Pathology in the gastrointestinal tract causing anaemia- lesion location and the role of capsule endoscopy.

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DECLARATION

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ABSTRACT

Iron deficiency anaemia (IDA) is a common clinical problem in the adult population. The prevalence of pan enteric pathology in IDA is unknown. Oesophagogastroduodenoscopy (OGD) is the gold standard examination, but it can be poorly tolerated and often requires the use of sedation. Meanwhile capsule endoscopy allows us to image the upper gastrointestinal tract (GI) and the small bowel in one sitting and it is well tolerated. The demand for capsule endoscopy is increasing, but evaluation capsule endoscopy videos is time consuming and requires the readers ongoing attention. Preliminary data has shown that the use of artificial intelligence (AI) in capsule endoscopy can significantly reduce reading times. With the growing demand for capsule endoscopy there is a need for biomarkers which can help risk stratify capsule endoscopy referrals. This thesis examines the role of capsule endoscopy in patients with IDA and also evaluated the role of faecal immunochemical test (FIT) for risk stratifying patients for small bowel capsule endoscopy.

As part of this thesis, a multicentre prospective study of 170 patients was carried out which investigated the prevalence of pan enteric pathology in patients with IDA. The diagnostic yield of lesions responsible for blood loss on OGD, capsule endoscopy and colonoscopy were 27.6%, 49.4% and 20% respectively ($p < 0.0001$).

We also compared the use of magnetically controlled capsule endoscopy (MACE) with OGD in the assessment of the upper gastrointestinal tract prospectively in 158 patients with IDA. This study showed that MACE identified significantly more lesions compared with OGD in the upper GI tract 119 vs 57 (95% CI 0.0- 0.08; $P < 0.001$). No adverse events were recorded and there was no capsule retention.

In the setting of IDA and the small bowel, a multicentre prospective study of 128 patients evaluated the role of AI- assisted reading in small bowel (SB) capsule endoscopy. In this study AI- assisted SB reading significantly reduced the reading time [mean standard read 18.13 min (SD 8.34) vs AI assisted SB reading time 2.27 (SD 2.05) ($p<0.0001$)]. The per patient diagnostic yield between standard read and AI assisted read was non-inferior [48.4%, 95%CI (40.0- 57.0) vs 53.9%, 95%CI (45.3- 62.3)].

The role of FIT in the detection of small bowel pathology is yet to be defined. In this single centre prospective study the role of FIT in predicting small bowel pathology in 79 patients with IDA was evaluated. We did not find that FIT conferred any additional benefit in the detection of small bowel pathology in patients with IDA, however the diagnostic yield of small bowel capsule endoscopy in patients with IDA is high at 40.2%.

In conclusions this thesis supports the use of MACE in the evaluation of the upper GI tract and small bowel in patients with first presentation and /or refractory IDA. It also supports the role of artificial intelligence in SB capsule endoscopy. There is a pressing need for biomarkers to help triage SB capsule endoscopy referrals, however FIT is not a reliable biomarker for the presence of SB pathology in patients with IDA.

PUBLICATIONS ARISING FROM THE BODY OF WORK PRESENTED IN THIS THESIS

The work presented in chapters one and six has been published and hence these chapters reproduce whole of the publication with minor additions. 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.

Chapter 1: Oka P, McAlindon M, Sidhu R. Capsule endoscopy - a non-invasive modality to investigate the GI tract: out with the old and in with the new. Expert Rev Gastroenterol Hepatol. 2022 Jul;16(7):591-599. doi: 10.1080/17474124.2022.2089113. Epub 2022 Jun 23. PMID: 35695266.

Chapter 3: Professor McAlindon conceptualised the study and sought ethics approval. In total 183 patients were recruited out of which 131 were recruited in Sheffield. I recruited all the patients in Sheffield. Prof. McAlindon performed 60 of 131 MACE procedures. I co-ordinated the multicentre trial, did the remaining procedures, collected and analysed the data and wrote the manuscript.

Chapter 4: Professor McAlindon conceptualised the study and sought ethics approval.
I co-ordinated the multicentre trial, collected and analysed the data and wrote the manuscript.

Chapter 5: Professor McAlindon conceptualised the study and sought ethics approval.

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Chapter 6: Oka P, Johnson CM, McAlindon M, Sidhu R. Does FIT have a role in the detection of small bowel pathology: a prospective study. Therapeutic Advances in Gastrointestinal Endoscopy. 2024;17. doi:10.1177/26317745241301553

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LIST OF ABREVIATIONS AND ACRONYMS

AI	Artificial intelligence
CCE	Colon capsule endoscopy
CD	Crohn's disease
CE	Capsule endoscopy
CNN	Convolutional neural network
CT	Computerised tomography
CTC	Computerised tomography colonography
DBE	Double balloon enterosocpy
FIT	Faecal immunochemical test
GI	Gastrointestinal
IDA	Iron deficiency anaemia

MACE Magnetic controlled capsule endoscopy

MDCT Multidetector row computerised tomography

MRE Magnetic resonance enterography

NSAID Non steroidal anti inflammatory drugs

OGD Oesophagogastroduodenoscopy

PEG Polyethylene glycol

SB Small bowel

SBCE Small bowel capsule endoscopy

UGICE Upper gastrointestinal tract capsule endoscopy

LIST OF APPENDICES

Chapter-1: INTRODUCTION

Iron deficiency anaemia (IDA) affects 2-5% of men and post-menopausal women(1). It is thought to occur as a consequence of gastrointestinal blood loss in the majority of cases. Studies suggest that gastroscopy and colonoscopy identifies a possible cause in a third of cases(2-5). Because pathologies in both upper and lower gastrointestinal(GI) tract can occur simultaneously in up to 26% of cases(2-6), current UK guidelines recommend both gastroscopy and colonoscopy for patients with IDA(1).

Wireless capsule endoscopy (CE) is a non-invasive form of endoscopy using a pill camera which is swallowed and produces images that can be viewed as a video. It is used routinely in clinical practice to examine the small bowel and colon and its role in upper GI tract investigations is emerging(7-10). It is much better tolerated than conventional endoscopy (11) which requires oral or anal intubation, often following the administration of intravenous sedation and analgesia and incurs a small risk of perforation. The main risk of CE is retention of the capsule behind a stricture, occurring in 1% of patients with IDA but this is always due to the pathology previously undiagnosed by conventional tests, some of which (tumours in particular) require surgical resection anyhow(12).

Pathology in the small bowel was historically considered to account for only 5% of all gastrointestinal causes of anaemia(13). Consequently, current guidelines recommend small bowel capsule endoscopy only when IDA has recurred after treatment(1). However, it is accepted that in as many as two thirds of the patients with IDA undergoing bidirectional

endoscopy have no significant abnormality identified(2, 5), raising the possibility that the cause is located in the small bowel. Meta-analyses now show significantly better diagnostic yields of CE compared to small bowel radiology in patients with IDA (42% and 6%, respectively)(14).

Although mostly performed in patients with recurrent or refractory (as opposed to first presentation of) anaemia, CE studies show a diagnostic yield of small bowel pathology in 40-66% and a tumour detection rate of as much as 10%(15, 16). Even in patients under 50 years of age, 5% of patients are found to have tumours(17). Given the uncertainties about which pathologies cause anaemia, the failure to identify a cause using conventional bidirectional endoscopy in over 60% and the availability of a highly sensitive, well tolerated small bowel investigative tool, our primary aim is to determine the incidence, nature and location of pathology in the gastrointestinal tract by performing small bowel capsule endoscopy in patients referred for gastroscopy and colonoscopy for the investigation of IDA.

Prior to passage through the pylorus and into the small bowel, capsule endoscopy can now be manoeuvred around the stomach using a joystick-controlled robot magnet (Ankon Technologies, Shanghai, China). A multicentre study using this device showed a 90% sensitivity in the detection of gastric focal lesions compared to gastroscopy, irrespective of size or location of the lesion(10). We have also demonstrated that the diagnostic ability of capsules manoeuvred around the stomach either using simple patient positional change (7) or external handheld magnets (18, 19) is comparable to that of gastroscopy. Patient tolerance significantly favoured CE in these studies with no adverse effects. The diagnostic yield using magnet controlled capsule endoscopy (MACE) of the upper gastrointestinal tract will be

compared with gastroscopy as a secondary outcome measure in this study of patients with IDA.

Software which eliminates sequential images which are almost identical has been shown to significantly reduce small bowel capsule endoscopy video reading time without reducing diagnostic yield of diffuse mucosal diseases (such as inflammatory bowel disease) and is routinely available in several different capsule endoscopy systems. This may not be the case for isolated lesions, of which several studies reported an unacceptable miss rate(20-22). Computer-aided diagnosis has progressed further with the development of artificial intelligence(23). If fed many examples of visual images of a specific lesion, machines develop their own recognition criteria (over and above those of shape, colour, texture, contour etc. conventionally used by the human brain). A deep convolutional neural network (CNN) has been developed for small bowel capsule endoscopy lesion recognition. Developed using images collected from 5000 patients, the CNN-based auxiliary model identifies abnormalities with 99.88% sensitivity in the per patient analysis and 99.90% sensitivity in the per-lesion analysis. Such software could significantly shorten the reading time(24). This software has been introduced into the Ankon NaviCam system and a recent prospective study shows promising results(25). The diagnostic yield of AI read versus SD a swell as the difference in reading time will be measured as one of the secondary outcomes.

FIT is an immunoassay used to detect human blood in stool(26). It has largely replaced the traditional faecal occult blood tests (FOBTs) due to higher sensitivity for colorectal cancer as well as advanced neoplasia(27-30). It is also thought to be more specific for distal gastrointestinal bleeding and the results are not affected by the use of NSAID and oral

anticoagulation(26, 28, 31). Over all the acceptability of FIT is higher compared to traditional FOBT(32, 33). Currently FIT is used for colorectal cancer (CRC) screening and also for risk stratifying patients with IDA in England(34, 35). The literature suggests that in up to 60% of the individuals with a positive FIT no significant colorectal lesion is identified. This raises the possibility of the lesions being located in the small bowel(36-38). Currently the role of FIT as a screening tool for small bowel pathology in patients with IDA remains unclear.

The GI tract can be examined by flexible fibre-optic endoscopy, radiological imaging and, capsule endoscopy since its introduction in 2000. Conventional endoscopy of the upper GI tract and the colon although considered the gold standard, can be uncomfortable, often requires sedation and comes with the inherent risks of perforation and bleeding. Cross sectional imaging is superseding barium contrast radiology, at least in the colon and magnetic resonance imaging has the advantage of not involving any radiation. Capsule endoscopy has rapidly been established as a first line investigation for small bowel examination particularly for the indication of obscure gastrointestinal bleeding. A prototype to image the colon has since been developed and more recently a capsule for the upper GI tract, thus providing clinicians with three investigative modalities for assessing GI symptoms and the different parts of the GI tract.

1.1 Upper GI tract investigations

1.1.1 Gastroscopy:

Gastroscopy is the gold standard investigation for examination of the upper GI tract, however gastroscopy is an uncomfortable procedure. It has been shown that patient satisfaction is significantly better with sedation, although it increases the risk of hypoxia 6% (95% CI 4%-7%) and hypotension 7% (95% CI 5%-10%) during the procedure(39). A recent cohort study showed that the unexpected hospital admission after an elective day case gastroscopy was 5.1% within 30 days of the procedure(40). Pneumonia was the most frequent cause for an emergency hospital admission after an endoscopy(40). The demand for gastroscopies is growing worldwide. In 2019 there were 866844 gastroscopies performed in National Health Services (NHS) in the UK with a 6% increase in demand since 2017(41). The vast majority of gastroscopies performed for dyspepsia are normal and gasto oesophageal malignancy is identified in less than 0.5% of the patients(42). It does allows direct mucosal visualisation, and also the ability for tissue sampling and therapy when required. Whilst there is a three-fold increase in the diagnosis of gastric cancer and dysplasia when the procedure time is at least seven minutes, many procedures that are performed do not follow this guidance. A study by Tai and colleagues show a 7.7% missed cancer rate with fibreoptic gastroscopy(43). A study by Paul Moayyedi shows that the number of gastroenterologists per 100,000 of the population was 3.9 in the United States, 3.48 in France, 2.1 in Australia, 1.83 in Canada, and 1.41 in the UK(44). To meet the growing demand and also to ease pressure on endoscopy units, non-invasive techniques warrants consideration as an alternative.

1.1.2 Radiology:

In patients who are unwilling or unable to undergo gastroscopy, radiology might be considered. However, the detection rate of early gastric cancer, using axial computerized tomography (CT) is low (53 % - 65%)(45, 46). Barium contrast is used as an alternative examination for patients presenting with dysphagia. Double contrast barium has been shown to have sensitivity of >95% in detecting oesophageal cancer(47, 48). A meta-analysis which compared barium contrast with gastroscopy for detection of gastric cancer in a screening population showed that gastroscopy is significantly better than barium contrast for gastric cancer detection(49). The multidetector row CT (MDCT) gastrography is an imagining technique which can generates 3D images of the stomach and this has enhanced the detection rate of early gastric cancers on imaging(50, 51). MDCT is mainly used for staging prior to endoscopic resection of gastric cancers. Whilst imaging does have a role, it also has some limitations; there is exposure to radiation and more so with MDCT. Patients with suspicious findings on imaging need a gastroscopy for direct visualization and biopsies if required. MDCT is also a more time consuming procedure and requires a longer reading time by the radiologist.

1.1.3 Capsule endoscopy of the upper gastrointestinal (GI) tract:

Capsule endoscopy is better tolerated than fibreoptic endoscopy(52, 53). Capsule endoscopy of the oesophagus was first approved by the Food and Drug Administration in U.S in 2004(54).

A meta analysis of the first and second generation oesophageal capsule showed a moderate sensitivity of 77% for the diagnosis of Barrett's oesophagus(55). There were concerns about inadequate visualization of the gastro-oesophageal junction (GOJ). Due to rapid transit of the capsule through the oesophagus it was recognised that increasing image capture rate was necessary. The most recent technological advance in this field is the Upper GI capsule (Medtronic Ltd, Dublin, Ireland; originally Given imagining) which was approved in 2014 (Table-1, Image-1). This dual headed capsule can capture as many as 35fps for 10 min followed by 18fps for a further 80 min with a field of view of 174 degrees for each head. A study by Ching et al. using the upper GI capsule visualised the GOJ in its entirety in 92.5% of patients, it was also possible to examine a water filled stomach using a sequence of position changes(53). In 40% the recording ceased before the capsule entered the duodenum and reading the videos was time consuming(53). To enable the routine use of capsule endoscopy in the upper GI tract the capsule needs to overcome a few challenges; the transit time in the oesophagus and the duodenum is very rapid and the stomach is capacious and non uniform. Steerable capsules with tails, fins and rotating blades have been developed to overcome the structural challenges of the stomach, but more progress has been made with external magnetic control in capsule endoscopy(56, 57). The use of magnets in capsule endoscopy was initially described by Carpi in 2006(58). The MiroCam-Navi was a hand-held magnet developed by Intromedic Ltd (Seoul, South Korea). Although it had advantages like portability and excellent patient tolerance, it was difficult to maneuver a 1kg magnetic device over a supine patient due to operator fatigue, also the views obtained of the fundus were suboptimal(59-61). In France an electromagnetic coil system was developed in a joint project by the Olympus Medial Systems Corporation (Tokyo, Japan) and Siemens Healthcare (Erlangen, Germany). A blinded study which compared this system to conventional gastroscopy showed that it had a sensitivity of 62%

when compared with conventional gastroscopy in identifying major lesions (62) but its size and cost was a limitation. . Ankon technologies Co LTD developed a system in Shanghai, China where the capsule movement was controlled with the help of magnetic attraction generated by the robotic arm (Image-1A). The capsule contained a magnet in its dome which allowed the capsule to be steered around the stomach with the help of two joysticks (Image-1C).A multicentre study of 350 patients showed that magnetically controlled capsule endoscopy (MACE) had a sensitivity of >90% when compared with gastroscopy at detecting focal gastric lesions(10).

The main aim of upper GI tract examination is to detect treatable neoplasia. A major concern is whether or not this new technology is capable of identifying early, treatable neoplasia. MACE identified neoplasia in all patients of a cohort awaiting ESD and accurately localised the lesion and size when compared to gastroscopy(63). It missed one of the two lesions in one patient. Capsule endoscopy is widely used for population screening for early gastric cancer in China. A review of over 3000 patients who were investigated for screening purposes found 0.22% with cancer and 17.8% with focal lesions (polyps, ulcers or submucosal tumours). All cancers identified were adenocarcinomas and occurred in individuals of over 50 years of age. Moreover, it demonstrated that the procedure was safe, with no long-term capsule retentions occurring(64). However, its uptake in the rest of the world has been slow.

Figure 1: Ankon system with A. robotic arm. B. Screen with controls. C. Close up of the joystick controls.

Histological samples including those for H. Pylori testing cannot be obtained using capsule endoscopy. However, information often provided by histology can be obtained using alternative, non-invasive methods, such as urea breath test or stool antigen test for H. Pylori or serum pepsinogen levels as a marker of gastric atrophy. Furthermore, whilst most endoscopists have a low threshold for obtaining biopsies, our previous study suggested that histology only impacted on patient management in 16%(65). Currently the capsule is also for single use only which increases the costs. A cost comparison of the two modalities is also needed.

Parameters	**Upper GI capsule (Medtronic)**	**NaviCam 2nd Generation (Ankon)**	**OMOMRC (Jinshan)**
Size (mm)	12x32	27x 12	30x 11.5
Frames per second(fps)	18-35	2-6	2- 10
Battery life (hrs)	1.5	12	12
Camera	Dual	Single	Single
Field of view (degree)	340	150	172
Image resolution (pixel)		720x 720	512 x 512
Magnetic control and automated	No	Yes	Yes
Small bowel examination	No	Yes	Yes

Table 1: Current upper gastrointestinal capsules

1.2 Small bowel investigations

1.2.1 Small bowel radiology

Prior to the advent of capsule endoscopy, radiology was the main stay of investigation for the small bowel. Traditionally, this included cross sectional imaging and small bowel follow through(66). Ultrasound has also been used for small bowel examination and has the advantages of being free of ionising radiation and easily available, however accuracy of findings is operator dependent(67). Magnetic resonance enterography (MRE) has become a useful modality for assessing disease activity in small bowel Crohns disease. In a large metanalysis the sensitivity and specificity was 0.88 (95% CI 0.86 to 0.91) and 0.88 (95% CI 0.84 to 0.91) respectively when compared with surgery, ileocolonoscopy and/or histolopathology, confirming a high sensitivity and specificity of MRE at identifying small bowel Crohns disease(68) .

1.2.2 Small bowel capsule endoscopy (SBCE):

Capsule endoscopy was first introduced in the field of medicine in 2000. The tubular shape and a small diameter of the small bowel makes it an ideal organ to be examined with the capsule. It provides a non -invasive method for complete visualisation of the small bowel

mucosa.There are a few different manufacturers for SBCE (PillCam, Medtronic, Dublin, Ireland; Endocapsule, Olympus Optical Co, Tokyo, Japan; Miro-Cam, IntroMedic, Seoul, Korea; OMOM capsule, Jinshan Science and Technology Group, Chongqing, China, Navicam , Ankon, Shanghai, China). These models have three parts; capsule, a sensor belt with receiver and a work station to download and read the images. The images are transmitted to a data recorder from which a video is created following download on to a computer. The capsocam (CapsoVision, Cupertino, California, USA) provides panoramic views of the small bowel. This capsule does not have a data recorder and the capsule needs to be collected after expulsion from the stool for retrieval of data(69). The capsocam retains imaging data in-situ and this is subsequently transferred onto a computer using bluetooth following capsule retrieval. All the capsules are for single use only. Head to head comparison in majority of the studies have shown similar diagnostic yields, image quality and completion rates for all the commercially available small bowel capsules(70-73). Majority of the studies have been done using the PillCam capsule (Image-5). Studies have shown the overall diagnostic yield of SBCE in patients with iron deficiency anaemia to be between 41%- 65%(15, 69, 74, 75). A systematic review by Liao et al has also shown that the diagnostic yield for SBCE is up to 50% for all indication(76).

Whilst bowel preparation is imperative prior to colonic investigations, the benefit of laxative-based preparation protocols prior to small bowel capsule endoscopy is less clear. A systematic review and meta-analysis on the use of bowel prep for small bowel capsule endoscopy showed that bowel preparation did not increase the diagnostic yield of small bowel findings, however the small bowel visualisation quality was improved(77). Bowel preparation is recommended for identification of subtle lesions. Small bowel cleanliness is one of the key factors for a good quality study with a high diagnostic yield. Currently 2 litres of polyethylene

glycol (PEG) based laxative the day before the procedure is the most commonly used regime in clinical practice(78). European Society of Gastrointestinal Endoscopy (ESGE) recommends an early SBCE (within 48 hours) in obscure GI bleeding as the yield is significantly higher compared to a delayed examination(79-81). This is the most common indication for SBCE worldwide(82). In patients with iron deficiency anaemia who have negative bidirectional endoscopy ESGE also recommends a SBCE(69).

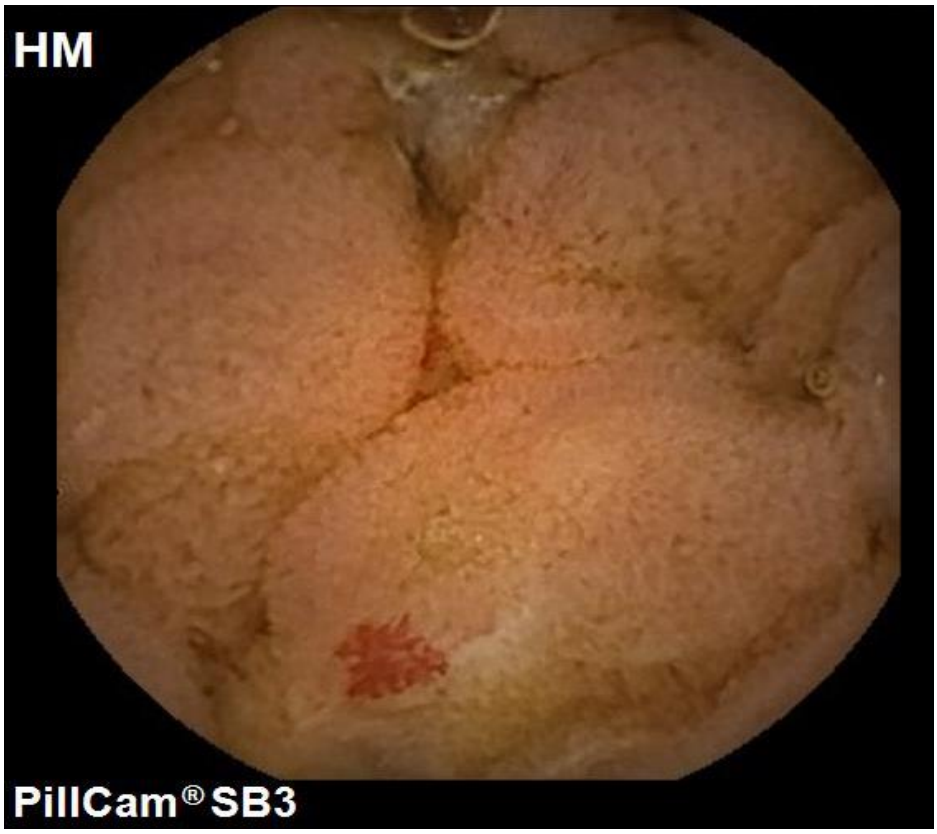

Figure -2: Small bowel capsule image of angioectasia

CE is a safe procedure. It is imperative to screen for risk factors such as obstructive symptoms, Crohn's disease and long term use of non steroidal anti-inflammatory drugs (NSAID). The only procedure related complication which is associated with SBCE is capsule retention, which can occur in 1-2% of the cases for all indications(76, 83). The risk of capsule retention however is

notably higher in patients with Crohn's disease. A recent meta analysis by Pasha et al showed that the capsule retention rates were 4.63% in established disease (95% CI, 3.42%-6.25%) and 2.35% (95% CI, 1.31%-4.19%) in suspected small bowel Crohns disease respectively(84). A patency capsule (PC) (Given Imaging, Yoqneam Israel) which is similar in size to a standard CE, is useful in patients with suspected small bowel stenosis to minimise the risk of capsule retention. It is a radiopaque and dissolves in a timely fashion. The two timer plugs at either end dissolve at approximately 30 hours due to contact with luminal fluid(85). A study by Rozenderen et al showed that MRE has a low positive predictive value (40%) and low specificity (59%) for predicting small bowel patency. Hence patients with a positive MRE or those with a high suspicion for small bowel strictures should undergo a patency capsule prior to capsule endoscopy(86)

Apart from the risk of retention, capsule endoscopy does have some limitations. Due to a rapid transit through the duodenum focal lesions in the proximal small bowel can be missed(87). It is also unable to take histological samples or provide therapy when disease is identified. Table 2 summaries the current small bowel capsule endoscopy prototypes .

Parameters	**PillCam SB3 (Medtronic)**	**OMOMHD (Jinshan)**	**MiroCam MC2000 (Intromedic)**	**Capsocam (CapsoVision)**	**Endocapsule-10 (Olympus)**	**NaviCam 2nd Generation (Ankon)**
Size (mm)	26 x 11	25 x 11	30 x 11	31 x 11	26 x 11	27x 12
Frames per second(fps)	2-6	2-10	6	20	2	2-6
Battery life (hrs)	8	12	12	15	12	12
Camera	Single	Single	Dual	4	Single	Single
Field of view (degree)	156	172	340	360	160	150
Image resolution (pixel)	340 x 340	512 x 512	320 x 320	221 x 184		720x 720

TABLE 2: Current small bowel capsules

1.2.3 Device assisted enteroscopy (DAE)

There are two techniques which are being utilised for deep enteroscopy. namely double balloon enteroscopy (DBE) and single balloon enterosocpy (SBE). DBE is the most commonly

used DAE procedure which lends a therapeutic arm to capsule endoscopy(69). It was first described in 2001 and has made it possible to perform diagnostic and therapeutic procedures during the same examination. It is also useful for obtaining histological samples and placing tattoos prior to surgical intervention. In recent years DBE has largely replaced push enteroscopy as well as intra operative enteroscopy as DBE achieves greater depth of insertion in the small bowel and is less invasive compared to an intra-operative enteroscopy. However, a SBCE has a higher rates of completion enteroscopy with a much lower complication rate and is less invasive. Hence DBE is often used as a confirmatory tool when other less invasive techniques like SBCE or imagining identify a lesion which needs therapy or histological sampling. The Single balloon enteroscopy (SBE) system (Olympus Optical Co, Tokyo, Japan) uses only one latex-free balloon, which is attached to the distal end of the overtube. A recent meta-analysis has shown no difference in the diagnostic yield or therapeutic yield of DBE or SBE(88).

1.3 Colonic Investigations

1.3.1 Colonoscopy:

Currently colonoscopy is the gold standard investigation for the large bowel. It can be challenging and associated with infrequent but serious complications. A population based study in the US which looked at 165527 colonoscopies, documented a perforation in (n=101), and splenic injury in (n=12)(89). A study which looked at post colonoscopy infection rates from six states in the U.S showed the 30-day infection-related unplanned visits per 1000

procedures were 4.0 for screening colonoscopy, 5.4 for non-screening colonoscopy compared with 2.9 for screening mammography(90). There is also the added risk of sedation which is used to improve patient tolerance(39). The demand for colonoscopies is increasing worldwide. There were 704125 colonoscopies performed in UK in 2019, with a 13% increase in standard colonoscopies and 30% increase in screening for bowel compared to 2017(41). However, colonoscopy can miss significant lesions. A systematic review and meta-analysis of tandem colonoscopies ((in which patients undergo a second colonoscopy by endoscopists who are blinded to each other's findings) has shown a miss rates of 26% for all adenomas, 9% for advanced adenomas and 27% for serrated polyps(91). A stool test is used for screening for colorectal cancer in some countries in Europe. The uptake of this test for screening for colorectal cancer is still very low (66%)(92). A qualitative study has shown that one of the reasons for the poor uptake is because of unwillingness of the participants to undergo a colonoscopy in case of a positive result(93). The diagnostic yield of colonoscopy in the symptomatic population is low, with 46%–75% of patients having a normal examination(94, 95). However, colonoscopy has an advantage that it allows active intervention such as suction, position change and inflation which improves the views and colonoscopy completion rates. In the future with improved non-invasive technology colonoscopy may be reserved for only those patients who need a biopsy or a polypectomy.

1.3.2 Computerised Tomographic colongraphy (CTC)

CTC is considered to be the gold standard radiological examination for the colon. A recent meta-analysis which compared CTC and colon capsule (CC) in a group of patients with

incomplete colonoscopies, showed the completion rate of CTC was higher compared to CC (86%- 100% vs 65%-93%) respectively. However, the diagnostic yield of polyps was lower for CTC compared to CC (4%-22% vs 8%- 41% for polyps >5mm) and (0-11% vs 3%-22% for polyps >9mm) respectively(96). A potential advantage of CTC is its ability to evaluate for any extra colonic pathology during colonic examination. This can provide reassurance to adults and also early detection of potentially significant pathology. A systematic review and meta analysis which evaluated the extracolonic findings at CTC showed a 4% rate for identifying potentially important extracolonic findings. The rate of identifying unsuspected extracolonic malignancy ranging from 0.3% to 2.5%(97). Currently CTC is offered as an alternative test for suspected CRC and also for completion for incomplete/ inadequate colonoscopy. It has been proposed as an alternative imaging modalities for examination of the colonic mucosa by the European Society of Gastrointestinal Endoscopy(98).

1.3.3 Colon capsule endoscopy:

Colon capsule endoscopy is a non-invasive technique used to examine the colon without the need for air insufflation or sedation (Image-5). Colon capsule (PillCam given imagining, Yokneam, Israel) was first introduced in 2006. A second generation colon capsule is currently in use with a variable image capture rate of 4-35fps based on the speed of peristalsis and almost a 360 degree field of view (Image-6). A colon capsule captures images from oesophagus and stomach for 3 minutes before entering the sleep mode for 1hour and 45 minutes to conserve battery life. Systematic reviews which looked at the use of the second generation capsules in screening for colorectal cancer showed that for polyps >6mm, sensitivity was 79 % - 96 % and specificity was 66 % - 97 %(99, 100). For polyps ≥ 10 mm,

sensitivity of the second-generation colon capsule was 84 % - 97 %, which was superior to computed tomographic colonography (CTC)(99, 100). The colorectal cancer detection rate for completed capsules was 93% (25/27)(99). It is an innovative technique as it can be carried out in the community minimising hospital attendance. The procedure involves administrating the oral capsule and fitting a receiver belt after which the patient is sent home. This can be done in a outpatient clinic setting. After completion of the test the patient returns the receiver from which the images can be downloaded and read(101).

A study which looked at patient acceptability of colon capsule endoscopy versus colonoscopy showed that 77.5% (n = 31/40) of patients would prefer colon capsule endoscopy for further lower GI investigation in the future. Of these, 77.4% (n = 24/31) still preferred CCE despite the potential need for a follow-up colonoscopy(102). The European Society of Gastrointestinal endoscopy guidelines recommended a colon capsule endoscopy in cases of incomplete traditional colonoscopy and also in patients who refuse a colonoscopy(103, 104). The use of colon capsule endoscopy in high risk individuals is being established. In the UK a national pilot is underway to evaluate its use in those with a positive FIT test (10-100 microgms hb/gm). Patients referred on the suspected cancer pathway are being offered a colon capsule as a first line diagnostic test(105). Data from the ScotCAP study shows that Colon capsule endoscopy reduced colonoscopy by 37% in the symptomatic patients. Polyps identified needing therapy was the main reason for requiring a repeat colonoscopy in this cohort (92%) and the completion rate was 72%(106). A study which looked at the role of prucalopride in improving completion rates has shown that completion rates were higher in the prucalopride group with 74.9% complete investigations compared to 56.7%in the control group. Bowel preparation quality was also better in the prucalopride group (75.9%) compared

to the control (57.1%)(107). There are some challenges that a colon capsule needs to overcome; with traditional colonoscopy mucosal visualisation can be improved if the bowel prep is not perfect with the help of air insufflation and suction where as good bowel prep is essential for a successful colon capsule.

A multicentre prospective study comparing Crohn's capsule, magnetic resonance enterography (MRE) and colonoscopy in detecting active Crohn's disease in the small bowel and the colon showed that the overall sensitivity of Crohn's capsule was 94% compared to 100% of MRE and /or colonoscopy (p=0.125) and specificity was 74% vs 22% (p=0.001). (108).

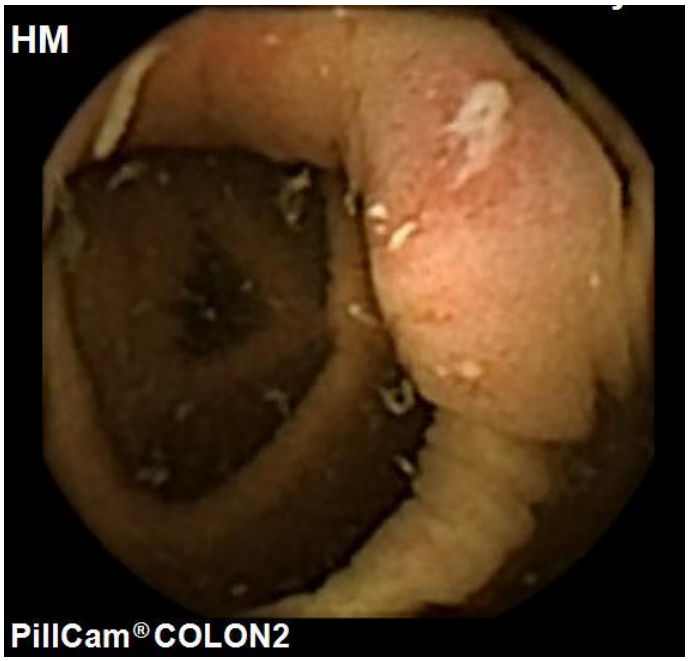

Figure-3: Colon capsule image of ileocecal valve with ulceration

Most patients with inflammatory bowel disease require several endoscopic and radiological procedures in their life time to assess for disease activity and response to therapy along with surveillance for bowel cancer. A Crohn's capsule allows for a non-invasive pan-enteric examination of the entire gastrointestinal tract. Up to 30% of patients with Crohn's disease can have isolated small bowel involvement(109). In a population-based cohort study, the cumulative probability of stricturing in Crohn's disease after long term follow-up was 12.4% at 5 years, 15.2% at 10 years and 21.6% at 20 years, respectively(110).The role of colon capsule has been studied in patients with inflammatory bowel disease to evaluate its role in assessing for mucosal healing and/or response to therapy(111-113). The PillCam Crohn's system (Medtronic, Yoqneam, Israel) was approved by the US FDA in 2017. It is similar to the colon capsule as it is a double headed capsule with a field of view of 336 degrees. It also has an adaptive image capture rate of 4-35 fps based on the speed of transit. This capsule starts taking images as soon as it is ingested and has an extended battery life of up to 12 hrs, hence obtaining pan enteric images. A multicentre feasibility study which included 41 patients (n= 29 established CD; n= 5 established UC; n= 7 suspected CD) showed a high functionality and no adverse events for the Crohns capsule (CC)(114). The bowel preparation regime for colon capsule and Pillcam Crohn's capsule is more rigorous compared to a routine colonoscopy as bowel cleanliness has to be excellent or at least good for adequate sensitivity of the examination. The European Society of Gastrointestinal Endoscopy guidelines recommend a liquid diet the day before the procedure and a split preparation of 4 lts polyethylene glycol electrolyte solution the day before and on the day of the examination. An oral promotility agent is administered if gastric emptying is longer than 1 h, and two further boosters of low-dose sodium phosphate may be given to propel the capsule through the small bowel into the colon(103).

Parameters	Colon 2 (Medtronics)	NaviCam(Ankon)
Size (mm)	32 x 12	31x 11
Frames per second(fps)	4- 35	0.5- 16
Battery life (hrs)	10	>10
Camera	2	2
Field of view (degree)	340	340
Image resolution (pixel)	512 x 512	480 x 480

Table 3: Current colon capsule

Chapter- 2: HYPOTHESIS AND AIMS

NULL HYPOTHESIS: Capsule endoscopy does not improve the detection of gastrointestinal pathology in patients with iron deficiency anaemia.

The body of work aims to address whether capsule endoscopy has a diagnostic role in patients with IDA. Chapter 3, looks at the prevalence of pan enteric pathology in patients with IDA. The diagnostic yield of OGD for the upper GI tract, capsule endoscopy for small bowel and colonoscopy for colonic pathology is assessed for all comers of IDA. In Chapter 4, the diagnostic yield of pathology which can cause IDA is assessed using Magnet controlled capsule endoscopy (MACE) and conventional OGD in the upper GI tract. This provides a platform to demonstrate the clinical relevance of capsule endoscopy in upper GI territory in patients with IDA. In Chapter 5, the role of artificial intelligence in small bowel capsule endoscopy is assessed for patients who have iron deficiency anaemia. Can AI add clinical benefit over standard reading in small bowel capsule endoscopy? and finally in Chapter 6, the role of the biochemical marker FIT is assessed in patients with IDA undergoing a small bowel capsule endoscopy. Can FIT be used to risk stratify capsule endoscopy referrals?

CHAPTER 3: BLEEDING LESIONS IN THE GASTROINTESTINAL TRACT: BLITGIT STUDY

3.1 Abstract

Introduction: Current guidelines suggest oesophagogastro duodenoscopy (OGD) and colonoscopy to investigate iron deficiency anaemia (IDA) because of a perceived low risk of small bowel pathology. This is the first study to investigate the entire gastrointestinal tract to localise lesions suspected of causing blood loss in patients with IDA.

Methods: Patients referred to three centres (Sheffield, Hong Kong and Szekesfehervar, Hungary) for the investigation of IDA underwent a small bowel (SB) capsule endoscopy (CE) (Navicam, AnX Robotica, Plano, USA) a week prior to OGD and colonoscopy. All lesions were described using terms selected from a predetermined diagnostic list and according to the perceived likelihood of bleeding (P0: unlikely; P1: suspected; P2: highly likely based on the adapted Saurin classification). All lesions were reviewed by an expert panel of three specialists and a consensus of the lesions was obtained.

Results: Assuming a true prevalence of small bowel lesions of 10% in patients with IDA, a sample size required to have 80% power of getting a 95% confidence interval for the prevalence no wider than 10 percentage points is 160 patients. During the study period 183 patients attended for CE. Total of 170 patients were included in the final analysis [median age 61 year (IQR 46- 71); 44% female] had a median haemoglobin of 102 g/L (IQR 90- 117), ferritin 11ug/L (IQR 7-18) and iron 6 umol/L (4-10). The completion rates for OGD, CE and colonoscopy were 99.4% (n=169), 88.2% (n=150) and 95.2% (n=162) respectively. The diagnostic yield of P1 and P2 lesions for OGD, CE and colonoscopy were 27.6%, 49.4% and 20% respectively ($p < 0.0001$). In 4.7% (n=8) patients there was synchronous pathology seen on OGD and colonoscopy. In 13.5%(n=23) patients there was synchronous pathology on OGD and CE and in 10% (n=16) patients there was synchronous pathology on colonoscopy and CE.

There was a high level of agreement between experts during the consensus read (Gwet AC inter-rater coefficient of 0.98).

Conclusion: Pathology suspected of, or likely to be, causing blood loss in patients with IDA appears to be commoner in the small bowel (SB) than the proximal gastrointestinal (GI) tract or colon. Small bowel examination should be performed routinely to maximise diagnostic yield.

3.2 Introduction

IDA is a cause of significant morbidity worldwide. Bleeding lesions in the GI tract are the most common cause of IDA in men and postmenopausal women in the developed world. Significant synchronous lesions can be identified on endoscopy in patients with IDA and hence single visit upper and lower endoscopic investigations are recommended(1, 115-117). Previous literature has consistently shown that potentially significant pathology is identified only in a third of the patients undergoing bidirectional endoscopy(115, 118-120). The identified lesions are also not standardized regarding their bleeding potential which adds to the uncertainty about the lesions contributing to IDA.

CE is the accepted reference modality for SB investigations and is extremely well tolerated(12). Although CE is mostly performed for recurrent or refractory (as opposed to first presentation of) IDA a meta-analysis has shown that the diagnostic yield of CE is as high as 66.6% (95% CI, 61.0%-72.3%; I^2 = 44.3%) with a tumour detection rate of 6.6% in patients with IDA(15).

To date, whilst it is accepted that disease processes in the upper and lower GI tract might be responsible for IDA, no study of a panenteric endoscopic assessment, including endoscopic

assessment of the SB, has identified the prevalence, location and nature of significant lesions. It is also unknown what the rate of synchronous pathology is in the SB in those patients who have been deemed to have a cause found on OGD or colonoscopy.

3.3 Materials and Methods

Study design and participants

Patients were recruited from Sheffield Teaching Hospitals NHS Foundation Trust (Sheffield, UK), Endo-Kapszula Health Centre (Székesfehérvár, Hungary) and the Chinese University of Hong Kong (Hong Kong). Inclusion criteria for participation were non-pregnant adults (aged ≥ 18 years and ≤ 80 years) with IDA confirmed on blood tests and defined by the World Health Organisation (WHO) as a haemoglobin (Hb) concentration below 130 g/L in men over 15 years of age, below 120 g/L in non-pregnant women over 15 years of age and a ferritin level of less than 30 gms/L(121). Exclusion criteria included dysphagia, gastroparesis, suspected or previous gastric outlet or small bowel obstruction, Crohn's disease, long term daily use of non-steroidal anti-inflammatory drugs (with the exception of low dose aspirin), previous oesophagogastric or small bowel surgery or abdominopelvic radiotherapy and the presence of any implantable electronic or magnetic device. Patients provided written informed consent before study procedures. The study protocol and all research procedures performed in this study were done in accordance with the ethical guidelines outlined in the Declaration of Helsinki. The study was approved by the regional ethics committee (Ref. No. 18/NW/0588) and has been registered on INRCTN registry (ISRCTN85978758). A detailed study protocol is attached in appendix (2).

Capsule endoscopy protocol

CE was performed using NaviCam SB system (Ankon, China and AnX Robotica, USA). CE was performed within a week before OGD and colonoscopy. Participants were advised to stay on clear fluids for 24 hours before the CE and to drink 2 litres of polyethylene glycol (PEG) solution the day before the procedure as a split dose. If the participants were unable to tolerate some or all of the PEG, CE was performed if the participants had followed fasting instructions. Four hours after capsule ingestion a light meal was allowed. Participants were advised to wear the data recorder for 10 hours after swallowing the capsule. CE examination was completed if the capsule reached the colon within the recording time. Capsule retention was defined as capsule remaining in the digestive tract after two weeks. CE videos were read using ES View (version 2.0) software. The generated CE videos were read in standard mode according to the recommendations of the European Society of Gastrointestinal Endoscopy (ESGE)(69). After completion of reading the entire video, findings were labelled according to their bleeding potential (P0, P1, or P2) and in accordanceccording to the adapted Saurin classification (Appendix-6) (122). Location of findings was reported according to a simplified location protocol which divides the SB in three tertiles according to the small bowel transit time.

OGD and colonoscopy was performed according to standard clinical practice by an endoscopist blinded to the MACE results who recorded all potential pathology and reported using the same predefined diagnostic list as was used for MACE and the adapted Saurin classification. Anonymised images of all pathology identified at OGD and MACE were

reviewed by a panel of three gastroenterologists who were expert in both procedures (MEM, AF and FLMW) and a consensus regarding lesion definition and bleeding potential was agreed and used as the gold standard. Only the lesions with P1 or P2 bleeding potential were included in the final analysis.

Outcome:

The primary endpoint of this study was to assess the prevalence and nature of lesions in the upper GI tract, small bowel and colon that cause IDA. We also looked at synchronous lesions between the upper GI tract, small bowel and colon.

Sample size calculation:

We assumed that the true prevalence of small bowel lesions in patients with IDA was 10%, a sample size required to have 80% power of getting a 95% confidence interval for the prevalence no wider than 10 percentage points is 160 patients. We estimated a dropout rate of 15% and therefore aimed to recruit 180 patients.

Statistical analysis

We used descriptive statistics to present continuous variables as medians with interquartile ranges (IQR) and categorical variables as numbers and percentages. Categorical variables were compared using Fisher's exact test with Bonferroni correction to account for multiple testing. We used Cohen's kappa coefficient (k) to assess inter-rater agreement during the consensus read. A two-sided p-value of 0.05 was considered statistically significant. All statistical analyses were performed using Stata version 18 (StataCorp, College Station, TX,

Ethical approval

The study protocol and all research procedures performed in this study were done in accordance with the ethical guidelines outlined in the Declaration of Helsinki. The study was approved by the regional ethics committee (Ref. No. 18/NW/0588) and has been registered on INRCTN registry (ISRCTN85978758). A detailed study protocol is attached in appendix (2).

3.4 Results

Patient characteristics

For the study 680 patient referrals were screened to identify eligible patients. Out of these 250 patients were contacted to participate. During the study period 183 patients attended for CE. Total of 170 patients were included in the final analysis [median age 61 year (IQR 46-71); 44% female] had a median haemoglobin of 102 g/L (IQR 90- 117), ferritin 11ug/L (IQR 7-18) and iron 6 umol/L (4-10). The baseline demographic and clinical characteristics of the study participants are provided in Table 1. The main inclusions criteria was IDA but there were 84(49%) patients who also had symptoms associated with IDA (bleeding, n=27; abdominal discomfort, n= 35; diarrhoea, n= 19; constipation, n=9; altered bowel habit, n= 15; weight loss, n= 17). 31 patients had more than one symptom. 92 patients had a faecal immunochemical test (FIT) done and 55 patients had a level of >4 ug Hb/g [median 25(14-105)]. In 93% of the patients the CE was performed within one week of their endoscopic evaluation.

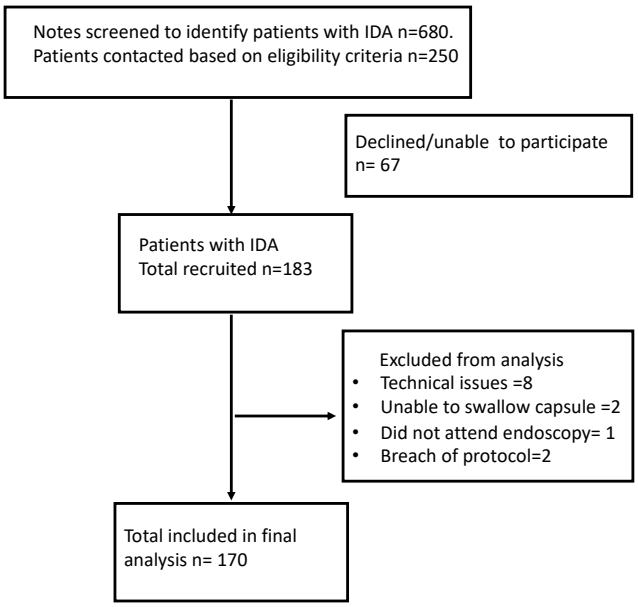

Figure 4: Patient selection for study

Sex, n (%)	
Female	81 (47.6)
Male	89 (52.4)
Age, median (IQR)	60 (46 – 71)
Blood results, median (IQR)	
Haemoglobin g/L	102 (90- 117)
Ferritin ug/L	11 (7-18)

Iron umol/L	6 (4-10)
Symptoms, n (%)	
Abdominal discomfort	35 (20.6)
Diarrhoea	19 (11.2)
Altered bowels	15 (8.8)
Constipation	9 (5.3)
Weight loss	17 (10)
Rectal bleeding	27(15.8)
Medication, n (%)	
Anticoagulation	8.8 (41.6)
Antiplatelet	4.1 (46.9)
NSAID use	8.8 (3.7)

Table 4 – Baseline demographics and clinical data of the study participants

Pan-enteric pathology and diagnostic yield:

There were 226 P1 or P2 lesions identified on OGD, small bowel capsule endoscopy and colonoscopy, of which 5.8% (13/226), 8% (18/226) and 7.1% (16/226) respectively were P2 lesions. The per patient diagnostic yield of P1 and P2 lesions for OGD, small bowel capsule endoscopy and colonoscopy was 27.6% (47/170), 49.4% (85/170) and 20% (34/170) respectively ($p < 0.0001$) and for P2 lesions alone, 6.5% (11/170), 10% (17/170) and 9.4% (16/170) respectively ($P = 0.48$). The distribution of P1 and P2 lesions in the gastrointestinal tract was as follows: 5.5% (12/219) in the oesophagus, 18.3% (40/219) in the stomach, 63.0% (138/219) in the small bowel and 13.2% (29/214) in the colon (Figure 6). Seven small bowel

lesions were detected by OGD (in the duodenum) or colonoscopy (in the terminal ileum) as well as capsule endoscopy. Oesophageal lesions were varices 0.9% (n=2), ulcers 1.8% (n=4) and erosions 2.7% (n=6); gastric lesions were erosions 10.5% (n=23), ulcers 2.3% (5), gastric antral vascular ectasia 1.4% (n=3), eroded polyp 2.3%(n=5), gastric tumour 0.9% (2), angioectasia 0.5% (n=1) and portal hypertensive gastropathy 0.5% (n=1); small bowel lesions were angioectasia 30.6% (n=67) ,ulcers 10.5% (n=23), erosions 16.4% (n=36), ulcerated stenosis 1.8% (n=4), eroded polyp 1.4% (n=3), fresh blood 1.8% (n=4), vascular lesion 0.9% (n=1) and colonic lesions were colon cancer 4.1% (n=9), haemorrhoids 4.1% (n=9), eroded polyps 1.4% (n=3), angioectasia 1.8% (n=4) and ulcers 1.8% (n=4). On OGD 78% (47/60) were P1 lesions and 21.7% (13/60) were P2 lesions. On capsule endoscopy 86.2% (112/130) of small bowel pathology was P1 and 11.5% (18/130) was P2. Of these 40%, 27% and 31% being located in first, second and third tertile respectively. At colonoscopy 55.5% (20/36) were P1 and 44.4% (16/36) P2 lesions (Figure 5).

Colorectal cancer was identified in nine (5.3%) patients. Eight of these patients had a faecal immunochemical test (FIT) performed and all had a FIT level of >10ug Hb/g. There were two patients with gastric neoplasia: one was a primary gastric adenocarcinoma and the other a gastric metastasis from a B cell lymphoma diagnosed by biopsy of a breast lesion. No small bowel tumours were identified. Four patients also had a new diagnosis of coeliac disease: all had evidence of villous atrophy alone which was graded as a P0 lesion.

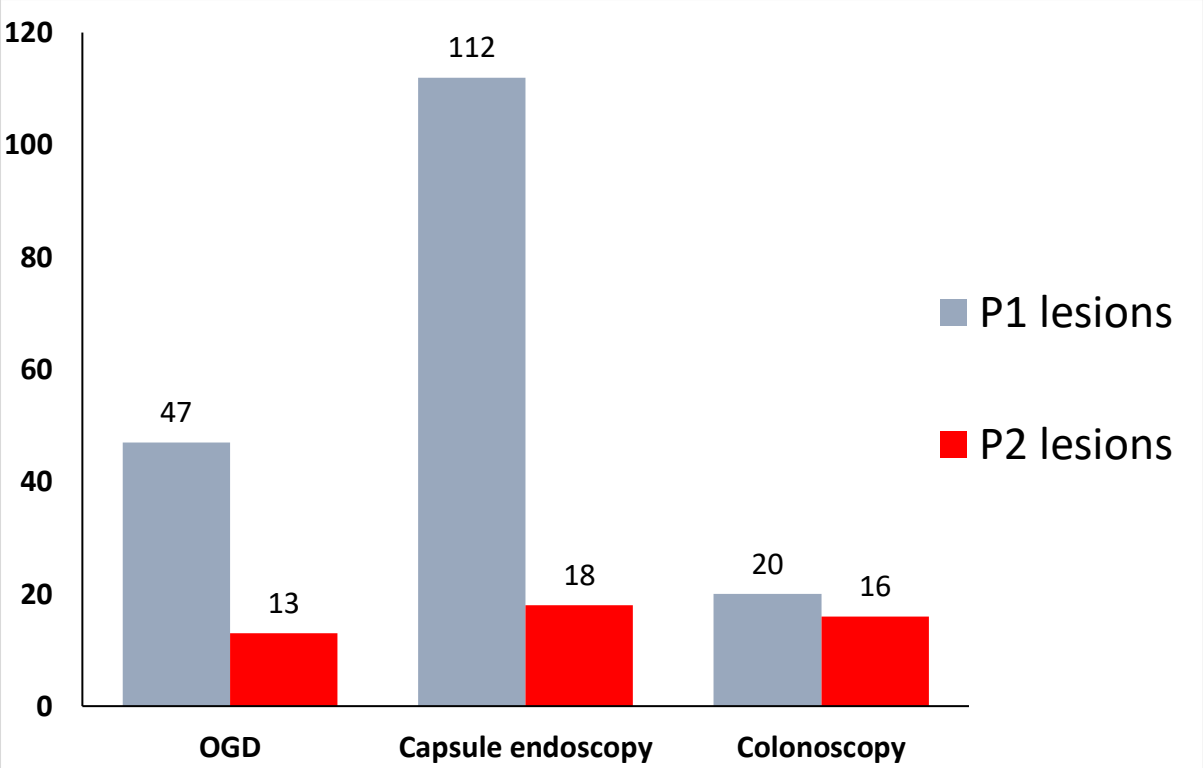

Figure 5: P1 and P2 pathology identified on colonoscopy, gastroscopy and capsule endoscopy

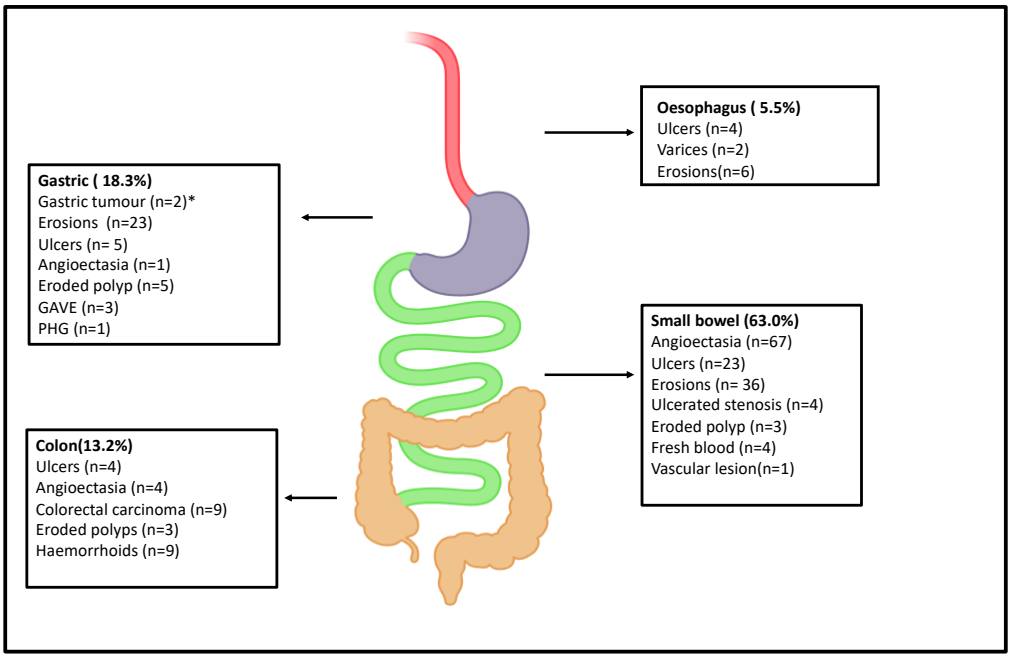

Figure 6: Pan enteric P1 and P2 pathology in patients with IDA. Some patients had more than one P1/P2 pathology. * gastric adenocarcinoma (n=1), gastric metastasis from B-cell

lymphoma (n=1). PHG (portal hypertensive gastropathy), GAVE (gastric antral vascular ectasia)

Completion rates and reading time

The completion rates for gastroscopy, CE and colonoscopy were 99.4% (n=169), 88.2% (n=150) and 95.2% (n=162) respectively. The reasons for incomplete procedure included the following: unable to intubate on gastroscopy (n=1); delayed gastric emptying of CE (n=8), detached kit before capsule enters caecum (n= 8); inflammatory SB stricture (n=4); poor colonic prep (n=3), poor tolerance of colonoscopy (n= 3), obstructing colorectal carcinoma (n=2). There were no procedure-related complications for OGD or colonoscopy. There was capsule retention. The mean small bowel reading time was 17.42min (SD 9.43min).

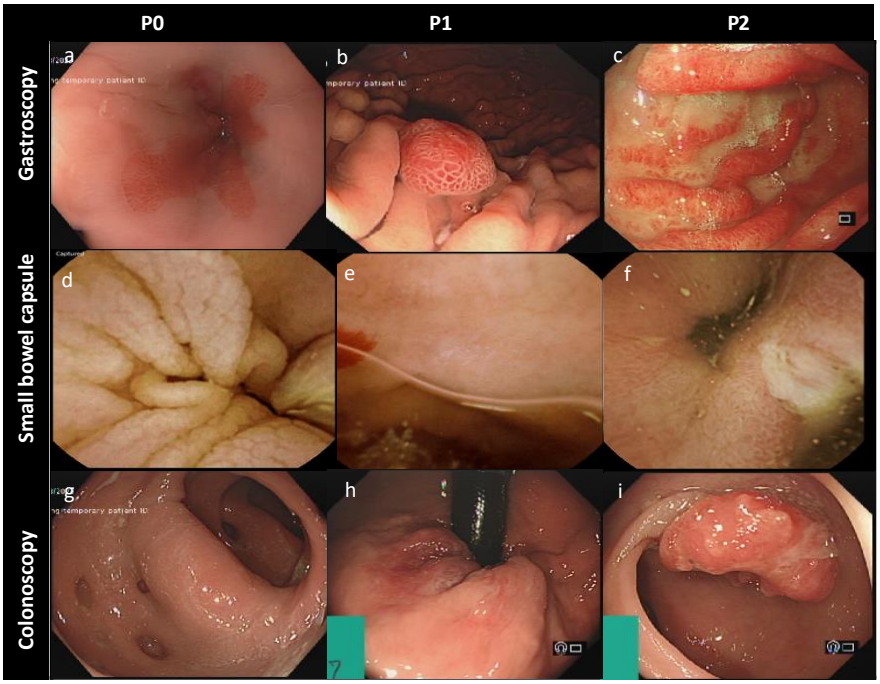

Figure 7 - Examples of lesions identified and graded according to the adapted Saurin classification. a. Barrett's oesophagus, b. Eroded gastric polyp, c. Gastric antral vascular angioectasia GAVE, d. Villous atrophy, e. Angioectasia, f. Ulcerated stricture, g. Diverticulosis, h. Haemorrhoids, i. Adenocarcinoma.

Synchronous lesions:

There were P1 or P2 lesions in more than one location in 47 patients (27.6%). In 4.7% (n=8) patients there was synchronous pathology seen on gastroscopy and colonoscopy. In 13.5%(n=23) patients there was synchronous pathology on gastroscopy and SB and in 10% (n=16) patients there was synchronous pathology on colonoscopy and SB.

Consensus read:

There was a high level of agreement between experts during the consensus read (Gwet AC inter rater coefficient of 0.98).

3.5 Discussion

Our study comprehensively evaluates 170 patients with recurrent / refractory as well as first presentation of IDA who underwent an OGD, CE and a colonoscopy. Twice as many patients had small bowel pathology when compared with the upper and the lower GI tract. There were four patients who had a new diagnosis of coeliac disease in our cohort who were not included in the final analysis as coeliac disease is a known cause of IDA however, it is not classed as a bleeding lesion. These findings are comparable to previous literature which have consistently shown a high diagnostic yield forof CE in patients which IDA although the studies have only

included patients with recurrent/refractory anaemia (15). Third of the patients had pathology identified on OGD and a fifth on colonoscopy. We standardised the identified lesions by using the adapted Saurin classification and grading them based on the bleeding potential. While it is known that bleeding lesions in the GI tract are the most common cause of IDA, there is variability in classifying the lesions identified in patients with IDA. Also, most studies which have looked at the prevalence of pathology in the upper and the lower GI tract have been retrospective. This could be the reason for the difference in prevalence of pathology compared to our study (118, 123-125). Malignant lesions were identified in 6.5% (11/170) of the patients. There were 5.3% with adenocarcinoma of the colon and primary gastric malignancy was identified in <1%. Small bowel tumours are rare; however, the risk is higher in younger patients with IDA(126, 127). No small bowel tumours were identified which is unexpected, but it could be explained by the selection criteria as we did not recruit any patients with obstructive symptoms into the study. The risk of malignancy increases with age in patients with IDA increases with age(128, 129). Our cohort of patients included patients who were fit for endoscopic investigations with the median age of 60 years. This could explain the lower prevalence of GI malignancy. Current guidelines recommend OGD and colonoscopy as first line investigations for patients with IDA based on a 1-10% risk of synchronous pathology in the upper and lower GI tract (116). In the study synchronous lesions were identified in 13.5% of patients on gastroscopy and CE and 10% patients on colonoscopy and CE supporting the use of CE as a first line modality to investigate the GI tract.

This is the first study to our knowledge which evaluates the prevalence of pan enteric pathology in patients with IDA. A symptom-guided approach to investigation: OGD for patients with dysphagia or vomiting, cross sectional imaging for those with obstructive

symptoms and capsule endoscopy of upper and mid GI tract for the remainder is recommended.

CHAPTER 4: A MUTICENTRE, PROSECTIVE BLINDED COMPARISON OF MAGNET- CONTROLLED CAPSULE ENDOSCOPY AND OESOPHAGOGASTRODUODENOSCOPY IN THE ASSESSMENT OF THE UPPER GASTROINTESTINAL TRACT

4.1 Abstract:

Introduction: Magnet-controlled capsule endoscopy (MACE) is a new, non-invasive technology which allows examination of the upper gastrointestinal tract. This study compared MACE with oesophagogastroduodenoscopy (OGD) in the detection of lesions with bleeding potential in patients referred for the investigation of iron deficiency anaemia (IDA).

Methods: MACE was performed within one week before OGD using the NaviCam (Ankon, China and AnX Robotica, USA) capsule endoscopy system.. All lesions considered to have bleeding potential were photographed and described according to a common diagnostic register and the endoscopist performing OGD was blinded to the MACE results. Anonymised images were reviewed by a consensus panel comprising three endoscopists who defined each lesion as P0 (no bleeding potential, P1 (possible bleeding source) or P2 (likely cause of bleeding). The aim of our study was to compare the diagnostic yield of lesions contribute to IDA seen on MACE and on OGD. We also looked at the complete detection of the various anatomical landmarks in the upper GI tract by MACE. Data was analysed using Graph pad Prism software.

Results: All patients were enrolled between Jan 2022- Jan 2024. Total of 158 patients were included in the final analysis with a median age 61 year (IQR 46- 72); 44.9% female, had a median haemoglobin of 103 g/L (IQR 90- 117.2), ferritin 11ug/L (IQR 7-18) and iron 6.4 umol/L (4-10). MACE identified significantly more lesions compared with OGD in the upper GI tract 119 vs 57 (95% CI 0.0- 0.08; P <0.001). The complete detection rate of oesophagel, gastric and

duodenal landmarks by MACE was 66.9% (95% CI 62.6-71), 94.1% (95% CI 92.5%- 95.5%), 78.5% (95% CI 92.5- 95.5). The mean completion time for MACE was 19.8minutes (SD +/-7.46 min) and 84.8% (134) patients also had a complete passive small bowel examination. No adverse events were recorded and there was no capsule retention.

Conclusions: The improved diagnostic yield of MACE compared to OGD is accounted for mainly by minor mucosal abnormalities which could, nonetheless, contribute to occult bleeding and anaemia. Although speculative this could be because of better tolerance of MACE and a longer examination time. An increased frame capture rate, with or without a second camera, is needed to improve oesophageal visualisation.

4.2 Introduction

Lesions in the gastrointestinal (GI) tract are a common cause of iron deficiency anaemia (IDA) and hence oesophagogastroduodenoscopy (OGD) and colonoscopy is the recommended investigation(115, 130). A second look OGD is suggested prior to small bowel examination for recurrent /refractory anaemia as lesions identified on capsule endoscopy are within reach of the OGD in 25% of the patients, suggesting that they were missed during the initial examination(115, 131, 132). However, OGD is an invasive procedure and comes with its own set of risks(133). Unsedated OGD is also unpleasant for some and can generate procedure related anxiety(134, 135).

Capsule endoscopy is a first line small bowel investigative modality, colon capsule endoscopy (CCE) is being used to investigate symptomatic patients in national programmes in England and Scotland(106) and a device which images the whole small and large bowel is marketed as

a Crohn's capsule. (53, 54, 136, 137). However, passive examination of the stomach with a capsule is challenging because it is capacious and irregular in shape. The use of magnets in capsule endoscopy has helped overcome this challenge and preliminary studies suggest that it may be possible to perform a complete gastric examination with magnetically controlled capsule endoscopy (MACE)(62, 63, 138-140). If indicated, the same device can be allowed to pass distally and provide a small bowel examination within the same procedure.

The aim of our study was to compare the diagnostic yield of lesions with bleeding potential seen on MACE and on OGD in patients with IDA. We also looked at the complete detection of the various anatomical landmarks in the upper GI tract by MACE.

4.3 Materials and Methods

Study design and participants

Patients with iron deficiency anaemia were recruited as part of the Bleeding Location in The Gastrointestinal Tract (BLITGIT) study (INRCTN registry (ISRCTN85978758)) in which they underwent small bowel capsule endoscopy as well as gastroscopy and colonoscopy with the primary aim being to identify the site of lesions with bleeding potential. As a combination of magnetic control using the Navicam Stomach System (AnX Robotica) and patient position movement allows an upper gastrointestinal as well as (uncontrolled) small bowel examination, MACE was also performed before the capsule entered the small bowel in order to compare the findings with those of OGD.

Patients were recruited from Sheffield Teaching Hospitals NHS Foundation Trust (Sheffield, UK), Endo-Kapszula Health Centre (Székesfehérvár, Hungary) and the Chinese University of

Hong Kong (Hong Kong). Inclusion criteria for participation were non-pregnant adults (aged ≥ 18 years and ≤ 80 years) with IDA confirmed on blood tests and defined by the World Health Organization (WHO) as a haemoglobin (Hb) concentration below 130 g/L in men over 15 years of age, below 120 g/L in non-pregnant women over 15 years of age and a ferritin level of less than 30 gms/L(121). Exclusion criteria included dysphagia, gastroparesis, suspected or previous gastric outlet or small bowel obstruction, Crohn's disease, long term daily use of non-steroidal anti-inflammatory drugs (with the exception of low dose aspirin), previous oesophagogastric or small bowel surgery or abdominopelvic radiotherapy and the presence of any implantable electronic or magnetic device. Patients provided written informed consent before study procedures.

Preparation for MACE

Patients were prepared for both MACE and small bowel examination. They were asked to have a low residue diet the day before and drink two litres of polyethylene glycol the evening before the procedure and fast from midnight (clear fluids were permitted). On the day of the MACE procedure patients drank 100mls water containing simethicone 80mg (Infacol, from wherever) 30 minutes before swallowing the capsule(141). The patients were then asked to drink up to one litre of water for gastric distension and mucosal visualisation(19). The protocol used was in keeping with the protocol used by Liao et al(10). The MACE procedure was performed within one week prior to the OGD.

MACE system

The MACE system used (figure 1) consists of a capsule (28 x 12mm) which has an incorporated permanent magnet, capturing images at 2-6 frames per second using a CMOS (complementary metal oxide silica) imaging device. The capsule has a field of view of 160 degrees and the depth of view 0 to 50 mm. The magnetic robot used to guide the capsule controls movement within two degrees of rotation and three of translation and can be operated either manually using a joystick controller or automatically by default mode. Images are transmitted to a data recorder which the patient wears in a belt.

MACE procedure:

The procedure was conducted as previously described by Jiang et al (142). Briefly, the patients swallowed the capsule with a few sips of water in the left lateral decubitus position with the magnet near the right shoulder. They were asked to adopt the supine position immediately on swallowing the capsule to capture the device in the oesophagus before transit into the stomach. After oesophageal inspection, the capsule was allowed to pass into the stomach (if necessary with further sips of water) and starting in the left lateral position (followed by the supine and right lateral position), magnet control was used to inspect cardia, fundus, body and antrum at an imaging rate of six frames per second. The capsule was then switched to small intestinal mode (two frames per second), the data recorder detached from the system and the patient allowed to go home. They were asked to wear the belt for a further 10 hours and return the equipment the following day for data download and video reporting.

Post MACE exam

The videos were processed using ES View (version 2.0) software. Pathology reporting was standardised using a pre-defined list to minimize interobserver variation (appendix 1). All

identified pathology was also described according to the perceived bleeding potential [none (P0), suspected (P1), or high bleeding potential (P2)] adapted from the Saurin classification(122). (appendix 2) Reporters recorded if each landmark was seen adequately (sufficient to identify significant pathology): adequate views of the distal oesophagus included visualisation of the whole gastro-oesophageal junction. Inadequate visualisation was described as either due to technical reasons (rapid transit or inadequate control) or luminal content (cloudy or containing food or mucoid secretions or bubbles)

OGD was performed according to standard clinical practice by an endoscopist blinded to the MACE results who recorded all potential pathologies and reported using the same predefined diagnostic list as was used for MACE and the adapted Saurin classification. Anonymised images of all pathology identified at OGD and MACE were reviewed by a panel of three gastroenterologists who were expert in both procedures (MEM, AF and FLMW) and a consensus regarding lesion definition and bleeding potential was obtained and used as the gold standard. Only the lesions with P1 or P2 bleeding potential were included in the final analysis.

Outcome

The main outcome parameter was the diagnostic sensitivity, specificity, positive and negative predictive value and accuracy of MACE and OGD compared to the consensus panel decisions as the gold standard. Secondary outcomes included the rate of complete detection of the various anatomical landmarks in the upper gastrointestinal tract (upper oesophagus, mid oesophagus, lower oesophagus, cardia, fundus, proximal corpus, distal corpus, antrum, pylorus, first and second part of duodenum) and also the time taken to perform MACE. A

Cohen's kappa (κ) was calculated to evaluate the strength of agreement between the findings on MACE and OGD.

Statistical analysis

We used descriptive statistics to present continuous variables as medians with interquartile ranges (IQR) and categorical variables as numbers and percentages. Categorical variables were compared using Fisher's exact test. A two-sided p-value of 0.05 was considered statistically significant. All statistical analyses were performed using Graph pad Prism for MAC OS version 10.3.0 GraphPad Software, Boston, Massachusetts USA.

Ethics

The study protocol and all research procedures performed in this study were done in accordance with the ethical guidelines outlined in the Declaration of Helsinki. The study was approved by the regional ethics committee (Ref. No. 18/NW/0588) and has been registered on INRCTN registry (ISRCTN85978758).

4.4 Results

Patient characteristics

All 183 patients were enrolled between Jan 2022- Jan 2024. We excluded 25 patients from the final analysis due to the following reasons: technical issues with the capsule (n=8); unable to swallow capsule (n=2), did not attend OGD (n=1); breach of protocol (n=2); OGD performed

>1 week after the MACE (n=12) (Figure-1). A total of 158 patients included in the final analysis had a median age of 61 years (IQR 46- 72), 44.9% were female and they had a median haemoglobin of 103 g/L (IQR 90- 117.2), ferritin 11ug/L (IQR 7-18) and iron 6.4 umol/L (4-10). The main inclusion criterial was IDA but there 74 (46.8%) patients who also were symptomatic (rectal bleeding (n=26), abdominal discomfort (n=33), diarrhoea (n=19), constipation (n=9), altered bowel habit (n=12), weight loss (n=15) and 30 (19.1%) patients presented with more than one symptom. There were 13 (8.2%) prescribed anticoagulants, 7(4.4%) taking antiplatelet agents and 15(9.5%) using non-steroidal anti-inflammatory drugs (NSAIDS) (Table-1).

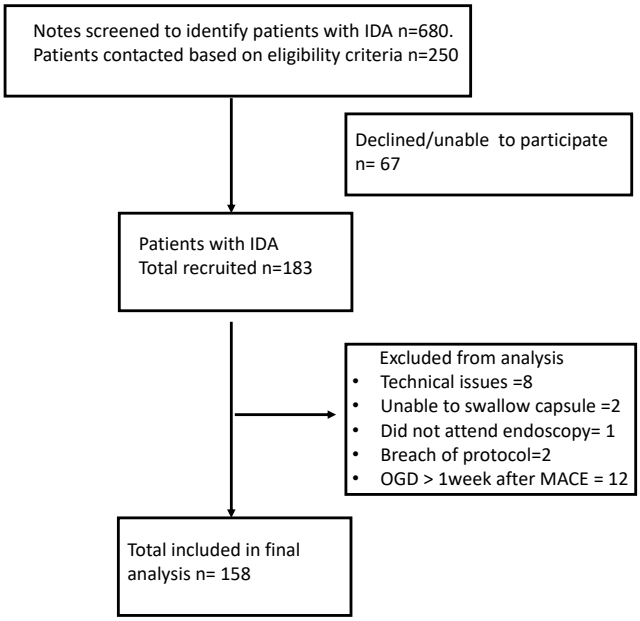

Figure-8: Patient selection for study

Sex, n (%)	
Female	71 (44.9)
Male	87 (55.0)
Age, median (IQR)	61 (46 – 72)
Blood results, median (IQR)	
Haemoglobin g/L	103 (90- 117.25)
Ferritin ug/L	11 (7-18)
Iron umol/L	6.4(4-10)
Symptoms, n (%)	
Abdominal discomfort	33 (20.9)
Diarrhoea	19 (12.0)
Altered bowels	12 (7.6)
Constipation	9 (5.7)
Weight loss	15 (9.5)
Rectal bleeding	26(16.5)
Medication, n (%)	
Anticoagulation	13 (8.2)
Antiplatelet	7 (4.4)
NSAID use	15 (9.5)

Table 5 – Baseline demographics and clinical data of the study participants (n= 158)

Diagnostic yield of MACE and OGD in the upper gastrointestinal tract:

In the upper GI tract 92 (58.2%) patients had 139 P1/P2 lesions identified by MACE and/or OGD and as defined by the consensus panel. MACE identified significantly more number of patients with pathology compared to OGD [89 vs 44 95% CI (6.2- 64.0); p< 0.0001]. Out of the 40 P2 lesions MACE identified 37 P2 lesions and OGD identified 12 P2 lesions in the upper GI tract. MACE did not identify one haematin stained duodenal ulcer, one eroded gastric polyp and one hemorrhagic gastric erosion that was identified by OGD. MACE identified significantly more P2 lesions compared to OGD. Of the total lesions MACE alone identified 12 (50%), 53 (60.9%) and 17 (60.7%) of the oesophageal, gastric and duodenal lesions respectively. Both modalities concomitantly identified 3 (12.5%), 31 (34.5%) and 3 (10.7%) of the oesophageal, gastric and duodenal lesions respectively. OGD alone identified 9 (37.5%), 3 (3.5%) and 8 (28.6%) of the lesions in the oesophagus, stomach and duodenum respectively. MACE identified significantly more lesions compared to OGD on gastric examination [84 vs 33 (95% CI 3.2- 35.7); p<0.0001]. There was no significant difference in the number of lesions identified by MACE or OGD in the oesophagus [15 vs 9 (95% CI 0.83- 12.68); p=0.12] or duodenum [20 vs 11; (95% CI 0.65- 9.55) p=0.19]. MACE detected 119 lesions versus 57 lesions by OGD in total (95% CI 0.0- 0.08; P <0.001). Significant lesions were missed by both modalities (Table-6). The Cohen's kappa agreement between MACE and OGD was poor (kappa <0.2).

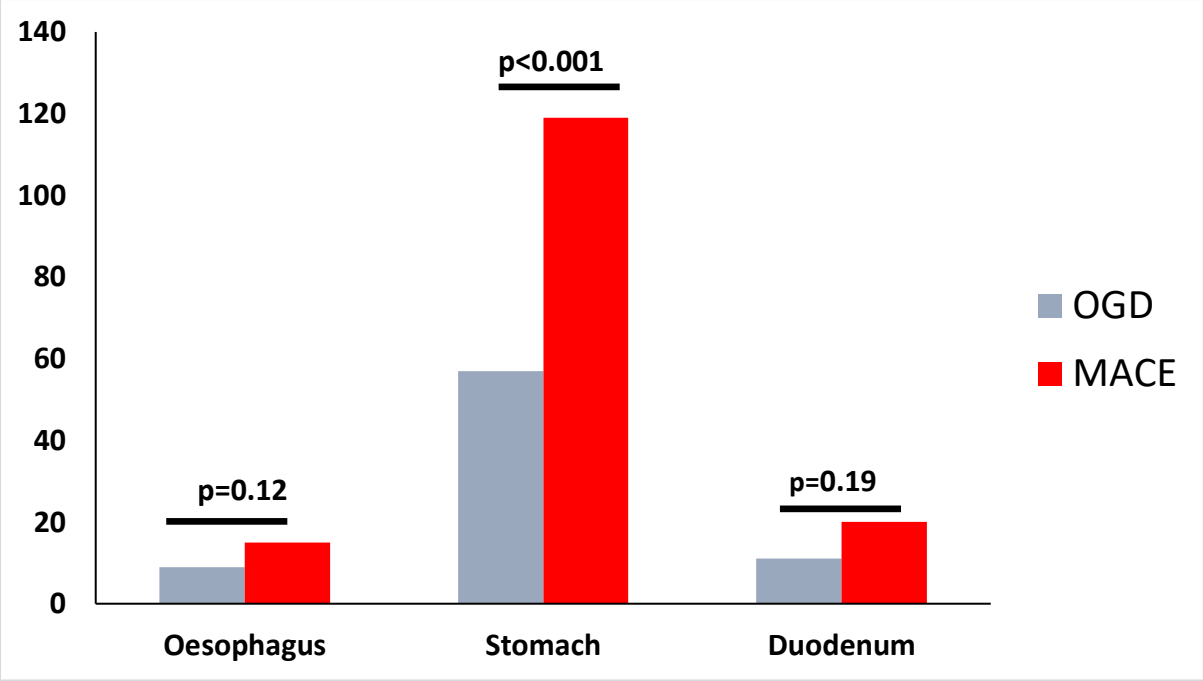

Figure-9: Graph depicting lesion detection by OGD and MACE in oesophagus, stomach and duodenum.

Pathology	**OGD only**	**MACE & OGD**	**MACE only**	**P -value**
Oesophagus				0.12
Ulcers &erosions	7	3	11	
Angioectasia			1	
Varices	2			
Gastric				**<0.0001**
Ulcer and erosions	2	22	37	
Eroded polyp	1	2	3	
GAVE		3	3	
PHG		1		
Angioectasia		1	10	
Gastric cancer *		2		
Duodenum				0.19
Ulcers & erosions	5	3	14	
Eroded polyp	1			
Angioectasia	2		3	

Table-6: Pathology seen on Oesophagogastroduodenoscopy (OGD) only; magnetically controlled capsule endoscopy (MACE) and OGD; MACE only. GAVE gastric antral vascular ectasia; PHG portal hypertensive gastropathy, * primary gastric adenocarcinoma and gastric metastasis of B cell lymphoma.

For oesophageal lesions MACE had a sensitivity of 62.5% (15/24), specificity 100% (115/115), positive predictive value of 100% (15/15) and negative predictive value of 92.7% (115/124). For gastric pathology MACE had a sensitivity of 96.5% (84/87), specificity 100% (52/52), positive predictive value of 100% (84/84) and negative predictive value of 94.5% (52/55). For duodenal bulb lesions MACE had a sensitivity of 71.4%% (20/28), specificity 100% (111/111), positive predictive value of 100% (20/20) and negative predictive value of 93.3% (111/119).

For oesophageal lesions OGD had a sensitivity of 50% (12/24), specificity 100% (115/115), negative predictive value of 90.6%(115/127) and a positive predictive value of 100% (12/12). For gastric lesions OGD had a sensitivity of 39.1% (34/87), specificity 100% (52/52), positive predictive value of 100% (34/34) and a negative predictive value of 49.5% (52/105). For duodenal bulb pathology OGD had a sensitivity of 39.3% (11/28), specificity of 100% (111/111), positive predictive value of 100% (111/111) and a negative predictive value of 86.7% (111/1128). For further details see supplementary table 1b.

Magnetically controlled capsule endoscopy

The complete detection rate of the various anatomical landmarks for oesophagus, gastric and duodenal examination was 66.9% (95% CI 62.6-71), 94.1% (95% CI 92.5%- 95.5%), 78.5% (95% CI 92.5- 95.5). The detection of the upper esophagus , lower oesophagus as well as the first part of the duodenum was the lowest at 62% (95%CI 54.3- 69.6), 58.2% (95% CI 50.5- 66.0) and 60.8% (95% CI 53.1- 68.5; Table-3) respectively. There was a statistically significant difference between the complete detection rates of the lower oesophagus and cardia (58.2% (95% CI 50.5- 66.0) vs 85.4 (79.9- 91.0); p<0.0001) as well as the duodenal bulb and cardia (60.8% (95% CI 53.1- 68.5) vs 85.4 (79.9- 91.0); p<0001). In 55 (34.8%) patients inadequate

views were because of technical reasons and in 13 (8.2%) patients the views were obscured by luminal content. The mean completion time for MACE was 19.8minutes (SD +/-7.46 min). As part of the BLITGIT study, all patients also had a small bowel examination: those in whom this was incomplete had a plain abdominal X-ray four weeks after the procedure and no capsule retentions were identified.

Location	**Complete visualization (n=158)**	
	Number	**% (95% CI)**
Oesophagus		
Upper oesophagus	98	62 (54.3- 69.6)
Mid oesophagus	127	80.4 (74.1- 86.6)
Lower oesophagus	92	58.2 (50.5- 66.0)
Gastric		
Cardia	135	85.4 (79.9- 91.0)
Fundus	149	94.3 (90.7- 98.0)
Proximal corpus	153	96.8 (94.1- 99.6)
Distal corpus	153	96.8 (94.1- 99.6)
Antrum	152	96.2 (93.2- 99.2)
Pylorus	149	94.3 (90.7- 98.0)
Duodenum		
First part	96	60.8 (53.1- 68.5)
Second part	152	96.2 (93.2- 99.2)

Table 7: Results of complete visualisation of the various locations in the upper GI tract by MACE.

4.5 Discussion

Potential bleeding lesions were identified in the upper gastrointestinal tract in 58.2% of patients with iron deficiency anaemia. MACE identified significantly more lesions than OGD and had a better diagnostic sensitivity in the stomach, but not oesophagus or duodenum. Rapid transit was the commonest reason for inadequate visualisation of the oesophagus and duodenum by MACE. Mean examination time was 20 minutes and no capsule retentions occurred.

This is the first study of MACE performed using a freestanding joystick-controlled robot magnet to identify suspected bleeding lesions in patients with iron deficiency anaemia. The findings are similar to those of our previous study in patients with recurrent or refractory anaemia in which MACE using a handheld magnet identified more total lesions, as well as those considered to cause anaemia, than OGD(61). Handheld magnet-controlled upper gastrointestinal capsule endoscopy also identified more pathologies than OGD in patients admitted with suspected upper gastrointestinal bleeding(59). They are also consistent with the 350 patient multicentre study reported by Liao et al who showed that MACE using the same Navicam Stomach System (AnX Robotica) identified focal gastric lesions in patients with dyspepsia with a sensitivity of 90.4% compared to OGD (irrespective of the size or site of the lesion), 84.6% of the false positive MACE diagnoses subsequently proving to be lesions missed by OGD when later repeated(10). That OGD misses pathology is not unexpected: there is significant interobserver variation in the reporting of all benign pathologies(143) and

systematic review and meta-analysis has shown a miss rate of gastric cancer by OGD of 9.4%-11.3%(144).

Although further comparative studies are needed, how might gastric capsule endoscopy provide a more reliable examination? The diagnostic yield of gastric cancer by 'slow' endoscopists is three-fold that of 'fast' endoscopists and a minimum seven-minute examination has been recommended(145, 146). It seems likely that endoscopists curtail examination time to minimise patient distress rather than to increase throughput as most of an endoscopy list is taken up by turnover time (of 20-23 minutes) between patients (the time between extubation of one patient and intubation of the next) rather than time taken to perform the procedures themselves(43). MACE is much better tolerated than OGD(147) therefore allowing longer examination times and, perhaps, a better diagnostic yield. Of course, a procedure which takes so much longer than OGD might mean slower throughput and the only cost analysis published to date does suggest that even with endoscopy lists of equal size, MACE costs over twice that of OGD(148). However, whilst a 20 minute examination time is similar to that reported in other clinical trials(10) , it was half that in over 3000 patients having a routine screening procedure (perhaps as operator expertise improved with experience) which is still measurably more than the minimum seven minute procedure recommended for a high quality OGD(64). Without the need for sedation, the main impact on turnover time is the time taken for the patient to drink the water, something which could be done before the patient enters the MACE room. The introduction of fully automated procedures using artificial intelligence as described by Xiao et al(149) may further tip the balance in favour of a longer examination time at the expense of turnover time.

The main limitation of MACE as it currently stands, at least if it is expected to replace diagnostic OGD in a like-for-like manner, is the unreliability of oesophageal and duodenal imaging. In this study, adequate visualisation of the distal oesophagus required complete visualisation of the Z line and was only achieved in 58.2% of cases. These specifications may have been more stringent than in the 40 patient study of Melzer et al(150) whose two reviewers observed the Z line (to what degree is not clear) in 77% and 85% of cases. Using a handheld magnet and the Mirocam Navi (Intromedic Ltd., Seoul, Korea) capsule (which, however, captured only three frames per second), Ching et al. Identified the Z line in only 33.3% and 53.1% of patients investigated respectively for suspected gastrointestinal bleeding and anaemia(59, 61). One solution to this problem is to slow transit through the oesophagus by applying traction on the capsule using a detachable tether, or string(151). Wang et al. found that string capsule endoscopy had a 97.5% sensitivity in diagnosing oesophagogastric varices compared to OGD. Flushing air through the hollow string detaches the capsule and allows MACE to proceed whilst the string is removed. However, swallowing the capsule with string might be more difficult than capsule alone, potentially increasing the risk of capsule inhalation(152). Regarding duodenal bulb imaging, we obtained complete views in 60.8%, which correlates with a diagnostic sensitivity of 62.5% reported by Yu et al. in their study of patients with suspected upper gastrointestinal bleeding using the Navicam(153). The challenges of both oesophageal and duodenal imaging could be remedied by increasing the specifications of the device: the UGI PillCam (Medtronic etc) is no longer commercially available, but captured 35 frames per second from a double ended camera capsule and visualised the Z line in 92.5% of cases in our experience. Furthermore, views of first and second part of duodenum were no less good than proximally, although the 90 minute battery life meant that capsule imaging beyond the pylorus only occurred in 64%(53). Improving

battery life, or perhaps more intelligent use of power available, to incorporate these improvements might allow a complete and thorough upper gastrointestinal examination which replicates the reach of OGD with a non-invasive tool.

CHAPTER 5: THE ROLE OF ARTIFICIAL INTELLIGENCE ASSISTED READING IN SMALL BOWEL CAPSULE ENDOSOCPY: A MULTICENTRE PROSPECTIVE STUDY

5.1 Abstract

Introduction: A typical capsule endoscopy video generated tens of thousands of images with abnormality being located over a few images only. The role of artificial intelligence (AI) in traditional endoscopy has shown immense potential exceeding human performance. The primary aim of our study was to assess the accuracy of AI-assisted video reading versus standard reading (SD) for potentially bleeding lesions in the small bowel.

Methods: This multicenter prospective study took place across three centres Sheffield, Hong Kong and Szekesfehervar, Hungary. Patients were invited to undergo a small bowel capsule endoscopy using the Navicam SB system (Ankon, China) . This system is equipped with the ProScan system which is a deep convolutional neural network (CNN) and it has been developed for small bowel capsule endoscopy lesion recognition. Videos were analyzed in a step wise fashion. Initial read was done in standard reading (SD) mode at the recruiting centre, following which the videos were anonymized and then the first blinded AI read (AI-1) was done using the proscan mode with the same reading instructions used in SD. Finally, a second unblinded AI read (AI-2) was done to assess lesions missed by AI-1 read and identify if the missed lesions was missed by the human reader or if it was a true missed AI lesion.

Results: Between Jan 2022- 24 128 patients [62 (48.4%) female; age 58 years (IQR 45-70; Hb 102g/L (IQR 91.25- 121.0); ferritin 11ug/L (IQR 7- 18)] were analysed. There was a significant reduction in the mean SB reading time from 18.13 minutes (SD 8.34) in SD mode to 2.27 minutes (SD 2.05) in AI assisted mode ($p<0.0001$). P1 and P2 lesions were identified in 62 of the 128 patients [standard reading (SD), diagnostic yield 48.4% 95%CI (40.0- 57.0)] and 69 of the 128 patients [AI-1 assisted reading, diagnostic yield 53.9% 95%CI (45.3- 62.3)]. On AI-2 assisted read 76 of the 128 patients had P1/P2 lesions [diagnostic yield 59.4% 95% CI (50.7- 67.5)]. Difference in diagnostic yield of SD and AI-1 assisted read was 5.5% [95%CI (2.6- 10.8);

p= 0.28] . This difference increased to 11% [95% CI (6.6- 17.5); p=0.008] when SD was compared with AI-2 assisted read.

Conclusions: The use of AI mode can safely reduce reading times without reduction in accuracy.

5.2 Introduction:

Small bowel capsule endoscopy is a safe and minimally invasive procedure which is being used in clinical practice for over 20 years(76, 154). Each capsule endoscopy video can generate on an average 50,000 still frames and analysing them can be a tedious process which requires the readers ongoing concentration. Several capsule endoscopy software systems have been developed and tested and have shown a significant reduction in reading times without reducing the diagnostic yield of diffuse mucosal diseases (such as inflammatory bowel disease). This may not be the case for isolated lesions, of which several studies reported an unacceptable miss rate(20-22). Convoluted neural networks (CNN) which is a deep learning model is the most popular machine learning algorithm for image analysis and has been widely developed for the detection for polyps and cancers in conventional endoscopy(155, 156). Preliminary reports in capsule endoscopy suggest that AI, in particular deep convoluted neural networks, are able to efficiently recognize specific images among a large variety, exceeding human performance in visual tasks(157-159). A CNN algorithm which can reduce the reading time of capsule endoscopy videos as well as improve lesion detection will help develop the field of capsule endoscopy further. A recent multicentre study evaluating the use of AI in capsule endoscopy has shown AI assisted reading is non inferior ($p<0.0001$) and superior ($p=0.0213$) to standard reading (SD) (82[62.4%] of 133 patients; 95% CI 3.6-19.0) and significantly reduced the reading time [AI- assisted reading time 3.8 min ($\pm$3.3) Vs 33.7 ($\pm$22.9) min in SD ($p <0.0001$)](25). The primary aim of our study is to assess the accuracy (sensitivity, specificity, PPV, NPV) of AI-assisted video reading versus SD with conventional software, in a per-patient and per-lesion analysis based on P1 / P2 lesions. We also compared the reading time of AI-assisted reading compared with SD.

5.3 Methods

Study design

We conducted a multicentre prospective study in three centres, Sheffield Teaching Hospitals, Sheffield; Endo-Kapszula Health Centre, Székesfehérvár, Hungary and The Chinese University of Hong Kong, Hong Kong. Patients with iron deficiency anaemia (IDA) were invited to participate in the study. Inclusion criteria were non-pregnant adults (aged $\geq$ 18 years and $\leq$ 80 years) with IDA confirmed on blood tests and defined by the WHO as a haemoglobin (Hb) concentration below 130 g/L in men over 15 years of age and below 120 g/L in non-pregnant women over 15 years of age. Iron deficiency was also confirmed with a ferritin levels < 30μgms/L. Patients provided a written informed consent before study procedures. Exclusion criteria are summarised in appendix.

Capsule endoscopy protocol

CE was performed using NaviCam SB system (Ankon, China and AnX Robotica, USA). The capsule videos were read using ES View (version 2.0) software. The system was also equipped with ProScan system which is a deep convolutional neural network (CNN) and it has been developed for small bowel capsule endoscopy lesion recognition. This system has been trained using images collected from 5000 patients, the CNN-based auxiliary model identifies abnormalities with 99.88% sensitivity in the per patient analysis and 99.90% sensitivity in the per-lesion analysis(24). Patients were asked to have a low residue diet the day before, and drink two litres of polyethylene glycol the evening before, the procedure and fast from midnight (clear fluids were permitted). If the participants were unable to tolerate some or all of the PEG, CE was performed if the patients had followed fasting instructions. Four hours

after capsule ingestion a light meal was allowed. Patients were advised to wear the recorder for 10 hours after swallowing the capsule. CE examination was completed if the capsule reached the colon within the recording time. Capsule retention was defined as capsule remaining in the digestive tract after two weeks.

Procedure

Videos were assessed in a step wise fashion. First the generated capsule videos were read in standard reading (SD) mode according to the recommendations of the European Society of Gastrointestinal Endoscopy (ESGE)(160). Landmarks (first image of the gastrointestinal tract, first duodenal image, first caecal image) were manually selected by the reader; findings were captured by mouse click with the stopwatch running. After completion of reading, findings were labelled according to their bleeding potential as P0 (none), P1 (suspected), or P2 (high), as per the adapted Saurin classification(122). This classification is a description of the lesions based on an impression of the identified lesions in the small bowel. Location of findings was reported according to a simplified location protocol which divides the SB into three tertiles according to the small bowel transit time. Only the lesions with suspected (P1) or a high (P2) bleeding potential were included in the final analysis. SD was done in the enrolment centre where the patients were recruited. Investigators from the enrolment centres converted and anonimised the videos which were randomly reallocated to another centre for a second blinded AI- assisted reading (AI-1). The AI assisted reading was done with the same reading instructions used in SD. Finally, a second AI read (AI-2) was done which was an unblinded read to assess lesions missed by AI-1 read and identify if the missed lesions was missed by the human reader or if it was a true missed AI lesion. Lesions were matched for type and timing. At per lesion analysis, lesions were considered matching when they were described in 5-

minute intervals by the readers in each modality. All lesions which were identified on SD and the two AI assisted reading were reviewed by an expert panel of three specialists who were from the three recruiting centres. A consensus was obtained for the identified lesions as well as the bleeding potential. The consensus read was used as the gold standard to compare SD and AI assisted read findings.

Outcomes

The primary aim of our study is to assess the accuracy (sensitivity, specificity, PPV, NPV) of AI-assisted video reading versus SD with conventional software, in a per-patient and per-lesion analysis based on the identification of P1 and P2 lesions. We also compared the reading time of AI-assisted reading compared with SD.

Statistical analysis

We used descriptive statistics to present continuous variables as medians with interquartile ranges (IQR) and categorical variables as numbers and percentages. Accuracy performance of categorical variables was evaluated by assessing sensitivity, specificity, positive predictive value and negative predictive value. Categorical variables were compared using Fisher's exact test. A two-sided p-value of 0.05 was considered statistically significant. Mann- Whitney test was used to analyse unpaired data. All statistical analyses were performed using Graph pad Prism for MAC OS version 10.3.0 GraphPad Software, Boston, Massachusetts USA.

Ethics

The study protocol and all research procedures performed in this study were done in accordance with the ethical guidelines outlined in the Declaration of Helsinki. The study was

approved by the regional ethics committee (Ref. No. 18/NW/0588) and has been registered on INRCTN registry (ISRCTN85978758).

5.4 Results

Between Jan 2022- Jan 2024, 128 patients [62 (48.4%) female; age 58 years (IQR 45-70; Hb 102g/L (IQR 91.25- 121.0); ferritin 11ug/L (IQR 7- 18)] were analysed. Capsule endoscopy was complete in 119 (92.9%) of 128 patients (Table-8).

Sex, n (%)	
Female	62 (48.4)
Male	66 (51.6)
Age, median (IQR)	58 (45 – 70)
Blood results, median (IQR)	
Haemoglobin g/L	102 (91.25 - 121.0)
Ferritin ug/L	11 (7-18)
Symptoms, n (%)	
Abdominal discomfort	28 (21.8)
Diarrhoea	15 (11.7)
Altered bowels	14 (10.9)
Constipation	8 (6.25)
Weight loss	11 (8.6)
Rectal bleeding	21(16.4)
Medication, n (%)	
Anticoagulation	9 (7.0)
Antiplatelet	6 (4.7)
NSAID use	12 (9.4)

Table 8 – Baseline demographics and clinical data of the study participants (n= 128)

P1 and P2 lesions were identified in 62 of the 128 patients [standard reading (SD), diagnostic yield 48.4% 95%CI (40.0- 57.0)] and 69 of the 128 patients [AI-1 assisted reading, diagnostic yield 53.9% 95%CI (45.3- 62.3)]. On AI-2 assisted read 76 of the 128 patients had P1/P2 lesions [diagnostic yield 59.4% 95% CI (50.7- 67.5)]. Comparing the diagnostic yield of SD and AI-1 assisted read a 5.5% increase [95%CI (2.6- 10.8); p= 0.28 McNemer's test] in diagnostic yield was observed. This difference increased to 11% [95% CI (6.6- 17.5); p=0.008 McNemer's test] when SD was compared with AI-2 assisted read. The per patient miss rate of standard read was (14 [18.4%] of 76) and AI-1 read was (7 [9.2%] of 76). The sensitivity, specificity, positive predictive value and negative predictive value of standard and AI- assisted reading for P1 and P2 lesions as well as only P2 lesions is shown in Table-9.

In total 129 P1/P2 lesions were identified. Of these 91 lesions were identified on SD [diagnostic yield 71.3% 95% CI (63.0- 78.4)], AI-1 read identified 101 lesions [diagnostic yield 78.3% 95% CI (70.4- 84.5)] and AI-2 read identified 113 lesions [diagnostic yield 88.3% ;95% CI (81.6- 92.8)]. The difference in diagnostic yield between SD and AI-1 read was 7% ;95% CI (3.7- 12.7 p =0.26 McNemer's test) and the difference in diagnostic yield between SD and AI-2 read was [16.3% ;95% CI 10.9- 23.6 P=0.004 McNemer's test]. The per lesion miss rate of standard read was (38 [29.5%] of 129) and AI-1 read was (28 [21.7%] of 129). There were 15 P2 lesions identified in total. Both SD and AI-1 read identified 13 of these 15 lesions. AI-2 read identified all 15 P2 lesions.

	P1 &P2 lesions			P2 lesions		
	Standard reading(95%CI)	AI-1 reading (95%CI)	AI-2 reading (95%CI)	Standard reading(95%CI)	AI-1 reading (95%CI)	AI-2 reading (95%CI)
Sensitivity	76.5% (66.3-84.4)	85.2% (75.9-91.3)	93.8% (86.3-97.3)	85.7% (60.1-97.5)	85.7% (60.1-97.5)	100.0% (78.5- 100.0)
Specificity	100% (92.4-100)	100% (92.4-100)	100% (92.4-100)	100% (96.8-100)	100% (96.8-100)	100% (96.4-100)
PPV	100% (94.2-100)	100% (94.7-100)	100% (95.2-100)	100% (75.8-100)	100% (75.8-100)	100% (78.5-100)
NPV	71.2% (59.4-80.7)	79.7% (67.7-88.0)	90.4% (79.4.- 95.8)	98.3 (94.0-99.7)	98.3 (94.0-99.7)	100% (96.7 – 100.0)
Diagnostic accuracy	85.2% (78.0-90.2)	90.3% (84.3-94.6)	96.8% (91.2-98.3)	98.4% (94.5-99.7)	98.4% (94.5-99.7)	100% (96.7-100)

Table 9: Diagnostic performance of standard reading and the two AI reads in per patient analysis (consensus read of identified pathology used as gold standard)

Reading time

The mean SB reading time on standard read was 18.13 minutes (SD 8.34) and the mean SB reading time on AI assisted reading was 2.27 minutes (SD 2.05). There was a significant difference in the reading time ($p<0.0001$; Mann-Whitney test).

5.5 Discussion:

This study demonstrates that the use of AI assisted reading compares favourably with standard reading with a sensitivity of 85.2% for detecting clinically significant lesions. The use of AI was also associated with a significant reduction in reading time with an average case taking only 2.5 minutes to interpret instead of 18 minutes in standard mode.

Although the diagnostic yield of AI- assisted read was higher in the per patient and per lesion analysis compared to standard read this difference was not statistically significant. However, the unblinded AI read (AI-2) read did identify significantly more lesions compared to standard read. The unblinded AI read (AI-2) confirmed that when the lesions were being missed by the AI read (AI-1) it was mainly because of other factors such as reading speed and image displayed rather than a true missed lesion by the proscan software. The sensitivity, specificity, PPV and NPV of AI read was higher when compared to standard read. In fact when we compare the sensitivity, specificity, PPV and NPV of the unblinded AI mode (AI-2) with the SD mode these values are even higher which suggests that the lesions are being identified by the AI system but are being missed by the human reader. These results are supported by previous studies with a 93.3% sensitivity and a diagnostic accuracy of 94.5% for P1 lesions at a per-patient analysis(25). Our study has some limitations. In view of the known interobserver variability in capsule reading(161) and interpretation, all identified lesions went through an expert consensus to evaluate reading discrepancies and formulate a standardised coding system for interpretation (appendix-1). The diagnostic yield of our cohort is comparable to

that seen in previous studies(15). All lesions were also graded based on their bleeding potential using the adapted Saurin classification(122). For example, an angioectasias was graded as a P1 lesion if there was no evidence of active bleeding. Only actively bleeding angioectasias were graded as a P2 lesion (appendix-6). Only P1 or P2 lesions were included in the final analysis as P0 lesions do not have any bleeding potential. All our patients had IDA and hence the focus of the AI functionality was for angioectasia which is the most common finding in this setting(15).

This study was mainly designed to test the accuracy and the reading times of AI-assisted reading. With the reduced reading time the capsule reader gets more time to focus on the identified lesions which are of clinical significance. Moreover, AI- based reading is not attempting to replace the physician but to support them in making a clinical diagnosis for their patients. In conclusion, our study supports the use of AI assisted reading for SBCE in patients with IDA. Further prospective studies evaluating AI-assisted reading for isolated SB pathology is needed to bring its use in routine practice.

CHAPTER 6: DOES FIT HAVE A ROLE IN THE DETECTION OF SMALL BOWEL PATHOLOGY- A PROSPECTIVE STUDY

6.1 Abstract

Background: FIT is an immunoassay used to detect human blood in stool. The role of FIT as a screening tool for small bowel pathology remains unclear.

Objectives: The aim of this study was to investigate the role of FIT in predicting small bowel pathology in patients with iron deficiency anaemia (IDA).

Design: This was a single tertiary centre prospective study. Inclusion criteria was adults (≥ 18 years and < 80 years) with IDA who were referred to secondary care for endoscopic investigations.

Methods: All patients had a FIT test done in primary care. Eligible patients were invited to have a small bowel capsule endoscopy (SBCE) prior to endoscopy. Patients with subsequent upper or lower gastrointestinal tract malignancy were excluded from the study. IDA was defined as a Hb < 131g/L for men and < 110 g/L for women with ferritin< 30ug/L and/ or iron levels < 11umol/L. A further 100 patients with recurrent/ refractory IDA who did not have a FIT test done and had a SBCE were used as the control group.

Results: In total 179 patients were included in the final analysis with a median age of 64.5 years (IQR 51-75); haemoglobin 101 (IQR 90- 111) and ferritin 11(7-20). In the prospective FIT group of 79 patients there were 35 (44%) patients with significant findings on SBCE which was classed as contributing to IDA. These findings included angioectasia in 21 (26.6%) patients which was the most common finding. The other findings included erosions and ulcers 5 (7.6%); inflammatory strictures 3 (3.8%); active Crohn's 1 (1.3%); visible blood with no clear source n=3 (3.8%) and bleeding angioectasia 1 (1.3%). A positive FIT (>10) had a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 34.29%,

54.55%, 37.5% and 51.08% respectively. In the control group of 100 patients 37% of the patients had significant pathology on SBCE. On logistic regression analysis age (OR 1.06; 95% CI 1.03 - 1.11) was the only factor related to the probability of having a positive finding on SBCE.

Conclusion: Over a third of the patients with IDA have significant findings on SBCE. However, in this study we did not find that FIT conferred any additional benefit in the detection of small bowel pathology.

6.2 Introduction

FIT is an immunoassay used to detect human blood in stool(26). It has largely replaced the traditional faecal occult blood tests (FOBTs) due to higher sensitivity for colorectal cancer as well as advanced neoplasia(27-30). It is also thought to be more specific for distal gastrointestinal bleeding and the results are not affected by the use of NSAID and oral anticoagulation(26, 28, 31). Overall the acceptability of FIT is higher compared to traditional FOBT(32, 33). Currently FIT is used for colorectal cancer (CRC) screening and also for risk stratifying patients with IDA in England(34, 35). We also know that in up to 60% of the individuals with a positive FIT no significant colorectal lesion is identified. This raises the possibility of the lesions being located in the small bowel(36-38). Currently the role of FIT as a screening tool for small bowel pathology in patients with IDA remains unclear.

Iron deficiency anaemia (IDA) is a common clinical problem and it occurs in 2-5% of men and postmenopausal women in the developed world(115, 162-164). Although most studies for

anaemia include only patients with recurrent/ refractory IDA, it has been shown that potentially significant small bowel pathology is identified in up to 60% of the cases(115, 118).

Capsule endoscopy is an accepted first line modality for investigating the small bowel particularly in the setting of obscure GI bleeding(160). It is minimally invasive and very well tolerated. In a metanalysis SBCE was superior to push enteroscopy as well as small bowel barium radiography for diagnosing clinically significant pathology in patients with obscure GI bleeding(14). Currently there are no biomarkers available which could be used to triage these patients who are being referred for a SBCE.

The aim of this study was to investigate the role of FIT in predicting small bowel pathology in patients with iron deficiency anaemia and negative bidirectional endoscopy.

6.3 Methods

Study design and patient selection

This was a single tertiary centre prospective study conducted in Sheffield, United Kingdom. Inclusion criteria was adults (≥ 18 years and < 80 years) with the presence of IDA who were referred for endoscopic evaluation (oesophagogastroduodenoscopy + colonoscopy) based on national guidelines(115). Prospective patients were recruited from Jan 2022- Jan 2024. Patients identified with IDA in primary care are advised to have a FIT test done before being referred into secondary care. This is routine practice for risk stratification of the referrals. All patients recruited into the study had IDA and a FIT test done in primary care. SBCE was

performed prior to their endoscopic investigations in the prospective group. Patients with subsequent upper or lower gastrointestinal tract malignancy were excluded from the study as this was considered to be the most likely cause of IDA. IDA was defined as a Hb < 131g/L for men and < 110 g/L for women with ferritin< 30ug/L and/ or iron levels < 11umol/L. A control group of a 100 adult patients (≥ 18 years and < 80 years) who had a SBCE for IDA (who did not have a FIT test done in primary care) were collated from the existing SBCE database (Jan 2022- Jan 2024). The database contains all patients who have had a SBCE at Sheffield Teaching Hospitals. Search term like IDA and anaemia were used to identify eligible patients. All patients included in the control group were referred for a SBCE for further evaluation of their recurrent/refractory IDA. Patient demographics and medical history were collected to look for correlation between age, sex, comorbidities (ischaemic heart disease, diabetes, hypertension, atrial fibrillation and stroke), medication (anticoagulation, antiplatelet, NSAID) and the level of haemoglobin on small bowel pathology. Sample size calculation was based on previous studies which have used a similar sample size. The reporting of this study conforms to the STARD checklist(165).

Small Bowel Capsule endoscopy (SBCE)

AnX Robotica magnet system and Navicam capsule (single camera capsule, frame rate 2-6/sec: Wuhan, China) was used for small bowel examination. All patients were offered the capsule endoscopy within 1 week prior to their endoscopic procedures. All capsule studies were read by a single Professor in gastroenterology with decades of experience in endoscopy and small bowel capsule (> 1000 life time CE reported). The reader was blinded to the FIT results and the endoscopic findings. A capsule endoscopy was deemed positive if it identified

small bowel pathology which could potentially cause IDA. These lesions were classified as angioectasias, ulcers, erosions, strictures, active Crohn's and fresh blood of unknown aetiology. All identified lesions were classified using the adapted Saurin classification and only those lesions with a suspected bleeding potential (P1 – angioectasia, erosions and ulcers) and a high bleeding potential (P2- bleeding angioectasia, active Crohn's, inflammatory stricture, fresh blood with no clear source, neoplasia, large eroded polyps) were included in the final analysis(122, 166).

Statistical analysis

Statistical analyses were conducted using GraphPad Prism version 10.0.2 for Mac (GraphPad Software, San Diego, California, USA). A two-tailed p-value less than 0.05 was considered statistically significant. Descriptive statistics were used to summariese continuous data as median (IQR, Interquartile range) and categorical data as total numbers (percentages). Fisher's exact test was used to compare the diagnostic yield of SBCE in IDA. The correlation between different variables such as age, sex , comorbidities, medication and level of IDA was assessed with small bowel pathology using multivariant logistic regression analysis. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) in predicting small bowel pathology was calculated for different levels of FIT.

Ethics approval and consent to participate:

Ethical approval was obtained from the Health Research Authority (IRAS project ID: 295838) and Sheffield Teaching Hospitals (STH21615). All participants completed a consent prior to

participation. All data was anonymised during collection. No personal data that would allow the patient to be identified has been included in this study

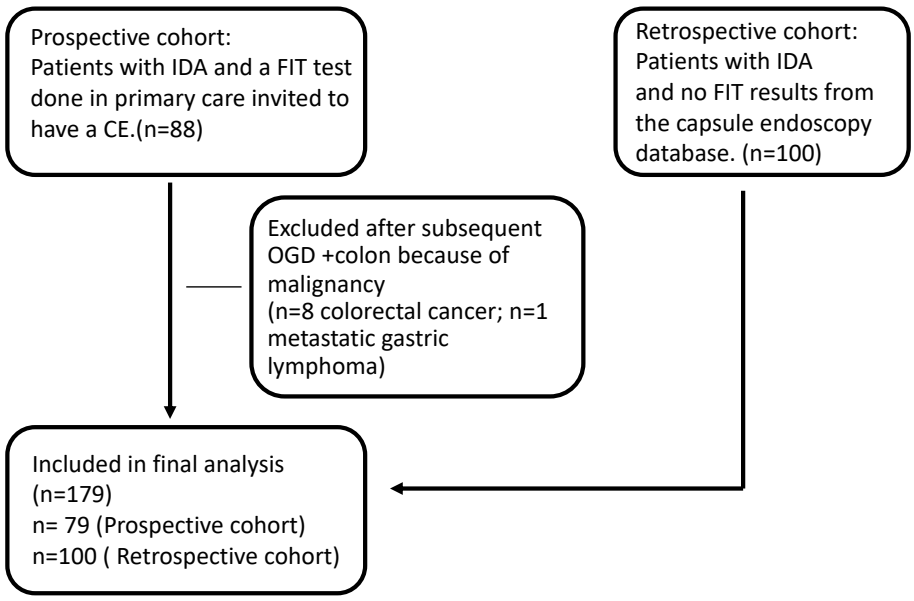

Figure-10: Flowchart shows selection of patients for the study. CE is capsule endoscopy.

6.4 Results

Patient characteristics

There were 179 patients in total. Out of these 88 patients were recruited prospectively. Nine patients were excluded from the prospective group after their endoscopic evaluation because of malignancy (colorectal carcinoma=8, metastatic gastric lymphoma=1). There were 79 prospective patients and 100 controls included in the final analysis (Figure-1). The median age was 64.5 years (IQR 51-75); haemoglobin 101g/L (IQR 90- 111) and ferritin ug/L 11(7-20). There were 54% female patients in total. There were 16 patients on NSAID's, 37 on anticoagulation and 12 on antiplatelets at the time of their investigations. A detailed

breakdown of patient characteristics in the prospective and the control group has been mentioned in Table-1.

Capsule endoscopy results

There were 179 patients with IDA and significant small bowel pathology identified in 72 (40.2%) of the patients. Group 1 included prospective patients with IDA who had a FIT test done in primary care. Group 2 included a retrospective cohort of control patients with recurrent or refractory IDA and no FIT sampling done in primary care.

Characteristic	**Group-1** Prospective Group	**Group-2** Retrospective
Sex n (%)		
Female	40 (50.6)	57 (57)
Male	39 (49.4)	43 (43)
Age, median (IQR)	67 (52-74)	63 (51-75)
Blood results, median (IQR)		
Haemoglobin(g/L)	103 (95-118)	98.5(86.8-108)
Ferritin (ug/L)	11 (6-11)	12 (7-23)
Medications n		
NSAID	13	2
Anticoagulation	11	26
Antiplatelet	5	7

Table-10: Patient characteristics of Group-1 (IDA and FIT) and Group-2 (IDA and no FIT). NSAID (non- steroidal anti-inflammatory drugs

In Group -1 there were 35 (44.3%) patients with significant findings on SBCE which was potentially contributing to IDA. These findings included angioectasia in n= 21 (26.6%) patients which was the most common finding. The other findings included erosions and ulcers = 6 (7.6%); inflammatory strictures= 3 (3.8%); active Crohn's n=1 (1.3%); visible blood with no clear source n=3 (3.8%); and bleeding angioectasia n=1 (1.3%). In Group 2 there were 37(37%) patients with significant findings on SBCE which was potentially contributing to IDA. These findings included angioectasia in n=20, bleeding angioectasia n= 1, new Crohn's disease, neoplasia n=4, erosions and ulcers n= 7, large eroded polyp n= 3, ulcerated stricture n= 1. There was no significant difference in the diagnostic yield between the two groups (95% CI 0.73- 2.51; P= 0.35) (Table-2). In some patients more than one finding was identified on SBCE. In these cases the P2 pathology was included in the analysis for diagnostic yield. No patients had more than one P2 pathology.

	Total with FIT n=79 (%)	**FIT <10ugHb/g**	**FIT ≥ 10ugHb/g**	**Total no FIT n=100 (%)**
Insignificant finding on SBCE	44 (55.7%)	24	20	63 (63%)
Significant finding on SBCE	35 (44.3%)	23	12	37 (37%)
Angioectasia	21 (26.6%)	14	7	20 (20%)
Bleeding angioectasia	1 (1.3%)	0	1	1 (1%)
Active Crohn's disease*	1 (1.3%)	1	0	1 (1%)
Inflammatory stricture	3 (3.8%)	1	2	1 (1%)
Fresh blood	3 (3.8%)	3	0	0
Erosions and ulcers	6 (7.6%)	4	2	7 (7%)
Neoplasia	0	0	0	4 (4%)
Large eroded polyp	0	0	0	3 (3%)

Table-11: Findings on small bowel capsule endoscopy (SBCE) in patients with IDA and FIT results (Group-1). *A finding was described as Crohn's on SBCE when ulcerative pattern was specific for Crohn's disease. Finding was described as ulcers and erosions when the pattern on SBCE was non-specific for Crohn's but abnormal. In a patient with more than one finding, P2 pathology was included in the diagnostic yield.

FIT results and capsule endoscopy

There were 79 patients who had IDA and a FIT test done. Median time from obtaining FIT results to complete investigations (SBCE and dual endoscopy) was 8 weeks. All patients with a FIT level > 10ugHb/g were investigated within 4 weeks. In total there were 35 (44%) patients with significant findings on SBCE which was the most likely contributing to IDA. Out of these

12 patients had a FIT >10ugHb/g and 23 had a FIT <10ugHb/g (p= 0.36). The sensitivity of FIT >10ugHb/g was 0.37 (95% CI 0.25 to 1.63); specificity 0.51 (0.37 to 0.64); PPV 0.34 (0.21-0.50); NPV 0.54 (0.40- 0.68) for detecting small bowel pathology. These results were also calculated for different FIT levels as shown in Table -3.

FIT (ugHb/g)	**Sensitivity %** **(95% CI)**	**Specificity %** **(95% CI)**	**PPV %** **(95% CI)**	**NPV %** **(95% CI)**	**FIT level(ugHb/g)**
>4 **(n= 43)**	41.9% (28.4- 56.7)	43.18% (37.01- 68.01)	41.86% (35.6- 67.0)	52.78% (29.7- 57.8)	>4
>10 **(n=32)**	37.5% (22.9- 54.0)	51.06% (37.2- 64.0)	34.1% (20.8- 50.8)	54.6% (40.07- 68.2)	>10
>45 **(n=11)**	50.0% (23.7- 76.3)	56.5% (44.8- 67.6)	14.3% (62.6- 29.4)	88.6% (76.0- 95.0)	>45
>75 **(n= 9)**	44.4% (18.9- 73.3)	55.7% (44.1- 66.6)	11.4% (4.5- 25.9)	88.6% (76.0- 95.0)	>75

Table- 12: Performance of Fecal immunochemical test (FIT) for the detection of significant small bowel lesions. PPV (positive predictive value); NPV (negative predictive value).

Several variables were significantly associated with positive findings using a univariant logistic regression analysis on our retrospective cohort of 100 patients. Age (OR 1.06; 95% CI 1.03 - 1.11) was the only factor that was significant on multivariable logistic regression for the small bowel pathology in patients with IDA (Table -4).

Variable	**Univariable**		**Multivariable**	
	Odds ratio(95%CI)	P- value	Odds ratio(95%CI)	P-value
Age	**1.07 (1.03- 1.11)**	**0.0002**	**1.06 (1.03 - 1.11)**	**0.002**
Sex	0.61 (0.26- 1.4)	0.25		
IHD	2.1 (0.75- 6.34)	0.15		
AF	1.3 (0.40- 4.10)	0.65		
Stroke	3.4 (0.32- 76.54)	0.32		
T2DM	1.08 (0.36 - 3.05)	0.88		
HTN	**3.18 (1.29 - 8.01)**	**0.01**		
CKD	**9.53 (1.45- 186.7)**	**0.04**		
Anticoag	1.33 (0.52 - 3.30)	0.5		
Antiplatelet	0.65 (0.09 - 3.20)	0.62		
Haemoglobin	0.99 (0.97 - 1.01)	0.56		
Ferritin	1.01 (1.00 -1.01)	0.08		

Table-13: Factors predicting small bowel pathology. Ischaemic Heart Disease (IHD), Atrial Fibrillation (AF), T2DM (Type-2 diabetes), Hypertension (HTN), Chronic Kidney Disease (CKD).

6.5 Discussion:

In the study we have shown that significant small bowel pathology was identified in over a third of the patients with IDA on SBCE. There was also no significant difference in the diagnostic yield between the prospective group with IDA (first presentation and recurrent IDA) and the retrospective group with recurrent and/ or refractory IDA. All identified lesions were standardised using the adapted Saurin classification and only those lesions with a suspected bleeding potential (P1) or a high bleeding potential (P2) were included in the final analysis. Our findings are supported by previous literature which have consistently shown a high diagnostic yield of small bowel pathology in patients with IDA(118, 127, 167). In spite of these findings small bowel investigations are only recommended for patients with recurrent or refractory anaemia(115). The study has also shown that age is a predictor of small bowel pathology which is also supported by previous literature suggesting that there is increased likelihood of small bowel pathology in older patients with IDA(168).

In the study FIT has a low sensitivity, specificity, PPV and NPV for small bowel pathology at all levels. These findings are supported by a previous meta-analysis which included five studies. In the metanalysis the overall sensitivity for SB pathology in patients with a FOBT test was 0.60 (95%CI 0.50-0.69) and specificity was 0.72 (95%CI 0.52-0.86)(169). When only the four studies which used FIT in the analysis were included the sensitivity of FIT for SB pathology on CE was 0.48 (95%CI 0.36-0.61) and the specificity was 0.60 (95%CI 0.42-0.76)(169-173). A more recent study by Judge et al has shown that a combination of anemia and positive FIT was statistically significant in predicting SB pathology (R = 0.39, P = 0.009); PPV of 66.7%, and a NPV of 82.1% (OR 9.14, 95% CI [1.39 – 60.12], P = 0.025(174). The reason for this difference could be the timing of the FIT test. Judge et al performed all FIT tests with in 24 hrs of the

SBCE. Small bowel lesions such as angioectasia do bleed intermittently and hence the timing of the FIT can potentially have an impact on lesion detection. Previous literature suggests that in patients with overt GI bleeding the diagnostic yield of SBCE is higher when performed close to the bleeding episode(81, 175). In a study by Kobayashi et al the timing of the FIT influenced the association between FIT result and SB pathology in patients with obscure bleeding(172). In our study although the diagnostic yield of SBCE was comparable to other studies, FIT had a low accuracy in predicting small bowel pathology. This could be because in our cohort of patients the median time from obtaining the FIT results to having endoscopic investigations was eight weeks.

One of the limitations of our study is the small sample size of the FIT group. However, the diagnostic yield of potentially significant pathology was comparable to previous studies.

Currently there is no validated tool used for grading capsule endoscopy referrals. With the expanding role of CE there is an increasing demand for rationalising these referrals and also for grading them as urgent or routine.

CHAPTER 7: DISCUSSION

The body of work presented in this thesis examines the in-depth role of capsule endoscopy in patients with iron deficiency anaemia. We first looked at the pan enteric prevalence of P1 and P2 pathology in patients with both recurrent/refractory and first presentation of IDA. This multicentre prospective study which included 170 patients showed that two thirds of patients with iron deficiency anaemia had GI lesions with bleeding potential and one in four had dual site pathology. Lesions were about twice as common in the small bowel than the upper and lower GI tract although those with high bleeding potential (P2) were more likely to be identified in the upper GI tract and all but one cancer was found in the colon. The small bowel was the site of 63.0% of GI pathologies with bleeding potential in patients with iron deficiency anaemia, in contrast to the widely quoted disease prevalence of 5-10%(115, 160, 176, 177). This is unsurprising given that the small bowel accounts for most of the GI mucosal surface area and is affected by common diseases. The discrepancy can be explained by the use of radiological imaging as the means to examine the small bowel in these studies, which since the advent of capsule endoscopy is known to be much less sensitive a diagnostic tool, particularly given its inability to identify flat vascular and inflammatory lesions, the commonest lesions seen at capsule endoscopy(115, 160, 177). The lack of adequate small bowel investigation is likely to be a major factor in the reported failure to identify causative lesions in between one and two thirds of patients with iron deficiency anaemia, a recurrence rate after adequate iron replacement therapy in 12-67% and need for reinvestigation in 35%(115, 178). The dual pathology rate of 25.7% is also much greater than the 1-10% rate previously reported: this is largely accounted for by small bowel pathologies identified in patients who also had upper or lower GI pathologies.

No small bowel tumours were identified, perhaps unexpectedly in a study of this size in light of yields of 1.3-4.5% previously reported(17, 176). It may be explained by the exclusion of patients with any symptoms which could be due to partial small bowel obstruction: we know of two patients who were screened for consideration of study participation but who were not enrolled because CT scan performed as the first investigation identified small bowel thickening suspicious of tumours. Nonetheless, it begs the question as to whether or not a policy of non-examination of the small bowel might continue in patients presenting with anaemia for the first time. However, this would risk missing significant benign pathology in the 10% of patients with P2 small bowel lesions such as ulcerated strictures and Crohn's disease. The yield of upper GI cancers was also likely to have been affected by the exclusion criteria which included dysphagia and vomiting. There were no capsule retentions in the study which supports previous literature that CE is a safe procedure with a risk of capsule retention of <1% (179). This is the first study to our knowledge which has looked at the pan-enteric prevalence of pathology in patients with IDA. This is important as it shows that pathology is the small bowel is a very likely cause of anaemia and hence we should routinely consider investigating the small bowel in all patients with IDA.

In the following study we have looked at the performance of MACE when compared with OGD. MACE identified more gastric lesions than OGD with a diagnostic sensitivity of 96.5% but, and consistent with the assessment of the quality of views of different landmarks, performed less well in oesophagus and duodenum. Rapid transit was the main reason for poor views of the oesophagus and duodenum. MACE proved to be a highly sensitive diagnostic tool in the stomach. This is consistent with previous data showing that diagnostic sensitivity is over 90% compared to OGD, irrespective of site or size of the lesion(10, 180).

This is likely to be comparable to OGD: no back-to-back or 'tandem' studies have been performed, but studies of repeat OGD, push enteroscopy and small capsule endoscopy studies in patients with recurrent anaemia suggest an OGD lesion miss rate of 2-28%(115, 177). Missed lesions relate to the speed with which OGD is performed: Park et al. reported a mean examination time of two minutes and 53 seconds, with slow endoscopists (taking more than three minutes) significantly more likely to detect neoplasia (odds ratio 1.52; 95% CI, 1.17-1.97) and Ge et al. achieving a significantly increased yield of high risk lesions by increasing examination time to at least six minutes(146, 181). MACE does not cause gagging, choking or discomfort and patients prefer it to OGD(147), so unlike with OGD, patient tolerance is not a limiting factor in the time needed to perform a high quality examination. Some might feel that a 20 minute MACE examination time is excessive, but outside the context of a clinical trial, experienced operators perform examinations in about 15 minutes(64).

Gastric cancer is commoner in China(64), where MACE was first developed, whereas oesophageal pathology is a greater concern in the West, so whilst diagnostic sensitivity in the oesophagus was similar for MACE and OGD, an adequate visualisation rate of 58.2% needs improvement. This has been addressed by attaching a hollow tether via a sleeve rolled over one end of the capsule which allows the examiner to hold the capsule in the oesophagus after it has been swallowed. Air flushed down the tether blows the capsule out of the sleeve, following which the tether can be withdrawn. This method was shown in a 582 patient, multicentre study to have a 97.5% sensitivity compared to OGD in the detection of oesophagastric varices(182). However, swallowing tether and capsule may be more difficult than capsule alone and excellent oesophageal imaging is possible using a double ended capsule camera capable of 35 frames per second(152). Our previous costing analysis has shown the cost of MACE is twice that of OGD. Further cost comparison analysis is required

which compares upper GI and small bowel examination done in one sitting versus done as two separate procedures.

We have assessed the accuracy of AI-assisted video reading mode versus standard reading (SD) mode in patients with IDA. Using the artificial intelligence software, Proscan, allowed a much quicker and reliable small bowel examination than human expert capsule endoscopy video readers and is likely to be incorporated into upper and lower GI tract capsule endoscopy devices in the future. One of the limitations in further expanding the role of CE is its prolonger reading time which is due to the large number of images which are generated during the procedure. This has shown to cause reader fatigue. Several capsule endoscopy software systems have been developed and tested and have shown a significant reduction in reading times without reducing the diagnostic yield for diffuse mucosal diseases (such as inflammatory bowel disease). This may not be the case for isolated lesions, of which several studies reported an unacceptable miss rate(20-22).

FIT is a routinely used for bowel cancer screening in England and is thought to be more specific for lower GI bleeding(26, 33). Hence in the final study we looked the role of FIT in predicting small bowel pathology in patients with IDA and negative bidirectional endoscopy. Although in this cohort of patients the diagnostic yield on SBCE was high, FIT had a low sensitivity, specificity, PPV and NPV for small bowel pathology at all levels. In previous studies which have shown a positive correlation between FIT and SB pathology(37, 174), FIT has been performed within a week of the CE. Also, the most common small bowel lesions in patients with IDA are angioectasia which was also the most common finding in our study. Further

studies are needed which evaluate the role of FIT in identification of other isolated SB pathology like tumours.

In conclusions the body of work presented in this thesis supports the role of CE in patients with IDA. Symptom-guided approach to investigation: OGD for patients with dysphagia or vomiting, cross sectional imaging for those with obstructive symptoms and capsule endoscopy of upper and mid GI tract for the remainder. Further studies looking at the long term follow up of patients with IDA are required to assess of recurrence and further management in this cohort.

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APPENDICES

APPENDIX-1 STANDARDISED CODING USED FOR ALL IDENTIFIED FINDINGS IN THE GASTROINTESTINAL TRACT

Code	Diagnosis	Bleeding potential – possible entries
01	Small ulcer coated with fibrin	P1 / P2
02	Large ulcer coated with fibrin	P1 / P2
03	Ulcer with haematin spot	P2
04	Ulcer with visible vessel	P2
05	Ulcer with active bleeding	P2
06	Dieulafoy lesion	P2
07	Erosions	P1 / P2
08	Small angioectasia	P1 / P2
09	Medium/large angioectasia	P1 / P2
10	Tumour without ulceration	P1 / P2
11	Tumour with ulceration	P2
12	Polyp	P0 / P1 / P2
13	Polyp with eroded surface	P1 / P2
14	Diverticula	P0 / P1 / P2
15	Multiple diverticulae	P0 / P1 / P2
16	Meckel’s diverticulum	P0 / P1 / P2
17	Small varices	P1 / P2

18	Large varices or varices with red spots	P1 / P2
19	Helminths	P0 / P1 / P2
20	Perforation	P2
21	Stenosis	P0 / P1 / P2
22	Blood or clots	P2
23	Haematin	P2
24	Pseudopolyp	P0 / P1 / P2
25	Red spot	P0
26	Erythema	P0
27	Oedema	P0
28	Petechiae	P0 / P1
29	Absent villi	P0 / P1
30	Nodules	P0 / P1
31	Oesophagitis	P0 / P1 /P2
32	Mallory Weiss tear	P1 / P2
33	Gastric antral vascular ectasia	P1 / P2
34	Portal hypertensive gastropathy	P1 / P2
35	Haemorrhoids	P1 / P2
36	Ulcerative colitis	P1 / P2
37	Crohn’s disease	P1 / P2
38	Segmental (diverticular) colitis	P1 / P2
39	Cystic lymphangiectasia	P0
40	Other (free text for lesion description)	P0 / P1 /P2

APPENDIX-2 DATA COLLECTION FORM USED FOR OGD

2. GASTROSCOPY

Date performed __ / __ / ____

Medications (one or more)

	Dose
Midazolam (mg)	____
Fentanyl (□g)	____
Buscopan (mg)	____

Examination extent

Examination extent: please check ALL areas visualised **adequately**

Oesophagus	Proximal / mid / distal
Stomach	Cardia / fundus / proximal corpus / distal corpus / antrum / pylorus
Duodenum	Duodenal bulb / second part of duodenum

Pathological findings 1:

Code _____ Number of lesions _____

Location:	Organ	Part of organ
	Oesophagus	Proximal / mid / distal
	Stomach	Cardia / fundus / proximal corpus / distal corpus / antrum / pylorus
	Duodenum	Duodenal bulb / second part of duodenum

Bleeding potential (select one)

P0 / P1 / P2

Pathological findings 2:

Repeat all items as for pathological findings 1 above.

Pathological findings 3.

Repeat all items as above

Pathological findings 4 -10

Repeat all items for each as above

APPENDIX-3 DATA COLLECTION FORM FOR COLONOSCOPY

3. COLONOSCOPY

Date performed __ / __ / ____

Medications (one or more; only add if performed on a different day from gastroscopy)

	Dose
Midazolam (mg)	____
Fentanyl (□g)	____
Buscopan (mg)	____

Examination extent

Terminal ileum /caecum/ascending/transverse/descending/sigmoid/rectum

Duration of examination (minutes) _____

Pathological findings 1:

Code _____ Number of lesions _____

Location:	Organ	Part of organ
	Small bowel	Terminal ileum
	Colon	Caecum/ascending/transverse/descending/sigmoid/ rectum

Bleeding potential (select one)

P0 / P1 / P2

Pathological findings 2:

Repeat all items as for pathological findings 1 above.

Pathological findings 3.

Repeat all items as above

Pathological findings 4 -10

Repeat all items for each as above

APPENDIX-4 DATA COLLECTION FORM FOR MAGNET CONTROLLED CAPSULE ENDOCOPY

(STANDARD READ)

Date performed __ / __ / ____

Examination extent: please check ALL areas visualised **adequately**

Oesophagus Proximal / mid / distal

Stomach Cardia / fundus / proximal corpus / distal corpus / antrum / pylorus

Duodenum Duodenal bulb / second part of duodenum

Duration of magnet controlled capsule examination of upper GI tract (minutes) _____

Did the capsule enter the duodenum prior to completion of magnet controlled exam?

Yes/no

Examination extent:

Small bowel Not entered / incomplete/ complete examination to caecum

Duration of small bowel capsule examination (minutes) _____

Time taken to read small bowel video (first duodenal to first caecal image; minutes) _____

Pathological findings 1:

Code _____ Number of lesions _____

Location:	Organ	Part of organ
	Oesophagus	Proximal / mid / distal
	Stomach	Cardia / fundus / proximal corpus / distal corpus / antrum / pylorus
	Duodenum	Duodenal bulb / second part of duodenum
	Small bowel	uncertain (incomplete exam) / 1st tertile / second tertile / third tertile

Bleeding potential (select one)

P0 / P1 / P2

Pathological findings 2:

Repeat all items as for pathological findings 1 above.

Pathological findings 3.

Repeat all items as above

Pathological findings 4 -10: Repeat all items for each as above

APPENDIX-5 DATA COLLECTION FORM FOR AI-ASSISTED CAPSULE READING

Time taken to read small bowel video (first duodenal to first caecal image; minutes) _____

Pathological findings 1:

Code _____ Number of lesions _____

Location:	Organ	Part of organ
	Duodenum	Duodenal bulb / second part of duodenum
	Small bowel	uncertain (incomplete exam) / 1st tertile / second tertile / third tertile

Bleeding potential (select one)

P0 / P1 / P2

Pathological findings 2:

Repeat all items as for pathological findings 1 above.

Pathological findings 3.

Repeat all items as above

Pathological findings 4 -10

Repeat all items for each as above

APPENDIX-6 THE ADAPTED SAURIN CLASSIFICATION

Lesion type	**Bleeding potential**	**Example**
P0	None	Red spots, erythema, diverticuli without blood, polyps without mucosal break, absent villi cystic lymphangictasia
P1	Suspected	Polyps with mucosal break, ulcers and erosions with a clean base, angioectasia with evidence of bleeding, small varices, portal hypertensive gastropathy
P2	High	Actively bleeding angioectasia, ulcers and erosions with blood and haematin staining, tumous, gastric antral vascular ectasia, polyps with blood clot/haematin staining.