

# **The role of capsule endoscopy in the upper gastrointestinal tract**

**Dr. Hey-Long Ching MBBS, BSc, MRCP(UK)**

Academic Department of Gastroenterology and Hepatology,  
Royal Hallamshire Hospital,  
Sheffield Teaching Hospitals NHS Foundation Trust, United Kingdom

Supervisors: Professor Mark E McAlindon and Professor Nigel Hoggard

## **Statement of Probity**

I confirm that I shall abide by the University of Sheffield's regulations on plagiarism and that all written work shall be my own and will not have been PLAGIARISED from other paper-based or electronic sources. Where used, material gathered from other sources will be clearly cited in the text.

Date: 31.12.18

Name (Print): Dr. Hey-Long Ching

## **Acknowledgments**

I would like to first and foremost thank my supervisors Professor Mark McAlindon and Professor Nigel Hoggard for their guidance and everlasting encouragement during this endeavour and Professor David Sanders for giving me this opportunity of a lifetime.

I would also like to thank the entire department of gastroenterology at Sheffield Teaching Hospitals. In particular Dr. Reena Sidhu, Sister Vicky Thurston and Sister Ailish Healy for their invaluable support.

As for everything in my life, my family are always there for me and I am eternally grateful. I would like to specially thank my wife, Michelle, for always being by my side. Lastly, I would like to thank God for placing me on Earth to serve his people. I shall continue to turn to Him for all aspects of my short-lived worldly life.



## Abstract

Oesophagogastroduodenoscopy (OGD) is invasive, may be poorly tolerated and is not without risk. Meanwhile, capsule endoscopy is well tolerated and adaptable to upper gastrointestinal (GI) territory. The null hypothesis of my thesis is that there is no role for capsule endoscopy in the investigation of the upper GI tract. The aim was to reject the null hypothesis using five studies.

Chapter 3: A retrospective cohort study of 500 patients undergoing OGD for dyspepsia. Diagnoses made endoscopically or histologically that would not have been adequately managed by *Helicobacter pylori* testing (and treating if positive) and trial of a proton pump inhibitor were only seen in 16.2%.

Chapter 4: A prospective cohort study of 156 patients assessing the tolerance and acceptability of OGD. More than 59% were worried about and 36% experienced significant gagging, choking and discomfort related to endoscopic intubation of the oropharynx. Despite this most patients regarded OGD as acceptable.

Chapter 5: A prospective cohort study of 49 patients with recurrent or refractory iron deficiency anaemia. Magnetically assisted capsule endoscopy (MACE) by manipulating a capsule inside the stomach with an external handheld magnet demonstrated better diagnostic yield and patient tolerance than OGD.

Chapter 6: A prospective cohort study of 33 patients with suspected acute upper gastrointestinal bleeding. MACE had higher diagnostic yield for focal lesions and identified additional small bowel bleeding compared to OGD and correctly predicted safe discharge for patients.

Chapter 7: A prospective cohort study of 50 patients undergoing examination with the novel upper GI capsule and following a nurse-led series of positional changes to move the capsule around the stomach. The upper GI capsule achieved excellent views of the upper GI tract.

In conclusion, these results suggest diagnostic OGD has limitations and upper GI capsule endoscopy has potential as a non-invasive alternative to OGD. These findings are sufficient to reject the null hypothesis.

## **Publications arising from the body of work presented in this thesis**

The work presented in several chapters of this thesis is already published. Therefore some chapters reproduce part or all of these publications with, in some cases, minor additions, explanatory notes or references. Permission to include the publications in this fashion has been sought and approved by all named co-authors and journals. Summarised below are my independent contributions to each thesis chapter and relevant articles.

**Chapter 1:** Ching HL, Hale MF, McAlindon ME. Current and future role of magnetically assisted gastric capsule endoscopy in the upper gastrointestinal tract. *Therap Adv Gastroenterol.* 2016;9(3):313-21. doi: 10.1177/1756283X16633052. I independantly wrote this chapter and article with guidance from Dr. Hale and Professor McAlindon on the key topics to address.

**Chapter 3:** Ching HL, Hale MF, Sidhu R, McAlindon ME. Reassessing the value of gastroscopy for the investigation of dyspepsia. *Frontline Gastroenterol.* 2018;9(1):62-6. doi: 10.1136/flgastro-2017-100838. I designed the study with guidance from Professor McAlindon. I sought approval from the Sheffield Teaching Hospitals Clinical Effectiveness Unit for the project. I independently collected, analysed and interpreted the data and wrote the chapter and article.

**Chapter 4:** I designed the study with guidance from Professor McAlindon. I sought approval from the Sheffield Teaching Hospitals Clinical Effectiveness Unit for the project. Dr. Raju and Ms. Marks distributed and collected the patient questionnaires. I independently collected, analysed and interpreted the data and wrote the chapter and manuscript.

**Chapter 5:** Ching HL, Hale MF, Kurien M, Campbell JA, Zammit SC, Healy A, Thurston V, Hebden JM, Sidhu R, McAlindon ME. Diagnostic yield of magnetically assisted capsule endoscopy versus gastroscopy in recurrent and refractory iron deficiency anemia. *Endoscopy.* October 2018. doi: 10.1055/a-0750-5682.Epub ahead of print. I contributed to the design of the study. I performed

magnetically assisted capsule endoscopy and collected data for 31 patients (Dr. Hale collected the data for 19 patients). I independently processed, analysed and interpreted the data for all patients and wrote the chapter and manuscript.

**Chapter 6:** I designed the study with guidance from Professor McAlindon. I sought ethical approval for the study from the Yorkshire & The Humber - Leeds West Research Ethics Committee. I independently collected, analysed and interpreted the data and wrote the chapter and manuscript.

**Chapter 7:** Ching HL, Healy A, Thurston V, Hale MF, Sidhu R, McAlindon ME. Upper gastrointestinal tract capsule endoscopy using a nurse-led protocol: First reported experience. *World J Gastroenterol*. 2018;24(26):2893-901. doi: 10.3748/wjg.v24.i26.2893. I designed the study with guidance from Professor McAlindon. I sought approval from the Sheffield Teaching Hospitals Clinical Effectiveness Unit for the project. I independently collected, analysed and interpreted the data and wrote the chapter and manuscript.

**Chapter 8 and 9:** I independantly wrote these chapters.

## Table of Contents

<b>Acknowledgments .....</b>	<b>2</b>
<b>Abstract .....</b>	<b>3</b>
<b>Publications arising from the body of work presented in this thesis .....</b>	<b>5</b>
<b>List of figures .....</b>	<b>9</b>
<b>List of tables .....</b>	<b>10</b>
<b>List of abbreviations .....</b>	<b>11</b>
<b>Chapter 1: Introduction .....</b>	<b>13</b>
<b>1.1 Oesophagogastrroduodenoscopy .....</b>	<b>13</b>
<b>1.2 Small bowel capsule endoscopy .....</b>	<b>16</b>
1.2.1 Background .....	16
<b>1.3 Developments in upper gastrointestinal capsule endoscopy.....</b>	<b>17</b>
<b>1.4 MACE using hand-held magnets.....</b>	<b>18</b>
1.4.1 Pilot studies.....	18
1.4.2 MiroCam® Navi .....	19
<b>1.5 Robot-assisted magnetic control.....</b>	<b>21</b>
1.5.1 Olympus and Siemens .....	21
<b>1.6 Robot-arm magnetic control.....</b>	<b>23</b>
1.6.1 Ankon NaviCam®.....	23
<b>1.7 Summary of current literature.....</b>	<b>25</b>
<b>Chapter 2: Aims.....</b>	<b>27</b>
<b>2.1 Null hypothesis.....</b>	<b>27</b>
<b>2.2 Phase 1 .....</b>	<b>27</b>
<b>2.3 Phase 2 .....</b>	<b>27</b>
<b>Chapter 3: Reassessing the value of gastroscopy for the investigation of dyspepsia .....</b>	<b>29</b>
<b>3.1 Abstract.....</b>	<b>29</b>
3.1.1 Introduction.....	29
3.1.2 Materials and Methods.....	29
3.1.3 Results .....	29
3.1.4 Conclusion .....	29
<b>3.2 Introduction .....</b>	<b>30</b>
<b>3.3 Materials and Methods .....</b>	<b>31</b>
<b>3.4 Results .....</b>	<b>32</b>
<b>3.5 Discussion .....</b>	<b>34</b>
<b>Chapter 4: Patient tolerability and acceptability of gastroscopy: a prospective study....</b>	<b>40</b>
<b>4.1 Abstract.....</b>	<b>40</b>
4.1.1 Introduction.....	40
4.1.2 Methods .....	40
4.1.3 Results .....	40
4.1.4 Conclusion .....	41
<b>4.2 Introduction .....</b>	<b>41</b>
<b>4.3 Methods and materials .....</b>	<b>43</b>
<b>4.4 Results .....</b>	<b>45</b>
<b>4.5 Discussion .....</b>	<b>49</b>
<b>Chapter 5: Magnetically assisted capsule endoscopy has higher diagnostic yield than gastroscopy in recurrent and refractory iron deficiency anaemia.....</b>	<b>53</b>

<b>5.1 Abstract.....</b>	<b>53</b>
5.1.1. Introduction.....	53
5.1.2 Methods.....	53
5.1.3 Results.....	53
5.1.4 Conclusion.....	54
<b>Introduction.....</b>	<b>54</b>
<b>Methods.....</b>	<b>55</b>
<b>Results.....</b>	<b>60</b>
<b>Discussion.....</b>	<b>68</b>
<b>Chapter 6: Magnetically assisted capsule endoscopy in acute upper gastrointestinal bleeding.....</b>	<b>73</b>
<b>6.1 Abstract.....</b>	<b>73</b>
6.1.1. Introduction.....	73
6.1.2 Materials and Methods.....	73
6.1.3 Results.....	73
6.1.4 Conclusion.....	74
<b>6.2 Introduction.....</b>	<b>74</b>
<b>6.3 Methods.....</b>	<b>75</b>
<b>6.4 Results.....</b>	<b>78</b>
<b>6.5 Discussion.....</b>	<b>87</b>
<b>Chapter 7: Upper gastrointestinal tract capsule endoscopy using a nurse-led protocol: first reported experience.....</b>	<b>93</b>
<b>7.1 Abstract.....</b>	<b>93</b>
7.1.1 Introduction.....	93
7.1.2 Methods.....	93
7.1.3 Results.....	93
7.1.4 Conclusion.....	94
<b>Introduction.....</b>	<b>94</b>
<b>Methods.....</b>	<b>95</b>
<b>Results.....</b>	<b>99</b>
<b>Discussion.....</b>	<b>105</b>
<b>Chapter 8: Discussion.....</b>	<b>111</b>
<b>Chapter 9: Conclusion.....</b>	<b>118</b>
<b>Chapter 10: Bibliography.....</b>	<b>119</b>
<b>Chapter 11: Appendix.....</b>	<b>131</b>
<b>Appendix 1: Modified Endoscopy Concerns Scale (mECS).....</b>	<b>131</b>
<b>Appendix 2: Hospital Anxiety and Depression Scale (HADS).....</b>	<b>132</b>
<b>Appendix 3: Grading scheme for visibility at major gastric landmark.....</b>	<b>133</b>
<b>Appendix 4: Pathology Reporting Form.....</b>	<b>133</b>
<b>Appendix 5: Participant comfort questionnaire before and after MACE and OGD.....</b>	<b>134</b>

## List of figures

- Figure 1. Indications for OGD.
- Figure 2. MiroCam Navi® system.
- Figure 3. Olympus and Siemens magnetically assisted capsule endoscopy system.
- Figure 4. Ankon NaviCam® system.
- Figure 5. Box and whisker plot of anticipated physical and social distress experienced by patients undergoing oesophagogastroduodenoscopy.
- Figure 6. Box and whisker plot of anticipated and actual physical symptoms experienced by patients undergoing oesophagogastroduodenoscopy.
- Figure 7. Normal views of major upper gastrointestinal landmarks achieved by MACE using the MiroCam Navi® system.
- Figure 8. Pathology in the upper gastrointestinal tract only detected by MACE and not seen at OGD in patients with recurrent or refractory iron deficiency anaemia.
- Figure 9. A gastric ulcer identified by both oesophagogastroduodenoscopy and magnetic assisted capsule endoscopy on the greater curvature.
- Figure 10. One case of oesophageal ulcers and four cases of ulcers in the first part of the duodenum identified at magnetic assisted capsule endoscopy and missed at oesophagogastroduodenoscopy.
- Figure 11. Schematic of the simple positional interchange technique (SPIT).
- Figure 12. Indications for assessment with the upper GI capsule.
- Figure 13. Normal views of the upper gastrointestinal (GI) tract seen with the upper GI capsule.
- Figure 14. Suboptimal views in the fundus with the upper GI capsule.
- Figure 15. Pathology detected by the upper GI Capsule.

## List of tables

Table 1.	Strengths and limitations of upper gastrointestinal capsule endoscopy systems
Table 2.	Diagnoses made at OGD performed to investigate dyspepsia.
Table 3.	Patient demographics and procedural factors did not influence experience of the most distressing symptoms associated with gastroscopy
Table 4.	Sequences of patient and magnet positions used in gastric examination by the MiroCam Navi®.
Table 5.	Frequency of visibility grades reported at each major upper gastrointestinal landmark during magnetically assisted capsule endoscopy.
Table 6.	Upper gastrointestinal pathology detection by magnetically assisted capsule endoscopy and oesophagogastroduodenoscopy for each study patient with recurrent or refractory iron deficiency anaemia.
Table 7.	Frequency of upper gastrointestinal pathology seen by MACE and OGD.
Table 8.	Case-by-case illustration of focal and significant pathology detected by MACE and OGD in patients presenting with suspected acute upper GI bleeding.
Table 9.	Number of upper gastrointestinal pathology seen by MACE and OGD.
Table 10.	Patients with suspected upper GI bleeding not appropriate for discharge based on MACE findings.
Table 11.	Summary of the evolution from the oesophageal capsule to the novel upper GI capsule.
Table 12.	Capsule transit time in the upper GI tract.
Table 13.	Visualisation scores of the upper GI capsule using the simple positional interchange technique.



## List of abbreviations

ASIC	Application-specific integrated circuit
BSG	British Society of Gastroenterology
CCD	Charge-couples device
CEU	Clinical Effectiveness Unit
CMOS	Complementary metal oxide silicon
CT	Computed tomography
D1	Duodenum, first part
D2	Duodenum, second part
ECS	Endoscopy Concerns Scale
FPS	Frames per second
GI	Gastrointestinal
GORD	Gastro-oesophageal reflux disease
HADS	Hospital anxiety and depression scale
HADS-A	Hospital anxiety and depression scale: anxiety component
HADS-D	Hospital anxiety and depression scale: depression component
HLC	Dr. Hey-Long Ching
IDA	Iron deficiency anaemia
KPI	Key Performance Indicator
LED	Light emitting diode
MACE	Magnetically assisted capsule endoscopy
mECS	Modified endoscopy concerns scale
MEM	Professor Mark E McAlindon
MFH	Dr. Melissa F Hale

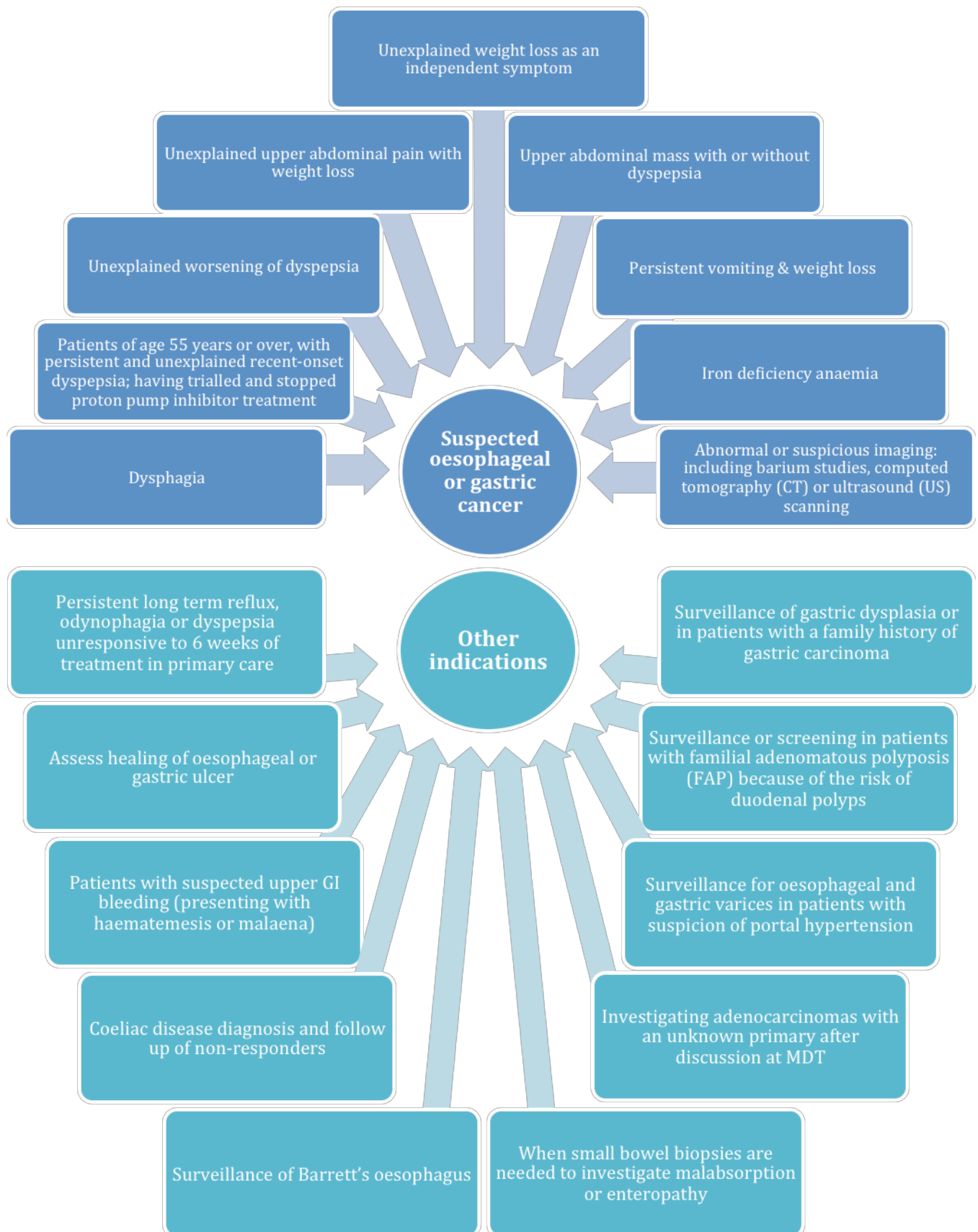
MRI	Magnetic resonance imaging
mT	milliTesla
NICE	National Institute for Health and Care Institute
NSAID	Non-steroidal anti-inflammatory drug
OGD	Oesophagogastroduodenoscopy
PC	Personalised computer
RHS	Dr. Reena H Sidhu
SB	Dr. Sabina Beg
SBCE	Small bowel capsule endoscopy
SIP	Simplified ingestion protocol
STH	Sheffield Teaching Hospitals NHS Foundation Trust
USA	United States of America
UK	United Kingdom

## Chapter 1: Introduction

### 1.1 Oesophagogastroduodenoscopy

Endoscopes were originally designed to visualise the internal aspect of hollow organs and cavities of the human body. From Kussmaul's rigid gastroscope (1868) and Schindler's semi-flexible endoscope (1932) we evolved to Hirschowitz's fiberoptic endoscope in 1957. (1) Our current era of high definition video-endoscopy is built on the latter. (2) Oesophagogastroduodenoscopy (OGD), otherwise known as gastroscopy, is the gold standard endoscopic investigation of the upper gastrointestinal (GI) tract. There are clear indications for OGD set by the British Society of Gastroenterology (BSG) (3) (figure 1). These national guidelines are a reminder that OGD is a mindful act; balancing clinical need, patient safety and available resources. OGD is invasive but generally accepted as safe. Complications exist as with any procedure and common minor problems include a mild sore throat in 9.5% and abdominal discomfort in 5.3% of cases. (4) More significant complications can occur but are uncommon. These include risks of infection, bleeding and perforation (in approximately 0.03%). (5) The risk of OGD can only be fully appreciated by also considering the risks of peri-procedural sedation: respiratory depression, aspiration pneumonia, angina, myocardial infarction and stroke. (6)

**Figure 1.** Indications for oesophagogastroduodenoscopy



The uptake of OGD remains high with approximately 1% of the population in the United Kingdom (UK) undergoing procedures annually (7) and the demand is climbing globally. (8, 9) However, the impact of performing OGDs on a large scale is unclear. While malignancy appears to be detected in less than 1% according to a meta-analysis of OGDs performed for dyspepsia (10), there is also evidence suggesting that 11.3% of upper GI malignancies are missed at endoscopy (up to 3 years before diagnosis). (11) Recent national key performance indicators (KPI) aim to improve the quality and diagnostic yield of OGD (8). This may shed more light on the true prevalence of upper GI pathology. Unlike its lower GI counterpart (colonoscopy) (12-15), patient tolerance and acceptability of OGD requires further understanding. The association between OGD and poor tolerance has been made, particularly in the absence of sedation (16-20). Studies on transnasal endoscopy report less gagging and discomfort and better tolerance and acceptability compared to OGD. (21-23) This would suggest that the primary source of distress for patients originates from stimulation of the gag reflex. In a randomised crossover trial by Choe et al. patients reported median scores of 71.4 and 62.7 (out of 100 max) for choking and globus respectively when undergoing OGD. (24) Further studies that focus on the experience, tolerance and acceptance of OGD as its primary outcome are required. The coexistence of high case volumes of OGD being performed and the suboptimal understanding of the patient experience is an oxymoron. Meanwhile, capsule endoscopy is an established form of GI endoscopy (25) that is well tolerated (26-28), adaptable to upper GI territory and would avoid triggering of the gag reflex. (29, 30) Thus, exploring capsule endoscopy as an alternative means to upper GI endoscopy is logical.

## **1.2 Small bowel capsule endoscopy**

### **1.2.1 Background**

When Gavriel Iddan and Paul Swain introduced wireless capsule endoscopy in the year 2000 it revolutionised investigation of the small bowel. (31) This was built using the technology of transistors and complementary metal oxide silicon (CMOS) image sensors, application-specific integrated circuit (ASIC) devices, and white-light emitting diode (LED) illumination. The result was a compact camera system small enough to swallow and energy efficient while also maintaining integrity of the captured image quality. (32) Within 10 years of release 1.5 million capsules had been performed. (33) Capsule endoscopy is now the gold standard small bowel investigation and guidelines worldwide advocate first-line use for multiple clinical indications. (25, 34, 35)

### **1.2.2 Risks**

The main risk of small bowel capsule endoscopy (SBCE) is capsule retention. It is contraindicated in patients with known strictures and some patients are also known to have a higher risk of retention. This includes patients with regular non-steroidal anti-inflammatory drug (NSAID) use, known extensive Crohn's disease and those who have been exposed to radiation injury to the abdomen. (34) In these cases a patency capsule can be performed prior to capsule endoscopy. Within the patency capsule is a radiofrequency emitting identification tag. Using a specifically designed external detector, if the radiofrequency tag is detectable beyond the time which the capsule is expected to be expelled from the patient, then patency capsule retention is suspected. (36) Further imaging to confirm the exact location of the capsule can be useful. (37) The patency capsule eventually dissolves so that retention is only short-lived but pre-assessment using the patency

capsule is helpful to either confirm or refute the risk of retention with capsule endoscopy. Regardless, the overall risk of capsule retention is low and approximates 2% only. (38) Moreover, bowel obstruction secondary to capsule retention is a rare event and most cases of capsule retention remain asymptomatic. If endoscopic or surgical retrieval of the capsule is necessary this is usually associated with the appropriate identification and intervention for the offending pathology. (39, 40) The risk of aspiration of capsule endoscopes is rare occurring in approximately 0.1% with only half of these patients requiring intervention (such as bronchoscopy) to retrieve the capsule. (41, 42) Previous concerns regarding interference between capsule endoscopy and pacemakers or implantable cardiac defibrillators have also proven insubstantial. (43-46)

### **1.3 Developments in upper gastrointestinal capsule endoscopy**

The concept of minimally invasive GI endoscopy is attractive (47) and the concept of pan-enteric capsule endoscopy continues to be tested. (48, 49) Capsules designed to visualise the oesophagus and colon are already in commercial use although not recommended as first-line investigations. (50, 51) Oesophageal capsule endoscopy has existed for over 10 years. Eliakim et al. first demonstrated feasibility of the PillCam ESO® (Given Imaging Ltd, Yoqneam, Israel) in 2004: an adaptation of the PillCam small bowel capsule with cameras installed at opposite ends. (52) In this pilot study of 17 patients the PillCam ESO® detected oesophageal pathology with 100% sensitivity and 80% specificity compared to OGD. The majority (16 out of 17 patients) preferred capsule endoscopy to OGD. The PillCam ESO2® capsule (Given Imaging Ltd, Yoqneam, Israel) was released four years later with a wider angle of view, higher quality images and faster image capture rate (18 compared to the 4 frames per second (fps) of the PillCam ESO®). When compared to OGD, the PillCam ESO2® identified Barrett's oesophagus and oesophagitis with 100% and 80% sensitivity and

74% and 87% specificity respectively. (53) Although initially adapted for oesophageal views, examination of the stomach using the PillCam ESO2® has also been reported. (54) Capsule endoscopy of the stomach is, however, not straightforward.

The stomach poses several challenges that can impair mucosal visualisation: it is capacious, irregular in shape and is influenced by peristalsis. Furthermore, it is collapsed in its natural state. (55) Commercially available capsules passively transit through and are unable to negotiate the obstacles of the stomach. The ability to somehow purposefully steer capsules would allow adaptation to gastric terrain. This can be achieved by internal or external actuation methods (56, 57) and external magnetic control of capsules appears to be a promising field. This was first introduced in 2006 (58) but several adaptations have since exploited the concept of magnetically assisted capsule endoscopy (MACE).

## **1.4 MACE using hand-held magnets**

### **1.4.1 Pilot studies**

In 2010, Swain et al. were the first to demonstrate external control of a capsule inside a human oesophagus and stomach. (29) The prototype system was based on the PillCam COLON® capsule (Given Imaging Ltd, Yoqneam, Israel). Ferromagnetic material was incorporated into the capsule to allow magnetic control. The system also included an external paddle-like magnet and a real-time imager (Given Imaging Ltd). In this single case study, OGD was performed at the same time to assess capsule movements live. Movements of the capsule in the oesophagus (rotation) and stomach (rotation and translocation) were successfully achieved. This was possibly made easier by the artificial gas distension from OGD. Subsequently, the same group failed to reproduce the same



level of control consistently. (18, 59) In a study of 10 volunteers, increasing the distance between the external magnet and the capsule (e.g. with a thicker abdominal wall) reduced responsiveness to magnetic manipulation. The magnetic force was also unable to withstand the peristaltic movements of a migrating motor complex in the stomach. (18) Visualisation of the gastric mucosa was variable: an estimated 75% to 90% of the mucosa could be examined in seven volunteers while only 50% to 60% in the remainder. Opaque gastric contents and a collapsed stomach were responsible for suboptimal views. Despite the technical challenges associated with performing upper GI MACE, also reported by other groups (60), patient tolerance was excellent.

#### **1.4.2 MiroCam® Navi**

The MiroCam® Navi (Intromedic Ltd, Seoul, South Korea) (figure 2) is a modified MiroCam® small bowel capsule (with an 11 hour battery-life) that has an integrated magnetic inclusion body. This permits magnetic steering in the upper GI tract using an external hammer-like handheld magnet (magnetic flux density 380 milliTesla (mT)), not dissimilar to the prototype equipment presented by Swain et al. (18, 29, 59) Images can be viewed real-time using Wi-Fi transmission from the data recorder to an electronic tablet or personal computer (PC). Feasibility of the MiroCam® Navi has been demonstrated in a cohort study of 26 volunteers. (60) MACE was performed followed by a standard OGD within 3 days in this study. To improve views during MACE the stomach was distended by asking subjects to drink water prior to swallowing the capsule and during MACE examination (median 800mls, range 200mls to 1500mls). Visualisation of each major upper GI landmark by the MiroCam® Navi was achieved in 88% to 100% of cases (oesophagogastric junction, 92%; cardia, 88%; fundus, 96%; body, 100%; incisura, 96%; antrum, 96%; and pylorus, 100%). The Z-

line was only visualised in 46%, as the magnetic force was not always able to overcome the capsule's speed of entry into the stomach.

**Figure 2.** The MiroCam Navi® system allows magnetically assisted capsule endoscopy (MACE) followed by conventional small bowel capsule endoscopy. 1, MiroCam Navi® capsule; 2, external hand-held magnet for steering; 3, data recorder allowing subsequent docking to workstation for video download; 4, mucosal live-views on tablet via Wi-Fi connection to assist MACE



Other challenges met by the MiroCam® Navi resonate with the pilot studies of Swain's group. (18, 29, 59) Manipulation of the capsule was particularly troublesome in the proximal stomach. This was likely due to the distance from the skin surface to the capsule sitting in the fundus, through which magnetic forces would have to transverse. Gastric cleanliness also affected visualisation but obstructed views from rugal folds could mostly be overcome by distension of the stomach with additional water ingestion. Despite ingesting large volumes of water in some cases, MACE was well tolerated by all participants. In this study, concordance between MACE and OGD was seen in the

detection of eight out of nine minor pathologies: the overall low diagnostic yield was likely related to the recruitment of healthy volunteers. However, in an ex vivo study comparing the MiroCam Navi® against OGD, Hale et al. reported comparable rates of identifying beads sewn onto the mucosa of porcine stomachs. (61) In a subsequent study, Hale et al. used MACE to guide MiroCam Navi® capsules towards the pylorus to determine whether it would improve small bowel capsule endoscopy completion rates (which it did not). (62) This was the first study to demonstrate feasibility of using the MiroCam Navi® in patients but MACE examination of the upper GI tract mucosa was not performed. To date there are no patient trials on the quality of views or diagnostic yield of upper GI MACE using the MiroCam Navi®. Meanwhile, the diagnostic accuracies of other more advanced MACE technology have been demonstrated in patients. (63, 64)

## **1.5 Robot-assisted magnetic control**

### **1.5.1 Olympus and Siemens**

MACE using a hand-held magnet is simple, requires less operating space and is relatively inexpensive. However, studies in porcine models show that the precision of capsule movement is superior with robot-controlled systems. (65) The joint effort of Olympus Medical Systems Corporation (Tokyo, Japan) and Siemens Healthcare (Erlangen, Germany) is one such system. (63, 66, 67) In 2010, Rey et al. demonstrated the feasibility of combining an Olympus magnetically responsive capsule with a Siemens magnetic navigation system (figure 3). (66) The navigation equipment is similar in appearance to a magnetic resonance imaging (MRI) machine but the magnetic field produced is weaker (up to 100mT, 150–500 times less than a conventional MRI scanner). The capsule contains ferromagnetic material and two image sensors, which relay real-

time images to a PC screen. Magnetic steering of the capsule is controlled by two joysticks: giving the operator access to capsule movement in the x, y and z-axes in addition to tilting, rotation and translocation.

**Figure 3.** Olympus and Siemens magnetically assisted capsule endoscopy system. With permission.



A total of 29 volunteers and 24 patients were recruited to this feasibility study. MACE was performed 24 hours after gastroscopy. 1300mls of water was used to distend the stomach for MACE and patient position changes were used to facilitate steering of the capsule. The distal gastric landmarks were identified in the majority of cases (96%, gastric pylorus; 98%, antrum; 96%, gastric body) but the proximal regions were more challenging (73%, fundus; 75%, cardia). Similar to the findings of Rahman (60) and Keller et al. (18) a collapsed proximal stomach and resistant mucus impaired visualisation. The magnetic force was not always able to overcome the force of peristalsis and in two cases uncontrolled rapid transpyloric exiting of the capsule meant incomplete gastric examination. One patient had transient abdominal pain (that spontaneously resolved). Otherwise there were no adverse effects with MACE or the large volume of ingested water and subsequent studies have shown that patients favour robotic MACE over OGD. (63, 67)

In a follow-up trial of 61 patients, Rey et al. compared the diagnostic yield of MACE with OGD. (67) 108 pathological findings were detected in total, of which 63 were identified by both modalities (58.3% concordance). MACE failed to identify 14 lesions but detected 31 lesions that were missed by OGD. This may have related to the longer examination time of MACE compared to OGD (17 versus 5 minutes respectively). Furthermore, MACE was performed soon after OGD and lesions identified only by MACE were minute and of an inflammatory or erosive nature. Thus minor trauma or biopsy sites from OGD could have been misinterpreted as primary pathology during MACE. This limitation has been addressed in the latest output from the same authors. (63) A multicenter, blinded, comparative trial of 189 patients was conducted where MACE was performed before gastroscopy. Simethicone was also used as an anti-foaming agent to improve gastric views. Lesions in this study were classified as major (requiring biopsy or removal) or minor. Of the 23 major lesions, MACE was able to identify these with 94.1% specificity but only 61.9% sensitivity. The specificity and sensitivity for minor lesion detection was also only 70% and 89%, respectively. In contrast, other robot MACE systems have demonstrated high diagnostic accuracy. (64)

## **1.6 Robot-arm magnetic control**

### **1.6.1 Ankon NaviCam®**

The NaviCam® system (Ankon, Wuhan, Shanghai, China) consists of a capsule containing a permanent magnet and a single image CMOS sensor. Live images are available to the operator on a PC screen during steering of the capsule. The guidance system is a robot of the C-arm type with a large permanent magnet (magnetic flux density up to 200mT) (figure 4) and the capsule is

navigated either manually via two joysticks or automated via pre-programmed software. Preparation for the procedure involves ingestion of 500 to 1000mls of water. (64, 68)

**Figure 4.** The Ankon NaviCam® system. 1, robot-steered permanent magnet; 2, patient examination bed; 3, dual joystick control; 4, live-image display



The feasibility of the NaviCam® was demonstrated in 34 healthy volunteers in 2012 by Liao et al. (68) Mucosal views of the gastric cardia, fundus, body, angulus, antrum and pylorus were reported as 82.4%, 85.3%, 100%, 100%, 100% and 100%, respectively. Views of the proximal stomach were suboptimal as seen with other MACE systems. (60, 63, 66, 67) Opaque gastric fluid obstructed views in six volunteers in the most gravity-dependent part of the stomach. No significant improvement was seen in four subjects despite additional water ingestion. Magnetic steering towards the fundus and cardia was not achieved in 14.6% of subjects. This, along with early transpyloric exiting of the capsule in one case reduced the number of complete gastric examinations.

Zou et al. led the group to complete a pilot study comparing the diagnostic accuracy of the NaviCam® with OGD in 68 patients. (69) This has now been superseded by a large statistically powered study by the same authors: 350 patients were recruited to this most recent multicenter trial. (64) Patients underwent MACE two hours prior to OGD and the detection of focal lesions (defined as ulcers, polyps, submucosal tumours and others lesions e.g. diverticulae) was compared between the two modalities. Overall, MACE detected gastric focal lesions with a sensitivity of 90.4% and specificity of 94.7% compared to OGD. After subgroup analysis of upper and lower stomach focal lesions, the sensitivity (90.2% versus 90.6% respectively) and specificity (96.7% versus 97.9% respectively) was still similar. This was despite gastric cleanliness and visualisation being worse in the proximal stomach (cardia and fundus) compared to the rest of the stomach. The examination time for MACE was reduced to 26.4 minutes, compared to 43.8 minutes reported in their first feasibility study (68), and probably related to the increase in number of procedures performed per examiner. Adverse events (including abdominal distension, nausea, headache, vomiting and a sensation of a foreign body) occurred in only 1.4% of examinations, and were unrelated to MACE or possibly caused by the volume of water ingested prior to the procedure. Nevertheless, 335 out of 350 patients preferred MACE to OGD (95.7%).

## **1.7 Summary of current literature**

OGD is the gold standard investigation for the upper GI tract and is performed frequently. However, the impact of performing OGDs in high volume on patient management should be justified. The understanding of patient tolerance and acceptability of OGD requires further studying. Meanwhile, MACE has potential as an alternative means to achieve upper GI endoscopy. Currently available MACE systems demonstrate different strengths and limitations when compared to oesophageal

capsule endoscopy using the ESO2 (table 1). The Ankon NaviCam® system has been studied most extensively: recent reports include shorter capsule gastric transit time, improved small bowel capsule endoscopy completion rates and use in gastric cancer screening. (70-72) In contrast, there is less reported experience with the MiroCam Navi®. This has the advantage of portability (using a handheld magnet) and is less costly than large robotic MACE systems. However, the diagnostic yield of the MiroCam Navi® in patients has not been previously tested. It is also uncertain whether magnetic steering is actually necessary. Positional change of a patient may suffice to move capsules by gravity around the stomach, a technique not previously used. Capsule endoscopy is well tolerated by patients but for this technology to establish a place in the investigation of the upper GI tract then it must first demonstrate diagnostic accuracy comparable to OGD.

**Table 1:** Strengths and limitations of upper gastrointestinal capsule endoscopy systems. Fps, frames per second. GI, gastrointestinal. MACE, magnetically assisted capsule endoscopy.

	ESO2	MiroCam Navi®	Olympus & Siemens system	Ankon NaviCam®
<b>Strengths</b>	<ul style="list-style-type: none"> <li>• Double-ended capsule</li> <li>• High video capture frame rate (18 fps)</li> <li>• Simple to use, limited training required</li> </ul>	<ul style="list-style-type: none"> <li>• Active capsule steering</li> <li>• Handheld magnet cheaper than robotic magnets</li> <li>• Portable system</li> <li>• Combined upper GI and small bowel examination available</li> </ul>	<ul style="list-style-type: none"> <li>• Active robotic capsule steering</li> <li>• Double-ended capsule</li> <li>• 94.1% specificity for major lesion detection (63)</li> </ul>	<ul style="list-style-type: none"> <li>• Active robotic capsule steering</li> <li>• Combined upper GI and small bowel examination available</li> <li>• Largest statistically powered study on MACE to date: 90.4% sensitivity and 94.7% specificity for focal lesion detection in stomach (64)</li> </ul>
<b>Limitations</b>	<ul style="list-style-type: none"> <li>• Limited to 30 minute battery life</li> <li>• Predominantly for oesophageal examination only</li> <li>• Passive capsule movement only</li> </ul>	<ul style="list-style-type: none"> <li>• 3 fps</li> <li>• Single-ended capsule</li> <li>• Diagnostic yield in patients not reported</li> </ul>	<ul style="list-style-type: none"> <li>• Expensive and large space required to store apparatus</li> <li>• 4 fps</li> <li>• Training required to use MACE system</li> <li>• 61.9% sensitivity for major lesion detection (63)</li> </ul>	<ul style="list-style-type: none"> <li>• Expensive equipment</li> <li>• 2 fps</li> <li>• Single-ended capsule</li> <li>• Training required to use MACE system</li> </ul>



## **Chapter 2: Aims**

### **2.1 Null hypothesis**

There is no role for capsule endoscopy in the investigation of the upper gastrointestinal tract.

The body of work aims to address whether capsule endoscopy has a diagnostic role in the upper GI tract. The hypothesis is tested in two phases. Firstly the impact of current upper GI endoscopic practice, OGD, is challenged. The influence of diagnostic OGD on the patient management pathway is questioned. Patient tolerance and acceptability is also examined. The first two studies of this thesis assess whether an alternative means of upper GI endoscopy, other than OGD, is required. Next, the diagnostic yield of capsule endoscopy in patients is examined in common clinical scenarios requiring upper GI endoscopy: providing a platform to demonstrate the clinical relevance of capsule endoscopy in upper GI territory. This is tested with specific reference to MACE using the MiroCam Navi® (in those with recurrent and refractory iron deficiency anaemia and suspected acute upper gastrointestinal bleeding) and the novel upper GI capsule (Medtronic Ltd, Dublin, Ireland; in those declining conventional OGD). These points will be addressed by the five studies in the chapters to follow.

### **2.2 Phase 1**

**Chapter 3:** Reassessing the value of gastroscopy for the investigation of dyspepsia.

**Chapter 4:** Patient tolerability and acceptability of gastroscopy: a prospective study.

### **2.3 Phase 2**

**Chapter 5:** Magnetically assisted capsule endoscopy has higher diagnostic yield than gastroscopy in recurrent and refractory iron deficiency anaemia.

**Chapter 6:** Magnetically assisted capsule endoscopy in acute upper gastrointestinal bleeding.

**Chapter 7:** Upper gastrointestinal tract capsule endoscopy using a nurse-led protocol: first reported experience.

## **Chapter 3: Reassessing the value of gastroscopy for the investigation of dyspepsia**

### **3.1 Abstract**

#### **3.1.1 Introduction**

Dyspepsia is common and the demand for OGD is rising. OGD can be uncomfortable and is associated with the risk of perforation and sedation. The aim of this study was to evaluate the diagnostic yield of investigating dyspepsia with OGD with or without mucosal biopsy.

#### **3.1.2 Materials and Methods**

We conducted a retrospective cohort study of 500 patients, 55 years of age and over, who underwent OGD for investigation of dyspepsia. The study period included a 4-month window. All OGDs were performed on an outpatient basis. Data was extracted from electronic records within the study period to analyse procedural data, diagnostic yield provided by endoscopic examination and histological assessment.

#### **3.1.3 Results**

378 patients (75.6%) were reported to have some form of endoscopic abnormality and 417 patients (83.4%) had biopsies taken. The most common findings at OGD were gastritis (47.2%) and oesophagitis (24.4%). Oesophagogastric malignancy was seen in 1%. Diagnoses made endoscopically or histologically that would not have been appropriately managed by empirical therapies were seen in 16.2%.

#### **3.1.4 Conclusion**

OGD in dyspepsia influences patient management in approximately one sixth of cases. However,

the majority of patients are sufficiently managed with *Helicobacter pylori* testing and eradication and/or a trial of proton pump inhibitor therapy. Further non-invasive approaches are needed to identify patients who need endoscopy for biopsy or therapy.

### 3.2 Introduction

Dyspepsia is defined as a group of persistent symptoms including heartburn, upper abdominal discomfort or pain, and nausea or vomiting. These symptoms are common, affecting up to 25.9% of the European population. (73) The definitive diagnostic test is OGD, which is invasive, may be poorly tolerated and incurs the small risks of perforation and sedation (16, 17, 19).

The National Institute for Health and Care Excellence (NICE) first developed management guidelines for dyspepsia in an attempt to ensure appropriate referral for OGD in 2004, updating them in 2014. (74) American guidelines for managing dyspepsia adopt a similar approach. (75) For uninvestigated dyspepsia, NICE guidelines recommend a *Helicobacter pylori* 'test and treat' approach or an empirical four week trial of full dose proton pump inhibitor treatment and step down therapy to the lowest dose needed to control symptoms. This would effectively treat the majority of patients with peptic ulcer or reflux disease without recourse to invasive investigation. Urgent direct referral for OGD (the 'two week wait' pathway) is recommended for patients with suspected cancer: those over 55 years of age who have dyspepsia or reflux symptoms which are treatment resistant, associated with weight loss, nausea, vomiting or a raised platelet count. (75) This was introduced as part of the UK Department of Health Cancer Plan to improve early cancer detection and treatment. (76)

Therefore recent guidelines and health campaigns may have affected the nature of referral practice and the rate of diagnostic findings, particularly malignant disease. This study was performed to determine the diagnostic yield and the nature of the diagnoses made both macroscopically and microscopically (following histological analysis of mucosal biopsy) based on current referral and endoscopic practice.

### **3.3 Materials and Methods**

A retrospective cohort study of consecutive patients 55 years of age and over, who underwent OGD between September 2015 and January 2016 to investigate dyspepsia was performed at Sheffield Teaching Hospitals NHS Trust (STH). The study was registered and approved by the Clinical Effectiveness Unit, Sheffield Teaching Hospitals NHS Foundation Trust (registration number 7073). All procedures are automatically logged and data collated by InfoFlex software (Chameleon Information Management Services Ltd).

Data on patient demographics, use of sedation, procedure indication(s), endoscopic diagnoses (including site), histological diagnoses (including site) and any rapid urease tests performed was collected. Diagnoses were considered in terms of whether or not endoscopy (with or without biopsy) had influenced management over and above the NICE recommendations for the management of uninvestigated dyspepsia.

Statistical analysis was performed using SPSS v22.0 (IBM). Continuous data was expressed as mean  $\pm$  standard deviation (SD). Categorical variables were expressed as absolute numbers  $\pm$

percentages. The Fisher exact probability test was used to compare differences in categorical variables.  $p < 0.05$  (two-sided) was considered statistically significant.

### 3.4 Results

Over a 4-month study period, 500 OGDs were performed for patients with dyspepsia (table 2). A small proportion of patients presented with concomitant symptoms in addition to dyspepsia: dysphagia (6%), anaemia (4%), vomiting (4.2%) and suspected gastrointestinal (GI) bleeding (0.6%). 39.8% of patients were male and the mean age ( $\pm$ SD) of patients was 58 ( $\pm$ 16.1) years. 145 (29%) patients were sedated with midazolam (mean ( $\pm$ SD), 2.0mg ( $\pm$ 1.0)) and, in some cases, concurrent fentanyl (50 $\pm$ 23mcg).

**Table 2.** Diagnoses made at OGD performed to investigate dyspepsia. Those in bold required OGD to obtain histology or cytology and would not have been appropriately managed by empirical *H. pylori* ‘test and treat’ or proton pump inhibitor therapy. GAVE, gastric antral vascular ectasia; PHG, portal hypertensive gastropathy.

Oesophagus			Stomach			Duodenum		
	n	%		n	%		n	%
<b>Ulcer</b>	3	0.6	<b>Ulcer</b>	9	1.8	Ulcer	1	0.2
<b>Malignant tumour</b>	1	0.2	<b>Malignant tumour</b>	4	0.8			
<b>Barrett’s oesophagus</b>	39	7.8	Gastritis	268	47.2	Duodenitis	55	11
<b>Candidiasis</b>	10	2	Atrophy	1	0.2			
<b>Stricture</b>	7	1.4	GAVE	2	0.4			
Oesophagitis	122	24.4	Hiatus hernia	178	35.6			
Benign polyps	9	1.8	Benign polyps	34	6.8	Benign polyps	1	0.2
Schatzki ring	4	0.8	PHG	2	0.4			
Benign plaques	2	0.4						
Diverticula	1	0.2						

378 patients (75.6%) underwent an OGD with some form of endoscopic abnormality reported. Patients were described as having one (26.4%), two (21.8%), three (15.8%), four (8.0%), five (2.8%), six (0.4%) or seven (0.2%) endoscopic findings. In addition, 417 patients (83.4%) had biopsies taken: 15.8% for histological assessment, 27.4% for rapid urease tests and 40.2% for both. Patients had biopsies taken from one (37.8%), two (14.6%), three (3.0%) or four (0.6%) different sites.

Findings of uncertain relevance, or which could have been managed with empirical therapy, were seen in 309 patients (61.8%). These findings (Table 2) included oesophagitis (n=122), Schatzki rings (n=4), benign oesophageal plaques (n=2), oesophageal diverticulae (n=1), hiatus hernias (n=178), benign polyps (n=44), gastritis (n=269), benign gastric ulcers (n=9), gastric antral vascular ectasia (GAVE) (n=2), portal hypertensive gastropathy (PHG) (n=2), duodenitis (n=55) and a duodenal ulcer (n=1). Conversely, diagnoses made endoscopically and from biopsies that would not have been appropriately managed by empirical therapies, numbered 81 (16.2%; Table 2). These included 69 (13.8%) patients with Barrett's oesophagus (n=39), an oesophageal stricture (n=7), oesophageal cancer (n=1) and gastric cancer (n=4). Twelve (2.4%) patients had a diagnosis made solely by histology (without evidence of endoscopic abnormality), which included eosinophilic oesophagitis (n=1), eosinophilic gastritis (n=1), intestinal metaplasia (without atrophy, n=3) and coeliac disease (n=7).

Subgroup analysis by referral status according to national guidelines (74) was performed. Patients were grouped into those referred for urgent OGD for investigation of suspected cancer (within two weeks as recommended by NICE (75)) in the presence of alarm symptoms (including patients with dysphagia or aged 55 years and over with weight loss and upper abdominal pain and/or reflux and/or dyspepsia) and those only requiring a routine OGD. There was no significant difference in

the frequency of endoscopic findings that required management other than empirical proton pump inhibitor or a 'test-and-treat' approach between the two groups (urgent vs. routine, 15% vs 13.1%,  $p=0.61$ ). The number of oesophagogastric cancers in patients requiring urgent OGD was four (0.8%) while those undergoing non-urgent investigation was one (0.2%). However, this difference did not reach statistical significance ( $p=0.4$ ). Of those referred for urgent OGD, one case of oesophageal cancer had concomitantly reported dysphagia. In the remaining three cases of gastric cancer, one had iron deficiency anaemia, another with symptoms of dysphagia (not related to the diagnosis) and one patient only had symptoms of dyspepsia. One patient with gastric cancer diagnosed under the non-urgent pathway reported unrelated symptoms of dysphagia retrospectively.

### 3.5 Discussion

In this study, 75.6% patients who were referred for OGD to investigate dyspepsia had endoscopic abnormalities identified. However, only 16.2% had a diagnosis that required endoscopy, of whom 13.8% had a macroscopic abnormality. Although biopsies were taken for histological analysis or rapid urease testing in 83.4% of patients, these added to the diagnostic yield in only 2.4%. Malignant tumours were diagnosed in only 1% of patients with dyspepsia.

Despite the introduction of guidelines for managing benign symptoms in the community without recourse to invasive investigation and for direct urgent referral for OGD of patients with suspected cancer, diagnostic yield, including that of cancer, remains low. In fact disease detection is largely unchanged since introduction of the guidelines: meta-analysis of studies from 1950 to 2010 demonstrated that OGD performed to investigate dyspepsia was normal in 78% of cases, identified oesophagitis in 13%, peptic ulcer disease in 8% and other diseases (including cancer) in only 1%.



(10) The NICE guidelines recommend the same management approach for reflux and other dyspeptic symptoms. (74) This is in recognition of the fact that upper gastrointestinal symptoms are not specific to one disease process. (77) However hiatus hernia and oesophagitis were by far the commonest diagnoses in this cohort of patients, neither of which need routine endoscopic biopsy, reinforcing the importance of future research in distinguishing benign oesophageal from other gastroduodenal disease causing dyspeptic symptoms.

Peptic ulcer disease was rather less common. This would be consistent with a decline in peptic ulcer disease noted before the introduction of proton pump inhibitors (PPIs) (78), and may have been further affected by the increasing use of PPIs since. (79) It may be that the NICE guidelines along with other cancer campaigns (10), have increased awareness of symptoms amongst the patient population and actually reduced the threshold of referral for OGD by general practitioners, primarily to exclude malignant disease. While the 'test and treat' approach and PPI therapy adequately manages the symptoms of many patients, it may run the risk of delaying the diagnosis of upper GI malignancy. A normal OGD examination may not change the patient management pathway but potentially provides reassurance to patients and physicians alike by excluding cancer. (80) This would account for the 30% increase in demand for OGDs in the United Kingdom in the last 5 years. (81)

The diagnostic yield of malignant disease was low and all cancers were detected at an advanced stage. Meta-analyses suggest that individual alarm symptoms in isolation have limited ability to specifically identify the likelihood of malignancy (82, 83) and when they do so, disease is advanced; the value of combining symptoms to predict risk remains uncertain. The lack of specificity and low positive predictive value in current models incur a high number needed to treat in order to avoid

missing cancers. (84, 85) Disappointingly, approximately 11.3% of patients presenting with upper GI cancer have had an OGD within the preceding three years, suggesting that early stage disease is often missed. (11) This might be because of time pressures resulting in OGD being performed too rapidly, a lack of training in recognition of early malignant disease or poor tolerance of the procedure, resulting in inadequate insufflation or an abbreviated examination. The use of anti-foaming agents and mucolytics may also improve mucosal visualisation and early lesion detection. (86) The new national BSG guidelines on upper GI endoscopy address many of these issues but the effect on the detection of early malignancy is yet to be seen. (8) Cheung et al. showed that alarm features were significantly less likely at presentation in these patients than those identified at first OGD. (87)

As many as 83.4% of patients had biopsies, 56% for histological analysis and 67.6% for rapid urease testing. This practice may be driven by guidelines that recommend taking biopsies from normal looking mucosa in dyspeptic patients. (88, 89) The rate of biopsy at gastroscopy varies widely, based on the practice of individual endoscopists and can range from 22% to 66%. (90-92) While biopsy rates for histology were similar in this study, it is unclear whether this affects long-term outcomes. There may be a desire not to miss any histological diagnoses by endoscopists who may not always be familiar with the patients' symptoms and who want to avoid the risk of the patient being referred for a second invasive procedure. In our study this practice only increased diagnostic yield by 2.4% and half of these patients were referred for OGD specifically for biopsy (five with positive endomysial antibodies and one patient with dysphagia for oesophageal biopsies to diagnose eosinophilic oesophagitis). Based on previous local costings at our institute (93), this approximates to a total cost of over £21000 (£10,100 for biopsy forceps, £10,600 for histology and £1,100 for rapid urease testing). These data would support the findings of Nelsen et al. who found

that a practice of having a low threshold to take biopsies for histology had a low yield at high cost.

(94)

Better diagnostic capability at reduced cost might be addressed to some extent within the boundaries of current practice. Colonic polyp detection rates can be improved by increasing the examination time to allow more careful mucosal inspection. Although similar studies are yet to be conducted, it seems likely that the same will apply to OGD. (95-98) Poor tolerance of OGD may be associated with a reduced lesion detection rate (11) and some studies suggest that sedation, particularly for anxious patients, may improve tolerance (99, 100). Patients should have had their *Helicobacter pylori* status checked prior to referral (74) and appropriate notification on the referral form should render rapid urease testing unnecessary for most. Malignant lesions can be differentiated from benign lesions by chromoendoscopy in the hands of experts and studies have shown that training improves lesion recognition (98, 101, 102). As with the 'resect and discard' policy for small colonic polyps, this might lead to a reduced need for histological analysis (103, 104).

Multiple factors are likely to affect how diagnostic OGD will impact on patient outcomes in the near future. While the management pathway was only changed in one sixth of patients in our study, overall OGD still misses early gastric cancers in more than one in ten cases. The implementation of new national standards (8) for upper GI endoscopy may improve diagnostic yield. The biopsy rate at OGD is high and may be subject to the inexperience of endoscopists' and concerns not to miss premalignant lesions. Endoscopists with a 7 minute total examination time (105) and 3 minute withdrawal time (after reaching the second part of the duodenum) (92) have higher detection rates for early gastric malignancies. Longer examination times and improved mucosal cleanliness (8, 98) may influence the rate of biopsy: a pristine mucosa and time for careful examination may

provide endoscopists the confidence to exclude precancerous lesions, avoiding the need to blindly take biopsies for reassurance. Conversely, more thorough examinations may increase the detection of what would have been missed premalignant lesions, leading to more biopsies for histological diagnosis. A reduction in biopsy rates would favour the use of novel non-invasive tests: selecting only the minority of those needing histological sampling.

The availability of non-invasive testing to help differentiate benign from potentially malignant disease is more relevant than ever and in the future might allow diagnosis in the community and selection of the minority of patients who need referral for OGD for biopsy. Early data suggests that breath testing for five volatile organic compounds have been shown to have a sensitivity of 80% and specificity of 81% in detecting oesophagogastric cancer, although this was in patients with mostly advanced disease (106). A swallowable 'cytosponge' attached to a thread, from which cells are analysed following retrieval, has a 79.9% sensitivity in detecting Barrett's oesophagus and is capable of detecting a variety of other oesophageal diseases (107, 108). A panel of serological biomarkers of gastric atrophy (pepsinogen I and II, amidated G-17) and *H. pylori* IgG antibodies identifies gastric atrophy of the corpus and antrum with sensitivities and specificities of 70.2% and 51.6% and 93.9% and 84.1% respectively (109). However individual non-invasive tools to date predominantly screen for a single specific condition. (109-111) Of the novel screening tools capsule endoscopy provides the most comprehensive examination, potentially assessing all types of mucosal lesions. However, it is currently limited to the detection of disease in the distal oesophagus (Barrett's oesophagus, oesophageal varices) (28, 112) and stomach (64): the proximal oesophagus is a common site of missed malignancy. (113) Studies are required to demonstrate reliable capsule endoscopy assessment of the entire upper GI tract and further research is needed to determine the

role of these exciting non-invasive technologies in the identification of significant upper gastrointestinal disease and the selection of appropriate patients for endoscopic biopsy or therapy.

## **Chapter 4: Patient tolerability and acceptability of gastroscopy: a prospective study**

### **4.1 Abstract**

#### **4.1.1 Introduction**

Oesophagogastroduodenoscopy is commonly performed but can be poorly tolerated by patients.

#### **4.1.2 Methods**

In this prospective cohort study, patient tolerance and acceptability of OGD was examined. Patient concerns about, and experiences of, OGD were quantified on a visual analogue scale (1-10). Acceptability was also scored and assessed by the likelihood that patients would undergo OGD again or recommend it to a friend.

#### **4.1.3 Results**

156 patients were included in the study (mean age 56 years, 51.9% male). Anticipated and actual experiences respectively were (median and interquartile range): gagging 5 (IQR 6), 3 (IQR 6),  $p=0.15$ ; choking 5 (IQR 6), 2 (IQR 5),  $p=0.86$ ; discomfort 4 (IQR 4), 3, (IQR 5),  $p=0.32$ ; and the physical act of endoscopic intubation 4 (IQR 7), 3 (IQR 5),  $p=0.9$ . More than 36% (range 36.1% to 49.9%) of patients experienced a score of six and above for each of these symptoms. Baseline anxiety and depression nor use of sedation predicted these patient experiences ( $p>0.05$  for all parameters) or acceptability. The median acceptability score for OGD was 9 (range 0-10, completely unacceptable to perfectly acceptable): more than 90% of patients were willing to have a repeat test and advise a friend to have an OGD.

#### 4.1.4 Conclusion

Gagging, choking and discomfort related to endoscopic intubation of the oropharynx were major concerns for patients and predicted their actual experience. Nonetheless, OGD was regarded as acceptable by patients. Reducing patient concerns about, and improving experience of, OGD, will require interventions that minimise or avoid stimulating the gag reflex.

#### 4.2 Introduction

In the UK 1% of the population undergo OGD annually. (7) The number of OGDs performed in the UK rose by 48% between 2014 and 2015 in response to upper gastrointestinal cancer awareness campaigns (114) while in the United States of America (USA) a 54% rise was observed between 2000 and 2009. (115) However in Chapter 3 we demonstrate OGD in patients with dyspepsia, the most common indication for OGD (115), only changes management in 16.2%. Furthermore, allowing for some variation in definition, between 31 to 78% of patients report at least moderate discomfort with unsedated OGD (14, 16, 20, 26, 100, 116), 8-10% fail to tolerate it (20, 116) and 27 to 35% prefer not to have another. (116, 117) Even with sedation, Abraham et al. reported that 19% would rather not have a repeat OGD. (116) Although adding to cost and inconvenience to patients (116), many national societies recommend offering moderate sedation for OGD (118-121), but whilst this improves patient satisfaction and willingness to undergo another procedure (122), it is not known if this is due to a reduction in anxiety and pain or amnesia. A better understanding of how OGD causes distress may allow the development of safer and more effective methods of investigation.

Tolerance of the procedure is only one measure of the impact that a test has on a patient. To address the broader concept of acceptability of a test, Condon et al. devised an Endoscopy Concerns Scale (ECS), a composite of individual measures of emotional, social and anticipatory physical reactions to endoscopy as well as the actual experience of the procedure itself. (14) Comprising 14 questions answered on a visual analogue scale (VAS), it showed good internal consistency, convergent validity and evidence of discriminatory validity. In this study, patients had the same level of concern about OGD as they did about colonoscopy prior to their procedures and suffered similar levels of procedure-related discomfort, but sensations specific to OGD were not described. However, this was primarily a study of colonoscopy patients and the OGD patient cohort was small.

Poor acceptability of a test is likely to affect compliance with investigation of symptoms and surveillance procedures. (123, 124) A better understanding of factors which have a negative impact on procedural acceptability and the specific nature of the distress caused by OGD would help to determine at what point in the pathway patients need support, the nature of the support needed, whether the test can be delivered in a more acceptable way or a more appropriate alternative identified.

The primary aim of this study was to assess the patient tolerance and acceptability of OGD. Quantification of patient concerns pre-procedure, comparison between anticipated and actual experience and assessment of acceptability of OGD was achieved using the Hospital Anxiety and Depression Scale (HADS) and a modified version of the ECS (mECS) (appendix 1). Acceptability was also scored by asking patients how likely they were to undergo the test again or recommend the test to a friend. (14)



### 4.3 Methods and materials

#### Patient questionnaires

We performed a prospective cohort study of consecutive patients presenting for OGD at Sheffield Teaching Hospitals NHS Trust, UK. Exclusion criteria for the study were patients under the age of 18 years and non-English speakers. The study was registered with the Clinical Effectiveness Unit (CEU number: 7073), STH. Prior to their procedure, participants were asked to score (from 1-10 on a visual analogue scale) their level of concern about a range of social, emotional and physical experiences related to OGD described in the mECS (appendix 1) and completed a HADS questionnaire. Two members of the study team (who were not part of the endoscopy department) collected data. The Hospital Anxiety and Depression Scale consists of two subscales of seven questions each to assess the baseline state of anxiety (HADS-A) and depression (HADS-D) in the clinical setting (appendix 2). (125) HADS-A and HADS-D components have a maximum score of 21 each. A score of 8 or more has a sensitivity and specificity for anxiety of 91% and 78% respectively; for depression, this is 83% and 79% respectively. (126)

Following the procedure whilst awaiting discharge, patients were asked to complete the post-procedural section of the mECS to allow comparison of anticipated with actual experiences. Patients who received sedation were approached in the same way as unsedated patients as answers to questionnaires do not differ significantly from those collected at a later date. (127) Patients also scored the acceptability of OGD as a diagnostic test on a visual analogue scale (0-10: completely unacceptable to perfectly acceptable). As a second measure of acceptability, they were asked if they would be prepared to undergo an OGD again or advise a friend to have the test under the same circumstances and if they would have an OGD as a screening test for cancer in one to two years time. (14)

## **Gastroscopy**

OGD was performed in a standard fashion. All procedures were automatically logged by InfoFlex software (Chameleon Information Management Services Ltd, UK). All patients received Lignocaine 100mg/g throat spray (Xylocaine®). Sedation was given according to patient choice. Endoscopists recorded their assessment of patient comfort on Infoflex as good, acceptable, poor or not tolerated (assigned scores of 0-3 respectively for data analysis). Endoscopists were made aware that service evaluation was being undertaken during the study period but were not privy to which procedures were being assessed and did not have access to study data.

## **Statistics**

IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, New York: IBM Corp.) was used for statistical analysis. Parametric continuous data (Shapiro-Wilk test,  $p$ -value  $\geq 0.05$ ) is presented as mean  $\pm$  standard deviation (SD) and non-parametric continuous data (Shapiro-Wilk,  $p < 0.05$ ) as median with an inter quartile range (IQR). Categorical variables were expressed as absolute numbers  $\pm$  percentages. Multiple (or binomial where dependent variables were dichotomous) or hierarchical regression was performed to assess the ability of independent variables to influence an ordinal dependent variable. A Kruskal-Wallis H test was used to compare non-parametric variables when there were more than two independent variables and Bonferroni-adjusted Mann-Whitney U test for post hoc analysis. A  $p$ -value less than 0.05 was considered statistically significant.

## 4.4 Results

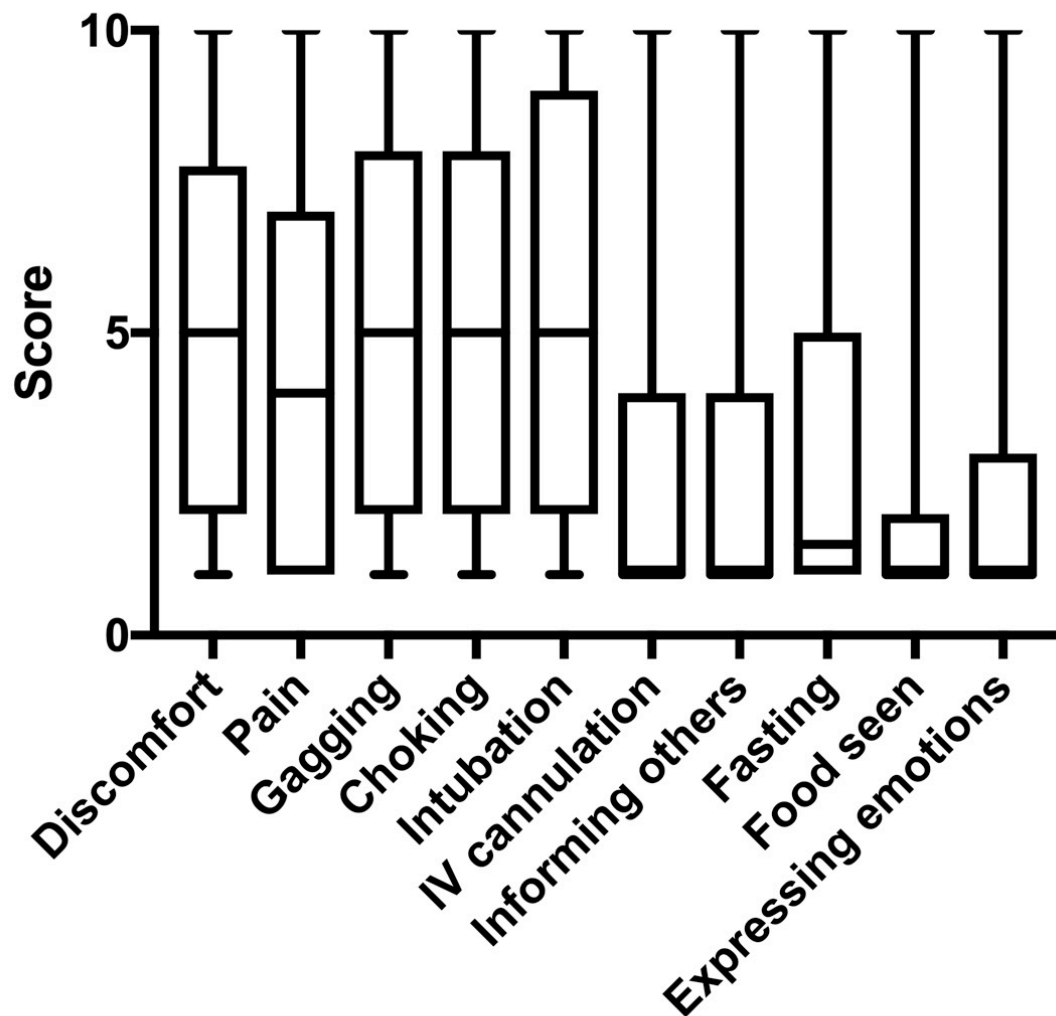
### Patient demographic and procedural data

One hundred and fifty nine patients were recruited between November 2016 and June 2017. Three patients provided incomplete questionnaires and were excluded, leaving 156 patients for analysis. The mean age of patients was 56 years ( $\pm 17$ ) with 51.9% of patients being male. The median HADS-A and HADS-D scores observed were 5 (IQR=7) and 3 (IQR=6) respectively. Pre-procedural sedation was given in 39.1% of cases (37.8% had midazolam alone and 16% had fentanyl in addition). When used, the median doses of midazolam and fentanyl were 2mg (IQR 1) and 50mcg (IQR 50) respectively.

### Patients' anticipated and actual experience of OGD

Patients scored their anticipated concerns regarding gagging (5 (IQR 6)), choking (5 (IQR 6)), discomfort (4 (IQR 4)), pain (4 (IQR 4.5)) and the physical act of endoscopic intubation (4 (IQR 7)) higher than those regarding intravenous cannulation (1 (IQR 1)) and the four social embarrassment factors of telling friends about the test (1 (IQR 3)), fasting (1 (IQR 4)), the doctor seeing food in the stomach (1 (IQR 1)) and expressing emotions during the test (1 (IQR 2)) (Kruskal-Wallis H test,  $p=3.6 \times 10^{-65}$ ; Bonferroni adjusted post-hoc analysis for all comparisons,  $p < 0.05$ ) (figure 5). Scores of greater than five were given by patients for expected gagging in 64.4%, choking in 60.1%, discomfort in 53.8%, pain in 46.1% and intubation in 59.3%. A higher HADS-A score did not predict more concern about these physical factors but predicted distress from the four social embarrassment factors ( $p < 0.05$  for all comparisons). Otherwise there was no association between HADS (anxiety or depression) scores with any other factor. Lesser anticipated concerns for patients were bloating (3, (IQR 4)) and vomiting (2, (IQR 6)).

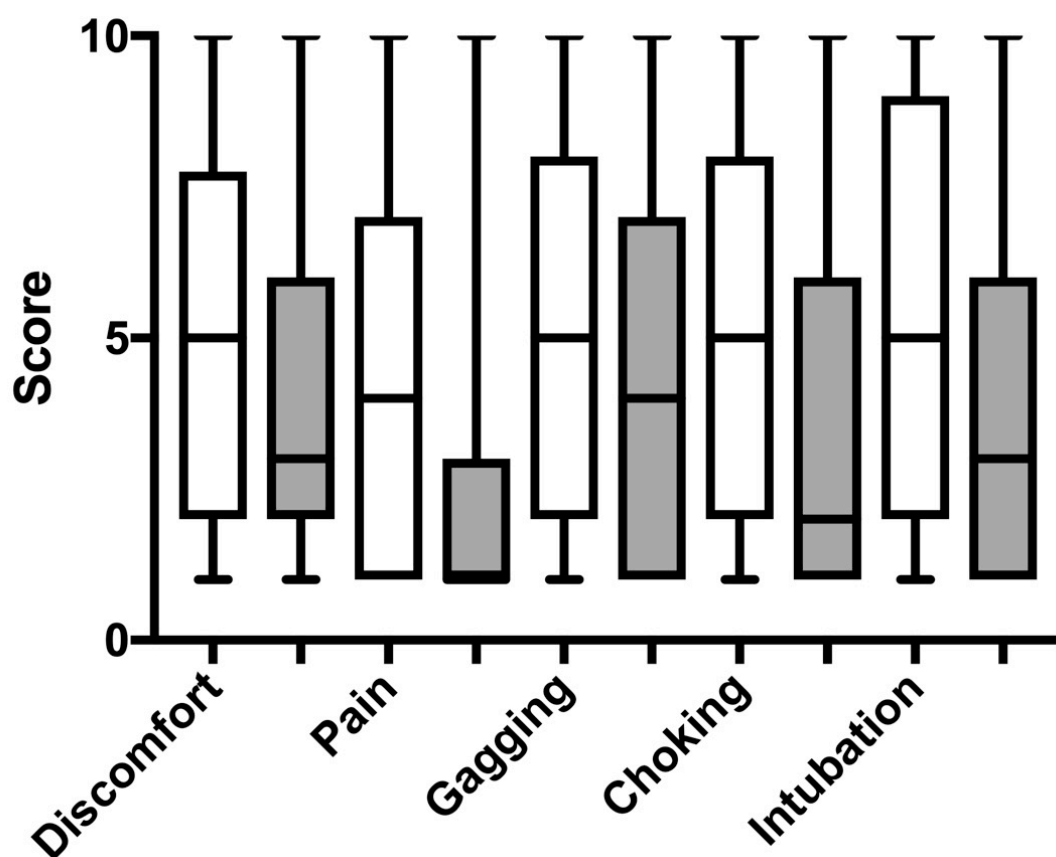
**Figure 5.** Box and whisker plot of anticipated physical and social distress experienced by patients undergoing oesophagogastroduodenoscopy. IV, intravenous.



Patients' actual experiences showed that they correctly predicted which aspects they would find most unpleasant: gagging (3 (IQR 6),  $p=0.15$  when compared to anticipated experience), choking (2 (IQR 5)),  $p=0.86$ , discomfort (3, (IQR 5)),  $p=0.32$ , pain (1 (IQR 2)),  $p=0.57$  and endoscopic intubation (3 (IQR 5)),  $p=0.9$  (figure 6). The endoscopy-specific symptoms of gagging, choking and distress from intubation were not associated with general discomfort ( $p=0.07$ ,  $0.88$  and  $0.64$  respectively) or pain ( $p=0.07$ ,  $0.29$  and  $0.53$  respectively). Bloating, vomiting and intravenous cannulation scored 2 ((IQR 2)),  $p=0.28$ , 1 ((IQR 1.5)),  $p=0.56$  and 1 ((IQR 1)),  $p=0.8$  respectively.

Scores of the actual experience of greater than five were given by patients for gagging in 49.9% ( $p=0.07$  compared to the percentage of patients anticipating a score of over five), choking in 36.1% ( $p=0.001$ ), discomfort in 36.5% ( $p=0.01$ ), pain in 13.9% ( $p=0.0001$ ) and intubation in 47.6% ( $p=0.002$ ).

**Figure 6.** Box and whisker plot of anticipated (white) and actual (grey) physical symptoms experienced by patients undergoing oesophagogastroduodenoscopy.



Neither the HADS-A and HADS-D scores, nor the use of sedation, statistically predicted the patients' actual experience of discomfort ( $p=0.55$ ,  $0.82$  and  $0.69$  respectively), pain ( $p=0.53$ ,  $0.89$  and  $0.52$  respectively), gagging ( $p=0.79$ ,  $0.65$  and  $0.28$  respectively), choking ( $p=0.7$ ,  $0.94$  and  $0.4$  respectively) or distress from intubation ( $p=0.5$ ,  $0.44$  and  $0.7$  respectively) (table 3). Endoscopists'

scores did not correlate with patients' scores of discomfort ( $p=0.41$ ) or pain ( $p=0.80$ ), nor did it predict actual experience of gagging ( $p=0.94$ ), choking ( $p=0.41$ ) or distress from intubation ( $p=0.56$ ).

**Table 3:** Patient demographics and procedural factors did not influence experience of the most distressing symptoms associated with gastroscopy

	Gagging	Choking	Distress from intubation	Discomfort
<i>p-values from hierarchical multiple regression</i>				
<b>Age</b>	0.54	0.74	0.99	0.34
<b>Female gender</b>	0.20	0.15	0.44	0.70
<b>HADS-A score</b>	0.79	0.70	0.50	0.55
<b>HADS-D score</b>	0.65	0.94	0.44	0.82
<b>Sedation</b>	0.28	0.40	0.70	0.69
<b>Endoscopist rating of patient comfort</b>	0.94	0.41	0.56	0.41

### Acceptability of OGD

The median acceptability score was 9 (IQR 4) and was not associated with age, gender, HADS, use of sedation, endoscopists' rating of comfort or any individual actual experience of physical symptoms ( $p>0.05$  for all parameters). However, a higher total ECS score (sum of all scores for anticipated and actual experiences) was associated with a lower acceptability VAS score (beta =  $-0.261$ ,  $p=0.016$ ). Only 8.6% of patients assigned an acceptability score of less than six. Overall patients found OGD acceptable with 92.9% willing to have a repeat test and advise a friend to have an OGD and 91.7% willing to engage with further OGD surveillance.

## 4.5 Discussion

Patients correctly predicted that gagging, choking, discomfort and the physical act of intubation were the most distressing aspects of OGD although less so than anticipated. None of these symptoms correlated with either the pain or discomfort that they actually suffered and whilst pain was feared, this proved to be an uncommon experience. Severity of the symptoms did not differ between sedated and unsedated patients. Factors related to OGD which might cause inconvenience or embarrassment, vomiting or bloating and intravenous cannulation were of much less concern. A high HADS-A score predicted greater concerns about the inconvenience and embarrassing aspects of OGD but otherwise there was no association with other anticipated factors or the actual experience. Nonetheless, all measures suggested that patients found the test highly acceptable.

This study demonstrates that it is the physical sensations related to the gag reflex induced by pharyngeal intubation that cause most patient distress during OGD and indeed throughout most of the care pathway. It is, however, consistent with studies showing that a strong gag reflex (in response to topical anaesthetic spray or digital palpation of the pharynx) predicts poor tolerance of OGD. (16, 116) Patients were anxious about suffering pain, and guidelines recommend the use of sedation to minimise it, (120-122) but in fact the median score for pain was the same as that for intravenous cannulation and only 13.9% of patients assigned a severity score of more than five. 'Discomfort' is a broader term which might be applied to a range of unpleasant sensations and patients anticipated and suffered discomfort almost as commonly as they did gagging and the experience of intubation. This is consistent with the data of Irvine et al., who found that patients gave much higher discomfort than pain scores to unsedated OGD. (26) The median score for actual discomfort in our cohort was three with 36.5% of patients reporting discomfort with a score of six or more. This is similar to the reports of Mulcahy et al. where, using a similar VAS, the median score

for discomfort was five with 9% of patients reporting very high levels (score 8 to 10). (20) Assessing discomfort rather than pain would be more appropriate in future studies. However, as the most distressing symptoms of gagging and choking related to endoscopic intubation did not correlate with discomfort, assessment of these specific symptoms should be considered.

Although the median scores for anticipated gagging, choking, discomfort, pain and distress from intubation were mid-range (5, 5, 4, 4 and 4 respectively), the non-parametric distribution of data and the large interquartile ranges mean that more than 45% (range from 46.1% to 64.4%) of patients anticipated a score of six and above for each of these symptoms. Previous studies have suggested that OGD-related anxiety may be associated with poor tolerance, but this is not universally the case. (16, 20) Curiously, our study suggested that a higher HADS-A score predicted greater concerns about socially embarrassing factors related to the procedure, but not aspects related to procedural tolerance or overall acceptability. Therefore, whilst appropriate explanation and reassurance may reduce anxiety about these factors (20, 100), it seems unlikely that psychological therapies would have a significant impact on overall patient outcomes.

There are limitations to our study. The ECS was validated in a study where acceptability of colonoscopy was the primary outcome being assessed (14): validation of the ECS tool may not apply to the assessment of OGD. Our study was exploratory. Future efforts should seek to validate tolerance and acceptability assessment tools for upper GI endoscopy, which at present do not exist, using large studies to achieve statistical power. Before considering how better to minimise the most distressing aspects of OGD, it is worth interrogating the data from this and previous studies. Sedation did not appear to have an impact as might have been expected in light of a meta-analysis suggesting that it improves overall patient experience and likelihood of having a repeat test.



However, the studies included in this meta-analysis used a mean of 4.8-10.3mg midazolam, several times the dose used in most of our patients. (122) The widespread practice of unsedated OGD or the use of relatively small doses of medication in the UK are a result of national drive to minimise sedation-related morbidity and mortality. (128, 129) As a consequence, sedative doses used are less than those demonstrated as having any measurable benefit. Furthermore, sedation use was not randomised in our study. Use of sedation was based on patient choice but may have also been influenced by the endoscopist and encouraged if they felt that the patient was particularly anxious: this would impose a selection bias and a randomised control trial in the future may provide better insight regarding the effects of sedation on tolerance and acceptability.

Whether alternative agents can improve the patient experience without incurring greater risk remains to be proven. Propofol, a hypnotic agent, used alone or in combination with midazolam and/or an opioid, is commonly used in the USA and parts of Europe, but without clear evidence of benefit over midazolam alone. (122, 130) Development of sedation protocols should be evidence based: this and other studies show that endoscopists tend to underestimate patient discomfort. (100, 131, 132) Non-pharmacological approaches to improving patient acceptability have been studied. Smaller calibre endoscopes are less likely to be associated with patient reported discomfort than larger instruments (20, 121) and a randomised trial has shown that unsedated ultrathin OGD is as well accepted as sedated OGD using a standard instrument. (21) Transnasal endoscopy avoids stimulating the base of the tongue, which is partly responsible for the gag reflex, and is associated with an improved tolerance compared to OGD. (133) Finally, the lack of an endoscopic cable means that capsule endoscopy removes the pharyngeal stimulus entirely and is extremely well tolerated by patients. (64, 134, 135)

The discrepancy between the symptoms caused by OGD and the high level of acceptability of the test is difficult to explain. This could be due to patients knowing that OGD is the accepted gold standard and a perception that there is no viable alternative. A previous study also reported a very high level of acceptability when assessed post-procedure, which was significantly higher than when assessed pre-procedure. (14) Other findings suggest that patients may have significant anxieties about possible diagnoses (20) which are allayed following a reassuring examination, perhaps contributing to an improved acceptability post-procedure.

In summary, the most distressing aspects of OGD are the gagging and choking caused by pharyngeal intubation and the symptoms experienced are better described as discomfort rather than pain. Future studies aiming to improve the experience of upper gastrointestinal assessment should consider assessing the impact of novel pharmacological therapies on these symptoms or consider technologies that avoid inducing the gag reflex.

## **Chapter 5: Magnetically assisted capsule endoscopy has higher diagnostic yield than gastroscopy in recurrent and refractory iron deficiency anaemia**

### **5.1 Abstract**

#### **5.1.1. Introduction**

Small bowel capsule endoscopy is advocated and repeat upper GI endoscopy should be considered for recurrent and refractory iron deficiency anaemia (IDA). The MiroCam Navi® allows MACE of the stomach followed by passive small bowel examination and might satisfy both requirements as a single procedure.

#### **5.1.2 Methods**

In this prospective cohort study, MACE and OGD were performed in patients with recurrent/refractory IDA. Comparisons of total (upper GI and small bowel) and upper GI diagnostic yields, gastric mucosal visibility and patient tolerance scores were the primary endpoints.

#### **5.1.3 Results**

Forty-nine patients were recruited (median age 64 years, 39% male). Combined upper and small bowel examination using the MiroCam Navi® yielded more pathology than OGD alone (113 vs. 52,  $p=0.0001$ ). Comparing only upper GI examination (proximal to the 2<sup>nd</sup> part of the duodenum, D2), MACE identified more total lesions than OGD (88 vs. 52,  $p<0.0001$ ). If only IDA-associated lesions are included (oesophagitis, altered/fresh blood, angioectasia, ulcers and villous atrophy), a difference remains (20 vs. 10,  $p=0.04$ ). Pathology distal to D2 was identified in 17 patients (34.7%). Median scores (worst-best=0-10) for pain (0 vs 2), discomfort (0 vs 3) and distress (0 vs 4) were lower for MACE than OGD respectively ( $p=0.0001$ ).

### 5.1.4 Conclusion

Combined examination of the upper and small bowel with the MiroCam Navi® detects more pathology than OGD alone in patients with recurrent/refractory IDA. MACE also has better diagnostic yield than OGD in the upper GI tract and is better tolerated.

### Introduction

Iron deficiency anaemia (IDA) is commonly due to GI blood loss. (136, 137) However, first-line endoscopic investigations, OGD and colonoscopy fail to identify a cause in approximately 30% of cases. (138) SBCE is reserved for those with recurrent or refractory IDA (25, 139) in whom diagnostic yield ranges between 44-66%. (35, 140) Of note, up to 25% of pathologies detected at SBCE are benign lesions within reach of OGD. (141-145) Repeat OGD should therefore also be considered in the investigation of recurrent and refractory IDA. (50) OGD is, however, invasive, not without risk (146, 147), may not be well tolerated (16, 26) and yet any pathology is almost always benign. (142-145)

In addition to the ability to perform upper GI MACE, the MiroCam Navi® has an 11-hour battery life that allows follow-on small bowel examination using the same capsule. (62) It might, therefore, provide examination of both the upper and mid-gut required for recurrent and refractory IDA. The primary aims of the study were to compare diagnostic yields and patient comfort of the MiroCam Navi® and OGD in patients with recurrent or refractory IDA and to assess gastric mucosal visibility achieved using MACE. Secondary outcomes included a comparison of the Mirocam Navi® and OGD

in assessment of the oesophagus, stomach and proximal duodenum. The study was executed as an exploratory trial in order to generate a hypothesis for further confirmatory trials.

## **Methods**

### **Patients**






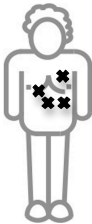



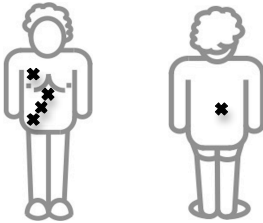
A prospective, single blinded, cohort study was conducted in Sheffield Teaching Hospitals NHS Trust, UK. All patients aged 18 years or over with recurrent or refractory IDA who were referred for both upper GI and small bowel investigation by OGD and SBCE respectively as part of routine clinical investigation were eligible for the study. SBCE was performed using the MiroCam Navi® which, prior to entering the small bowel, was used to examine the upper GI tract with the handheld magnet. Patients with pacemakers, intra-cardiac devices, magnetically or electrically controlled devices or those who were pregnant, had Crohn's disease or long-term use (over six months) of non-steroidal anti-inflammatory drugs were excluded.

### **Magnetically-assisted capsule endoscopy (MACE)**

MACE was performed using the MiroCam Navi® by one of two investigators (Dr. Hey-Long Ching (HLC) or Dr. Melissa F Hale (MFH)). Patients drank two litres of Klean Prep® (Norgine, Uxbridge, UK) the evening before the procedure as per standard protocol for SBCE. Immediately prior to capsule endoscopy, one litre of water (containing 40mg of simethicone) was given orally to distend and optimise gastric views as previously described. (62) Patients swallowed the capsule in the right lateral position to view the oesophagus according to the simplified ingestion protocol described by Gralnek et al. (148) The hand-held magnet was placed over the lower sternum to try and capture the capsule before it reached the gastro-oesophageal junction (GOJ). This was followed by a series

of patient positional changes to help carry the capsule to a new location in the flow of swallowed water. The patient was asked to lie supine and the magnet moved through a sequence of positions to view the proximal stomach. Once in position, subtle changes in rotation (altering the polarity) and distance (altering the strength of attraction) of the magnet from the capsule were used to swivel the capsule around its vertical axis to obtain a near 180° view. (60) Similar sequences (described in detail in table 4) were followed with the patient in the left lateral, supine and right lateral positions to further image the proximal stomach, the gastric body and distal stomach respectively. If felt necessary, the patient was also examined in the upright seated position.

**Table 4.** Sequences of patient and magnet positions used in gastric examination by the MiroCam Navi®. Patient positions are illustrated as a birds-eye view. Magnet positions are marked with an 'x'.

Patient position	Sequence of magnet positions
<b>1</b> Right lateral 	Lower sternum 
<b>2</b> Supine 	Lower sternum, right xiphisternum, left pectoral, left xiphisternum 
<b>3</b> Left lateral 	Left pectoral, right xiphisternum, left upper quadrant, epigastrium 
<b>4</b> Supine 	Right xiphisternum, left upper quadrant, umbilicus, right upper quadrant 
<b>5</b> Right lateral 	Epigastrium, right umbilicus, right pectoral, right lower quadrant, right thoracolumbar spine (posteriorly) 

Visibility at major anatomical landmarks was graded on a 1-5 scale (poor to excellent, appendix 3) using an adapted protocol. (68) A single reporter (MEM) reviewed all capsule videos and reported upper GI pathology and graded mucosal visibility while blinded to the live-MACE findings to avoid inter-observer bias. To minimise variation in pathology reporting between MACE and OGD, endoscopists were required to describe pathology using terms selected from a pre-defined diagnostic list (appendix 2). Once gastric MACE was complete, the capsule was allowed to pass into the small bowel under the action of peristalsis for small bowel examination to be completed. Standard practice in the unit was followed, such that intramuscular metoclopramide (10mg, Hameln Ltd, Gloucester, UK) was administered if the capsule endoscope had not traversed the pylorus within 45 minutes of ingestion. The effect of small bowel preparation was rated overall as good, fair, or poor.

### **Gastroscopy (OGD)**

A member of the study team (accredited by the UK Joint Advisory Group on GI Endoscopy for independent OGD practice), (8) blinded to MACE findings, performed OGD using Olympus GF-260 gastroscopes (Olympus, Tokyo, Japan). Sedation for OGD was administered according to patient choice. Oesophagogastrroduodenal pathology detected at OGD was documented in a similar fashion to MACE using terms selected from the same predefined diagnostic list (appendix 2). In addition, patient tolerance of the two modalities was compared using a previously validated visual analogue scale (VAS) (score 0 to 10, none to extreme) (appendix 3). (26, 149)



## Ethics

This study was approved and performed in accordance with the ethical standards of the Yorkshire & The Humber -South Yorkshire NHS Research Ethics Committee (14/YH/1010. Clinicaltrials.gov number: NCT02282553) and the 1964 Helsinki declaration and its later amendments.

## Statistics

Advice was sought from the University of Sheffield Mathematics and Statistics Resource Centre. Upper gastrointestinal pathology within reach of OGD is detected in up to 25% of patients with recurrent/refractory iron deficiency anaemia. (141-145) The diagnostic yield of capsule endoscopy in this cohort is between 44% and 66%: a 55% yield was therefore assumed for the purpose of this study. (35, 140) In order to achieve 80% power and 5% two-sided significance, it was estimated that a sample size of 41 patients would be needed to show a difference in diagnostic yield between the two modalities. The study aimed to recruit 50 patients to allow for patients withdrawing from the study between the two examinations.

Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, NY: IBM Corp.). Continuous data is presented as a mean value  $\pm$  standard deviation (SD) or median  $\pm$  inter quartile range (IQR). Categorical variables are expressed as absolute numbers  $\pm$  percentages. Total study population and subgroup analysis was performed with similar statistical methods. Binomial regression was used to compare one or more independent variables with a dichotomous dependent variable. The McNemar's test was used to compare paired proportions. The Kruskal-Wallis H test was used for rank-based nonparametric comparison. Statistical significance was defined as  $p < 0.05$ . All co-authors had access to the data, reviewed and approved the final manuscript.

## Results

### Demographics

Fifty patients (39% male; median age 66 years (IQR=15)) were consecutively enrolled in the study between December 2014 and August 2017. All patients had previously had bidirectional endoscopy after their initial presentation with IDA. Forty patients had recurrent- and nine patients refractory IDA. One patient completed MACE but subsequently declined OGD and was excluded from analysis. The majority of patients (n=39, 79.6%) had MACE prior to OGD with 10 patients undergoing MACE after OGD (20.4%). The median duration between OGD and MACE was two days (IQR=13). The mean haemoglobin was 101.1g/dL ( $\pm 20$ ), ferritin 15.8 $\mu$ g ( $\pm 15$ ) and mean cell volume 79.6fL ( $\pm 7.9$ ). Sedation was given to 38.8% of OGD patients. Mean midazolam and fentanyl doses in these cases were 2.5mg ( $\pm 0.8$ ) and 50mcg ( $\pm 11.8$ ), respectively.

### Diagnostic yield of MACE and OGD

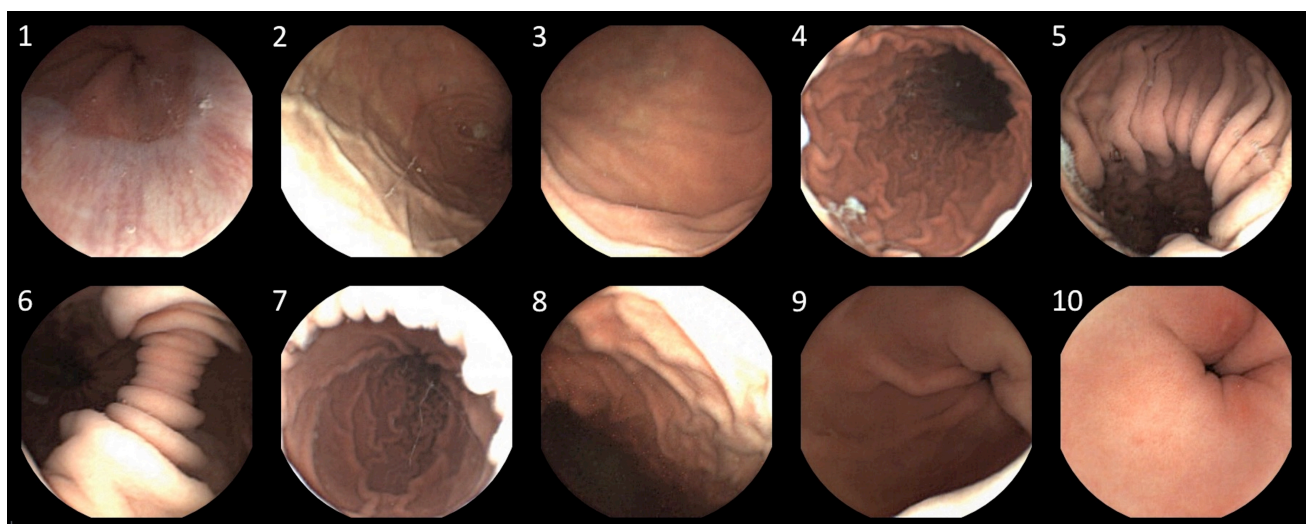
Capsule endoscopy of the upper GI tract using MACE combined with conventional (passive) examination of the small bowel identified more lesions than OGD (113 vs. 52, 95% confidence interval (CI) 0.41 to 0.53,  $p=0.0001$ ).

### Magnetically assisted capsule endoscopy

Mean examination time for upper GI MACE was 23 minutes (mins) ( $\pm 10$ ). The median time for the capsule to traverse the pylorus (gastric transit time) was 62 mins (IQR=50). Visualisation of upper GI major landmarks was achieved in most cases: oesophagus, 89.8%; GOJ, 53.1%; gastric cardia, 95.9%; fundus, 98%; greater and lesser curvature, 98% each; anterior and posterior gastric body, 98% each; antrum, pylorus, first and second part of the duodenum (D1 and D2), 100% each (figure 7). A statistically significant difference was detected with the GOJ being less visualised by MACE

than all other areas ( $p=0.0002$ ). The MiroCam Navi® capsule was magnetically steered into the duodenum in 11 patients (22.4%). In the remainder, passive entry into the duodenum occurred (with or without metoclopramide). The median visibility scores were: oesophagus, 4 (IQR 4); GOJ, 1 (IQR 3); gastric cardia 5, (IQR 3); fundus, 3(IQR 2); greater curvature, 5 (IQR 1); lesser curvature, 5 (IQR 0); gastric cardia 5, (IQR 3); fundus, 3(IQR 2); greater curvature, 5 (IQR 1); lesser curvature, 5 (IQR 0); anterior body, 5 (IQR 0.5); posterior body, 5 (IQR 0.5); antrum, 5 (IQR 0); pylorus, 5 (IQR 0); D1, 3 (IQR 1); D2, 5 (IQR 0). The frequencies of visibility grades for each anatomical landmark are illustrated in table 5. There was a statistically significant difference between visualisation scores of different areas ( $\chi^2=209.5$ ,  $p<0.05$ , Kruskal-Wallis H test). Better visualisation scores were seen in the greater and lesser curvatures, anterior and posterior body, antrum, pylorus and second part of the duodenum. Compared to these areas, lower visualisation scores were seen in the oesophagus, GOJ, cardia, fundus and D1: apart from the cardia, this difference reached statistical significance with post-hoc analysis ( $P < 0.05$ , with Bonferroni correction).

**Figure 7.** Normal views of major upper gastrointestinal landmarks achieved by MACE. 1, gastro-oesophageal junction; 2, cardia; 3, fundus; 4, greater curvature; 5, lesser curvature; 6, incisura angularis; 7; anterior gastric body wall; 8; posterior gastric body wall; 9, antrum; 10, pylorus.



**Table 5.** Frequency of visibility grades reported at each major upper gastrointestinal landmark during magnetically assisted capsule endoscopy

	Frequency of visibility grades (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Oesophagus	40.9	0	2.3	9.1	47.7
Gastro-oesophageal junction	23.1	26.9	15.4	12	23.1
Cardia	17	8.5	8.5	12.8	53.2
Fundus	14.6	14.6	20.8	31.3	18.8
Greater curve	0	0	12.5	12.5	75
Lesser curve	0	0	6.3	14.6	79.2
Anterior gastric body	0	0	10.4	12.5	77.1
Posterior gastric body	0	0	10.4	12.5	77.1
Antrum	0	0	2	14.3	83.7
Pylorus	2	0	2	12.2	83.7
1 <sup>st</sup> part of duodenum (D1)	8.2	10.2	38.8	22.4	20.4
2 <sup>nd</sup> part of duodenum (D2)	0	0	6.1	14.3	79.6

### Upper gastrointestinal pathology detection

Two patients had both normal MACE and OGD examinations. In the remaining 47 patients, MACE and/or OGD identified a total of 102 lesions proximal to D2 (table 6); Thirty-eight of these lesions (37.3%) were identified concomitantly by both modalities. A statistically significant difference was detected with more overall lesions identified in the upper GI tract (oesophagus, stomach and duodenum up to and including D2) by MACE alone (50 lesions, 49%) (figure 8) compared to OGD alone (14 lesions, 13.7%; 95% CI 0.21 to 0.48,  $p<0.0001$ ). This difference remained during subgroup analysis with MACE detecting more total upper GI lesions than OGD with or without sedation ( $p=0.0033$  and  $0.0031$  respectively). More gastric lesions were detected by MACE alone compared to OGD alone (36 vs. 5 respectively,  $p=0.0001$ , table 6). No statistically significant difference was seen in lesion detection by MACE or OGD alone in the oesophagus (7 vs. 6 respectively,  $p=1$ ) or duodenum (7 vs. 3 respectively,  $p=0.18$ ). Subgroup analysis demonstrated similar results: more gastric lesions were detected by MACE than OGD alone whether OGD was performed with (16 vs. 1

respectively,  $p=0.0007$ ) or without sedation (19 vs. 4 respectively,  $p=0.0035$ ). No statistically significant difference was seen in oesophageal or duodenal lesion detection irrespective of whether sedation was given for OGD ( $p>0.05$  for all).

**Table 6:** Upper gastrointestinal pathology detection by magnetically assisted capsule endoscopy (MACE) and oesophagogastroduodenoscopy (OGD) for each study patient. D1, first part of duodenum; D2, second part of duodenum.

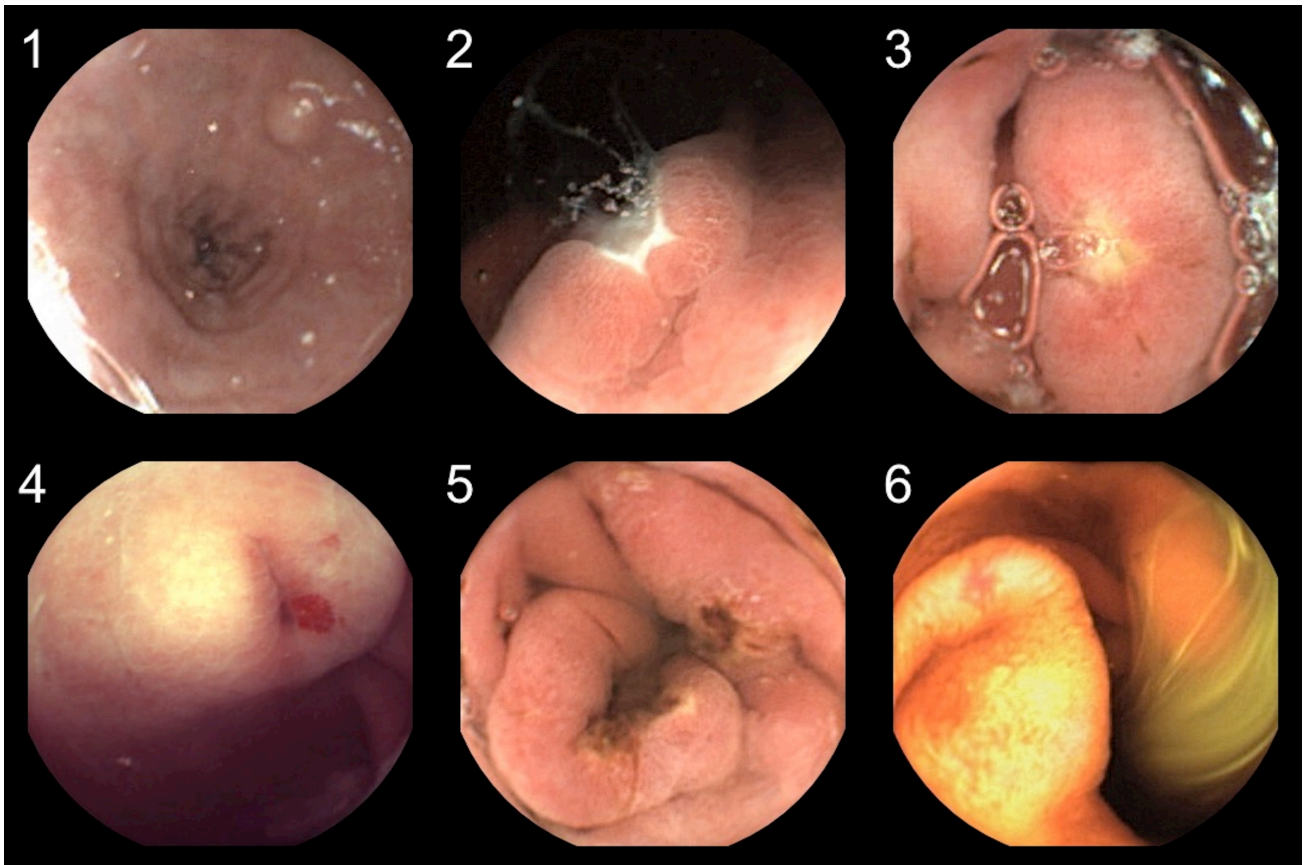
Case	Pathology detected by MACE and OGD	Pathology only detected by MACE	Pathology only detected by OGD
1		Gastritis, D1 duodenitis	
2			Hiatus hernia, D2 angioectasia
3		Gastritis, D1 duodenitis	
4		Gastritis	
5	Gastritis	D1 duodenitis	
6	Hiatus hernia, gastritis		Gastric polyp, gastric angioectasia
7	Gastritis	Gastric polyp	
8		Gastritis	
9	Gastritis, gastric polyp	Hiatus hernia, gastric angioectasia	
10	Gastritis		
11	Gastritis	Gastric angioectasia	Gastric polyp
12	Gastritis	Gastric polyp	
13		Gastritis	
14		Gastric angioectasia	Gastritis
15		Gastritis	
16	Gastritis, gastric polyp	Atrophic gastric mucosa	
17	Gastritis	Gastric polyp, gastric angioectasia	Hiatus hernia
18	Gastritis		
19	Gastritis, gastric polyp		
20	Oesophagitis, gastritis, pancreatic rest		
21	Gastritis	Gastric ulcer, hiatus hernia	
22	Hiatus hernia	Oesophagitis, gastritis, two gastric ulcers, altered blood in the stomach, D1 and D2 ulcer and D2 angioectasia	
23		Gastritis, gastric polyp	
24		Gastritis, gastric polyp	

Table 6 (continuation)

Case	Pathology detected by MACE and OGD	Pathology only detected by MACE	Pathology only detected by OGD
25	Hiatus hernia		D1 duodenitis
26	Active bleeding in D2	Hiatus hernia	
27			Barrett's oesophagus
28		D2 diverticulum	
29	Hiatus hernia, D1 duodenitis	Gastritis	
30		Gastritis, gastric ulcer	
31	Oesophagitis		
32		Gastritis	
33	Hiatus hernia	Gastric polyp	
34		Gastric polyp	
35		Gastric polyp	
36	Gastric angioectasia		D1 ulcer
37	Hiatus hernia	Barrett's oesophagus, gastric polyp	
38	Gastric polyp	Gastritis, gastric angioectasia	
39	Gastritis		
40	Hiatus hernia	Gastric polyp	Oesophagitis
41	Normal		
42	Hiatus hernia	Oesophagitis	
43	Hiatus hernia, gastritis		
44	Gastritis	Oesophageal nodule	
45	Excluded from study		
46	Normal		
47	Hiatus hernia	Atrophic gastric mucosa	
48	Gastric polyp		
49	D2 villous atrophy		Gastritis
50		Gastric polyp	Oesophagitis, hiatus hernia

**Figure 8.** Pathology in the upper gastrointestinal tract only detected by MACE and not seen at OGD.

1, oesophageal nodule; 2, gastric ulcer (mid-body); 3, pre-pyloric gastric ulcer; 4, gastric angioectasia; 5, D2 ulcers; 6, D2 angioectasia.



**Table 7:** Frequency of upper gastrointestinal pathology seen by MACE and OGD. Pathologies considered as possible sources of recurrent or refractory iron deficiency anemia (source lesions) are highlighted in **bold**. Pathologies considered as likely causes of recurrent or refractory iron deficiency anemia (major lesions) are identified by an asterisk\*. D1, first part of duodenum; D2, second part of duodenum; MACE, magnetically assisted capsule endoscopy; OGD, oesophagogastroduodenoscopy.

Findings	MACE & OGD	MACE only	OGD only
<b>*Oesophagitis</b>	2	2	2
Barrett's oesophagus	-	1	1
Hiatus hernia	10	3	3
Oesophageal submucosal lesion	-	1	-
<b>*Altered blood in stomach</b>	-	1	-
<b>Gastritis</b>	16	13	2
<b>*Gastric ulcer</b>	-	4	-
Gastric polyp (benign)	5	11	2
<b>*Gastric angioectasia</b>	1	5	1
<b>Atrophic gastric mucosa</b>	-	2	-
Pancreatic rest	1	-	-
<b>Duodenitis</b>	1	3	1
<b>*D1 ulcer</b>	-	1	1
<b>*Villous atrophy</b>	1	-	-
<b>*D2 ulcer</b>	-	1	-
<b>*Duodenal angioectasia</b>	-	1	1
Duodenal diverticulum	-	1	-
<b>*Active bleeding in duodenum</b>	1	-	-

If only upper GI lesions recognised as possible sources of IDA are included in subgroup analysis (denoted in bold in table 7), then 22 pathologies were identified concomitantly by both modalities. MACE alone identified more source lesions than OGD alone (33 vs. 8 respectively,  $p=0.0002$ ). Even if only major lesions recognised as likely causes of IDA are included during analysis (denoted by an asterisk in table 7: oesophagitis, altered/fresh blood, angioectasia, ulcers and villous atrophy), a statistically significant difference still remains with MACE detecting more lesions than OGD alone (15 vs. 5 respectively (5 detected by both modalities),  $p=0.04$ ). No pathologies identified when



MACE was performed after OGD were likely to be due to biopsy trauma. The patient with villous atrophy identified by MACE had this subsequently confirmed histologically.

### **Small bowel pathology**

A total of 41 patients (83.7%) had complete small bowel examination. A statistically significant association between gastric transit time and completion of small bowel examination was not observed ( $p=0.1$ ). The mean small bowel transit time was 5 hours ( $\pm 2$  hours). The bowel prep was rated good, fair and poor in 89.8%, 6.1% and 4.1% respectively. Twenty-five patients had normal small bowel capsule endoscopy beyond D2. In the remaining 24 patients, pathologies included angioectasia ( $n=15$ ), erosions ( $n=6$ ), polyps ( $n=1$ ), active bleeding ( $n=1$ ), small bowel varices ( $n=1$ ) and a diverticulum ( $n=1$ ). Logistic regression did not detect a statistically significant difference in small bowel pathology detection by SBCE with increasing age ( $p=0.55$ ). Seventeen patients were deemed to have a small bowel cause (beyond D2) for recurrent or refractory IDA, of which 15 patients concomitantly had an upper GI cause (proximal to D2) identified by MACE, OGD or both. Cases with IDA-associated small bowel lesions included: 14 patients with angioectasia, one patient with both small bowel angioectasia and small bowel varices, one patient with active bleeding but without a witnessed focal lesion and one patient with a bleeding diverticulum.

### **Patient tolerance**

VAS scores for pain (0 (IQR=0) vs. 2 (IQR=3)), discomfort (0 (IQR=0) vs. 3 (IQR=5.5)) and distress (0 (IQR=0) vs. 4 (IQR=5)) were all lower for MACE than OGD respectively ( $p=0.0001$  for all three parameters). A statistically significant difference remained after subgroup analysis irrespective of whether sedation was given (Kruskal-Wallis H test:  $\chi^2=33.5$ , 35.9 and 48 respectively;  $p<0.05$  for all parameters). No complications were seen with MACE or with OGD.

## Discussion

Capsule endoscopy using magnetic control (MACE) to examine the upper GI tract followed by passive examination of the small bowel improved the diagnostic yield compared to OGD alone in patients with recurrent or refractory iron deficiency anaemia and was better tolerated by patients. This is partly explained by the ability of capsule endoscopy to image the small bowel, but whilst both modalities missed lesions and overall pathology detection concordance was disappointing, MACE was more sensitive in the detection of upper GI lesions than OGD.

The findings suggest that examination of the upper GI tract and the small bowel might be performed safely and comfortably using a single MACE procedure rather than separate OGD and SBCE in patients with recurrent or refractory anaemia. Such an approach would avoid the need for OGD, a test that is not always well tolerated, reduce hospital visits and may allow cost saving by reducing the number of tests being performed.

The poor diagnostic concordance between the two modalities and the pathology miss rate by OGD, the accepted gold standard, is surprising. The diagnostic yield of OGD for major lesions associated with recurrent and refractory IDA was 20%, suggesting that no more pathology was being missed by OGD than in other studies of similar patient cohorts. (50, 141-145) To our knowledge, there are no 'back to back' or 'tandem' studies in which OGD is compared to itself in patients undergoing a second procedure by an endoscopist blinded to the results of the first. However, several such studies of colonoscopy performed in expert centres consistently show a miss rate of significant polyps of between 10-20%. (150) The fact that 11.3% of patients with upper GI cancers have had an OGD within the previous three years suggests that important focal lesions are missed. (11) Spencer et al. showed a significant difference between endoscopists in the rate of reporting of all

upper GI pathologies, with the exception of cancer. (151) This might partly be explained by a difference in the use of terminology, (152) but may also be explained by some endoscopists missing pathology. The recently published statement on quality standards for upper GI endoscopy acknowledges that endoscopist experience, case volume and duration of endoscopic examination (with a recommended minimum of seven minutes) may affect diagnostic yield. (8) The quality of examination may also be affected by patient tolerance, may be incomplete and may require a repeat examination. It is possible that the better endoscopic control offered by OGD is offset by the better tolerance of capsule endoscopy and much longer examination time (a mean of 23 minutes).

We have already discussed above that capsule endoscopy may compare favourably to OGD in terms of upper GI diagnostic yield. Using the MiroCam Navi®, preliminary studies demonstrated similar sensitivities between conventional flexible endoscopy and MACE in detecting beads sewn inside a porcine stomach model. (61) The MACE system developed by Olympus and Siemens demonstrated 62% and 89% sensitivity for major and minor lesions respectively, compared to OGD. This is slightly disappointing, but the study may not have been adequately powered given that only 23 major lesions were found in 189 patients. (63) In comparison Liao et al. adequately powered their study based on results from pilot studies (69), recruiting 350 patients to their multicentre trial and demonstrating 90.4% sensitivity in the detection of focal lesions using the Ankon NaviCam® (64)

The handheld magnet affords a relatively crude level of control of capsule movement. Our experience was that despite a magnetic flux density of up to 0.38T, it was insufficiently powerful to hold the position of the capsule in the presence of strong peristaltic contractions. Movement of the capsule from one region to another is usually achieved in the flow of gastric water induced by

changing the patient's position. Relatively small approximations of the magnet towards the abdomen can result in the capsule jumping from posterior to anterior gastric wall. Slow, subtle movements of a handheld device weighing 1005g becomes more difficult during a prolonged examination as operator fatigue develops. However, once the capsule is in position, magnet rotation alters the polarity resulting in swivelling of the capsule head enabling the endoscopist to obtain a near 180° view. Thus, whilst not helpful in moving the device against peristalsis or through the pylorus, our previous study showed that this level of control was helpful in hastening the identification of landmarks (62) and perhaps, therefore, pathology. Nonetheless, the data does suggest that visualisation of the oesophagus, GOJ, fundus, duodenal bulb, and, to a lesser extent, the cardia, could be improved. These data are consistent with the previous experience of other studies of upper GI capsule examination. (60, 63, 64, 134, 148) Liao et al. found the majority of focal gastric lesions in patients with dyspepsia located in the body and distal stomach (77%) rather than the fundus/cardia (23%). (64) It may be that the suboptimal visualisation of the cardia and fundus by MACE did not impact on its diagnostic yield because of the low prevalence of proximal pathology in this study. The MiroCam Navi® reduces energy consumption by utilising electric-field propagation (using human tissue as a transmission medium) (153) and image capture seems to be slightly delayed following ingestion, perhaps because of the need for full tissue/water contact. Our experience was that occasionally the magnet failed to capture the capsule in the oesophagus and no oesophageal images were obtained. Furthermore, image capture rate is 3 frames per second from one camera compared to 18 frames per second from two cameras (at either end of the capsule) in the ESO-2 oesophageal capsule (Medtronic, Dublin, Ireland), which compares very favourably to OGD in oesophageal imaging (but has a battery life of only 30 minutes). (53, 134) Views of the GOJ may be inadequate if the blind end of the capsule is leading as it may only see it from a retrograde perspective as it passes into the stomach, although this often provides excellent

views of the cardia. If the camera end of the capsule is leading, GOJ views may be adequate but cardiac views may not be obtained at that point (but may be seen later in the examination). These problems are likely to be addressed by developing a double-ended capsule with a higher frame rate, although this may require further development of battery technology to power the device for the required time. This is also likely to improve views in the duodenal bulb, through which rapid transit becomes less critical if image capture rate is high and a double-ended camera allows a near 360° view. Better fundal views may require further improvements in control. However, this problem may not be confined to MACE: fundal views at OGD require endoscopic retroflexion and insufflation, which is not always possible in patients who cannot retain air.

This study has several limitations. The discrepancy in total lesion detection between the two modalities should be interpreted with caution. MACE and OGD both detected 16 cases of gastritis while MACE detected an additional 13 cases alone (and OGD an additional two cases alone). This would suggest better detection of gastritis with MACE. However, although villous atrophy identified by MACE was subsequently confirmed histologically, this was not the case with gastritis, gastric atrophy and Barrett's oesophagus. Despite this there remained a significant difference in detection rates between the two modalities when these less certain diagnoses were excluded. Nonetheless, the possibility that some pathologies identified by MACE but not by OGD were false positive diagnoses cannot be excluded and might have been addressed by independent review of photodocumented lesions or unblinding the endoscopist prior to extubation and allowing repeat examination. Recently published guidelines recommend a minimum examination duration of seven minutes, inclusion of at least eight photographic landmark images and routine grading of mucosal visualisation quality. (8) These were not routinely assessed in our cohort and should be considered in future comparative studies. A pragmatic approach of allowing patients to choose whether or not

to have OGD with sedation means that the study may not have been adequately powered to address any effect of sedation on pathology detection. Ten patients had MACE following OGD and previous groups report misinterpretation of OGD or biopsy-induced trauma as erosive pathology during subsequent MACE examination. (67) This was not the case in our study as additional pathologies detected in these patients were of a vascular or polypoid nature but future studies should refrain from performing MACE after OGD.

Our study was designed to compare the diagnostic yield of MACE with OGD as its output. MACE diagnosed an additional 15 major lesions. Of these findings oesophagitis (n=2), gastric ulcers (n=4) and duodenal ulcers (n=2) may have prompted PPI therapy and a repeat gastroscopy to ensure healing of the gastric ulcers, while gastric and duodenal angioectasia (n=5 and n=1 respectively) may have benefitted from argon plasma coagulation treatment. However, patient outcomes, including the need for endotherapy and transfusion dependency, were not investigated. A recent systematic review suggests similar re-bleeding rates from small bowel angioectasia despite endotherapy. (155) In these cases, patients presenting for investigation of recurrent and refractory anaemia may benefit from the reassurance of an upper GI and small bowel examination that is negative for cancer but remain symptomatic from their anaemia or dependant on blood transfusion or iron supplementation. Follow-up of patients would allow the impact of pathology detection to be assessed. Finally, there is limited data on the cost-effectiveness of upper GI capsule endoscopy in clinical practice (154) and capsule technology remains purely diagnostic. (57) Future studies should consider the cost implications of equipment, capsule video reading time, training required to perform MACE and the need for biopsy.

## **Chapter 6: Magnetically assisted capsule endoscopy in acute upper gastrointestinal bleeding**

### **6.1 Abstract**

#### **6.1.1. Introduction**

Acute upper gastrointestinal bleeding is common and requires investigation with OGD but endotherapy is not always necessary. Magnetically assisted capsule endoscopy uses a capsule steerable by an external magnet and allows examination of the upper gastrointestinal tract and small bowel but its role in acute upper gastrointestinal bleeding has not been assessed.

#### **6.1.2 Materials and Methods**

We conducted a prospective cohort study comparing the diagnostic yield of MACE and OGD in patients with suspected acute upper gastrointestinal bleeding. Patient tolerance, mucosal visibility by MACE and frequency of small bowel bleeding were assessed. Whether or not MACE could safely predict discharge of patients was also determined.

#### **6.1.3 Results**

Thirty-three patients were included for analysis (median age 60 years, 75.8% male). MACE detected more focal lesions (peptic, vascular and fresh/altered blood without a clear source) than OGD (40 versus 25 respectively,  $p=0.02$ ) but statistical significance was not reached for significant lesions (considered to be the bleeding source; 14 versus 13 respectively,  $p=1$ ). Capsule endoscopy identified an additional cause for bleeding in the small bowel in 18%. Visualisation by MACE was excellent in most areas: views of the oesophagus, gastroesophageal junction, fundus and duodenal bulb were suboptimal. MACE was better tolerated than unsedated OGD and correctly identified all 73% of patients safe for discharge.

### 6.1.4 Conclusion

MACE had higher diagnostic yield for focal lesions, was better tolerated and identified additional bleeding sources in the small bowel when compared to OGD. It also correctly predicted safe discharge for patients with acute upper gastrointestinal bleeding.

## 6.2 Introduction

Acute upper gastrointestinal haemorrhage occurs with an incidence of 50 to 170 per 100,000 population (156, 157) and is associated with significant morbidity and mortality (158-160). It often requires hospital admission (161) and OGD is recommended within 24 hours of presentation. (162, 163) Endotherapy for bleeding lesions is required in up to 24% of cases. (164) Capsule endoscopy is first-line for small bowel investigation. (25, 50) It has also been used in the upper GI tract to assess oesophagitis, Barrett's oesophagus and oesophageal varices. (28, 165, 166) Moreover, it may have a role in acute upper GI bleeding as a risk-stratifying tool: identifying those who require OGD. (54, 161, 167) In a small prospective study capsule endoscopy had a sensitivity of 67.5% for detecting peptic and inflammatory lesions in acute GI bleeding (54): the PillCam ESO2 (Given Imaging, Ltd., Yoqneam, Israel) was used and relies on passive movement of the capsule within the stomach. The advent of MACE now allows a modified capsule to be steered within the stomach by an external magnet. The MiroCam Navi<sup>®</sup> (Intromedic Ltd, Seoul, Korea) utilises a hand-held magnet to achieve MACE. Real-time imaging is displayed on a monitor during examination and the video recording can be viewed on completion of the examination. The capsule has an 11-hour battery life allowing subsequent passive examination of the small bowel in the same sitting. The MiroCam Navi<sup>®</sup> has demonstrated excellent sensitivity for detecting simulated gastric lesions *ex-vivo* (61) and feasibility *in-vivo* (62).



The primary objective of the study was to compare the diagnostic yield of MACE with that of conventional OGD in patients with suspected acute upper GI bleeding. Secondary outcomes included a comparison of tolerance of the two endoscopic modalities. The quality of upper GI mucosal visualisation achieved by MACE, the frequency of small bowel bleeding (distal to the second part of the duodenum) and the potential for MACE to avoid unnecessary OGD or hospital admission were also investigated.

## **6.3 Methods**

### **Patients**

We conducted a prospective, single blinded, cohort study in two teaching hospitals in the United Kingdom (UK). Patients presenting with suspected acute upper GI bleeding, defined as having haematemesis (fresh blood or coffee ground vomiting) and/or melaena within the previous 48 hours, who were haemodynamically stable (systolic blood pressure of over 100mmHg and a pulse rate of less than 100 beats per minute) and requiring an OGD as part of their diagnostic workup were eligible for the study. Exclusion criteria included: age below 18 and above 80 years; permanent pacemakers or other magnetically or electrically controlled devices; high risk of capsule retention (known Crohn's disease, small bowel strictures or daily non-steroidal anti-inflammatory drug use) and pregnancy.

### **Magnetically-assisted capsule endoscopy**

Patients swallowed one litre of water containing 40mg of simethicone to distend and optimise views of the gastric mucosa immediately before MACE. (19) Ingested water has an intra-gastric half-

life of 13 minutes (168) such that a load of 1000mls should return to less than the mean resting volume (of 35mls) within one hour of ingestion. MACE using the MiroCam Navi® was performed by one of two investigators (HLC and Dr. Sabina Beg (SB)) up to, but not less than, one hour from their scheduled inpatient OGD. The capsule was swallowed with patients lying in the right lateral position (148) with the handheld magnet placed adjacent to the lower sternum to try and hold the capsule in the oesophagus and maximise views of the oesophagus and gastroesophageal junction. Once live views confirmed gastric entry of the capsule, the same set sequence of patient position changes and magnet manoeuvres were used to move and spin the capsule respectively to achieve complete gastric mucosa examination as described in Chapter 5 (table 2). (169)

Pathology reporting was standardised using a pre-defined diagnostic list to minimise inter-observer reporting variability (appendix 2). Focal lesions were defined as peptic lesions (oesophageal, gastric and duodenal erosions and ulcers), vascular lesions (angioectasia, oesophageal varices of all grades, gastric and duodenal varices) and fresh/altered blood (without an obvious source). Significant lesions were those considered to be the cause of bleeding and included peptic ulcers (oesophageal, gastric and duodenal), oesophageal varices of at least grade two and gastric varices. Visibility at major upper GI landmarks was graded on a 1-5 scale (poor to excellent) (appendix 3). (169) A single reporter (MEM), blinded to OGD findings, reviewed all MACE videos and reported upper GI pathology, and a decision was documented as to whether patients required inpatient OGD or were safe for discharge. All patients proceeded to OGD irrespective of the decision made on MACE findings. On completion of gastric MACE, the capsule was allowed to pass distally under the action of peristalsis to complete a small bowel examination. Intramuscular metoclopramide (10mg, Hameln Ltd, Gloucester, UK) was administered if the capsule had not entered the duodenum within 30 minutes of ingestion.

### **Oesophagogastroduodenoscopy**

OGD was performed using Olympus GIF-H260 or Q260 gastroscopes (Olympus, Tokyo, Japan) after MACE by a gastroenterology consultant or supervised trainee (all accredited by the UK Joint Advisory Group on GI Endoscopy for independent OGD practice). (8) Patients admitted during daylight hours had MACE at the end of the working day and OGD the following morning. Those admitted after hours had MACE the following morning with OGD on the same morning or afternoon. Endoscopists were blinded to MACE findings. Pathology was documented using the same pre-defined diagnostic list for reporting MACE pathology. Based on findings at OGD (and blinded to MACE findings) an opinion was documented by the endoscopist as to whether patients could be discharged (assuming there were no other clinical indications requiring further inpatient treatment).

### **Patient tolerance**

Visual analogue scales (VAS) (26, 149) were used to assess and compare patient anxiety, discomfort and pain between gastric MACE and OGD on a 1 to 10 scale (none to extreme) (appendix 3).

### **Ethics**

This study was performed in accordance with the ethical standards of the Yorkshire & The Humber - Leeds West Research Ethics Committee (16/YH/0039; Clinicaltrials.gov number: NCT02690376), the 1964 Helsinki declaration and its later amendments.

### **Statistics**

Advice was sought from the University of Sheffield Mathematics and Statistics Resource Centre. OGD fails to identify a cause for acute upper GI bleeding in 3 to 19% of cases. (164, 170, 171) In a

pilot study examining the diagnostic yield of capsule endoscopy, 20 possible lesions (including peptic ulcers, varices and fresh blood) causing acute upper GI bleeding were identified in 46 patients. (54) Assuming a diagnostic yield of 80% and 45% for OGD and capsule endoscopy respectively, a sample size of 29 patients would be needed to demonstrate a statistically significant difference in diagnostic yield between the two modalities with 80% power and 5% two-sided significance.

IBM SPSS Statistics for Macintosh, Version 24.0 (Armonk, NY: IBM Corp.) was used for statistical analysis. Data is presented and processed with the same standards as those used in Chapter 5.

## **6.4 Results**

### **Demographics**

Thirty-four patients were recruited between June 2016 and August 2017. One patient could not swallow the capsule, withdrew consent and was excluded, leaving 33 patients for analysis. The median age of patients was 60 years (IQR 24) (75.8% male). The median Glasgow-Blatchford Score at presentation was 8 (IQR 7.3). OGD was performed within 8 hours of MACE in 22 and within 24hrs) in 11. Nineteen patients (57.6%) had sedation for their OGD. The median dose of midazolam used was 1.5mg (IQR 2.3). Fentanyl was only used in 4 cases (12%) where the dose range was 50-100mcg.

### **Diagnostic yield of MACE and OGD in the upper GI tract**

Overall diagnostic yield of focal lesions (peptic, vascular and evidence of fresh/altered blood without a clear source) were detected more often with MACE than OGD: MACE detected 40 focal

lesions while OGD detected 25 ( $p=0.02$ ) (table 8). Subgroup analysis of significant lesions (i.e. pathology thought to have likely bled) was performed. OGD and MACE concomitantly identified oesophageal varices (grade three ( $n=2$ )), gastric varices ( $n=2$ ), gastric ulcers ( $n=2$ ) (figure 9) and duodenal bulb ulcers ( $n=3$ ) in 10 patients. OGD alone identified one additional gastric ulcer (not requiring endotherapy) and three additional duodenal bulb ulcers (one of which required endotherapy where fresh bleeding, but not the ulcer, was identified during MACE). However, MACE alone additionally identified one case of oesophageal ulcers and four duodenal bulb ulcers (figure 10): these patients did not require a second look OGD as they remained haemodynamically stable with improving haemoglobin levels. A statistically significant difference was not observed in the detection of significant lesions between the two modalities ( $p=1$ ).

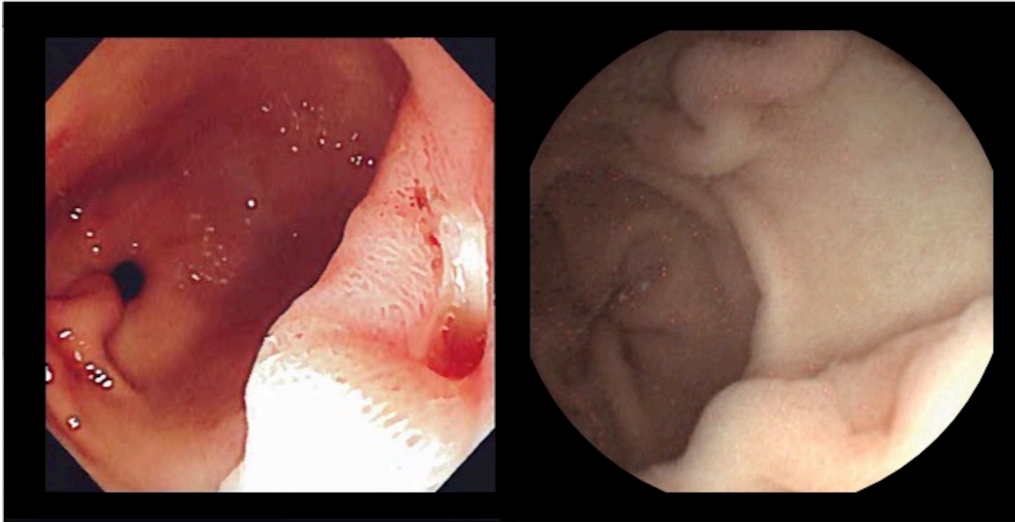
**Table 8.** Case-by-case illustration of focal and significant (in bold type) pathology detected by MACE and OGD. Blank spaces imply either a normal examination, or the presence of only minor findings (e.g. erythema), or findings unrelated to upper GI bleeding (e.g. fundic gland polyps). D1, first part of duodenum; D2, second part of duodenum.

Case	Detected by MACE and OGD	Detected by MACE only	Detected by OGD only
1	<b>Gastric ulcer (antrum)</b>	Gastric erosion (body) Gastric angioectasia	
2	Gastric erosion (antrum)	Fresh blood in stomach	Gastric erosion (body)
3			
4	Grade 1 oesophageal varices <b>Gastric varices</b>		
5			
6		Gastric erosion	
7		Gastric erosion	
8			
9		<b>D1 ulcer</b>	
10		Gastric erosion	Gastric angioectasia

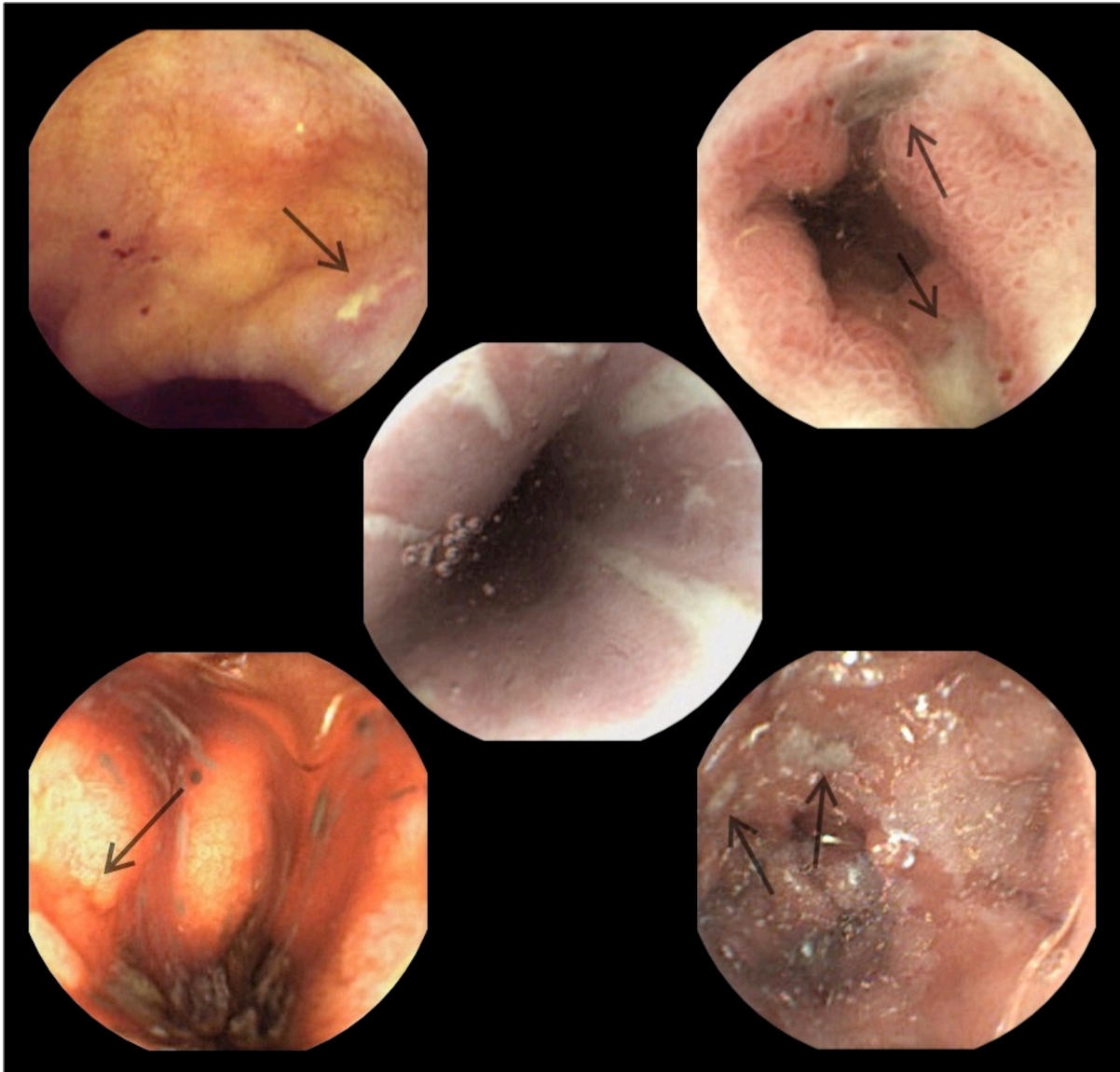
Table 8 (continuation)

Case	Detected by MACE and OGD	Detected by MACE only	Detected by OGD only
11		Fresh blood in stomach, D1 and D2 Gastric erosion <b>D1 ulcer (superior wall)</b> D2 erosion	<b>D1 ulcer (anterior wall) with visible vessel</b>
12			
13		<b>D1 ulcer</b> D1 and D2 erosions	
14			<b>D1 ulcer</b>
15		<b>Oesophageal ulcers</b>	
16			
17	<b>Grade 3 oesophageal varices</b> <b>Gastric varices</b> Blood in stomach, D1 and D2	Gastric erosion Duodenal varices	
18			Grade 1 oesophageal varices
19			<b>D1 ulcer</b>
20		Fresh and altered blood in stomach, <b>D1 ulcer</b>	Grade 1 oesophageal varices
21			
22	<b>D1 ulcer</b>		
23			Gastric erosion
24			
25		Gastric erosion	
26		Fresh and altered blood in stomach, D1 and D2	
27	<b>Gastric ulcer</b> <b>D1 ulcer</b>		
28		Grade 1 oesophageal varices Gastric erosion D1 erosion	
29	<b>Grade 3 oesophageal varices</b>		
30	<b>D1 ulcer</b>		
31			Gastric angioectasia
32	Gastric erosion	D2 angioectasia	D1 erosion
33	Gastric erosion	D1 erosion	<b>Gastric ulcer</b>

**Figure 9.** Gastric ulcer identified by both oesophagogastroduodenoscopy (left) and magnetic assisted capsule endoscopy (right) on the greater curvature



**Figure 10.** One case of oesophageal ulcers (central image) and four cases of ulcers in the first part of the duodenum (peripheral images) identified at magnetic assisted capsule endoscopy and missed at oesophagogastroduodenoscopy.



When considering all pathologies reported by each modality (including diffuse lesions and structural abnormalities not considered to be significant as well as focal lesions), MACE of the upper GI tract detected more lesions overall than OGD in 30 patients (82 vs. 49 respectively,  $p=0.0004$ ) and three patients had normal examinations using both modalities (table 9).



**Table 9.** Number of upper gastrointestinal pathology seen by MACE and OGD. Focal peptic and vascular pathology and evidence of fresh blood are denoted in **bold**. Significant lesions likely to have been the source of upper GI bleeding are highlighted further by an asterisk \*. <sup>†</sup>All grade 1 varices demonstrated no features of recent bleeding. D1, first part of duodenum; D2, second part of duodenum.

Pathology	Detected by both MACE and OGD	Detected only by MACE	Detected only by OGD
Oesophagitis	1	2	1
Barrett's oesophagus	-	-	1
Hiatus hernia	-	2	3
<b>*Oesophageal ulcer</b>	-	1	-
<b>Oesophageal varices (grade 1)<sup>†</sup></b>	1	1	2
<b>*Oesophageal varices (grade 2 or 3)</b>	2	-	-
Oesophageal candida	-	1	-
Shatzki ring	-	-	1
Gastric erythema	4	9	2
<b>Gastric erosion</b>	3	8	2
<b>*Gastric ulcer</b>	2	-	1
Gastric polyps	1	7	-
<b>*Gastric varices</b>	2	-	-
<b>Gastric angioectasia</b>	-	1	2
Portal hypertensive gastropathy	3	2	1
D1 duodenitis	2	3	3
<b>D1 erosion</b>	-	3	1
<b>*D1 ulcer</b>	3	4	3
D2 duodenitis	-	5	1
<b>Duodenal varices</b>	-	1	-
<b>Duodenal angioectasia</b>	-	1	-
<b>D2 erosion</b>	-	2	-
<b>Fresh/altered blood</b>	1	4	-

### **Magnetically assisted capsule endoscopy (MACE)**

Intra-gastric magnetic steering was achieved using the MiroCam Navi<sup>®</sup> in all cases. Patients were able to swallow the capsule in the right lateral position in 69.7% (some patients had to be elevated in order to swallow the capsule) and the operator was able to catch and hold the capsule above the gastroesophageal junction using the magnet in 50%. The median duration of MACE was 20 minutes (IQR 11.3). Gastric and duodenal landmarks were identified by MACE in most cases (cardia, 94%; fundus, greater and lesser curve, anterior and posterior body and pylorus, 97%; first and second part of duodenum, 100%) but less so for the oesophagus (oesophagus, 63.6%; gastroesophageal junction, 33.3%). The median visualisation scores were: oesophagus, 5 (IQR 5); gastroesophageal junction, 0 (IQR 4.5); cardia, 5 (IQR 1); fundus, 3 (IQR 2); greater curvature, 5 (IQR 2.5); lesser curvature 5 (IQR 2); anterior body wall, 5 (IQR 2.5); posterior body wall, 5 (IQR 2.5); antrum, 5 (IQR 0); pylorus, 5 (IQR 0); first 3 (IQR 2) and second part of the duodenum, 5 (IQR 1). A statistically significant difference in the visualisation scores of the upper GI landmarks was observed (Kruskal-Wallis H test:  $\chi^2=88.6, p=3.1 \times 10^{-14}$ ) with the lowest mean rank visualisation scores seen at the oesophagus, gastroesophageal junction, fundus and duodenal bulb. Post-hoc comparison (with Bonferroni correction) of these challenging areas with the rest of the upper GI tract (greater and lesser curvatures, anterior and posterior body, antrum, pylorus and second part of the duodenum) was performed. A statistically significant difference was detected between the lower score of the gastroesophageal junction and the higher scores of the rest of the upper GI tract and also between the fundus and most of the remaining areas (except the anterior and posterior body,  $p=0.37$  and  $0.17$  respectively). The lower score of the duodenal bulb reached statistical significance when compared to the distal upper GI tract (antrum ( $p=0.0003$ ), pylorus ( $p=0.001$ ) and second part of the duodenum ( $p=0.003$ )). Although views of the oesophagus by MACE were absent in more than a

third of patients, the difference between the visualisation scores for the oesophagus and the remaining upper GI tract did not reach statistical significance.

A post-hoc analysis was also performed on the visualisation scores of areas where focal lesions were missed by MACE (and only detected by OGD). Visualisation by MACE was suboptimal in areas where pathology was missed in most cases: two grade one oesophageal varices, visualisation score 2.5 ( $\pm 2.5$ ); two gastric erosions, 4.6 ( $\pm 0.4$ ); one gastric ulcer, 2.0; two gastric angioectasia, 1.5 ( $\pm 0.5$ ); one duodenal erosion, 5.0; three duodenal ulcers 1.0 ( $\pm 0$ ).

### **Small bowel pathology**

Review of small bowel images identified an additional cause for GI bleeding distal to the second part of the duodenum in six cases (18%): small bowel lymphoma ( $n=1$ ), angioectasia ( $n=3$ ), fresh bleeding in the proximal and distal small bowel with no culprit lesion seen ( $n=1$  for each). In three of these cases there was a concomitant lesion causing upper GI bleeding proximal to the second part of the duodenum. In one case there were grade one oesophageal varices and an angioectasia in the mid-small bowel (neither of which were seen to be actively bleeding). In another, two ulcers in the duodenal bulb were detected but also fresh bleeding (without an obvious source) in the distal small bowel. In the third case an ulcer in the duodenal bulb was identified in addition to fresh bleeding in the proximal small bowel, but distal to the duodenal ulcer.

### **Tolerance**

Patient reported median VAS scores for pain (0 (IQR 0) vs. 2 (IQR 4)), discomfort (0 (IQR 0) vs. 3 (IQR 4.5)) and distress (0 (IQR 0) vs. 3 (IQR 6)) were all lower with MACE than OGD respectively ( $p<0.05$  for all parameters). Following subgroup analysis, this difference remained in all tolerance

parameters when comparing MACE to unsedated OGD ( $p=0.01$ ,  $0.002$  and  $0.001$  respectively). However, a statistically significant difference was not reached when MACE was compared to sedated OGD ( $p=0.4$ ,  $1$  and  $0.5$  respectively). No adverse events occurred with MACE or OGD.

### **Decision to discharge**

Based on the findings of MACE (and blinded to the findings of OGD), 24 (73%) patients were identified as potentially being safe for discharge as no evidence of active bleeding or lesion identified requiring further endoscopic assessment or endotherapy was detected. In all cases, the findings at OGD concurred with the decision that these patients were safe for discharge. The mean hospital stay of these patients where MACE suggested discharge, in whom had uncomplicated admissions, was 53 hours ( $\pm 23$ ). Nine patients were deemed not fit for discharge based on the findings of MACE (table 10).

**Table 10.** Patients not appropriate for discharge based on MACE findings. MACE views of ulcers in the duodenal bulb were suboptimal so that the examiner could not confidently discharge them based on MACE findings alone: some ulcers required endotherapy at OGD (Forest classification Ib and IIa in case 11 and 22 respectively) and some did not (Forest III in cases 20 and 30). Oesophageal varices detected at MACE required endotherapy at OGD. In case 2 and 26, fresh bleeding was seen at MACE but no bleeding lesion identified even at OGD. A decision to discharge could not be advised in case 10 due to excess food debris in the stomach hence an incomplete examination of the gastric mucosa by MACE. Subsequent OGD revealed only non-bleeding small gastric angioectasia that did not require endotherapy.

Case	MACE findings				
	Duodenal bulb ulcer	Oesophageal varices	Gastric varices	Fresh bleeding in stomach	Food in stomach
2				✓	
10					✓
11	✓				
17		✓	✓	✓	
20	✓			✓	
22	✓				
26				✓	
29		✓			✓
30	✓				

## 6.5 Discussion

MACE had a better diagnostic yield than OGD in terms of identifying focal and total (including diffuse and structural) lesions, although the identification of significant lesions thought to be the cause of upper GI bleeding did not differ between the two modalities with statistical significance. It was also better tolerated than OGD. Visualisation of the oesophagus, gastroesophageal junction, fundus and duodenal bulb by MACE were suboptimal. MACE identified potential bleeding sources

in the small bowel distal to the duodenum in 18% of examinations and correctly predicted safe discharge for almost three quarters of those admitted with suspected upper GI bleeding.

This is the first study to suggest that capsule endoscopy has a better diagnostic yield than OGD in suspected GI bleeding. Although OGD is regarded as the gold standard, there are no studies in which OGD has been compared to itself in back-to-back studies, but such studies of colonoscopy show a 10-20% miss rate of significant polyps. (150) It is presumed that OGD also misses lesions as push enteroscopy and capsule endoscopy studies of patients with anaemia show proximal lesions (within reach of OGD) in 10-42% of cases. (145, 172, 173) It is well accepted that early gastric and oesophageal cancers are missed in approximately 11.3% of cases. (11) We previously showed that MACE was no less likely to miss beads sewn into an *ex-vivo* porcine stomach than OGD. (61) In a patient study, Rey et al. found that whilst both modalities identified 14 of 30 pathologies, OGD alone identified six and MACE, 10, three of which were ulcers. (66) However, OGD only missed one major lesion (an angioectasia) in 21 patients in another study where endoscopists were unblinded to the MACE findings after completion of the OGD but before extubation. (63) Liao et al. performed a multicenter study of 350 patients comparing MACE using the Ankon robot magnet with OGD. Compared to OGD, MACE had a sensitivity of 90.4% in detecting focal lesions. In fact, patients with an apparent false positive MACE diagnosis of a focal lesion went on to have a second OGD a week later and proved that in the majority of cases there had been an initial false negative OGD rather than false positive MACE: OGD was as likely to miss lesions as MACE. (64) Endoscopists were aware of their involvement in our study and were asked to report any lesions from the same pre-set diagnostic proforma used by MACE reporters in order to maintain consistency in reporting. However, it remains possible that in the context of a potential emergency scenario that their focus on locating a bleeding source may have made them more susceptible to underreporting of trivial

lesions than the MACE reporter. This potential limitation to the protocol may partly explain why there was such discordance in lesion detection between the two modalities and might have been addressed by unblinding of the endoscopists on completion of the examination and second-look OGD if required.

The concordance of pathology detection in previous studies between capsule endoscopy and OGD in acute upper GI bleeding is variable. Chandran et al used a Pillcam ESO2 (14 frames per second, battery life of 20 minutes) and reported concordant findings in 55% of patients, and whilst the ESO2 missed 38% of lesions identified by OGD, this was mainly due to power loss before duodenal entry in one third and OGD missed 25% of significant lesions detected by ESO2. (174) The ESO2 missed no oesophageal pathologies and in the 53% of patients in whom the capsule was still imaging when it exited the stomach, 92% of duodenal pathologies were identified. Gralnek et al. used an ESO2 capsule modified to allow a 90-minute battery life and found no overall difference between the two in detection of peptic or inflammatory lesions. (54) The ESO2 identified most oesophageal pathologies but, despite a 97.8% rate of duodenal entry, detected only half the number of duodenal ulcers as OGD. Gastric yield by ESO2 might have been further improved by the use of water distension (62) and whilst promotility agents were routinely administered to improve gastric cleansing, it is possible that more rapid gastric emptying might have reduced stomach and/or duodenal imaging.

Examination time is considered to be an important factor in diagnostic yield. The time taken to perform OGD was not assessed in this study. Guidelines have adopted the recommendations of studies suggesting that the duration of an OGD should be at least seven minutes to minimise the risk of missed pathology. (8, 105) The median time to perform MACE was 20 minutes and an OGD

examination of this duration may have provided higher diagnostic yield than if performed within the suggested seven minutes. Short examination times might be determined by the endoscopist, but may also be limited by patient tolerance. All studies of upper gastrointestinal endoscopy show that capsule endoscopy is significantly better tolerated than OGD. (64, 134, 169) This is likely to be a contributory factor in the much longer examination times (between 10-24 minutes) reported in this and other studies of upper gastrointestinal capsule endoscopy. The experience of using the MiroCam Navi® to perform MACE echo those in chapter 5: what MACE lacks in terms of the responsive instrumental control and facility for mucosal cleansing offered by OGD may be balanced by the better tolerance and ability to perform a longer examination. The difference in timing between MACE and OGD may have also influenced diagnostic yield. MACE was performed prior to OGD in all patients. There is evidence to suggest that early capsule endoscopy is associated with higher diagnostic yield and location of the bleeding source. (175, 176) While it would not have been feasible to perform OGD in the emergency department or the acute medical admissions unit, the later timing of OGD may have reduced its diagnostic yield in comparison to MACE. This may explain why bleeding was seen at MACE in four cases which subsequent OGD did not detect. Future studies should design protocols where MACE is performed immediately prior to (but not within one hour of) OGD to minimise the time-lag effect on diagnostic yield.

The oesophagus, gastroesophageal junction, fundus and duodenal bulb were less reliably seen by MACE than other landmarks. This is consistent with the findings above. (169) Both oesophagus and duodenal bulb are common sites of disease where inadequate views would be of concern, but technological developments are already demonstrating that these issues can be addressed. On swallowing the Mirocam Navi® there is sometimes a short delay in image capture such that the oesophagus was not seen in a third of the cases studied. This delay, and the possibility that some



patients will have swallowed the single camera capsule blind end first, means that the gastroesophageal junction was not seen in two thirds of patients. However, we describe in chapter 7 below that the upper GI capsule (Medtronic Ltd, Dublin, Ireland), a capsule with cameras at both ends which captures images at 35 frames per second for the first 10 minutes, has a mean oesophageal transit time of 28 seconds (equating to 980 oesophageal images). Both landmarks were seen in all cases and using the same scoring system as used in this study, oesophageal and gastroesophageal junction visualisation scores were 4.8. Furthermore, although the upper GI capsule only reached the duodenum in 64% of cases within the 90 minutes battery life, the visualisation score was 4.7 when the duodenal bulb was seen (135), compared to 3.0 in this study. In cases where transit through the bulb is rapid, it is likely that the 360° view provided by a double headed capsule will improve completeness of examination.

The value of capsule endoscopy in suspected upper gastrointestinal bleeding as a specific indication remains to be clarified. A decision to discharge was appropriately made in 73% of cases in this study immediately after the MACE procedure was completed, an action which would avoid unnecessary intervention (in the form of sedation and OGD), reduce patient inconvenience and be economically desirable. However, duodenal pathologies were identified in 17/24 cases only after the data was downloaded and video reviewed. In this study, failure to see the duodenal bulb live did not affect the outcome, but it is possible that a decision to discharge could have been made based on a normal, clean oesophagus and stomach seen at MACE only for a duodenal ulcer with stigmata of recent haemorrhage to be revealed later in the examination and only recognised following review of the downloaded video. It seems likely that clinicians would want to see the duodenal bulb before considering discharging the patient which would mean keeping the patient until at least later in the day following completion of the study, data download and review of the whole video.

This would also allow identification of the small bowel pathologies that occurred in 18% of patients. Therefore the use of capsule endoscopy in suspected bleeding might be dictated by local availability of facilities and expertise. It may be a useful tool in emergency centers which do not have ready access to expert endoscopy, but may be less so in centers which have rapid access endoscopy service unless the non-invasive alternative is used because of patient preference or significant comorbidity.

In conclusion, in our cohort of haemodynamically stable patients MACE detects more upper GI lesions and appears to be comparable to OGD in the detection of lesions suspected as being the cause of bleeding, although both modalities miss pathologies. It is a well-tolerated procedure that predicted safe early patient discharge in this study. MACE also detected small bowel bleeding in 18% of our cohort. Further studies are needed to determine if MACE has a role in upper GI bleeding whether as a diagnostic alternative to OGD, localising bleeding site (proximal, mid or hindgut) (176), stratifying high versus low risk patients to avoid admission (167) or prioritising patients for endoscopy (within the first 24 hours of bleeding (162, 163)) and exploring cost saving implications. (154)

## **Chapter 7: Upper gastrointestinal tract capsule endoscopy using a nurse-led protocol: first reported experience.**

### **7.1 Abstract**

#### **7.1.1 Introduction**

Without active control of movement the visualisation of the upper GI tract by capsule endoscopy is limited only to the dependent parts of the stomach when passively transiting through. Several MACE systems can steer capsules within the gastric cavity, but movement in water flow induced by patient positional change might offer an effective, simpler and less expensive alternative. The aim of this study was to test the feasibility and performance of a novel upper GI capsule endoscope (Medtronic Ltd, Dublin, Ireland) using a nurse-led protocol.

#### **7.1.2 Methods**

We conducted a prospective cohort study of patients who declined OGD but who consented to upper GI capsule endoscopy. Patients swallowed the upper GI capsule following ingestion of 1 liter of water (containing simethicone). A series of positional changes were used to exploit the effects of water flow and move the upper GI capsule from one gravity-dependent area to another using a nurse-led protocol. Capsule transit time, video reading time, mucosal visualisation, pathology detection and patient tolerance was evaluated.

#### **7.1.3 Results**

Fifty patients were included in the study. The median capsule transit times in the oesophagus and stomach were 6.5 seconds and 78.3 minutes respectively. Visualisation of the following major anatomical landmarks was achieved (graded 1-5: poor to excellent): oesophagus, 5 (IQR 0); gastro-oesophageal junction (GOJ), 5 (IQR 0); cardia, 5 (IQR 0); fundus, 4 (IQR 2); greater curvature, 5 (IQR

1); lesser curvature, 5 (IQR 0.5); anterior body, 5 (IQR 0); posterior body, 5 (IQR 0); antrum, 5 (IQR 1); pylorus, 5 (IQR 0); duodenal bulb (D1), 5 (IQR 5); D2, 5 (IQR 5). The upper GI capsule reached D2 in 64% of patients. The mean video reading time was 48 minutes with standard playback mode and 20 minutes using Quickview ( $p=0.0001$ ). No pathology was missed using Quickview. Procedural tolerance was excellent. No complications were seen with the upper GI capsule.

#### **7.1.4 Conclusion**

The upper GI capsule achieved excellent views of the upper GI tract using the nurse-led protocol. Future studies should compare the diagnostic accuracy between the upper GI capsule and OGD.

## **Introduction**

Oesophageal capsule endoscopy was introduced in 2004 with the PillCam<sup>®</sup> ESO2 being the latest in the series (table 11). It has cameras at both ends and is capable of high image acquisition rates (18 frames per second) to maximise oesophageal visualisation and a 30-minute battery life. Meta-analyses have shown that it can detect Barrett's oesophagus, oesophageal varices and oesophagitis. (28, 165, 166) Although designed for the oesophagus, it has been used and adapted to examine the rest of the upper GI tract. Three studies have shown that it can be used to identify patients with suspected upper gastrointestinal bleeding who need gastroscopy. (54, 161, 167) In a comparative study in dyspeptic patients, Marelli et al. identified all major pathology detected by gastroscopy using an ESO2. (134) However, as the battery of the ESO2 only lasts for half an hour, this may explain why the rate at which it enters the duodenum can be as low as 48% to 61%. (134, 177)

The upper GI capsule (Medtronic Ltd, Dublin, Ireland) represents the most recent technological advance in this field. Preserving dual-camera image capture, each with a 174° field of view, the UGI capsule captures as many as 35 frames per second for 10 minutes followed by 18 frames per second for a further 80 minutes. The capsule is designed to capture images of the entire upper GI tract. This study describes the first reported experience of upper GI capsule endoscopy using a simple, nurse-led protocol comprising a sequence of patient positional changes following the ingestion of water and simethicone.

**Table 11.** Summary of the evolution from the oesophageal capsule to the novel upper GI capsule.

	Prototype PillCam ESO	PillCam ESO®	PillCam ESO2®	Upper GI Capsule®
<b>Generation</b>	-	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>
<b>Designed for</b>	Oesophagus	Oesophagus	Oesophagus	Entire upper GI tract
<b>Cameras</b>	2: double-ended capsule	2: double-ended capsule	2: double-ended capsule	2: double-ended capsule
<b>Size (mm)</b>	11 × 30	11 × 26	11 × 26	11 × 26
<b>Field of view (per camera)</b>	-	140°	169°	174°
<b>Total image capture rate</b>	4 fps	14 fps	18 fps	35 fps for first 10 mins. 18 fps for next 80 mins.
<b>Battery life (mins)</b>	-	30	30	90
<b>Depth of field (mm)</b>	-	0-20	0-30	0-30
<b>Real-time viewer</b>	No	No	RAPID® Real-time Viewer (Given Imaging) separate to PillCam® Recorder	RAPID® Real-time Viewer (Given Imaging) built into PillCam® Recorder
<b>Video review software</b>	RAPID Workstation®	RAPID Workstation®	RAPID Workstation®	RAPID Workstation® version 9

## Methods

### Study population

We performed a prospective observational study at our tertiary hospital. Patients were offered upper GI capsule endoscopy if they refused OGD. All indications were considered. Those who had

Crohn's disease were required to undergo a PillCam Patency capsule (Medtronic Ltd) examination first.

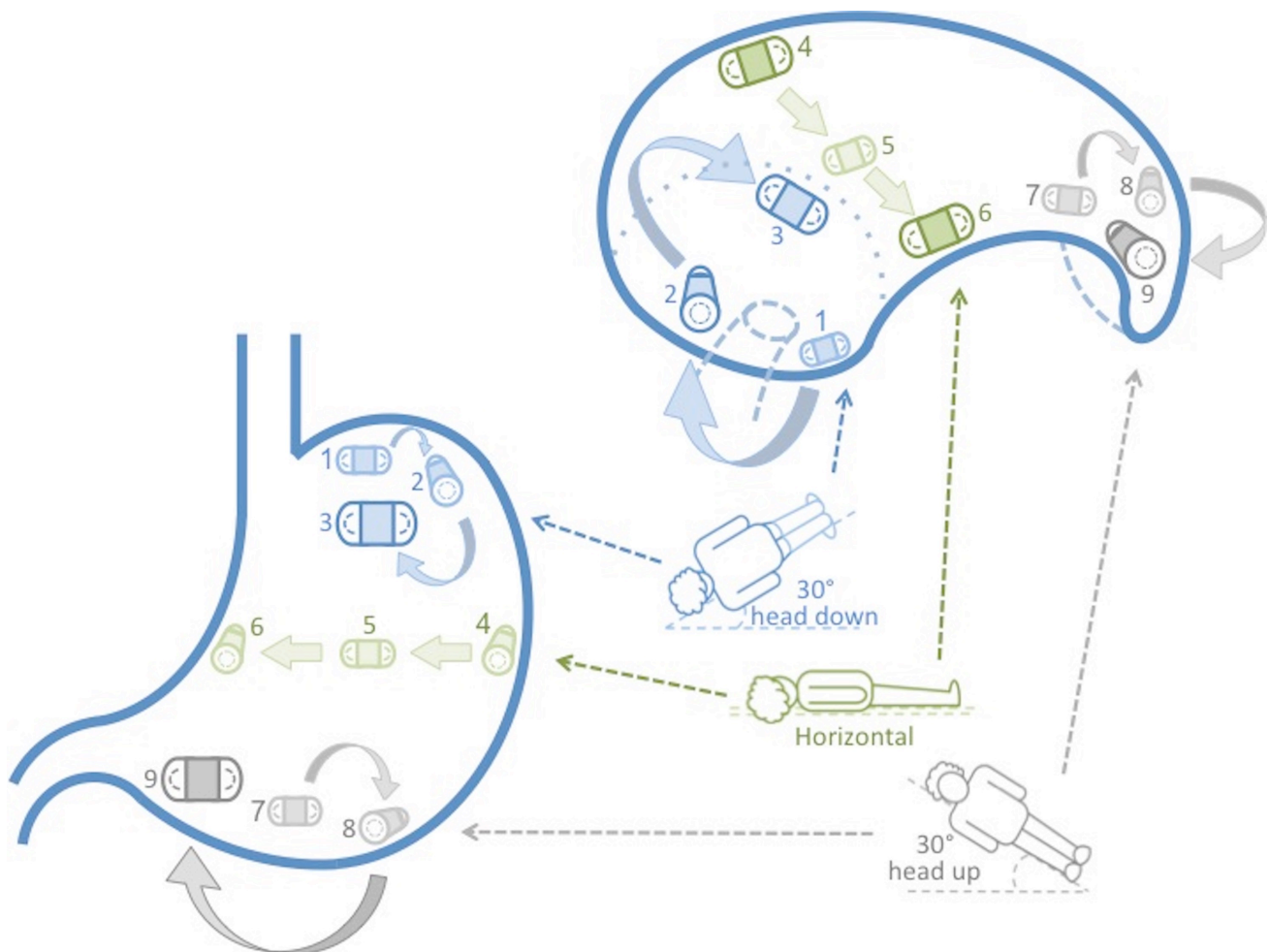
### **Simple positional interchange technique (SPIT)**

The upper GI capsule endoscopy system includes an external portable data recorder. The recorder is connected to the patient by an array of leads on the chest and abdominal skin during the examination. This interface supports data export from the capsule to the memory drive of the data recorder. A small monitor in the recorder allows real-time viewing. When the procedure is complete, the data recorder is docked onto a workstation installed with Rapid 9<sup>®</sup> software (Medtronic Ltd.) and video images are exported for further analysis by the physician.

The SPIT was performed by nursing staff on the Clinical Investigation Unit, Royal Hallamshire Hospital. Patients first drank one litre of water containing 80mg simethicone. Immediately before swallowing the UGI capsule, 20mg of hyoscine butylbromide was given intramuscularly to reduce gastric peristalsis (98) and optimise gastric views. Patients were asked to swallow the UGI capsule in the right lateral position using an adaptation of the previously described simplified ingestion procedure (SIP). (148) If patients were unable to swallow the capsule while lying in the horizontal plane, the head of the bed was incrementally elevated until swallowing was successful. If this failed, then patients swallowed the capsule sitting upright. The real-time views detected when the UGI capsule entered the stomach. Once the capsule entered the stomach, patients were asked to position themselves to face three planes (left/right lateral decubitus and supine/prone) at three angles (30° head down/up and horizontal) for 2 minutes per position (figure 11). Additional positional changes and sips of water were used to improve views of the gastric mucosa as necessary. When complete gastric mucosal assessment was achieved patients were asked to sit

upright to assist passive capsule movement towards the pylorus. If the capsule had not reached the first part of the duodenum 60 minutes after ingestion then 10mg of intramuscular metoclopramide was administered as per our standard protocol. (62) Patient tolerance in the form of procedural pain, discomfort and distress scores were recorded using the same visual analogue scales as those used in previous chapters (appendix 3). (26, 149)

**Figure 11.** Schematic of the simple positional interchange technique (SPIT). Coronal views are illustrated on the left and transverse views (with the cranial end closest to the reader) on the right. Capsule movement is achieved by exploiting the effects of water flow from one gravity dependent area to another with patient positional change. Once the UGI capsule enters the stomach, the examination bed is tilted 30° head down (depicted in blue) and patients lie supine (position 1), on their left lateral (position 2) and then prone (position 3). The bed is returned to the horizontal plane (depicted in green) and patients lie on their left lateral (position 4), supine (position 5) and then right lateral (position 6). The bed is finally adjusted to 30° head up (depicted in grey) and patients lie supine (position 7), on their left lateral (position 8) and then prone (position 9).





## **Video interpretation and analysis**

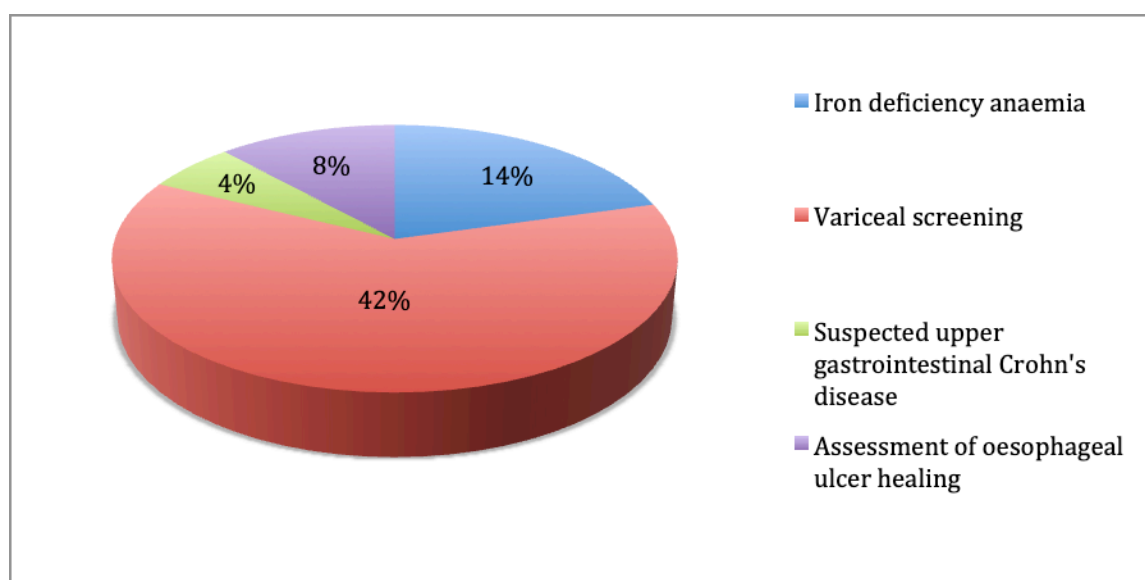
UGI capsule videos were reported by one of two co-authors (RS and MEM), each with experience of reading over 1000 small bowel capsule endoscopy videos. Rapid 9<sup>®</sup> software (Medtronic Ltd) was used to review videos and has the capacity to playback recordings up to 100 frames per second in an accelerated reading mode. Analysis of videos included grading of mucosal visualisation (appendix 3) . Capsule transit time, video reading time, completion of examination to the second part of the duodenum (D2), pathology detection and procedural complications were recorded. The service evaluation was registered with the Clinical Effectiveness Unit (registration number 7073), Sheffield Teaching Hospitals NHS Foundation Trust (STH), UK.

SPSS V.22.0 (IBM) was used for statistical analysis. Continuous parametric and non-parametric data was represented as mean  $\pm$  standard deviation (SD) and median  $\pm$  IQR respectively: the student's t-test or Wilcoxon signed-rank test (Kruskall-Wallis H test when more than two independent variables) was used for comparisons of parametric and non-parametric data respectively. Categorical data was represented as an absolute number and/or percentage

## **Results**

### **Patient demographics**

Fifty patients (40% male) with a mean age of 57 ( $\pm 15.7$ ) years were included in the study protocol. Indications for investigation are illustrated in figure 12.

**Figure 12.** Indications for assessment with the upper GI capsule.

### Performance characteristics

SPIT was achieved in 90% of patients: five had difficulty lying prone. Complete examination to D2 was achieved in 64%. The median times of capsule transit are illustrated in table 12. The average time oesophageal transit time was 28 seconds. Routine administration of hyoscine was abandoned after the first 33 patients because of concern that it might be delaying capsule entry into the duodenum. Analysis, however, failed to demonstrate any delaying effect of the drug on gastric transit: a Wilcoxon signed-rank test did not elicit a statistically significant change in gastric transit time with buscopan ( $Z = -0.71$ ,  $p = 0.94$ ) (Shapiro-Wilk test  $p < 0.05$ ).

**Table 12:** Capsule transit time in the upper GI tract.

Area	Median transit time (IQR)
Oesophagus	6.5 seconds (11.9)
Stomach (all cases)	78.3 minutes (37.2)
Stomach (with hyoscine butylbromide)	78.6 minutes (36.6)
Stomach (without hyoscine butylbromide)	76.2 minutes (51)
Duodenum	6.6 minutes (15)

### **Mucosal visualisation and pathology detection**

The mean reading time for capsule videos was 48 ( $\pm 18$ ) minutes with standard mode. All 50 studies were subsequently de-identified and re-read by one reader (MEM) in a randomised, blinded fashion using the Quickview (Medtronic Ltd.) option in the pre-set mode (the software selecting 10% of the most relevant lesions for viewing by the reader) to examine the stomach (oesophagus and duodenum being read in standard mode with frame rate selected by the reader according to his usual practice): reading time was significantly reduced to 20 ( $\pm 5$ ) minutes (Shapiro-Wilk test  $p = 0.51$ , student t-test  $p=0.0001$ ).

Visualisation scores of the upper GI tract and examples of views achieved with SPIT are shown in table 13 and figure 13 respectively. Withdrawal of hyoscine administration did not affect any visualisation scores. A Kruskal-Wallis H test showed that there was a statistically significant difference in visualisation between the different areas of the upper GI tract,  $\chi^2 = 64.8$ ,  $p = 1.15 \times 10^{-9}$ . This reached statistical significance in certain cases after post-hoc analysis with Bonferroni adjustment: visualisation scores in the fundus were significantly lower compared to those of the oesophagus, GOJ, cardia, lesser curve and anterior and posterior gastric body ( $p < 0.05$  for all) (figure 14). Views of D1 and D2 were also statistically significantly less than those of the oesophagus, GOJ and cardia ( $p < 0.05$  for all comparisons). The whole circumference of the Z-line was seen in 92.5% of cases. Inability to achieve prone positions during SPIT did not render lower overall gastric visualisation compared to complete SPIT; combined median scores of cardia, fundus, body, antrum and pylorus visualisation were 5 (IQR 1.75) vs. 5 (IQR 1), respectively (Shapiro-Wilk test  $p < 0.05$ ; Wilcoxon signed-rank test,  $Z = -2.013$ ,  $p=0.06$ ). Detected pathology included: oesophagitis ( $n=12$ ), Barrett's oesophagus ( $n=1$ ), hiatus hernias ( $n=7$ ), Cameron's ulcer ( $n=1$ ), gastric inlet patch ( $n=1$ ), oesophageal varices ( $n=8$ ), gastric varices ( $n=2$ ), portal hypertensive gastropathy ( $n=5$ ), gastritis

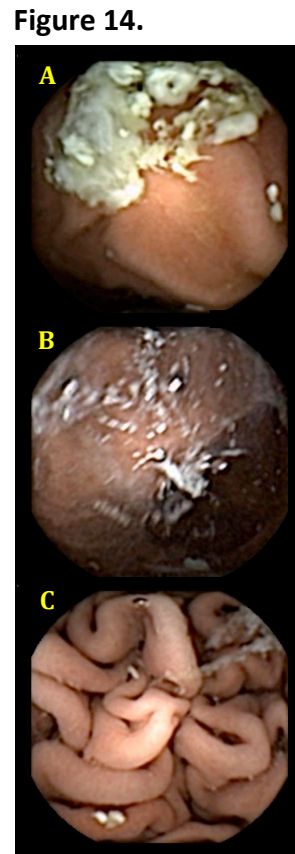
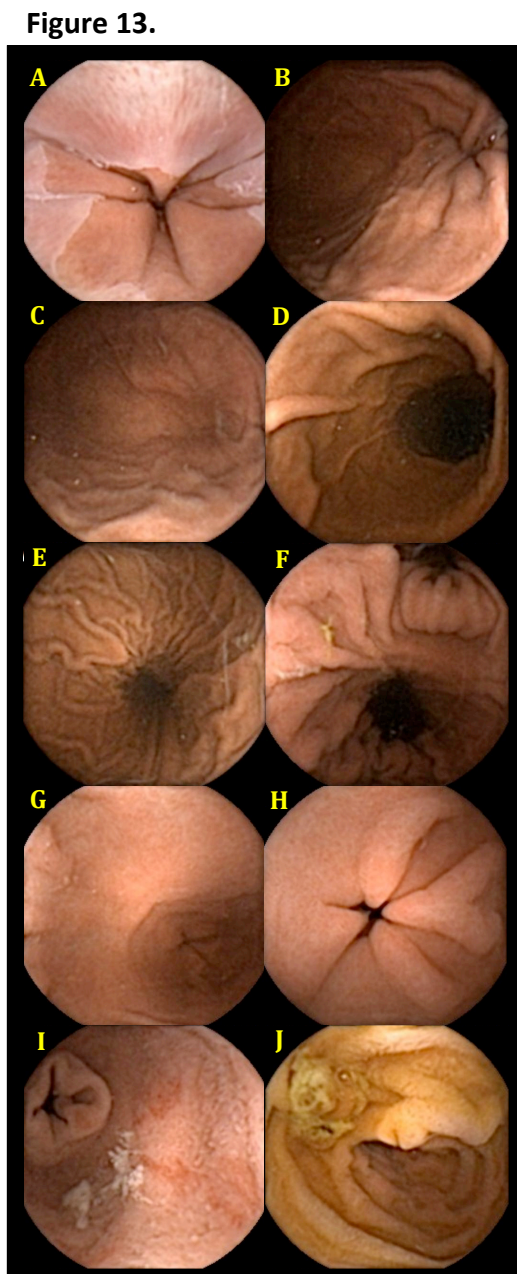
(n=20), benign gastric polyps (n=10), gastric ulcers (n=2), duodenitis (n=4), duodenal polyp (n=1), villous atrophy (n=1) and angioectasia (n=7) (figure 15). No pathology was missed using the Quickview reading software in the stomach when compared to standard mode.

**Table 13:** Visualisation scores of the upper GI capsule using the simple positional interchange technique.

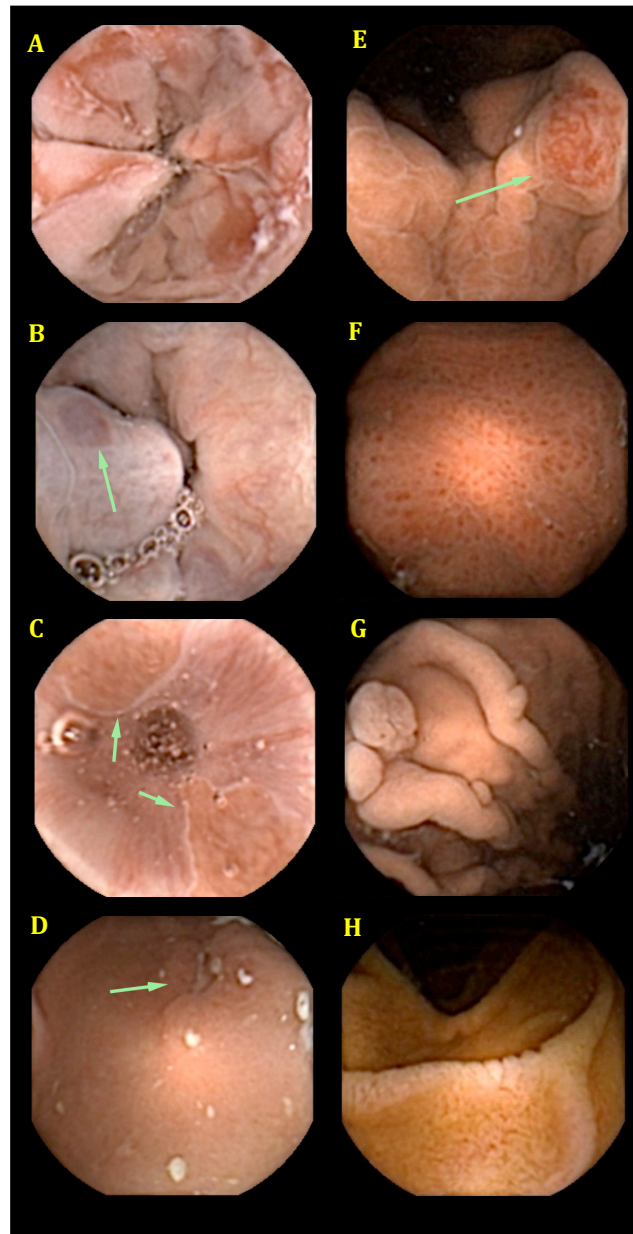
Area	Median visualisation score (IQR)
Oesophagus	5 (0)
Gastro-oesophageal junction	5 (0)
Cardia	5 (0)
Fundus	4 (2)
Greater curvature	5 (1)
Lesser curvature	5 (0.5)
Anterior body	5 (0)
Posterior body	5 (0)
Antrum	5 (1)
Pylorus	5 (0)
Duodenal bulb (D1)	5 (5)
D2	5 (5)

**Figure 13.** Normal views of the upper gastrointestinal (GI) tract seen with the upper GI capsule. A, gastroesophageal junction; B, cardia; C, fundus; D, greater curvature; E, lesser curvature; F, incisura angularis; G, antrum; H, pylorus; I, first part of duodenum (retrograde view); J, second part of duodenum (ampulla also seen).

**Figure 14.** Suboptimal views in the fundus. A, mucus; B, bubbles; C, insufficient distension.



**Figure 15.** Pathology detected by upper GI Capsule. A: Erosive oesophagitis; B: Oesophageal varices; C: Barrett's oesophagus; D: Gastric ulcer; E: Gastric angioectasia; F: Portal hypertensive gastropathy; G: Benign cystic fundic gland polyps; H: Coeliac disease.



### Patient tolerance and safety

Mean procedural pain, discomfort and distress scores were: 0.4 ( $\pm 1$ ), 0.4 ( $\pm 1$ ) and 0.3 ( $\pm 0.9$ ) respectively. No complications were seen. All patients were willing to undergo a repeat procedure if it was necessary.

## Discussion

UGI capsule endoscopy achieved oesophagogastric examination in all patients, although limited battery life precluded duodenal examination in a third. All studies using swallowed water for gastric distension, simethicone and the SPIT was performed by nursing staff according to protocol. Patients were able to comply with the SPIT in 90% of cases although difficulties with lying prone in the remainder did not affect outcome. SPIT provided excellent views of all areas of the oesophagus and stomach, both D1 and D2 were visualised clearly when the capsule traversed the pylorus within the 90-minute time frame and pathology was identified throughout. The procedure was extremely well tolerated and no complications occurred.

Unlike the small and large bowel, which are long, relatively straight with constant lumina, the upper gastrointestinal tract comprises three quite different structures: the short, tubular, small diameter oesophagus and duodenum and the voluminous stomach, the gastroduodenum being convoluted in shape. Technologies to date have tried to address these challenges by developing capsules with cameras at both ends, maximising image capture rate and battery life and controlling capsule movement. Although there is no equivalent data for the oesophagus, there is evidence that a double-ended pill camera is better than a single-ended one in terms of diagnostic yield in the small bowel. (178, 179) Intuitively it seems likely that a single-ended capsule leading with the blind end is less likely to get complete views of the GOJ than one with cameras at both ends. Similarly, from our experience in chapter 6, a single ended device may miss proximal lesions in the duodenal bulb if transit through the bulb is rapid. (180)

The Pillcam<sup>®</sup> ESO, capturing a total of fourteen frames (seven from each end) per second (181) was superseded by the ESO2 (182), capturing a total of 18 frames per second. The 35 frames per second

delivered by the UGI capsule would deliver almost 1000 oesophageal images in the average transit time of 28 seconds shown in our evaluation (and still more than 220 images if based on a median time of 6.5 seconds). This improvement is likely to have resulted in better oesophageal views: the entire GOJ was seen in only 50% of ESO2 studies (183) compared to 92.5% in this series. Whether or not this translates to better diagnostic yield in the oesophagus and the rest of the upper gastrointestinal tract needs to be confirmed.

While our results above and from other previous studies suggest that MACE may be useful in the upper GI tract (60, 63, 64) such techniques, however, require expertise and cost-effectiveness studies are needed. Therefore, the prospect of a simple, nurse-led, protocol driven UGI examination is attractive: cost and expertise required is mainly limited to the capsule and the interpretation of the videos. The SPIT protocol is easy to follow in clinical practice. The patient is asked to rotate along their longitudinal axis almost 360° from the right lateral to prone position, a series of manoeuvres which are performed 30° head down, horizontal and 30° head up. This aims to achieve complete gastric imaging as was reported for capsule endoscopy using handheld external (184) and static robot magnets. (185) Qian et al. demonstrated the benefits of the left lateral, supine and right lateral positions for imaging the fundus, cardia and antropyloric regions respectively. (185) Rahman et al. found that visualising incisura, antrum and pylorus was best achieved by using the handheld magnet to position the capsule opposite the gravity-dependent positions on the greater curve and antrum in the supine patient. (184) We have used the prone position to achieve the same capsule position and viewpoints. The combination of patient positional changes in Rahman's study achieved good to excellent views of all areas of the upper gastrointestinal tract. These previous studies were performed using single ended camera capsules: it is likely that greater coverage is obtained using a double-ended capsule providing a view of



almost 360°. Studies comparing diagnostic yield of the two modalities are warranted. Five patients were unable to achieve the prone position but otherwise completed SPIT without obvious impact on landmark visualisation. Nonetheless, SPIT may not be feasible for those with mobility restrictions or those who are particularly frail.

Capsule reading was time consuming at 48 minutes and most of the viewing is repetitive gastric imaging making reading a tedious task. However, image recognition software continues to be developed which can exclude sequentially identical images, or select images which are different or identified as pathological, thereby reducing the size of the video to be viewed. The Quickview system is such a software and in its previous iteration in the Pillcam® SB2 (Given Imaging Ltd.) was shown to have a sensitivity of 92.3% in detecting small bowel pathology. (186) Perhaps such software may prove more useful in the large volume stomach in which the capsule images the same areas repeatedly, compared to the small bowel in which transit distally is more constant and subject to less repetitive imaging of the same region. No pathology was missed when Quickview was used to view the stomach. In this study, videos were re-read with Quickview in a randomised order and anonymised. Even so, they were re-read by MEM, one of the co-authors involved in the initial video interpretation using standard mode. Unbiased Quickview video interpretation by an independent reader, blinded to the findings at standard reading would provide more reliable comparison. Future larger comparative studies are needed to confirm the value of Quickview in UGI capsule endoscopy.

The UGI capsule visualised the fundus less well. This is consistent with other studies using capsule endoscopy, even with external actuation techniques such as magnetic steering (60, 68) which includes our findings using the MiroCam Navi® above. During gastroscopy, gas insufflation is used

to inspect the proximal stomach, which is collapsed in the fasted state. While varying amounts of water have been used to distend the stomach during upper GI capsule endoscopy, (62, 134) we have previously shown that 1000mls improves mucosal clarity and distension compared to 200mls. (62) Some UGI videos were obscured by adherent mucus in the proximal stomach. The use of mucolytics such as N-acetylcysteine or pronase has been shown to be of benefit in improving mucosal visibility during gastroscopy, (86, 187, 188) although this did not translate to the only capsule endoscopy study to date. (189) Routine use of hyoscine has been advocated to improve visualisation in OGD. (98) This did not appear to make a difference in our experience, although as with water- and gas- distension techniques and mucolytics, the potential benefits of these agents should be investigated further.

Achieving complete examination to D2 in only 64% was disappointing. Hyoscine may delay gastric emptying (190), but although this was not a study powered to investigate its effects, hyoscine did not appear to have an obvious effect on gastric transit in this small cohort. Meltzer et al. found that only one half of their ESO2 (30 minute) examinations reached the duodenum. (177) Using a modified version of the ESO2 (with a 90-minute battery life) and pre-procedural intravenous erythromycin, Gralnek et al. achieved duodenal entry of the capsule in 97.8% of cases. (54) Therefore the use of promotility agents might be considered, unless rendered redundant by further improvements in battery life.

The development of transnasal and single-fibre endoscopy as well as Cytosponge acknowledges the need for less-invasive technologies for upper gastrointestinal screening and surveillance. (191) In this feasibility study, anxiety, discomfort and pain scores associated with the UGI capsule and SPIT were excellent, consistent with previous studies of capsule endoscopy of the oesophagus (52, 53),

small bowel (26) and colon (13). Furthermore, Gupta et al. found that adult subjects expressed a preference for capsule endoscopy compared to sedated endoscopy for Barrett's oesophagus screening (192), raising the possibility that compliance with investigation might be better if less-invasive techniques are offered.

There are limitations to this study and with the technologies. This is an observational cohort study that suggests that UGI capsule endoscopy is feasible, and when technological development allows more reliable duodenal imaging, randomised controlled trials of diagnostic yield compared to gastroscopy are needed. The upper GI capsule did not always achieve complete visualisation of a landmark by views from just one position of the SPIT protocol. It was not uncommon that the head down tilt position allowed better views of the proximal aspects of the greater curvature followed by the head up tilt to complete views of the distal part. Future studies should aim to validate the visualisation achieved with SPIT with case-control studies comparing views from the upper GI capsule and OGD (as the gold standard). Alternatively, comparative trials of patients with pathology detected at OGD who are subsequently examined with the upper GI capsule (to determine if the same pathology can be identified) would also validate whether visualisation of the pathology-harboured area is adequate.

Cost effectiveness studies should consider the costs of the supporting systems and their maintenance (endoscopes, stack systems, monitors, computer software), disinfection, accessories and disposables (which includes the capsule), training requirements and the time taken to perform procedures (including interpreting images). Capsule endoscopy at present remains only diagnostic. The technology to biopsy lesions has been reported but remains in the experimental phase. (57) However, whilst most endoscopists have a low threshold for taking biopsies, the use of non-

invasive tests for *Helicobacter pylori* might reduce this and our experience of investigating patients with dyspepsia above (Chapter 3) is that biopsies only increased diagnostic yield by 2.4%. (193)

Within the context of the limitations, this study shows that upper GI capsule endoscopy can be performed by nurses in a protocol-driven manner using the novel UGI capsule (Medtronic Ltd.). The SPIT, combined with gastric insufflation using water and simethicone appears to allow excellent visualisation of the whole stomach, albeit with slightly reduced visibility in the fundus. The oesophagus and gastro-oesophageal junction are well seen although further work is needed to allow more reliable visualisation of the duodenum. The procedure is extremely well tolerated by patients.

## Chapter 8: Discussion

The body of work presented in this thesis aims to examine the role of capsule endoscopy in the investigation of the upper GI tract. We first interrogate the current practice of OGD to determine if there is a need for an alternative means of upper GI endoscopy. Upper GI examination with OGD changed the management pathway in only one sixth of our patients with dyspepsia, the most common indication for OGD. (115, 194) Malignant tumours were diagnosed in 1% reinforcing the need for endoscopy. However assessing patient tolerance revealed that more than one third of patients worry about and suffer significant gagging, choking, discomfort and distress from the physical act of intubation during OGD. Endoscopists do not recognise the stress of the patient experience and sedation does not improve tolerance. In spite of this, patients find OGD highly acceptable but whether this is related to the lack of an alternative means of investigation or the reassurance from a normal examination is unclear. We continue with the evaluation of MACE in common clinical settings requiring upper GI endoscopy. In recurrent and refractory IDA and suspected upper GI bleeding upper GI MACE followed by passive small bowel capsule endoscopy (using the MiroCam Navi®) has higher diagnostic yield compared with conventional OGD alone. Upper GI MACE alone (excluding follow-on small bowel capsule endoscopy) still identifies more culprit lesions than OGD in recurrent and refractory IDA and is comparable to OGD in detecting lesions likely to be responsible for patients presenting with suspected acute upper GI bleeding. Follow-on small bowel capsule endoscopy additionally detects a small bowel cause for recurrent/refractory IDA in more than a third of patients and a sixth of patients with acute upper GI bleeding. Moreover MACE is safe in patients and is superior to OGD in terms of patient tolerance, even when sedation is used for the latter. The advantage of magnetic steering as opposed to just gravity-dependent maneuvering of the capsule is uncertain: high-quality oesophagogastric mucosal

examination with the Medtronic® upper GI capsule, using a simple positional change protocol, is feasible and well tolerated.

In our experience diagnoses made at OGD in patients with dyspepsia only changed the patient management pathway, beyond what would be adequately managed by the NICE guidelines for uninvestigated dyspepsia, in 16.2%. However, as we conducted a retrospective study the impact of diagnoses made at OGD were inferred and would be better assessed by follow-up studies of patients. As OGD potentially misses 11.3% of early upper GI cancers (11) and new national standards for OGD (8) aim to improve the detection of potentially curable premalignant lesions, this suggests that the impact of diagnostic OGD is also likely to improve. Individual alarm symptoms are poor at predicting malignant disease (82, 83) where individual symptoms of anaemia, dysphagia and weight loss all have sensitivities less than 50% for the detection of upper GI malignancy. (83) Endoscopic assessment is therefore invaluable and while non-invasive screening with capsule endoscopy is attractive in principle several barriers must first be address. Biopsy rates at OGD are still high: 56% in our cohort and reported to be as high as 66% by others. (90) Capsule endoscopy with the ability to biopsy remains experimental. (57) Without a significant reduction in biopsy rates diagnostic upper GI capsule endoscopy would be superfluous. Nevertheless, our findings suggest that patient management pathways are only affected by biopsy findings alone in 2.4%. In our cohort of patients with dyspepsia benign gastric polyps and benign ulcers were detected at OGD. Arguably lesions such as gastric ulcers are confirmed as benign only following histological sampling and assessment. Nevertheless, peptic ulcers are present in only 8% of patients with dyspepsia (10) and international guidelines do not support routine biopsy of all gastric ulcers (although there may be a role for this). (195) Further studies are needed to determine patient outcomes by assessing the prevalence of lesions requiring histological analysis (polyps, ulcers, atrophy), the likelihood of these

lesions harbouring dysplastic or neoplastic change and whether diagnostic screening of patients with upper GI capsule endoscopy would be a cost-saving exercise.

The role of follow-up OGD for gastric ulcers (195) and second-look OGD for acute upper GI bleeding from peptic ulcers (196) is unclear and would likely only require biopsy or endotherapy, respectively, in the minority of cases. (196) Upper GI capsule endoscopy may be useful in this setting, particularly as novel capsule technologies continue to emerge: chromoendoscopy (197, 198), ultrasound (199) and electron microscopy (200) may improve lesion detection and provide sufficient information at the submucosal and cellular level respectively to reduce the need for biopsy in the future. It is also worth highlighting that the MiroCam Navi® detected additional relevant small bowel pathology in the same sitting, inaccessible to OGD, which in our experience (in those with recurrent/refractory iron deficiency anaemia and suspected acute upper GI bleeding) was not insignificant (one third and one sixth of patients respectively).

Upper GI capsule endoscopy will be competing with other novel variants of upper GI endoscopy. Transnasal endoscopy demonstrates better patient tolerance and acceptability compared to conventional OGD, not only when assessed using patient questionnaires but also objective measuring of cardiac function and oxygen saturations. (22) Interestingly, in a randomised control study, Chak et al. reported that 12.6% of patients undergoing transnasal endoscopy found it intolerable, compared to no patients randomised to oesophageal capsule endoscopy ( $p=0.001$ ). Large randomised control trials are required to determine which technology is better tolerated but it is clear that the tolerance of OGD can be poor in comparison. Using the ECS we demonstrated that more than 59% of patients were worried about, and 36% experienced, significant gagging, choking and distress related to endoscopic intubation of the oropharynx. The

symptoms of gagging, choking and globus during OGD (22) have been assessed in studies comparing transnasal endoscopy with OGD. (201, 202) Other studies assessing the tolerance of OGD as their primary outcome report similar levels of discomfort (20, 116) but did not assess the specific symptoms associated with intubation of the oesophagus. Our findings did not detect a statistically significant association between discomfort and gagging, choking or intubation-associated distress. Thus studies may underestimate the true distress experienced by patients if only assessing for general discomfort. Future studies assessing the tolerance of upper GI endoscopy should measure the distress from triggering of the gag reflex.

The ECS has been validated for the assessment of tolerance and acceptability in colonoscopy. (14) Further validation of the ECS in the assessment of OGD is required. Over 90% of patients found OGD acceptable in our cohort: this may be from reassurance of a normal examination following the procedure (80) but we postulate that this might also be influenced by the lack of an available alternative to OGD. Gralnek et al. found that significantly more patients were willing to have a repeat capsule endoscopy than repeat OGD in their comparative study of patients presenting with acute upper GI bleeding. (54) The tolerance and acceptability of upper GI capsule endoscopy is universally superior in previous trials when compared to OGD (63, 64, 134) and is also demonstrated in our data. Future studies assessing the acceptability of OGD should be performed in comparative studies where a novel alternative is available.

In our cohort of patients with recurrent and refractory iron deficiency anaemia and those presenting with haemodynamically stable acute upper GI bleeding the diagnostic yield of MACE for culprit lesions using the MiroCam Navi® was comparable or higher than that of OGD in the upper GI tract. However, in both cohorts there was a significant discordance in lesion detection between



MACE and OGD. Approximately 10-20% of colonic polyps can be missed between tandem procedures. (150) While tandem studies have not been performed on OGD, the fact that 25% of pathologies detected at SBCE are within reach of OGD (141-145) and 11.3% of patients diagnosed with an upper GI cancer have had an OGD within the last 3 years, both suggest a diagnostic miss rate with current OGD practice. A minimum duration of 7 minutes is now advised for OGD examination and may improve diagnostic yield. (8) We did not measure the time duration of OGDs but future studies comparing upper GI capsule endoscopy and OGD should assess whether this influences lesion detection concordance. While MACE seemingly detected more total lesions than OGD (in both patients with recurrent and refractory anaemia and suspected upper GI bleeding), we did not confirm whether lesions only detected by MACE (and presumably missed by OGD) were false positives. This could be achieved by video recording or photodocumentation of the index OGD, second-look OGD or unblinding of the endoscopist prior to extubation. Future trials should take this into account while planning their study protocol.

Upper GI capsule endoscopy struggled to gain views in the fundus compared to other areas of the stomach in our studies, which resonates with previous reports. (60, 69) Water distension was used in our studies but other methods also exist. The use of gas-producing powder was not very effective in preliminary trials. (18, 68, 69) However, visualisation of the proximal stomach was not the primary outcome, nor was gas-production the main intervention tested. The role of anti-peristalsis agents is unclear. Hyoscine did not affect visualisation by the upper GI capsule in our experience, but our study was not powered adequately to test this. Incomplete capsule examination of the stomach has been associated with rapid pyloric expulsion (18, 67, 68) or contractions repeatedly pushing the capsule forwards and backwards through the pylorus obscuring antral views. (67) In contrast, we found that views of the antrum were excellent with SPIT using the upper GI capsule

and with MACE using the MiroCam Navi®. The effect of hyoscine on fundal views and diagnostic accuracy of upper GI capsule endoscopy is to be determined. Interestingly performing SPIT (water distension and position change alone) with the upper GI capsule achieved better views of the fundus than MACE with the MiroCam Navi® (median 4 (IQR 2) vs. 3 (IQR 2)). It is unclear why this is but may be related to the dual-cameras of the upper GI capsule versus the single camera of the MiroCam Navi®, differences in field of view (174° versus 170° respectively), improved water distension of the fundus by the head-down tilt position during SPIT or the difficulty met when attempting to steer the MiroCam Navi® capsule in the fundus during MACE. Utilising CT modelling, Rahman et al. found the distance between the ventral skin surface and the fundus to be more than 20 cm in up to 20% of cases. (184) This would explain why MACE in this area is difficult given that magnetic strength exponentially decreases with distance. The visualisation scoring tool used in this thesis (appendix 3) requires further validation but future trials should compare visualisation by the two methods of bedside upper GI capsule endoscopy: MACE using the MiroCam Navi® and SPIT using the Medtronic® upper GI capsule.

Upper GI tract radiology is unlikely to replace OGD. There is insufficient evidence to encourage barium contrast imaging of the upper GI tract as an alternative to OGD. (203, 204) Evidence to support the use of CT virtual gastroscopy is also sparse. (205-207) The lack of development in upper GI radiology may be related to the more attractive option of visualising the mucosa directly with OGD: upper GI capsule endoscopy is also capable of direct mucosal visualisation and less invasive. The importance of gastric mucosa cleanliness is worthy of mention. Recent guidelines promote the use of water flushing, antifoaming agents and suction to achieve a pristine surface for OGD examination. (8, 98) Various combinations of simethicone (208), pronase (187, 209), N-acetylcysteine (208) and dimethylpolysiloxane (210) have been used for OGD. Our previous

collaborative work with Zhu et al. in Shanghai, China, demonstrated that adding simethicone (400mg) to water produces better mucosal visualisation by MACE than water alone but that the combination of simethicone and pronase together is no better than simethicone alone. (189)

Achieving a clean mucosal surface with cleansing reagents is particularly relevant to upper GI capsule endoscopy given that suction (of excess fluid, bubbles and debris) is not available, unlike with OGD. Further randomised control trials will be needed to determine the prime cocktail of gastric cleansing agents. In summary, the technique of upper GI capsule endoscopy needs refining: the optimal gastric preparation (cleanliness of the mucosal surface and distension of the proximal stomach), value of double versus single-headed cameras and the benefit of magnetic steering (whether with a hand-held or robotic-arm magnet and the magnetic strength needed) compared to repositioning of the capsule just using gravity need to be determined.

## Chapter 9: Conclusion

In conclusion, we argue that the body of work justifies further research of upper GI capsule endoscopy. We demonstrate evidence of at least comparable diagnostic ability to OGD with the current technology and technique of MACE, which is only in its infancy. The data shows that upper GI capsule endoscopy is well tolerated and that OGD is not for a significant proportion of patients. Several follow-on studies are worthy of pursuit. A validated tool to assess the tolerance and acceptability of upper GI endoscopy is required. The diagnostic yield and biopsy rate of OGD should be re-evaluated following the implementation of new national standards (8) and its impact on patient outcomes. Future studies on upper GI capsule endoscopy need to establish a validated assessment tool for mucosal visualisation. The discordance of pathology detection between OGD and MACE needs to be reduced: this can be achieved by photo or video-documentation of index OGD procedures, second-look procedures or unblinding of endoscopists to confirm if lesions only seen with upper GI capsule endoscopy have been missed by OGD. Finally, the cost-effectiveness of upper GI capsule endoscopy should be assessed. At this time, upper GI capsule endoscopy cannot replace diagnostic OGD. Our experience however has convinced us of its potential as a non-invasive alternative to investigating the upper GI tract and sufficient to reject the null hypothesis of this thesis.

## Chapter 10: Bibliography

1. Edmonson JM. History of the instruments for gastrointestinal endoscopy. *Gastrointest Endosc.* 1991;37(2 Suppl):S27-56.
2. Demling L, Hagel HJ. Video endoscopy. Fundamentals and problems. *Endoscopy.* 1985;17(5):167-9.
3. Harris A. Guidance on the indications for diagnostic upper GI endoscopy, flexible sigmoidoscopy and colonoscopy. BSG Guidelines.2013.
4. Zubarik R, Eisen G, Mastropietro C, Lopez J, Carroll J, Benjamin S, et al. Prospective analysis of complications 30 days after outpatient upper endoscopy. *Am J Gastroenterol.* 1999;94(6):1539-45.
5. Riley S. Complications of upper gastrointestinal endoscopy. In: Alderson D, editor. BSG Guidelines in Gastroenterology.2006.
6. Quine MA, Bell GD, McCloy RF, Charlton JE, Devlin HB, Hopkins A. Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods. *Gut.* 1995;36(3):462-7.
7. Provision of gastrointestinal endoscopy and related services for a district general hospital. Working Party of the Clinical Services Committee of the British Society of Gastroenterology. *Gut.* 1991;32(1):95-105.
8. Beg S, Ragunath K, Wyman A, Banks M, Trudgill N, Mark Pritchard D, et al. Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS). *Gut.* 2017.
9. Sonnenberg A, Amorosi SL, Lacey MJ, Lieberman DA. Patterns of endoscopy in the United States: analysis of data from the Centers for Medicare and Medicaid Services and the National Endoscopic Database. *Gastrointest Endosc.* 2008;67(3):489-96.
10. Ford AC, Marwaha A, Lim A, Moayyedi P. What is the prevalence of clinically significant endoscopic findings in subjects with dyspepsia? Systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2010;8(10):830-7, 7.e1-2.
11. Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. *Endosc Int Open.* 2014;2(2):E46-50.
12. Valori RM, Damery S, Gavin DR, Anderson JT, Donnelly MT, Williams JG, et al. A new composite measure of colonoscopy: the Performance Indicator of Colonic Intubation (PICI). *Endoscopy.* 2018;50(1):40-51.
13. Ojidu H, Palmer H, Lewandowski J, Hampton J, Blakeborough T, Epstein O, et al. Patient tolerance and acceptance of different colonic imaging modalities: an observational cohort study. *Eur J Gastroenterol Hepatol.* 2018;30(5):520-5.
14. Condon A, Graff L, Elliot L, Illyckyj A. Acceptance of colonoscopy requires more than test tolerance. *Can J Gastroenterol.* 2008;22(1):41-7.
15. Gavin DR, Valori RM, Anderson JT, Donnelly MT, Williams JG, Swarbrick ET. The national colonoscopy audit: a nationwide assessment of the quality and safety of colonoscopy in the UK. *Gut.* 2013;62(2):242-9.
16. Campo R, Brullet E, Montserrat A, Calvet X, Moix J, Rué M, et al. Identification of factors that influence tolerance of upper gastrointestinal endoscopy. *Eur J Gastroenterol Hepatol.* 1999;11(2):201-4.
17. Bell GD. Preparation, premedication, and surveillance. *Endoscopy.* 2004;36(1):23-31.
18. Keller J, Fibbe C, Volke F, Gerber J, Mosse AC, Reimann-Zawadzki M, et al. Inspection of the human stomach using remote-controlled capsule endoscopy: a feasibility study in healthy volunteers (with videos). *Gastrointest Endosc.* 2011;73(1):22-8.

19. Brandt LJ. Patients' attitudes and apprehensions about endoscopy: how to calm troubled waters. *Am J Gastroenterol*. 2001;96(2):280-4.
20. Mulcahy HE, Kelly P, Banks MR, Connor P, Patchet SE, Farthing MJ, et al. Factors associated with tolerance to, and discomfort with, unsedated diagnostic gastroscopy. *Scand J Gastroenterol*. 2001;36(12):1352-7.
21. Garcia RT, Cello JP, Nguyen MH, Rogers SJ, Rodas A, Trinh HN, et al. Unsedated ultrathin EGD is well accepted when compared with conventional sedated EGD: a multicenter randomized trial. *Gastroenterology*. 2003;125(6):1606-12.
22. Parker C, Alexandridis E, Plevris J, O'Hara J, Panter S. Transnasal endoscopy : no gagging no panic! *Frontline Gastroenterology*. 2016;7(4):246-56.
23. Trevisani L, Cifalà V, Sartori S, Gilli G, Matarese G, Abbasciano V. Unsedated ultrathin upper endoscopy is better than conventional endoscopy in routine outpatient gastroenterology practice: a randomized trial. *World J Gastroenterol*. 2007;13(6):906-11.
24. Choe WH, Kim JH, Ko SY, Kwon SY, Kim BK, Rhee KH, et al. Comparison of transnasal small-caliber vs. peroral conventional esophagogastroduodenoscopy for evaluating varices in unsedated cirrhotic patients. *Endoscopy*. 2011;43(8):649-56.
25. Pennazio M, Spada C, Eliakim R, Keuchel M, May A, Mulder CJ, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*. 2015;47(4):352-76.
26. Irvine AJ, Sanders DS, Hopper A, Kurien M, Sidhu R. How does tolerability of double balloon enteroscopy compare to other forms of endoscopy? *Frontline Gastroenterology*. 2015.
27. Lapalus MG, Dumortier J, Fumex F, Roman S, Lot M, Prost B, et al. Esophageal capsule endoscopy versus esophagogastroduodenoscopy for evaluating portal hypertension: a prospective comparative study of performance and tolerance. *Endoscopy*. 2006;38(1):36-41.
28. Bhardwaj A, Hollenbeak CS, Pooran N, Mathew A. 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(6):1533-9.
29. Swain P, Toor A, Volke F, Keller J, Gerber J, Rabinovitz E, et al. Remote magnetic manipulation of a wireless capsule endoscope in the esophagus and stomach of humans (with videos). *Gastrointest Endosc*. 2010;71(7):1290-3.
30. Chak A, Alashkar BM, Isenberg GA, Chandar AK, Greer KB, Hepner A, et al. Comparative acceptability of transnasal esophagoscopy and esophageal capsule esophagoscopy: a randomized, controlled trial in veterans. *Gastrointest Endosc*. 2014;80(5):774-82.
31. Iddan G, Meron G, Glukhovsky A, Swain P. Wireless capsule endoscopy. *Nature*. 2000;405(6785):417.
32. Swain P. Wireless capsule endoscopy. *Gut*. 2003;52 Suppl 4:iv48-50.
33. Adler SN, Bjarnason I, Metzger YC. New balloon-guided technique for deep small-intestine endoscopy using standard endoscopes. *Endoscopy*. 2008;40(6):502-5.
34. Sidhu R, Sanders DS, Morris AJ, McAlindon ME. Guidelines on small bowel enteroscopy and capsule endoscopy in adults. *Gut*. 2008;57(1):125-36.
35. Enns RA, Hookey L, Armstrong D, Bernstein CN, Heitman SJ, Teshima C, et al. Clinical Practice Guidelines for the Use of Video Capsule Endoscopy. *Gastroenterology*. 2017;152(3):497-514.
36. Spada C, Spera G, Riccioni M, Biancone L, PetruzzIELLO L, Tringali A, et al. A novel diagnostic tool for detecting functional patency of the small bowel: the Given patency capsule. *Endoscopy*. 2005;37(9):793-800.

37. Assadsangabi A, Blakeborough A, Drew K, Lobo AJ, Sidhu R, McAlindon ME. Small bowel patency assessment using the patency device and a novel targeted (limited radiation) computed tomography-based protocol. *J Gastroenterol Hepatol*. 2015;30(6):984-9.
38. Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc*. 2010;71(2):280-6.
39. Li F, Gurudu SR, De Petris G, Sharma VK, Shiff AD, Heigh RI, et al. Retention of the capsule endoscope: a single-center experience of 1000 capsule endoscopy procedures. *Gastrointest Endosc*. 2008;68(1):174-80.
40. Cheon JH, Kim YS, Lee IS, Chang DK, Ryu JK, Lee KJ, et al. Can we predict spontaneous capsule passage after retention? A nationwide study to evaluate the incidence and clinical outcomes of capsule retention. *Endoscopy*. 2007;39(12):1046-52.
41. Yung DE, Plevris JN, Koulaouzidis A. Short article: Aspiration of capsule endoscopes: a comprehensive review of the existing literature. *Eur J Gastroenterol Hepatol*. 2017;29(4):428-34.
42. Bandorski D, Kurniawan N, Baltes P, Hoeltgen R, Hecker M, Stunder D, et al. Contraindications for video capsule endoscopy. *World J Gastroenterol*. 2016;22(45):9898-908.
43. Bandorski D, Irnich W, Brück M, Beyer N, Kramer W, Jakobs R. Capsule endoscopy and cardiac pacemakers: investigation for possible interference. *Endoscopy*. 2008;40(1):36-9.
44. Bandorski D, Lotterer E, Hartmann D, Jakobs R, Brück M, Hoeltgen R, et al. Capsule endoscopy in patients with cardiac pacemakers and implantable cardioverter-defibrillators - a retrospective multicenter investigation. *J Gastrointest Liver Dis*. 2011;20(1):33-7.
45. Bandorski D, Höltgen R, Stunder D, Keuchel M. Capsule endoscopy in patients with cardiac pacemakers, implantable cardioverter defibrillators and left heart assist devices. *Ann Gastroenterol*. 2014;27(1):3-8.
46. Stanich PP, Kleinman B, Betkerur K, Mehta Oza N, Porter K, Meyer MM. Video capsule endoscopy is successful and effective in outpatients with implantable cardiac devices. *Dig Endosc*. 2014;26(6):726-30.
47. Bouchard S, Ibrahim M, Van Gossum A. Video capsule endoscopy: perspectives of a revolutionary technique. *World J Gastroenterol*. 2014;20(46):17330-44.
48. Hale M, McAlindon ME. Capsule endoscopy as a panenteric diagnostic tool. *Br J Surg*. 2014;101(3):148-9.
49. Hosoe N, Naganuma M, Ogata H. Current status of capsule endoscopy through a whole digestive tract. *Dig Endosc*. 2015;27(2):205-15.
50. Ladas SD, Triantafyllou K, Spada C, Riccioni ME, Rey JF, Niv Y, et al. European Society of Gastrointestinal Endoscopy (ESGE): recommendations (2009) on clinical use of video capsule endoscopy to investigate small-bowel, esophageal and colonic diseases. *Endoscopy*. 2010;42(3):220-7.
51. Spada C, Hassan C, Costamagna G. Colon capsule endoscopy. *Gastrointest Endosc Clin N Am*. 2015;25(2):387-401.
52. Eliakim R, Yassin K, Shlomi I, Suissa A, Eisen GM. A novel diagnostic tool for detecting oesophageal pathology: the PillCam oesophageal video capsule. *Aliment Pharmacol Ther*. 2004;20(10):1083-9.
53. Gralnek IM, Adler SN, Yassin K, Koslowsky B, Metzger Y, Eliakim R. Detecting esophageal disease with second-generation capsule endoscopy: initial evaluation of the PillCam ESO 2. *Endoscopy*. 2008;40(4):275-9.
54. Gralnek IM, Ching JY, Maza I, Wu JC, Rainer TH, Israelit S, et al. Capsule endoscopy in acute upper gastrointestinal hemorrhage: a prospective cohort study. *Endoscopy*. 2013;45(1):12-9.

55. Rahman I, Afzal NA, Patel P. The role of magnetic assisted capsule endoscopy (MACE) to aid visualisation in the upper GI tract. *Comput Biol Med.* 2015;65:359-63.
56. Ciuti G, Menciassi A, Dario P. Capsule endoscopy: from current achievements to open challenges. *IEEE Rev Biomed Eng.* 2011;4:59-72.
57. Koulaouzidis A, Iakovidis DK, Karargyris A, Rondonotti E. Wireless endoscopy in 2020: Will it still be a capsule? *World J Gastroenterol.* 2015;21(17):5119-30.
58. Carpi F, Galbiati S, Carpi A. Magnetic shells for gastrointestinal endoscopic capsules as a means to control their motion. *Biomed Pharmacother.* 2006;60(8):370-4.
59. Keller J, Fibbe C, Volke F, Gerber J, Mosse AC, Reimann-Zawadzki M, et al. Remote magnetic control of a wireless capsule endoscope in the esophagus is safe and feasible: results of a randomized, clinical trial in healthy volunteers. *Gastrointest Endosc.* 2010;72(5):941-6.
60. Rahman I, Pioche M, Shim CS, Lee SP, Sung IK, Saurin JC, et al. Magnetic-assisted capsule endoscopy in the upper GI tract by using a novel navigation system (with video). *Gastrointest Endosc.* 2015.
61. Hale MF, Rahman I, Drew K, Sidhu R, Riley SA, Patel P, 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(7):650-3.
62. Hale MF, Drew K, Sidhu R, McAlindon ME. Does magnetically assisted capsule endoscopy improve small bowel capsule endoscopy completion rate? A randomised controlled trial. *Endosc Int Open.* 2016;4(2):E215-21.
63. Denzer UW, Rösch T, Hoytat B, Abdel-Hamid M, Hebuterne X, Vanbiervliet G, et al. Magnetically guided capsule versus conventional gastroscopy for upper abdominal complaints: a prospective blinded study. *J Clin Gastroenterol.* 2015;49(2):101-7.
64. Liao Z, Hou X, Lin-Hu EQ, Sheng JQ, Ge ZZ, Jiang B, et al. Accuracy of Magnetically Controlled Capsule Endoscopy, Compared With Conventional Gastroscopy, in Detection of Gastric Diseases. *Clin Gastroenterol Hepatol.* 2016;14(9):1266-73.e1.
65. Ciuti G, Donlin R, Valdastrì P, Arezzo A, Menciassi A, Morino M, et al. Robotic versus manual control in magnetic steering of an endoscopic capsule. *Endoscopy.* 2010;42(2):148-52.
66. Rey JF, Ogata H, Hosoe N, Ohtsuka K, Ogata N, Ikeda K, et al. Feasibility of stomach exploration with a guided capsule endoscope. *Endoscopy.* 2010;42(7):541-5.
67. Rey JF, Ogata H, Hosoe N, Ohtsuka K, Ogata N, Ikeda K, et al. Blinded nonrandomized comparative study of gastric examination with a magnetically guided capsule endoscope and standard videoendoscope. *Gastrointest Endosc.* 2012;75(2):373-81.
68. Liao Z, Duan XD, Xin L, Bo LM, Wang XH, Xiao GH, et al. Feasibility and safety of magnetic-controlled capsule endoscopy system in examination of human stomach: a pilot study in healthy volunteers. *J Interv Gastroenterol.* 2012;2(4):155-60.
69. Zou WB, Hou XH, Xin L, Liu J, Bo LM, Yu GY, et al. Magnetic-controlled capsule endoscopy vs. gastroscopy for gastric diseases: a two-center self-controlled comparative trial. *Endoscopy.* 2015;47(6):525-8.
70. Jiang X, Qian YY, Liu X, Pan J, Zou WB, Zhou W, et al. Impact of magnetic steering on gastric transit time of a capsule endoscopy (with video). *Gastrointest Endosc.* 2018;88(4):746-54.
71. Luo YY, Pan J, Chen YZ, Jiang X, Zou WB, Qian YY, et al. Magnetic Steering of Capsule Endoscopy Improves Small Bowel Capsule Endoscopy Completion Rate. *Dig Dis Sci.* 2019.
72. Zhao AJ, Qian YY, Sun H, Hou X, Pan J, Liu X, et al. Screening for gastric cancer with magnetically controlled capsule gastroscopy in asymptomatic individuals. *Gastrointest Endosc.* 2018;88(3):466-74.e1.
73. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut.* 2014;63(6):871-80.



74. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. NICE guidelines. [Available from: <https://www.nice.org.uk/guidance/CG184>.
75. Shaukat A, Wang A, Acosta RD, Bruining DH, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in dyspepsia. *Gastrointest Endosc*. 2015;82(2):227-32.
76. Department of Health. The NHS Cancer Plan 2000 [Available from: [http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/documents/digitalasset/dh\\_4014513.pdf](http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4014513.pdf).
77. Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. *Gastroenterology*. 2005;129(5):1756-80.
78. Bardhan KD, Royston C. Time, change and peptic ulcer disease in Rotherham, UK. *Dig Liver Dis*. 2008;40(7):540-6.
79. Lanas A. We Are Using Too Many PPIs, and We Need to Stop: A European Perspective. *Am J Gastroenterol*. 2016;111(8):1085-6.
80. Sonnenberg A, Vakil N. The benefit of negative tests in non-ulcer dyspepsia. *Med Decis Making*. 2002;22(3):199-207.
81. Monthly diagnostic waiting times and activity. NHS England Statistics. [Available from: <https://www.england.nhs.uk/statistics/statistical-work-areas/diagnostics-waiting-times-and-activity/monthly-diagnostics-waiting-times-and-activity/>.
82. Fransen GA, Janssen MJ, Muris JW, Laheij RJ, Jansen JB. Meta-analysis: the diagnostic value of alarm symptoms for upper gastrointestinal malignancy. *Aliment Pharmacol Ther*. 2004;20(10):1045-52.
83. Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. *Gastroenterology*. 2006;131(2):390-401; quiz 659-60.
84. Khademi H, Radmard AR, Malekzadeh F, Kamangar F, Nasser-Moghaddam S, Johansson M, et al. Diagnostic accuracy of age and alarm symptoms for upper GI malignancy in patients with dyspepsia in a GI clinic: a 7-year cross-sectional study. *PLoS One*. 2012;7(6):e39173.
85. Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. *Gut*. 2005;54(1):40-5.
86. Basford PJ, Brown J, Gadeke L, Fogg C, Haysom-Newport B, Ogollah R, et al. A randomized controlled trial of pre-procedure simethicone and N-acetylcysteine to improve mucosal visibility during gastroscopy - NICEVIS. *Endosc Int Open*. 2016;4(11):E1197-E202.
87. Cheung D, Menon S, Hoare J, Dhar A, Trudgill N. Factors Associated with Upper Gastrointestinal Cancer Occurrence After Endoscopy that Did Not Diagnose Cancer. *Dig Dis Sci*. 2016;61(9):2674-84.
88. Allen JI, Katzka D, Robert M, Leontiadis GI. American Gastroenterological Association Institute Technical Review on the Role of Upper Gastrointestinal Biopsy to Evaluate Dyspepsia in the Adult Patient in the Absence of Visible Mucosal Lesions. *Gastroenterology*. 2015;149(4):1088-118.
89. Yang YX, Brill J, Krishnan P, Leontiadis G, Committee AGACPG. American Gastroenterological Association Institute Guideline on the Role of Upper Gastrointestinal Biopsy to Evaluate Dyspepsia in the Adult Patient in the Absence of Visible Mucosal Lesions. *Gastroenterology*. 2015;149(4):1082-7.
90. Januszewicz W, Wieszczy P, Bialek A, Karpinska K, Szlak J, Szymonik J, et al. The endoscopists' biopsy rate as a quality indicator for outpatient gastroscopy: a multicenter cohort study with validation. *Gastrointest Endosc*. 2019.
91. Hosokawa O, Tsuda S, Kidani E, Watanabe K, Tanigawa Y, Shirasaki S, et al. Diagnosis of gastric cancer up to three years after negative upper gastrointestinal endoscopy. *Endoscopy*. 1998;30(8):669-74.

92. Park JM, Huo SM, Lee HH, Lee BI, Song HJ, Choi MG. Longer Observation Time Increases Proportion of Neoplasms Detected by Esophagogastroduodenoscopy. *Gastroenterology*. 2017;153(2):460-9.e1.
93. Lau MS, Mooney P, White W, Appleby V, Moreea S, Haythem I, et al. 'Pre-endoscopy point of care test (Simtomax- IgA/IgG-Deamidated Gliadin Peptide) for coeliac disease in iron deficiency anaemia: diagnostic accuracy and a cost saving economic model'. *BMC Gastroenterol*. 2016;16:115.
94. Nelsen EM, Lochmann-Bailkey A, Grimes IC, Benson ME, Gopal DV, Pfau PR. Low Yield and High Cost of Gastric and Duodenal Biopsies for Investigation of Symptoms of Abdominal Pain During Routine Esophagogastroduodenoscopy. *Dig Dis Sci*. 2017;62(2):418-23.
95. Rondonotti E, Andrealli A, Amato A, Paggi S, Conti CB, Spinzi G, et al. Technical interventions to increase adenoma detection rate in colonoscopy. *Expert Rev Gastroenterol Hepatol*. 2016;10(12):1349-58.
96. Kumar S, Thosani N, Ladabaum U, Friedland S, Chen AM, Kochar R, et al. Adenoma miss rates associated with a 3-minute versus 6-minute colonoscopy withdrawal time: a prospective, randomized trial. *Gastrointest Endosc*. 2016.
97. Kashiwagi K, Inoue N, Yoshida T, Bessyo R, Yoneno K, Imaeda H, et al. Polyp detection rate in transverse and sigmoid colon significantly increases with longer withdrawal time during screening colonoscopy. *PLoS One*. 2017;12(3):e0174155.
98. Veitch AM, Uedo N, Yao K, East JE. Optimizing early upper gastrointestinal cancer detection at endoscopy. *Nat Rev Gastroenterol Hepatol*. 2015;12(11):660-7.
99. Hazeldine S, Fritschi L, Forbes G. Predicting patient tolerance of endoscopy with conscious sedation. *Scand J Gastroenterol*. 2010;45(10):1248-54.
100. Trevisani L, Sartori S, Gaudenzi P, Gilli G, Matarese G, Gullini S, et al. Upper gastrointestinal endoscopy: are preparatory interventions or conscious sedation effective? A randomized trial. *World J Gastroenterol*. 2004;10(22):3313-7.
101. Taghavi SA, Membari ME, Eshraghian A, Dehghani SM, Hamidpour L, Khademalhoseini F. Comparison of chromoendoscopy and conventional endoscopy in the detection of premalignant gastric lesions. *Can J Gastroenterol*. 2009;23(2):105-8.
102. Baptista V, Singh A, Wassef W. Early gastric cancer: an update on endoscopic management. *Curr Opin Gastroenterol*. 2012;28(6):629-35.
103. Ignjatovic A, East JE, Suzuki N, Vance M, Guenther T, Saunders BP. Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. *Lancet Oncol*. 2009;10(12):1171-8.
104. Rees CJ, Rajasekhar PT, Wilson A, Close H, Rutter MD, Saunders BP, et al. Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect InSpect Characterise Resect and Discard 2 (DISCARD 2) study. *Gut*. 2017;66(5):887-95.
105. Teh JL, Tan JR, Lau LJ, Saxena N, Salim A, Tay A, et al. Longer examination time improves detection of gastric cancer during diagnostic upper gastrointestinal endoscopy. *Clin Gastroenterol Hepatol*. 2015;13(3):480-7.e2.
106. Markar S, Hanna G, editors. Breath test could help detect stomach and esophageal cancers. The European CanCer Organisation (ECCO); 2017.
107. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, Walker E, Varghese S, Lao-Sirieix P, 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):e1001780.
108. Paterson AL, Lao-Sirieix P, O'Donovan M, Debiram-Beecham I, di Pietro M, Miremadi A, et al. Range of pathologies diagnosed using a minimally invasive capsule sponge to evaluate patients with reflux symptoms. *Histopathology*. 2017;70(2):203-10.

109. Syrjänen K. A Panel of Serum Biomarkers (GastroPanel®) in Non-invasive Diagnosis of Atrophic Gastritis. Systematic Review and Meta-analysis. *Anticancer Res.* 2016;36(10):5133-44.
110. Iyer PG, Taylor WR, Johnson ML, Lansing RL, Maixner KA, Yab TC, et al. Highly Discriminant Methylated DNA Markers for the Non-endoscopic Detection of Barrett's Esophagus. *Am J Gastroenterol.* 2018;113(8):1156-66.
111. Iqbal U, Siddique O, Ovalle A, Anwar H, Moss SF. 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(11):1261-9.
112. 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.* 2016.
113. Chadwick G, Groene O, Hoare J, Hardwick RH, Riley S, Crosby TD, et al. A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. *Endoscopy.* 2014;46(7):553-60.
114. Siau K, Yew AC, Hingley S, Rees J, Trudgill NJ, Veitch AM, et al. The 2015 upper gastrointestinal "Be Clear on Cancer" campaign: its impact on gastroenterology services and malignant and premalignant diagnoses. *Frontline Gastroenterol.* 2017;8(4):284-9.
115. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology.* 2012;143(5):1179-87.e3.
116. Abraham NS, Fallone CA, Mayrand S, Huang J, Wiczorek P, Barkun AN. Sedation versus no sedation in the performance of diagnostic upper gastrointestinal endoscopy: a Canadian randomized controlled cost-outcome study. *Am J Gastroenterol.* 2004;99(9):1692-9.
117. Garg PK, Singh AP, Jain BK, Bansal A, Mohanty D, Agrawal V. Safety and acceptance of non-sedated upper gastrointestinal endoscopy: a prospective observational study. *J Laparoendosc Adv Surg Tech A.* 2012;22(4):315-8.
118. Riphaus A, Wehrmann T, Weber B, Arnold J, Beilenhoff U, Bitter H, et al. S3 Guideline: Sedation for gastrointestinal endoscopy 2008. *Endoscopy.* 2009;41(9):787-815.
119. Cohen LB, Ladas SD, Vargo JJ, Paspatis GA, Bjorkman DJ, Van der Linden P, et al. Sedation in digestive endoscopy: the Athens international position statements. *Aliment Pharmacol Ther.* 2010;32(3):425-42.
120. Igea F, Casellas JA, González-Huix F, Gómez-Oliva C, Baudet JS, Cacho G, et al. Sedation for gastrointestinal endoscopy. *Endoscopy.* 2014;46(8):720-31.
121. Early DS, Lightdale JR, Vargo JJ, Acosta RD, Chandrasekhara V, Chathadi KV, et al. Guidelines for sedation and anesthesia in GI endoscopy. *Gastrointest Endosc.* 2018;87(2):327-37.
122. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. *Gastrointest Endosc.* 2008;67(6):910-23.
123. Badurdeen DS, Umar NA, Begum R, Sanderson AK, Jack M, Mekasha G, et al. Timing of procedure and compliance with outpatient endoscopy among an underserved population in an inner-city tertiary institution. *Ann Epidemiol.* 2012;22(7):531-5.
124. El-Serag HB, Duan Z, Hinojosa-Lindsey M, Hou J, Shakhathreh M, Naik AD, et al. Practice patterns of surveillance endoscopy in a Veterans Affairs database of 29,504 patients with Barrett's esophagus. *Gastrointest Endosc.* 2012;76(4):743-55.
125. Stern AF. The hospital anxiety and depression scale. *Occup Med (Lond).* 2014;64(5):393-4.

126. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002;52(2):69-77.
127. Brooks AJ, Hurlstone DP, Fotheringham J, Gane J, Sanders DS, McAlindon ME. Information required to provide informed consent for endoscopy: an observational study of patients' expectations. *Endoscopy.* 2005;37(11):1136-9.
128. Cullinane M, Gray AJG, Hargraves CMK, Lucas S, Schubert M, Sherry KM, et al. Scoping our practice 2004 [Available from: <https://www.ncepod.org.uk/2004report/>].
129. Sneyd R, Benger J, Blayne M, Furniss S, Holden C, Ibbetson R, et al. Safe sedation practice for healthcare procedures 2013 [Available from: <https://www.rcoa.ac.uk/system/files/PUB-SafeSedPrac2013.pdf>].
130. Behrens A, Kreuzmayr A, Manner H, Koop H, Lorenz A, Schaefer C, et al. Acute sedation-associated complications in GI endoscopy (ProSed 2 Study): results from the prospective multicentre electronic registry of sedation-associated complications. *Gut.* 2018.
131. Walmsley RS, Montgomery SM. Factors affecting patient tolerance of upper gastrointestinal endoscopy. *J Clin Gastroenterol.* 1998;26(4):253-5.
132. Kim LS, Koch J, Yee J, Halvorsen R, Cello JP, Rockey DC. Comparison of patients' experiences during imaging tests of the colon. *Gastrointest Endosc.* 2001;54(1):67-74.
133. Sami SS, Subramanian V, Ortiz-Fernández-Sordo J, Saeed A, Singh S, Guha IN, et al. Performance characteristics of unsedated ultrathin video endoscopy in the assessment of the upper GI tract: systematic review and meta-analysis. *Gastrointest Endosc.* 2015;82(5):782-92.
134. Marelli L, Jaboli FM, Jackson L, Palmer H, Erian G, Hamilton M, et al. A pilot study comparing ESO-2 capsule endoscopy with conventional upper endoscopy for the assessment of uncomplicated heartburn and dyspepsia. *Frontline Gastroenterology* 2013. p. 96–101.
135. Ching HL, Healy A, Thurston V, Hale MF, Sidhu R, McAlindon ME. Upper gastrointestinal tract capsule endoscopy using a nurse-led protocol: First reported experience. *World J Gastroenterol.* 2018;24(26):2893-901.
136. Kepczyk T, Kadakia SC. Prospective evaluation of gastrointestinal tract in patients with iron-deficiency anemia. *Dig Dis Sci.* 1995;40(6):1283-9.
137. McIntyre AS, Long RG. Prospective survey of investigations in outpatients referred with iron deficiency anaemia. *Gut.* 1993;34(8):1102-7.
138. Riccioni ME, Urgesi R, Spada C, Cianci R, Pelecca G, Bizzotto A, et al. Unexplained iron deficiency anaemia: Is it worthwhile to perform capsule endoscopy? *Dig Liver Dis.* 2010;42(8):560-6.
139. Goddard AF, James MW, McIntyre AS, Scott BB, Gastroenterology BSo. Guidelines for the management of iron deficiency anaemia. *Gut.* 2011;60(10):1309-16.
140. Koulaouzidis A, Rondonotti E, Giannakou A, Plevris JN. Diagnostic yield of small-bowel capsule endoscopy in patients with iron-deficiency anemia: a systematic review. *Gastrointest Endosc.* 2012;76(5):983-92.
141. Zaman A, Katon RM. Push enteroscopy for obscure gastrointestinal bleeding yields a high incidence of proximal lesions within reach of a standard endoscope. *Gastrointest Endosc.* 1998;47(5):372-6.
142. Descamps C, Schmit A, Van Gossum A. "Missed" upper gastrointestinal tract lesions may explain "occult" bleeding. *Endoscopy.* 1999;31(6):452-5.
143. Tee HP, Kaffes AJ. Non-small-bowel lesions encountered during double-balloon enteroscopy performed for obscure gastrointestinal bleeding. *World J Gastroenterol.* 2010;16(15):1885-9.
144. Fry LC, Bellutti M, Neumann H, Malfertheiner P, Mönkemüller K. Incidence of bleeding lesions within reach of conventional upper and lower endoscopes in patients undergoing

- double-balloon enteroscopy for obscure gastrointestinal bleeding. *Aliment Pharmacol Ther.* 2009;29(3):342-9.
145. Lara LF, Bloomfield RS, Pineau BC. The rate of lesions found within reach of esophagogastroduodenoscopy during push enteroscopy depends on the type of obscure gastrointestinal bleeding. *Endoscopy.* 2005;37(8):745-50.
  146. Kavic SM, Basson MD. Complications of endoscopy. *Am J Surg.* 2001;181(4):319-32.
  147. Ben-Menachem T, Decker GA, Early DS, Evans J, Fanelli RD, Fisher DA, et al. Adverse events of upper GI endoscopy. *Gastrointest Endosc.* 2012;76(4):707-18.
  148. Gralnek IM, Rabinovitz R, Afik D, Eliakim R. A simplified ingestion procedure for esophageal capsule endoscopy: initial evaluation in healthy volunteers. *Endoscopy.* 2006;38(9):913-8.
  149. Elphick DA, Donnelly MT, Smith KS, Riley SA. Factors associated with abdominal discomfort during colonoscopy: a prospective analysis. *Eur J Gastroenterol Hepatol.* 2009;21(9):1076-82.
  150. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol.* 2006;101(2):343-50.
  151. Spencer HL, Lobo AJ, Riley SA. Variations in the reporting of endoscopies by different endoscopists. *Clin Med (Lond).* 2007;7(1):23-7.
  152. Asfeldt AM, Straume B, Paulssen EJ. Impact of observer variability on the usefulness of endoscopic images for the documentation of upper gastrointestinal endoscopy. *Scand J Gastroenterol.* 2007;42(9):1106-12.
  153. Choi EH, Mergener K, Semrad C, Fisher L, Cave DR, Dodig M, et al. A multicenter, prospective, randomized comparison of a novel signal transmission capsule endoscope to an existing capsule endoscope. *Gastrointest Endosc.* 2013;78(2):325-32.
  154. Meltzer AC, Ward MJ, Gralnek IM, Pines JM. The cost-effectiveness analysis of video capsule endoscopy compared to other strategies to manage acute upper gastrointestinal hemorrhage in the ED. *Am J Emerg Med.* 2014;32(8):823-32.
  155. Romagnuolo J, Brock AS, Ranney N. Is Endoscopic Therapy Effective for Angioectasia in Obscure Gastrointestinal Bleeding?: A Systematic Review of the Literature. *J Clin Gastroenterol.* 2015;49(10):823-30.
  156. Tsoi KK, Chan HC, Chiu PW, Pau CY, Lau JY, Sung JJ. Second-look endoscopy with thermal coagulation or injections for peptic ulcer bleeding: a meta-analysis. *J Gastroenterol Hepatol.* 2010;25(1):8-13.
  157. Siau K, Chapman W, Sharma N, Tripathi D, Iqbal T, Bhala N. Management of acute upper gastrointestinal bleeding: an update for the general physician. *J R Coll Physicians Edinb.* 2017;47(3):218-30.
  158. Wuerth BA, Rockey DC. Changing Epidemiology of Upper Gastrointestinal Hemorrhage in the Last Decade: A Nationwide Analysis. *Dig Dis Sci.* 2017.
  159. Laine L, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol.* 2012;107(8):1190-5; quiz 6.
  160. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. *N Engl J Med.* 2008;359(9):928-37.
  161. Meltzer AC, Pinchbeck C, Burnett S, Buhumaid R, Shah P, Ding R, et al. Emergency physicians accurately interpret video capsule endoscopy findings in suspected upper gastrointestinal hemorrhage: a video survey. *Acad Emerg Med.* 2013;20(7):711-5.
  162. Dworzynski K, Pollit V, Kelsey A, Higgins B, Palmer K, Group GD. Management of acute upper gastrointestinal bleeding: summary of NICE guidance. *BMJ.* 2012;344:e3412.

163. Hwang JH, Fisher DA, Ben-Menachem T, Chandrasekhara V, Chathadi K, Decker GA, et al. The role of endoscopy in the management of acute non-variceal upper GI bleeding. *Gastrointest Endosc.* 2012;75(6):1132-8.
164. Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: results of a nationwide audit. *Gut.* 2010;59(8):1022-9.
165. Colli A, Gana JC, Turner D, Yap J, Adams-Webber T, Ling SC, et al. Capsule endoscopy for the diagnosis of oesophageal varices in people with chronic liver disease or portal vein thrombosis. *Cochrane Database Syst Rev.* 2014(10):CD008760.
166. Lu Y, Gao R, Liao Z, Hu LH, Li ZS. Meta-analysis of capsule endoscopy in patients diagnosed or suspected with esophageal varices. *World J Gastroenterol.* 2009;15(10):1254-8.
167. Sung JJ, Tang RS, Ching JY, Rainer TH, Lau JY. Use of capsule endoscopy in the emergency department as a triage of patients with GI bleeding. *Gastrointest Endosc.* 2016;84(6):907-13.
168. Mudie DM, Murray K, Hoad CL, Pritchard SE, Garnett MC, Amidon GL, et al. Quantification of gastrointestinal liquid volumes and distribution following a 240 mL dose of water in the fasted state. *Mol Pharm.* 2014;11(9):3039-47.
169. Ching HL, Hale MF, Kurien M, Campbell JA, Zammit SC, Healy A, et al. Diagnostic yield of magnetically assisted capsule endoscopy versus gastroscopy in recurrent and refractory iron deficiency anemia. *Endoscopy.* 2018.
170. Enestvedt BK, Gralnek IM, Mattek N, Lieberman DA, Eisen G. An evaluation of endoscopic indications and findings related to nonvariceal upper-GI hemorrhage in a large multicenter consortium. *Gastrointest Endosc.* 2008;67(3):422-9.
171. Holster IL, Kuipers EJ. Management of acute nonvariceal upper gastrointestinal bleeding: current policies and future perspectives. *World J Gastroenterol.* 2012;18(11):1202-7.
172. Sidhu R, Sanders DS, Kapur K, Hurlstone DP, McAlindon ME. Capsule endoscopy changes patient management in routine clinical practice. *Dig Dis Sci.* 2007;52(5):1382-6.
173. Hayat M, Axon AT, O'Mahony S. Diagnostic yield and effect on clinical outcomes of push enteroscopy in suspected small-bowel bleeding. *Endoscopy.* 2000;32(5):369-72.
174. Chandran S, Testro A, Urquhart P, La Nauze R, Ong S, Shelton E, et al. Risk stratification of upper GI bleeding with an esophageal capsule. *Gastrointest Endosc.* 2013;77(6):891-8.
175. Kopylov U, Yung DE, Engel T, Avni T, Battat R, Ben-Horin S, et al. Fecal calprotectin for the prediction of small-bowel Crohn's disease by capsule endoscopy: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2016;28(10):1137-44.
176. Marya NB, Jawaid S, Foley A, Han S, Patel K, Maranda L, et al. A randomized controlled trial comparing efficacy of early video capsule endoscopy with standard of care in the approach to nonhematemesis GI bleeding (with videos). *Gastrointest Endosc.* 2019;89(1):33-43.e4.
177. Meltzer AC, Ali MA, Kresiberg RB, Patel G, Smith JP, Pines JM, et al. Video capsule endoscopy in the emergency department: a prospective study of acute upper gastrointestinal hemorrhage. *Ann Emerg Med.* 2013;61(4):438-43.e1.
178. Triantafyllou K, Papanikolaou IS, Papaxoinis K, Ladas SD. Two cameras detect more lesions in the small-bowel than one. *World J Gastroenterol.* 2011;17(11):1462-7.
179. Remes-Troche JM, Jiménez-García VA, García-Montes JM, Hergueta-Delgado P, Roesch-Dietlen F, Herreras-Gutiérrez JM. Application of colon capsule endoscopy (CCE) to evaluate the whole gastrointestinal tract: a comparative study of single-camera and dual-camera analysis. *Clin Exp Gastroenterol.* 2013;6:185-92.
180. Ching H-L, Hale MF, Sidhu R, Beg S, Ragunath K, McAlindon ME. Magnetically assisted capsule endoscopy (MACE) of the upper GI tract to select patients for endoscopy and reduce hospital admissions.: Presented at the BSG Annual Meeting 2017. Manchester, UK. BSG2017-942.

181. Koslowsky B, Jacob H, Eliakim R, Adler SN. PillCam ESO in esophageal studies: improved diagnostic yield of 14 frames per second (fps) compared with 4 fps. *Endoscopy*. 2006;38(1):27-30.
182. Laurain A, de Leusse A, Gincul R, Vanbiervliet G, Bramli S, Heyries L, et al. Oesophageal capsule endoscopy versus oesophago-gastroduodenoscopy for the diagnosis of recurrent varices: a prospective multicentre study. *Dig Liver Dis*. 2014;46(6):535-40.
183. Krok KL, Wagennar RR, Kantsevov SV, Thuluvath PJ. Esophageal capsule endoscopy is not the optimal technique to determine the need for primary prophylaxis in patients with cirrhosis. *Arch Med Sci*. 2016;12(2):365-71.
184. Rahman I, Kay M, Bryant T, Pelitari S, Salter S, Dimitrov B, et al. Optimizing the performance of magnetic-assisted capsule endoscopy of the upper GI tract using multiplanar CT modelling. *Eur J Gastroenterol Hepatol*. 2015;27(4):460-6.
185. Qian Y, Wu S, Wang Q, Wei L, Wu W, Wang L, et al. Combination of Five Body Positions Can Effectively Improve the Rate of Gastric Mucosa's Complete Visualization by Applying Magnetic-Guided Capsule Endoscopy. *Gastroenterol Res Pract*. 2016;2016:6471945.
186. Koulaouzidis A, Smirnidis A, Douglas S, Plevris JN. QuickView in small-bowel capsule endoscopy is useful in certain clinical settings, but QuickView with Blue Mode is of no additional benefit. *Eur J Gastroenterol Hepatol*. 2012;24(9):1099-104.
187. Lee GJ, Park SJ, Kim SJ, Kim HH, Park MI, Moon W. Effectiveness of Premedication with Pronase for Visualization of the Mucosa during Endoscopy: A Randomized, Controlled Trial. *Clin Endosc*. 2012;45(2):161-4.
188. Kim GH, Cho YK, Cha JM, Lee SY, Chung IK. Effect of pronase as mucolytic agent on imaging quality of magnifying endoscopy. *World J Gastroenterol*. 2015;21(8):2483-9.
189. Zhu SG, Qian YY, Tang XY, Zhu QQ, Zhou W, Du H, et al. Gastric preparation for magnetically controlled capsule endoscopy: A prospective, randomized single-blinded controlled trial. *Dig Liver Dis*. 2017.
190. Stacher G, Bergmann H, Havlik E, Schmierer G, Schneider C. Effects of oral cyclopropium bromide, hyoscine N-butylbromide and placebo on gastric emptying and antral motor activity in healthy man. *Gut*. 1984;25(5):485-90.
191. di Pietro M, Chan D, Fitzgerald RC, Wang KK. Screening for Barrett's Esophagus. *Gastroenterology*. 2015;148:912-23.
192. Gupta M, Beebe TJ, Dunagan KT, Schleck CD, Zinsmeister AR, Nicholas J, Locke III GR, et al. Screening for Barrett's Esophagus: Results from a Population-Based Survey. *Dig Dis Sci*. 2014;59(8):1831-50.
193. Ching H-L, Hale MF, Sidhu RH, McAlindon ME. Reassessing the value of gastroscopy for the investigation of dyspepsia. Data submitted to the British Society of Gastroenterology annual meeting. ; 2016.
194. Tahir M. Appropriateness of Upper Gastrointestinal Endoscopy: Will the Diagnostic Yield Improve by the use of American Society of Gastroenterology Guidelines? *Euroasian J Hepatogastroenterol*. 2016;6(2):143-8.
195. Selinger CP, Cochrane R, Thanaraj S, Sainsbury A, Subramanian V, Everett S. Gastric ulcers: malignancy yield and risk stratification for follow-up endoscopy. *Endosc Int Open*. 2016;4(6):E709-14.
196. Park SJ, Park H, Lee YC, Choi CH, Jeon TJ, Park JC, et al. Effect of scheduled second-look endoscopy on peptic ulcer bleeding: a prospective randomized multicenter trial. *Gastrointest Endosc*. 2018;87(2):457-65.
197. Rimbaş M, Negreanu L, Ciobanu L, Benguş A, Spada C, Băicuş CR, et al. Is virtual chromoendoscopy useful in the evaluation of subtle ulcerative small-bowel lesions detected by video capsule endoscopy? *Endosc Int Open*. 2015;3(6):E615-20.

198. Boal Carvalho P, Magalhães J, Dias de Castro F, Gonçalves TC, Rosa B, Moreira MJ, et al. Virtual chromoendoscopy improves the diagnostic yield of small bowel capsule endoscopy in obscure gastrointestinal bleeding. *Dig Liver Dis*. 2016;48(2):172-5.
199. Cox BF, Stewart F, Lay H, Cummins G, Newton IP, Desmulliez MPY, et al. Ultrasound capsule endoscopy: sounding out the future. *Ann Transl Med*. 2017;5(9):201.
200. Gora MJ, Quénéhervé L, Carruth RW, Lu W, Rosenberg M, Sauk JS, et al. Tethered capsule endomicroscopy for microscopic imaging of the esophagus, stomach, and duodenum without sedation in humans (with video). *Gastrointest Endosc*. 2018;88(5):830-40.e3.
201. Preiss C, Charton JP, Schumacher B, Neuhaus H. A randomized trial of unsedated transnasal small-caliber esophagogastroduodenoscopy (EGD) versus peroral small-caliber EGD versus conventional EGD. *Endoscopy*. 2003;35(8):641-6.
202. Dumortier J, Ponchon T, Scoazec JY, Moulinier B, Zarka F, Paliard P, et al. Prospective evaluation of transnasal esophagogastroduodenoscopy: feasibility and study on performance and tolerance. *Gastrointest Endosc*. 1999;49(3 Pt 1):285-91.
203. Dooley CP, Larson AW, Stace NH, Renner IG, Valenzuela JE, Eliasoph J, et al. Double-contrast barium meal and upper gastrointestinal endoscopy. A comparative study. *Ann Intern Med*. 1984;101(4):538-45.
204. Stevenson GW, Norman G, Frost R, Somers S. Barium meal or endoscopy? A prospective randomized study of patient preference and physician decision making. *Clin Radiol*. 1991;44(5):317-21.
205. Springer P, Dessl A, Giacomuzzi SM, Buchberger W, Stöger A, Oberwalder M, et al. Virtual computed tomography gastroscopy: a new technique. *Endoscopy*. 1997;29(7):632-4.
206. Chen CY, Kuo YT, Lee CH, Hsieh TJ, Jan CM, Jaw TS, et al. Differentiation between malignant and benign gastric ulcers: CT virtual gastroscopy versus optical gastroendoscopy. *Radiology*. 2009;252(2):410-7.
207. Takahashi S, Hirayama M, Kuroiwa G, Kawano Y, Takada K, Sato T, et al. Diagnostic validity of CT gastrography versus gastroscopy for primary lesions in gastric cancer: evaluating the response to chemotherapy, a retrospective analysis. *Gastric Cancer*. 2013;16(4):543-8.
208. Neale JR, James S, Callaghan J, Patel P. Premedication with N-acetylcysteine and simethicone improves mucosal visualization during gastroscopy: a randomized, controlled, endoscopist-blinded study. *Eur J Gastroenterol Hepatol*. 2013;25(7):778-83.
209. Chang CC, Chen SH, Lin CP, Hsieh CR, Lou HY, Suk FM, et al. Premedication with pronase or N-acetylcysteine improves visibility during gastroendoscopy: an endoscopist-blinded, prospective, randomized study. *World J Gastroenterol*. 2007;13(3):444-7.
210. Asl SM, Sivandzadeh GR. Efficacy of premedication with activated Dimethicone or N-acetylcysteine in improving visibility during upper endoscopy. *World J Gastroenterol*. 2011;17(37):4213-7.



## Chapter 11: Appendix

### Appendix 1: Modified Endoscopy Concerns Scale (mECS)

<sup>a</sup>Questions answered by patients only prior to gastroscopy. <sup>b</sup>Question answered by patients only after gastroscopy. All remaining questions are answered by patients before and after for comparison of expectation and experience.

Modified Endoscopy Concerns Scale (mECS)											
With regards to your gastroscopy, how much, if any, have you been distressed by concerns about:											
<sup>a</sup> Telling friends/colleagues about the nature of my upcoming test	1	2	3	4	5	6	7	8	9	10	
<sup>a</sup> Fasting prior to the test	1	2	3	4	5	6	7	8	9	10	
Gagging during the test	1	2	3	4	5	6	7	8	9	10	
Sensation of choking during the test	1	2	3	4	5	6	7	8	9	10	
Sensation of bloating during the test	1	2	3	4	5	6	7	8	9	10	
Vomiting during the test	1	2	3	4	5	6	7	8	9	10	
Doctor seeing my food in the stomach during the test	1	2	3	4	5	6	7	8	9	10	
Expressing emotions during the test	1	2	3	4	5	6	7	8	9	10	
Insertion of the scope into my gullet	1	2	3	4	5	6	7	8	9	10	
Insertion of intravenous line into my hand	1	2	3	4	5	6	7	8	9	10	
<sup>a</sup> Discomfort prior to the test	1	2	3	4	5	6	7	8	9	10	
Discomfort during the procedure	1	2	3	4	5	6	7	8	9	10	
Discomfort after the procedure	1	2	3	4	5	6	7	8	9	10	
<sup>a</sup> Pain prior to the test	1	2	3	4	5	6	7	8	9	10	
Pain during the procedure	1	2	3	4	5	6	7	8	9	10	
Pain after the procedure	1	2	3	4	5	6	7	8	9	10	
<sup>b</sup> Overall acceptability of test	0	1	2	3	4	5	6	7	8	9	10

## Appendix 2: Hospital Anxiety and Depression Scale (HADS)

<b>I feel tense or 'wound up':</b>		<b>I feel as if I am slowed down:</b>	
Most of the time	3	Nearly all the time	3
A lot of the time	2	Very often	2
From time to time (occasionally)	1	Sometimes	1
Not at all	0	Not at all	0
<b>I still enjoy the things I used to enjoy:</b>		<b>I get a sort of frightening feeling like "butterflies" in the stomach:</b>	
Definitely as much	0	Not at all	0
Not quite as much	1	Occasionally	1
Only a little	2	Quite often	2
Hardly at all	3	Very often	3
<b>I get a sort of frightening feeling as if something awful is about to happen:</b>		<b>I have lost interest in my appearance:</b>	
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care	0
<b>I can laugh and see the funny side of things:</b>		<b>I feel restless as I have been on the move:</b>	
As much as I always could	0	Very much indeed	3
Not quite so much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
<b>Worrying thoughts go through my mind:</b>		<b>I look forward with enjoyment to things:</b>	
A great deal of the time	3	As much as I ever did	0
A lot of the time	2	Rather less than I use to	1
From time to time, but not often	1	Definitely less than I use to	2
Only occasionally	0	Hardly at all	3
<b>I feel cheerful:</b>		<b>I get sudden feelings of panic:</b>	
Not at all	3	Very often indeed	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0
<b>I can sit at ease and feel relaxed:</b>		<b>I can enjoy a good book or radio/TV program:</b>	
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

### Appendix 3: Grading scheme for visibility at major gastric landmark

Grade	Description
1	Poor view. More than 75% obscured by debris/bubbles/poor image clarity/illumination
2	Sub-optimal view. More than or equal to 50% obscured by debris/bubbles/poor image clarity/illumination
3	Reasonable view. Less than 50% obscured by debris/bubbles/poor image clarity/illumination
4	Good view. Less than 25% obscured by debris/bubbles/poor image clarity/illumination
5	Excellent. 100% complete view of the landmark

### Appendix 4: Pathology Reporting Form

Please tick the box(es) that correspond to the findings at gastroscopy

	<i>Tick (or state number)</i>	<i>Location*</i>
Oesophagitis		
Mallory-Weiss tear		
Gastric antral vascular ectasia (GAVE)		
Portal hypertensive gastropathy		
Small ulcer <1cm		
Large ulcer ≥1cm		
Ulcer with visible vessel		
Ulcer with active bleeding		
Dieulafoy lesion		
Erosion		
Nodules		
Erythema		
Oedema		
Bile reflux		
Angioectasia		
Tumour without ulceration		
Tumour with ulceration		
Polyp		
Diverticulum		
Varices		
Fresh blood or clots		
Haematin/old blood		

\*Please report location as follows:

Oesophagus: proximal, mid, distal

Stomach: cardia, fundus, greater/lesser curvature, antrum

## Appendix 5: Participant comfort questionnaire before and after MACE and OGD

This information is being collected as part of a research study looking at a new way of performing capsule endoscopy. All data will be treated as confidential. Please complete sections 1.0 before your endoscopy and 2.0 and 3.0 after your procedure.

Thank you for taking the time to complete this questionnaire.

Section 1.0: Please complete this section ***before*** your endoscopic test:

For the following questions please score your feelings from 0-10 where 0 is none and 10 is the worst imaginable.

How anxious are you about the procedure? (Please place an X on the line)

A horizontal number line with vertical tick marks at every integer from 0 to 10. The number 0 is written below the first tick mark on the left, and the number 10 is written below the last tick mark on the right.

How much abdominal discomfort are you expecting during the procedure?

[illegible]

How much abdominal pain are you expecting during the procedure?

[illegible]

How much abdominal discomfort are you currently in?

[illegible]

How much abdominal pain are you currently in?

[illegible]

Section 2.0: Please complete this section **after** your endoscopic test.

Overall how much abdominal pain did you experience during the procedure?

[illegible]

