16–21). We demonstrated better sensitivity for the presence of Barrett's than was seen with these older technologies, pooled sensitivity of 86% c.f. 93.8% in the current study (22)

Implications for clinical practice

There is increasing interest in developing minimally invasive, community-based techniques for investigation of the UGI tract. MACE meets this brief, with the additional value of providing pan-endoscopy within a single procedure. The current cost of capsule equipment has thus far been prohibitive for routine use. However this may be offset with the potential of performing this procedure with the aid of non-medical endoscopists or physician extenders and within the community setting without the requirement for sedation or decontamination equipment (23). Whilst capsule endoscopy does not allow for the acquisition of histological samples, it is known that the majority of EGDs are diagnostic with no requirement for biopsies or intervention for many indications, with as many as 78% of those undergoing endoscopy for dyspepsia demonstrating no mucosal abnormalities (24). With a high negative predictive value UGI capsule could be regarded as a scouting technique, in order to detect those with major pathology or with pre-malignant change, who warrant more detailed assessment with advanced imaging or the acquisition of histology.

This technology exists within an environment that includes alternatives such as trans-nasal endoscopy and esophageal capsule, as well as non-endoscopic techniques such as the cytosponge. Limitations of the ESO capsule include its short battery life, which limits imaging to the esophagus and stomach. The Cytosponge allows for the acquisition of cytological specimens to evaluate specific esophageal pathology, but no endoscopic images and with evaluation limited to the esophagus (14,25). Unsedated nasal endoscopy is perhaps the most comparable modality being performed in the community, with no sedation and high levels of patient acceptability. Further on in its development, there has been an improvement in the

quality of images obtained and high levels of diagnostic accuracy demonstrated (12,26–28). Specific benefits of MACE would be in those who have a condition which would benefit from pan endoscopy, such as those being investigated for iron deficiency ananemia or in those who decline flexible endoscopy. Further developments in the field of MACE include automation, the Ankon system (Ankon Optoelectronic Technology Co. Ltd, China) utilizes a computer controlled robotic arm, which can be either directly controlled or adopt a pattern of programmed movements. This has been used in a variety of populations, with promising results (29–32). There are no direct comparisons between this robotically controlled system and the MiroCam Navi system, however studies using these systems that examined the ability to pull the capsule past the pylorus, suggested whilst this was not possible with a hand held magenet it could be achieved with the Ankon system, suggesting stronger or more effective magnetic capture (10,33).

Study strengths and limitations

This study was conducted within a single centre, with all MACE procedures performed by a single operator. While this ensures consistency in technique and environment, the reproducibility of these results outside of this setting is unknown.

The endoscopic diagnosis made from the MACE procedures were made in real time. The operator was not blinded to the appearances of the patient. Given that a proportion of the participants had underlying liver disease it could be argued that the phenotype of these patients may influence the operator of the pre-test suspicion of esophageal varices. This potential bias is thought to be of minimal influence, given that the control cohort included patients with suspected EV and BE, which were correctly diagnosed as normal at both EGD

and MACE. Additionally review of the post procedural images demonstrated similar Kappa Values for both MACE and EGD. Similiarly, a potential bias in favor of conventional endoscopy was introduced, with the possibility of reviewing previous endoscopy reports and being aware of the indication pre-procedure, compared to the blinded performance of MACE. The choice for this approach was a pragmatic one, in our institution BE and EV are placed on specialist lists and as such we did not want to deviate from standard practice in conventional endoscopy for participants. Unanswered questions include whether the results of the MACE procedure would be as promising in an unselected population with a wider variation of pathology, in particular focal lesions.

Conclusions

The findings from this pilot study demonstrate that the MACE procedure is safe and well tolerated by patients. Acceptable accuracy was demonstrated for the diagnosis of esophageal lesions but this will require validation through larger studies. There is scope to optimize the available technology to improve upon these results further.

References

1. Brandt LJ. Patients' attitudes and apprehensions about endoscopy: How to calm troubled waters. Am. J. Gastroenterol. 2001;280–284.
2. Campo R, Brullet E, Montserrat A, *et al.* Identification of factors that influence tolerance of upper gastrointestinal endoscopy. Eur. J. Gastroenterol. Hepatol. 1999;11:201–204.
3. Shenbagaraj L, Thomas-Gibson S, Stebbing J, *et al.* Endoscopy in 2017: A national survey of practice in the UK. Frontline Gastroenterol. 2018;7–15.
4. Ojidu H, Palmer H, Lewandowski J, *et al.* Patient tolerance and acceptance of different colonic imaging modalities: An observational cohort study. Eur. J. Gastroenterol. Hepatol. 2018;30:520–525.
5. Sánchez-Yagüe A, Caunedo-Álvarez Á, García-Montes JM, *et al.* Esophageal capsule endoscopy in patients refusing conventional endoscopy for the study of suspected esophageal pathology. Eur. J. Gastroenterol. Hepatol. 2006;977–983.
6. Eliakim R. Where do I see minimally invasive endoscopy in 2020: clock is ticking. Ann. Transl. Med. 2017;5:202.
7. Rahman I, Pioche M, Shim CS, *et al.* Magnetic-assisted capsule endoscopy in the upper GI tract by using a novel navigation system (with video). Gastrointest. Endosc. 2016;83:889–895.
8. Hale MF, Rahman I, Drew K, *et al.* Magnetically steerable gastric capsule endoscopy is equivalent to flexible endoscopy in the detection of markers in an excised porcine stomach model: Results of a randomized trial. Endoscopy 2015;47:650–653.
9. Mudie DM, Murray K, Hoad CLCL, *et al.* Quantification of Gastrointestinal Liquid Volumes and Distribution Following a 240 mL Dose of Water in the Fasted State. Mol.

Pharm. 2014;11:3039–3047.

10. Hale MF, Drew K, Sidhu R, *et al.* Does magnetically assisted capsule endoscopy improve small bowel capsule endoscopy completion rate? A randomised controlled trial. Endosc. Int. open 2016;4:E215–E221.

11. Siau K, Li J, Fisher NC, *et al.* Intubation failure during gastroscopy: Incidence, predictors and follow-up findings. J. Gastrointest. Liver Dis. 2017;26:339–344.

12. Peery AF, Hoppo T, Garman KS, *et al.* Feasibility, safety, acceptability, and yield of office-based, screening transnasal esophagoscopy (with video). Gastrointest. Endosc. 2012;75:945–953.

13. Sami SS, Dunagan KT, Johnson ML, *et al.* A randomized comparative effectiveness trial of novel endoscopic techniques and approaches for barrett's esophagus screening in the community. Am. J. Gastroenterol. 2015;110:148–158.

14. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, *et al.* Evaluation of a Minimally Invasive Cell Sampling Device Coupled with Assessment of Trefoil Factor 3 Expression for Diagnosing Barrett's Esophagus: A Multi-Center Case–Control Study. PLoS Med. 2015;12:1–19.

15. Marelli L, Jaboli FM, Jackson L, *et al.* A pilot study comparing ESO-2 capsule endoscopy with conventional upper endoscopy for the assessment of uncomplicated heartburn and dyspepsia. Frontline Gastroenterol. 2013;4:96–101.

16. Laurain A, Leusse A de, Gincul R, *et al.* Oesophageal capsule endoscopy versus oesophago-gastroduodenoscopy for the diagnosis of recurrent varices: A prospective multicentre study. Dig. Liver Dis. 2014;46:535–540.

17. 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;38:31–35.

18. Ahn D, Guturu P. Meta-analysis of capsule endoscopy in patients diagnosed or suspected with esophageal varices. World J. Gastroenterol. 2010;16:785–786.

19. Frenette CT, Kuldau JG, Hillebrand DJ, *et al.* Comparison of esophageal capsule endoscopy and esophagogastroduodenoscopy for diagnosis of esophageal varices. World J. Gastroenterol. 2008;14:4480–4485.

20. Sacher-Huvelin S, Calès P, Bureau C, *et al.* Screening of esophageal varices by esophageal capsule endoscopy: Results of a French multicenter prospective study. Endoscopy 2015;47:486–492.

21. McCarty TR, Afinogenova Y, Njei B. Use of wireless capsule endoscopy for the diagnosis and grading of esophageal varices in patients with portal hypertension: A systematic review and meta-analysis. J. Clin. Gastroenterol. 2017;51:174–182.

22. Bhardwaj A, Hollenbeak CS, Pooran N, *et al.* A meta-analysis of the diagnostic accuracy of esophageal capsule endoscopy for Barrett's esophagus in patients with gastroesophageal reflux disease. Am. J. Gastroenterol. 2009;104:1533–1539.

23. Rubenstein JH, Inadomi JM, Brill J V., *et al.* Cost Utility of Screening for Barrett's Esophagus With Esophageal Capsule Endoscopy Versus Conventional Upper Endoscopy. Clin. Gastroenterol. Hepatol. 2007;5:312–318.

24. Ford AC, Marwaha A, Lim A, *et al.* What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. Clin. Gastroenterol. Hepatol. 2010;830–837.

25. Iqbal U, Siddique O, Ovalle A, *et al.* Safety and efficacy of a minimally invasive cell sampling device ('Cytosponge') in the diagnosis of esophageal pathology: A systematic review. Eur. J. Gastroenterol. Hepatol. 2018;30:1261–1269.

26. Despott EJ, Baulf M, Tripoli E, *et al.* The SCENT Trial: The UK's First Prospective Randomised Head-to-Head Trial of Transnasal Endoscopy Against Conventional Oral Endoscopy - Preliminary Results. Gastrointest. Endosc. 2009;69:AB319.

27. Sami SS, Iyer PG, Pophali P, *et al.* Acceptability, Accuracy, and Safety of Disposable Transnasal Capsule Endoscopy for Barrett's Esophagus Screening [Internet]. Clin. Gastroenterol. Hepatol. 2019;17:638-646.e1.Available from: https://doi.org/10.1016/j.cgh.2018.07.019

28. S.S. S, E. W, M. J, *et al.* Evaluation of a novel, portable, probe-based transnasal endoscope: Superior patient preference and acceptable diagnostic accuracy for oesophageal varices compared to conventional endoscopy. United Eur. Gastroenterol. J. 2014;2:A132–A605.

29. Qian YY, Zhu SG, Hou X, *et al.* Preliminary study of magnetically controlled capsule gastroscopy for diagnosing superficial gastric neoplasia [Internet]. Dig. Liver Dis. 2018;50:1041–1046.Available from: https://doi.org/10.1016/j.dld.2018.04.013

30. Zou W Bin, Hou XH, Xin L, *et al.* Magnetic-controlled capsule endoscopy vsgastroscopy for gastric diseases: A two-center self-controlled comparative trial. Endoscopy 2015;72:525–528.

31. Qian Y, Bai T, Li J, *et al.* Magnetic-guided capsule endoscopy in the diagnosis of gastrointestinal diseases in minors. Gastroenterol. Res. Pract. 2018;2018:1–8.

32. 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;14:1266–1273.

33. Jiang X, Qian YY, Liu X, *et al.* Impact of magnetic steering on gastric transit time of a capsule endoscopy (with video) [Internet]. Gastrointest. Endosc. 2018;88:746–754.

Appendix 1: Visulaisation grading system of upper gastro intestinal landmarks.	
Grade	**Description**
0	No image obtained
1	Poor quality views with less than 50% visualization of the landmark.
2	Reasonable quality views with approximately 50% visualization of the landmark
3	Good quality views with approximately 75% visualization of the landmark
4	Excellent quality views with 100% visualization of the landmark

Figure 1: The components of the MiroCam Navi MACE system

A. Hand held Magnet: 26 cm x 3.5 cm hand held magnet.
B. Computer: Real time and saved images of the MACE procedure can be viewed using a tablet or laptop with proprietary MiroCam interpretation software.
C. Magnetically Steerable Capsule : 11x 24mm capsule, with a weight of 4.2g. Images are obtained at a rate of 3 frames per second at a resolution of 320 x 320. The capsule has a field of view of 170 degrees and depth of field of 30mm.
D. Sensing system: The sensing system consists of 9 sensing pads that are placed at pre-designated points across the torso. Images are transmitted from the sensing box to a computer using Wi-Fi, allowing real time assessment.

Figure 2. A flow diagram summarising study recruitment

Figure 3. Example pictures of esophageal lesions detected on MACE
A & B: Esophageal Varices
C&B: Barrett's Esophagus
E: Esophagitis above a Barrett's segment F: Cervical Inlet Patch

Figure 4. Example pictures of non-Esophageal lesions detected on MACE
A&B Portal hypertensive gastropathy
C: Gastric angioectasia D: Gastric polyp
E: Duodenitis F: Active small bowel bleed