Small-Bowel Capsule Endoscopy

Optimising Capsule Endoscopy in Clinical Practice

A thesis submitted to the University of Dublin

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On research carried out with

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Declaration

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Summary

This thesis evaluated three aspects of the clinical application of small bowel capsule endoscopy (SBCE).

The first section looked at the use of the patency capsule in clinical practice and evaluated its limitations. Our retrospective study demonstrated that while patency assessment reduces the risk of capsule retention to almost zero, it has its drawbacks due to the likely excessive false positive rate of the test as it stands, with functional patency confirmed in only 55.3% of patients having the test. We performed a single-centre prospective study of an extended-time protocol, which increased the confirmation of functional patency by 17%, a significant improvement. Still, there is likely room to improve this further.

The second section of this work evaluated completion rates in capsule endoscopy. Completion rates in the literature are heterogeneous, with rates ranging from 64% to 96% (median 80%) [1] Real-time monitoring and prokinetics have been shown to be of value only in patients with risk factors for delayed gastric emptying. Still, they are time-consuming and require the IV administration of prokinetics. Our group has demonstrated the efficacy and drawbacks of the standard approach where the completion rates (90.2% vs 96.3%) and rates of significant findings (37.7% vs 32.5%) were similar in our population with risk factors for delayed gastric emptying who received prokinetics with real-time monitoring in comparison to a control group [2, 3].

Peppermint water has been shown to aid gastric emptying, and in a pilot study, its possible benefit has been demonstrated as an aid to completion in those with risk factors for delayed gastric transit. Here we performed a single centre prospective open-label non-inferiority trial comparing orally administered peppermint water solution versus real time monitoring protocol as an aid to completion of SBCE in patients with risk factors for delayed gastric transit. We demonstrated completion rates comparable to real-time monitoring and a control group without risk factors for delayed gastric emptying. Completion rates overall were high and were similar in the 3 groups 94.7% Peppermint vs 90.7% Real time monitoring vs 95.3% in a control group. All 3 groups met the European Society of Gastrointestinal Endoscopy (ESGE) minimum completion KPI of 80%, with the peppermint and control groups meeting the higher target of >/=95% [1]. Peppermint water solution given at the time of capsule ingestion in patients with risk factors for delayed gastric emptying is equivalent in terms of completion rates to the current standard protocol involving the administration of prokinetics and has advantages, it is safe, well tolerated and reduces patient time in the department.

In the final section of this thesis, we looked at the use of an artificial intelligence-enabled capsule reading platform to aid in the analysis and reporting of small bowel capsules. Capsule reading is a time-consuming and often tedious process with average reading times in the literature ranging between 30–120 minutes [2]. It demands a high level of concentration without distractions to avoid missing pathology [3]. Our study of 40 small bowel procedures has shown; Overall diagnosis correlated 100% between AI

and standard reading. In a per-lesion analysis, AI-assisted reading captured 1268 (98.1%, 95% CI 97.15–98.7) of lesions, while standard reading captured 1114 (86.2%, 95% confidence interval 84.2–87.9), P < 0.001. But most interestingly, mean reading time went from 29.7 minutes with standard reading to 2.3 minutes with AI-assisted reading (P < 0.001), for an average time saving of 27.4 minutes per study. This would be a game changer if further data confirms the software's superiority to human readers for exclusion of normal and duplicate images.

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Dedication

To my wife Karen, whose support, encouragement, and patience have gotten me to this point.

Acknowledgments

This dissertation, submitted for the degree of Doctor of Medicine to the University of Dublin, describes my research work carried out in the School of Medicine Trinity College, the Trinity Academic Gastroenterology group, and the Department of Gastroenterology Tallaght University Hospital under the supervision of Professor Deirdre McNamara.

Firstly, I would like to thank my supervisor, Professor McNamara. I am incredibly grateful to her for allowing me to undertake this MD under her supervision and expert guidance. She has provided invaluable support to me throughout this project and beyond. I will always be in debt for the advice and encouragement she has provided me over these years.

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Finally, a huge thank you to my family, especially my partner in life, Karen. She has shown tremendous support and encouragement throughout my journey in medicine. I am eternally grateful for her continued encouragement.

List of Abbreviations

ACG	American College of Gastroenterology
AI	Artificial Intelligence
ALICE	Active Locomotive Intestinal Capsule Endoscope
CADe	Computer-aided detection
CD	Crohn's Disease
CE	Capsule Endoscopy
CEST	Capsule endoscopy structured terminology
CI	Confidence Interval
CNN	Convolutional neural network
CT	Computed Tomography
DM	Diabetes Mellitus
ECCO	European Crohn's and Colitis Organization
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESGE	European Society of Gastrointestinal Endoscopy
FDA	Food and Drug Administration
FICE	Flexible spectral colour enhancement
GI	Gastrointestinal
GIE	Gastrointestinal Endoscopy
GTT	Gastric Transit Time
HD	High Definition
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome

ICCE	International Conference on Capsule Endoscopy
ICV	Ileocaecal valve
IDA	Iron Deficiency Anaemia
IQR	Interquartile range
ISG	Irish Society of Gastroenterology
IV	Intravenous
JAMA	The Journal of the American Medical Association
KPI	Key performance indicators
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
NSAID	Non-steroidal anti-inflammatory
OR	Odds Ratio
PA	Posteroanterior view
PC	Patency Capsule
PEG	Polyethylene Glycol
PP	Peppermint Protocol
PPV	Positive Predictive Value
RCT	Randomised control trial
RR	Relative Risk
RTM	Real-time monitoring
SB	Small bowel
SBCE	Small bowel capsule endoscopy
SBFT	Small bowel follow-through
SBTT	Small bowel transit time

SD	Standard Deviation
SR	Standard Reading
TAGG	Trinity Academic Gastroenterology Group
UEG	United European Gastroenterology
US	Ultrasound

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Published Papers and Presentations

Part of this thesis has been published and or presented at both national and international meetings as follows:

Published Papers

2 O'Hara F, McNamara D. Capsule endoscopy with artificial intelligence-assisted technology: Real-world usage of a validated AI model for capsule image review. Endoscopy International Open 2023 Oct 11;11(10): E970-E975.

3 O'Hara F, Walker C and McNamara D. Patency testing improves capsule retention rates but at what cost? A retrospective look at patency testing. Frontiers in Medicine 2023 Vol. 10

4 O'Hara F, McNamara D. Small-Bowel Capsule Endoscopy—Optimizing Capsule Endoscopy in Clinical Practice. Diagnostics 2021, 11(11), 2139.

Presentations at National Meetings

1. Capsule endoscopy with artificial intelligence: AI in clinical practice. ISG meeting winter 2022

2. Orally administered peppermint oil solution as an aid to prevent delayed gastric emptying in capsule endoscopy. ISG meeting winter 2022

3. Retrospective Analysis of The Utility of Patency Capsule Prior To Capsule Endoscopy. ISG Winter Meeting 2021

Presentations at International Meetings

1. Audit of the Use of Prokinetics to Improve Completion Rates of Small Bowel Capsule Endoscopy. ESGE Days 2021. O'Hara F, Seminov S, McNamara D.

2. The Use of Bowel Preparation to Improve Diagnostic Yield in Small Bowel Capsule Endoscopy. A Prospective Randomised Nested Case-Control Study of Moviprep Versus Dietary Measures. ESGE Days 2021. O'Hara F, Seminov S, McNamara D.

3. Orally administered peppermint oil solution as an aid to prevent delayed gastric emptying in capsule endoscopy. UEG week 2022 (Moderated Poster Session)

4. Capsule endoscopy with artificial intelligence assisted technology: AI in clinical practice. UEG week 2022

5. Retrospective analysis of the utility of the patency capsule. ESGE Days 2022. O'Hara F, Costigan C, McNamara D

Awards

1. Capsule endoscopy with artificial intelligence: AI in clinical practice.
    - Best Clinical Abstract ISG Winter Meeting 2022

2. Retrospective analysis of the utility of patency capsule prior to capsule endoscopy
    - First Prize - Endoscopy Poster Awards ISG Winter Meeting 2021

Chapter 1 - Introduction

The small bowel is the longest organ within the gastrointestinal tract. Until the turn of the century, it was an obscure area in terms of endoscopic imaging, limited by the distance to which enteroscopes could be pushed into the small bowel. The emergence of small bowel capsule endoscopy (SBCE) has since revolutionized the investigation and diagnosis of small bowel pathology [4] Its utility as a noninvasive and well-tolerated procedure that can be performed in an outpatient setting has made it a valuable tool for the gastroenterologist. However, it was not always thus.

1.1. A brief history of small bowel investigation

The first imaging procedure used to investigate the small bowel was the X-ray. In traditional abdominal X-rays, the small bowel appears in the centre surrounded by the colon. The mucosal folds can be delineated, but the image quality is often poor due to overlapping structures. Consequently, identifying and diagnosing related pathologies is challenging.

A significant advancement in the visibility of various characteristics of the small bowel in an X-ray came with the prior ingestion of a contrast agent, which emphasized specific areas within the acquired images. Bismuth preparations were first used for this purpose at the end of the 19th century but in 1910, Krause, Bachem, and Gunther recommended barium sulphate as a replacement since bismuth was considered too toxic [5]. Barium has two very important properties: it adheres to the small intestine wall and

absorbs X-rays. The small bowel was more visible on the new X-rays, in almost white shades making pathological lesions easier to spot.

The development of CT technology in 1989 led to a new direction regarding imaging investigations, so in the early 90s, CT enterography brought new perspectives on the small bowel. Other radiology techniques without radiation exposure were also used: magnetic resonance imaging, magnetic resonance enteroclysis and enterography, ultrasound or contrast-enhanced ultrasound [6]. These techniques are less invasive and better accepted by patients, but they lack the possibility to perform biopsies.

Endoscopic techniques, such as push enteroscopy, ileocolonoscopy, and intraoperative enteroscopy, are invasive and uncomfortable for patients. Still, from an imaging point of view, they offer real-time images of the small bowel acquired with miniature cameras, not images reconstructed by various techniques, such as radiology investigations [7].

All these investigations have advantages and disadvantages and offer complementary data on the small bowel. But what was missing was an investigation that would allow a complete and accurate visualization of the small bowel.

1.2. A new concept

Endoscopic techniques thus far required a wire, a cable, or a similar physical element that could not be extended enough to cover the entire length of the small bowel.

The next step was to either create a device long enough to traverse the entire small bowel or develop a device small enough to be swallowed by the patient and capture images from inside the gastrointestinal (GI) tract.

In 1981, Gavriel Iddan, an Israeli engineer, together with Eitan Scapa, a gastroenterologist, laid the foundation of what would later become capsule endoscopy. It took 10 years to come up with an initial solution: a small device with a video camera that would take pictures of the inside of the small bowel and an electrical 'umbilical cord' that would provide the power supply [8]. This device was not practical due to the length of the electrical cord needed. Thus, a wireless solution had to be identified.

By 1997, Paul Swain was independently studying the use of mini cameras for the same purpose. He succeeded in sending real-time images from a pig's stomach during an endoscopy to a video screen [9].

By 1997, Iddan and Swain, having joined forces two years earlier, developed the first working prototypes being produced by Given Imaging R&D. In 2000, Iddan and his team performed and reported the first successful studies on animals [4]. Not long afterwards, the first studies performed on humans were also completed in 2001. In the same year, this new device received clearance from the US Food and Drug Administration and thus Given Imaging produced the first wireless capsules for small bowel investigation, PillCam SB [10].

1.3. Clinical Application

The emergence of SBCE in clinical practice in Western countries from about 2005 has since revolutionized the investigation and diagnosis of small bowel pathology [4]. Its utility as a non-invasive and well-tolerated procedure, which can be performed in an out-patient setting, has made it an invaluable tool for the gastroenterologist.

Indications for SBCE include obscure gastrointestinal bleeding, small bowel Crohn's disease (CD), and less frequent screening in polyposis syndromes, celiac disease, or other small bowel pathologies [11]. Several small bowel capsules from different manufacturers are currently on the market; however, they share many technological features and to date remain solely an imaging modality.

1.4. Challenges and Opportunities

Many areas related to capsule endoscopy still feature a degree of uncertainty as to how to optimize performance. The European Society of Gastrointestinal Endoscopy (ESGE), as late as 2018, published technical guidance on the optimal use of SBCE [2] and has only recently developed a set of performance measures to guide quality standards in this area [1].

The risk of capsule retention, incomplete studies due to slow transit, and poor imaging secondary to inadequate preparation continue to frustrate its optimum clinical appli-

cation. Other challenges SBCE face is the risk of missed pathology due to the subtle nature of lesions and the often-fleeting images of pathology obtained as well as the time commitment required to accurately read the capsule videos.

1.5. Capsule Retention

Capsule retention is defined as the identification of a capsule on abdominal radiological imaging ≥ 14 days after capsule ingestion or the need for its surgical removal due to small bowel obstruction [12]. It remains a feared complication during capsule endoscopy. The identification of risk factors at patient triage and the use of the patency capsule (PC) have ameliorated this risk.

1.5.1. Risk Factors/Rates

We now possess a good understanding of the risk factors associated with capsule retention. The presence of a combination of symptoms suggestive of bowel obstruction (abdominal pain, abdominal distension, and nausea/vomiting) before capsule endoscopy is associated with a significantly higher rate of capsule retention [13-15]. Furthermore, previous small-bowel resection, abdominal/pelvic radiation therapy, an established diagnosis of Crohn's disease and the chronic use of high-dose nonsteroidal anti-inflammatory drugs (NSAIDs) have all been shown to increase the risk of capsule retention [13, 14, 16].

The most cited meta-analysis of capsule retention rates stated that retention occurs in approximately 2% of patients undergoing evaluation for small-bowel bleeding and between 4% and 8% in patients with suspected or known IBD [17]. This analysis likely overestimates the real-world retention rate in CD as it excluded studies that performed small bowel patency assessments routinely. Indeed, these rates decreased by half in those studies that used either a patency capsule or CT enterography to assess patency before performing CE [17].

Wang's 2020 systematic review of 108,079 capsule endoscopy procedures showed a retention rate of 0.73% (Table 1.1). The retention rate (coefficient = −0.34%, 95%CI −0.53 to −0.14%, $p = 0.0006$) decreased significantly over the 20 years examined due to improved patient selection and the use of the patency capsule. The incomplete examination rate of SBCE also significantly declined over time ($p < 0.0001$). As to the causes of capsule retention, CD was the most common retention reason (35.4%). Among the 766 retained capsules, surgery was the most frequently used intervention ($n = 352$, 45.9%), followed by endoscopic management ($n = 199$, 25.9%), no intervention ($n = 176$, 22.9%), and medical therapy ($n = 39$, 5.0%) [18]. Although there was no significant change in time-trend analysis of retention interventions, surgery had a downward trend and other interventions had upward trend. The very high surgical rate in this meta analysis and the other large meta analysis where a rate of 57% of capsule retentions underwent surgical management is multifactorial. Not all were due to the development of obstructive symptoms. Indeed both authors commented that it was difficult to determine whether a decision for surgical management was due to expertise at the study center, availability of endoscopic

method of capsule retrieval, or the need to avoid possible future adverse events from a retained capsule [17, 18].

When capsule retention does occur, it is usually asymptomatic [17], and the capsule can remain in the small bowel without symptoms for prolonged periods or be naturally egested during subsequent follow-up [19]. In a recent population study, only 1.9% of 104 capsule retentions developed into symptomatic bowel obstruction [19]. Thus, conservative observation is justified for the management of capsule retention in the majority of cases unless malignancy is strongly suspected. During this period, targeted treatment with medications (including corticosteroids as appropriate) may promote capsule egestion in up to 20–30% of patients with capsule retention [2]. The ESGE recommends observation in cases of asymptomatic capsule retention. In cases where capsule retrieval is indicated, they recommend device-assisted enteroscopy as the method of choice [2].

Table 1.1. Rates of capsule retention and trend over time [27]

(n = 108,079)	**Rate**	**95% CI**
Pooled Retention Rate	0.73%	0.59%–0.89%
Established CD	4.29%	1.46%–7.12%, (p = 0.0029)
Retention Post-Patency Assessment	0.09%	0.00%–0.34%

1.5.2. Patency Assessment

Patency capsule testing and dedicated small-bowel cross-sectional imaging techniques have both been found to be effective at assessing patency of the small bowel (see Table 1.2) [20, 21]. In a meta-analysis of patency capsule usage, which included five

Table 1.2 Key Comparison Studies between PC and Radiographic or Other Cross-Sectional Imaging Methods

Author, Year	Diagnostic Comparison	Patients with Intestinal Stenosis, n	Patients with Successful PC Test, n (%)	Patients with Retained PC, n (%)	Capsule retention after successful PC n (%)
Herrerías JM, 2008 [23]	CT, SBFT	106	59 (56%)	47 (44%)	none
Spada C, 2005[20]	SBE, SBFT, colonoscopy	34	20 (67%)	14 (33%)	N/A
Boivin ML, 2005[24]	SBFT, CT, Mrec	22	13 (59%)	9 (41%)	none
Rozendorn N, 2016[25]	Mreg	30	18 (76%)	12 (24%)	none
Yadav A, 2011[26]	CT, Cteg,MRI, SBFT	42	33 (78.6%)	9 (21.4%)	none

CT, computed tomography; eg, enterography; ec, enteroclysis; MR, magnetic resonance; MRI, magnetic resonance imaging; N/A, nonapplicable; SBE, small bowel enteroclysis; SBFT, small bowel follow-through.

studies and 203 patients, the pooled data showed a patency capsule sensitivity of 97% (95%CI 93–99%) and a specificity of 83% (95%CI 65–94%) [22].

As stated previously, retention rates are falling. Compared with a 2010 study, Wang et al.'s 2020 systematic review detected a lower pooled retention rate of 0.73% vs. the 1.4% rate seen previously [14, 18].

This could be attributed to the usage of patency capsules, which predicts small bowel strictures in patients at high risk for retention. The patency capsule is a dissolvable dummy capsule that first appeared in 2005 due to deficiencies in radiological imaging techniques, including MRI and CT, to predict the functional patency of the gastrointestinal tract during capsule endoscopy [20]. The patency assessment procedure involves the ingestion of the dummy capsule with follow-up assessment for its intact passage, thus

confirming whether an object the size of a capsule can pass through the patients intestine [20]. Wang's systematic review showed a retention rate after negative patency testing of 0.09%, and patency testing demonstrated a significantly decreased retention rate by 5.04% in multivariate meta-regression [20]. These findings and others confirm that performing an initial patency capsule test before SBCE in patients with a high retention risk is useful in avoiding retention [18].

In studies published over the past five years, where assessment for patency was the standard procedure, retention rates in patients with established CD were much lower (up to 2.5%); indeed, in the largest study to date of 343 CE procedures performed in patients with established CD, a retention rate of 2.3% was observed [40].

The evaluation of small bowel patency in patients with established CD utilizing a patency capsule or imaging is now the standard practice endorsed by the recent European Crohn’s and Colitis Organization (ECCO)/ESGE guidelines [2].

However, ESGE does not recommend offering a patency capsule procedure indiscriminately to all patients undergoing capsule endoscopy [2]. The rates of positive patency tests range from 30% to 43% in published data [27, 28]. These rates are far higher

than any retention rates seen in real-world SBCE data, indicating a high false positive rate with this test. Thus, the overuse of patency capsules results in the follow-on exclusion of patients who may have benefited from the test.

SBCEs after positive patency tests have been shown to have high retention rates: In 18 patients who underwent SBCE after a positive patency capsule test, a retention rate of 11.1% was seen [22]. Although this was a high result, the real capsule was still passed on 89% of positive patency tests.

Are there ways of reducing the rates of "false positive" patency tests without affecting the retention rates? Extending the time for confirming functional patency up to 72 hours only in cases in which an intact capsule or intact body of PC is observed directly may be acceptable. It may enhance the probability of performing CE safely. A recent Japanese study looked at this and in 6 of 19 patients (31.6%) in whom patency was not confirmed at 30 hours, patency was confirmed within 72 hours and no capsule retention occurred [29].

Great strides have been made in reducing the rate of capsule retention over the last twenty years (Table 1.3). Refining the use of the patency capsule with further study will hopefully help to reduce the exclusion of patients from capsule endoscopy unnecessarily.

Table 1.3. Trends in retention rates (data from Wang et al. [18]).		
(n = 108,079)	**Co-Efficient**	**95% CI**
Retention Reduction Post-Patency	−5.04%	−8.75% to −1.33%, (p = 0.0077)
Trend in Retention Rates 2006-2016	−0.34%	−0.53 to −0.14%, (p = 0.0006)

1.5.3. Procedural Issues

1.5.3.1. Small Bowel Preparation

Bowel preparation remains an area of much debate in SBCE. Given Imaging, the manufacturer of the first capsules did not recommend preprocedural purgative use for SBCE; the only recommended requirements were a low-fiber diet the day before the procedure with clear liquids only in the evening and a 12-hour fast. ESGE recommends a modified diet pre-procedure, as well as the ingestion of 2 L of a PEG-based purgative to improve visualization [2]. Several meta-analyses have concluded that 2 L of PEG solution before capsule ingestion improves the visibility of the small bowel, but the question of whether this improves completion rates and diagnostic yield is still inconclusive, and the optimal timing of the purgative's use is unclear [30, 31]. The largest published meta-analysis showed that in comparison with a clear-liquid diet, purgative bowel preparation did not increase the diagnostic yield (RR 1.17 (95%CI 0.97 to 1.40); p = 0.11), the quality of small-bowel mucosal visualization (RR 1.14 (95%CI 0.96 to 1.35); p = 0.15) nor the completion rate for the examination (RR 0.99 (95%CI 0.95 to 1.04); p = 0.76) [32].

The most recent meta-analysis looking at bowel preparation for small bowel capsule endoscopy which looked at purgative preparation schedules including day-before,

split and same-day preparation protocols showed fasting alone vs overall purgative preparations a pooled rate difference (RD) of 0.15 I2=81.5% p: 0.000.

Sub-analysis for preparation schedule (day-before, split and same-day) and the time lapse showed that administration of PEG after the ingestion of the capsule had the highest rate of adequate small bowel cleansing with an RD 0.33, administration between 1 and 6 h before SBCE had an RD 0.28, 6 to 12 h had an RD 0.21 and ≥12 h had an RD 0.05. However, despite improved views an improvement in diagnostic yield was not demonstrated[33].

1.5.3.2. Anti-Foaming Agents

Three RCTs have demonstrated that anti-foaming agents improve the quality of mucosal visualization, and two meta-analyses have concluded that simethicone significantly decreases the presence of small-bowel bubbles/foam [30, 34]. There is no consensus on the optimal dose of simethicone, with ranges between 80 to 200 mg used [30]. A recent trial of high-dose simethicone (1125 mg in 750 ml of water) did not show any benefit for the high dose versus a standard dose of 300 mg [35]. ESGE recommends anti-foaming agents before capsule ingestion [2].

1.5.3.3. Diving Method

The ingestion of 500 mL of water every hour, administered after the capsule reaches the small bowel [36] has shown endoscopic images in the proximal third and middle third of the small bowel in the "diving group" were significantly higher than those in the control group (3.47 ± 0.60 vs. 3.11 ± 0.63 (p = 0.007) and 3.24 ± 0.59 vs. 2.78 ± 0.74 (p = 0.002), respectively). The diagnostic yield in the distal third of the small bowel was significantly higher in the "diving group" (p = 0.005), as was the overall completion rate (92.19% vs. 76.32%, respectively; p = 0.012). However, disappointingly, the lesion detection rates were similar in the two groups (p = 0.577). No adverse events were reported, except complaints of frequent urination from 5 patients out of 64 [36].

1.5.3.4. Prokinetics/Real-Time Viewer

The major cause for incomplete examination of the small bowel is prolonged gastric transit time [37]. Prokinetics have been used to aid the passage of the capsule from the stomach to the small bowel. But prokinetic use alone is ineffective at increasing SBCE completion rates [38]. However, patients with risk factors for an incomplete SBCE study (i.e., those with previous history of abdominal surgery, delayed gastric emptying, diabetic neuropathy, severe hypothyroidism, or use of psychotropic drugs) may benefit from the administration of certain prokinetics (metoclopramide, domperidone or erythromycin) when the capsule remains in the stomach for more than 30–60 min, as confirmed by real-

time monitoring [38]. The ESGE recommends prokinetic usage/or endoscopically assisted capsule delivery into the duodenum in patients for whom delayed gastric emptying has been confirmed by real-time monitoring [2].

A prospective study from Japan compared SBCE in 80 patients with or without real-time viewing. If the capsule remained in the stomach for more than 60 min in the real-time viewing group, a prokinetic was administered, followed by PEG. The completion rate in the real-time viewing group was significantly higher than in the control group (90% vs. 72.5%) [39]. A further Japanese study [40] compared the proportion of completed exams and positive findings among a group of patients studied before the introduction of real-time viewing and a group in which capsule transit was regularly monitored, and action was taken (the administration of water or IV metoclopramide) if it was delayed. Using a real-time viewer increased the SBCE completion rates from 66% to 86% ($p = 0.002$). Our group has also demonstrated similar data, where the completion rates (90.2% vs. 96.25%, p = 0.825) were similar in our at-risk population who received prokinetics for delayed gastric emptying compared to a control group without risk factors [41]. There were no serious adverse events in the prokinetic group, but 7% of patients reported side effects including nausea, dizziness, and pain at the cannula site. A significant (15%) proportion were administered a second prokinetic, increasing the potential for adverse events, given that using metoclopramide and erythromycin as prokinetics can pose a significant risk of cardiac adverse effects in elderly cohorts.

Alternative prokinetic interventions would be advantageous given the possible adverse effects of commonly used prokinetics as well as the time and resources needed

for real-time monitoring. Peppermint has been shown to function as a prokinetic when administered orally and provides a possible alternative to IV-administered medications [42].

1.6. How Should Capsules Be Read/The Introduction of Artificial Intelligence

1.6.1. Who

The reading of capsule studies is time-consuming, with a mean reading time of 45–60 min [43, 44]. This raises the question of who the most appropriate person is to read these studies. Previous evidence confirms that, with adequate training, nurses and/or other technical staff can identify pathology as well as physicians [45, 46]. The ESGE recommends the acceptance of qualified nurses and trained technicians as prereaders of capsule endoscopy with the important caveat that “the responsibility of establishing a diagnosis must remain with the treating physician” [2]. The ESGE has agreed on the suggestion that a minimum of 30–50 SBCEs is required to acquire proficiency and that 30–50 procedures per year are needed to maintain competence[2]. The ESGE has also developed a curriculum for training in small-bowel endoscopy[47].

1.6.2. How

ESGE recommends a maximum reading speed of 10 frames per second (less in the proximal small bowel) for SBCE. Double- and multiple-view modes, if available, at a maximum speed of 20 frames per second have also been shown to be acceptable [2]. Imaging

enhancing modes, collectively known as virtual chromoendoscopy, such as FICE “blue mode” and ALICE, have shown no benefit over white light imaging to date and are not recommended for routine usage [48, 49].

1.6.3. The Future

Capsule endoscopy appears to be ideally suited to machine learning and artificial intelligence, as in its current guise it entails pattern recognition from still images. As technology improves, this offers the potential to speed up reading times by eliminating normal images, removing near-identical images, and, in the future, recognizing and identifying pathology. Indeed, in a recent meta-analysis of 19 retrospective studies, deep learning applications for capsule endoscopy detection accuracy were above 90% for most studies and diseases [50]. The pooled sensitivity and specificity for ulcer detection were 0.95 (95% confidence interval [CI], 0.89–0.98) and 0.94 (95%CI, 0.90–0.96), respectively. The pooled sensitivity and specificity for bleeding or bleeding sources were 0.98 (95%CI, 0.96–0.99) and 0.99 (95%CI, 0.97–0.99), respectively (Table 1.4). However, these retrospective studies featured an elevated risk of bias and further, larger-scale prospective studies are required to raise confidence in their clinical utility. Early prospective data point to comparable results in the real-world application of some of these technologies. AI mode showed a sensitivity, specificity, NPV, and PPV of 94.6%, 100%, 83.3%, and 100%, respectively, in a 48-patient prospective study of a Mirocam Express view system published as an abstract. The mean reading time was 84.13 ± 53.63 min in the standard arm and 14.79 ± 11.2 min in the Express View arm ($p < 0.001$) [51].

The use of machine learning for the detection of multiple pathologies and lesion localization in SBCE is also under investigation, with continuing improvements refining the technology [52, 53].

The assessment of bowel preparation quality is another area where computer algorithms are likely to be extremely useful. Currently, the main issue with the assessment of preparation quality and the various scores used is that they are operator-dependent and time-consuming [54]. Indeed, a universally accepted scale for grading small-bowel cleansing is still lacking. The available grading systems feature different technical characteristics, assessing different parameters and portions of the video. The ESGE does recommend that Brotz and Park scores should be used for SBCE [1].

To date, studies have used computer-generated scores using red-to-green pixel ratios that correlate well with operator-dependent scores. The concept of the R/G ratio is based on the principle that properly visible mucosa are associated with red colours, whereas a faecal-contaminated lumen is associated with green colours. In a study by Ali et al., their small bowel computer assessment of cleaning score demonstrated a sensitivity of 91.3% and a specificity of 94.7% compared to an experienced reader's score assessing adequate small-bowel visualization [55].

Table 1.4. Deep learning for detecting bleeding/bleeding sources and ulcers in capsule endoscopy (data from Soffer et al. [49]).

Bleeding/Bleeding Source	Sensitivity (95% CI)	Specificity (95% CI)	Ulcer Detection	Sensitivity (95% CI)	Specificity (95% CI)
Aoki et al., 2019[56]	0.99 (0.96–1.00)	1.00 (1.00–1.00)	Alasker et al., 2019[57]	1.00 (0.95–1.00)	1.00 (0.86–1.00)
Jia et al., 2017[58]	0.91 (0.84–0.96)	0.98 (0.97–0.99)	Aoki et al., 2019[56]	0.87 (0.83–0.90)	0.91 (0.90–0.91)
jia et al., 2017[59]	0.99 (0.98–1.00)	1.00 (0.99–1.00)	Fan et al., 2019[60]	0.97 (0.95–0.98)	0.95 (0.94–0.96)
Leenhardt et al., 2019[61]	1.00(0.99–1.00)	0.98 (0.93–0.98)	Klang et al., 2019[62]	0.98 (0.97–0.98)	0.97 (0.97–0.97)
Tsuboi et al., 2019[63]	0.99(0.97–1.00)	0.98 (0.98–0.99)	Wang et al., 2019[64]	0.90 (0.89–0.91)	0.90 (0.89–0.91)
Pooled Estimate	0.98 (0.96–0.99)	0.99 (0.94–0.99)	Pooled Estimate	0.95 (0.89–0.98)	0.94 (0.90–0.96)

Goals of this dissertation

The overall objectives of this dissertation are to examine current practice of small bowel capsule endoscopy both globally and locally and to further research the optimisation of technical aspects of SBCE in the following areas:

i) Patency Capsule

   (1) Retrospective analysis of the current use of the patency capsule in SBCE.

   (2) Prospectively investigate the role of an extended patency assessment to improve the pass rate of the patency assessment.

ii) Prokinetics

   (1) Retrospective analysis of the current usage of prokinetic and their effect on completion rates.

   (2) Prospective analysis of the use of Peppermint water as a novel prokinetic in SBCE.

iii) Artificial Intelligence in SBCE

Chapter 2. Patency Testing

2.1. Introduction

Adverse events in SBCE are a relatively infrequent occurrence. The most serious of these is capsule retention, which is defined as the identification of a capsule on abdominal radiological imaging ≥ 14 days after capsule ingestion, or the need for its surgical removal due to small bowel obstruction [2].

The patency capsule is a dissolvable dummy capsule that first appeared in 2005 due to deficiencies in radiological imaging techniques including MRI and CT to predict the functional patency of the gastrointestinal tract during capsule endoscopy [20]. These techniques are associated with a high radiation dose, and false−negative results may emerge in patients with obstruction, especially when intermittent or is partial.

A recently published meta-analysis showed that the capsule retention rate was 2.1% for patients with suspected small-bowel bleeding (95%CI 1.5%– 2.8%) and 2.2% (95%CI 0.9%–5.0%) for those having evaluation because of abdominal pain and/or diarrhoea [17]. The retention rate for patients with suspected IBD was 3.6% (95%CI 1.7%– 8.6%), and for patients with established IBD was 8.2% (95%CI 6.0%–11.0%) [17]. Capsule retention is usually asymptomatic and can be egested during follow-up but there is a risk of bowel obstruction and the need for surgery or endoscopic intervention for its removal [19, 65]. It remains the feared complication during capsule endoscopy.

We now possess a good understanding of the risk factors associated with capsule retention. [18]The presence of a combination of symptoms suggestive of bowel obstruction (abdominal pain, abdominal distension, and nausea/vomiting) before capsule endoscopy is associated with a significantly higher rate of capsule retention [13-15]. Furthermore, previous small-bowel resection, abdominal/pelvic radiation therapy, and the chronic use of high-dose nonsteroidal anti-inflammatory drugs (NSAIDs) and a previous diagnosis of Crohn's disease have all been shown to increase the risk of capsule retention [13-15].

The most cited meta-analysis of capsule retention rates published in 2017 showed retention occurs in approximately 2% of patients undergoing evaluation for small-bowel bleeding and between 4% and 8% in patients with suspected or known IBD [17]. This analysis likely over-estimates the real-world retention rate in IBD as it excluded studies that performed small bowel patency assessments routinely. In this meta analysis rates decreased by half in those studies that used either a patency capsule (PC) or CT enterography to assess patency before performing CE [4].

Wang's 2020 systematic review of 108,079 capsule endoscopy procedures showed a retention rate of 0.73% [18]. The retention rate (coefficient = −0.34%, 95%CI −0.53 to −0.14%, p = 0.0006) decreased significantly over the 20 years examined due to improved patient selection and the use of PCs. As to the causes of capsule retention, CD was the most common retention reason (35.41%). Among the 766 retained capsules, surgery

was the most frequently used intervention (n = 352, 45.95%), followed by endoscopic management (n = 199, 25.98%), no intervention (n = 176, 22.98%), and medical therapy (n = 39, 5.09%) [18].

The evaluation of small bowel patency in patients with established CD using a PC or imaging is now the standard practice endorsed by the recent ECCO/ESGE guidelines [66].

While capsule endoscopy after failed patency tests has been shown to have high retention rates (in 18 patients who underwent SBCE after a failed PC a retention rate of 11.1% was seen [27]) The real capsule was still passed by 89% of those who failed their patency tests. Thus, there is a risk of overuse of the PC; indeed, ESGE does not recommend offering a PC procedure indiscriminately to all patients undergoing capsule endoscopy [2].

2.2. Patency Retrospective Study

While it is proper to err on the side of caution, denying access to capsule endoscopy to a significant proportion of patients unnecessarily based on a false positive test could also negatively impact patient care and warrants further examination and the development of strategies to reduce its occurrence. The aim of this study was to retrospectively evaluate the real-world use of the patency capsule to assess its benefits and limitations.

2.2.1. Materials and Methods

We performed a retrospective study to evaluate patients who were referred for capsule endoscopy over a period of 12 months from July 2020 to July 2021 in our capsule endoscopy service. All patients referred for capsule endoscopy who underwent patency assessment were included. Patients referred for capsule endoscopy were pre-assessed for risk factors for retention. Risk factors for retention were previous abdominal surgery, known CD, long-term or high-dose NSAID use, known GI obstruction, and previous capsule retention. Those with at least one risk factor were sent for patency assessment prior to capsule endoscopy.

The Pillcam Patency Capsule (Medtronic, Dublin, Ireland) was used for the patency assessment. This is the same shape and size as the Pillcam SB3 small bowel capsule but has a soluble body consisting of lactose-containing 10% barium sulphate covered with an impermeable film coating. Intestinal fluid enters via 2-timer plugs, and the capsule begins to dissolve by 33 h after oral administration. Retention of the PC in the intestine is designed to result in complete disintegration of the capsule body leaving behind only the impermeable film coating, which can then pass through narrow stenotic areas.

All patients were consented prior to the procedure. The PC was ingested with water. Patients were free to have any food before and after PC ingestion. No prokinetic medications were used as part of the protocol.

The definition of the confirmation of functional patency of the GI tract was that the PC passed out of the body intact within 28 hours. Patients who self-reported passage of intact capsules in their stool were deemed to have functional patency. Those who didn't report capsule passage had a plain film abdominal x-ray, which was examined for the presence of a capsule within the GI tract. Evidence of a capsule remaining in the GI tract was deemed as not having functional patency. This was due to the difficulty in device localization on a 2-dimensional abdominal X-ray. If the PC was not observed on the x-ray at 28 hours, the intact PC was considered to have been excreted from the body without the patient's knowledge, confirming functional patency of the GI tract. Abdominal ultrasound, tomosynthesis, and computed tomography (CT), including low-dose CT scans, were not used to assess the PC location in this study.

Patients with confirmed functional patency went forward for capsule endoscopy. The primary endpoint was the capsule retention rate in patients who had confirmed functional patency by PC. Secondary endpoints were the rates of confirmed functional patency and by what means (self-reported or via radiology), small bowel transit time (SBTT) on follow-up capsule, and adverse events.

Statistical Analysis

The results are reported using descriptive statistics (median and interquartile range) for patient characteristics. Comparisons between groups were made using the

Mann-Whitney U test, chi-square test (if needed, with Yates' correction) or Fisher's exact test as appropriate. Differences at $p < 0.05$ were considered to be significant.

2.2.2. Results

2.2.2.1. Demographics

1127 patients who were referred for capsule endoscopy in our unit over 12 months from July 2020 to July 2021 were included. At preassessment, 169 (15%) patients were deemed to have a risk factor for capsule retention and were sent for patency assessment.

Table 2.1 Study Population Demographics

	n = 169
male, no. (%)	77, (45.6%)
female, no. (%)	92, (54.4%)
age (IQR)	48.2 years (34.7 – 64.3)
Indication for Capsule Endoscopy	
Suspected CD	84 (49.7%)
CD Assessment	37 (22.5%)
IDA	29 (17.7%)
GI bleeding	4 (2.4%)
Other	13 (7.7%)

Of this group with risk factors for retention, 77 were male (45.6%) with a mean age of 48.2 years (Table 2.1). This mean age was lower than the overall cohort of 1127 patients referred for capsule endoscopy which had a mean age of 60 (SD +/- 18.1).

The indication for capsule endoscopy in the patency assessment group was a history of CD in 49.7% and suspected CD in 22.5%. Iron deficiency anaemia and GI bleeding were the most common other causes, at 17.7% and 2.4%, respectively (Table 2.1).

2.2.2.2. Retention Rates

In those patients who passed the patency assessment and went forward to capsule endoscopy (n=84), no patient experienced capsule retention. 82 patients had a complete small bowel study, while in one patient, the capsule stayed in the stomach for the entire duration of the study, and a second patient had incomplete small bowel imaging. Both had asymptomatic passage of the capsule on radiological assessment after 14 days.

In our entire cohort of patients who had capsule endoscopy during the period of analysis (n =761), only one confirmed case of capsule retention was recorded, giving a retention rate of 0.13%. This patient did not have a patency test as was not deemed to have a risk factor for capsule retention on pre-assessment. While asymptomatic from the retained capsule, they went on to have a surgical resection of a complex small bowel diverticulum, which was felt to be the cause of their original symptoms.

2.2.2.3. Indication for Patency

When the indication for patency assessment was reviewed, it was found to be appropriate in 87.0% (n=147) compared to ESGE guidelines (Table 2.2) [2]. Of the 13.0% that fell outside guidelines, 81.8% (n=18) were for suspected CD, while a further 4 had no clear indication documented.

Table 2.2. Indication for Patency

	n = 169	
Valid Indication	**147**	**(87.0%)**
Previous Abdominal Surgery	51	(30.2%)
Known CD	37	(21.9%)
Radiological findings	20	(11.8%)
Long term NSAID use	20	(11.8%)
Endoscopic findings	9	(5.3%)
Obstructive Symptoms	9	(5.3%)
Previous Abdominal Radiation	1	(0.6%)
Invalid Indication	**22**	**(13.0%)**
Suspected CD	18	(10.6%)
None documented	4	(2.4%)

2.2.2.4. Patency Assessment Results

Of 169 patients referred for patency 152 had the procedure. Of the 17 who did not have the test, 10 did not attend and were returned to the referring physician, 4 declined the test and 3 were still awaiting the test at time of analysis.

Functional patency was confirmed in 55.3% (n=84) of these. 8.3%(n=7) of patients reported passage of intact capsule within 28 hours, while in 91.7%(n=77), the passage was confirmed via abdominal x-ray.

There was no statistically significant difference in confirmed patency rates between sexes. While those aged over sixty had a significantly lower patency rate. (41.5% vs 60.4%, p = 0.0442) (Table 2.3).

Table 2.3. Patency Rates by Age, Sex

	n	% of total	Confirmed patency	Unconfirmed patency	Patency Rate	*p-value*
Male	70	46.1%	42	28	60.0%	
Female	82	53.9%	42	40	51.2%	0.3271
Age </=60	111	73.0%	67	44	60.4%	
Age > 60	41	27.0%	17	24	41.5%	0.0442

Patency rates, when analysed by risk factors for retention at pre-assessment, showed some variability. However, the only risk factor to show a statistically significant variation was known CD, which interestingly showed a higher patency rate than the group (72.7% vs 55.3%, p = 0.0292). (Table 2.4) This, we believe, is likely due to selection bias, as patients with known complex CD aren't referred for capsule endoscopy due to the perceived risk of retention in this group. The rates were similar between those with a valid vs. invalid indication for patency assessment using ESGE guidelines (55.6% vs 52.6%, p = 0.8106) [2].

Table 2.4. Patency Rates by Indication

	n	% of total	Con-firmed patency	Uncon-firmed patency	Patency Rate	Univariate analysis, *p* value
Previous Abdominal Surgery	42	27.6%	21	21	50.0%	0.4680
CD	33	21.7%	24	9	72.7%	0.0292
NSAIDs	19	12.5%	11	8	57.9%	1.0000
Radiological Findings	20	13.2%	7	13	35.0%	0.0573
Endoscopic findings	8	5.3%	4	4	50.0%	1.0000
Obstructive symptoms	9	5.9%	7	2	77.8%	0.1888
Radiation (Ab-dominal/Pelvic)	2	1.3%	0	2	0.0%	0.205
Suspected CD	16	10.5%	9	7	56.3%	1.0000
None documented	3	2.0%	1	2	33.3%	0.5869
Total, n (% of total)	152	100%	84	68	55.3%	

2.2.2.5. Adverse Events

Two patients (1.2%) reported abdominal pain and bloating during the patency test. Both were managed conservatively and had passed the PC on radiological assessment at 28 hours. Both were excluded from capsule endoscopy and were referred for radiological small bowel imaging.

2.2.2.6. Capsule Endoscopy Results

50.0% (n=42) of patients who proceeded to capsule endoscopy had clinically significant findings on their test (Table 2.5). Enteritis/Ileitis was the most common finding, seen in 34.5% (n=29). The mean SBTT was 241 minutes (SD +/- 135 minutes).

Table 2.5 Capsule findings post patency

	n	
Normal Study	42	50.0%
Enteritis/ileitis	29	34.5%
Angiodysplasia	2	2.4%
Duodenitis	3	3.6%
Small bowel polyp	2	2.4%
Colonic polyp	2	2.4%
Submucosal bulge	1	1.2%
Meckel's Diverticulum	1	1.2%
Gastric Retention	1	1.2%
Incomplete study	1	1.2%

2.2.3. Discussion

Current imaging techniques can identify long or medium stenosis of the GI tract with associated luminal narrowing. However, short stenoses are difficult to exclude by standard imaging methods. There have been many reported cases of capsule retention in patients who had prior radiological imaging that failed to diagnose short intestinal strictures that were clearly identifiable on capsule endoscopy.[67] Pennazio et al. also reported that capsules were retained in 5 of 100 patients with obscure GI bleeding [68]. None of these patients had small bowel strictures based on previous small bowel follow-through (SBFT). Conversely, no retention of diagnostic capsule endoscopy was seen in 10 patients who had strictures previously confirmed by radiological evaluation [13]. As such patency capsule has become a recognised gold standard for the assessment of luminal patency prior to capsule endoscopy [1].

In this retrospective study, we assessed our current use of the PC and evaluated its real-world utility in reducing capsule retention rates in SBCE. In our unit, with preassessment for risk factors for capsule retention a retention rate of 0.14% was found. This is low compared to published data; indeed, the largest meta-analysis showed that the capsule retention rate was 2.1 % for patients with suspected small-bowel bleeding (95%CI 1.5%– 2.8 %) while for established inflammatory bowel disease, the rate reached 8.2 % (95 %CI 6.0 %– 11.0 %) [17].

In our study, 84 patients with confirmation of patency safely underwent capsule endoscopy without retention. 50.0% of these patients who underwent the SBCE procedure had clinically significant findings. Therefore, this study demonstrated that the PC can allow us to carry out SBCE safely and effectively in patients at an increased risk for capsule retention.

Radiological localization of the PC in those patients who don't self-report passage within 28 hours was only available by plain film x-ray. Given the difficulty in accurately localizing within the colon against the small bowel on this modality, any visualized capsule was deemed unconfirmed functional patency. 44.7% of patients failed the patency assessment by these criteria. This compares to a recent meta-analysis where failure rates of between 21.4 and 44% were seen. [69]

Preferably, CT or X-ray tomosynthesis would have been used, but resource limitations prevented this routine usage. Thus, 43.1% is likely to contain a high number of false positives.

This data has several limitations. The subjects were consecutive patients in clinical practice, but the clinical data were retrospectively collected at a single referral centre. Guidelines for using the PC were based on ESGE technical guidance; however, some patency studies were performed that fell outside these criteria, or the indication was unclear.

The high false positive rate is likely related to procedural aspects of the test, which warrants further investigation to avoid the unnecessary exclusion of patients from capsule endoscopy.

2.3. Extended time protocol to improve rates of confirmed functional patency with the patency capsule. A prospective study.

2.3.1. Introduction

Given the findings of in our retrospective data from the use of the PC detailed above we performed a prospective study of an extended patency protocol in order to improve rates of the confirmation of functional patency without increasing the risk of capsule retention.

Previously published data from a single study has suggested that patient-reported passage of an intact capsule up to 72 hours post-ingestion was safe for confirmation of functional patency [33].

2.3.2. Materials and Methods

We performed a single-centre prospective open-label study over 6 months from January to July of 2023. Ethical approval for the study was obtained from the Joint Research Ethics Committee of Tallaght/St James Hospital. All patients over the age of 18 referred for capsule endoscopy deemed to have at least one risk factor (in accordance with ESGE guidance) for capsule retention at preassessment were enrolled. Risk factors for retention were previous abdominal surgery, known CD, long-term or high-dose NSAID use, known GI obstruction, previous capsule retention, and obstructive symptoms [9]. Patients were consented before the procedure and advised of the protocol.

2.3.2.1. Procedure

The Pillcam Patency Capsule (Medtronic, Dublin, Ireland) was used for functional patency assessment. The PC was ingested with water on the morning of the assessment. No fasting was required before the procedure, and no prokinetic medications were used as part of the protocol.

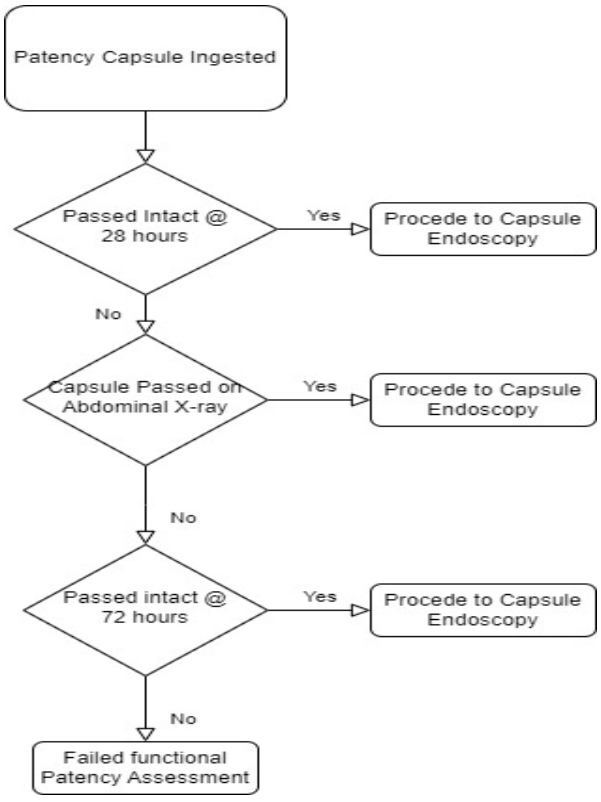
The definition of confirmed functional patency of the GI tract was that the PC passed out of the body intact within 28 hours. Patients who self-reported passage of an intact capsule in their stool by 28 hours post-ingestion were deemed to have functional patency. Those who didn't report capsule passage had a plain film abdominal X-ray. If the PC was not observed on the x-ray at 28 hours, the intact PC was considered to have

been excreted from the body without the patient's knowledge, confirming functional patency. Any individual with radiological evidence of a capsule remaining in the GI tract was deemed not to have functional patency. Of note, any patients who reported symptoms consistent with transient obstruction during the patency test period were also deemed not to have functional luminal patency and were excluded.

Patients without passage of the patency capsule at 28 hours went into the extended patency arm of the study. These patients were contacted by phone 72 hours post-PC ingestion. Patients who verbally confirmed passage of an intact capsule up to 72 hours post-ingestion were deemed as having confirmed functional patency and went forward for a capsule endoscopy (Figure 2.1). This study did not use abdominal ultrasound, tomosynthesis, or computed tomography (CT) to assess the PC location.

The primary endpoint was the capsule retention rate in patients who had confirmed functional patency by PC. Secondary endpoints were the rates of confirmed functional patency and by what means (self-reported or via radiology), SBTT on follow-up capsule and adverse events were also recorded.

FIGURE 2.1 STUDY DESIGN



Statistical Analysis

The results are reported using descriptive statistics (median and interquartile range) for patient characteristics. Comparisons between groups were made using the Mann-Whitney U test, chi-square test (if needed, with Yates' correction) or Fisher's exact test as appropriate. Differences at $p < 0.05$ were significant.

2.3.2.2. Results

2.3.2.2.1. Demographics

135 patients who underwent patency assessment before capsule endoscopy over a period of 6 months from January to July 2023 were enrolled in the study. Of this group, 75 were female (56%) with a mean age of 50.1 years (Table 2.6). The indication for capsule endoscopy was suspected CD in 49.7%, CD assessment in 23.7%. Iron deficiency anaemia and GI bleeding were indications for capsule endoscopy in 17.7% and 2.4%, respectively.

Table 2.6 Study Population and Indication for Capsule Endoscopy

Demographics	n = 135	
male, no. (%)	60	(44%)
female, no. (%)	75	(56%)
age (IQR)	50.1 yrs. (29.0)	
Indication for Capsule Endoscopy		
Suspected CD	67	(49.7%)
CD Assessment	30	(22.5%)
IDA	24	(17.7%)
GI bleeding	3	(2.4%)
Other	10	(6.5%)

2.3.2.2.2. Indication for Patency

The indications for patency assessment included surgery in 31.9%, a history of CD in 23.7%, NSAIDs in 13.3%, and Radiological findings in 13.3%, Endoscopic findings at 6.7% (which included findings of ileitis, or suspected strictures) (Table 2.7).

Table 2.7 Indication for patency

	n = 135	
Previous Surgery	43	31.9%
CD	32	23.7%
Radiology	18	13.3%
NSAIDs	18	13.3%
Endoscopic findings	9	6.7%
Obstructive Symptoms	9	6.7%
Prior Abdominal Radiation	3	2.2%
No clear indication	3	2.2%

2.3.2.2.3. Patency Assessment Results

Of the 135 patients referred for patency assessment functional patency was confirmed in 66 (48.9%) patients at 28 hours. Of these, 23 patients reported passage of intact capsule within 28 hours, while a further 43 patients had functional patency confirmed via abdominal x-ray.

69 patients had radiological evidence of the patency capsule on abdominal x-ray at 28 hours and went on to assessment at 72 hours. At 72 hours, a further 12 (17%) of 69 patients confirmed passage of an intact patency capsule and were deemed to have functional patency by the study protocol. The extended protocol increased the overall confirmed functional patency rate from 48.9% (n=66) to 57.8% (n=78) of patients from the cohort of 135 patients. A further three patients reported passage of a damaged capsule up to 72 hours and were deemed not to have confirmed functional patency by the study protocol.

2.3.2.2.4. Capsule Endoscopy Results

In all, 50.0% (n=39/78) of patients who proceeded to capsule endoscopy after a patency test had clinically significant findings (Table 2.8). Enteritis/Ileitis was the most common finding seen in 34.6% (n=27). The mean SBTT was 241 minutes (SD +/- 135 minutes).

Table 2.8 Capsule findings post patency

	n = 78	
Normal Study	39	50.0%
Enteritis/ileitis	27	34.6%
Angiodysplasia	2	2.6%
Duodenitis	3	3.8%
Small bowel polyp	2	2.6%
Colonic polyp	2	2.6%
Submucosal bulge	1	1.3%
Meckel's Diverticulum	1	1.3%
Gastric Retention	1	1.3%

There was no significant difference in SBTT between those who passed patency before 28 hours and those who passed patency up to 72 hours (241 minutes vs 243 minutes (p= 0.9637)) (Table 2.9).

Table 2.9 Small Bowel Transit Time

	n	SBTT (mean, min)	SD
Patency @ 28 hours	66	241	145
Patency @ 72 hours	12	243	102

2.3.2.2.5. Capsule Retention

There was no capsule retention in patients with confirmed functional patency in the standard or extended patency protocol. Of interest, however, one retained capsule occurred in a patient with a failed patency assessment but went on to have a normal MRI small bowel and was deemed appropriate for capsule endoscopy. The capsule was retained in an area of ulcerated small bowel mucosa. The patient had an asymptomatic passage of the capsule by the time of an abdominal x-ray 6 weeks post-procedure. A small bowel lymphoma was diagnosed at a follow-up enteroscopy.

2.3.2.2.6. Adverse Events

Two patients (1.2%) reported abdominal pain and bloating during the patency assessment. Both were managed conservatively and had passed the PC on radiological assessment at 28 hours. Both were excluded from capsule endoscopy and were referred for radiological small bowel imaging.

2.3.2.3. Discussion

Patency capsules have been shown to be a safe means of confirming functional patency prior to capsule endoscopy and to reduce the risk of capsule retention [54] significantly. Our retrospective data has shown that while the patency capsule reduces the risk of capsule retention, there is likely a cohort of patients who fail functional patency assessment due to the nature of the test [59].

Limited radiation CT based protocols have been shown to be effective in accurately assessing the location of patency capsules. Indeed a UK study has shown in a protocol based on the use of a PC and targeted, limited CT scan to confirm small bowel patency in those failing to excrete the PC 30 h post-ingestion, the sensitivity, specificity, positive, and negative predictive value were 99.4%, 90.0%, 99.7%, and 81.0%, respectively[70]. However, in high-volume capsule endoscopy centres the availability of cross-sectional imaging to confirm capsule location can be limited, and 2-dimensional imaging assessment can be inaccurate in localizing the patency capsule location in the colon, one study showed 5 SBCE retentions in 963 cases led by misinterpretation of PC localization[71]. Thus, modifications to the current methodologies are needed to reduce the number of patients excluded from capsule endoscopy by false positive functional patency assessments.

Radiological localization of the PC in those patients who don't self-report passage within 28 hours is routinely only available by plain film x-ray in our unit. Given the difficulty in accurately localizing within the colon against the small bowel on this modality,

any visualized capsule is considered a failure, with no functional patency confirmed. Our retrospective data has shown a high failed patency assessment by this criterion of 43.1% [59]. This compares to a recent meta-analysis where failure rates of between 21.4 and 44% were seen for functional patency assessment [58].

This prospective study has shown that of the 69 patients who failed patency assessment at 28 hours, 12 (17.4%) went on to have functional patency confirmed by the extended protocol and went on to have capsule endoscopy without capsule retention. This improved the overall functional patency rate from 48.9% to 57.8% without an increase in risk, as all subsequently passed the capsule. Thus, the extended patency protocol can allow us to conduct capsule endoscopy safely and effectively in patients without increasing the risk of capsule retention.

The previously reported data with an extended window to 72 hours showed in 6 of 19 patients (31.6%) in whom patency was not confirmed at 30 h, patency was confirmed within 72 h and no capsule retention occurred [33]. This was a higher rate again than achieved in our study.

This present study has several limitations. The subjects were consecutive patients in clinical practice at a single referral centre. The number of patients having capsules post-extended patency was small and requires ongoing monitoring for retention risk. The request for patients to examine their stool for the capsule was based on gross visual inspection only. More thorough stool inspection measures may have further increased the rate of confirmed functional patency but may not be acceptable to patients. Also,

we depended on the patient to report accurately whether the capsule was passed intact or not. Based on low subsequent retention rates in our cohort, future assessment with a digital image would appear not to be necessary. No data was available at the time of analysis of outcomes for those patients who failed patency assessment and didn't proceed to capsule endoscopy.

While this protocol improves overall functional patency rates by 17.4%, further investigation is needed to reduce the false positive rate further. What we do with the patient who fails a patency assessment also warrants further study. Currently, in our tertiary referral centre, the decision is made on a case-by-case basis for our own patients whether further radiological imaging or direct to enteroscopy is appropriate. Those from external centres are sent back to their treating physician.

To conclude, the patency capsule significantly reduces the retention risk in those with risk factors in capsule endoscopy. It is recognized as the safest assessment method in high-risk cohorts compared to other radiological techniques. However, it remains an imperfect measure of functional patency before capsule endoscopy, with a high exclusion rate for CE. Extended patency assessment up to 72 hours by this protocol has improved the functional patency rate in our cohort without increasing the risk of capsule retention in an easy-to-implement and cost-neutral manner. Taken together with the Japanese data, the safety to date suggests we should adopt this protocol with an ongoing audit of outcomes.

Chapter 3. Peppermint as a prokinetic

3.1. Orally administered peppermint oil solution as an aid to completion in capsule endoscopy.

3.1.1. Introduction

SBCE has revolutionized the diagnosis and management of small bowel diseases, offering a non-invasive and patient-friendly alternative to traditional methods. With its miniature camera housed in a swallowable capsule, SBCE provides high-resolution images of the small intestine, aiding in detecting various pathologies such as obscure gastrointestinal bleeding, CD, and small bowel tumours [11]. However, despite its widespread use and diagnostic efficacy, SBCE has limitations. One crucial aspect influencing its utility is the completion rate – the percentage of examinations where the capsule traverses the entire small bowel and reaches the caecum, enabling comprehensive evaluation. Understanding completion rates is pivotal, as incomplete examinations may lead to missed diagnoses and compromise clinical outcomes.[2]

Incomplete study rates remain problematic for capsule endoscopy. ESGE's recently published performance measures for capsule endoscopy suggest a minimum completion rate of 80%, with a target of >/= 95%. This performance indicator was based on data from 23 studies (18035 patient procedures) where the percentage of complete examinations was reported. The results of these studies were heterogeneous, with completion rates ranging from 64% to 96% (median 80%) [1]

Incomplete SBCE results in further costs owing to the repetition of SBCE and/or alternative investigations. In cases where the capsule did not reach the colon or the stoma within the duration of the recording and the patient does not confirm excretion within 2 weeks of ingestion, an abdominal radiograph will be needed to rule out capsule retention [1]. A completion rate of <80% may be associated with a higher risk of missing significant pathology, but the true magnitude of this risk is unclear.

The major cause of incomplete small bowel examination is prolonged gastric transit time[37, 72], comprising up to 30% of cases[73]. Prolonged gastric transit time is defined as delayed gastric transit resulting in SBCE remaining in the stomach for more than 30-120 minutes[37, 74].

Prokinetics have been used to aid the passage of the capsule from the stomach to the small bowel. However, prokinetic use alone is ineffective at increasing SBCE completion rates except in patients with risk factors for an incomplete SBCE study (i.e., those with previous history of abdominal surgery, delayed gastric emptying, diabetic neuropathy, severe hypothyroidism, or use of psychotropic drugs) who may benefit from the administration of certain prokinetics (metoclopramide, domperidone or erythromycin) when the capsule remains in the stomach for more than 30 minutes [11, 38].

In a prospective study from Japan comparing SBCE in 80 patients with or without real-time monitoring (RTM) (where in the RTM group if the capsule remained in the stomach for more than 60 min, a prokinetic was administered) the completion rate in the

RTM group was significantly higher than in the control group (90% vs. 72.5%)[39]. A further Japanese study recently compared the proportion of completed exams and positive findings among a group of patients studied before the introduction of RTM and a group in which capsule transit was regularly monitored, and action was taken (e.g., the administration of water or intravenous metoclopramide) if it was delayed [40]. Using the real-time viewer increased the SBCE completion rates from 66% to 86% (p = 0.002).

Our group has also demonstrated similar findings, where the completion rates (90.2% vs. 96.3%) and rates of significant findings (37.7% vs. 32.5%) were similar in our population with risk factors for delayed gastric emptying who received prokinetics in comparison to a control group [41]. There were no serious adverse events in the prokinetic group, but four (7%) reported side effects, including nausea, dizziness, and pain at the cannula site. A significant (15%) proportion required a second prokinetic, increasing the potential for adverse events, given that metoclopramide and erythromycin as prokinetics can risk adverse cardiac effects in an elderly cohort. There are also resource issues with RTM with patients spending prolonged time in the unit with repeated capsule position checks and the resources needed to administer further medications. Thus, alternative prokinetic interventions would be advantageous.

Current practice includes the patient staying in the department, time checks of capsule positioning, and the not infrequent administration of prokinetic medications. Metoclopramide and erythromycin are the most commonly used prokinetics.

Metoclopramide, a dopamine D2 receptor agonist, has a combination action of relaxing the pyloric sphincter and improving the antro-duodenal co-ordination[75]. It has good rapid oral absorption, with a peak plasma concentration at 56 min and a half-life of 5 h. Tardive dyskinesia and other extrapyramidal/dystonic reactions have been reported—not infrequently—as idiosyncratic adverse effects of its use. [72]

Erythromycin, a macrolide antibiotic, acts on motilin receptors of the endocrine cells of the duodenum [76] and has well-known prokinetic properties. It induces high-amplitude gastric propulsive contractions. As a result, it accelerates gastric emptying for both liquids and solids, including that of non-digestible particles [76]. Its commonest side effect is nausea, which in the case of SBCE may limit its use [72].

The largest meta-analysis to date on the use of prokinetics has not shown any serious adverse effects[38]. However, there is a time and resource commitment to keeping patients for potentially over an hour in the department with multiple interventions by the capsule staff.

Figure 3.1 Peppermint

Peppermint has been shown to function as a prokinetic when administered orally and provides a possible alternative to IV-administered medications [42]. Orally administered peppermint has been reported to aid gastric emptying and has a suitably safe side effect profile [77, 78].

Peppermint is of herbal origin and has menthol as its main constituent. It is a naturally occurring carminative that causes relaxation of the gastrointestinal smooth muscle through the blockade of Ca2+ channels [79]. Several meta-analyses have shown that it is effective in treating irritable bowel syndrome (IBS) symptoms [78, 80]. It has several proposed effects on the gastrointestinal tract, including intestinal smooth muscle relaxation, k-opioid receptor agonism modulation of transient receptor potential channel-mediated visceral nociception, 5-hydroxytryptamine antagonism, antimicrobial and antifungal effects [77, 78, 81]. Antispasmodic properties have shown a reduction in gastric antral spasms and a dramatic opening of the pyloric ring in endoscopic studies [42, 77].

A pilot study on the use of peppermint as an alternative to standard prokinetic interventions by our group showed in 143 patients with risk factors for delayed gastric emptying, peppermint had similar completion rates compared to metoclopramide (83.3% vs. 90.2% respectively) when given 30-60 minutes post-capsule ingestion if the

capsule remained in the stomach. Gastric transit times (GTT) were 111min vs 97min respectively (p = 0.1582). Interestingly, SBTT was shorter in the peppermint test group, 118min vs 193min (p = 0.0005) [82].

3.1.2. Aims

This study aimed to assess the efficacy of peppermint water as a prokinetic in patients with risk factors for delayed gastric transit undergoing SBCE. The primary endpoint was the completion rate. Secondary endpoints of GTT, SBTT, cleanliness score, and rates of significant findings were also assessed.

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3.1.3. Methods

3.1.3.1. Study design and population.

We performed a single-centre prospective open-label non-inferiority trial comparing orally administered peppermint water solution versus real-time monitoring (RTM) protocol as an aid to completion of SBCE in patients with risk factors for delayed gastric transit (Diabetes Mellitus, Hypothyroidism, Parkinson Disease, Prior Gastric Surgery, and certain medications). Ethical approval for the study was obtained from the Joint Research Ethics Committee of Tallaght/St James Hospital (Project ID 0495). All patients 18

years or older referred for SBCE without contraindications to administration of the study prokinetics were invited to participate over 4 months from February to May 2023. Contraindications included a history of cardiac arrhythmia, QT prolongation, and documented allergies to test prokinetics. Informed consent was obtained.

3.1.3.2. Procedure

SBCE was carried out using the Pillcam SB3 (Medtronic, Dublin, Ireland). Patients with risk factors for capsule retention (e.g., Known CD, Prior surgery of the GI tract, Abdominal radiation, Regular NSAID use, previous capsule retention, obstructive symptoms) completed a capsule patency test before capsule endoscopy. No purgative agents were used before the procedure, and patients fasted from 7 p.m. the evening before. Patients were randomized by a simple coin toss allocation method.

The real-time monitoring (RTM) group ingested the capsule with up to 200ml of water. They remained in the department for a capsule location check (Figure 3.2) 30 minutes after ingestion using the real-time viewer. If the capsule remained in the stomach 30 minutes after ingestion, the patients received 10mg of IV metoclopramide. A further site check was performed 60 minutes after ingestion, and if the capsule remained in the stomach, patients received 250 mg of erythromycin intravenously.

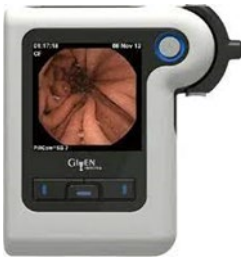


Figure 3.2 Capsule Endoscopy with RTM

The peppermint protocol (PP) group ingested the capsule with 200ml of a peppermint water solution (containing 90mg of peppermint). This has previously been shown to be safe and well tolerated dose of orally administered peppermint in IBS studies and use in upper endoscopy[83, 84]. They were then free to leave the department to return the equipment the following day. No position check or further prokinetics were administered to this group.

A control group of age and sex-matched patients with no risk factors for delayed gastric emptying were included in our capsule database for comparison purposes.

All studies were read and reported by experienced readers, and the final reports were reviewed at a departmental capsule review meeting before approval. The Pillcam software automatically generated transit times following landmark identification by the reader. Image quality was based on the reader's overall impression of the bowel preparation as per the Brotz score.

A nested case-control design was utilized. Basic demographics, completion rates, image quality, transit times, and diagnostic yield were compared between groups using

student t-tests or chi-square tests as appropriate. Adverse events and complications were documented.

Results were compared between the three patient groups. A P value of less than 0.05 was considered statistically significant. Analysis was performed on an intention-to-treat basis.

3.1.4. Results:

3.1.4.1. Demographics

Over the study period, 449 small bowel capsules were performed. Of these, 132 (29.4%) had risk factors for delayed gastric transit and were randomized: 57 in the PP group and 75 in the RTM group. A Control group of 193 with no risk factors for delayed transit was also included.

All patients in the peppermint group received peppermint water solution with capsule ingestion. One patient did not tolerate the solution and consumed only 25ml. In the standard group, 34/75 (45.1%) patients received metoclopramide; of these 8/75 (8.0%) also received erythromycin.

Demographics were similar between the PP and RTM groups (60.1 vs 64.0 years (p=0.2046); 42% vs 39% male (p=0.7226) respectively) Table 3.1.

Table 3.1 Demographics

	PP		RTM		Control	
n	57		75		193	
Male (n, %)	24	42.1%	29	38.7%	81	42.0%
Age (years)	60.1	(SD 19.0)	64.0	(SD16.1)	59.0	(SD16.0)
Risk Factor for Delayed Gastric Transit						
Medication	15	26.3%	25	33.3%		
DM	9	15.8%	16	21.3%		
Hypothyroidism	12	21.1%	14	18.7%		
More Than one	21	36.8%	20	26.7%		

3.1.4.2. Completion Rates

Completion rates overall were high and similar in the 3 groups: 94.7% (PP) vs 90.7% (RTM) vs 95.3% (C) (Table 3.2). There was no statistical difference in completion rates between the 2 study groups (p = 0.5135) or between the PP group and the control group (p=0.7385).

Table 3.2 Completion Rates

	n	complete	completion rate	
PP	57	54	94.7%	
RTM	75	68	90.7%	p = 0.5135
Control	193	184	95.3%	p = 0.7385

p values are measured compared to PP group

In the PP group, 54/57 had a complete study. Of the 3 patients with incomplete studies, 2 had delayed gastric emptying, with the capsule remaining in the stomach for the entire study duration, and 1 patient had capsule retention at a small bowel stricture.

In the RTM group of 68/75 patients had a complete study. 3 had delayed gastric emptying despite administration of both prokinetics with the capsule remaining in the stomach for the entirety of the study, while 4 had incomplete visualisation of the small bowel. The control group of patients without identified risk factors for delayed gastric emptying had a completion rate of 184/193 (95.3%). There was also no statistical difference between the PP group and the C group (P = 0.7385).

All 3 groups met the ESGE minimum completion KPI of 80%, with the peppermint and control groups meeting the higher target of >/=95%[1].

3.1.4.3. Transit Times

Gastric transit times (GTT) were 42.3 minutes (SD 34.2) (PP) vs 57.0 minutes (SD 45.144) (RTM). There was a statistical difference between the two test groups (P = 0.042). GTT in the control group was 34.4 minutes, which was not statistically significant compared to the PP group (P = 0.184).

Small Bowel Transit Time (SBTT) was 246.4 minutes in the PP group vs 193 minutes in the RTM group. There was a statistical difference between the two test groups (p =

0.012). The SBTT in the control group was 228.3min, which was not significantly different compared to the PP group (P = 0.301) (Table 3.3).

Table 3.3 Capsule Transit Times

	GTT (mins)	SD	p value	SBTT (mins)	SD	p value
PP	42.3	34.2		246.4	90.3	
RTM	57.0	45.1	p = 0.042	193.0	127.5	p = 0.012
Control	34.4	40.0	p = 0.184	228.3	110.9	p = 0.301

p value compared against PP group

3.1.4.4. Diagnostic Yield

Significant findings were identified in 24/56 (42.9%) in the peppermint group vs 28/75 (37.3%) of the standard group (p = 0.5895) and 63/193 (32.6%) in the control group (P = 0.2025 in comparison to peppermint group). These differences are not significant.

3.1.4.5. Bowel prep

Adequate bowel prep assessed by the Brotz score was similar in the 3 groups: 98.2% (PP) vs. 93.2% (RTM) vs. 95.3% (C) deemed adequate. There was no statistical difference in the comparison.

3.1.4.6. Adverse Events

No significant adverse events were recorded. One patient in the PP group tolerated the peppermint solution poorly and only consumed 25ml. In the RTM monitoring group, pain at the IV site was recorded in 2 patients and nausea in 2 further patients.

3.1.5. Discussion

Diagnostic yield of SBCE is only limited by two confounders that hamper the complete evaluation of small-bowel mucosal features: a) poor luminal visualization, and b) slow gastric and/or small-bowel transit time which can prevent the capsule from reaching the ICV/caecum within the capsule's battery life[85].

Therefore, various techniques and interventions have been developed aiming to improve the clinical chances for total enteroscopy. Prokinetics have been used to aid the passage of the capsule from the stomach to the small bowel. Prokinetic use alone is ineffective in increasing SBCE completion rates [38]. However, patients with risk factors for an incomplete SBCE study may benefit from the administration of certain prokinetics

(metoclopramide, domperidone, or erythromycin) when the capsule remains in the stomach for more than 30–60 minutes. The ESGE recommends prokinetic usage/or endoscopically assisted capsule delivery into the duodenum in patients for whom delayed gastric emptying has been confirmed by real-time monitoring [2].

This study shows that capsule ingestion with a peppermint water solution in patients with risk factors for delayed gastric emptying is well tolerated with minimal adverse effects.

The prokinetic effects are equivalent to the standard protocol for patients with delayed gastric emptying risk factors. Overall, completion rates were high and similar in the 3 groups: 94.7% (PP) vs 90.7% (RTM) vs 95.3% (C), with no effect on preparation quality or findings. GTT times were significantly shorter in the PP group than the RTM group, likely due to the timing of the interventions and duration of effect: 42.3 minutes (PP) vs 57.0 minutes (RTM), $p = 0.042$). But this didn't continue through to SBTT times, where an opposite result was recorded; 246.4 minutes (PP) vs. 193 minutes (RTM), $p = 0.012$).

Limitations of this study include it being a single-centre study, and the randomization method used resulted in slightly imbalanced study groups; however, demographics in both were similar. While very good outcomes with high completion rates in all groups a much larger number of patients would be required to show a NNT advantage. Apart from recording adverse events no patient feedback was assessed. A formal cost-effec-

tiveness study would help assess any potential financial savings. The cost of the medications themselves are peppermint water at €6.91 per dose, while metoclopramide is significantly cheaper at €0.40 per dose and erythromycin when used is €14.26 per dose. While RTM protocol will have significantly lower drug costs involved the potential savings in staff time may reverse the overall costs involved in the use of peppermint water.

3.1.6. Conclusion

Peppermint water, given during capsule ingestion in patients with risk factors for delayed gastric emptying, is equivalent to the current RTM protocol. The peppermint water protocol also reduces patient time in the department, as no position checks are required thus reducing the workload on the capsule laboratory in the repeated monitoring and potential administration of prokinetics before the patient can leave the department.

There is a potential role for peppermint in colon capsule endoscopy where completion rates are also an issue and RTM is used more broadly [86].

Chapter 4. AI reading

4.1. Introduction:

Capsule endoscopy (CE) has revolutionized the management of small bowel (SB) diseases owing to its convenience and non-invasiveness[4]. Its use is endorsed by international guidelines for the investigation and diagnosis of suspected small bowel bleeding, iron deficiency anaemia, suspected CD, polyposis syndromes and refractory coeliac disease. Capsule reading is a time-consuming and often tedious process with average reading times in the literature ranging between 30–120 minutes[2]. It demands a high level of concentration without distractions to avoid missing pathology [3].

Artificial intelligence (AI) use in CE is an attractive solution for reducing reading time by removing redundant images and identifying suspicious abnormalities [87]. Several previous studies have demonstrated impressive sensitivity and specificity in created datasets of capsule images [50, 52, 63, 87, 88]. They have performed well in detection of bleeding lesions, ulcers and protruding lesions (Table 4.1, 4.2 and 4.3).

Table 4.1: Studies assessing AI in detection of bleeding/potentially bleeding lesions.

Author	Year	Study design	Training dataset images	Testing dataset images	Sensitivity (%)	Specificity (%)	Accuracy (%)	
Jia[58]	2016	R	2050 GI bleeding frames 6150 normal	800 GI bleeding frames 1000 normal	99	100	-	-
Jia[89]	2017	R	200 GI bleeding frames 800 normal	100 GI bleeding frames 400 normal	91	98	-	-
Leenhardt[61]	2019	R	300 GIA 300 normal	300 GIA 300 normal	100	96	-	-
Tsuboi[63]	2020	R	2237 GIA	488 GIA 10000 normal	98.8	98.4	-	0.998
Aoki[56]	2019	R	6503 blood content 21344 normal	208 blood content 10000 normal	96.6	99.9		0.9998
Aoki[90]	2020	R	11097 GIA	29 pts GIA	97	-	-	0.871
			6503 blood content 21,344 normal	23 pts blood content	100	-	-	-
Ding[91]	2020	R	158235 abnormal images including Bleeding Vascular disease	113268334 abnormal images including Bleeding Vascular disease	100	100	-	-
					98.92	100	-	-
Otani[92]	2020	R	538 GIA 34 437 normal	288 pts 40 pts	-	-	-	0.950 0.884
Soffer[50]	2020	SR-MA	-	-	98	99	-	-

Legend: R = retrospective; GIA = gastrointestinal angioectasia SR-MA = systematic review and meta-analysis;

Table 4.2: Studies assessing AI in detection of ulcers.

Author	Year	Study design	Training dataset images	Testing dataset images	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC (%)
Fan[60]	2018	R	3250 ulcers, 5000 normal; 4910 erosions, 8000 normal	150 ulcers, 400 normal; 300 erosions, 800 normal	96.80	94.79	95.16	0.9891
Aoki[93]	2019	R	5360 ulcers, 21344 normal	440 ulcers, 10000 normal	88.2	90.9	90.8	0.958
Alaskar[57]	2019	R	256 ulcers, 80 normal	80 ulcers 25 normal	*G* = 100, 100, 76; A = 100, 100, 76	*G* = 100, 100, 0; A = 100, 100, 0	*G* = 100, 97.14, 76.19; *A* = 100, 100, 76.19	*G* & *A* = *1, 1, 0.50*
Wang[94]	2019	R	990 ulcers	283 ulcers	91.64	92.42	92.05	-
Otani[92]	2020	R	398 ulcers, 34437 normal	288 and 40 patients	-	-	-	0.996 and 0.928
Klang[62]	2020	R	7391 ulcers, 10249 normal	-	E1 = 92.5-97.1; E2 = 76.7-100	E1 = 96.0-98.1; E2 = 56.8-100	E1 = 95.4-96.7; E2 = 73.7-98.2	E1 = 0.989-0.994; E2 = 0.995-0.999
Soffer[50]	2020	SR-MA	-	-	95	94	-	-

Legend: R = retrospective; SR-MA = systematic review and meta-analysis; G = GoogLeNet; A = AlexNet; E1 = experiment 1; E2 = experiment 2

Table 4.3: Studies assessing AI in detection of protruding lesions (polyps and tumours).

Author	Year	Study design	Images of training dataset	Images of testing dataset	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC (%)
Barbosa[95]	2012	R	104 tumours, 100 normal	700 tumours, 2300 normal	93.9	93.1	-	-
Li[96]	2012	R	540 tumours, 540 normal	60 tumours, 60 normal	82.33	84.67	83.50	-
Constantinescu[97]	2016	P	-	-	93.75	91.38	-	-
Ding[91]	2019	R	158235	113268334	PPA = 100; PLA = 100	PPA = 100; PLA = 100	-	-
Otani[92]	2020	R	4590 ulcers, 34437 normal	288 and 40 patients	-	-	-	0.950 and 0.902
Saito[98]	2020	R	30584 protruding lesions	7507 protruding lesion, 10000 normal	90.7	79.8	-	-

Legend: R = retrospective; P = prospective; PPA = per-patient analysis; PLA = per-lesion analysis.

Despite these impressive results in created datasets real-world data is lacking and thus remains a barrier to the adoption of Artificial Intelligence AI in capsule endoscopy in clinical practice primarily due to the concern of missing a lesion without human review of the entire video, despite the knowledge that human reviewers are subject to a high lesion miss rate and early fatigue (Figure 4.1) [99].

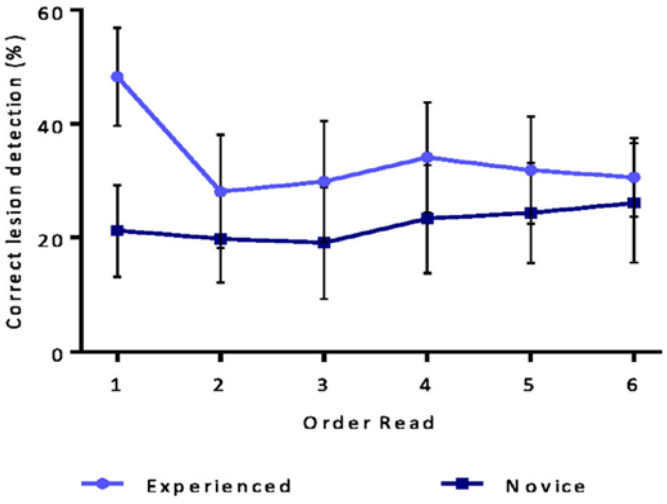


Figure 4.1 Reader fatigue effecting lesion detection after reading 1 capsule.[99]

The capsule's journey along the GI tract remains out of the control of the operator, and views of any abnormality may be fleeting and only partial. In the future, when AI will select a limited number of frames to be reviewed by the endoscopist it is likely that over 99% of frames will never get a human check thus the primary aim of AI in CE is currently to reduce reading times while maintaining a high sensitivity for the detection of abnormalities and possibly reducing the unknown but inevitable miss lesion rate.

Table 4.4: ESGE position statement Expected values for AI in Capsule endoscopy		
AI task	Description	Expected Value
Quality of Bowel Cleansing	AI assisted endoscopist scoring according to validated scales	Comparable to scoring as adequate/inadequate by experienced endoscopists (100% agreement)
Completeness of SBCE procedure	AI assisted identification of the caecum/colon landmarks	Comparable to caecum/colon identification be experienced endoscopists (100% agreement)
SBCE reading and lesion detection	1.Reading time 2. Detection of clinically significant small bowel lesions	1. No increase and possible reduction in reading time 2. Agreement >95% with experienced endoscopist for lesion detection.

Reflecting the arrival of AI in endoscopy ESGE have released a position statement [100] outlining expected value of AI in a number of areas of endoscopy including capsule endoscopy (Table 4.4). For acceptance AI assisted reading should be comparable to that of experienced endoscopists for lesion detection without increasing reading time. To date the evidence for this is lacking.

Figure 4.2 OMOM HD capsule

OMOM HD Capsule endoscopy system (Jinshan Science & Technology (Group), Yubei, China) introduced in 2020 with AI technology includes redundancy deletion, lesion detection, and classification software. It comprises 3 components: the capsule itself, the data recorder, and the computer workstation with the software for interpretation and reporting. The reporting software includes a CNN based computer aided detection (CADe) algorithm which can identify small bowel abnormalities and filter the video files for these. After downloading the video file, the software automatically processes the file.

The operator can select either to view the entire video as standard or to utilise the AI software which displays only the filtered images selected by the algorithm. The filtered images are played in a video format familiar to experienced capsule readers, or as a collection of still images with suggested findings.

Xie et al recently published a paper on the development and validation of this AI software for SBCE video review in a Chinese study encompassing 51 capsule endoscopy centres [101]. It was trained using convolutional neural networks (CNN) to detect 17 types of capsule endoscopy structured terminology (CEST) findings including venous structure, nodule, mass or tumour, polyps, angioectasia, red and white plaques, red spot, abnormal villi, lymphangiectasia, erythematous, oedematous, erosion, ulcer, aphtha, blood, and parasite (Figure 4.3) [102].

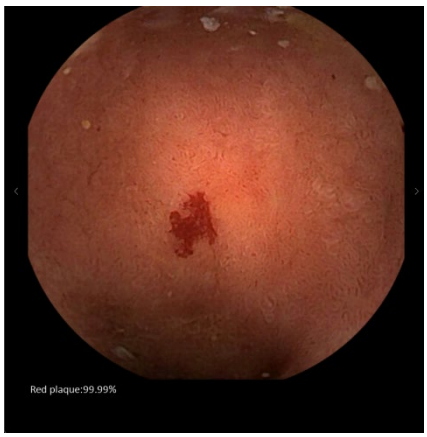


Figure 4.3 Capsule image with AI assisted assignment of CEST findings

During the validation phase they reported an extremely low miss rate of 1.0% using the AI algorithm when compared with the conventional reading group. In contrast, the conventional reading group had a miss rate of 9.6% when compared with the AI-assisted group.

Our primary aim was to evaluate the compare the diagnostic yield of the AI software against standard reading in the detection of clinically significant small bowel pathology when both are performed by experienced readers in a real-world setting. Secondary aims assessed reading times, assessment of bowel cleansing and identification of passage to the colon for AI vs Standard reading.

4.2. Methods

4.2.1. Study Population

In this single centre study, we looked at 40 sequential patient procedures performed using the OMOM HD capsule. These were performed in a single capsule referral centre over an 8-week period. All patients referred for SBCE had met our clinically established pathways for capsule endoscopy to investigate suspected small bowel bleeding, iron deficiency anaemia, CD assessment, suspected small bowel CD or small bowel polyps. Patients were screened for risk factors for capsule retention and had functional patency confirmed using a patency capsule if indicated.

4.2.2. Procedure:

The capsule was administered as per normal departmental protocol. Patients fasted from the night before and attended for capsule placement in the morning. No bowel prep was administered as is our local protocol. The recording device was worn for 12 hours and returned for download and analysis the following day. Recordings were downloaded to the OMOM HD capsule software platform. Standard reports were issued for all cases and clinical follow up arranged as standard.

The studies were retrospectively analysed using the AI software following a 3-month time delay from initial reporting with each filtered image evaluated for findings.

4.2.3. Recording modalities.

Following download and analysis of the video by the software the files were read in two modalities.

A. Standard reading (SR) which was performed as per ESGE standards [2]. Which was reading at a maximum of 10-fps single image mode.

B. Artificial Intelligence (AI) reading which was read at 5fps after image processing by AI-assisted technology.

Standard reading was performed first by two gastroenterologists experienced in capsule endoscopy who read approximately 150-200 capsules per year. This was performed at the time of data capture without reference to AI findings with data examined and results recorded. The findings and report generated by this method was reviewed by our expert group (consisting of two senior gastroenterologists reading>200 capsules/year for more than 15 years combined and three experienced readers reading 50-100 capsules/year) to agree on image interpretation and the text of a final report.

AI reading was performed by the same gastroenterologists 3 months later. The AI algorithm preread the examination and filtered out suspected CEST findings, each selected image was then evaluated for findings with data examined, results recorded, and a report generated.

Time of review began at examination of first small bowel image and ended at time of first colonic image and was recorded using a validated stopwatch. The reader was free to move between images as per their normal reviewing procedure including pausing the video and moving backward and forward through the images. A maximum reading rate of 5fps was used for AI reading due to the small number of images reviewed per study (mean of 375 (SD 329, IQR 139-684) and the high positivity rate per image (8.8%).

4.2.4. Statistics and Data Analysis

Data analysis was performed from July 2022 until September 2022 using excel and SPSS. For each study reading time, pathology identified, number of images for review in the AI mode, intestinal landmark identification timings, and bowel preparation assessment (Brotz Score) were recorded.

Qualitative measures were described by mean, median, maximum, and minimum values. Pearson's coefficient was used to compare bowel prep and identification of first colonic images. The Wilcoxon signed-rank test was used for comparing reading times and number of images in standard and AI assisted reading.

A paired chi-squared test was performed with the difference of accurate detection rate of finding types between the 2 reading modes. Where the value of the indicators reached 100%, the 95% CI calculation was based on the modified Wald method with all P values from 2-sided tests and results deemed statistically significant at $P < 0.05$.

4.3. Results

Table 4.5: Demographics

male (n, %)	26	65.0%
age (years, SD)	50.0	20.0
Indication (n, %)		
• Suspected Small bowel bleeding	20	50.0%
• Suspected CD	15	37.5%
• CD Assessment	3	7.5%
• Polyp surveillance	2	5.0%

4.3.1. Patient Demographics

40 SBCE procedures were included for analysis (26 male (65%); mean age 50.0 years (SD 20.0). The indications for CE were suspected small bowel bleeding 50% (n=20), suspected CD 37.5% (n=15), CD assessment in 7.5% (n=3) and follow up of

small bowel polyps in 5% (n=2) (Table 4.5). 1 patient had gastric retention of the capsule for the entire duration of the study and was excluded, leaving 39 studies included for analysis. No capsule retention was recorded.

4.3.2. Overall Patient Diagnoses

For both modalities 19 studies were reported with abnormalities giving a 48.7% diagnostic yield (Table 4.9) when normal variants such as lymphangiectasia were excluded. This is within the range seen in published data [11, 103]. 7 patients had ileitis to varying degrees, 4 cases of angiodysplasia were identified, with blood/melaena seen on a further 3 studies. A polyp was identified on a further study and a likely tumour was identified on another (confirmed as adenocarcinoma on follow-up enteroscopy).

There was excellent agreement between both modalities for overall diagnosis with 100% correlation. Sensitivity, specificity, positive and negative predictive values of AI reading compared to standard reading were 100% on overall diagnosis.

Table 4.6: Patient Diagnosis

Overall Findings	AI mode	(n, %)	SR mode	(n, %)
Normal	20	51.3%	20	51.3%
Ileitis	7	17.9%	7	17.9%
angiodysplasia	4	10.3%	4	10.3%
Blood/melaena	3	7.7%	3	7.7%
Meckel's	1	2.6%	1	2.6%
polyp	1	2.6%	1	2.6%
tumour	1	2.6%	1	2.6%
submucosal bulge	2	5.1%	2	5.1%
gastric retention	1	2.6%	1	2.6%

4.3.3. Per significant lesion analysis

In the 39 studies included, 1293 images of significant lesions were identified (lymphonodular hyperplasia was excluded from analysis) when both reading modes were combined. These included angiodysplasia, ulcers/erosions, polyps, submucosal bulges, lymphangiectasia, and p1 vascular lesions. AI captured 1268 (98.1%, 95% CI 97.15-98.7) of these findings while standard reading captured 1114 (86.2%, 95% CI 84.2-87.9). This result is significant with a p <0.001 (Table 4.7).

Table 4.7: Lesion Detection Sensitivity

	AI (n)	Sensitivity	SR (n)	Sensitivity	Combined findings (n)	p value (AI vs SR)
Venous Bleb	16	100.0%	14	87.5%	16	0.14
Mass/Tumour	68	100.0%	65	95.6%	68	0.08
Polyp	10	100.0%	10	100.0%	10	
Angiodysplasia	81	100.0%	76	93.8%	81	0.02
Red spot	84	95.5%	60	68.2%	88	<0.01
Lymphangiectasia	361	97.8%	296	80.2%	369	<0.01
Ulcer/Erosion	629	98.6%	570	89.3%	638	<0.01
Blood	14	100.0%	14	100.0%	14	
Endoscopic Clip	0	0.0%	4	100.0%	4	<0.01
Tattoo	5	100.0%	5	100.0%	5	
Overall		98.1% (95.5 - 100%)		86.2% (68.2 -100%)		

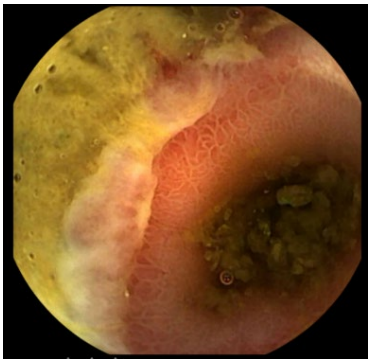
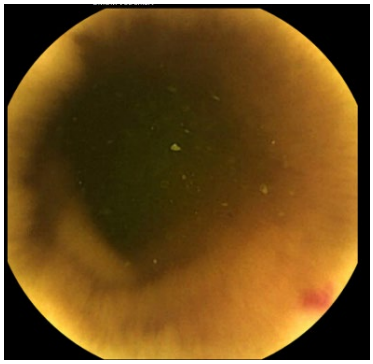
AI = Artificial Intelligence assisted reading; SR = standard reading

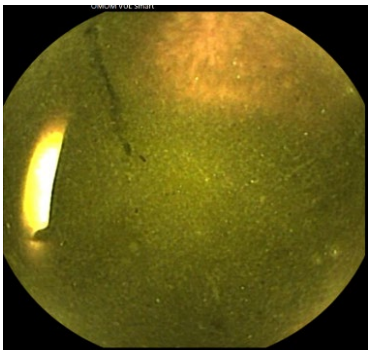
The enhanced AI sensitivity comes with many normal images included in the selected frames for review (false positives). AI selected 14640 small bowel images for review over the 39 studies, with 1293 positive findings, giving a true positive rate of just 8.8%. However, more significantly, the mean number of images for review for each study was reduced to 375.4 (SD 329.4, IQR 139-684).

4.3.4. Missed lesions

A total of 17 images of significant lesions were not noted in the AI mode (Table 4.7): 4 images of P1 angiodysplasia in an otherwise positive study for angiodysplasia, 9 images of a circumferential ulcer at the ICV in an area of poor prep, and 4 images of a clip placed during a recent antegrade enteroscopy (Figure 4.4). Additionally, 4 images of red spots and 8 images of lymphangiectasia were also not selected for review. Interestingly tattoo placement during previous enteroscopy was identified in 5 images.

Figure 4.4: Examples of missed lesions

a.  b. 



c.

a. Ulcer at ICV

b. Red spot

c. Endoscopic clip in area of poor prep

4.3.5. Reading time

AI assistance significantly reduces reading time. The mean (SD) reading time for small bowel images went from 29.7 (11.8) minutes by standard reading to 2.3 (1.4) minutes by AI mode ($z = -5.44$, $p < 0.001$). This gives a mean time saving of 92.3% or 27.4 minutes per study. (Table 4.8)

Table 4.8: Small Bowel Reading Time				
SBCE reading time (minutes)	AI (mins)	SR	Difference	p value
mean (SD)	2.29 (1.39)	29.69 (11.82)	27.40	<0.001
median	2	27	25	<0.001
range	1 - 4.5	15 - 63		

non-parametric paired Wilcoxon rank sum test : Z= -5.4424, p<0.0001

AI = Artificial Intelligence assisted reading; SR = standard reading

4.3.6. Quality of bowel cleansing

Bowel preparation assessment was performed using a validated scoring system described by Brotz [104]. Comparing overall cleansing evaluation scores, which is the standard set by ESGE[100], agreement was seen in 97.4%. 36/39 (92.3%) studies by standard reading mode vs. 37/39 (94.9%) by AI mode were deemed to have adequate cleansing, giving a fairly strong correlation (r= 0.805, p<0.001). Using the Brotz qualitative evaluation of prep as poor, fair, good, and excellent, results correlated moderately between the two reading methods with an agreement in 54% (r = 0.554, p <0.001).

4.3.7. Landmark identification/Completeness of procedure

Intestinal landmark identification is important for assessing the complete evaluation of the small bowel and localizing lesions for planning further investigations, such as

the direction of enteroscopy. The AI software marks what it believes to be the position of the start and end of the small bowel during processing by its CNN. These timestamps were compared to those recorded during standard reading.

Table 4.9 Intestinal Landmark Identification

Landmark	SR time	AI time	Mean Difference	Range	
First Duodenal Image (mins)	45.0	94.2	-49.2	-543 to +107	(r=0.222, p=0.275)
First Caecal Image (mins)	304.5	205.3	99.2	-567 to +337	(r=0.085, p =0.679)

Recognition of the intestinal landmarks by the software was poor (Table 4.9). Time of first caecal image showed a wide discrepancy between AI and standard reading of 99.2 minutes (range -567 minutes to +337 minutes, r = 0.085, p =0.68). Time of first duodenal image also showed a similar level of discrepancy between AI and standard reading with a mean difference of 49.2 minutes (range -543 to +165 minutes, r=0.22, p =0.27). As such the localisation of significant abnormalities as well as calculations of Lewis score[105] will likely be unreliable using the AI landmarks alone.

4.4. Discussion:

Currently, reporting SBCE is a task of single reviewers. It can be limited by human error and human reading performance is disappointing [106]. The reporting accuracy in SBCE declines after reading a single capsule study [107]. In its current iteration, AI in capsule endoscopy needs to recognize all lesions as it remains at this stage a filter of the normal from the abnormal before human review.

This is the first real-world study of using the recently validated OMOM AI system.

The correlation between AI-assisted reading and standard reading for the detection of pathology is excellent. Overall, in a per procedure analysis the diagnostic accuracy was equivalent between both modalities. Indeed, in these 39 cases reports generated by the 2 reading methods agreed 100% on overall diagnosis.

When the detection of each clinically significant small bowel lesion was examined. There was a higher rate of detection in the AI-assisted method (98.1% vs 86.2%). This met ESGE's expected value for AI in capsule endoscopy of >95% agreement with experienced endoscopists for lesion detection. Standard reading missed 179 lesions (13.8%), while AI-assisted reading missed only 25 (1.9%).

When missed lesions by AI-assisted reading were reviewed, bowel preparation was seen to be a factor in all cases. 4 were of small P1 lesions in areas of suboptimal prep, and 9 images were of a circumferential ulcer at the ileocaecal valve also in an area of unprepped colon while the prep around the endoscopic clip was particularly poor. While in colonoscopy the endoscopist can focus on an area of interest, clean any debris, and steady the endoscope in capsule endoscopy the software can only evaluate the images recorded with poor prep and partial or blurred images a fact of life when reading capsule endoscopy.

In the case of the endoscopic clip, which was not identified, this demonstrates one of the difficulties in training AI software for capsule endoscopy. The software is trained to identify atypical findings[101]. In the validation study, AI reading showed superior performance compared with conventional reading (1454 findings (23.9%) were missed by conventional reading and 250 findings (4.1%) were missed by AI reading). 13 findings missed by AI reading were associated with various reasons such as atypical image, a limited number of captured frames of specific findings, and/or overall image quality. This is an area for further refinement of the software.

AI-assisted reading showed superior performance compared to standard reading, with a 92.3% reduction in mean reading times to 2.29 minutes from 29.69 minutes per study.

Landmark identification by the AI software showed a poor correlation with the expert reader with a 49.2 minute average difference for the first caecal image (r=0.222, p=0.275) and thus didn't meet ESGE expected value of 100% agreement. From discussion with the manufacturer the validation of landmark identification was not part of the original validation but will be part of future software upgrades. This is necessary as in its current guise incorrect landmark identification will lead to issues with localization of lesions when planning further investigations and therapies as well as assessment of Lewis scores, which are based on the identification of tertiles of the small bowel.

AI in capsule endoscopy will not remove the known limitations of the test such as the use and timing of bowel preparation and delayed capsule transit [2]. Indeed, standard of bowel preparation may become a more significant issue as missed lesions in this study were associated with areas of suboptimal prep. Reduction in images reviewed to an average of only 375 per study will also limit the readers assessment for rapid transit through parts of the small bowel as well as areas of poor prep. The evaluation of the clinical relevance of any findings remains the role of the clinician.

Overall, the software meets the ESGE expected values of >95% agreement with human reader for the identification of lesions. Whether this is sufficient for adoption is unclear as liability for missed lesions remains with the clinician and abnormalities may be only seen on a single frame. Also, AI assisted reading didn't meet the ESGE expected values for assessment of completeness of the study or quality of bowel preparation. Given this, AI assisted reading software in its current form would seem more appropriately used as a preread or as a training aid for those beginning capsule reading.

This study does have a few limitations. This was a single centre study of a small number of capsules. The use of the standard reading mode as the reference standard is limited by the abilities of that reader. Ideally, each study would be reviewed by a panel of readers; however, the effort involved was deemed to be prohibitive.

In conclusion, with recognition of its limitations, AI software has the potential to significantly reduce reading time in CE without negatively affecting pathology recognition and diagnostic yield. Further studies to increase the dataset are required to evaluate the clinical utility of the software in its current form.

Chapter 5 Conclusions and Future Directions

Despite almost 20 years of clinical application, many aspects of the use of small bowel capsule endoscopy remain to be optimised. This thesis looked at three specific problem areas identified: the use of the patency capsule pre-procedure, the use of a novel prokinetic to improve completion rates in patients with risk factors for delayed gastric transit, and the clinical application of a recently validated AI-enabled capsule reading software to identify pathology and reduce reading times.

The first section looked at the use of the patency capsule in clinical practice and evaluated its limitations. Our retrospective study demonstrated that while patency assessment reduces the risk of capsule retention to almost zero, it has its drawbacks due to the likely excessive false positive rate of the test as it stands, with functional patency only confirmed in only 55.3% of patients having the test. Our prospective study of an extended-time protocol increased the confirmation of functional patency by 17%, a significant improvement, without any capsule retention.

There is likely room to improve this rate further. Synchronisation of the test with patient's bowel routine may help improve rates in patients who move their bowels less than every day. The use of prokinetics hasn't been shown to improve completion rates in capsule endoscopy itself, but their role in patency assessment is unknown. Caution may be needed here as bowel obstruction has been reported with the patency capsule itself [108, 109]. The addition of a lateral X-ray in combination with the PA view adds

more information for the radiologist and may increase the accuracy of capsule localisation.

A pathway for those excluded from capsule endoscopy due to a failed patency assessment needs to be developed. Currently in our tertiary referral centre the decision is made on a case-by-case basis for our own patients where those from external centres are sent back to their primary physician. Depending on indication for capsule endoscopy referral to radiology for dedicated small bowel imaging or proceeding to device assisted enteroscopy is often the pathway but a cohort often get no further investigation of their small bowel. Protocols should be developed to maximise the diagnostic capability of capsule endoscopy and device-assisted enteroscopy.

The second section of this work evaluated completion rates in capsule endoscopy. which in the literature are heterogeneous with rates ranging from 64% to 96% (median 80%) [1] Real-time monitoring and prokinetics have been shown to be of value only in patients with risk factors for delayed gastric emptying but are time-consuming and require the administration of IV prokinetics. Our group has demonstrated this where the completion rates (90.2% vs. 96.3%) and rates of significant findings (37.7% vs. 32.5%) were similar in our population with risk factors for delayed gastric emptying who received prokinetics with real-time monitoring in comparison to a control group [2, 3].

A novel prokinetic, peppermint water has been shown to aid gastric emptying and in a pilot study in those with risk factors for delayed gastric transit [82]. Here we performed a single centre prospective open-label non-inferiority trial comparing orally administered peppermint water solution versus existing RTM protocol as an aid to completion of SBCE in patients with risk factors for delayed gastric transit. We demonstrated completion rates comparable to RTM and a control group without risk factors for delayed gastric emptying. Completion rates overall were high in the 3 groups 94.7% PP vs 90.7% RTM vs 95.3% in a control group. All 3 groups met the European Society of Gastrointestinal Endoscopy (ESGE) minimum completion KPI of 80%, with the peppermint and control groups meeting the higher target of >/=95% [1].

This study has shown peppermint water solution given at the time of capsule ingestion in patients with risk factors for delayed gastric emptying is equivalent in terms of completion rates to the current RTM protocol involving the administration of prokinetics while reducing patient time in the department and freeing up capsule technician time.

Further studies in the use of this novel prokinetic should include its utility in Colon capsule where completion rates remain an issue. A cost benefit analysis could more accurately assess the perceived time and cost savings.

In the final section of this thesis, we looked at the use of an artificial intelligence-enabled capsule reading platform to aid in the reading of small bowel capsules. Capsule reading is a time-consuming process with average reading times in the literature ranging between 30–120 minutes [2]. It also has a significant fall off in lesion detection with prolonged time spent reading capsules[99]. It demands a high level of concentration without distractions to avoid missing pathology [3].

Our study of 40 small bowel procedures has shown a high degree of accuracy in lesion detection. Overall diagnosis correlated 100% between AI and standard reading. In a per-lesion analysis, AI-assisted reading captured 1268 (98.1%, 95% CI 97.15–98.7) of lesions, while standard reading captured 1114 (86.2%, 95% confidence interval 84.2–87.9), $P < 0.001$. One of the most interesting findings is that mean reading time went from 29.7 minutes to 2.3 minutes with AI-assisted reading ($P < 0.001$), for an average time saving of 27.4 minutes per study. It is perhaps in this area that the gastroenterologist needs most help and perhaps where AI in capsule should focus its development. The elimination of similar images and normal bowel resulted in an average of 375 images for review per study, this is likely to eliminate the fatigue factor. Clinicians trained in capsule endoscopy are likely less worried about correct identification of abnormalities if they can be confident that the abnormalities will be filtered for review and AI software should be optimised in this regard in the first instance.

Going forward Artificial Intelligence (AI) will likely become an increasingly integral part of capsule endoscopy. The literature surrounding the real-world application of AI in CE is expanding, this study was published as the first real-world data of the use of an AI platform in capsule endoscopy. Since then, a multicentre prospective study has demonstrated similar positive results using a different AI platform[110]. However, this study looked only at vascular lesions. Nevertheless, they showed at a per-patient analysis the diagnostic yield of P1 and P2 vascular lesions in AI-assisted reading (98 of 133 lesions (73·7%)) was non-inferior ($p<0·0001$) and superior ($p=0·0213$) to standard reading (82 of 133 lesions (62.4%)); 95% CI 3·6-19·0). Mean small bowel reading time was 33·7 min (SD 22·9) in standard reading and 3·8 min (3·3) in AI-assisted reading ($p<0·0001$).

The integration of AI into capsule endoscopy continues to evolve, with promising implications for clinical practice, education, and research. As AI tools are further validated and endorsed by regulatory bodies like ESGE, their utilization could significantly reshape the landscape of capsule endoscopy.

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