Advancing Minimally Invasive Aspects of Flexible Gastrointestinal Endoscopy

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Dedication

I dedicate this work to all those who have supported me; most especially my parents Karl and Maphine and my sister Maria who have constantly encouraged me 'to push on, regardless'.

Declaration

Whilst registered as a candidate for this doctorate, I have not been registered for any other research award. The results and conclusions of this thesis are the work of the named candidate and have not been submitted for any other academic award. This thesis is the result of original work carried out at the Wolfson Unit for Endoscopy at St Mark's Hospital and Academic Institute under the auspices of the Department of Surgery and Cancer (SORA) of Imperial College London, United Kingdom. Any reference made to the work of others has been duly acknowledged. This work was carried out under the supervision of Dr. Chris Fraser and co-supervision of Dr. Ailsa Hart of St Mark's Hospital and Academic Institute and Imperial College London.

My period in research for the conduct of the work described in this thesis was supported by an unrestricted grant, very kindly provided by Imotech Medical (UK) and Fujifilm Inc.

Abstract

The technological developments seen in recent years have facilitated remarkable progress in the field of flexible gastrointestinal (GI) endoscopy. Smaller high-resolution charge-coupled devices (CCDs) have facilitated the manufacture of ultrathin (UT) (<6mm) endoscopes, while the introduction of device assisted enteroscopy (balloon-assisted and spiral enteroscopy) has allowed endoscopists to access the deep small bowel (SB) without the need for recourse to major surgery. Furthermore, the application of double-balloon colonoscopy (DBC) has shown promise to improve outcomes in patients with 'technically difficult' colons. Although these 3 types of innovative endoscopic technologies all share the potential capacity to enhance minimally invasive patient care, research into their optimal role and effectiveness (particularly within UK clinical practice) remains limited.

This thesis has examined the potential role of this selection of advanced flexible GI endoscopic technologies for the enhancement of minimally invasive patient care. The first study evaluated transnasal upper GI endoscopy in the UK and confirmed that within this clinical paradigm, transnasal endoscopy using UT endoscopes, is a feasible, effective and more acceptable alternative to patients than conventional oral upper GI endoscopy. The next series of studies were dedicated to device assisted enteroscopy (DBE in particular) and showed that DBE is capable of providing a safe and effective, minimally invasive alternative to major surgery in selected cases. A comparison of spiral enteroscopy as an alternative to DBE, showed that spiral enteroscopy (in its current, manual form), appears to be inferior to DBE in its ability to facilitate deep enteroscopy. The final study evaluated technically difficult colonoscopy and included the development and validation of a score for technical difficulty which may in the future be applied to routine clinical practice. This study also highlighted the usefulness of DBC as a potentially more effective tool than conventional colonoscopy for technically difficult cases.

Acknowledgements

I owe a great debt to many individuals who have helped and supported me throughout the conduct of this work.

Heartfelt thanks go out to my main supervisor, Dr Chris Fraser for having confidence in me, for his patience and relentless encouragement (through thick and thin), for being a great mentor and also for being my friend. Likewise, I wish to thank my co-supervisor Dr Ailsa Hart for her sterling, on-going support and inspiration.

I have been fortunate enough to carry out my research within the unique environment that is 'the Wolfson Unit for Endoscopy at St Mark's'. In a league of its own, the Wolfson Unit is not only teeming with ideas and 'infectious' motivation but also provides a haven of family-like nurturing support which is so essential to the success of the fledgling academic. I therefore thank all those people who make the Wolfson Unit what it is. Special thanks go out to the Wolfson's director, Prof Brian Saunders for his wise guidance, support and constant encouragement, Ms Aine O'Rourke (who was so supportive and somehow also managed to put up with sharing an office with me), Mr Steve Preston (for teaching me some of his multimedia skills), Mr Eric Tripoli (for his tremendous support in helping me run our small bowel studies), NC Maggie Vance (for her ongoing encouragement and particular support), Dr Noriko Suzuki, Ms Jean Mannings, Ms Nicola Palmer, Ms Lisa Mackay and Sisters Mariann Baulf, Ripple Man and Jayne Butcher. I also wish to thank Drs Adam Haycock, Ana Ignjatovic, Aymer Postgate, Suresh Sivanesan, Jonathan Bromley, Zacharias Tsiamoulos and Adela Brigic, some of my 'Wolfson-fellows-in-arms', with whom I shared so much of the joy (and pain) that endoscopic research is known to bring. A special mention goes to the other Wolfson fellows, Drs Alberto Murino, Leonidas

Bourikas, Yoriaki Komeda and my dear friend Dr Sachin Gupta for regularly topping-up my zest and enthusiasm and for helping me to keep things in perspective. I very much appreciate the enormous support of our nurses and the clerical staff who did everything in their power for things to run smoothly and that of Mr Paul Basset for his statistical advice.

A special thank you goes out to Dr Jonathan Bromley and Sister Mariann Baulf for their invaluable contribution to the upper GI endoscopy study (**Chapter 2**), Dr Leonidas Bourikas for his significant contribution in obtaining the follow-up required for the study relating to patients with Peutz-Jeghers syndrome (**Chapter 6**), Dr Masanao Nakamura for his tremendous help with the pilot study evaluating the proposed colonoscopy 'technical difficulty score' (**Chapter 9**) and again to my colleague and friend Dr Alberto Murino for his remarkable efforts in helping me conclude the final 2 studies included in this thesis (**Chapters 8 and 9**).

I also wish to extend my appreciation to our enteroscopy colleagues from around the UK, namely: Prof David Sanders, Drs Reena Sidhu, Steve Hughes, Peter Marden, Ashibek Deo, Robert Willert, Jason Jennings, Mike Thompson, John Plevris, Ken Trimble, Simon Panter and David Nylander for contributing immensely to the successful creation of the UK DBE database. The sterling collaboration and wise counsel of other endoscopy researchers and experts from the UK and around the world, namely: Professors Hironori Yamamoto, Andrea May, Pradeep Bhandari, Rami Eliakim, Jonathan Leighton; Drs Mark McAlindon, Martin Keuchel, Paul Akerman, Peter Mensink, Kazuaki Kawada and NC Carolyn Davison is also greatly appreciated.

Finally I wish to express my deepest gratitude to all the patients who selflessly and generously, consented to taking part in this research and to the kind staff at Imotech Medical and Fujifilm

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Introduction

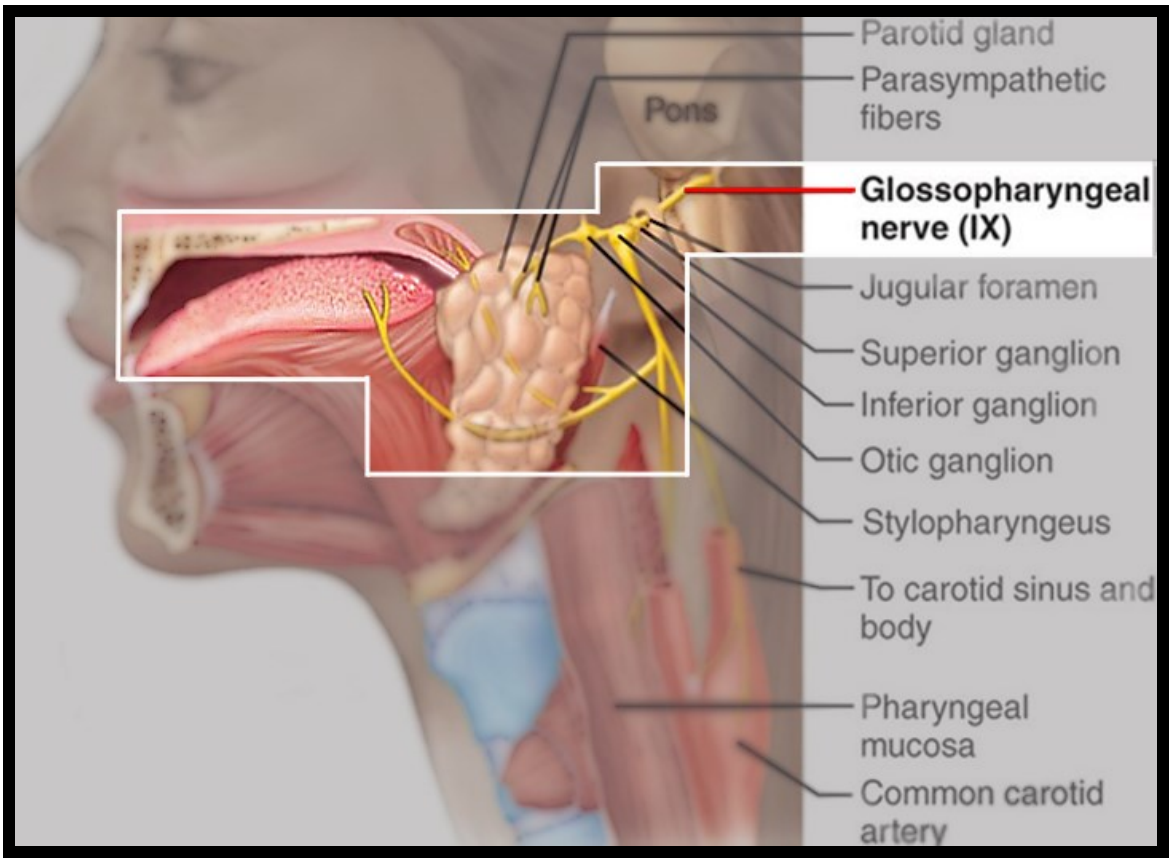
1.1 Minimally invasive aspects of gastrointestinal endoscopy: technological advancements in response to anatomical and physiological challenges

1.1.1 Upper gastrointestinal (GI) endoscopy

Although diagnostic oral upper GI endoscopy is one of the most common investigations performed in gastroenterology, it remains an uncomfortable procedure for patients [1-4]. This unpleasant experience is mainly the result of repeated triggering of the pharyngeal 'gag' reflex, caused by stimulation of afferent glossopharyngeal nerve fibres located in the tongue root, uvula and palatine arches (**Figure 1**), during insertion and withdrawal of the endoscope [1-4].

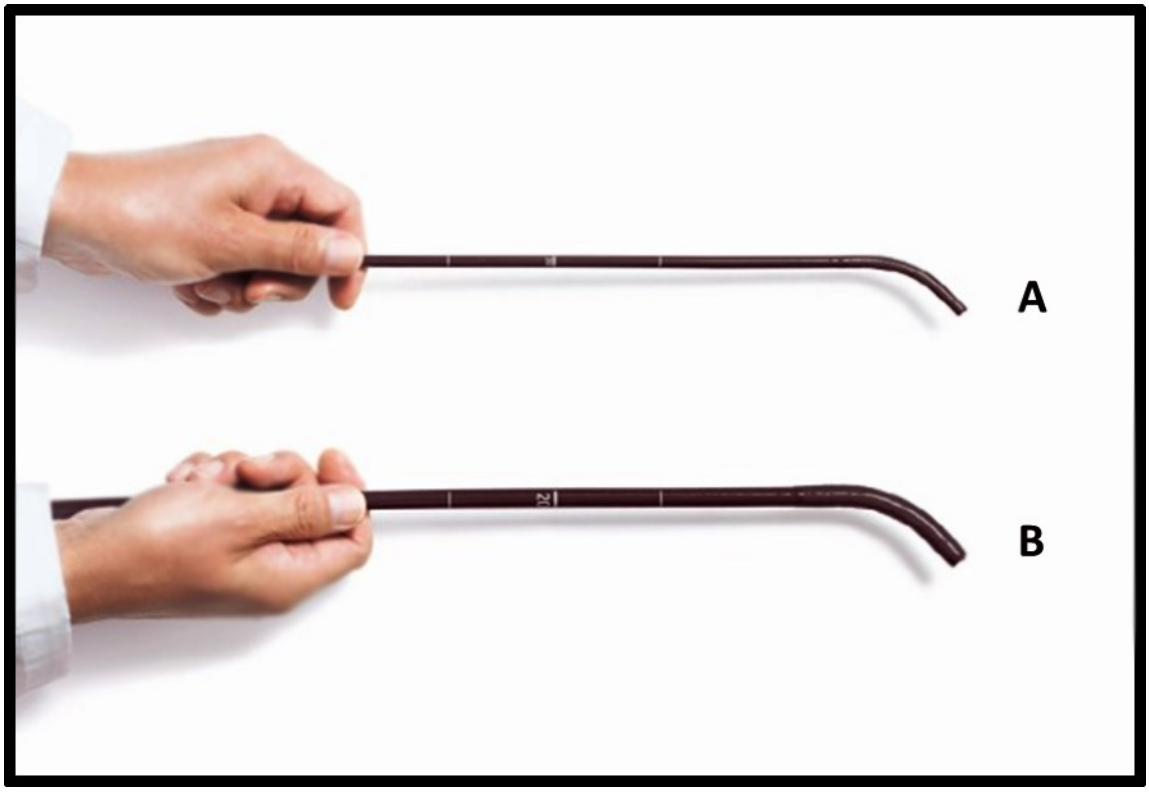
Upper GI endoscopy often remains unpleasant for patients despite the use of topical anaesthesia and/or intravenous conscious sedation. Furthermore, the use of sedation is associated with most of the serious adverse events relating to endoscopy, prolongs patient recovery time and introduces added costs (drugs, monitoring equipment, additional nursing, patient transportation and days-off-work) [1;3;5;6]. Improving patient tolerance of upper GI endoscopy such that sedation can be avoided has recognisable benefits.

Figure 1: *Anatomical dissection demonstrating the afferent pathway of the pharyngeal, 'gag' reflex conducted through glossopharyngeal nerve (CN IX) fibres, originating mainly at the root of the tongue, uvula and palatine arches. (Public domain image, modified by the author)*



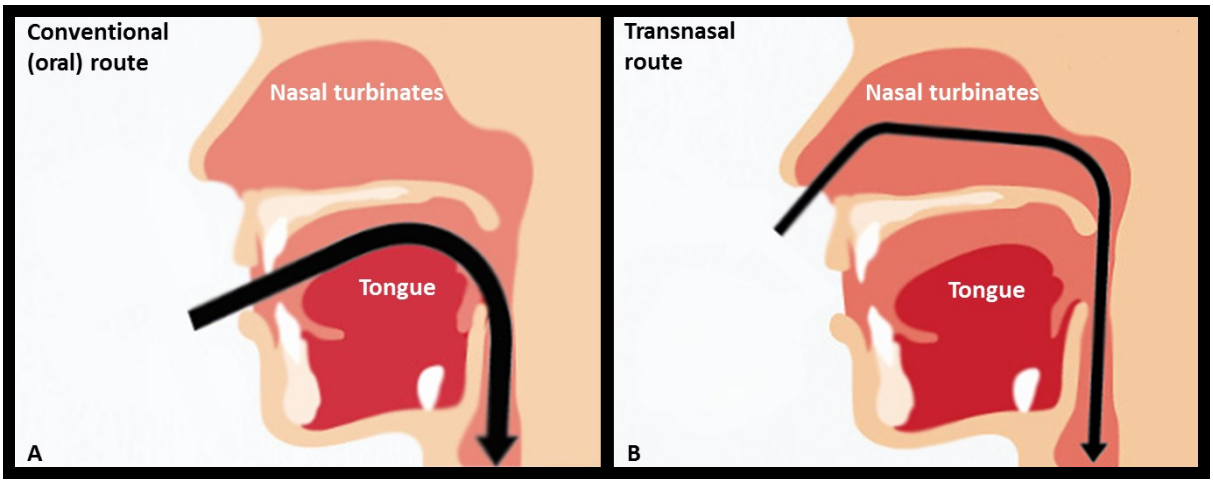
The introduction of the charge-coupled device (CCD) in the 1980s, led to development of video endoscope technology [7], which apart from facilitating improved endoscopic imaging, also enabled the manufacture of minimally invasive instruments with the potential capacity to improve patient tolerance during endoscopic procedures. An example of this has been the development of ultrathin (<6mm diameter) endoscopes for transnasal upper GI endoscopy (T-OGD) as an alternative to oral (conventional) upper GI endoscopy (C-OGD) (**Figure 2**) [4].

Figure 2: *Comparison of ultrathin (<6mm diameter) upper GI endoscope (**A**) with conventional (≥9.0mm diameter) upper GI endoscope, (**B**). (Image courtesy of Fujifilm, Saitama, Japan)*



In contrast to C-OGD, contact between the endoscope and the root of the tongue, uvula and palatine arches is minimized during T-OGD (**Figure 3**). This reduces stimulation of the gag reflex, and has been shown to enhance patient experience, obviating the need for sedation [2;8-13]. Since the first report of unsedated T-OGD as an alternative to C-OGD by Shaker in 1994 [4], several studies have confirmed its feasibility and improved patient tolerance [2;8-13]. However adoption of T-OGD into mainstream clinical practice has varied [14-17] and while its use in Japan is widespread, uptake in most Western countries has been slow [14-16]. Current endoscopy practice in the UK is typical of this and to date, there have been no studies to evaluate the potential benefits of T-OGD use in the UK.

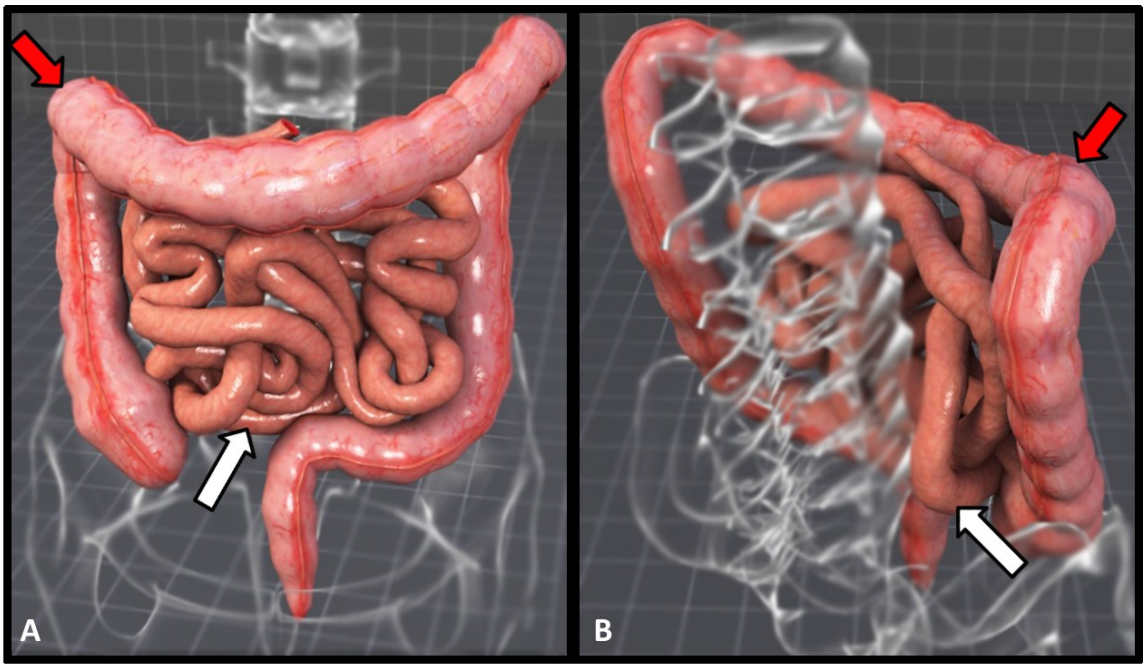
Figure 3: *Route of insertion and withdrawal used for conventional (oral) (**A**) (thick black arrow) and transnasal (**B**) (thin black arrow), upper GI endoscopy. During conventional endoscopy (**A**), the endoscope is in constant contact with the tongue, whereas using the transnasal route (**B**), tongue contact is virtually eliminated. (Image courtesy of Fujifilm, Saitama, Japan)*



1.1.2 Small bowel endoscopy (enteroscopy)

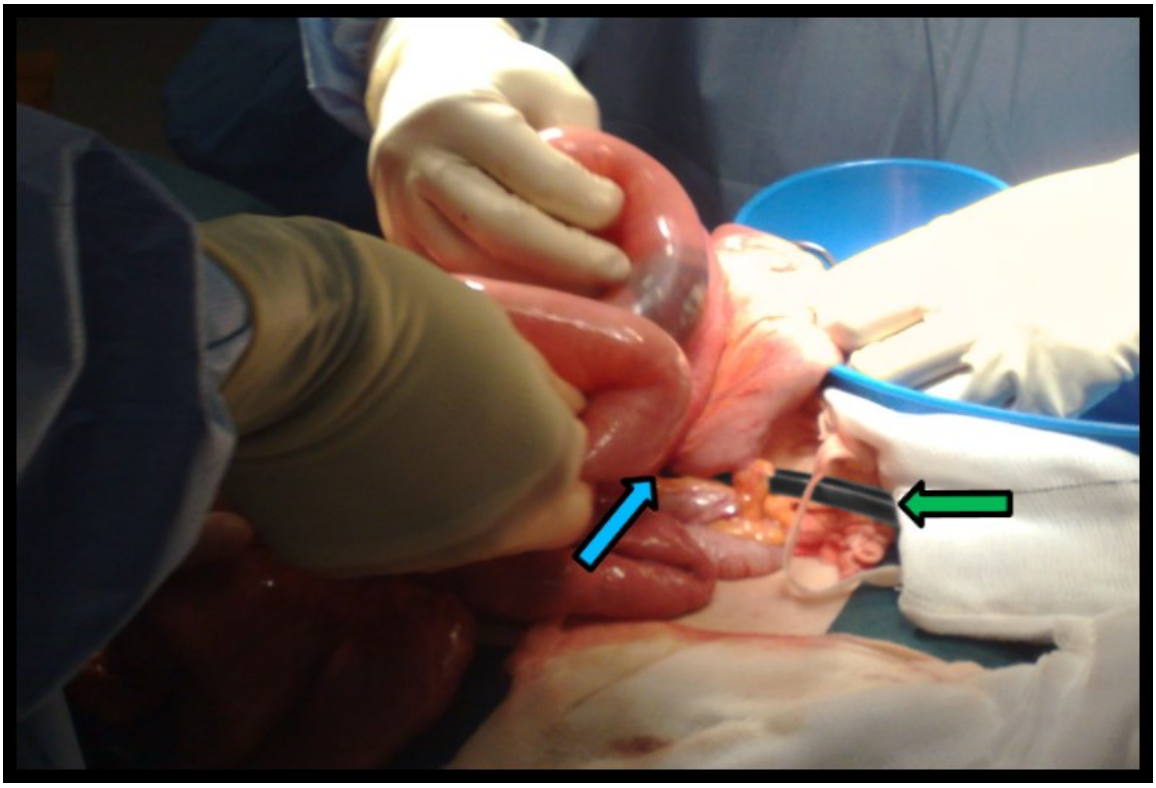
Comprising the longest part of the GI tract, the small bowel (SB) presents particular challenges to GI endoscopy. The anatomy of the SB consists of a coiled-up, loose tube, up to 8 metres long [18] (**Figure 4**), anchored only at the ligament of Treitz and the ileo-caecal valve [19], therefore predisposing to stretching and uncontrollable looping during endoscopic procedures [20].

Figure 4: *Computer generated 3D model (DigitalLab3D©, FallingPixel.com) antero-posterior view (**A**) and right postero-oblique view (**B**) of the small bowel (SB) (white arrow) in relation to the colon (red arrow). The 3D model demonstrates the anatomy of the SB as a long, coiled-up tube.*



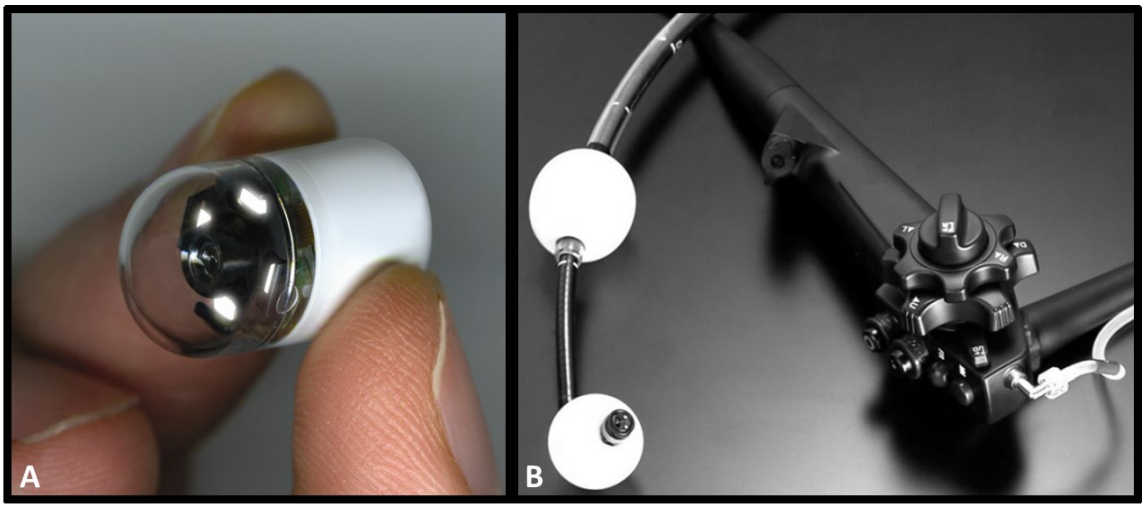
Until recently, non-surgically assisted flexible endoscopy of the SB has been limited to push enteroscopy (PE) and ileo-colonoscopy (IC) [21;22], limiting visualisation to the most-proximal or most-distal parts of the SB respectively. Achieving complete SB evaluation therefore required recourse to major surgery and the significantly more invasive intra-operative enteroscopy (IOE) [21;22] (**Figure 5**).

Figure 5: *Invasive nature of intraoperative enteroscopy (IOE). The enteroscope (green arrow) can be seen as it enters the exteriorised SB at the chosen site of enterotomy (blue arrow).*



The introduction of SB capsule endoscopy (SBCE) [23] and double-balloon enteroscopy (DBE) [20] in 2001 has revolutionised SB endoscopy, facilitating visualisation of the entire SB without the need for surgery. Although SBCE and DBE are complementary technologies, the role of SBCE is a diagnostic one and limited to the capture of endoscopic images while DBE offers tissue biopsy and the full range of therapeutic options of flexible endoscopy; DBE is frequently performed after SBCE when abnormalities have been identified [20;21;24-49] (**Figure 6**). Since SBCE is not classified as a flexible endoscopic technology, its role is beyond the scope of this thesis and shall therefore not be discussed further in this text.

Figure 6: *SB capsule endoscope (Given Imaging, Yoqneam, Israel) (**A**) and double-balloon enteroscope (**B**) (Fujifilm, Saitama, Japan). Although the SB capsule endoscopy (SBCE) is a less invasive procedure than double-balloon enteroscopy (DBE), SBCE is limited to image capture and is therefore frequently used to 'scout' for SB pathology which may biopsied or treated during a subsequent DBE procedure. (Image **6B** courtesy of Fujifilm, Saitama, Japan)*



DBE overcomes the challenge of deep intubation related to SB anatomy by the employment of 2 latex balloons and a stabilising plastic overtube [20;45;50-54] (**Figure 6B**). The 2 balloons allow for the application of gentle traction on the SB wall for plication of the SB onto the overtube during step-wise 'push-and-pull' manoeuvres in order to prevent SB stretching and minimise unfavourable looping (**Figure 7**) [20;45;50-54]. During the insertion phase, the endoscopist aims to enable deeper SB insertion by 'encouraging' the formation of favourable 'wide' spiral looping (**Figure 8**) while avoiding the formation of 'tight' and unfavourable 's-shaped' deep looping, which may hinder depth of insertion and eventual success of the procedure. In certain cases (particularly in patients with a history of abdomino-pelvic surgery), SB tethering (relating to the presence of post-surgical adhesions), this may still be challenging to achieve and may result in limited SB insertion depths.

Nonetheless, with its ability to be performed via both the oral (anterograde) and rectal (retrograde) routes, DBE facilitates deep enteroscopy and may also allow for pan-enteroscopy (**Figure 8**), thus providing a minimally invasive alternative to IOE [20;45;50-54]. In selected cases endotherapy facilitated by DBE [20;21;24-49], has been shown to obviate the need for operative surgery. Several international registries have also reported on the effectiveness and safety of DBE, but as yet, there are no reports which describe the performance, limitations and complications of DBE within the UK.

Figure 7: *Sequential steps involved during SB insertion at DBE performed via the anterograde route (**A**) and the retrograde route (**B**). Sequential inflation and deflation of the enteroscope (green circle) and overtube (blue circle) balloons coupled with advancement and withdrawal manoeuvres of the enteroscope (black line) and overtube (light-blue line) facilitates plication of the SB onto the overtube and allows enteroscope advancement into the SB in a 'caterpillar' like fashion. (Images courtesy of Sugano K, Yamamoto H & Kita H. Eds; Double-balloon Endoscopy (Nankodo Co Ltd.) (Tokyo) 2005)*

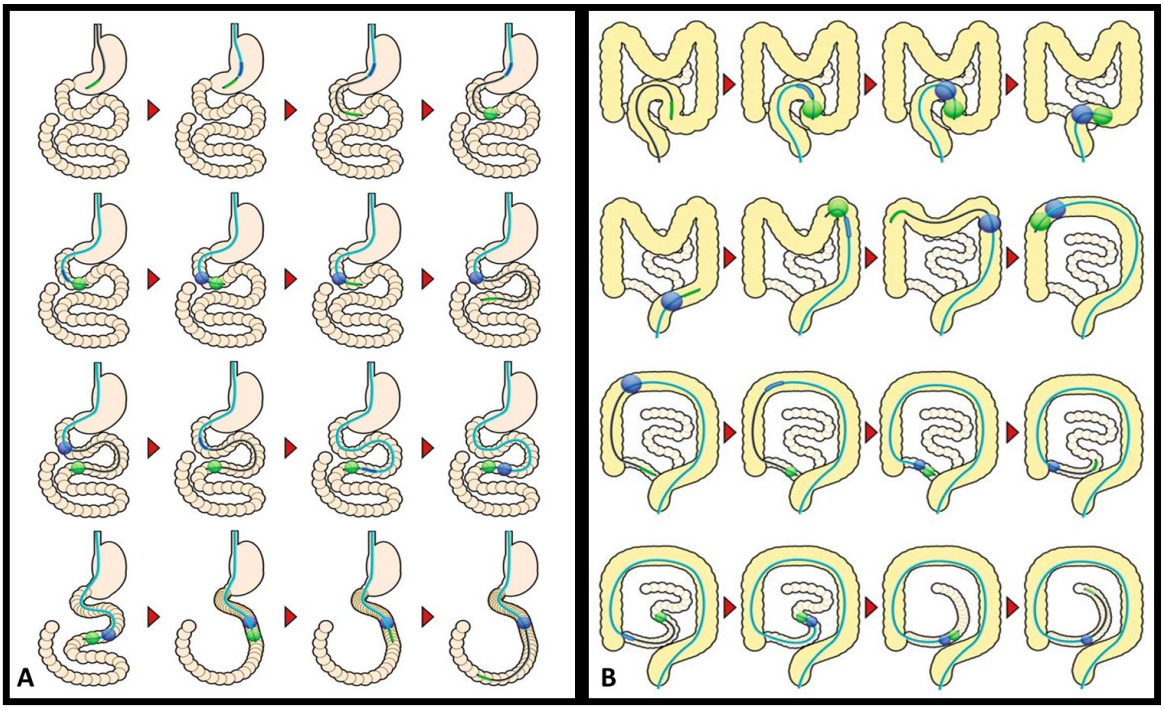
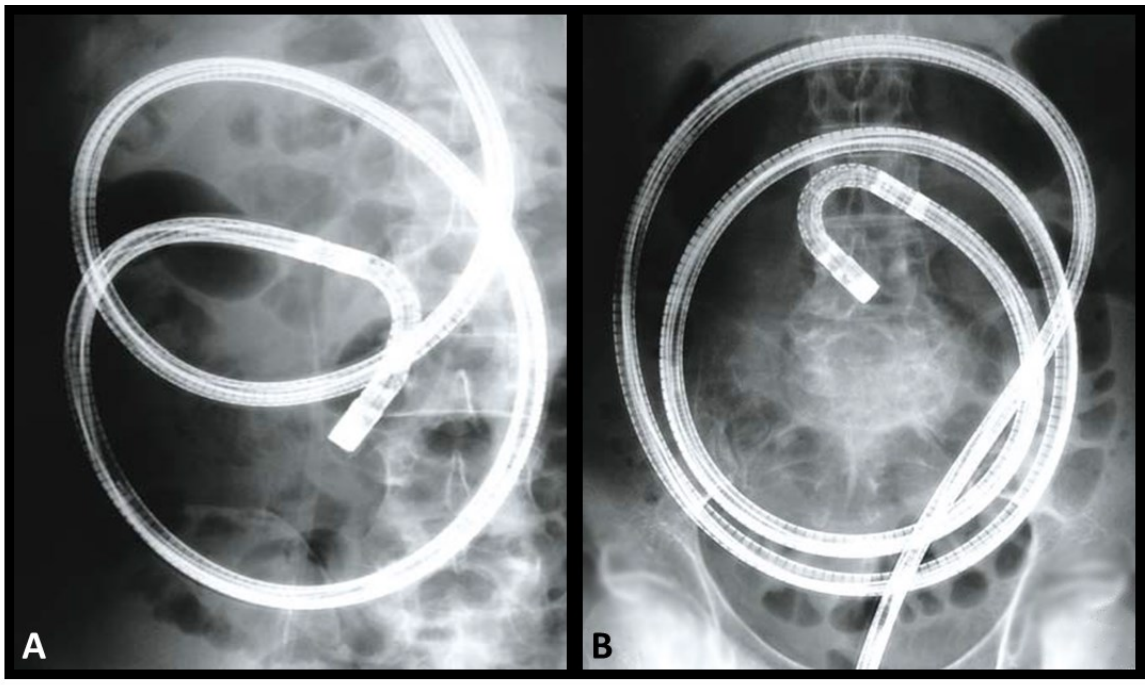


Figure 8: *Fluoroscopy demonstrating insertion of the double-balloon enteroscope through the whole of the SB (pan-enteroscopy) during DBE performed via the anterograde route (**A**) and retrograde route (**B**). In these 2 cases favourable, wide spiral looping has facilitated pan-enteroscopy (Images courtesy of Sugano K, Yamamoto H & Kita H. Eds; Double-balloon Endoscopy (Nankodo Co Ltd.) (Tokyo) 2005)*



Since the introduction of DBE, two other types of device assisted enteroscopy (DAE), namely single-balloon enteroscopy (SBE) [55;56] and manual spiral enteroscopy (SE) [57] have been introduced into clinical use in 2007 and 2008, respectively. While all 3 currently available technologies make use of a stabilising overtube, SBE and DBE use 1 or 2 additional balloons respectively, whereas SE uses a raised soft-plastic spiral (**Figure 9**) in order to provide traction for plication of the SB onto the overtube [20;45;50-52;54;57]. SBE (Olympus, Tokyo, Japan) [55;56] is another form of balloon-assisted enteroscopy which uses a similar principle to DBE (albeit with a single, overtube balloon) to advance an enteroscope (and overtube) through the SB. In view of these similarities and the fact that our unit only uses the double-balloon system, SBE shall not be discussed further in this text.

However, SE uses rotational-traction as an alternative to balloon-assisted traction and appears to enable faster enteroscopy than the DBE technique [57-62]. Nonetheless, it remains uncertain as to whether SE in its currently available (manually-driven) form is able to regularly achieve similar SB insertion depths to those attained during DBE [59-61].

Figure 9: *Spiral enteroscopy (SE) overtube, Endo-Ease Discovery® SB (Spirus Medical, LLC, MA, USA) demonstrating its raised soft-plastic spiral (**A**). 'Engagement' of the SB mucosa, in order to provide traction for forward propulsion of the overtube and enteroscope into the SB (**B**); Insertion of the overtube and enteroscope by clockwise rotation of the overtube (green arrow) during SE (**C**). (Images 9**A** & 9**B**, courtesy of Spirus Medical, LLC, MA, USA)*



1.1.3 Colonoscopy

Incomplete colonoscopy, defined as failure to achieve caecal intubation at colonoscopy is reported to occur in up to 10% of attempted cases [63-65]. If complete colorectal examination is needed after failed colonoscopy, patients may require alternative investigations which in turn, carry their own intrinsic risks (for example, radiation exposure from computed tomographic colonography (CTC)) [66]. These additional investigations may then detect proximal colonic

pathology, necessitating even further attempts at colonoscopy [66]; measures to improve caecal intubation therefore merit serious consideration.

Several studies have identified certain patient-related characteristics associated with technically difficult (TD) colonoscopy, higher risk of failure, increased patient discomfort and longer procedure duration [67-79]. These factors include: female gender [63;65;67;68;70-74;76;77;80-85], increasing age (>60 years) [68-72;74;83], chronic constipation [71;77] (often associated with a 'long redundant colon' (dolichocolon) [65;66;75;76;84;86-91]); small body habitus, as indicated by a low body mass index (BMI) or low waist-to-hip (W/H) ratio [67-70;72;73], a past history of abdominal/pelvic surgery [63;65;69;72;73;77;80;83;84] and a history of failed colonoscopy [65;66;84;92-100]. To date however, these factors have not been incorporated into an evidenced-based combined scoring-system. The development of such a scoring-system may enable endoscopists to predictively risk-stratify patients for TD colonoscopy and may allow strategic planning (e.g. allocation of extended time-slots and dedicated equipment) before such procedures are attempted.

Approaches which have been reported to facilitate successful intubation of the TD colon include: fastidious attention to the application of good basic technique, enhanced loop management aided by use of a magnetic endoscopic imager (MEI) (ScopeGuide® UPD, Olympus, Tokyo, Japan), switching to a paediatric colonoscope or an upper GI endoscope (slimmer instruments with shorter bending sections, which may allow negotiation of tight sigmoid angulations); the use of a colonoscope which incorporates a variable-stiffness shaft (designed to minimise re-looping), longer colonoscopes or enteroscopes and the attachment of a plastic hood to the tip of the chosen instrument (also designed to facilitate passage through an angulated sigmoid colon) [66;84;98;99;101-116]. Despite the use of these strategies and techniques, TD colonoscopy may

still result in failure to achieve caecal intubation, even in the hands of expert colonoscopists [66] and alternative technologies such as the recently developed balloon assisted colonoscopy, double-balloon colonoscopy (DBC) in particular, are being explored for this indication [66;113;117-123].

DBC, being directly derived from DBE, applies the use of gentle bowel wall traction by two latex balloons and a stabilising overtube, to advance a dedicated, slim colonoscope around the colon. The technique of DBC insertion and withdrawal is identical to that used for retrograde-route DBE [20;54;117;122;124] (**Figure 7B**).

DBC may have several potential advantages over conventional colonoscopy (CC):

i) The endoscope itself is narrower and more flexible than a standard colonoscope; this characteristic may allow it to 'slalom' past a sharply angulated and 'fixed-down' sigmoid colon while the overtube and its balloon stabilise the rest of the colon (**Figure 10**)

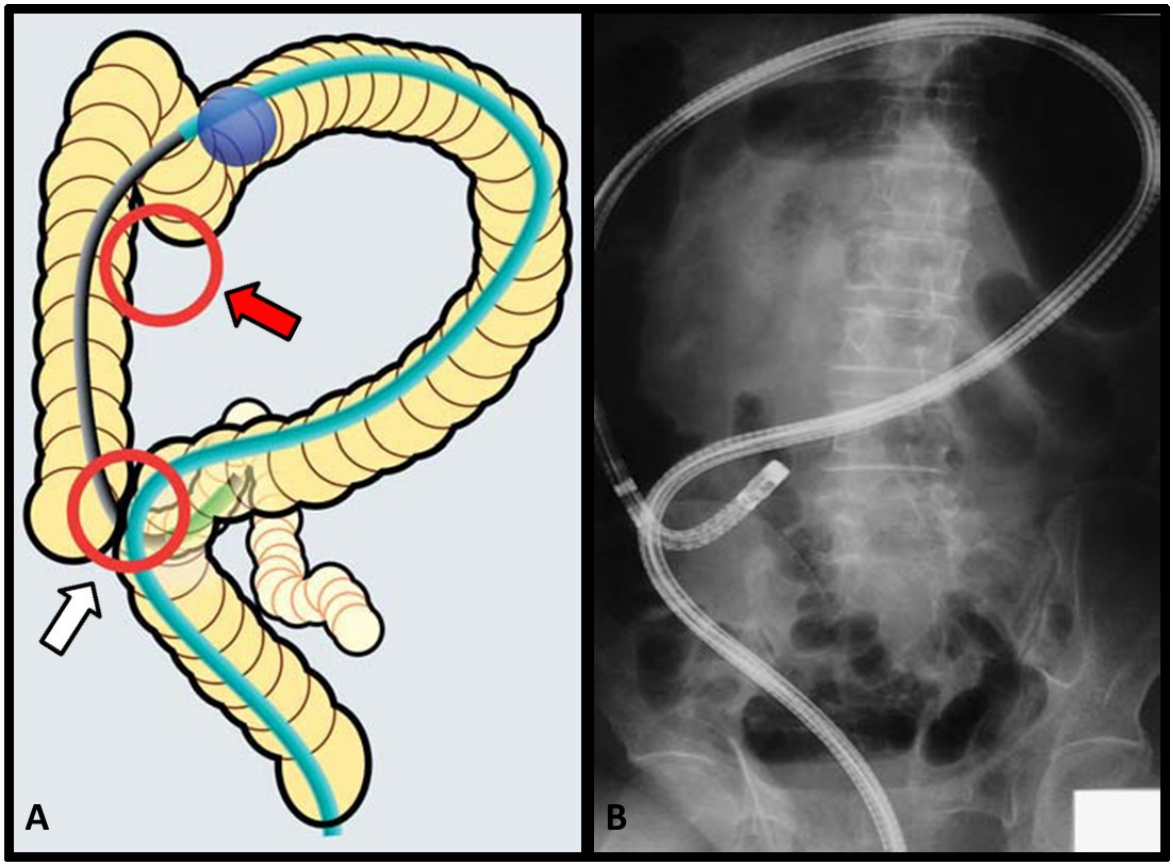
ii) The overtube provides additional stiffness when this is needed to negotiate lengths of redundant colon

iii) The sequential inflation and deflation of the latex balloons on the colonoscope and overtube provide additional stability, while also providing the capacity to plicate (and effectively 'shorten') the colon

Although these potential advantages of DBC have been suggested by 4 non-comparative studies [92;117;121;122], only one prospective randomised study comparing DBC and CC in TD cases has been published to date [113]. This study from Kanagawa, Japan showed that DBC allowed

significantly faster caecal intubation, a higher caecal intubation rate and improved patient comfort as compared to CC (with supplementary use of MEI and a plastic cap at the colonoscope tip). However, parameters relating to patient selection with regards to TD were based solely on the experience of a previous colonoscopy. Studies which incorporate an objective, evidence-based 'predictive' scoring-system for TD may add value to further DBC vs. CC comparisons.

Figure 10: *Cartoon (**A**) and corresponding fluoroscopic image (**B**) demonstrating complete colonoscopy achieved by the use of a double-balloon colonoscope. The red circles seen in (**A**) represent post-surgical adhesive disease affecting the sigmoid colon and caecum (white arrow) and the transverse and ascending colon (red arrow). (Images courtesy of Sugano K, Yamamoto H & Kita H. Eds; Double-balloon Endoscopy (Nankodo Co Ltd.) (Tokyo) 2005)*



1.2 Research rationale and hypothesis

1.2.1 Rationale

Research into the optimal role and effectiveness of these flexible endoscopic technologies in clinical practice remains limited.

- Although several investigators from other countries have studied the use of T-OGD vis-à-vis C-OGD, no studies on its potential role in a UK clinical paradigm have been performed.

- An evaluation of the performance, limitations and safety of DBE practice in the UK is also lacking. Furthermore, data on the impact of DBE endotherapy on Crohn's disease (CD) SB strictures, Peutz-Jeghers (PJS) SB polyposis and enteral feeding access are still required. Data evaluating for any potential benefits of the newer SE technology as compared with DBE are still sparse and to date only 2 prospective studies have attempted this comparison.

- Although several factors have been shown to be associated with TD colonoscopy, these have never been incorporated into a scoring-system which may allow colonoscopists to predict a TD procedure. The development of an evidence based scoring-system may allow pre-planning for TD cases e.g. with the allocation of longer time-slots and choice of ancillary equipment. Such a scoring-system may also facilitate more objective case-selection for research studies evaluating the use of new technologies (such as DBC) for

TD colonoscopy. No comparisons of DBC vs. CC for TD colonoscopy as defined by evidence-based criteria have been performed to date.

This research attempts to address some of these issues by investigating the performance, limitations and safety of advanced flexible endoscopic technologies, focusing particularly on the evaluation of patient comfort, diagnostic ability and new therapeutic indications in the provision of minimally invasive care.

1.2.2 Hypothesis

'Technological advancements in flexible GI endoscopy, in the form of ultrathin endoscopes and device assisted enteroscopy and colonoscopy systems will provide an alternative, minimally invasive option of care which is both safe and effective'

Specifically, the aims of this research were to:

i) Perform the first evaluation of performance of ultrathin T-OGD as an alternative to C-OGD in a UK setting (**Chapter 2**)

ii) Perform the first evaluation of performance, limitations and complications of DBE in clinical practice within the UK (**Chapter 3**)

iii) Describe original DBE techniques (developed by the author and the author's co-supervisor, during the conduct of this research), designed to surmount technical

challenges which may impede DBE in the setting of a retroverted ileo-caecal valve or unfavourable looping, relating to adhesive disease or a short SB mesentery (**Chapter 4**)

iv) Examine the effectiveness and safety of DBE facilitated dilatation of CD SB strictures (**Chapter 5**)

v) Examine the effectiveness and safety of DBE facilitated polypectomy of clinically significant SB polyps in patients with Peutz-Jeghers syndrome (PJS) (**Chapter 6**)

vi) Examine the feasibility and safety of DBE facilitated direct percutaneous endoscopic jejunostomy (DPEJ) tube placement (**Chapter 7**)

vii) Compare the performance of DBE and SE in the same cohort of patients (**Chapter 8**)

viii) Compare the performance of DBC and CC in TD colonoscopy (incorporating the use of a newly proposed, original, evidenced-based scoring-system for selection of TD cases) (**Chapter 9**)

2 Evaluating the role of transnasal upper gastrointestinal (GI) endoscopy as compared with conventional (oral) GI endoscopy in a UK clinical setting

2.1 Background

Patient discomfort during oesophagogastroduodenoscopy (OGD) via the conventional, oral route (C-OGD) is due mainly to repeated triggering of the gag reflex. Although C-OGD is employed in daily practice, patients often find it to be an unpleasant experience, which frequently warrants the use of intravenous sedation [1-3]. However, sedation use is associated with additional risks, prolonged patient recovery duration and added costs [1;3;5;6;125-128].

Since unsedated transnasal OGD (T-OGD) was introduced as alternative to C-OGD by Shaker [4], several studies done in other countries have demonstrated its feasibility and association with improved patient tolerance [2;8-13;16]. Despite these findings, adoption of T-OGD into mainstream clinical practice, possibly due to cultural or other perceptions has varied widely, with rapid adoption in Japan and less wide acceptance in parts of Europe [14-17]. In the UK for example, the potential role for T-EGD in clinical practice has not been formally evaluated to date. In order to address this and to explore the potential benefits of 2 different sized ultrathin

(UT) endoscopes for both T-OGD and C-OGD, we performed the St Mark's Conventional Endoscopy versus trans-Nasal endoscopy sTudy (SCENT).

2.2 Aims

The primary objective was to compare T-OGD using UT (5.9mm, 4-way angulation endoscopes, T-OGD1 or 4.9mm, 2-way angulation endoscopes, T-OGD2) with C-OGD using standard 9.0mm endoscopes, C-OGD1 or UT (5.9mm, 4-way angulation, or 4.9mm, 2-way angulation) endoscopes, C-OGD2 (**Table 1**) in a UK clinical setting. Parameters of patient tolerance, endoscopic quality, patient safety and feasibility of the OGD (patient preparation, procedure and recovery duration and technical ease of the procedure) were assessed. The secondary objective was to compare all groups (i.e. T-OGD1 vs. T-OGD2, C-OGD1 vs. C-OGD2 and C-OGD2 vs. T-OGD) in addition to T-OGD with C-OGD with or without sedation. A quick-reference guide to the type of procedure performed in each group is shown (**Table 2**).

Table 1: *Technical specifications of UT endoscopes used in SCENT*

Table 1: Technical specifications of UT endoscopes used in SCENT

Model /Make	Angulation	Field of view	Depth of field (mm)	Shaft diameter (mm)	Accessory channel diameter (mm)	Working length (mm)
EG-530N/ (Fujifilm, Saitama, Japan)	210˚up/90˚down 100˚ left/100˚ right	120˚	3-100	5.9	2.0	1100
EG-530NP/ (Fujifilm, Saitama, Japan)	210˚up/120˚down No left/right angulation	120˚	3-100	4.9	2.0	1100
GIF-N60/ (Olympus, Tokyo, Japan)	210˚up/120˚down No left/right angulation	120˚	3-100	4.9	2.0	1100

Table 2: *Quick reference guide to type of procedure performed in each group*

Table 2: Type of procedure performed in each group		
Group name	**Route of OGD**	**Shaft diameter of endoscope used (mm)**
C-OGD1	Oral	9.0
C-OGD2	Oral	4.9 or 5.9
T-OGD1	Transnasal	5.9
T-OGD2	Transnasal	4.9

2.3 Methods

2.3.1 Patients

The study was performed between September 2008 and November 2009; patients (both genders, over 18 years-of-age and able to give informed consent) referred to our institution for routine diagnostic OGD were invited to participate. Exclusion criteria were the following: patient reluctance to undergo a T-OGD or to participate in the study, history of major nasal trauma or nasal/sinus surgery, recurrent epistaxis, haemorrhagic tendency, use of anticoagulation, severe cardio-respiratory co-morbidity (American Society of Anesthesiologists physical status ≥4) and/or allergy to drugs used (lidocaine, phenylephrine and midazolam) during OGD. All patients fulfilling the entry criteria gave their written informed consent to participate. The research protocol and conduct of the study was approved by the regional research ethics committee and by the institution's research and development review board (Harrow REC (North London REC 3) Ref. 08/H0719/24; RD 8/038) and is registered with the International Standard Randomised Controlled Trial Number Register (ISRCTN77474635). The study was carried out

in accordance with the World Medical Association Declaration of Helsinki, 1964 (incorporating all later amendments) [129].

2.3.2 Study design

This was a prospective, randomized, comparative study (of parallel design). Participating patients were randomized 1:1 with a computer-generated random number sequence, to 1 of 4 groups: T-OGD1, T-OGD2, C-OGD1 or C-OGD2. Patients were allocated their designated procedure by an endoscopy research fellow or a research nurse.

2.3.3 Endoscopic procedures

Prior to OGD procedures, patients were instructed to withhold oral intake for 6 hours. All procedures were performed by 1 of 4 experienced endoscopists (1 consultant, 2 advanced endoscopy fellows and 1 senior nurse endoscopist) proficient in both oral and transnasal upper gastrointestinal endoscopy. Patients in the T-OGD group received local anaesthesia to the nasal passages in the form of fine-mist sterile nasal spray consisting of 5% lidocaine and 0.5% phenylephrine (co-phenylcaine nasal spray, Aurum Pharmaceuticals, Romford, UK), standardized to 4 sprays into each nostril (**Figure 11A**, Co-phenylcaine spray, with fine-mist spray nozzle attached). The phenylephrine component of the nasal spray served the purpose of a topical vasoconstrictor, to decongest the nasal passages and reduce the risk of peri-procedure epistaxis. Approximately 3 minutes after the application of the local anaesthetic, patients in the T-OGD group had a soft-silicone 6mm diameter dilatation catheter (N 18F-SS, Fujifilm, Saitama, Japan) (**Figure 11B**), (lubricated with non-proprietary 2%, aqueous lidocaine gel) inserted 80mm deep into either nasal passage (**Figure 11C**). This ensured the nasal passage

chosen for the T-OGD was wide enough and well lubricated to allow insertion and withdrawal of the endoscope.

Figure 11: *Co-phenylcaine spray (with fine-mist spray nozzle attached) (**A**); Soft-silicone, (6mm diameter) transnasal preparation catheter before transnasal insertion (**B**) and on transnasal insertion through patient's right nostril (**C**).*

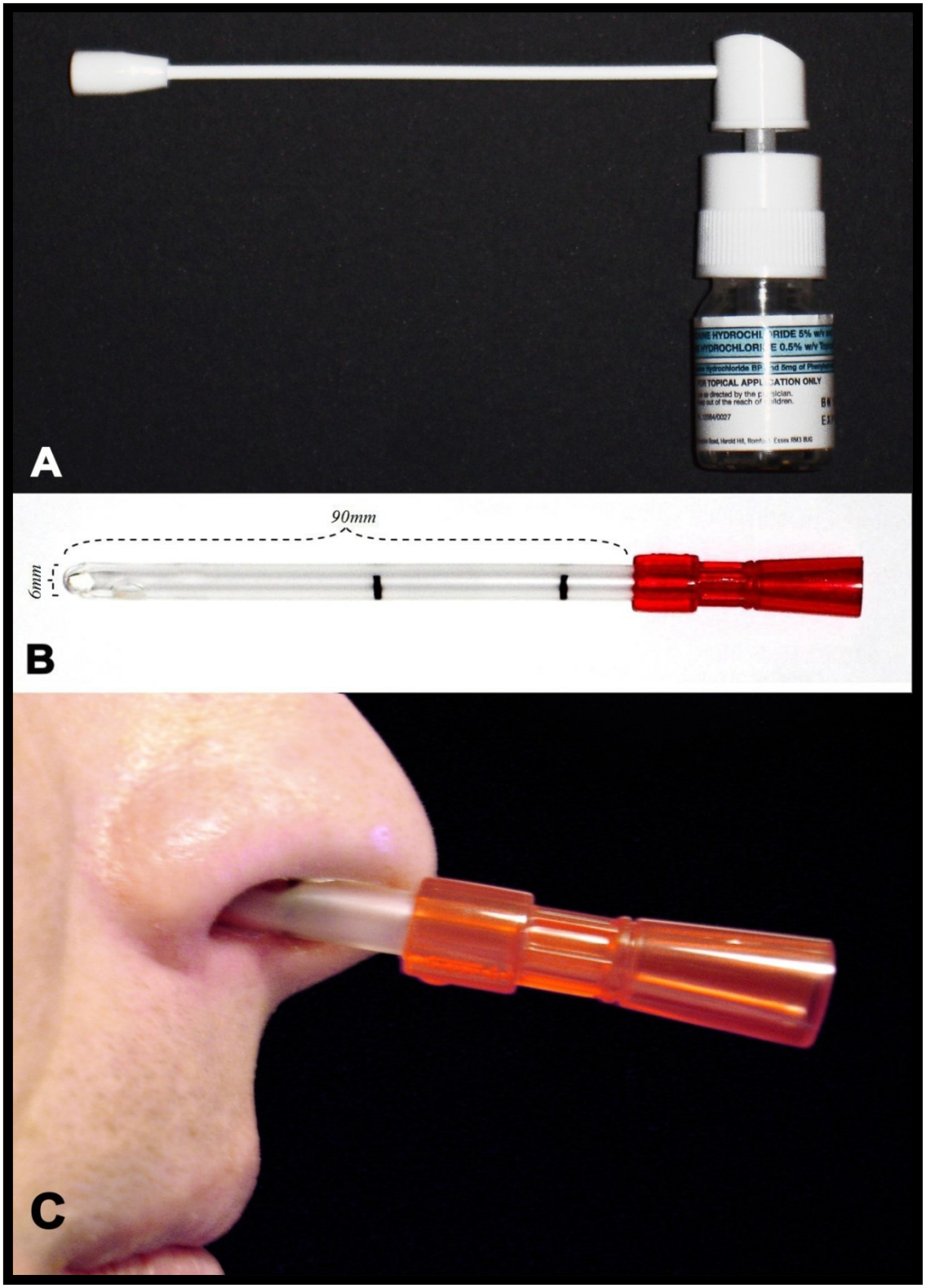
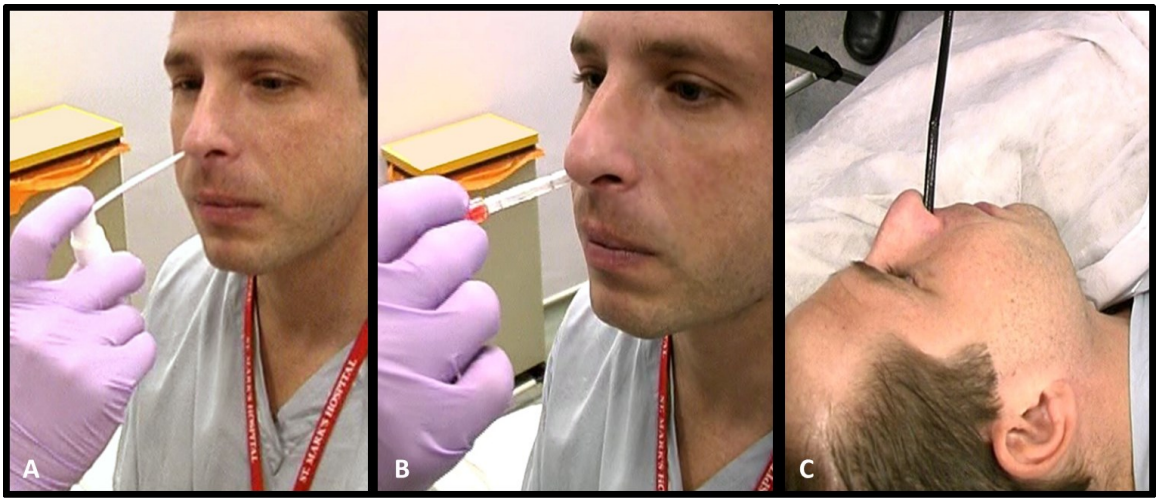


Figure 12: *Right nostril being prepared with co-phenylcaine spray (**A**); insertion of soft-silicone transnasal preparation catheter into right nostril (**B**) and transnasal endoscopy being performed through the right nostril (with the patient in the left lateral decubitus position) (**C**).*



If neither of the nasal passages allowed catheter insertion, the T-OGD was converted to a C-OGD2 procedure. Patients who underwent C-OGD received local anaesthesia to their oro-pharynx in the form of 10 sprays of 10% lidocaine (Xylocaine®, Astra Zeneca, London, UK) and intravenous conscious sedation (using low dose intravenous non-proprietary midazolam), given only on demand. Supplemental oxygen was only given to patients who required intravenous conscious sedation.

OGD procedures were carried out using a standardized method according to the study protocol with patients in the left lateral decubitus position. Upper gastrointestinal (GI) anatomical 'landmarks' (i.e. oesophageal, gastro-oesophageal junction, forward and retroflexed views of the stomach, views of the 1st (D1) and 2nd parts (D2) of the duodenum) were photo documented. Anti-foaming agent (bubble-breaker) in the form of 1% simethicone suspension (Infacol®, Forest

Laboratories, Dartford, UK) was sprayed down the endoscope working channel to improve endoscopic view quality as required.

All UT endoscopes were equipped with charge-coupled device (CCD) technology, giving optical characteristics comparable to the GIF-XQ260 (9.0mm diameter) endoscope (Olympus, Tokyo, Japan) used for C-OGD1 procedures. Technical specifications of the UT endoscopes are described (**Table 1**).

2.3.4 Questionnaires

Separate questionnaires incorporating 10cm visual analogue scales (VAS) [130] were used to evaluate i) patient tolerance, ii) endoscopic view quality, iii) patient safety and iv) technical ease of the procedure. Patient preparation, procedure and recovery duration were recorded. Patient satisfaction with the procedure undertaken was recorded on a 5-point Likert scale [131] (very satisfied, satisfied, neutral, dissatisfied or very dissatisfied).

i) Evaluation of patient tolerance

On recovery, the patients were assessed on their tolerance to the OGD procedure by marking a 10cm VAS (0, non-existent; 10, unbearable) to quantify 5 separate sensations: overall discomfort, pain, gagging sensation, nausea and anxiety. Similar VAS's for perceived patient overall discomfort and anxiety were completed by the endoscopist and the attending nurse.

ii) Evaluation of view quality

The following views of the upper GI tract were scored by the endoscopist, using a 10 cm VAS (0, very poor views; 10 very good views): oesophagus, forward (F) view and retroflexed (R) views of the stomach, D1 and D2 in addition to overall impression of quality of endoscopic view.

iii) Evaluation of patient safety

Measurements of patient vital parameters (lowest and highest systolic blood pressure, lowest and highest heart rates and lowest oxygen saturations) taken by nurses during the endoscopy were used as surrogate markers of patient safety.

iv) Evaluation of feasibility

Technical handling and ease of procedure performance were evaluated by the endoscopist using a 10cm VAS (0, very difficult; 10 very easy) to quantify 5 separate parameters relating to: technical difficulty or ease of endoscope insertion, general handling of the instrument, intubation of the 2nd part of duodenum and taking of random or targeted biopsies. In addition, the endoscopist's overall impression of practical feasibility of the procedure was evaluated. Duration of pre-procedure patient preparation (from the start of application of local anaesthetic spray to the start of insertion of the endoscope), actual OGD procedure duration (from start of insertion to end of withdrawal of the endoscope) and the post procedure recovery period (from end of OGD to when nurses were satisfied the patient was able to drink water without spluttering and to leave the endoscopy unit safely) were recorded as markers of overall practical feasibility.

2.3.5 Statistical analysis

Power calculation and statistical analyses were performed with the assistance of a nominated consultant medical statistician. By recruiting 50 patients into each group (C-OGD1, COGD2, T-OGD1 or T-OGD2) it was calculated that the study had 90% power to detect a difference of at least 2 units on the VAS between groups for the primary objective parameters (considering a standard deviation of 2.5). A *P* value of <0.05 was regarded to be statistically significant. Patient demographics (age and gender) in the different groups were analysed using the Kruskal-Wallis test and the χ^2 test respectively. Specific comparisons of the various recorded parameters between types of OGD were pre-determined before commencing the analysis of the data. The majority of the outcomes were measured on a continuous scale and the appropriate analysis method was dependent on the distribution of the outcome measure. For outcomes found to be normally distributed, analysis of variance (ANOVA) followed by linear contrasts were used to compare between the different OGD types. For outcomes that were not found to be normally distributed, the Mann-Whitney U test was used to compare between OGD groups. Categorical outcomes such as success of T-OGD procedures, diagnostic yield and biopsy quality were assessed using Fisher's exact test.

2.4 Results

2.4.1 Study population

Of a total number of 286 patients assessed for eligibility to participate in the study, 86 were excluded, due to a history of nasal trauma/surgery, recurrent epistaxis or on-going use of anticoagulation (n=12) or because of refusal to participate (n=74). The remaining 200 patients

(106 women and 94 men; median age, 54 years; range 19-95 years) were prospectively recruited over a period of 18 months as shown in the CONSORT [132] study flowchart (**Figure 13**).

Patient demographics and indications for OGD are shown (**Table 3**). There were no significant demographic differences among the patients in the 4 study groups. Passage of UT endoscopes via the transnasal route was possible in 48/50 (96%) T-OGD1 procedures and 46/50 (92%) T-OGD2 procedures (P=0.69). Failure of passage of catheter or UT endoscope was due to narrow (bilateral) nasal passages in all 6 patients. The failed procedures were converted to C-OGD2 procedures and analysed as such for the purposes of the study.

Figure 13: *SCENT flow diagram (CONSORT [132])*

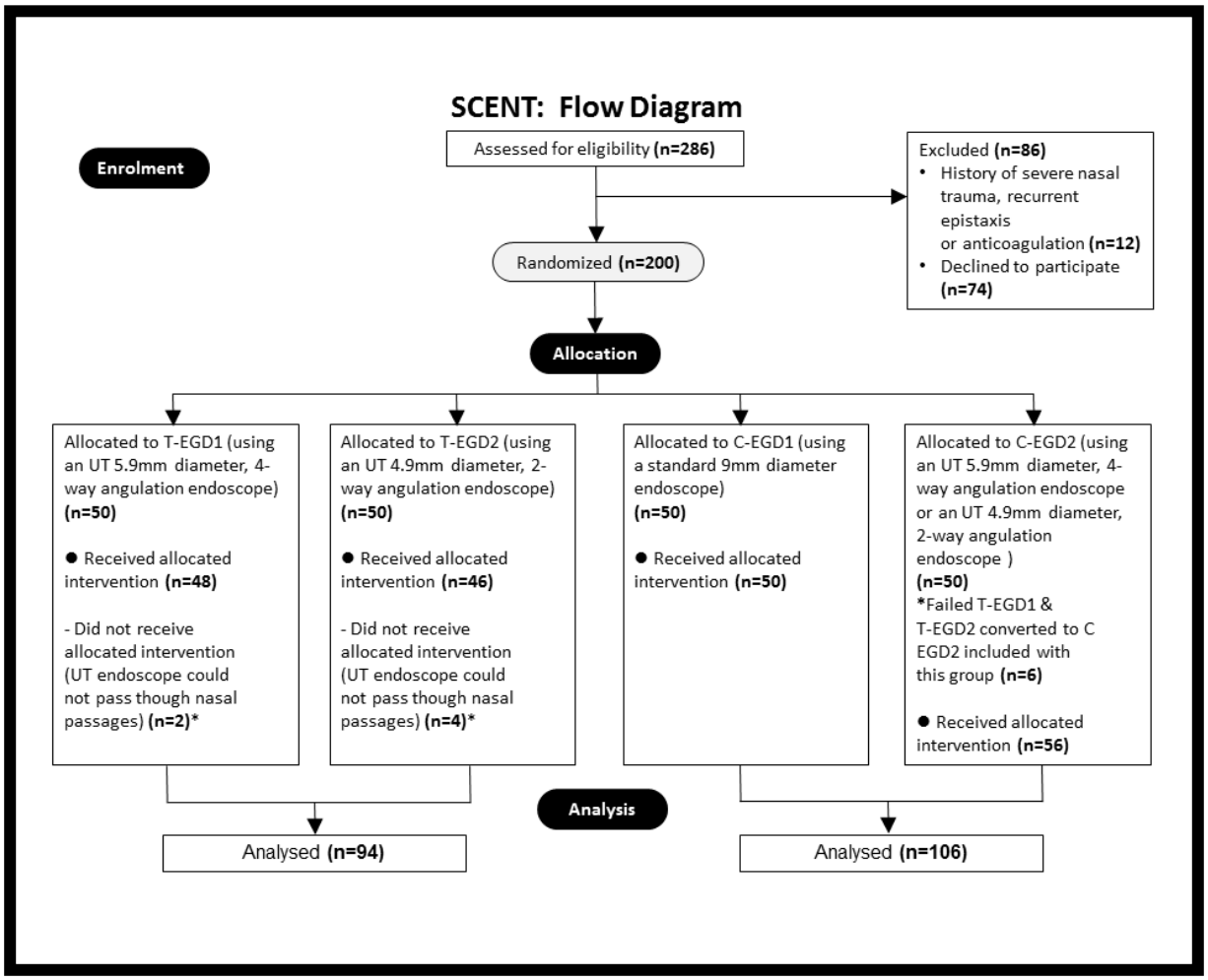


Table 3: *Patient demographics and indications for OGD *Kruskal-Wallis test; **χ2 test; P values compare the differences in demographic variables among the four study groups and show that there are no significant differences among the groups*

Table 3: Patient demographics and indications for esophagogastroduodenoscopy (OGD)					
	C-OGD1	**C-OGD2**	**T-OGD1**	**T-OGD2**	
Patients (n)	50	56	48	46	
Age (median; range)(years)	54 (23-87)	53 (22-95)	54 (19-89)	55 (26-84)	P=0.98*
Gender (women/men)	22/28	34/22	25/23	25/21	P=0.29**
Indications (n)					
Dyspepsia	22	27	25	22	
Iron deficiency anaemia	6	10	2	6	
Weight loss	7	4	7	5	
Reflux symptoms	5	6	6	3	
Dysphagia	4	1	5	4	
Barrett's surveillance	1	0	0	0	
Melaena	2	2	1	0	
Gastric ulcer follow-up	0	2	1	2	
Malabsorption	1	0	0	1	
Coeliac disease follow-up	0	2	0	1	
Nausea/vomiting	2	2	1	2	

2.4.2 Comparison of C-OGD1 and T-OGD

Outcomes between patients undergoing C-OGD1 (n=50) and T-OGD (n=94) were examined first (**Figure 14, Table 4A**). Median preparation and procedure times increased by 16% and 30% respectively for T-OGD compared with C-OGD1 (5.5 vs. 4.6 minutes, P <0.001 and 10.0 vs. 7.0 minutes, P=0.004). However, T-OGD was associated with a 50% reduction in recovery time (5 vs. 10 minutes, P <0.001). Mean systolic blood pressure (SBP) during procedures was lower in the C-OGD1 group compared with the T-OGD group (122 vs. 132 mm Hg, P <0.02). Median VAS scores reflecting patient tolerance were all lower (i.e. better tolerance) for T-OGD with a 60% reduction in overall discomfort score for T-OGD compared with C-OGD1 (1.6 vs. 4.0, P <0.001). Median pain, gagging, nausea and anxiety scores were reduced by 71% (0.7 vs. 2.4, P

<0.02), 73% (1.0 vs. 3.7, *P* <0.001), 83% (0.4 vs. 2.4, *P* <0.001) and 70% (1.0 vs. 3.3, *P* <0.001) respectively when compared with C-OGD1. Nurse and endoscopist VAS scores for perceived patient anxiety and discomfort mirrored the reduction in patient VAS scores for T-OGD (**Table 4A**). No differences were detected in quality of endoscopic views obtained (s**upplemental images, Appendix 2.5)** and in technical handling of instruments between T-OGD and C-OGD1.

Figure 14: *Box plots comparing preparation duration, procedure duration and recovery duration **(14A)** and patient tolerance VAS tolerance scores, **(14B)** for C-OGD1 and T-OGD procedures. Values are expressed as medians (horizontal lines) and 25th and 75th percentiles (boxes) of the interquartile range (IQR). The whiskers of the box plots are set at 1.5x the 25th and 75th percentile respectively; *Mann-Whitney test.*

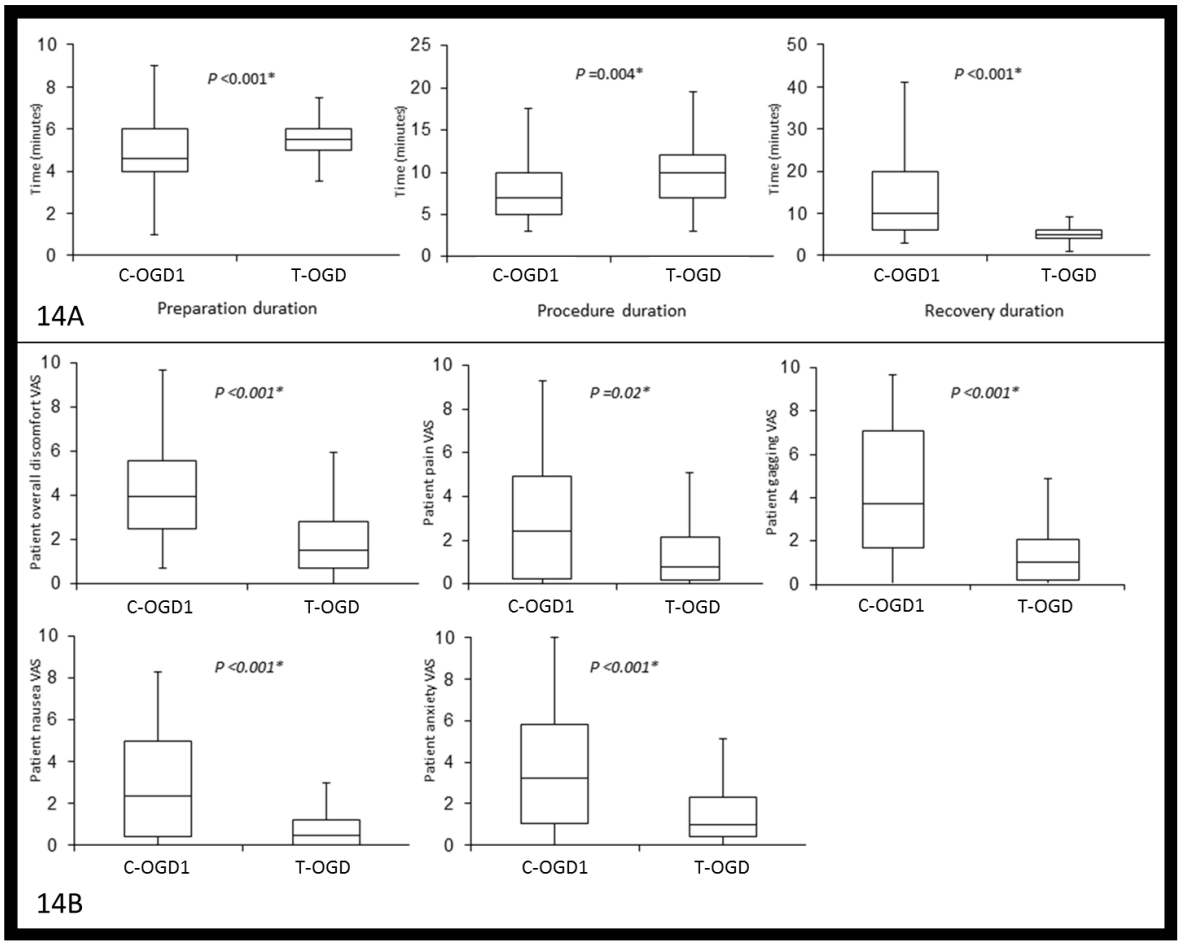


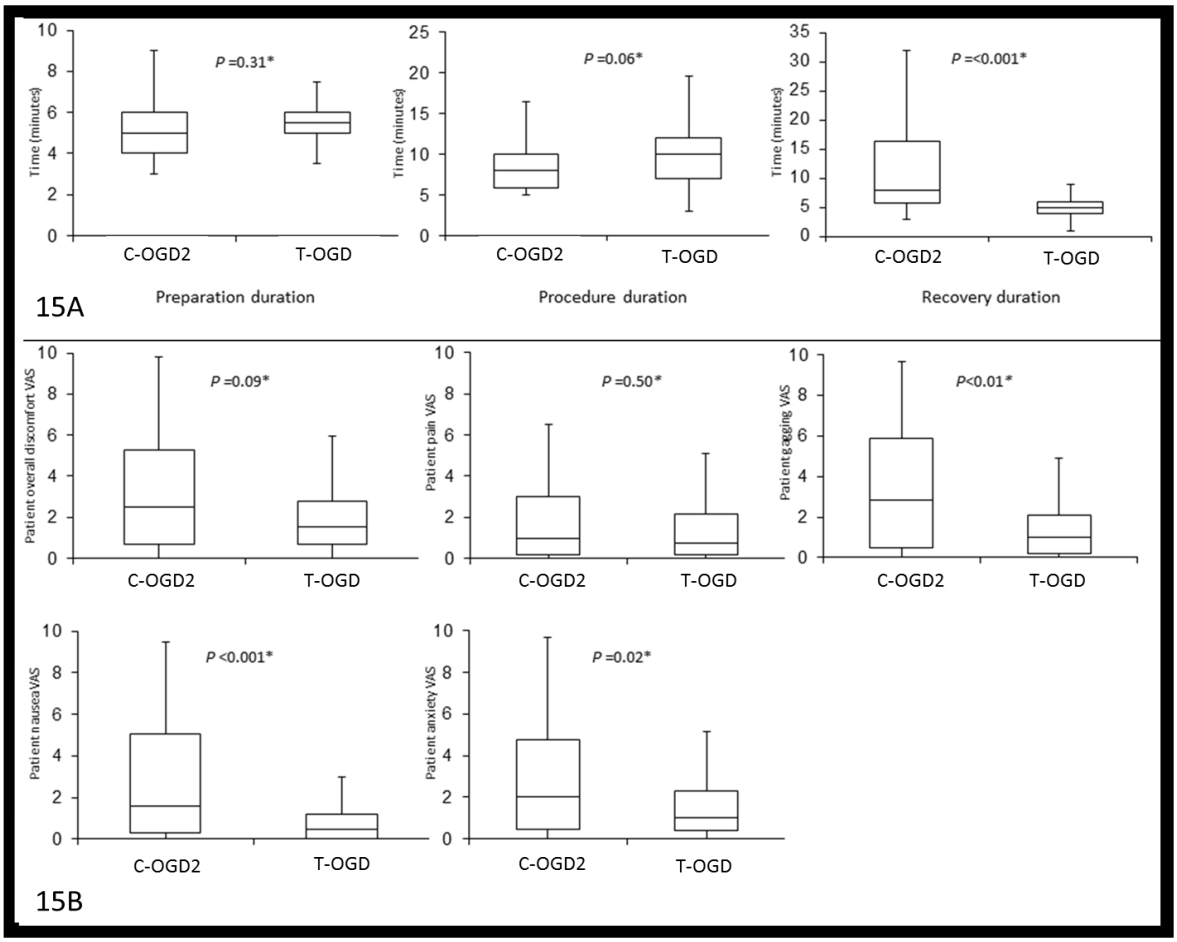
Table 4: *Overall comparative study of variables between C-OGD1 and T-OGD (T-OGD1 + T-OGD2), (**4A**) and between C-OGD2 and T-OGD, (**4B**); (Patient=patient's VAS score; Nurse=Nurses VAS score; Endosc. =Endoscopist's VAS score); IQR, interquartile range; †ANOVA, linear contrasts; ‡ Mann-Whitney test*

	4A			4B		
Variable	**C-OGD1 Mean (SD)**	**T-OGD Mean (SD)**	**P-value†**	**C-OGD2 Mean (SD)**	**T-OGD Mean (SD)**	**P-value†**
Lowest Systolic BP (mmHg)	122 (23)	132 (24)	**0.02**	128 (23)	132 (24)	0.34
Highest Systolic BP (mmHg)	140 (26)	145 (27)	0.22	143 (19)	145 (27)	0.87
Lowest Pulse Rate (beats per	79.4 (11.7)	76.6 (12.4)	0.21	78.1 (13.0)	76.6 (12.4)	0.97
Highest Pulse Rate (beats per	91.0 (13.9)	86.0 (13.5)	0.05	87.6 (15.9)	86.0 (13.5)	0.13
Lowest O_2 Saturation (%)	98 (97, 99)	97 (96, 99)	0.11	98 (95, 99)	97 (96, 99)	0.19
	C-OGD1 Median (IQR)	**T-OGD Median (IQR)**	**P-value‡**	**C-OGD2 Median (IQR)**	**T-OGD Median (IQR)**	**P-value‡**
Nurse - Discomfort	3.5 (1.3, 4.5)	1.3 (0.5, 2.2)	**<0.001**	2.2 (1.3, 4.5)	1.3 (0.5, 2.2)	**0.003**
Nurse - Anxiety	3.1 (1.2, 4.5)	1.2 (0.5, 2.5)	**<0.001**	2.0 (0.7, 4.3)	1.2 (0.5, 2.5)	**0.009**
Endosc. - Discomfort	4.2 (2.5, 7.3)	0.7 (0.4, 1.5)	**<0.001**	3.0 (0.5, 5.0)	0.7 (0.4, 1.5)	**<0.001**
Endosc. - Anxiety	4.4 (2.7, 7.5)	0.8 (0.4, 2.0)	**<0.001**	3.5 (1.2, 6.5)	0.8 (0.4, 2.0)	**<0.001**
Endosc. - Ease of insertion	9.0 (8.6, 9.3)	9.2 (8.7, 9.4)	0.25	9.2 (9.1, 9.5)	9.2 (8.7, 9.4)	0.97
Endosc. - Overall handling	9.2 (8.7, 9.4)	9.0 (8.6, 9.4)	0.75	9.3 (9.0, 9.5)	9.0 (8.6, 9.4)	0.41
Endosc. - D2 intubation	9.2 (8.6, 9.4)	9.0 (8.5, 9.4)	0.28	9.2 (9.0, 9.5)	9.0 (8.5, 9.4)	0.10
Endosc. - Random biopsies	9.2 (8.9, 9.4)	9.0 (8.6, 9.4)	0.06	9.2 (9.0, 9.5)	9.1 (8.6, 9.4)	0.08
Endosc. - Targeted biopsies	9.2 (8.8, 9.4)	9.0 (8.5, 9.3)	0.06	9.2 (9.0, 9.5)	9.0 (8.5, 9.3)	0.07
Endosc - Feasibility	9.1 (8.6, 9.3)	9.0 (8.7, 9.3)	0.99	9.2 (9.0, 9.5)	9.0 (8.7, 9.3)	0.39
Endosc. - View oesophagus	9.1 (8.6, 9.3)	9.0 (8.4, 9.3)	0.21	9.0 (8.8, 9.4)	9.0 (8.4, 9.3)	0.32
Endosc. - View stomach (F)	9.2 (8.7, 9.3)	9.0 (8.2, 9.2)	0.08	9.0 (8.8, 9.4)	9.0 (8.2, 9.2)	0.07
Endosc. - View stomach (R)	9.0 (9.0, 9.0)	9.0 (8.0, 9.0)	0.18	9.0 (9.0, 9.0)	9.0 (8.0, 9.0)	0.21
Endosc. - View D1	9.1 (8.7, 9.2)	9.0 (8.5, 9.2)	0.22	9.0 (8.7, 9.3)	9.0 (8.5, 9.2)	0.24
Endosc. - View D2	9.2 (8.9, 9.3)	9.1 (8.4, 9.3)	0.06	9.0 (8.8, 9.3)	9.0 (8.4, 9.3)	0.08
Endosc. - Overall view	9.1 (8.5, 9.2)	8.9 (8.4, 9.2)	0.47	9.0 (8.8, 9.4)	8.9 (8.4, 9.2)	0.50

2.4.3 Comparison of C-OGD2 (UT endoscopes) and T-OGD

Outcomes between C-OGD2 using ultrathin endoscopes (n=56) and T-OGD (n=94) were examined (**Figure 15, Table 4B**). No differences were found in vital parameters or preparation duration. There was a 30% increase in median procedure time for T-OGD (10.0 vs. 7.0 minutes, *P*=0.005) offset by a 38% reduction in median recovery time (8.0 vs. 5.0 minutes, *P* <0.001). Although there was no difference in median VAS score for pain, there was a trend in reduction of median overall discomfort for T-OGD (*P*=0.09). A 67% reduction in patient gagging median VAS score (1.0 vs. 3.0, *P* <0.001) for T-OGD compared with C-OGD2 (**Figure 15**) was noted. Nausea and anxiety median VAS scores were reduced by 75% and 50% (0.4 vs. 1.6, *P* <0.001and 1.0 vs. 2.0, *P*=0.02) respectively for T-OGD. Nurse and endoscopist VAS scores for perception of patient discomfort and anxiety were also significantly lower for T-OGD (**Table 4B**).

Figure 15: *Box plots comparing preparation duration, procedure duration and recovery duration, (**15A**) and patient tolerance VAS tolerance scores, (**15B**) for C-OGD2 and T-OGD procedures. Values are expressed as medians (horizontal lines) and 25th and 75th percentiles (boxes) of the interquartile range (IQR). The whiskers of the box plots are set*



2.4.4 Comparison of C-OGD without sedation (sub-group) and T-OGD

Outcomes between unsedated C-OGD (C-OGD1 and C-OGD2 unsedated, n=77) and T-OGD (T-OGD1 and T-OGD2, n=94) were examined (**Figure 16A, Table 5A**). Median T-OGD preparation and procedure times increased by 9% and 20% respectively (5.5 vs. 5 minutes, *P*=0.001 and 10.0 vs. 7.0 minutes, *P*=0.005) compared with unsedated C-OGD. Recovery time for T-OGD was 38% less than for unsedated C-OGD (5 vs. 8 minutes, *P* <0.001). Median patient VAS tolerance scores were generally lower (i.e.

better tolerance) for T-OGD with a 43% reduction in overall discomfort (1.6 vs. 2.8, *P*=0.001). Patient VAS scores for gagging, nausea and anxiety reduced by 71% (1.0 vs. 3.4, *P* <0.001), 78% (0.4 vs. 1.8, *P* <0.001) and 60% (1.0 vs. 2.5, *P* <0.001) respectively. Nurse and endoscopist VAS scores for patient anxiety and discomfort were also significantly lower for the T-OGD (**Table 5A**).

Figure 16: *Box plots comparing preparation duration, procedure duration and recovery duration, (**16A**) and patient tolerance VAS tolerance scores, (**16B**) for unsedated C-OGD and T-OGD procedures. Values are expressed as medians (horizontal lines) and 25th and 75th percentiles (boxes) of the interquartile range (IQR). The whiskers of the box plots are set at 1.5x the 25th and 75th percentile respectively; *Mann-Whitney test.*

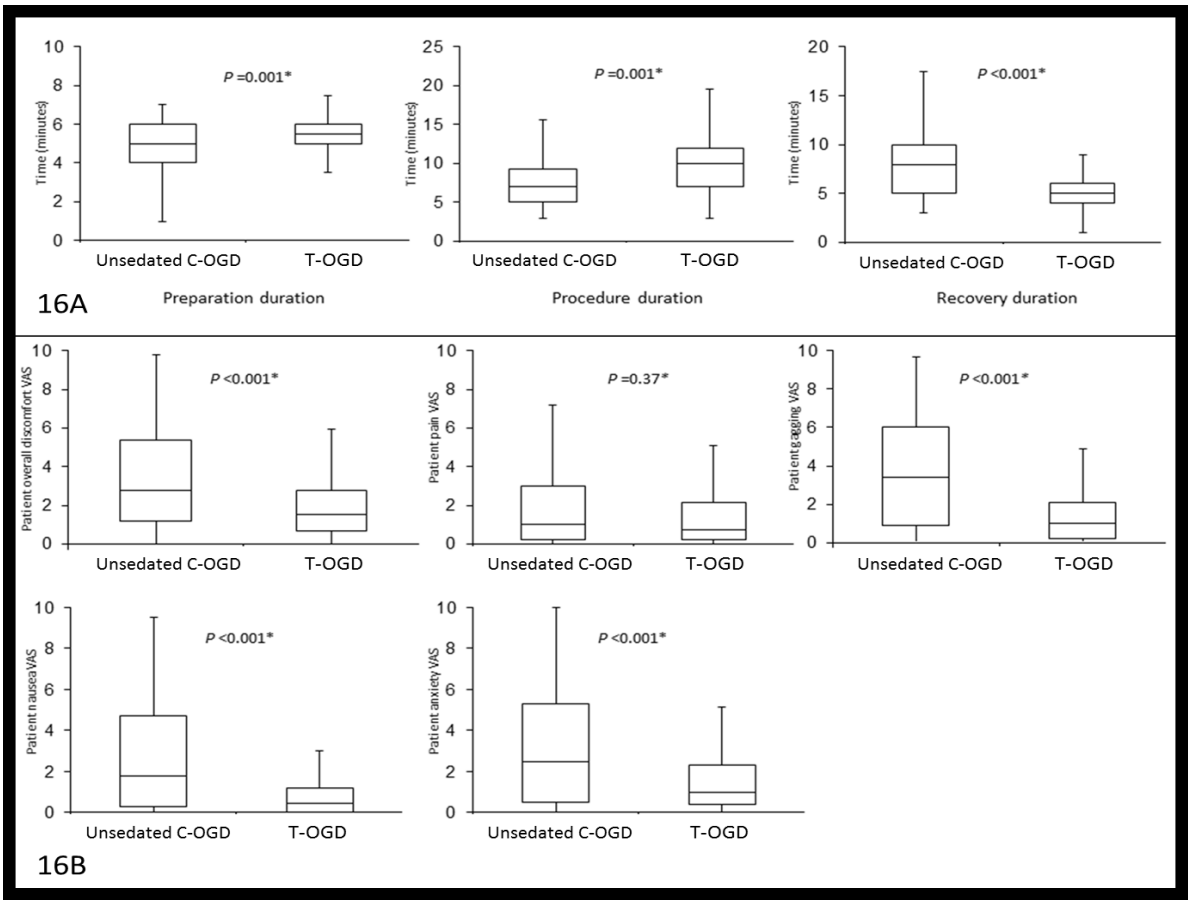


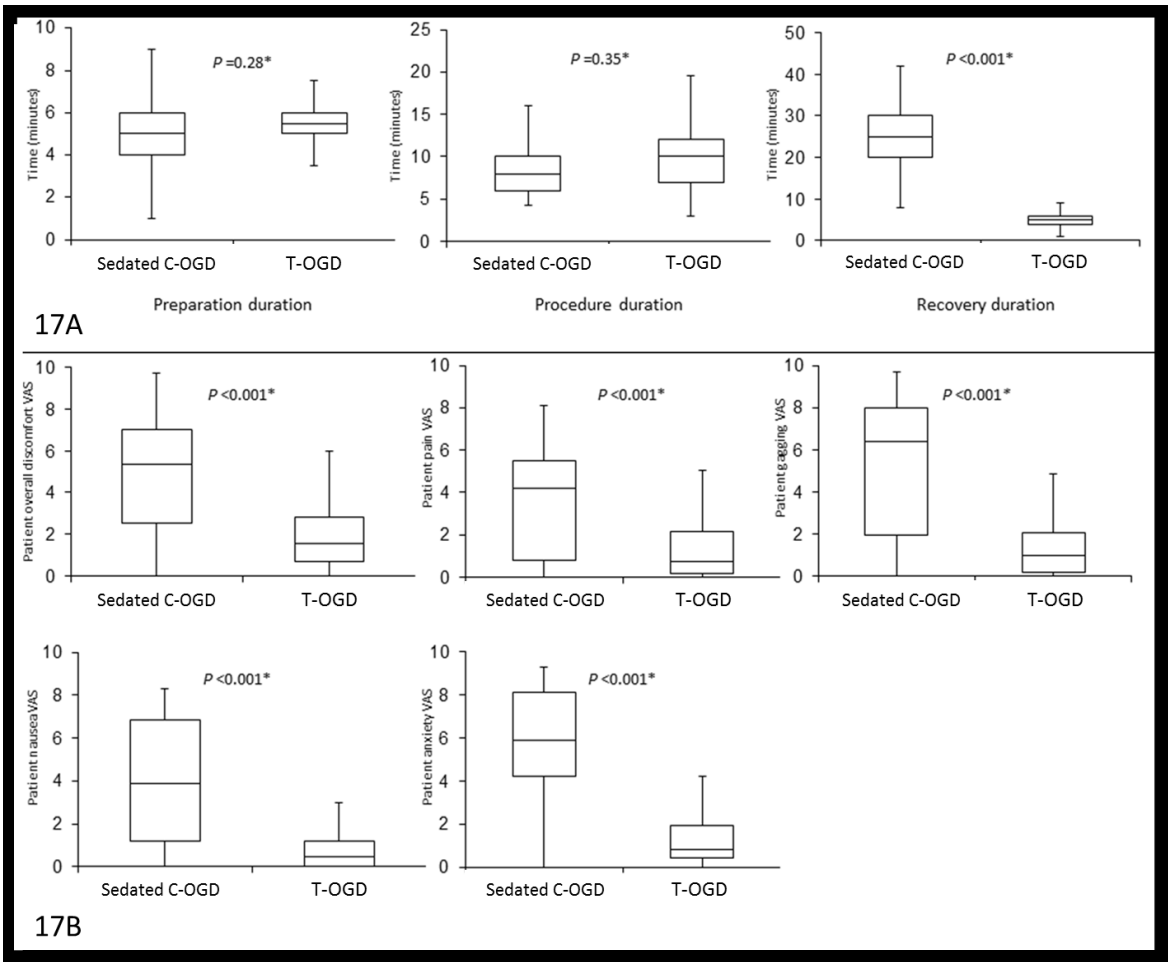
Table 5: *Overall comparative study of variables between unsedated C-OGD (unsedated C-OGD1+ unsedated C-OGD2) and T-OGD (T-OGD1 + T-OGD2), (**5A**) and between sedated C-OGD (sedated C-OGD1+ sedated C-OGD2) and T-OGD (T-OGD1 + T-OGD2), (**5B**); (Patient=patient's VAS score; Nurse=Nurses VAS score; Endosc. =Endoscopist's VAS score); IQR, interquartile range; †ANOVA, linear contrasts; ‡ Mann-Whitney test*

	5A			5B		
Variable	**Unsedated C-OGD Mean (SD)**	**T-OGD Mean (SD)**	**P-value†**	**Sedated C-OGD Mean (SD)**	**T-OGD Mean (SD)**	**P-value†**
Lowest Systolic BP (mmHg)	125 (25)	132 (24)	0.14	115 (17)	132 (24)	**0.01**
Highest Systolic BP (mmHg)	139 (27)	145 (27)	0.23	141 (25)	145 (27)	0.58
Lowest Pulse Rate (beats per minute)	79.3 (11.5)	76.6 (12.4)	0.29	79.6 (12.7)	76.6 (12.4)	0.40
Highest Pulse Rate (beats per minute)	91.5 (13.3)	86.0 (13.5)	0.05	89.9 (15.9)	86.0 (13.5)	0.35
Lowest O_2 Saturation (%)	98 (97, 99)	97 (96, 99)	0.20	98 (97, 99)	97 (96, 99)	0.20
	Unsedated C-OGD Median (IQR)	**T-OGD Median (IQR)**	**P-value‡**	**Sedated C-OGD Median (IQR)**	**T-OGD Median (IQR)**	**P-value‡**
Nurse - Discomfort	2.2 (1.0, 3.5)	1.3 (0.5, 2.2)	**0.003**	4.5 (3.7, 6.6)	1.3 (0.5, 2.2)	**<0.001**
Nurse – Anxiety	2.0 (1.0, 4.0)	1.2 (0.5, 2.5)	**0.002**	4.0 (2.4, 5.7)	1.2 (0.5, 2.5)	**<0.001**
Endosc. – Discomfort	2.9 (1.2, 5.2)	0.7 (0.4, 1.5)	**<0.001**	5.1 (2.7, 8.0)	0.7 (0.4, 1.5)	**<0.001**
Endosc. – Anxiety	3.3 (1.5, 5.4)	0.8 (0.4, 2.0)	**<0.001**	5.9 (4.2, 8.1)	0.8 (0.4, 2.0)	**<0.001**
Endosc. - Ease of insertion	9.2 (9.0, 9.4)	9.2 (8.7, 9.4)	0.47	9.1 (7.7, 9.3)	9.2 (8.7, 9.4)	0.08
Endosc. - Overall handling	9.2 (9.0, 9.5)	9.0 (8.6, 9.4)	0.15	9.0 (8.6, 9.3)	9.0 (8.6, 9.4)	0.43
Endosc. - D2 intubation	9.2 (9.0, 9.5)	9.0 (8.5, 9.4)	0.09	9.0 (8.7, 9.2)	9.0 (8.5, 9.4)	0.28
Endosc. - Random biopsies	9.2 (9.0, 9.5)	9.0 (8.6, 9.4)	0.07	9.1 (8.7, 9.3)	9.0 (8.6, 9.4)	0.89
Endosc. - Targeted biopsies	9.2 (8.8, 9.4)	9.0 (8.5, 9.3)	0.06	9.0 (8.9, 9.3)	9.0 (8.5, 9.3)	0.27
Endosc – Feasibility	9.1 (8.9, 9.4)	9.0 (8.7, 9.3)	0.11	8.9 (8.6, 9.3)	9.0 (8.7, 9.3)	0.31
Endosc. - View oesophagus	9.1 (8.7, 9.3)	9.0 (8.4, 9.3)	0.19	9.0 (8.7, 9.3)	9.0 (8.4, 9.3)	0.73
Endosc. - View stomach (F)	9.1 (8.9, 9.4)	9.0 (8.2, 9.2)	0.10	8.9 (8.6, 9.2)	9.0 (8.2, 9.2)	0.78
Endosc. - View stomach (R)	9.0 (9.0, 9.0)	9.0 (8.5, 9.0)	0.10	9.0 (9.0, 9.0)	9.0 (8.0, 9.0)	0.82
Endosc. - View D1	9.1 (8.7, 9.3)	9.0 (8.5, 9.2)	0.11	8.8 (8.6, 9.2)	9.0 (8.5, 9.2)	0.68
Endosc. - View D2	9.2 (8.9, 9.3)	9.0 (8.4, 9.3)	0.16	9.1 (8.7, 9.3)	9.0 (8.4, 9.3)	0.98
Endosc. - Overall view quality	9.1 (8.6, 9.2)	8.9 (8.4, 9.2)	0.13	8.9 (8.6, 9.3)	8.9 (8.4, 9.2)	0.67

2.4.5 Comparison of C-OGD with sedation (sub-group) and T-OGD

Outcomes between C-OGD with sedation (C-OGD1, n=14 and C-OGD2, n=15; total n=29) and T-OGD (T-OGD1 and T-OGD2, n=94) (**Figure 17, Table 5B**) were examined. The midazolam dose for sedation during C-OGD1 and C-OGD2 was the same (mean of 2.5 ±1mg). This was associated with a 13% reduction in mean SBP during procedures compared with T-OGD (115 vs. 132 mm Hg, P =0.01). While no differences in pre-procedure preparation time or procedure duration were noted, there was a reduction in median recovery time of 80% for T-OGD (5.0 vs. 25.5 minutes, $P < 0.001$) compared with C-OGD with sedation. Median VAS scores for patient tolerance were significantly lower (indicating better tolerance) for T-OGD across all parameters (Figure 6), with the greatest reduction in VAS score being 84% for gagging (1.0 vs. 6.4, $P < 0.001$). Nurse and endoscopist VAS scores for patient anxiety and discomfort were significantly lower for T-OGD (**Table 5B**).

Figure 17: *Box plots comparing preparation duration, procedure duration and recovery duration, (17A) and patient tolerance VAS tolerance scores, (17B) for sedated C-OGD and T-OGD procedures. Values are expressed as medians (horizontal lines) and 25th and 75th percentiles (boxes) of the interquartile range (IQR). The whiskers of the box plots are set at 1.5x the 25th and 75th percentile respectively; *Mann-Whitney test.*



2.4.6 Comparison of C-OGD1 and C-OGD2 (UT endoscopes)

Outcomes between the two C-OGD groups (C-OGD1, n=50 and C-OGD2 using ultrathin endoscopes, n=56) were examined (**Figure 18, Table 6A**). No differences were found in vital parameter observations, preparation duration or procedure duration. However there was a 38% reduction in median patient VAS score for overall patient discomfort for C-OGD2 using ultrathin endoscopes compared with C-OGD1 (2.5 vs. 4.0,

P=0.03). There was a trend towards reduced patient anxiety in the C-OGD2 group (2.1 vs. 3.6, *P*=0.09). C-OGD2 was associated with reductions in endoscopist and nurse median VAS scores for overall perceived patient discomfort of 29% and 37% respectively (3.0 vs. 4.2, *P*=0.03 and 2.2 vs. 3.5, *P*=0.03). Technical ease of insertion of the endoscope was rated marginally easier for C-OGD2 than C-OGD1 (9.2 vs. 9.0, *P* <0.001). No significant differences in endoscopic view quality or any of the other technical variables were found (**Table 6A**).

Figure 18: *Box plots comparing preparation duration, procedure duration and recovery duration, (**18A**) and patient tolerance VAS tolerance scores, (**18B**) for C-OGD1 and C-OGD2 procedures. Values are expressed as medians (horizontal lines) and 25th and 75th percentiles (boxes) of the interquartile range (IQR). The whiskers of the box plots are set at 1.5x the 25th and 75th percentile respectively; *Mann-Whitney test.*

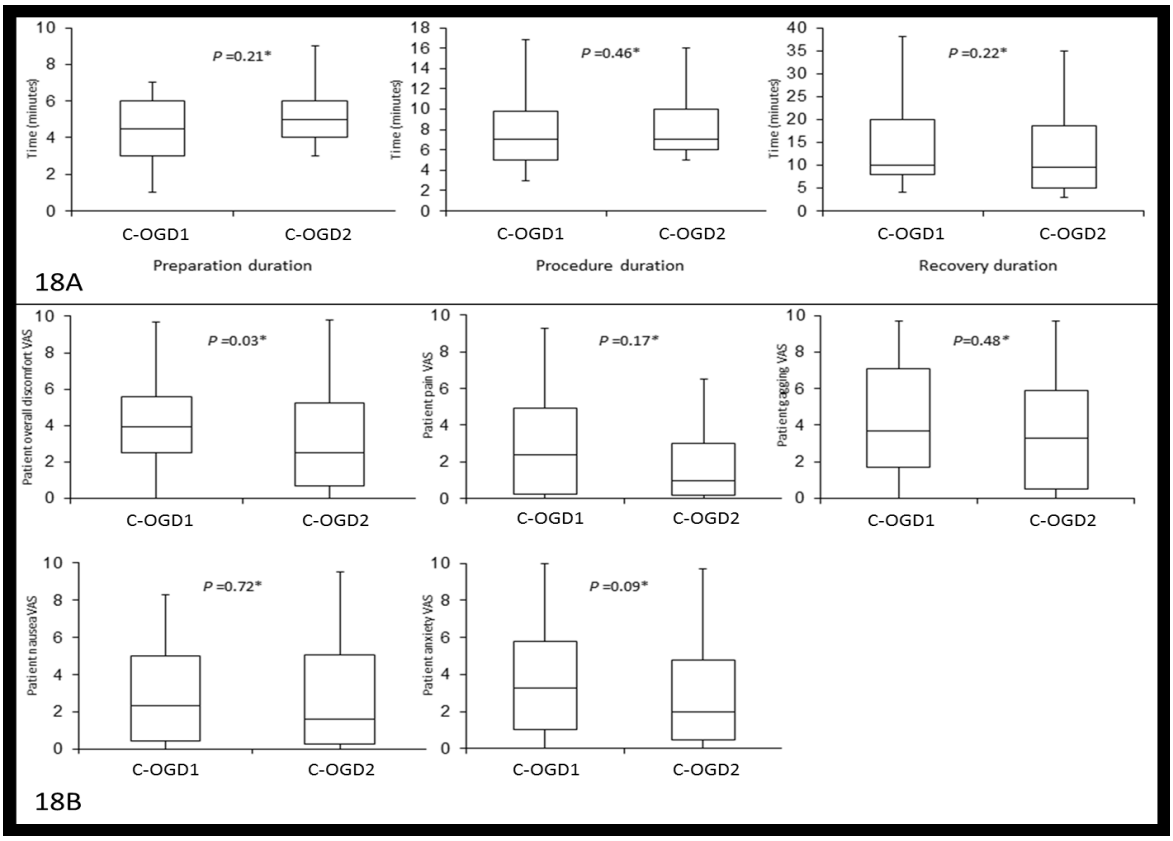


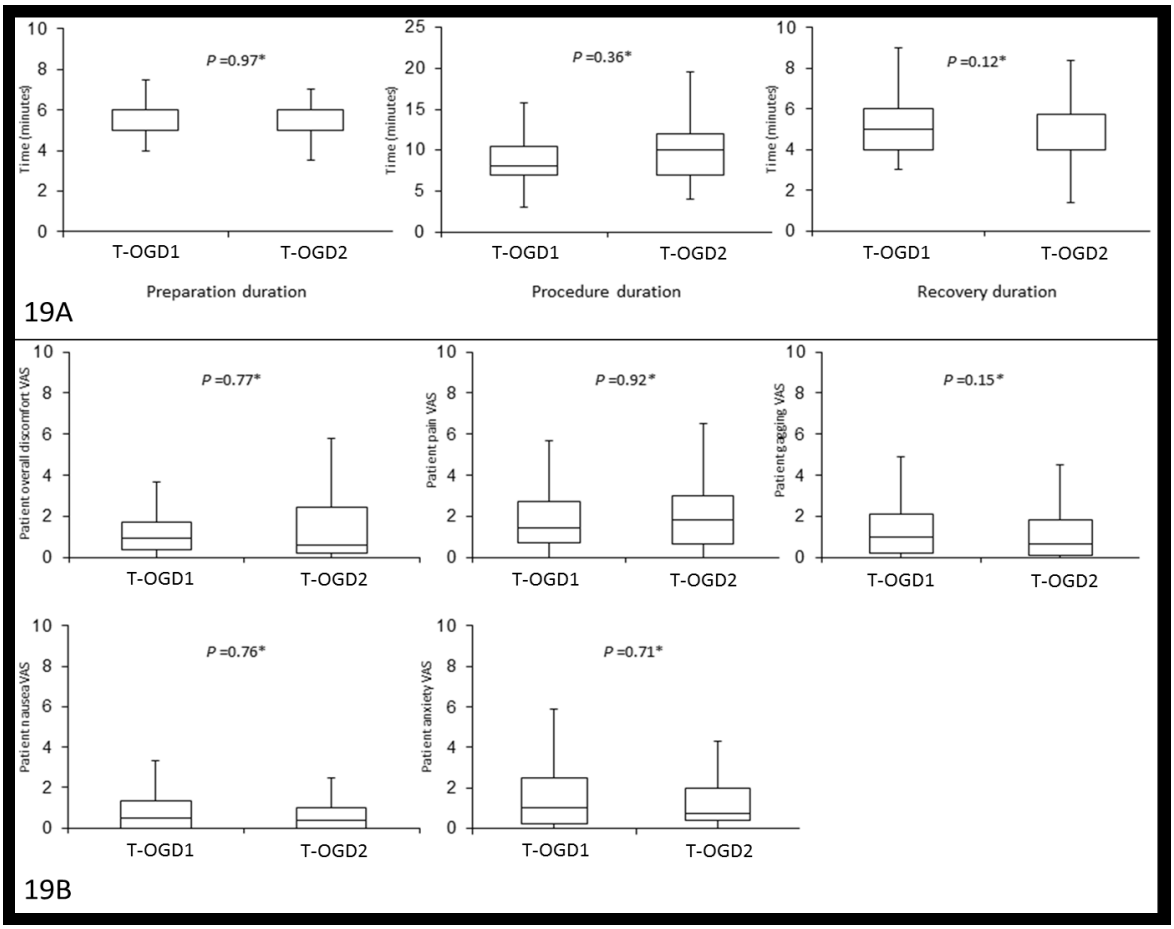
Table 6: *Overall comparative study of variables between C-OGD1 and C-OGD2, **(6A)** and between T-OGD1 and T-OGD2, **(6B)**; (Patient=patient's VAS score; Nurse=Nurses VAS score; Endosc. =Endoscopist's VAS score); IQR, interquartile range; †ANOVA, linear contrasts; ‡ Mann-Whitney test*

	6A			6B		
Variable	**C-OGD1 Mean (SD)**	**C-OGD2 Mean (SD)**	**P-value†**	**T-OGD1 (5.9mm) Mean (SD)**	**T-OGD2 (4.9mm) Mean (SD)**	**P-value†**
Lowest Systolic BP (mmHg)	122 (23)	128 (23)	0.23	97 (96, 99)	97 (96, 98)	0.17
Highest Systolic BP (mmHg)	140 (26)	143 (19)	0.54	132 (20)	132 (27)	0.87
Lowest Pulse Rate (beats per minute)	79.4 (11.7)	78.1 (13.0)	0.62	145 (23)	145 (31)	0.97
Highest Pulse Rate (beats per minute)	91.0 (13.9)	87.6 (15.9)	0.24	74.7 (11.9)	78.6 (12.8)	0.13
Lowest O_2 Saturation (%)	98 (97, 99)	98 (95, 99)	0.10	97 (96, 99)	97 (96, 98)	0.17
	C-OGD1 Median (IQR)	**C-OGD2 Median (IQR)**	**P-value‡**	**T-OGD1 (5.9mm) Median (IQR)**	**T-OGD2 (4.9mm) Median (IQR)**	**P-value‡**
Nurse - Discomfort	3.5 (1.3, 4.5)	2.2 (1.3, 4.5)	0.05	1.2 (0.5, 2.2)	1.4 (0.5, 2.2)	0.98
Nurse – Anxiety	3.1 (1.2, 4.5)	2.0 (0.7, 4.3)	0.09	1.1 (0.7, 2.6)	1.3 (0.5, 2.3)	0.75
Endosc. - Discomfort	4.2 (2.5, 7.3)	3.0 (0.5, 5.0)	**0.03**	0.8 (0.4, 1.5)	0.6 (0.4, 1.4)	0.65
Endosc. - Anxiety	4.4 (2.7, 7.5)	3.5 (1.2, 6.5)	0.05	1.0 (0.5, 2.2)	0.6 (0.4, 1.6)	0.13
Endosc. - Ease of insertion	9.0 (8.6, 9.3)	9.2 (9.1, 9.5)	**<0.001**	9.2 (8.8, 9.4)	9.1 (8.5, 9.3)	0.29
Endosc. - Overall handling	9.2 (8.7, 9.4)	9.3 (9.0, 9.5)	0.07	9.2 (8.7, 9.4)	8.9 (7.7, 9.5)	0.10
Endosc. - D2 intubation	9.2 (8.6, 9.4)	9.2 (9.0, 9.5)	0.49	9.2 (8.7, 9.5)	8.8 (7.3, 9.4)	**0.03**
Endosc. - Random biopsies	9.2 (8.9, 9.4)	9.2 (9.0, 9.5)	0.83	9.0 (8.6, 9.4)	9.0 (8.6, 9.4)	0.81
Endosc. - Targeted biopsies	9.2 (8.8, 9.4)	9.2 (9.0, 9.5)	0.21	9.0 (8.5, 9.4)	8.8 (8.2, 9.2)	0.22
Endosc - Feasibility	9.1 (8.6, 9.3)	9.2 (9.0, 9.5)	0.05	9.0 (8.9, 9.4)	8.9 (8.5, 9.1)	**0.02**
Endosc. - View oesophagus	9.1 (8.6, 9.3)	9.0 (8.8, 9.4)	0.84	9.0 (8.5, 9.3)	9.0 (8.3, 9.3)	0.50
Endosc. - View stomach (F)	9.2 (8.7, 9.3)	9.0 (8.8, 9.4)	0.64	9.0 (8.5, 9.2)	8.9 (8.0, 9.1)	0.21
Endosc. - View stomach (R)	9.0 (9.0, 9.0)	9.0 (9.0, 9.0)	0.39	9.0 (8.0, 9.0)	9.0 (8.0, 9.0)	0.59
Endosc. - View D1	9.1 (8.7, 9.2)	9.0 (8.7, 9.3)	0.34	9.0 (8.7, 9.2)	8.8 (8.0, 9.2)	**0.04**
Endosc. - View D2	9.2 (8.9, 9.3)	9.0 (8.8, 9.3)	0.80	9.2 (8.7, 9.4)	8.7 (8.0, 9.2)	**0.02**
Endosc. - Overall view quality	9.1 (8.5, 9.2)	9.0 (8.8, 9.4)	0.09	9.0 (8.5, 9.2)	8.7 (8.2, 9.2)	0.16

2.4.7 Comparison of T-OGD1 and T-OGD2

Finally outcomes in T-OGD1 (n=48) and T-OGD2 (n=46) groups were examined (**Figure 19, Table 6B**). There was no difference between the groups for most outcomes however small but significant differences were observed in endoscopic view quality of the duodenum (D1 and D2), which appeared inferior for T-OGD2 compared with T-OGD1 (8.8 vs. 9.0, *P*=0.02 for D1 and 8.7 vs. 9.2, *P*=0.02 for D2, respectively). There were also small but significant differences in technical feasibility and handling scores relating to the same anatomical location (9.2 vs. 8.8, *P*=0.03 for D2 intubation) and for overall feasibility (9.0 vs. 8.9, *P*=0.02) between T-OGD1 and T-OGD2.

Figure 19: *Box plots comparing preparation duration, procedure duration and recovery duration, (**19A**) and patient tolerance VAS tolerance scores, (**19B**) for T-OGD1 and T-OGD2 procedures. Values are expressed as medians (horizontal lines) and 25th and 75th percentiles (boxes) of the interquartile range (IQR). The whiskers of the box plots are set at 1.5x the 25th and 75th percentile respectively; *Mann-Whitney test.*



2.4.8 Level of patient satisfaction

Although none of the patients expressed dissatisfaction with any of the procedures, patient satisfaction as obtained using a 5-point Likert scale (i.e. very satisfied, satisfied, neutral, dissatisfied and very dissatisfied) significantly favoured T-OGD as compared with C-OGD1 and C-OGD2 (**Table 7**). No differences in satisfaction scores were found within the T-OGD1 vs. T-OGD2 and C-OGD1 vs. C-OGD2 comparisons.

Table 7: *Levels of patient satisfaction with procedures were obtained using a 5-point Likert scale (i.e. very satisfied, satisfied, neutral, dissatisfied and very dissatisfied); none of the patients expressed dissatisfaction with the procedure undertaken and therefore the last 2 points on the scale have been omitted from the table. The results are expressed as the percentage of relative satisfaction for each group; *Fisher's exact test.*

Variable	Category	C-OGD1 (%)	T-OGD (%)	P-value*
Patient Satisfaction	Very satisfied	40	64	**<0.001**
	Satisfied	46	25	
	Neutral	14	4	
		T-OGD (%)	C-OGD2 (%)	
Patient Satisfaction	Very satisfied	69	47	**0.03**
	Satisfied	27	39	
	Neutral	4	14	
		C-OGD (unsedated) (%)	T-OGD (%)	
Patient Satisfaction	Very satisfied	39	69	**0.004**
	Satisfied	58	27	
	Neutral	3	4	
		C-OGD (sedated) (%)	T-OGD (%)	
Patient Satisfaction	Very satisfied	29	69	**<0.001**
	Satisfied	21	27	
	Neutral	50	4	
		C-OGD1 (%)	C-OGD2 (%)	
Patient Satisfaction	Very satisfied	36	47	0.52
	Satisfied	48	39	
	Neutral	16	14	
		T-OGD1 (%)	T-OGD2 (%)	
Patient Satisfaction	Very satisfied	64	74	0.53
	Satisfied	32	22	
	Neutral	4	4	

2.4.9 Complications and other observations

None of the patients suffered any epistaxis or other adverse event during the course of the study. The yield of positive findings (diagnostic yield) of C-OGD1 procedures using the 9.0mm endoscope was similar to that of T-OGD and C-OGD2 procedures with UT endoscopes; 72% vs. 70% respectively (P=0.71). Biopsies for histopathological analysis were taken in 34 of the 50 patients in the C-OGD1 group (68%) and in 100 of the 150 patients (67%) who underwent an OGD procedure using an UT endoscope (P=0.80). In 98% of cases, the biopsies taken using UT endoscopes were adequate for analysis; in the 2 cases where the biopsies were deemed to be too small for histological analysis, suspected antral gastritis (because of antral erythema) could not be confirmed. None of the biopsies taken with the 9.0mm endoscope were considered too small for histological interpretation (P=0.69).

2.5 Discussion

SCENT is the first prospective, randomized study to evaluate the role of unsedated transnasal OGD as an alternative to per-oral OGD in the UK. The study compared the latest available UT endoscopes with the larger (9.0mm) diameter conventional gastroscope most commonly used in current clinical practice. SCENT is also one of the most comprehensive T-OGD studies reported to date. While study parameters included an assessment of patient tolerance from multiple perspectives (patient, nurse and endoscopist), T-OGD feasibility (procedure preparation, duration and recovery times), safety and endoscopic view and biopsy quality, the protocol also allowed us to examine the use of UT endoscopes in several ways. Aside from comparing T-OGD with C-OGD1 (OGD using 9.0mm endoscopes), we also examined insertion of UT endoscopes via both

the nasal and oral route (T-OGD compared with C-OGD2), T-OGD with C-OGD performed with and without (on-demand) sedation and T-OGD performed using different calibre UT endoscopes (T-OGD1 compared with T-OGD2).

2.5.1 Evaluation of patient tolerance

Our findings for the comparison of C-OGD1 (OGD using 9.0mm endoscopes) with T-OGD are in keeping with those of others and show that T-OGD is significantly better tolerated than C-OGD1 performed under low dose sedation or without [8;9;11-13;133;134]. All median VAS scores (patient, endoscopist and nurse derived) for patient discomfort, pain, gagging, nausea and anxiety significantly favoured T-OGD as the more comfortable procedure. The largest reductions in VAS scores were for gagging and nausea, which is likely to reflect the minimal stimulation of the pharyngeal reflex by T-OGD. These findings were mirrored by the Likert score comparisons showing that patients were significantly more satisfied with T-OGD.

For the comparison of C-OGD2 to T-OGD using UT endoscopes via the oral and transnasal route respectively, although differences in VAS scores were smaller in magnitude than those seen for C-OGD1 (using the 9.0mm endoscope) vs. T-OGD, a general reduction in patient tolerance scores (lower scores = better tolerated) and significantly higher satisfaction scores were seen favouring T-OGD over C-OGD2. Interestingly the comparison of C-OGD1 with C-OGD2 (using UT endoscopes) also showed a significant reduction in overall patient discomfort VAS score relating to C-OGD2, however this improvement appeared less substantial than that observed using UT endoscopes via the transnasal route. While use of UT endoscopes for C-OGD appeared to improve aspects of patient tolerance compared with C-OGD (using the 9.0mm

endoscope), our findings suggest that improved patient experience during OGD is more dependent upon the route used for the procedure than the endoscope calibre itself [2;12;13;16;135]. We found no difference in patient tolerance or satisfaction scores between either sized UT endoscope for T-OGD, however differences have been reported by others [136].

When C-OGD with or without sedation was compared with T-OGD we found that median VAS scores for patient tolerance were significantly lower (indicating better tolerance) for T-OGD across multiple parameters. While direct comparisons were not made, C-OGD VAS scores by patients, nurses and endoscopists for C-OGD with sedation appeared inferior to those for C-OGD without sedation. Patient satisfaction levels (% of patients 'satisfied' and 'very satisfied') were similarly reduced. One possible explanation is that the patients who requested sedation during C-OGD found it more uncomfortable and painful to begin with and therefore reported it so. In adherence to unit policy and national guidance [137], we used low doses of sedation (midazolam, mean dose 2.5mg ±1mg) which was only given on demand, according to study protocol. The scores relating to the subset of patients who requested sedation may have therefore been confounded by the possibility that this subset was also likely to also represent a 'self-selected' sub-group who had found the OGD procedure to be particularly uncomfortable. The benefit of on-demand sedation for GI endoscopy has recently been examined by Seip et al. [138] who found that giving sedation in this way (with median doses of 3mg midazolam and 50mg pethidine) was not associated with lower rates of painful colonoscopy or improved patient satisfaction despite accounting for factors related to more painful colonoscopy. This study did not examine the effect of pre-

procedure sedation for C-OGD on VAS scores for patient tolerance, which is intended to be the purpose of a future study.

2.5.2 Evaluation of endoscopic view and biopsy quality

No significant differences in endoscopic view quality or diagnostic yield were detected when procedures using UT endoscopes were compared with those performed using the conventional 9.0mm endoscope. The only significant differences in view quality were detected within the comparison of 5.9mm and 4.9mm UT endoscopes for T-OGD1 and T-OGD2 procedures respectively where views of the first and second part of the duodenum using 4.9mm UT endoscopes were found to be of significantly inferior quality. This may relate to the one-way bending plane of this endoscope, which requires reliance on additional torquing of the instrument shaft in order to obtain the desired views [139]. Although our main objectives did not include a formal analysis of size and quality of biopsy specimens obtained, we performed a brief comparison of biopsy specimens taken with the UT and 9.0mm endoscopes and showed no significant difference. This is in agreement with the findings of a recent large study dedicated to the quality of biopsies taken by small forceps used in UT OGD as compared with standard size OGD forceps which confirmed no overall difference in biopsy quality [140].

2.5.3 Evaluation of patient safety

Although T-OGD is associated with epistaxis that has been reported to occur in up to 2% of cases [141] no significant adverse events or complications were observed during this study. An interesting, albeit clinically inconsequential finding was that the SBP was found to be lower in C-OGD1 patents who received sedation. This observation may be

explained by pharmacologic effect of midazolam, which is known to lower the SBP even at the low doses used in this study [1;142;143].

2.5.4 Evaluation of feasibility

In our experience, T-OGD was technically possible in 94% of patients in whom it was attempted. The inability to pass the soft-silicone preparation catheter or UT endoscope through either of the patients' nasal passages in the remaining 6% is similar to the 3-8% failure rate reported by others [2;10;13;144]. Although some studies have shown that failure rates relate to a wider UT endoscope diameter [12;136], this trend was not evident in our experience since our failure rate was higher in the 4.9mm group. Regarding preparation and procedure duration, we found that it took longer to prepare for and to perform T-OGD. This was however offset by a shorter recovery time for T-OGD. As expected, this difference was greater when T-OGD was compared with C-OGD under sedation. Although no formal cost-effectiveness analysis was performed, two studies have demonstrated that the enhanced recovery relating to unsedated OGD using UT endoscopes versus sedated C-OGD may facilitate reductions in personnel and facility costs in the order of 20-36% [145;146].

2.5.5 Limitations of the study

This study was conducted in single academic endoscopy institute and incorporated multiple group comparisons, using subjective measures (VAS and Likert scores). Furthermore, although sub-analysis of comparisons of various sub-groups yielded statistically significant results, the original power calculation was based only on

comparisons for the primary objective. Another potential limitation of the study was that sedation was only given on demand and this may have derived a self-selected sub-group.

2.5.6 Conclusion

In summary, this is the first prospective study to compare T-OGD using the latest available UT 5.9mm and 4.9mm endoscopes with C-OGD in the UK. We have confirmed that unsedated transnasal endoscopy is associated with significantly higher levels of patient tolerance and satisfaction compared with C-OGD. In addition, we have also confirmed that T-OGD is a highly feasible and safe alternative to C-OGD with similar diagnostic quality. Use of UT endoscopes via the oral but more so the nasal route is associated with improved patient tolerance compared with C-OGD. In our experience, the thinner 4.9mm UT endoscope in its current form, does not appear to offer a significant advantage over the 5.9mm UT endoscope and may be more difficult to use. The encouraging findings of our study, which in many respects echo the results of others, may help to support a wider acceptance of transnasal endoscopy into routine clinical practice in the UK.

3 An evaluation of performance, limitations and complications of double-balloon enteroscopy (DBE) in the United Kingdom

3.1 Background

Recent advances in endoscopic technology have revolutionized endoscopy of the small bowel (SB) [147;148]. Since the introduction of SB capsule endoscopy (SBCE) [23] and double-balloon enteroscopy (DBE) [20], clinicians are able to visualize the entire SB without recourse to surgical intervention. These two technologies complement each other [149], with SBCE, being less invasive often used to 'scout' for potential SB pathology and help determine the best route of insertion for subsequent DBE [150].

DBE allows for controlled, direct endoscopic characterization of lesions, facilitates tissue biopsy and enables the application of endotherapy, such as argon plasma coagulation (APC), endoclipping and injection of vascular lesions; dilatation of strictures, polypectomy and direct percutaneous endoscopic jejunostomy (DPEJ) placement [20;21;24-49]. In selected cases, these endotherapeutic interventions may obviate the need for surgery [20;21;24-49]. Although initially described by Yamamoto et al. [20] a decade ago, there have been no published reports on the UK practice of DBE.

3.2 Aims

To assess the performance, limitations and complications of DBE within the UK by the evaluation of data collected into a large multi-centre database.

3.3 Methods

Since the introduction of DBE in the UK in 2005, a total of 8 tertiary referral centres (The UK DBE Users Group) which perform DBE on a regular (at least 2-weekly) basis have collected data on DBE procedures performed. Data collected from each centre were recorded using a standardized, electronic spread-sheet designed by the author (Microsoft® Excel 2003, Microsoft Corporation, WA, USA). These data were then collated into a dedicated database (by the author at St Mark's Hospital) and analysed retrospectively. Data were collected for i) patient related and ii) DBE procedure details.

i) Patient details

Data for patient demographics (age and gender), past history of abdominal/pelvic surgery, indications for referral for DBE and pre-DBE investigations were recorded.

ii) DBE procedure details

Data collected in relation to DBE procedures included: number of DBEs performed per patient, route of approach i.e. per oral (anterograde), per rectal or per ileostomy (retrograde) and details of sedation or general anaesthesia (GA) used. The type of gas used for SB insufflation (i.e. carbon dioxide (CO_2) or air), estimated depth of insertion, completeness of procedures, limitations encountered and time taken to perform DBE procedures were documented. Diagnostic findings, endotherapy applied and details of

DBE-related complications (including subsequent interventions/outcomes) were also collected.

3.3.1 Definitions

Diagnostic DBE procedures were defined as procedures performed with or without biopsy and with or without India ink tattooing (Spot® GI Supply, PA, USA) of the SB sub-mucosa. Therapeutic DBE procedures were defined as procedures involving the use of any form of endotherapy, including: argon plasma coagulation (APC), application of endoclips (Resolution®, Boston Scientific, MA, USA or Quickclip®, Olympus, Tokyo, Japan), therapy of varices by injection of human thrombin (Tisseel®, Baxter, IL, USA), endoscopic balloon-dilatation using through-the-scope (TTS) controlled radial expansion (CRE) balloon dilators (Boston Scientific, MA, USA), snare polypectomy and direct percutaneous endoscopic jejunostomy (DPEJ) enteral tube placement.

Pan-enteroscopy was defined as complete DBE examination of the SB, confirmed either by the identification of a submucosal India ink tattoo placed at a previous DBE done via the opposite end or by the identification of the ileo-caecal valve/colon during a procedure done via the oral route.

A complication was defined as a procedure-related event which negatively affected the health of a patient post-procedure [30]. Unfortunately, due to the retrospective design of the study and tertiary nature of the referrals for DBE, data on longer-term complications could not be secured and therefore complication data should be considered to mainly represent immediate (peri-procedure) adverse events. Complications were graded as mild, moderate or severe as defined by American Society of Gastrointestinal Endoscopy (ASGE) lexicon for endoscopic adverse events [151]. Pancreatitis was defined as post procedural, abdominal pain associated with a ≥3 fold rise in serum amylase/lipase above

the upper limits of normal, associated with ≥2 days of unintended post-procedure hospitalization [30;39].

3.3.2 DBE procedures

DBE procedures were carried out using the EN-450P5 (8.5mm diameter, 200cm working length and 2.2mm instrument channel) or the EN-450T5 (9.5mm diameter, 200cm working length 2.8mm instrument channel) enteroscopes, both manufactured by Fujifilm (Saitama, Japan). In cases where CO_2 was used as an insufflating agent, CO_2Efficient^{TM} systems (E-Z-EM Inc., NY, USA) were used. Patients having a DBE via the anterograde route were prepared with an 8-12 hour fast, while patients having a retrograde DBE received bowel preparation as per individual unit practice. Anterograde procedures were performed with the patient in the left lateral position. In DBEs performed via the rectal route, intubation of the colon was performed with the patient in the left lateral position; patients were then placed in the supine position for SB intubation. The route of DBE procedures was generally determined by the findings of pre-DBE investigations such as SBCE [150], barium follow-through (BaFT), computed tomographic enterography (CTE) and/or magnetic resonance enterography (MRE). Anti-foaming agent in the form of 1% simethicone suspension (Infacol®, Forest-Laboratories, Dartford, UK) was used as a wash to improve endoscopic view quality as required.

Conscious sedation was administered using intravenous generic midazolam in addition to an intravenous opioid (in the form of either generic pethidine or fentanyl), as per local unit policy. Five centres had access to GA and monitored anaesthesia care (MAC, for propofol sedation) services, which were used at the discretion of endoscopists as an alternative to intravenous conscious sedation [142]. Antispasmodic agents in the form of

intravenous hyoscine-N-butylbromide (Buscopan®, Boehringer Ingelheim Gmbh, Germany) or generic glucagon were administered to reduce SB peristaltic activity as necessary. Enteroscope depth of insertion into the SB (from the pylorus, terminal ileum or ileostomy) was estimated using the method described by May et al. [51]. This method, which has been validated on Erlangen-type ex-vivo animal training models [51], uses an estimated depth of SB insertion of 20-40cm per DBE insertion cycle.

3.3.3 Statistical analysis

Data were collated into a dedicated computer database and analysed at the lead centre (St Mark's Hospital and Academic Institute, Imperial College London) using Microsoft® Office 2010 (Microsoft Corporation, WA, USA) and GraphPad® InStat, version 3.0 software (GraphPad Software Inc., CA, USA). Descriptive statistics were used for examination of patient demographics and the Mann-Whitney U-test was used to compare independent ordinal variables such as SB insertion depths. Binomial distribution analyses were used to examine limitations encountered and diagnostic yields. A *P* value of <0.05 was regarded to be statistically significant. Two-tailed probability tests were used and data are presented as means ± SD, medians and ranges. Selected box-plots of medians and interquartile ranges (IQR) are also shown.

3.4 Results

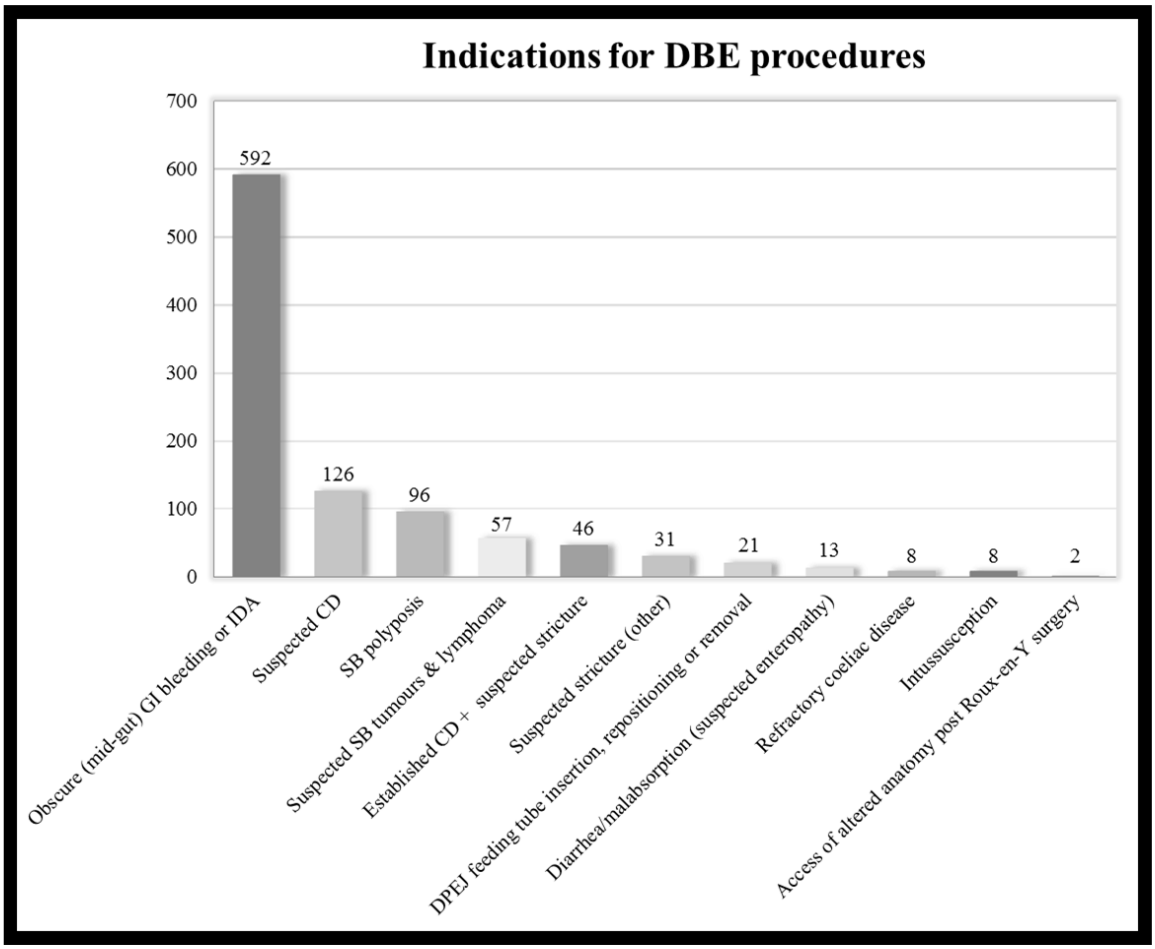
3.4.1 Patient details

Between February 2005 and February 2011, a total of 1000 DBE procedures were performed in 783 patients (439 men; 344 women). The mean age ±SD of patients was 54 ±18 (range 7-94) years. A past history of abdominal or pelvic surgery was present in 248

(31.7%) patients. Details regarding indications for DBE procedures are described (**Figure 20**). These data include those of 12 paediatric patients (mean age 14±3 (range 7-18) years) who all underwent DBE for removal of SB polyps in the setting of Peutz-Jeghers syndrome (PJS), and therefore a detailed evaluation of DBE procedures in this sub-group of paediatric patients is given in **Chapter 6**.

Pre-DBE SB investigations in the form of SBCE and/or diagnostic imaging (MRE or computed tomographic enterography (CTE) or SB barium follow through (SBFT)) were carried out prior to 966 (96.6%) of procedures.

Figure 20: *Indications for DBE procedures and respective number of cases performed. IDA, iron deficiency anaemia; CD, Crohn's disease; SB, small bowel; DPEJ, direct endoscopic percutaneous jejunostomy*



3.4.2 Procedure details

The number of DBEs performed per patient ranged from 1 (n=605) to 6 (n=1); full details are described (**Table 8**). The anterograde route of insertion was used for 682 procedures while the retrograde route was used for 318 DBEs. In total, 113 patients underwent a DBE via both the anterograde and retrograde routes. Laparoscopic assisted DBE (lap-DBE) was used in 4 cases (for the removal of large duodenal polyps).

Table 8: *Number of DBEs performed per patient; OGIB, obscure (mid-gut) GI bleeding; IDA, iron-deficiency anaemia; CD, Crohn's disease; PJS, Peutz-Jeghers syndrome*

Number of DBEs performed (n)	Patients (n)	Further details
1	605	OGIB/IDA (n=336) Suspected CD (n=80) PJS (n=65) Suspected SB tumour (n=41) Strictures (n=31) Enteropathy (n=21) DPEJ (n=21) Intussusception (n=8) Post Roux-en-Y (n=2)
2	150	OGIB/IDA (n=98) Suspected CD (n=20) PJS (n=14) Strictures (n=13) Suspected SB tumour (n=5)
3	19	OGIB/IDA (n=10) Strictures (n=4) Suspected CD (n=2) Suspected SB tumour (n=2) PJS (n=1)
4	8	OGIB/IDA (n=6) Strictures (n=2)
6	1	OGIB/IDA (n=1)

Intravenous sedation was given for 650 DBEs (including 4 procedures performed under MAC using anaesthetist delivered propofol sedation); GA was used for the remaining 350 procedures. Details of drug dosage for intravenous sedatives and antispasmodics are shown (**Table 9**). CO_2 was used as an insufflating agent in 730 cases while air was used in the remaining 270 procedures.

Table 9: *Dosage details of drugs used during DBE procedures; *glucagon was used in patients who had contraindications to the use of hyoscine-N-butylbromide; mcg, micrograms; MAC, monitored anaesthesia care*

Dosage details of drugs used for intravenous sedation and analgesia		
Drug	Mean dose (±SD)	Dose range
Midazolam (used for 646 DBEs)	5.56 (±2.88) mg	1.25-10 mg
Pethidine (used for 311 DBEs)	57.30 (±17.29) mg	12.5-100 mg
Fentanyl (used for 335 DBEs)	74.29 (±33.83) mcg	25-200 mcg
Propofol infusion by anaesthetist delivered MAC (used for 4 DBEs)		
Sedation maintained by intravenous infusion of propofol at a dose rate of 1.5-4.5mg/kg/hour (after 20-40mg bolus induction)		
Dosage details of drugs used as antispasmodics		
Drug	Mean dose (±SD)	Dose range
Hyoscine-N-butylbromide (Buscopan®) (used for 526 DBEs)	21.62 (±8.65) mg	10-40 mg
Glucagon* (used for 16 DBEs)	1.02 (±0.43) mg	0.5-2.0 mg

There was no significant difference in the median duration of DBEs performed via the anterograde route as compared with retrograde procedures (70 vs. 65 minutes respectively, P=0.36) (**Figure 21A**). However, the median estimated depth of insertion

for anterograde DBEs was found to be twice that of retrograde procedures (240 vs. 120 cm, respectively, $P < 0.0001$) (**Figure 21B**). Significant differences were also identified when median estimated insertion depths for procedures performed using CO_2 insufflation were compared with those performed using air (220 vs. 180 cm, respectively, $P=0.0001$) (**Figure 21C**). The median insertion depth at DBE in patients without a history of surgery was significantly higher than that for patients who had undergone abdominal and / or pelvic surgery (220 vs. 160 cm, respectively, $P < 0.0001$) (**Figure 21D**). Differences in median insertion depth relating to type of gas insufflation and past history of surgery were significant for both anterograde and retrograde DBE procedures (**Figure 22A-D**).

3.4.3 Rate of pan-enteroscopy

In the sub-group of 113 patients who underwent a DBE via both the anterograde and retrograde route patients, pan-enteroscopy was achieved in 20 (17.7%). In another sub-group of 7 patients, pan-enteroscopy was achieved during DBE procedures done via the anterograde route alone; 5 of these patients had a history of short bowel syndrome secondary to extensive SB resection.

Figure 21: *Duration of oral and rectal DBE procedures (**A**), Estimated depths of insertion for oral and rectal DBE procedures (**B**), Overall estimated depths of insertion (oral + rectal) in relation to a past history (Hx) of surgery (**C**) and Overall estimated depths of insertion (oral + rectal) in relation to the use of CO_2 or air (**D**). Values are expressed as medians (horizontal lines) and the 25^{th} and 75^{th} percentiles, boxes of the interquartile range (IQR). The whiskers of the box plots are set at 1.5x the 25^{th} and 75^{th} percentiles respectively; *Mann-Whitney test.*

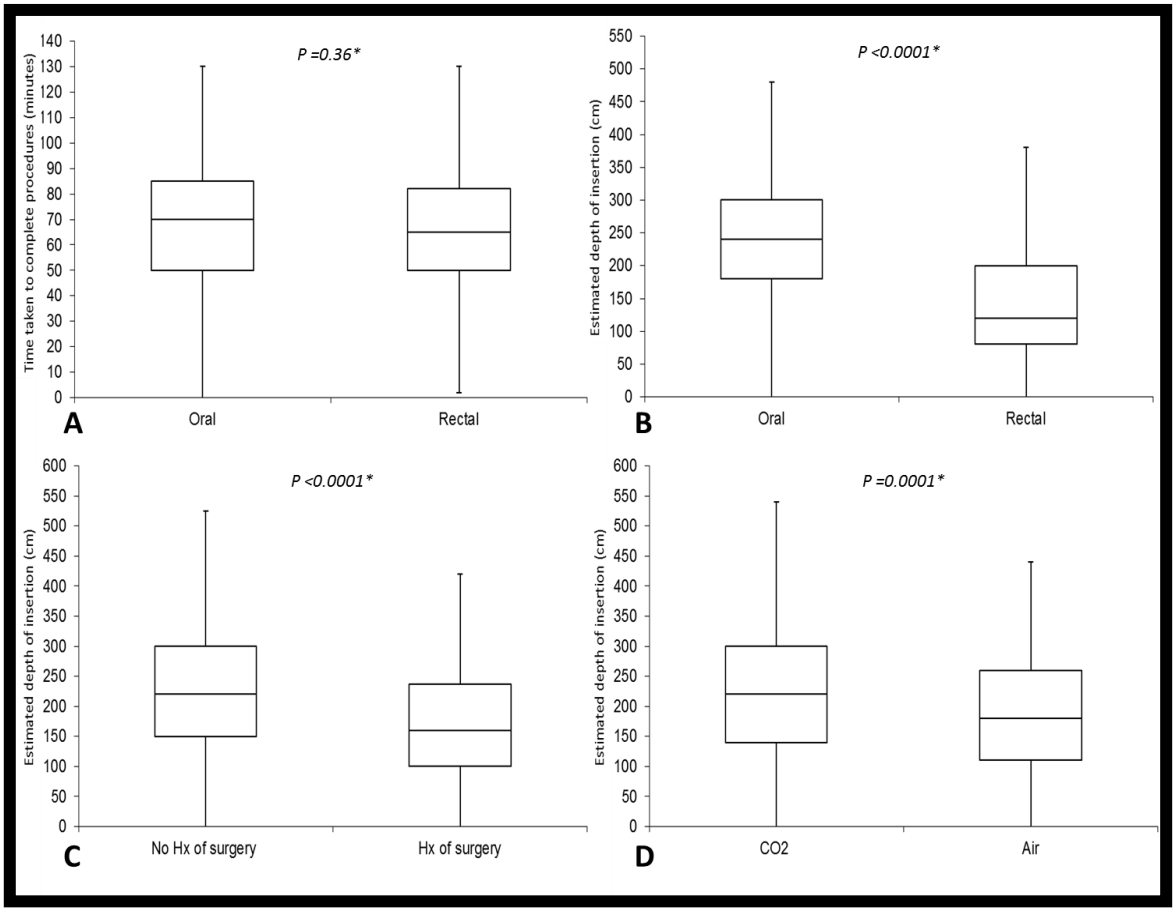
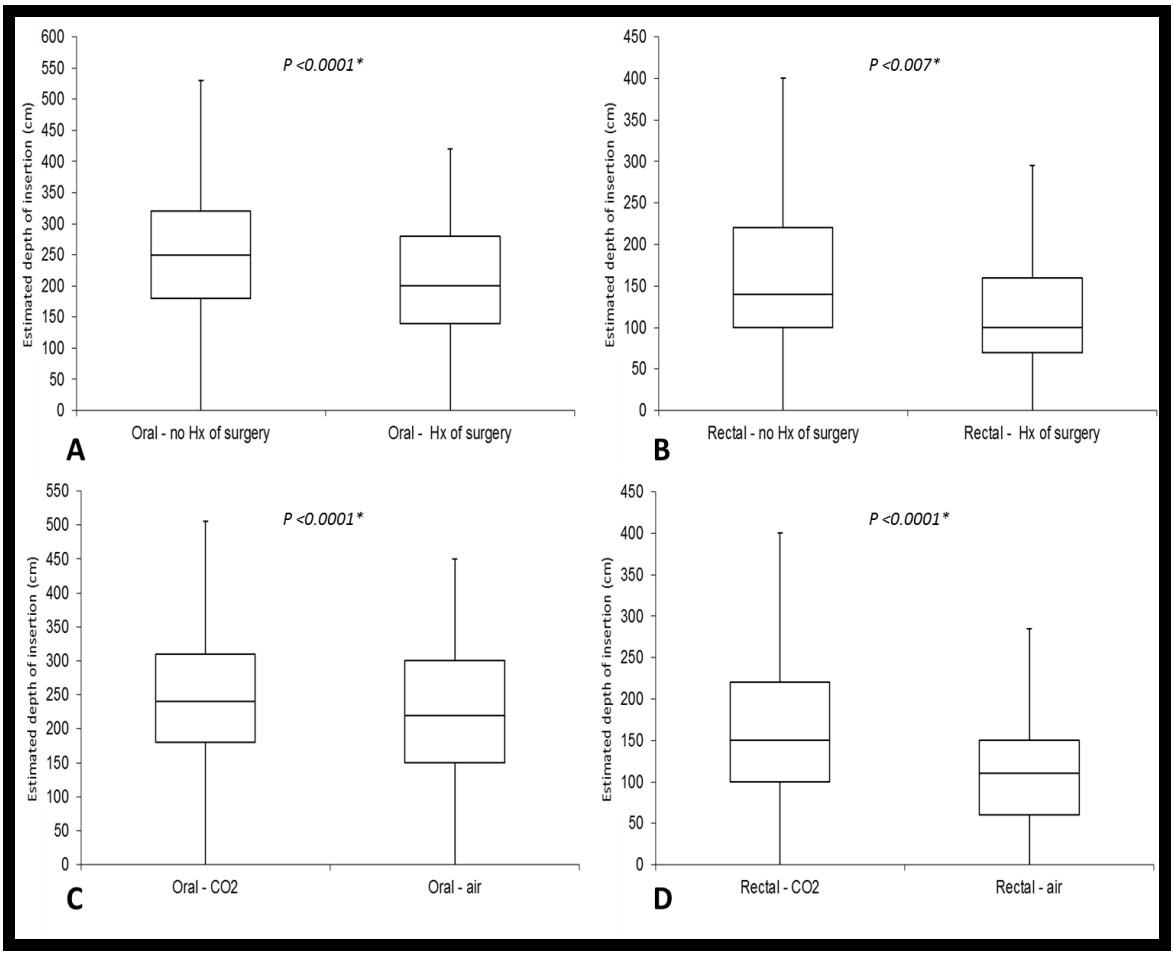


Figure 22: *Estimated depths of insertion in relation to a past history (Hx) of surgery for the oral route (**A**) or rectal route (**B**) or in relation to the use of CO_2 or air; oral route (**C**), rectal route (**D**). Values are expressed as medians (horizontal lines) and the 25th and 75th percentiles, boxes of the interquartile range (IQR). The whiskers of the box plots are set at 1.5x the 25th and 75th percentiles respectively; *Mann-Whitney test.*



3.4.4 Diagnostic yield

After exclusion of the 22 cases with an intrinsically therapeutic indication (DPEJ and ERCP in the setting of surgically altered anatomy), positive findings were identified in 565/978 (57.8%) of the remaining DBE procedures. There was no significant difference between diagnostic yield for either route (anterograde, 56.7% vs. retrograde, 56%, *P*=0.82). However, in the subgroup of 113 patients who underwent both anterograde and retrograde procedures, the combined overall diagnostic yield was significantly higher for the 20 patients in whom pan-enteroscopy was achieved as compared with that for the remaining 93 (80% vs. 64.5% respectively, *P*=0.02) in whom it was not.

3.4.5 Endoscopic therapy

Therapeutic interventions took place in 383 DBE procedures (38.3%). Most commonly, argon plasma coagulation (APC) of SB angioectasias was applied in 239/383 (62.4%) cases. Polypectomy of clinically-significant SB polyps in the setting of Peutz-Jeghers syndrome (PJS) was performed in another 79/383 (21%) of therapeutic DBE and balloon dilatation of SB strictures in 38/383 (9.9%). A total of 19/383 (5%) therapeutic DBEs involved direct percutaneous endoscopic jejunostomy (DPEJ) feeding tube placement (n=15), repositioning (n=2) or removal (n=2). The remaining 8/383 therapeutic procedures (2.1%) facilitated the application of other forms of haemostatic endotherapy, namely the deployment of endoclips (n=7) and thrombin injection of SB varices (n=1).

In 2 of the cases where DPEJ placement was intended, the procedures were abandoned due to inability to achieve adequate trans-illumination. In the only case intended for facilitation of endoscopic retrograde cholangio-pancreatography (ERCP) in a patient

with altered SB anatomy (post-orthotopic liver transplantation); no ERCP was performed since SB tethering hindered effective DBE insertion.

3.4.5.1 Factors identified by the endoscopists as having a negative effect on SB insertion depth

Specific factors which were identified by endoscopists as having a negative effect on SB insertion depth included 'SB tethering' and 'unfavourable SB looping'. These were encountered in 121 of 294 procedures (41.2%) in patients with a history of surgery and in 51 of 706 procedures (7.2%) done in surgically naïve patients ($P < 0.0002$). Other factors included 'technical faults', which occurred in 16 procedures (1.6%), 'poor bowel preparation' which caused 'friction' between the overtube and enteroscope in another 15 (1.5%) of DBEs and a 'retroverted (backward facing) or ileo-caecal valve' which was described in 8 procedures (0.8%). The retrograde route itself was also identified as having a negative impact on SB insertion depth; 86 of the 318 retrograde DBEs (27%), failed to achieve an estimated SB insertion depth of 100cm as compared with 39 of the 682 anterograde procedures (5.7%) which failed to achieve this ($P < 0.0002$).

3.4.6 DBE related complications

Unfortunately, due to the retrospective design of the study and tertiary nature of the referrals for DBE, data on longer-term complications could not be secured and therefore complication data should be considered to mainly represent immediate (peri-procedure) adverse events. Peri-procedure complications occurred in 9 DBE procedures involving endotherapeutic interventions and in 1 case where no endotherapy was applied. These

consisted of 4 perforations (2 post-polypectomy, 1 post-stricture dilatation and 1 diagnostic procedure in a patient with actively inflamed Crohn's disease distal SB strictures); 3 cases of mild post-polypectomy bleeding (requiring no transfusion), 1 case of acute coronary syndrome (ACS), 1 case of post-DBE pancreatitis and 1 case of a pelvic abscess related to an infected laparoscopy-port wound post lap-DBE. None of the complications was associated with mortality and all patients made a full recovery (**Table 11**).

Consequently, the overall DBE rate of adverse events in our experience was 1%. The complication rates for diagnostic and therapeutic DBEs were 1/617 (0.16%) and 9/383 (2.35%) respectively. The overall post-polypectomy complication rate was 5/79 (6.3%); post-polypectomy bleeding and perforation occurred in 3/79 (3.8%) and 2/79 (2.5%) respectively. Perforation occurred in 1/38 cases (2.6%) of dilatation of SB strictures. Post-DBE pancreatitis occurred in 1/682 (0.15%) of anterograde procedures but none of the retrograde cases.

Table 10: *Full details of peri-procedure DBE related complications. CT, computed tomography; Hx, history; IHD, ischemic heart disease; Mx, management; ECG, electrocardiogram; NSTEMI, non-ST segment elevation myocardial infarction; Dx, diagnosis; MRI, magnetic resonance imaging. *Severity was graded according to the American Society of Gastrointestinal Endoscopy (ASGE) lexicon of adverse events (2010) [151]*

Patient details			Indication for DBE / route of insertion / GA & sedation details	Complication type	Procedure/complication details	Outcome	Severity*
Number	Gender	Age (years)					
1	F	49	Dilatation of Crohn's disease (CD) small bowel (SB) strictures / oral route / general anaesthesia (GA)	Perforation (post-SB stricture dilatation)	Successful dilatation of 3 tight strictures in an angulated and adhered jejunal segment was followed by the development of severe abdominal pain 8 hours post procedure; Urgent CT confirmed delayed perforation of the jejunum.	The patient underwent emergency laparotomy with resection of the diseased segment of jejunum and formation of a temporary jejunostomy which has since been reversed with good recovery.	Severe
2	M	17	Emergency polypectomy in the setting of intussusception of a large, semi-pedunculated duodenal Peutz-Jeghers syndrome (PJS) polyp / oral route / GA	Perforation (post-polypectomy)	Emergency DBE was performed in attempt to avoid surgery in the setting of intussusception of a large semi-pedunculated duodenal polyp; an immediate post-polypectomy perforation occurred.	The procedure was immediately converted to an IOE through the full-thickness defect by the observing surgeon. The duodenal polyp was resected and the patient made an uneventful recovery.	Severe
3	F	39	Polypectomy of large, semi-pedunculated jejunal PJS polyp / oral route / GA	Perforation (post-polypectomy)	Immediate perforation following elective polypectomy of a large semi-pedunculated jejunal polyp.	The patient underwent emergency laparotomy and IOE with resection of the polyp through an enterotomy. Good recovery with no further complications.	Severe
4	M	42	Assessment of CD disease activity and evaluation of SB strictures / rectal route / GA	Perforation (not related to endotherapy)	The mesenteric wall of the distal ileum was involved by linear inflammation and stricturing with pre- and post-stenotic saccular dilatation. None of these strictures required endotherapy. On withdrawal of the enteroscope however, a 2cm perforation was noted on the mesenteric border. This may have been caused by trauma from angulation of the tip of the enteroscope.	At emergency laparotomy, the full-thickness perforation into the mesentery was confirmed and the diseased segment of ileum was resected without need for an ileostomy. The patient made a full recovery.	Severe
5	M	80	Argon plasma coagulation (APC) of SB angioectasias / oral route / sedation (5mg midazolam + 50mg pethidine)	Acute coronary syndrome (ACS)	The patient (who had a Hx of IHD) developed severe compressive chest pain during APC of jejunal angioectasias. The procedure was immediately aborted and the chest pain resolved after 30 minutes with medical Mx. ECG and serum troponin levels confirmed NSTEMI. The patient did not experience peri-procedure hypoxia or hypotension.	The patient was admitted for percutaneous coronary intervention (with bare metal stenting) and was discharged 5 days later after a good recovery.	Moderate
6	M	46	Polypectomy of a large jejunal PJS polyp / oral route / sedation (8mg midazolam + 100 mcg fentanyl)	Post-DBE pancreatitis	The patient (who had a Hx of laparotomy for PJS polyposis) underwent successful polypectomy of a large jejunal polyp. The procedure duration was 90 minutes and the estimated depth of insertion was 200cm; no significant procedure limitations were encountered. Shortly after the DBE, the patient developed moderately severe, persistent epigastric pain. Serum amylase and subsequent abdominal CT confirmed a Dx of pancreatitis.	The patient was admitted and the pancreatitis resolved with conservative, medical management. The patient did not require admission to a high dependency or intensive care unit and was discharged 6 days later without further complications.	Moderate
7	M	16	Laparoscopically assisted DBE (Lap-DBE) for polypectomy of a large duodenal PJS polyp / oral route / GA	Pelvic abscess (post-Lap-DBE)	Given the high risk nature of the duodenal polyp (large, sessile), a Lap-DBE was performed, during which successful polypectomy was undertaken. During post-op recovery, the patient developed signs of laparoscopic port-wound infection which eventually led to the development of a small pelvic abscess, as confirmed by MRI of the abdomen and pelvis.	The patient was treated as an inpatient with intravenous antibiotics and radiologically guided drainage of the abscess. A good recovery without further complications was followed by discharge home 10 days after the procedure.	Moderate
8	F	21	Polypectomy of large jejunal PJS polyp / oral route / GA	Mild bleeding (post-polypectomy)	Successful polypectomy of a large semi-pedunculated jejunal polyp was followed by some mild post-polypectomy bleeding.	The bleeding was immediately controlled by the use of endoclips but the patient was admitted for overnight observation. The patient did not require blood transfusion and no further complications ensued.	Mild
9	M	43	Polypectomy of 3 large jejunal PJS polyps / oral route / sedation (5mg midazolam + 100 mcg fentanyl)	Mild bleeding (post-polypectomy)	Successful polypectomy of 3 large pedunculated jejunal polyps was followed by mild post-polypectomy bleeding from 1 of the polyp stalks.	The bleeding was controlled by endoclip deployment and the patient was discharged home after uneventful overnight observation without transfusion.	Mild
10	M	76	Polypectomy of a large jejunal PJS polyp / oral route / sedation (5mg midazolam + 100 mcg fentanyl)	Mild bleeding (post-polypectomy)	Successful polypectomy of a large pedunculated polyp in the jejunum resulted in mild post polypectomy bleeding.	Successful haemostasis was achieved by endoclip use. The patient was admitted for overnight observation. There was no transfusion requirement and recovery was uneventful.	Mild

3.5 Discussion

3.5.1 Performance

Median depth of SB insertion during DBE was influenced by the route of approach, type of gas used for insufflation and the patients' past surgical history. The anterograde route was associated with significantly deeper SB insertion compared to the retrograde approach. Other investigators have also demonstrated lower insertion depths with retrograde procedures [39;152] which is likely to reflect the more technically challenging nature of retrograde DBE [152;153]. The use of CO_2 as an insufflating agent was also associated with deeper SB insertion, in keeping with the findings of Domagk et al. [154] whose two-centre randomized controlled study of CO_2 compared with air for SB insufflation at DBE showed a 30% increase in insertion depth associated with the use of CO_2.

Our overall diagnostic yield of positive findings at DBE was 57.8%. This is comparable to the overall pooled detection rate of 68.1%, reported by Xin et al. [148], in their recent systematic review including 45 studies with a total of 5615 patients. In our experience, there was no difference in diagnostic yield for procedures performed via the anterograde or retrograde approaches, however in the subgroup of patients where pan-enteroscopy was successful, the diagnostic yield increased significantly. This supports the view that although challenging, particularly in patients with a history of laparotomy, an attempt at achieving pan-enteroscopy in selected patients may be worthwhile [155].

3.5.2 Limitations of DBE

DBE procedures performed in patients with a history of abdominal or pelvic surgery were associated with a significantly lower median SB insertion depth as compared with procedures performed in surgically naïve patients. SB tethering and unfavourable

looping were reported more often in patients with a history of surgery. Our experience mirrors that of others [27;152;156;157]. Adhesive disease may account at least in part, for our pan-enteroscopy rate of 17.7%, which although similar to the pan-enteroscopy rate of 21%, reported by a prospective German database [39], is at the lower end of the range of pan-enteroscopy rates (8-66%) described by other European series [30;155;158].

3.5.3 Complications

The overall peri-procedure complication rate of 1% is well within the range (0.72-1.2%) reported by other international series [27;30;38;39;148]. Importantly, none of these complications was associated with mortality. Also, similar to other reports [27;30;38;39;148] most adverse events (9/10) related to use of endotherapy. The patient who suffered a perforation during diagnostic DBE (0.1% of all DBE procedures; 0.16% of diagnostic DBEs), had actively inflamed CD-related stricturing and it is suspected that trauma to the friable SB wall from angulation of the tip of the enteroscope (due to 'high stretch'/pressure during unfavourable looping) contributed to this unfavourable outcome. Complications relating to endotherapy (0.9% of all DBE procedures; 2.35% of endotherapeutic DBEs) consisted of perforations (n=3), mild post-polypectomy bleeding (n=3), ACS (n=1), pancreatitis (n=1) and a post-laparoscopic wound related infection, following laparoscopic assisted DBE (n=1). The endotherapeutic procedures carrying the highest risk were polypectomy of large PJS polyps (3.80% risk of bleeding and 2.53% risk of perforation) and dilatation of SB strictures (2.63% risk of perforation). The presence of active inflammation within strictures should alert the endoscopist to avoid proceeding with dilatation in patients with SB CD. In our experience, post-DBE pancreatitis only occurred during 1 anterograde case (0.1% of all DBE procedures, 0.15%

of anterograde DBEs); this compares favourably to figures reported by others (0.2%-0.49%) [27;30;38;39;148]. It must be re-iterated that the retrospective design of the study and tertiary nature of the referrals for DBE, data on longer-term complications could not be secured reliably. In view of this limitation, our complication data should be considered to mainly represent immediate (peri-procedure) adverse events, and may have therefore potentially underestimated the overall procedure-related complications.

3.5.4 Limitations of the study

This was a retrospective study and the intrinsic limitations of this design (such as the absence of a pre-data collection study protocol) should be borne in mind. The retrospective design and tertiary nature of DBE referrals also led to challenges in securing longer-term complication data. We consider this to be a major limitation and have therefore accepted that our complication data is more likely to represent peri-procedure (immediate) complications and that this may have potentially underestimated overall post-procedure complications. The collation of multiple data-sets from different centres across the country also has its limitations and challenges and although every effort was made to ensure that the data collected were complete and accurate, the absence of an audit mechanism may have allowed room for potential error. Since the establishment of DBE services in the UK has developed over the course of the last few years, it is also possible that cases performed by newer services were not included in this report. Another potential limitation may relate to heterogeneity of DBE user experience which may have confounded some of the results obtained. However, given these inherent limitations, our results are compatible with reports of other similar databases published to date [27;30;38;39;148].

3.5.5 Conclusion

In summary, our data from the first UK multicentre experience shows that DBE has an important role in the diagnosis and management of SB pathology. Factors which influence successful performance include the route of insertion, the presence or absence of intra-abdominal adhesive disease and the type of gas used for SB insufflation. Although pan-enteroscopy may be a challenge to achieve, it may help to increase the diagnostic yield. In our experience, DBE in the UK has an overall immediate complication rate of 1%, although SB polypectomy and stricture dilatation are associated with higher risks of complications which is in accordance with the findings of other large series [27;30;38;39;148].

4 Description of two original, alternative DBE insertion techniques

4.1 Background

Although DBE has the potential to facilitate deep enteroscopy without the need for surgical intervention, the procedure is labour-intensive and requires dedicated training. While some reports on DBE learning-curves have suggested that proficiency may improve after the performance of between 20 and 35 procedures [152;159], the author agrees with the findings of Gross et al. [160] who report that expertise in the procedure may require significantly more experience to be achieved (>100 – 150 procedures). Although competency in endoscopy should ideally be assessed by dedicated and validated competency assessment tools [161-165] (rather than the use of numbers of procedures performed as a surrogate marker of competency) this reported data suggests that training in DBE may best be achieved through dedicated, lengthy advanced endoscopy fellowships in specialist centres.

Furthermore, our experience and that of others [27;152;153;156;166] has found that SB insertion depth may be limited during procedures performed via the retrograde route or in the presence of SB tethering (e.g. secondary to post-surgical adhesive disease). In an attempt at overcoming these potential limitations, we developed 2 original, alternative DBE insertion techniques which are designed to enable deeper SB insertion during retrograde DBE and for the management of 'unfavourable' SB looping as caused by the presence of SB tethering, respectively [167;168].

4.2 Achieving successful ileal intubation during retrograde DBE: description of an original alternative technique

The retrograde approach is considered technically more challenging in DBE and failure rates for ileal intubation of up to 30% have been reported [152]. The original ileal intubation technique at DBE as described by Yamamoto et al. [20;123] involves a 'forward view' approach to the ileo-caecal valve (ICV) while the overtube (with its balloon inflated) is pulled-back within the ascending colon (**Figure 7B**) which helps to reduce the 'ileocolic' angle enabling improved visualisation and intubation of the ICV and the terminal ileum (TI) [123]. In our experience and that of others, ileal intubation can still fail despite the use of this technique [152;153].

We subsequently proposed an original, alternative method for ileal intubation when the standard manoeuvre [123] is unsuccessful. Our technique enables ileal intubation in situations where the 'ileocolic' angle cannot be reduced sufficiently by pull back of the overtube balloon or when the ICV is retroverted (i.e. backward-facing, away from direct endoscopic view).

4.2.1 Diagrammatic, step-wise description of the technique:

Figure 23: ***Step 1****: Both the enteroscope and overtube are passed into the caecum, the overtube balloon is inflated and the ICV visualised by the enteroscope in the retroflexed view; the enteroscope balloon remains deflated.*

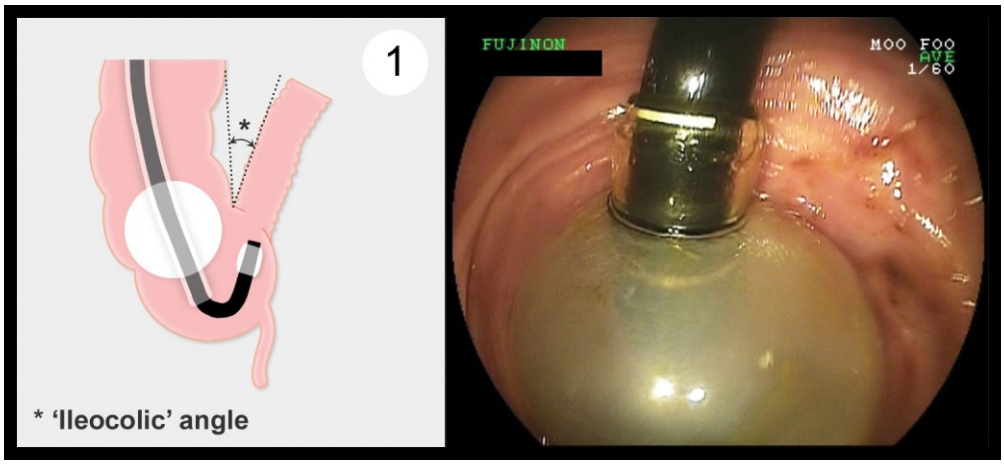


Figure 24: ***Step 2:*** *The enteroscope is advanced into the terminal ileum (TI), while in the retroflexed position. The enteroscope balloon is then inflated, allowing the enteroscope balloon to apply gentle traction to the TI in preparation for step 3.*

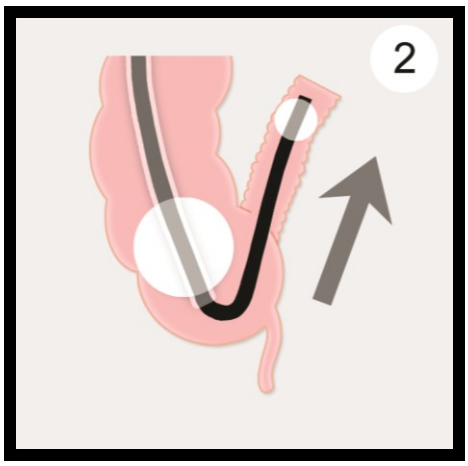


Figure 25: ***Step 3:*** *While the enteroscope balloon is inflated in the TI, the overtube balloon is deflated and the enteroscope and overtube are pulled back together, straightening the enteroscope in preparation for advancement of the overtube into the TI.*

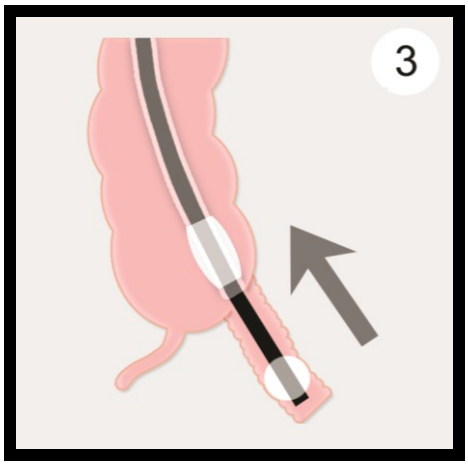


Figure 26: ***Step 4:*** *The overtube is advanced across the ICV into the TI and the overtube balloon is inflated.*

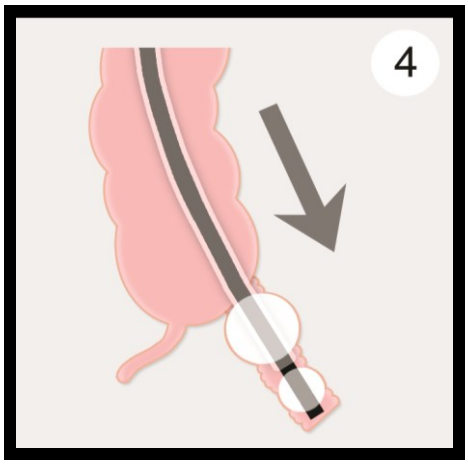
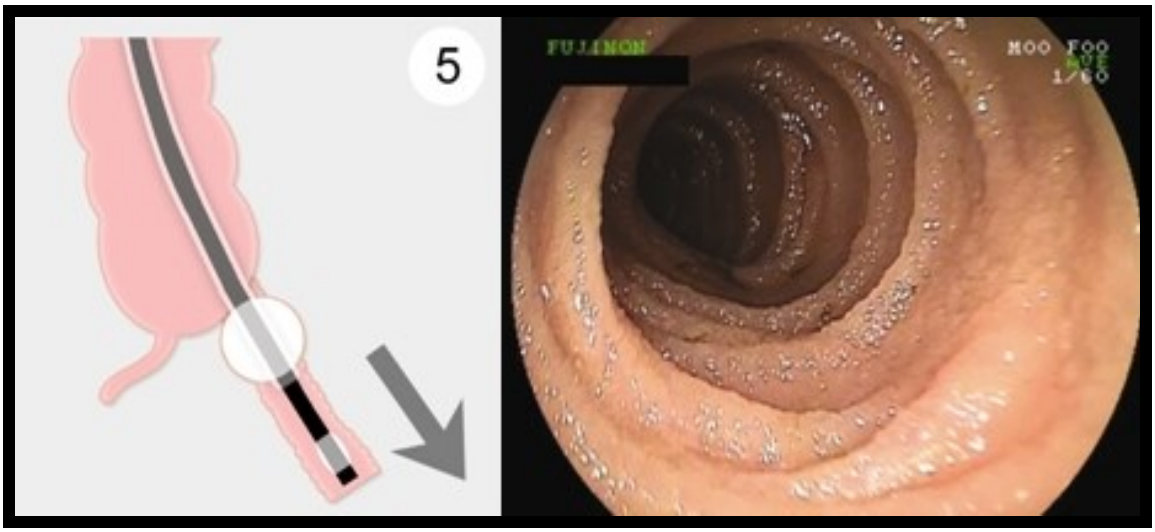


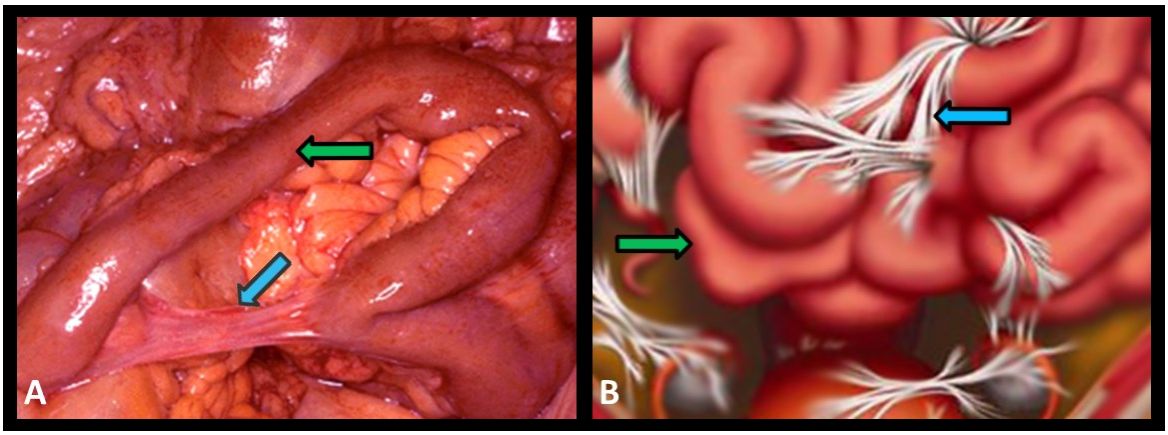
Figure 27: ***Step 5****: With enteroscope balloon deflated, the enteroscope is advanced deeper into the ileum while the overtube balloon remains inflated. The usual DBE insertion method [123] can then be resumed.*



4.3 Management of deep looping when failing to progress at DBE: description of an original alternative technique

The key principles of deep intubation of the SB by DBE as described by Yamamoto et al. [20;54;123] involve minimal SB stretching and loop reduction. This relies on gentle traction of the SB provided by the enteroscope and overtube balloons, and a "pull-back" manoeuvre which allows loop resolution and straightening of the mobile and un-tethered SB [123]. In patients with underlying SB tethering (e.g. due to intra-abdominal adhesions) (**Figure 28**), our experience and that of others [156] has found that this insertion method may be limited by the formation deep 's-shaped' loops that are difficult to reduce during enteroscope insertion, resulting in decreased insertion depth and procedure failure. We therefore developed an original adaptation of the conventional insertion method designed to improve SB insertion depths during DBE when such deep, unfavourable looping occurs.

Figure 28: *Photograph (courtesy of Dr Edward C. Klatt MD, 'WebPath', The Internet Pathology Laboratory for Medical Education, Mercer University School of Medicine, Savannah, Georgia, USA (http://library.med.utah.edu/WebPath)), demonstrating adhesions (blue arrow) of the SB (green arrow) as seen at laparotomy (**A**) and cartoon illustrating how adhesive disease (blue arrow) causes tethering of the SB (green arrow) (**B**)*



4.3.1 Diagrammatic, step-wise description of the technique:

Figure 29: ***Step 1A:*** *Failure to progress with enteroscope (**a**) as SB tethering (**b**) forms a deep loop* ***Step 1B:*** *The enteroscope balloon is inflated (a), the overtube balloon is deflated (**b**) and the overtube advanced (**c**).*

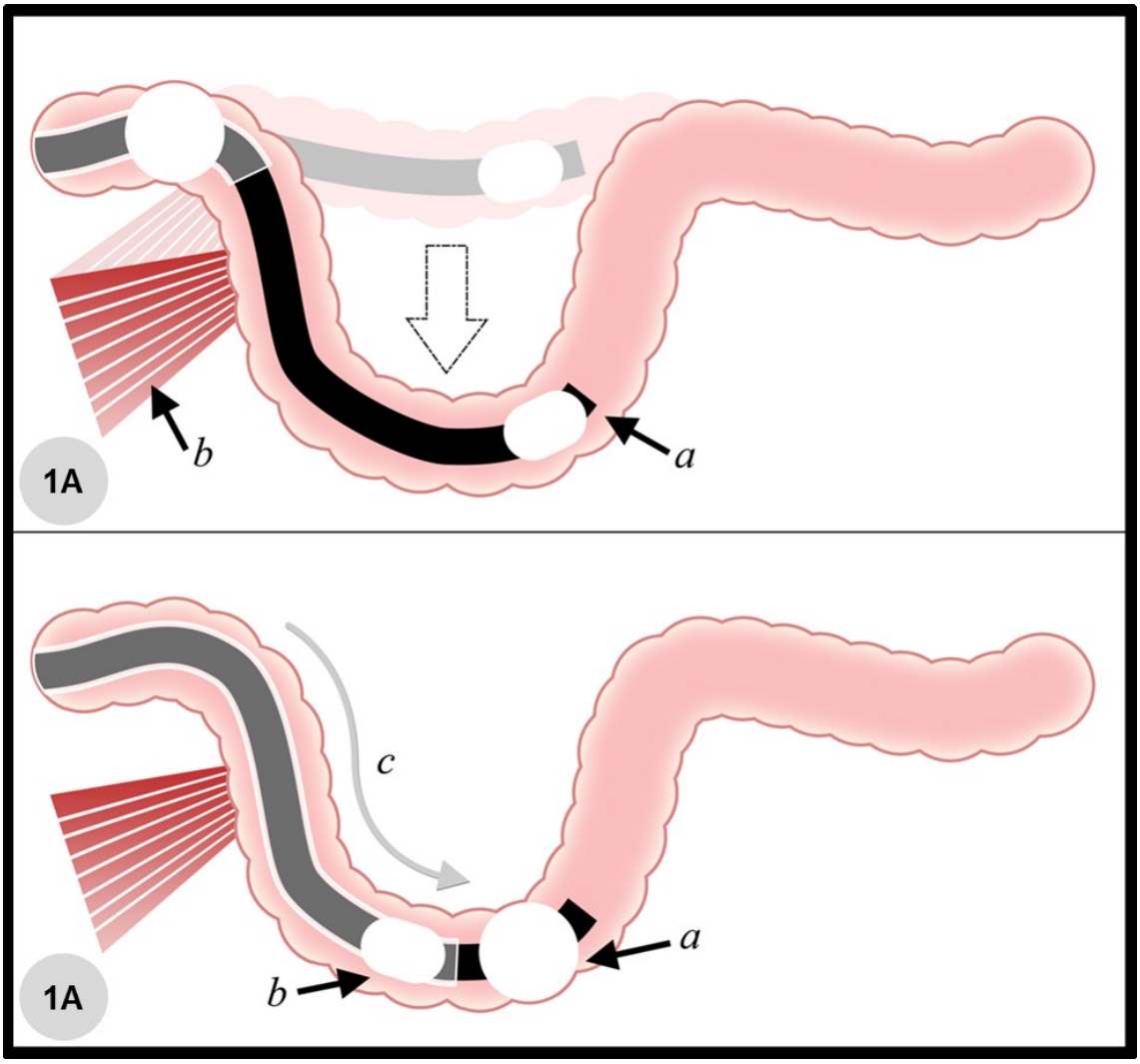


Figure 30: ***Step 2:*** *The overtube balloon is inflated (**a**) while the enteroscope balloon is deflated (**b**). The enteroscope is then advanced as the overtube pulled back (**c**).*

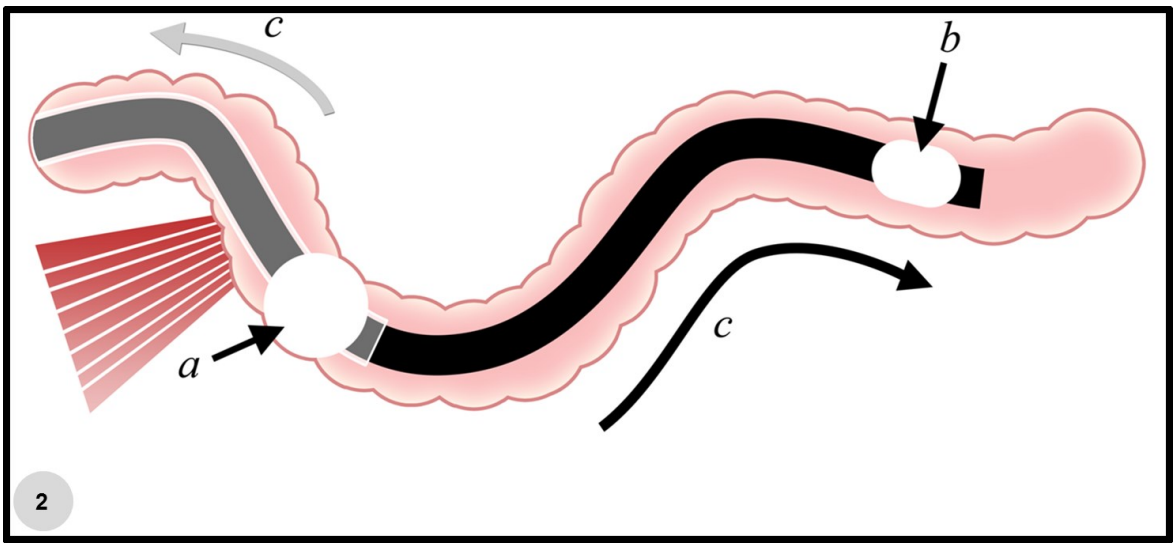


Figure 31: ***Step 3:*** *The enteroscope balloon is inflated (**a**) and the overtube balloon deflated (**b**). The overtube is then advanced as the enteroscope is pulled back (**c**). This step is fundamental to the success of this variation in insertion method and relies on the use of the enteroscope balloon alone (which is not available in other deep enteroscopy techniques such as single balloon or spiral enteroscopy).*

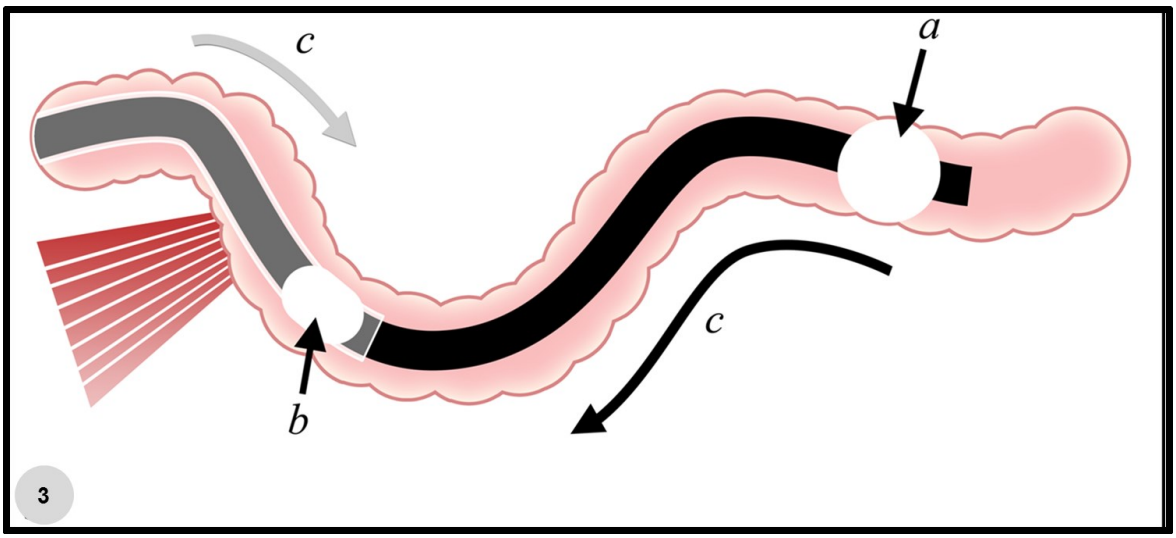
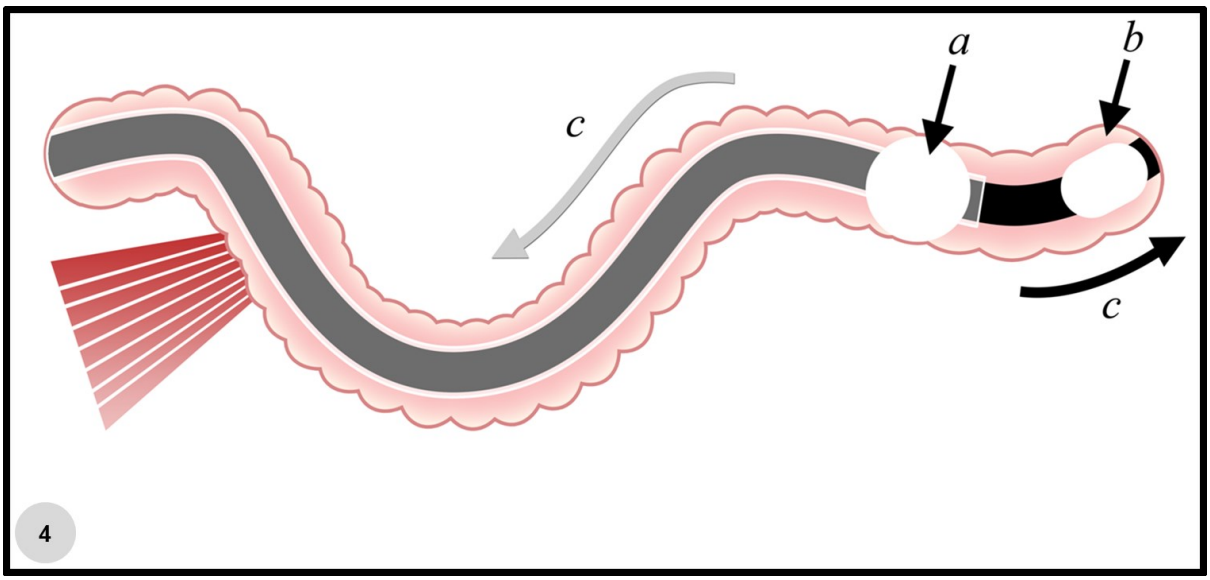


Figure 32: *Step 4: The overtube balloon is inflated (**a**) and the enteroscope balloon deflated (**b**). The enteroscope is then advanced as the overtube pulled back (**c**).*



4.4 Summary

Despite the ability of DBE in achieving effective, minimally invasive deep enteroscopy [27;152;153;156;166], it is a labour-intensive procedure which requires dedicated training. Although procedure proficiency may improve after the performance of the initial 35 procedures [152;159], it is likely that expertise in DBE may potentially only be achieved through the acquisition of significantly more experience [160]. Furthermore, SB insertion depth may be reduced during procedures performed via the retrograde route or in the presence of SB tethering. To address these limitations, we have developed 2 original, alternative DBE insertion techniques that may be applied when needed, in order to achieve successful intubation of the ICV and during looping, particularly when SB tethering due to adhesions is suspected [167;168].

5 Effectiveness and safety of DBE facilitated dilatation of Crohn's disease SB strictures

5.1 Background

Idiopathic inflammatory bowel disease (IBD) is classified into ulcerative colitis (UC) and Crohn's disease (CD), two major chronic inflammatory disorders of the gastrointestinal (GI) tract which are hallmarked by significant morbidity relating to frequent relapses [169]. Although both these conditions are lifelong disorders, each has its own distinct pathological and clinical features: UC is characterised by diffuse inflammation of the colonic mucosa while CD is heterogeneous, affecting any part of the GI tract with varying degrees of inflammation [170;171]. CD is also associated with transmural inflammation that may result in stricturing and penetrating disease [170] and a tendency for progression in severity with time [172]. CD most commonly affects the ileo-colic region, with SB involvement affecting up to 80% of cases and in about 30% of patients, the disease is limited to the SB alone [31;170;173].

Stricture formation in CD constitutes a major part of the disease burden and is a leading indication for surgical intervention and hospitalisation for patients with this condition1. The distal small bowel (SB) and ileo-colic anastomosis are the most common sites of involvement while colonic stricturing may occur in up to 17% of patients and proximal SB and upper gastrointestinal strictures occur in up to 5%.2 Although it is unclear why some patients develop stricturing disease while others are spared this complication, several factors such as the severity of CD, its duration, ileal involvement and the

presence of certain NOD2/CARD15 genetic polymorphisms appear to be linked with an increased risk of stricture development.3-5 There is also a tendency for the CD phenotype to worsen over time; one large series showed that up to 27% of patients progressed from a non-stricturing/non-penetrating phenotype to stricturing disease over a period of 10 years.6 Despite recent advances in the medical management of CD, stricturing disease remains a challenging issue since most strictures eventually develop a significant fibrostenotic component that is refractory to medical therapy and requires endoscopic or more invasive surgical intervention.

Stricturing disease causes gradual narrowing of the intestinal lumen that may remain clinically silent but often manifests itself sub-acutely with post-prandial bloating, colicky abdominal pain or with the signs and symptoms of frank, acute intestinal obstruction (frequently precipitated by a fibre-rich meal). Three types of CD related strictures are described: inflammatory, fibrostenotic and anastomotic.7 The inflammatory and fibrostenotic types illustrate the natural history of CD itself and represent the two ends of a progressive continuum; often there is co-existence of inflammation and fibrosis within the same CD stricture. Although an attempt at quantification of the inflammatory and fibrotic components can prove to be a challenging task, every effort should be made to rule out active inflammation, as this has the potential to respond (at least in part) to medical therapy. Post-surgical anastomotic strictures are often very short, frequently occur in the absence of CD recurrence and tend to be more amenable to endoscopic therapy.8 Pointers to active disease may be sought from C-reactive protein (CRP) levels, diagnostic imaging and endoscopic evaluation. While the CRP is usually raised in active CD, a rise in its level may be caused by inflammation elsewhere and corroboration with other investigations is advised; also the CRP level may be normal in the face of active disease in up to 10% of patients.9 Radiological investigations (**Figure 33**) that may demonstrate disease activity include barium studies and contrast enhanced computed

tomographic (CT) enterography/colonography. Contrast enhanced ultrasound scanning (with Doppler) may also help to clarify the scenario but the quality of this test relies heavily on a high level of operator expertise.8 Dynamic gadolinium enhanced magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), have also been shown to be excellent at highlighting active inflammation within a given stricture.10 Diagnostic imaging also provides additional information on the length and complexity of any stricturing disease; characteristics that will also influence the management strategy in their own right. Direct endoscopic visualisation of a stricture and its surrounding mucosa is also a key part of the assessment process; endoscopic findings that strongly support active disease include the presence of marked mucosal ulceration and sloughing (Fig. 2); endoscopic assessment also provides the opportunity to take biopsies for histopathological analysis. During the initial clinical work-up of patients who present with sub-acute symptoms associated with SB strictures, it is also important to consider the frequently overlooked co-existence of small intestinal bacterial overgrowth (SIBO) since treatment of this condition may have a significant impact on symptom alleviation.11

The acute or sub-acute symptomatic manifestation of a stricture is usually related to the plugging of the stenosis by indigestible dietary fibre or the presence of on-going mucosal oedema secondary to active inflammation. Unless the clinical scenario dictates otherwise, a conservative approach with medical and supportive therapy should be the first line strategy. The response to medical therapy is however dependent on the inflammatory component within the stricture and strictures that are actively inflamed have a greater potential to respond to steroids and immunomodulatory agents than lesions that are already significantly fibrosed. Strictures that are likely to have a significant inflammatory component should therefore be managed with high dose systemic steroids in the first instance; responders should then be maintained on long-

term immunomodulators. Although the subject remains controversial, concerns regarding the potential for anti-tumour necrosis factor-α (anti-TNF-α) agents to worsen or induce fibrostenotic disease may be unfounded as the findings of several small series show.8, 12 These data suggest that anti-TNF-α drugs may have a role to play in the management of active strictures that are refractory to initial treatment with steroids.

Although surgery is often unavoidable in the management of stricturing CD, it may be associated with significant morbidity and high post-operative recurrence rates. Up 70% of patients develop endoscopic recurrence within 1 year of surgery and up to 40% of patients will be symptomatic again within 4 years [174]. Apart from the inherent risks of surgery, up to 20% of patients may suffer serious postoperative complications [174]. One large series quoted a 30-day postoperative mortality rate of 3.2% [175]. Patients also face the hazard of loss of significant lengths of SB with the potential development of short bowel syndrome [176] and dependence on parenteral nutrition. In addition, surgically treated patients have an increased likelihood of further episodes of intestinal obstruction due to post-surgical SB adhesive disease [177] or to re-stricturing at anastomotic or stricturoplasty sites [174]. This has encouraged the development of surgical techniques such as stricturoplasty in order to preserve SB length by minimising the need for bowel resection. The length of stenosis that can be repaired by stricturoplasty is usually between 10 and 25cm17. The Heinecke-Mikulicz and Finney methods are the two most common techniques of stricturoplasty performed in current practice. In the Heinecke-Mikulicz technique, a linear incision is made through the antimesenteric border of the stricture; this is extended by about 3cm on either side of the stricture and then sutured transversely with interrupted sutures in order to widen the SB lumen at the anastomosis. The Finney method is useful for longer strictures and involves the arrangement of the affected SB into a ‘U’-shape, incising the stricture at the antimesenteric margin and closing this in a side-to-side fashion. A meta-analysis

comparing these two methods, reported a lower re-operation rate in patients treated with the Finney method.18 Traditionally, long strictures have been dealt with small bowel resection but in expert hands long stricturoplasties (Michelassi) have been associated with good long term success rates but can be associated with a higher rate of anastomotic leakage.19 Stricturoplasty is contraindicated in patients with on-going sepsis or in the presence of a fistula and is generally reserved for strictures involving the SB rather than the colon since colonic strictures are deemed to be at higher risk of harbouring the potential for malignant transformation in long-standing CD of the colon.20

Since its introduction in the early 1980s, endoscopic balloon dilatation (EBD) has been shown to be a suitable alternative to surgery for selected patients with CD related strictures. Most published series describing EBD relate to its use at colonoscopy for the management of ileo-colic anastomotic, terminal ileal and colonic strictures. Long-term follow-up data from the largest such series published to date (138 patients, 237 dilatations) demonstrate that after a median follow-up of 5.8 years, 76% of patients avoided the need for surgery and only 46% required repeat EBD.13

The introduction of DBE has made previously difficult to reach parts of the SB more accessible to endoscopic therapy [20;45;54;123;178;179] providing a potential alternative to surgery for selected CD patients with SB strictures [42]. We here describe our experience of DBE facilitated SB stricture EBD in a series of patients with CD referred to our unit.

5.2 Aims

The aim of this series was to assess the effectiveness and safety of DBE facilitated CD SB stricture EBD in routine clinical practice.

5.3 Methods

Data from patients with CD referred for SB stricture EBD was prospectively collected. Almost all patients presented with obstructive-type symptoms: abdominal pain and bloating with chronic dietary restriction. The following information was recorded: stricture characteristics, route of procedure, EBD success, symptom resolution and change in diet post EBD, need for repeated EBD, complications and surgery. Follow-up was carried out by telephone consultation. A total of 13 DBE procedures were done in 11 consecutive patients (4 males; mean age 46.4±7.8 years). Decisions relating to EBD management were undertaken through the institution's multi-disciplinary team and on-going medical management of these was determined by the patients' referring medical teams. Patient characteristics and details pertaining to each case are summarised (**Table 12**). In 9 patients, their CD was considered to be stable and no changes had been made to their medication regimens in the preceding year. One of the patients (Patient 9) had refractory CD requiring the on-going use of steroids and in another patient (Patient 10), the diagnosis of CD was made at DBE. The mean duration of CD in the 10 patients with a prior diagnosis of CD was 24 years (range 13-31 years).

Table 11: *Patient characteristics and case details*

Patient number	Age(years)/Gender	History of CD and medical therapy at the time of referral	Previous surgery	Findings at BFT or CTE
1	42/M	17-year history of ileocolonic CD; on longstanding AZA and mesalasine	Right hemicolectomy and ileal resection	BFT showed 2 short strictures in the distal ileum
2	52/F	21-year history of SB CD; on mesalasine only	Jejunal and ileal resection; right hemicolectomy	CTE showed a short mid-jejunal stricture
3	47/F	28-year history of ileocolonic CD; on no regular medical therapy	Right hemicolectomy and ileal resection	CTE showed a tight short stricture in the distal ileum
4	52/M	25-year history of SB CD; on longstanding AZA and mesalasine	1 ileal resection	BFT showed a mid-jejunal stricture
5	44/F	23-year history of SB; on mesalasine only	2 ileal resections and a jejunal stricturoplasty	BFT showed 2 jejunal strictures
6	49/F	30-year history of ileocolonic CD; on longstanding 6-MP and steroids	End ileostomy; 3 ileal resections and 1 ileal stricturoplasty	No lesions seen on BFT but CTE showed 2 distal ileal strictures
7	42/F	19-year history of ileocolonic CD; on longstanding AZA	4 ileal resections	CTE showed a mid-ileal stricture
8	30/M	13-year history of ileocolonic CD; on mesalasine only	Right hemicolectomy and ileal resection; 1 ileal stricturoplasty	BFT showed 2 distal ileal strictures
9	47/F	31-year history of SB CD; on longstanding AZA and steroids	5 SB resections (jejunal and ileal); end ileostomy in situ	BFT showed 3 strictures in the jejunum with likely adhesions
10	59/M	Referred for investigation of non-specific abdominal pain, minimally elevated inflammatory markers; normal OGD and colonoscopy but video-capsule retention; No history of NSAID use	No previous surgery	Plain abdominal radiograph revealed a retained video-capsule
11	58/F	37-year history of SB and colonic CD; on longstanding AZA	Jejunal resection, ileal resection and right hemicolectomy	BFT showed 2 jejunal strictures

The anatomy of the SB strictures considered for EBD was determined by diagnostic imaging i.e. barium follow through (BFT) or computerised tomographic enterography (CTE) in the work-up before DBE in all but 1 patient (**Figure 33**); fluoroscopy during procedures was not required. All SB strictures were short (<5cm) and were additionally classified as predominantly fibrotic or inflammatory based on endoscopic appearance (**Figure 34**). Longer (>5cm) strictures were considered unsuitable for EBD. As it was generally difficult to determine with certainty either by diagnostic imaging or endoscopically, which strictures were 'de novo' or primary CD in nature or due to post-surgical recurrence this was not recorded.

Figure 33: *Barium follow through (**A**) and CT enterography (**B**) showing a SB stricture (black and white arrows, respectively; different patients)*

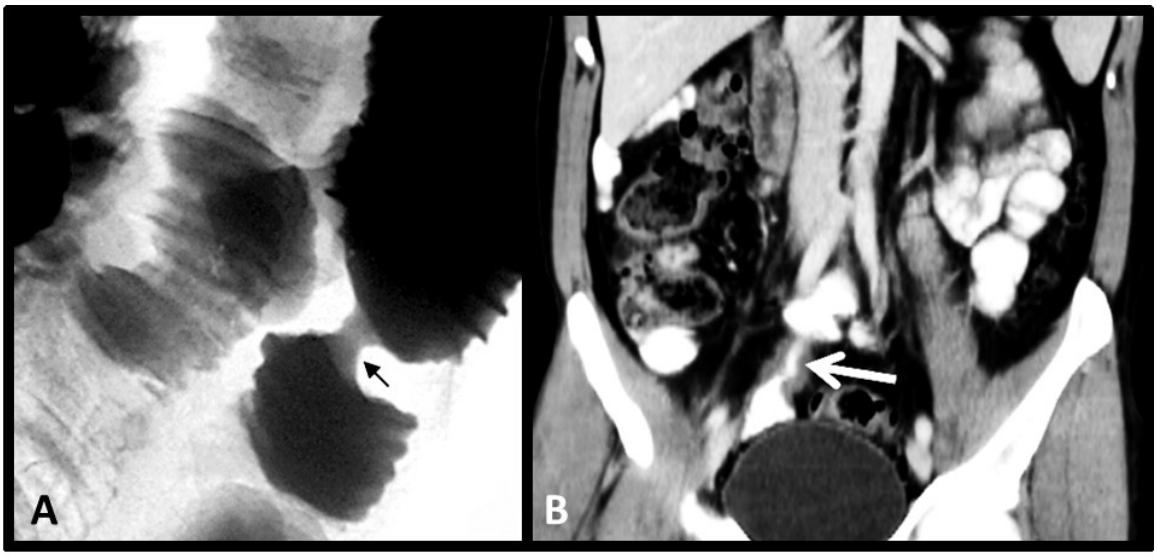
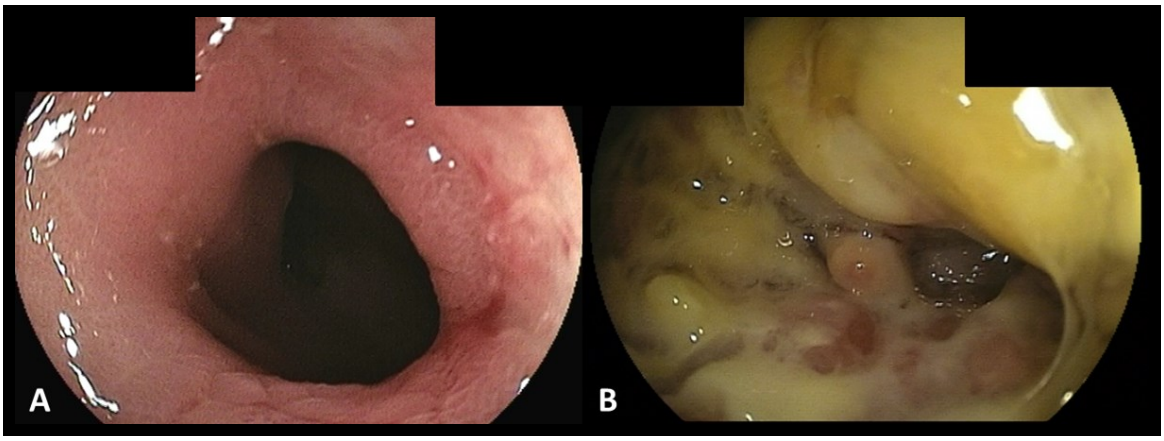
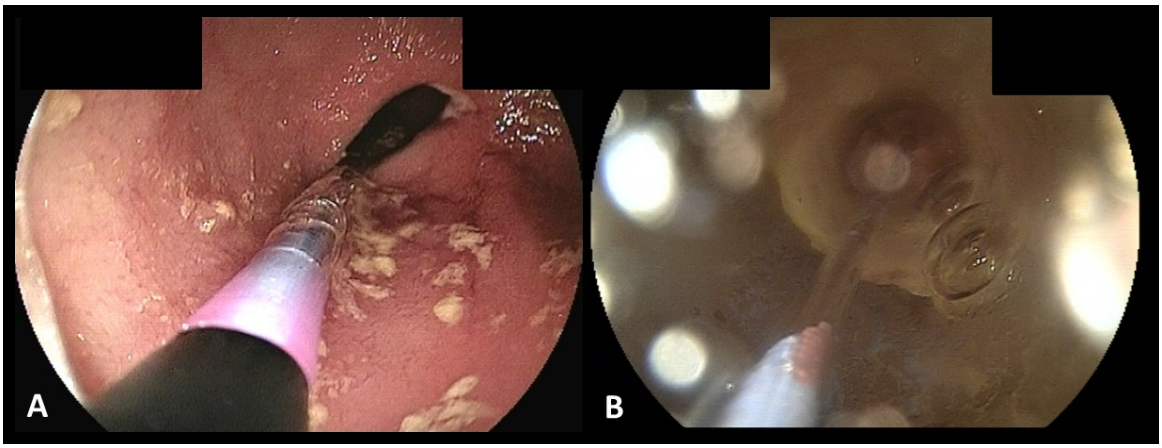


Figure 34: *CD related SB strictures; mainly fibrotic (**A**); severely inflamed with evidently active disease (**B**).*



Patients were fasted for 8 hours pre-procedure and in cases where the rectal route for DBE was used, additional bowel preparation was administered in the form of 13g of senna granules and 3 sachets of magnesium citrate (Citromag, Bioglan Laboratories, Hertfordshire, UK) on the day before and morning of the procedure. Nine of the procedures were performed under general anaesthesia, 2 procedures under conscious sedation with midazolam and pethidine and one case was done under Monitored Anaesthesia Care (MAC) (anaesthetist-delivered propofol sedation). Hysoscine-N-butylbromide (Buscopan®, Boehringer-Ingelheim, Germany) was used as an anti-peristaltic agent in each procedure. The procedures were performed using the therapeutic EN-450T5 double balloon enteroscope (Fujifilm, Saitama, Japan). Carbon dioxide gas (CO_2Efficient®, E-Z-EM, NY, USA) was used for SB insufflation and stricture EBD was performed using Controlled Radial Expansion (CRE) wire-guided balloon dilators (Boston Scientific, Natick, Mass, USA). The balloon dilators were inflated with water to the appropriate pressure (ATM) and balloon diameter as per instructions; EBD was maintained for 60 seconds once or twice per stricture under direct vision (**Figure 35**).

Figure 35: *Through-the-scope endoscopic balloon dilatation (EBD) of a short, fibrotic CD related SB stricture; deflated CRE-balloon catheter passed through stricture (**A**); stricture EBD with CRE-balloon insufflated under direct endoscopic vision (**B**).*



A standardised proforma was used to characterise the severity of symptoms (abdominal pain and bloating) including degree of dietary restriction present before DBE stricture EBD using a 10cm standard visual analogue scale (VAS). An identical proforma was used to collect data post-stricture EBD (by telephone consultation). At follow-up the requirement for interim, post-EBD surgical intervention was also noted. DBE procedures and stricture EBD were performed after written informed consent was obtained from the patients. The patients were informed about the risks of the endoscopic procedure itself, the risks of general anaesthesia or conscious sedation and the risks associated with endoscopic balloon EBD of CD SB strictures. On consultation with the regional and institutional review boards, it was deemed that no further dedicated ethics approval was required, since EBD of strictures is considered to be standard of care and that symptomatic follow-up of these patients post-EBD is part of the routine clinical paradigm.

5.3.1 Statistical analysis

Descriptive analysis was used for the patient demographic and clinical data. The t-Test (two-tailed) was used to analyse data collected from the VAS scores of patients before and after treatment.

5.4 Results

Overall in the 13 DBE procedures which were done during the period of study (February 2005 to October 2008), 18 SB stricture EBDs were performed in 9 of 11 patients. The mean stricture EBD diameter was 15.4mm (range 12-20mm). In the 2 patients in whom stricture EBD was not performed, DBE proved to be technically challenging. The presence of severe SB tethering secondary to adhesions from previous surgery and possibly also from the underlying CD itself, meant it was not possible to reach the strictures in these patients who subsequently went on to have successful surgical stricturoplasties. One of our patients in whom successful EBD of a complex set of strictures in a tethered and angulated segment of jejunum was achieved, developed sharp abdominal pain 8 hours post-procedure. An urgent CT scan of the abdomen and pelvis confirmed the presence of a perforation close to one of the dilated strictures. The patient underwent a laparotomy during which the diseased segment was resected and a defunctioning temporary jejunostomy was fashioned. Histopathological examination of the excised specimen confirmed the presence of active CD. The patient made a good recovery and the jejunostomy has since been reversed.

In the other 8 patients, successful DBE assisted SB stricture EBD was achieved, obstructive symptoms improved dramatically and by the end of November 2008 none of

these patients has required surgery with a mean follow-up 20.5 months (range 2-41 months). During follow-up 2 of the patients who had undergone stricture EBD required a repeat EBD of the same strictures due to recurrence of symptoms. The first of these 2 patients had a modest recurrence of symptoms at 6.5 months after the initial EBD and the second patient had a significant recurrence of her symptoms 13 months post-EBD. Both these patients proceeded to have straightforward repeat EBDs. In the penultimate patient in the series (Patient 10; **Tables 11, 12**), the diagnosis of CD only became clear at DBE. This patient was originally referred for further investigation of non-specific right iliac fossa abdominal discomfort, raised inflammatory markers and SB capsule endoscopy retention (**Figure 36**) in the setting of normal upper GI endoscopy and colonoscopy and no history of NSAID use. At DBE, two short ileal strictures were found and dilated, biopsies were taken and the retained capsule retrieved (**Figure 37**). Histopathology of the biopsies and a subsequent CT enterography were consistent with a new diagnosis of CD.

Although the numbers in this series are small, clinical improvement in pre- and post-EBD VAS scores (mean) was significant: 8.8 vs. 1.8, respectively (P <0.001). The procedure related details including VAS scores are shown (**Table 12**, **Figure 38**). None of the patients who underwent successful EBD required changes to their immuno-modulatory drug regimens during the follow-up period.

Figure 36: *Plain abdominal X-ray showing the retained video capsule (black arrow)*

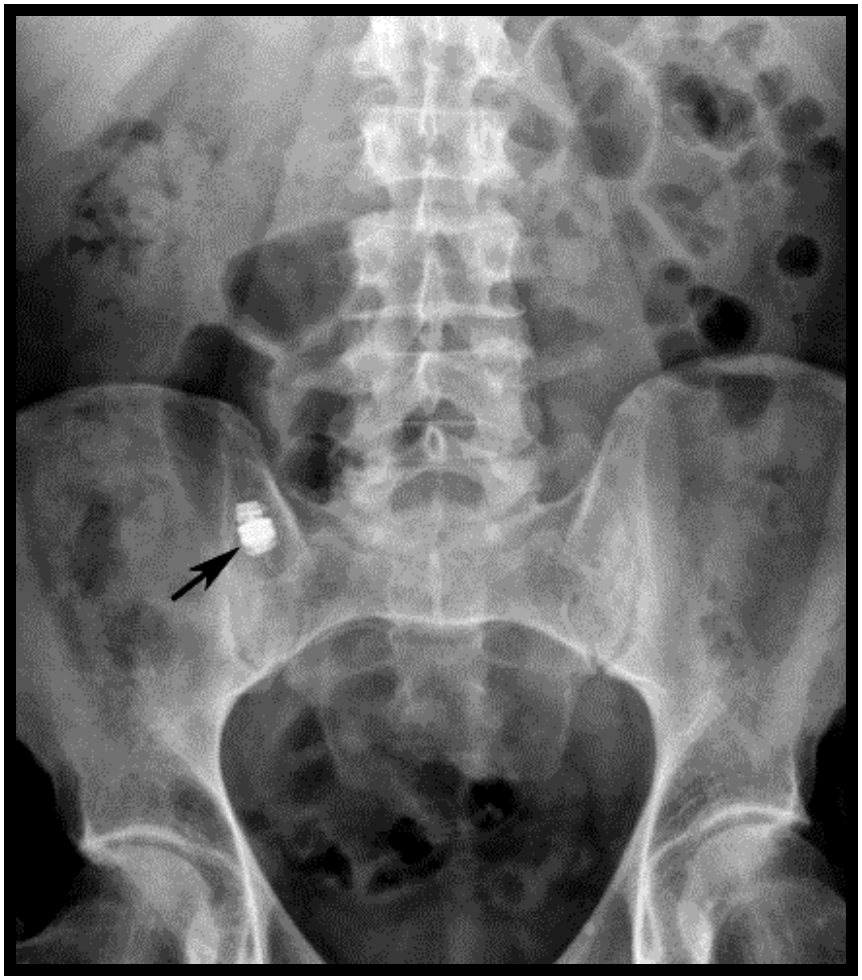


Figure 37: *Retained capsule endoscope at a short CD SB stricture (**A**); retrieval of the capsule with a Roth™ net (US Endoscopy, USA) after successful EBD of the culprit stricture, (**B**).*

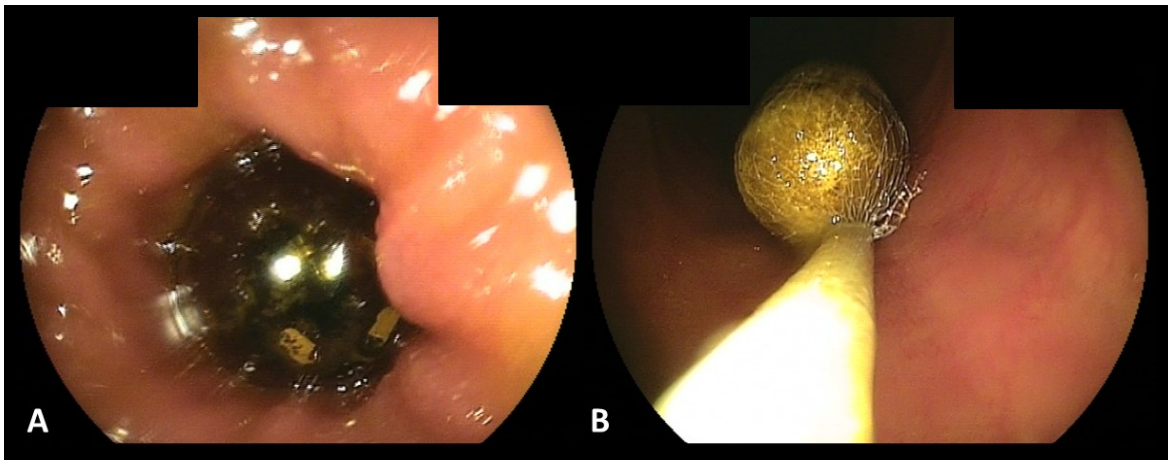
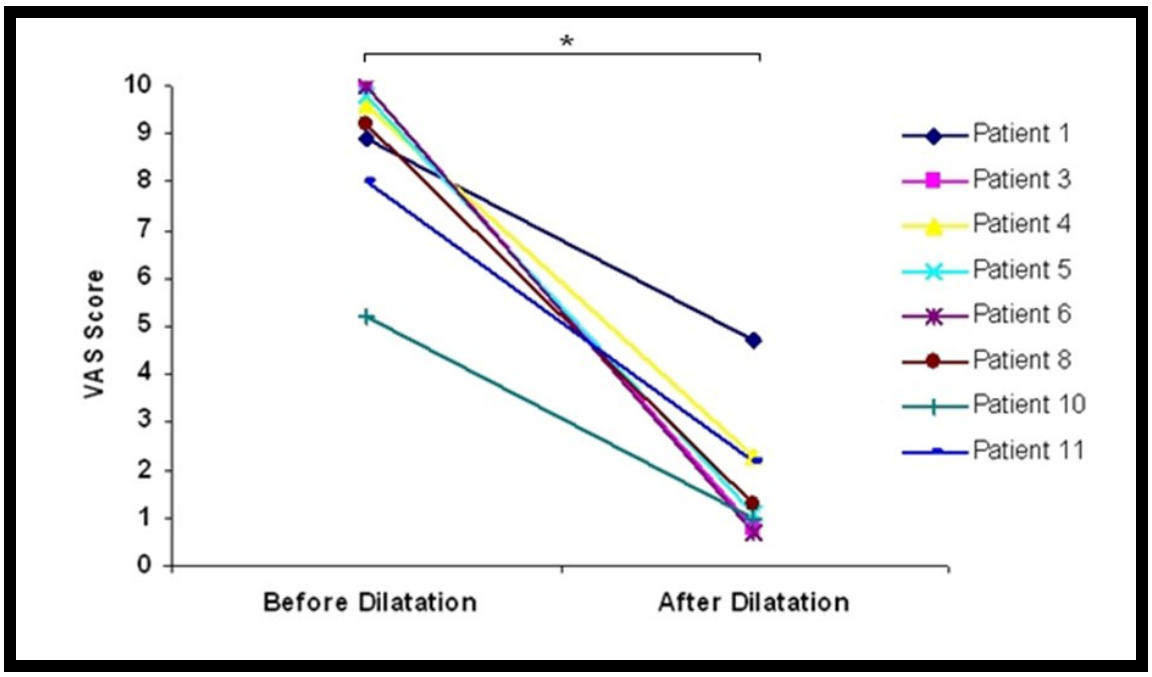


Table 12: *Intervention details and VAS symptom scores before and after DBE facilitated SB CD stricture EBD*

Patient number	Technical difficulties relating to adhesions	DBE stricture EBD performed	DBE route used	Number and type of strictures dilated	VAS symptom score before stricture EBD	VAS symptom score at latest post-procedure follow-up*	Need for a second DBE EBD procedure	Surgery required by latest follow-up
1	Minimal	Yes	Rectal	2 distal ileal; (fibrotic)	8.9	4.7	No	No
2	Significant	No	Oral	Not dilated	9.3	N/A	No	Surgical stricturoplasty
3	Minimal	Yes	Rectal	1distal ileal (fibrotic)	10	0.8	Yes (13 months after initial EBD)	No
4	Minimal	Yes	Oral	1 jejunal (fibrotic)	9.6	2.3	No	No
5	Minimal	Yes	Oral	3 jejunal (1 inflammatory and 2 fibrotic)	9.8	1.1	No	No
6	Minimal	Yes	Through end ileostomy	2 ileal (fibrotic)	10	0.7	No	No
7	Significant	No	Through transverse colostomy	Not dilated	9.5	N/A	No	Surgical stricturoplasty
8	Minimal	Yes	Rectal	2 ileal (Fibrotic)	9.2	1.3	Yes (6.5 months after initial EBD)	No
9	Moderate	Yes	Oral	3 jejunal (2 inflammatory and 1 fibrotic)	10	N/A	N/A	Emergency laparotomy due to perforation
10	None	Yes	Rectal	2 ileal (fibrotic); Retained video capsule retrieved by DBE; Biopsies of the stricture confirmed CD	5.2	1	No	No
11	None	Yes	Oral	2 jejunal (fibrotic)	8	2.2	No	No

Figure 38: *VAS scores for obstructive symptoms/dietary restriction before stricture EBD and at follow-up (where 0=no symptoms/restriction and 10=severe symptoms/restriction). *P <0.001*



5.5 Discussion

EBD of CD associated strictures has been used since the late 1980s [180] but the technique has been mainly applied to upper GI, ileo-colic or colonic strictures [181-183] since most of the SB has remained inaccessible to conventional flexible endoscopy. The ability to reach and dilate strictures deep within the SB endoscopically is now possible with DBE. Our case series adds to the currently small body of published evidence [42] which shows that DBE assisted SB stricture EBD in CD is feasible and effective. Our mean follow-up period of 20.5 months is among the longest published periods of follow-up to date. Morini et al. [184] showed that the first few months of follow-up after CD stricture EBD is an accurate predictor of long-term success, however EBD with DBE can be repeated if strictures recur. However, this should not be regarded as a failure,

particularly since the need for repeat surgery after stricturoplasty may be as high as 25% over a follow-up of 30 months [185].

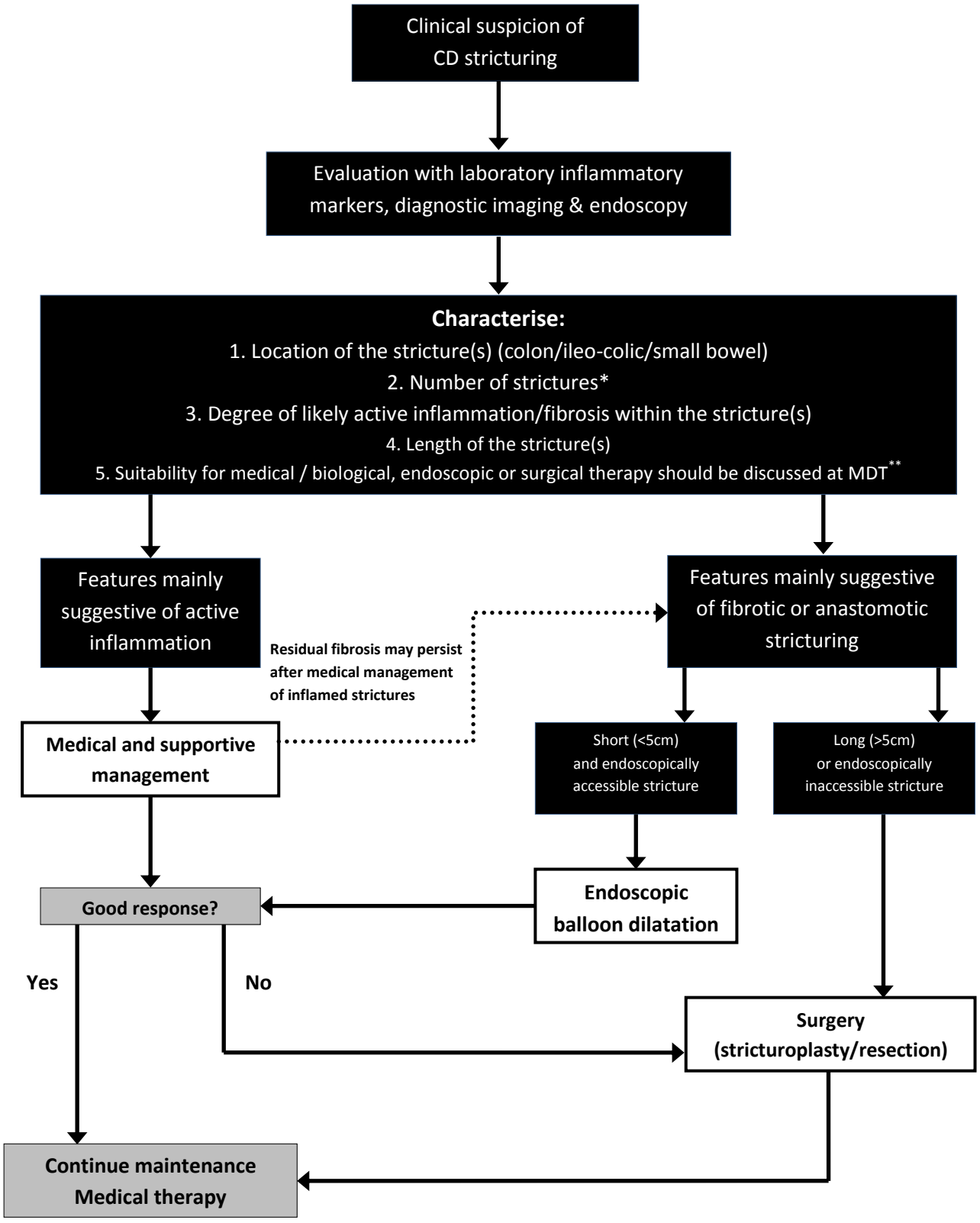
In our series, 1 patient unfortunately developed a delayed perforation requiring a temporary jejunostomy. The patient suffered from long-standing active CD that failed to respond to aggressive medical therapy with immunosuppressive drugs. As the patient had already lost significant lengths of SB from previous resections, stricture EBD with DBE was attempted with caution. The procedure was technically difficult due to adhesion related angulation and tethering of the affected segment of SB which contained several closely related, significantly ulcerated strictures. This case highlights the fact that although EBD of strictures is considered a relatively safe procedure, the risk of perforation in certain cases may be as high as 11% [186;187]. SB strictures that are long (>5cm), severely inflamed and ulcerated should therefore be considered high-risk and a potential contraindication to DBE assisted EBD [42]. However our series also shows that a history of previous surgery is not a contraindication to DBE: 10 of our patients had undergone previous surgery (often multiple) but the procedure was straightforward in most of them (both via the oral and rectal routes).

It is worth noting that 10 of the 11 patients in our series had undergone SB resections and/or stricturoplasties in the past. It is therefore possible that a significant number of the dilated strictures were post-surgical rather than primary in nature. Fifteen of the 18 strictures were considered predominantly fibrotic and the remainder inflammatory in appearance which may support this view. However in the series by Pohl et al. [42] all SB strictures in CD patients undergoing dilation were reported as fibrotic while 50% of patients had never undergone surgery. Therefore we would argue the exact aetiology of a fibrotic stricture i.e. whether it is of primary or post-surgical origin, is not particularly relevant if it is causing symptoms and can be successfully dilated by DBE. We recognise

that our study has its own limitations. One of these limitations relates to the small number of patients studied, while other limitations relate to the fact that 'a snapshot' of subjective measures was used (VAS scores) and that the follow-up questionnaire was completed at a long and variable time after EBD (mean follow-up 20.5 months (range 2-41 months) and this may have therefore been confounded by other variables which were not taken into account.

In summary, despite these recognised limitations, this series has shown that the technique of DBE facilitated SB stricture EBD for selected patients with CD is of significant benefit and may be considered an alternative to surgical resection or stricturoplasty. Since the publication of our series [188], a further study from Japan [189] has confirmed our findings. In their study, Hirai et al. showed that DBE facilitated EBD was successful in 18 of 25 cases; 2 patients suffered complications (bleeding and pancreatitis) and the cumulative surgery-free rates for all subjects were 83% and 72% at 6 and 12 months respectively [189]. In view of the growing evidence in support of the usefulness of EBD for CD SB strictures we propose an algorithm for the clinical management of patients afflicted by this condition (**Figure 39**). In the future, research into the use candidate molecules that may arrest or reverse fibrogenesis hold promise to expand the medical armamentarium available for this condition. Early work on removable self-expanding metal, plastic and biodegradable stent placement may also provide the foundations for additional alternative endoscopic options in the years to come; until then, EBD is likely to have an on-going role to play in the management of these patients.

Figure 39: *Proposed algorithm for the management of stricturing SB CD; *multiple strictures may predispose to surgical management (stricturoplasty/resection); **MDT, multi-disciplinary team meeting, comprising gastroenterologists, surgeons, radiologists and specialist nurses*



6 Effectiveness and safety of DBE facilitated polypectomy of clinically significant SB polyps in patients with PJS

6.1 Background

Peutz-Jeghers syndrome (PJS) is a high penetrance, autosomal dominant polyposis syndrome that is associated with a germline mutation in the STK11 (*serine/threonine kinase 11*) gene (19p13.3) in 80% - 94% of cases [190]. PJS has an incidence of about 1 in 50,000 to 1 in 200,000 live births [191;192] and is characterized by mucocutaneous melanin pigmentation (**Figure 40**), gastrointestinal (GI) hamartomatous polyps [193] and an increased risk of GI and extra-GI neoplasia [190;194-197]. SB polyposis forms a major part of the disease burden that often manifests itself early-on in life [191;198-200], leading to obstruction secondary to intussusception or bleeding and iron deficiency anaemia (IDA) [192;196;201]. The cumulative risk of SB intussusception may be as high as 50% at age 20 years [196]. Until recently, laparotomy with intraoperative enteroscopy (IOE) was the sole option available for removal of PJS polyps deep within the SB [202;203]. This intervention however, exposes patients to the hazards inherent to major surgery and may lead to post-operative complications such as intra-abdominal adhesions and short-bowel syndrome [177;204-206]. Double-balloon enteroscopy (DBE) permits endoscopic removal of SB polyps in adults and children [20;44;45;207;208] and potentially offers a lower morbidity alternative to surgery for patients with PJS [207-212]. This combined prospective series, which includes both an adult and a paediatric

cohort for the first time, examines the feasibility, efficacy and safety of DBE facilitated SB polypectomy.

Figure 40: *Macular melanin pigmentation of the lips and peri-oral region in one of our patients with PJS undergoing SB polypectomy by DBE*



6.2 Aims

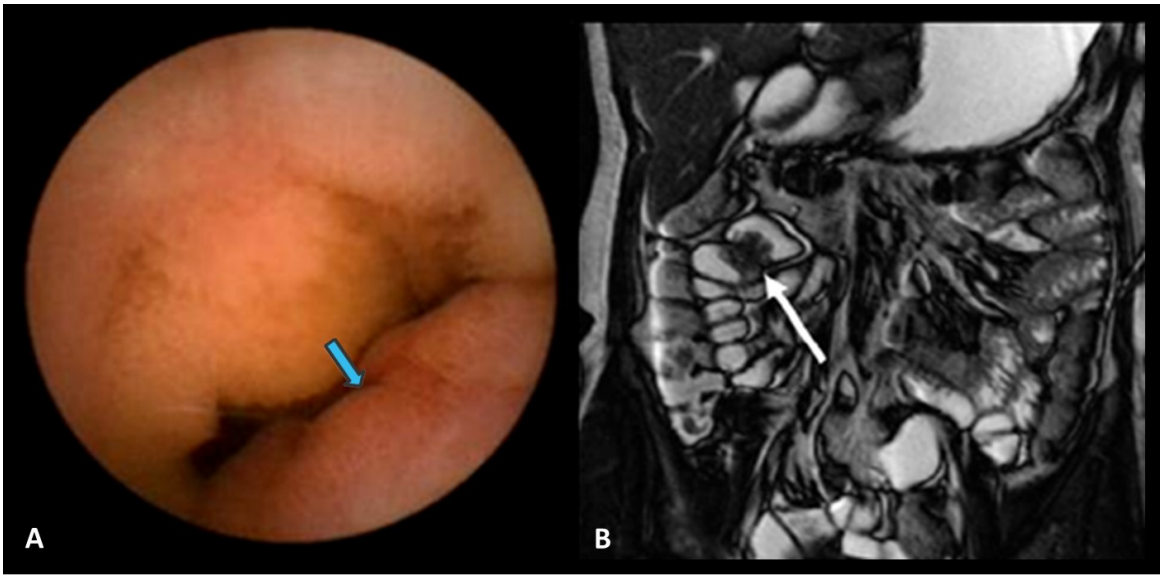
To assess the effectiveness and safety of DBE facilitated polypectomy of clinically significant SB polyps in patients with PJS.

6.3 Methods

6.3.1 Patients

Patients were referred from the St Mark's Hospital Polyposis Registry, London and a paediatric tertiary referral centre, the Centre for Paediatric Gastroenterology, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, which together manage the largest cohort of PJS patients in the UK. Since the introduction of the DBE service to our institutions, data for all patients with PJS [213] referred for SB polypectomy have been prospectively collected. As part of our PJS surveillance program, patients undergo a SB capsule endoscopy (SBCE) and/or radiological imaging (magnetic resonance enterography (MRE), computed tomographic enterography (CTE) or rarely SB barium follow-through (BFT)) triennially [191;194;195] for early detection of polyps deemed to be large enough to warrant prophylactic removal (**Figure 41**). As is the practice at our institutions [214] patients found to have SB polyps with an estimated diameter ≥1.5cm at surveillance were referred for DBE in the first instance.

Figure 41: *Large (>1.5cm) PJS SB polyp as seen at SBCE (blue arrow), (**A**) and at MRE (white arrow), (**B**)*



Adult (>18 years of age) and paediatric patient characteristics (including past history of abdominal surgery) are shown (**Table 13**). Since endoscopic polypectomy is a well-established technique with good efficacy, DBE facilitated SB polypectomy was considered clinically appropriate for suitable patients. Procedures were performed after routine written informed consent was obtained. The patients or parents/guardians were informed of the risks of the procedure and endoscopic polypectomy (including the potential need for surgery) and general anaesthesia. All PJS patients were kept under regular follow-up with prospective data collection. Final follow-up (for symptoms and complications) was carried out by another endoscopy research fellow (at St Mark's Hospital) and by a paediatric gastroenterology registrar (at the Sheffield centre) by review of the medical notes and if necessary by telephone consultation. The data was then analysed retrospectively. On consultation with the regional and institutional review boards, it was deemed that no further dedicated ethics approval was required, since

endoscopic polypectomy is considered to be standard of care and that symptomatic follow-up of these patients post-polypectomy is part of the routine clinical paradigm.

Table 13: *Paediatric (in grey) and adult (in white) patient characteristics; *patients with negative or unavailable genetic test results, fulfilled other World Health Organization criteria for PJS [213]; N/A: not available; +ve or –ve: positive or negative genetic testing*

Patient N$^{o.}$	Gender	Age at diagnosis (years)	Initial presentation	Genetic testing	Upper GI polyps	Colonic polyps	N$^{o.}$ of pre-DBE SB surgeries	N$^{o.}$ of SB resections	Age at 1st DBE	Other PJS related comorbidities
1	M	5	Genetic testing	+ve	Yes	Yes	0	0	15	No
2	M	5	Intussusception	+ve	Yes	Yes	1	1	7	No
3	F	16	Genetic testing	+ve	No	No	0	0	16	No
4	M	9	Genetic testing	+ve	No	Yes	0	0	13	No
5	M	11	Genetic testing	+ve	Yes	No	0	0	12	No
6	M	16	Genetic testing	+ve	Yes	No	0	0	16	No
7	M	10mths	Intussusception	+ve	Yes	No	0	0	11	No
8	M	6	Genetic testing	+ve	Yes	Yes	0	0	16	No
9	F	15	Intussusception	N/A*	Yes	No	1	1	18	No
10	F	7	Intussusception	N/A*	Yes	No	1	1	14	No
11	F	13	Genetic testing	+ve	Yes	Yes	0	0	16	No
12	F	10	Genetic testing	+ve	Yes	No	0	0	12	No
16	M	41	Abdominal pain	+ve	Yes	Yes	2	2	54	No
17	F	11	Genetic testing	+ve	Yes	Yes	0	0	19	No
18	M	14	Intussusception	+ve	Yes	Yes	2	2	34	No
19	F	28	Abdominal pain	+ve	Yes	Yes	0	0	43	No
20	F	5	Genetic testing	+ve	Yes	Yes	1	1	39	Sex cord ovary tumour
21	M	27	Abdominal pain	+ve	Yes	Yes	1	1	43	No
22	M	10	IDA	+ve	Yes	Yes	1	1	42	No
23	F	37	Abdominal pain	+ve	Yes	Yes	3	1	63	No
24	M	14	Intussusception	+ve	Yes	Yes	3	2	19	No
25	M	18	Intussusception	+ve	Yes	Yes	1	1	26	No
26	F	15	Intussusception	+ve	Yes	Yes	2	1	26	No
27	F	5	Intussusception	+ve	Yes	Yes	5	5	33	No
28	M	14	IDA+ Intussusception	+ve	Yes	Yes	1	1	30	No
29	F	4	Intussusception	+ve	Yes	Yes	6	6	40	No
30	F	23	Intussusception	+ve	Yes	Yes	1	1	31	No
31	F	8	Intussusception	N/A*	Yes	Yes	3	3	52	Thyroid cancer Breast cancer
32	M	22	IDA	N/A*	Yes	Yes	1	1	36	No
33	F	25	Abdominal pain	+ve	Yes	Yes	2	2	38	No
34	F	18	Intussusception	-ve *	No	No	3	1	31	No
35	F	37	Intussusception	+ve	Yes	Yes	2	1	37	No
36	M	2	Intussusception	+ve	Yes	Yes	5	4	45	No

6.3.2 DBE procedures

All DBE procedures were performed using the 2.8mm working channel Fujifilm EN-450T5 therapeutic double-balloon enteroscope (Fujifilm, Saitama, Japan), under general anaesthesia (GA). The route of approach for DBE (i.e. per-oral vs. per-rectal route), was determined by SBCE [150] and/or radiological findings [214]. All patients fasted for eight hours before the procedure and if the DBE was being performed through the rectal

route, adults received prior bowel preparation with three sachets of magnesium citrate (Citromag; Bioglan Laboratories, Hertfordshire, UK) and generic senna granules (13g by weight) while children received sodium picosulfate (Picolax; Ferring Pharmaceuticals, West Drayton, UK) 2.5-10g (depending on age) and Senokot (Reckitt Benckiser, Kingston-upon-Thames, UK) 1-2mg/kg (max 30g). The depth of SB insertion by DBE was estimated as described by May et al [51].

Prior to endoscopic snare resection, in order to minimize the risk of immediate bleeding or SB perforation, the stalks of pedunculated polyps were injected with a dilute solution of adrenaline (1 in 200,000) and methylene blue (0.025%) in normal saline; semi-pedunculated and sessile polyps were lifted using submucosal injection of the same solution (**Figure 42A,B**). Simple snare or endoscopic mucosal resection was performed using the VIO® 200D or ICC® 200 EA diathermy units (ERBE Elektromedizin GmbH, Tübingen, Germany) on Swift Coag™ mode (maximum power: 40W, effect 2) or Endo Cut™ mode (maximum power: 120W, effect 2) for adults and children, respectively. If required, endoscopic haemostatic clips (either Resolution® (Boston Scientific, Natick, MA, USA) or Quick Clip® (Olympus Medical, Tokyo, Japan)) were applied to the resection site to reduce the risk of post-polypectomy bleeding. In several cases, polyps required debulking by piecemeal resection to improve access and whenever possible, the resected polyps or their fragments were retrieved for histopathological analysis (**Figure 42C**). All DBE procedures were carried out with expert surgical support available if needed.

Figure 42: *Large semi-pedunculated PJS SB polyp as seen at DBE, (**A**); injection of the polyp stalk and base with a dilute solution of adrenaline (1 in 200,000) and methylene blue (0.025%) in normal saline prior to snare resection, (**B**); retrieval of the resected polyp*



*using a Roth™ net (US Endoscopy, USA), (**C**)*

6.4 Results

Between February 2005 to April 2011, 36 patients with PJS (17 males, median age 30.5 years; range: 7-63 years) were referred for SB polypectomy by DBE (Figure 1). All patients had at least 1 pre-DBE evaluation by SBCE (86%) or diagnostic imaging (75%) or both (58%). In the adult cohort, 92% of patients had a history of SB surgery (an average of 2 laparotomies per patient) with 87% having undergone a partial SB resection. In contrast only 25% of paediatric patients had a history of SB surgery (an average of 0.3 laparotomies per patient). A total of 53 DBE procedures were performed with the number of procedures required per patient ranging from 1 (n=22) to 4 (n=1). Twelve patients required 2 procedures each while another 1 patient required 3 DBEs. Forty DBE procedures were performed via the oral route and the remainder via the rectal approach. Estimated mean depth of insertion was 186±65cm post-pylorus and 93±61cm proximal to the ileo-caecal valve for oral and rectal procedures, respectively. Pan-enteroscopy, confirmed by visualization of a submucosal tattoo of sterile India ink (Spot®, GI Supply, Camp Hill, PA, USA) when placed at previous DBE via the opposite route, was achieved in 2 adult patients. In 2 paediatric patients who underwent DBE via the oral route, pan-enteroscopy was confirmed by visualization of the ileo-caecal valve. Mean duration for DBEs done via the oral and rectal routes was 91±19 minutes and 83±35 minutes respectively. Details of DBE procedure are shown (**Table 14**).

Table 14: *Paediatric (in grey) and adult (in white) patient DBE details; N/A not applicable*

Patient N$^{o.}$	Route	Depth of insertion (cm)	Significant polyps	Polyps removed	Maximum size (mm)	Limitations	Major Complications
1	PO PR	220 70	1 1	1 1	20 20	No	None
2	PO	120	7	4	20	No	None
3	PO PR	200 100	0	0	N/A	No	None
4	PO	220	1	1	20	No	None
	PR	35	0	0	N/A	No	None
5	PO PR	250 45	5	1	20	No	None
6	PO	200	7	7	30	lap-DBE	Pelvic abscess
7	PO	250	6	6	50	No	None
8	PO	120	1	1	20	Emergency setting	Perforation
9	PO	Complete enteroscopy	3	3	15	No	None
10	PO	Complete enteroscopy	2	2	40	No	None
11	PO	320	1	1	10	No	None
	PR	140	0	0	N/A	No	None
12	PO	230	1	1	50	lap-DBE	None
13	PO	190	2	2	35	No	None
14	PR	200	2	2	25	No	None
	PO	160	2	2	25	No	None
15	PO	250	3	3	35	Adhesions	None
16	PO	150	1	1	30	Adhesions	None
17	PO	140	1	5	40	None	None
18	PO	310	3	4	25	Adhesions	None
	PR	60	2		20	Adhesions	None
19	PO	170	1	1	25	No	None
20	PO	220	0	0	N/A	Adhesions	None
21	PO PR	250 50	2 4	3 4	30 20	Adhesions Adhesions	None None
22	PO	200	3	2	30	Sessile duodenal polyp	None
	PR	100	1	2	20	No	None
	PO	100	1	1	30	lap-DBE	None
	PO	100	0	0	N/A	No	None
23	PR PO	80 220	1 14	1 12	20 30	Retroverted ICV Severe adhesions	None None
24	PO	200	1	1	40	Severe adhesions	None
25	PO	240	5	5	30	Adhesions	None
26	PO	120	1	6	20	Adhesions	None
	PR	60	0	0	0	Adhesions	None
27	PR	75	0	0	0	Adhesions	None
28	PO	260	1	0	20	Adhesions + sessile polyp-endoscopically unresectable	None
	PO	160	0	0	N/A	Adhesions	None

Table 14 (continued): *Paediatric (in grey) and adult (in white) patient DBE details; N/A not applicable*

Patient No.	Route	Depth of insertion (cm)	Significant polyps	Polyps removed	Maximum size	Limitations	Major Complications
29	PR	240	1	1	40	Adhesions	None
	PO	260	1	2	30	Adhesions	None
30	PO	140	0	0	N/A	Adhesions-altered bowel anatomy	None
31	PO	160	10	13	25	Adhesions	None
32	PO	160	2	4	40	Large sessile polyp in distal duodenum	None
	PO	45	1	0	70		None
	PO	45	1	0	70	lap-DBE: difficulty in laparoscopic visualization	None
33	PO	150	8	6	30	Adhesions	None
34	PO	150	2	2	30	Adhesions	None
35	PO	160	7	11	30	No	None
36	PO	100	0	0	0	Adhesions	None
	PR	50	0	0	0	Adhesions	None

6.4.1 Successful clearance of large polyps by DBE or laparoscopic-assisted DBE

The aim at DBE was to attempt polypectomy of all significant polyps found (as detected by SBCE and/or SB radiology) in all 36 patients. Two patients (patients 3 and 20) did not undergo polypectomy at DBE as their polyps were considered non-significant due to likely overestimation of size at SBCE. Therefore 34 patients were considered suitable for DBE facilitated polypectomy. Of these, 25/34 patients (74%) underwent successful polypectomy by DBE alone (n=22) or else by lap-DBE facilitated polypectomy (n=3; patients 6, 12 and 22) for large, sessile duodenal polyps that were deemed high-risk for polypectomy by DBE alone. On average, 4 polypectomies per patient (range: 1-13 polypectomies) were performed. A total of 132 polyps were resected; the majority of these were stalked (85%) while the remainder were semi-pedunculated or sessile. The median diameter of excised polyps was 41mm (range: 10-50mm). Sixty-six per cent of polyps were located within the jejunum while 19% and 15% were located within the

ileum and duodenum respectively. The histopathology of all retrieved polyps confirmed their hamartomatous nature although a sessile duodenal polyp was also found to contain a small adenomatous component (low grade dysplasia); details of SB polyps including their location are described (**Table 15**).

Table 15: *Paediatric (in grey) and adult (in white) patient polyp location and characteristics; N/A not applicable; LGD, low grade dysplasia*

Patient No.	Significant polyps removed	DD	PJ	DJ	PI	DI	Pedunculated	Semi-pedunculated	Retrieved	Hamartomas	Mixed
1	2	0	2	0	0	0	2	0	2	2	0
2	2	0	2	0	0	0	1	1	0	N/A	N/A
3	0	0	0	0	0	0	0	0	0	0	0
4	1	0	1	0	0	0	0	1	1	0	1
5	1	0	0	1	0	0	0	1	1	1	0
6	7	2	1	2	2	0	3	4	7	4	3
7	6	1	2	3	0	2	3	3	6	4	2
8	1	0	1	0	0	0	1	1	1	1	0
9	1	0	0	0	0	1	0	1	1	1	0
10	2	0	0	1	0	1	1	1	2	2	0
11	1	0	1	0	0	0	1	0	1	1	0
12	1	1	0	0	0	0	1	0	1	1	0
13	2	1	1	0	0	0	1	1	2	2	0
14	2	0	0	0	2	0	2	0	2	2	0
15	3	0	3	0	0	0	3	0	3	3	0
16	1	1	0	0	0	0	1	0	1	1	0
17	5	0	5	0	0	0	5	0	1	1	0
18	4	0	0	0	2	2	4	0	4	4	0
19	1	0	0	1	0	0	1	0	1	1	0
20	0	0	0	0	0	0	0	0	0	N/A	N/A
21	7	0	3	0	0	4	7	0	7	7	0
22	5	1	2	2	0	0	4	1	3	2	1(LGD)
23	1	0	0	0	0	1	1	0	1	1	0
24	13	0	0	8	5	0	12	1	1	1	0
25	5	1	2	2	0	0	5	0	0	N/A	N/A
26	6	0	3	3	0	0	6	0	6	6	0
27	0	0	0	0	0	0	0	1	0	N/A	N/A
28	2	0	1	0	0	1	2	0	0	N/A	N/A
29	1	0	0	0	1	0	1	0	1	1	0
30	0	0	0	0	0	0	N/A	N/A	N/A	N/A	N/A
31	13	5	5	2	1	0	13	0	1	1	0
32	5	5	0	0	0	0	4	0	4	4	0
33	6	0	6	0	0	0	5	1	1	0	0
34	2	2	0	0	0	0	0	2	2	0	0
35	7	0	6	1	0	0	7	0	0	0	0
36	0	0	0	0	0	0	N/A	N/A	N/A	N/A	N/A

6.4.2 Need for additional laparotomy with intraoperative enteroscopy

Nine of the 34 patients with significant SB polyps (26%) required subsequent laparotomy with intraoperative enteroscopy (IOE) following incomplete DBE which in most cases was due to inadequate insertion depth. Small bowel tethering (causing tight angulation and unfavourable looping) likely due to adhesional disease was considered the main reason for this. In 7 of these patients, who were all adults (patients 24, 26, 27, 28, 29, 30, 36); none of the target polyps were reachable by DBE alone. Another patient (patient 32) required conversion of a lap-DBE to laparotomy, since adequate laparoscopic views of the duodenal wall involved by a large sessile polyp could not be obtained. Emergency DBE was performed for an episode of intussusception in 1 paediatric patient (patient 8) due to a large semi-pedunculated polyp; however an immediate post-polypectomy perforation occurred, necessitating conversion of the DBE into an IOE through the defect by the endoscopist and observing surgeon. The patient recovered fully and was subsequently discharged. The only other complication identified in the series, occurred in a paediatric patient after successful polyp clearance by lap-DBE (patient 6) who developed a pelvic abscess related to an infected laparoscopy-port wound that responded to well to drainage and conservative management. Although formal 30-day complication data was not actively pursued, long-term complication and outcome data was compiled at final follow-up (through case-note review and telephone consultation if required)).

6.4.3 Follow-up

At a median follow-up period of 24 months (range: 2-50 months); 25 of the 34 patients (74%) who underwent successful DBE or lap-DBE polypectomy without the need for a post-DBE laparotomy and IOE, remained asymptomatic, without need of further intervention. They continue with triennial surveillance (or earlier if symptoms develop)

by SBCE and/or MRE. Follow-up data for adult and paediatric patients are shown (**Table 16**).

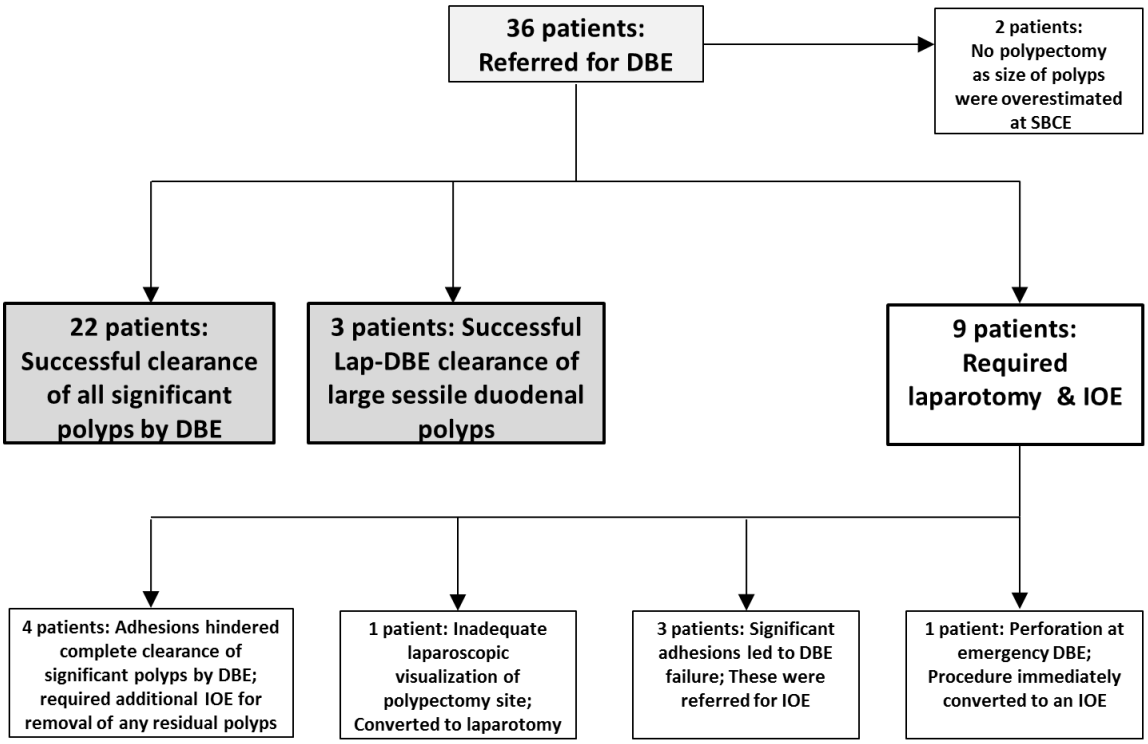
Table 16: *Paediatric (in grey) and adult (in white) patient follow-up details; N/A, not applicable; *Symptoms in this patient are likely to be related to adhesions since polyp size was deemed to be overestimated at SBCE (as confirmed by subsequent MRE and DBE)*

Patient N°	Symptoms pre-DBE	Months of F/U after DBE	Additional surgery/IOE after DBE	Symptoms post-DBE
1	None	12	No	No
2	None	12	No	No
3	None	N/A	No	No
4	None	20	No	No
5	None	26	No	No
6	None	50	No	No
7	Abdo pain	26	No	No
8	Abdo pain	N/A	Yes-DBE converted immediately to IOE due to perforation	N/A
9	Abdo pain	24	No	No
10	None	17	No	No
11	None	2	No	No
12	None	4	No	No
13	None	34	No	No
14	None	35	No	No
15	Abdo pain	30	No	No
16	Abdo pain	29	No	No
17	Abdo pain	23	No	No
18	None	28	No	No
19	None	31	No	No
20	Abdo pain	N/A	No	Yes*
21	None	38	No	No
22	None	21	No	No
23	Abdo pain	25	No	No
24	Abdo pain	N/A	Yes	N/A
25	Abdo pain	25	No	No
26	Abdo pain	N/A	Yes	N/A
27	Abdo pain	N/A	Yes	N/A
28	Abdo pain	N/A	Yes	N/A
29	Abdo pain	N/A	Yes	N/A
30	Abdo pain	N/A	Yes	N/A
31	None	10	No	No
32	Abdo pain	N/A	Yes	N/A
33	Abdo pain	9	No	No
34	None	9	No	No
35	None	7	No	No
36	None	N/A	Yes	N/A

6.5 Discussion

This study showed that DBE facilitated polypectomy can provide an effective alternative to laparotomy and IOE for selected adult and paediatric patients with PJS and significant SB polyposis. DBE (with or without laparoscopic assistance) facilitated significant polyp clearance in 74% of patients (**Figure 43**) who remain symptom and intervention free at a median follow-up of 2 years.

Figure 43: *STROBE [215] Flow-diagram representing the outcome of the original 36 patients with PJS referred for double-balloon enteroscopy (DBE); SBCE (small bowel capsule endoscopy); Lap-DBE (laparoscopic assisted DBE); IOE (intraoperative enteroscopy)*



DBE procedures were incomplete in several cases. SB tethering causing tight angulations and irreducible looping, resulting in inadequate depth of insertion was encountered solely in adults but none of the children. Ninety-two per cent of adults had a history of previous, often multiple laparotomies, compared with just 25% of children. Laparotomy is a recognized cause of SB adhesional disease and therefore tethering. The findings suggest that removal of significant SB polyps for selected patients with PJS by DBE is likely to be more successful earlier-on in life, before multiple surgeries have been performed and should be considered where possible.

A limited endoscopic view caused by the presence of large, sessile polyps particularly within the duodenum reduces the ability to perform polypectomy safely by DBE. These are high risk lesions to and overcome this limitation; we employed the use of laparoscopic assistance [216]. Although more invasive than DBE alone, lap-DBE is less invasive than laparotomy and was successful in 3 of 4 patients undergoing this procedure. The other patient in whom lap-DBE facilitated polypectomy was attempted, required conversion to laparotomy since adequate laparoscopic visualisation of the involved duodenal wall was unobtainable.

Due to the limitations of DBE (26% of patients in our cohort ultimately required surgery) as well as the natural history of PJS, laparotomy with IOE has and will continue to have a major role in the therapeutic management of PJS SB polyposis. In addition the necessity to ensure expert surgical back-up in case of DBE induced complications is highlighted. Patient 8 suffered an acute post-polypectomy perforation during emergency DBE for intussusception which was rapidly converted to an uneventful laparotomy and IOE by the attending surgeon. We recognise that our study has its own limitations. One of these limitations relates to the absence of formal 30-day complication data and that follow-up regarding longer-term complications and recurrence of symptoms was

completed at a long and variable time after polypectomy 24 months (range: 2-50 months). Although we are confident that no longer-term procedure related complications were missed by our follow-up process, we recognise that symptom recurrence may have potentially been under-reported.

In summary, this combined series of adult and paediatric patients with PJS (the largest such series reported to date) demonstrates that DBE facilitated polypectomy can provide an effective therapeutic alternative to laparotomy with IOE for selected patients [207-210;212]. The introduction of a DBE-based approach to therapy earlier-on in life to remove SB polyps will help to avoid the need for future surgery and the risk and complications associated with this. Nevertheless ideal management of patients affected by this condition requires a dedicated, multi-disciplinary approach that is individualized according to the needs of each patient.

7 Feasibility and safety of DBE facilitated direct percutaneous endoscopic jejunostomy (DPEJ) tube placement

7.1 Background

In clinical scenarios where long-term enteral nutritional support is required, access to the GI tract is usually provided by an endoscopically placed percutaneous endoscopic gastrostomy (PEG) feeding tube [217;218]. In patients with previous gastric surgery however, where PEG tube placement is not possible or in circumstances where PEG feeding is associated with recurrent aspiration of gastric contents (such as in patients with chronic gastroparesis or gut dysmotility), jejunal feeding may be preferred [219-221].

Long-term jejunal feeding is frequently provided through a percutaneous endoscopic gastrostomy with a jejunal tube extension (PEG-J). The PEG-J relies on a narrow bore (size 9 Fr, 1.9mm internal diameter) feeding tube extension that passes via a standard PEG tube and through the pylorus to deliver enteral feed into the distal duodenum or proximal jejunum [222-227]. Due to its narrow calibre, the jejunal extension is prone to frequent blockage; there is also a tendency for the extension tube to ‘flip-back’ into the stomach by retrograde migration [217;221;228;229].

Direct percutaneous endoscopic jejunostomy (DPEJ) tube feeding is an alternative to the PEG-J method that allows the endoscopic placement of a wider bore feeding tube directly into the jejunum [217;224;228;230-232]. Unlike a PEG-J, the intrinsic jejunal location of the DPEJ tube eliminates the possibility of retrograde migration into the stomach while the wider calibre makes occlusion less likely [228;229]. A recent study by Panagiotis et al. from the University of Utah [233] has also shown that DPEJ placement appears to significantly decrease recurrent aspiration pneumonia; this has not been shown to be the case with PEG-J.

The original DPEJ technique which was first described by Shike et al. [232] more than 20 years ago, relies on push enteroscopy (PE) to facilitate DPEJ placement and is therefore considerably more technically challenging than PEG-J insertion. The key to successful placement is endoscopic intubation of a suitable superficial loop of jejunum. The chosen jejunal loop should allow adequate trans-illumination and digital indentation as this minimizes the risk of inadvertently "skewering" other loops of bowel that may be interspersed between the chosen jejunal loop and the abdominal wall [232;234]. The inability to intubate a suitable jejunal loop with these desired characteristics accounted for 95% of the failed procedures in one series with a reported overall success rate of DPEJ placement of 68% [231]. Double-balloon enteroscopy (DBE) which has the ability to apply light traction to the small bowel and move along its length using inflatable balloons, allows the operator to identify a superficial loop of jejunum easily [20;54;123]; this capability, along with the relative stiffness provided by the overtube is likely to improve control of jejunal intubation, potentially facilitating DPEJ placement. Although a retrospective case note review presented by Orlando-Lopez et al. at digestive disease week in San Diego, USA, 2008 [235] described that DBE assisted DPEJ placement had been successful in 5 of 6 cases where the PE technique had failed and

Mehdizadeh et al. [152] reported 2 cases of successful DBE assisted DPEJ placement as part of a general DBE experience, at the time of our study, there were no published dedicated reports on prospectively collected cohorts; this prospective series aimed to address this.

7.1 Aims

The aim of this series was to assess the feasibility and safety of DBE facilitated DPEJ placement for enteral nutrition.

7.2 Methods

Since the start of the DBE service at our institution in February 2005, data on DBE assisted DPEJ tube placement was prospectively collected. We report a case series of 10 consecutive patients (done between February 2005 and July 2009) highlighting the feasibility of the technique. The procedure is described in an illustrated step-by-step format and the underlying indications and management of each case are summarised (**Table 17**). Post-procedure, patients were observed for the occurrence of immediate complications and patients remained under the long-term care and follow-up by our nutrition team.

Table 17: *Patient characteristics and indications for DBE facilitated DPEJ insertion; NJ, Naso-jejunal*

Case Number	Gender	Age (years)	Underlying Condition	Management of patients before DBE assisted DPEJ insertion	Indication for DBE assisted DPEJ insertion
1	F	64	Chronic pseudo-obstruction and vagotomy and pyloroplasty	Persistent vomiting and aspiration with PEG feeding → PEG-J	Repeated blockage of PEG-J extension
2	M	32	Neurogenic dysphagia due to Pelizaus-Merzbacher disease	Persistent regurgitation and aspiration with PEG feeding → PEG-J	Repeated retrograde migration of PEG-J extension
3	M	47	Chronic gastroparesis due to diabetic autonomic neuropathy	Gastroparesis with persistent regurgitation and aspiration → PEG-J	Repeated retrograde migration of PEG-J extension
4	M	39	Partial gastric resection and Roux-en-Y due to recurrent peptic ulcer disease	Delayed gastric emptying with persistent regurgitation and aspiration → surgical jejunostomy	Repeated displacement of surgically placed jejunostomies
5	M	64	Neurogenic dysphagia due to intra-cerebral haemorrhage and Bilroth I partial gastrectomy	Persistent regurgitation and aspiration with PEG feeding → PEG-J	Repeated blockage and retrograde migration of PEG-J extension
6	F	40	Idiopathic gastroparesis and chronic dysmotility	Persistent regurgitation and aspiration with PEG feeding→ PEG-J	Repeated blockage of PEG-J extension
7	M	46	Neurogenic dysphagia secondary to cerebral trauma in a road traffic accident	PEG feeding complicated by persistent regurgitation and aspiration	Persistent regurgitation and aspiration with PEG feeding
8	M	26	VATER syndrome requiring gastric transposition; complicated by severe dumping syndrome	Trial of NJ feeding with a view to long term jejunal feeding via DPEJ	NJ feeding was well tolerated, with weight gain, a long term jejunal feeding method was sought
9	F	68	Chronic pseudo-obstruction secondary to visceral neuropathy	Complete gut amotility necessitated TPN and the insertion of a venting PEG	Venting PEG not providing adequate drainage of enteral contents
10	F	18	Neurogenic dysphagia secondary to basilar artery thrombosis syndrome (BATS)	Persistent regurgitation and aspiration with PEG feeding→ trial of NJ feeding	As the patient tolerated NJ feeding well, and gained weight, a long term jejunal feeding method was sought

Since DPEJ tube placement is a well-established technique, the procedures were performed after routine written informed consent was obtained; patients were informed of the risks of the endoscopic procedure itself, the risks of general anaesthesia or conscious sedation and the risks associated with jejunal feeding tube placement. On consultation with the regional and institutional review boards, it was deemed that no further dedicated ethics approval was required, since DPEJ feeding tube insertion is considered to be standard of care and that follow-up of these patients post-procedure is part of the routine clinical paradigm. DPEJ feeding tube insertions were performed using a 9.4mm diameter 200cm EN-450T5 DBE enteroscope (Fujifilm, Saitama, Japan) and a commercially available size 15 Fr Freka® (3.6mm internal diameter, 35cm length) PEG feeding tube (Fresenius Kabi AG, Germany). All patients with impaired gastric emptying had extended fasting for 12 hours and received antibiotic cover in the form of 1.2g of co-amoxiclav intravenously 30 minutes before the procedure, to reduce the risk of infection at the site of skin puncture as per the American Society of Gastrointestinal Endoscopy guidelines [236]. Skin puncture was performed using strict aseptic conditions. All patients were given an anti-peristaltic agent, 20mg of hyoscine-N-butylbromide, intravenously during the procedure and the skin wound was infiltrated with 2mls of the long-acting local anaesthetic bupivocaine (0.25%) to reduce post-procedural pain. All cases were performed under general anaesthesia by 2 experienced endoscopists. Although lateral fluoroscopy guidance was used for the first 4 cases, in our experience this did not convey any more useful information than trans-illumination and digital indentation of the small bowel alone; it was therefore not used for the remaining 6 cases.

7.2.1 Step-wise description of DBE facilitated DPEJ placement technique

Step 1: Localisation of superficial loop of jejunum

The DBE is inserted orally post-pylorus into the distal duodenum. The insertion is continued past the ligament of Treitz (LoT) into the proximal jejunum using the standard technique as described by Yamamoto et al [20]. Our technique for identifying the correct site for jejunal DPEJ insertion is to first fully confirm the position of the LoT – this includes insertion and withdrawal of the enteroscope and overtube across the distal duodenum and proximal jejunum on a number of occasions until the location is clear. Slow insertion of the enteroscope from the LoT into the proximal jejunum is then combined with frequent trans-illumination with digital indentation to identify a superficial loop. The quality of trans-illumination is very similar to that seen during PEG insertion and visibility is improved by dimming the external lighting as much as possible (**Figure 44**). DPEJ placement should be avoided if trans-illumination cannot be achieved. In our series, the mean depth of insertion of the endoscope was calculated as 86±20cm from the pylorus using the method described by May et al [51].

Figure 44: *Trans-illumination and digital indentation (room view)*



Step2: Cleansing of the abdominal wall skin and insertion of 'seeker' needle

The site for insertion of a 19 gauge seeker needle is marked and the overlying abdominal wall skin is cleaned with a chlorohexidine or povidone-iodine solution as per local hospital policy. The seeker needle is then inserted into the jejunum as described by Baron [234] (**Figure 45**).

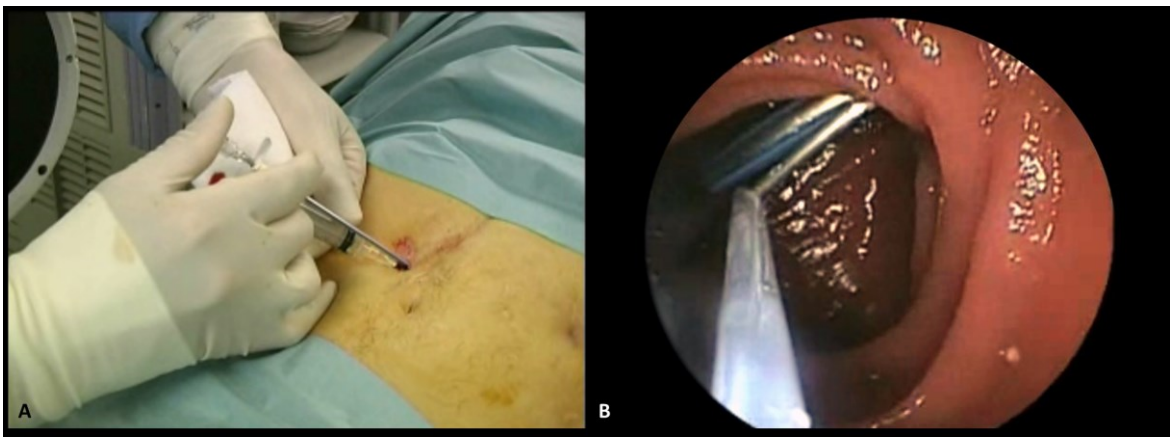
Figure 45: *Seeker needle inserted into jejunum (DBE view)*



Step 3: Snaring of seeker needle, insertion of trocar and retrieval of DPEJ thread

The seeker needle is grasped and held in place endoscopically using a 25mm snare (Olympus, Tokyo, Japan). Snaring of the needle allows anchoring of the jejunum to the abdominal wall, minimising the risk of displacement of the jejunal loop during insertion of the trocar and sheath alongside the seeker needle (**Figure 46**) [234]. Once the trocar and sheath are inserted into the jejunum the snare is transferred over to the trocar sheath to secure it in place during passage of the double thread (120cm length, supplied with the Freka® PEG kit) and the trocar is withdrawn. The thread is then passed into the jejunum, snared and pulled out though the mouth by withdrawal of the enteroscope.

Figure 46: *Insertion of trocar and sheath alongside seeker needle (held in place by snare), room view (**A**); DBE view (**B**)*



Step 4: DPEJ tube pull-through, bumper site check and aftercare

The distal end of the Freka® PEG tube is attached to the thread by the fashioning of a simple loop and thread and feeding tube pulled through the skin puncture site, as per original PEG tube pull-through technique as described by Ponsky and Gauderer [237]. After pull-through, the position of the internal bumper is confirmed by direct enteroscopic visualisation (**Figure 47**); the distance between the internal bumper and skin exit site is noted (range 2-4cm) and the feeding tube external tip connectors applied. The tube is then clearly marked "PEJ tube" to avoid confusion with any PEG tube (if in situ) as the external appearances are identical.

Figure 47: *DPEJ tube bumper in situ within the jejunum (DBE view)*



7.3 Results

DPEJ tube insertion by DBE was successful in 9 of 10 cases. In the first case that was attempted, the procedure was abandoned due to inadequate trans-illumination; this patient went on to have a surgically placed jejunostomy feeding tube. In the other 9 cases, DBE facilitated DPEJ insertion without difficulty. In each of these cases, a suitable superficial loop of jejunum was easily identified and by gentle pull-back of the DBE endoscope and overtube (with both balloons inflated), the jejunal loop could be straightened to ensure a stable endoscopic platform throughout the procedure. The mean time taken to complete the procedure was 35 minutes (range 25-50 minutes) and there were no immediate procedure related complications. Although no formal 30-day complication data were collected, these patients remained under regular follow-up (mean follow-up 14 months, range: 3-24 months) by our specialist nutrition team. During this time, no serious DPEJ related complications were identified and enteral feeding by DPEJ

was well tolerated and uncomplicated, avoiding the need for surgical jejunostomy or parenteral nutrition.

7.4 Discussion

This case series is the first prospective series focused on the feasibility and technique of DBE assisted DPEJ insertion. Although similar in principle to the original method described by Shike et al. [232], we consider the use of DBE rather than push enteroscopy to facilitate jejunal access as an improvement in the technique. Successful DPEJ placement relies on the ability to reach, identify and stabilise a suitable superficial segment of jejunum. This is likely to be easier to achieve by DBE as more controlled endoscopic insertion is possible with prevention of looping and stretching of the small bowel [20;45;54;152]. Although our experience was not associated with major complications, we recognize the limitations of this series in that it is a report of a small cohort, in a single tertiary referral institution and that we have no formal data of 30-day follow-up. It is likely that DBE assisted DPEJ placement may be linked with similar major complications that have been associated with the PE technique from which it is derived. These complications (which have been reported to be as high as 10%), include small bowel perforation, major bleeding, fistula formation and small bowel volvulus [231]. Although our cohort illustrates feasibility of DBE assisted DPEJ placement as an alternative technique, larger comparative studies are required to clearly illustrate any potential advantages or improvement in success rates compared with PE.

8 A direct (back-to-back) comparative study of the performance of DBE and manual spiral enteroscopy (SE) in the same cohort of patients

8.1 Background

Since the introduction of DBE in 2001 [20], two other forms of device assisted enteroscopy have become available: single-balloon enteroscopy (SBE) [55;56] and spiral enteroscopy (SE) [57]. For DBE and SBE an inflatable balloon is incorporated onto an overtube (**Figure 6B**), whereas SE uses a raised soft-plastic spiral in order to provide traction for plication of the SB onto the overtube [1-4] (**Figure 9**). Although DBE is a safe and useful modality and facilitates complete enteroscopy [20;33-39;41;45;50-54;147;148;154;155;178;179;188;210;211;220;235;238-261], procedures may last over 60 minutes [61]. Studies which have compared DBE with SBE have demonstrated similar duration for SBE procedures [155;262;263].

The more recently developed SE, with its use of rotation of a soft-plastic spiral as an alternative to balloon-assisted traction appears to enable faster enteroscopy than the DBE technique [57-59;62;264;265], however it remains uncertain if SE in its current form can achieve equivalent insertion depth. Estimation of SB insertion depth is somewhat subjective but perhaps more reliable for DBE using the method described by May et al. [51], since this is based on step wise advancement during insertion through the SB of a measured length of enteroscope, while insertion depth at SE is estimated during withdrawal according to number of SB folds visualised [57]. Although two prospective studies [60;61] have directly compared SE to DBE, both of these studies have used

different methods to estimate SB insertion depths achieved during SE and DBE. Following a literature review and based on our centre's deep enteroscopy experience [59], we conducted the SPiral Enteroscopy Comparative Study (*SPECS*); a prospective, back-to-back study comparing insertion depths achieved at SE and DBE respectively. In this study, both types of enteroscopy procedures were carried out in tandem (during the same session), in the same cohort of patients, using the same method for SB insertion depth estimation [51].

8.2 Aims

The primary end-point of the study was to compare SB insertion depths by SE and DBE procedures performed in immediate succession, in the same cohort of patients, using the same method of SB insertion depth estimation. The secondary end-points included comparisons of procedure duration and procedure difficulty (based on the VAS score recorded by the endoscopist performing the enteroscopy).

8.3 Methods

8.3.1 Patients

The study was conducted between August 2010 and September 2011. All patients ≥18 years of age referred to our institution for oral deep enteroscopy under GA were considered for recruitment. Exclusion criteria included: unwillingness of patients to undergo deep enteroscopy or to take part in the study, contraindications to deep enteroscopy (bleeding tendency, pregnancy); contraindications to GA and latex allergy

since the balloons used by the DBE system are made of latex). All patients who participated in the study gave their written informed consent.

The research protocol and conduct of the study was approved by the regional research ethics committee and by the institution's research and development review board (North London REC 3 Ref. 10/H0709/48; RD 10/32). The study was carried out in accordance with the World Medical Association Declaration of Helsinki, 1964 (incorporating all later amendments) [129].

8.3.2 Procedures and equipment

Deep enteroscopy procedures were carried out by two experienced enteroscopists. Although both enteroscopists primarily employed the DBE technique in their routine clinical practice (and had therefore acquired more experience with this modality), both of them had also received dedicated training in SE [59]. All procedures were performed via the oral route with patients in the left-lateral position under GA after a 6 to 8 hour fast. Carbon dioxide (CO_2), (CO_2Efficient™ systems, E-Z-EM Inc., NY, USA) was used for SB insufflation.

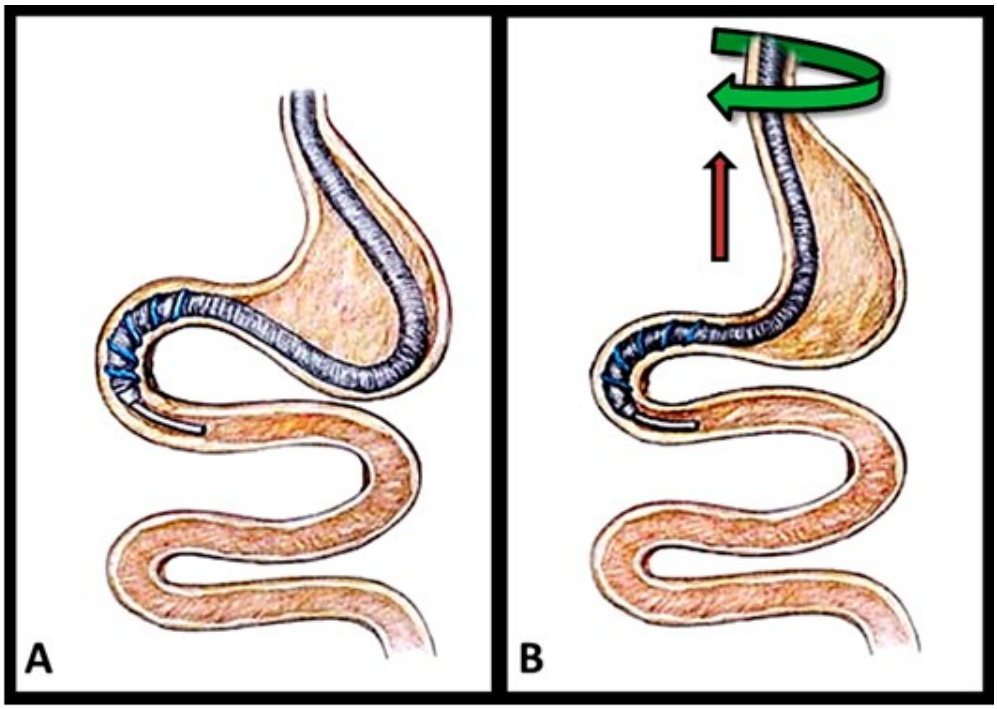
The Endo-Ease Discovery® SB overtube (Spirus Medical, LLC, MA, USA) over the EN-450T5 (9.5mm, 200cm working length and 2.8mm instrument channel) enteroscope (Fujifilm Inc., Saitama, Japan) were used for SE procedures. The Endo-Ease Discovery® SB is 118cm long with an outer diameter of 16mm. The oral-end incorporates a 21cm long, soft-plastic (compressible) spiral, 5.5mm in profile in order to 'engage' the SB and provide gentle-traction. Insertion and withdrawal are achieved by respective clockwise and counter-clockwise rotation of the overtube handle [4] (**Figure 9**).

The EN-450P5 (8.5mm diameter, 200cm working length and a 2.2mm instrument channel) enteroscope, also manufactured by Fujifilm Inc., was used for DBE. During DBE, the two balloons which are attached to the tip of the overtube and enteroscope respectively, are inflated or deflated sequentially using a dedicated pressure-controlled pump and DBE insertion is achieved using the push-and-pull technique as described by Yamamoto et al. [20] (**Figure 7A**).

Each patient first underwent a SE procedure immediately followed by a DBE. Although we recognise that this may have introduced the potential for intrinsic bias, our rationale for this, rather than a randomised procedure order was to enable us to use a single method for estimation of SB insertion depth (as described by May et al. [51;61]), which would in turn provide us with a more reliable comparison of insertion depths for both procedures. Maximal SB insertion depth at SE was considered to have been achieved when further SB intubation was not possible despite rotation of the overtube or use of ancillary techniques such as the 'Cantero manoeuvre' (an ancillary measure designed to reduce enteroscope and overtube looping within the stomach) [57;58;264] (**Figure 48**), the 'over-the-scope manoeuvre' (another alternative technique involving separate advancement of the enteroscope and overtube) [57;58;264] and the use of external abdominal counter-pressure [59]. The deepest point of SB insertion reached at SE was marked by a submucosal tattoo of sterile India ink (Spot®, GI Supply, PA, USA). Maximal SB insertion depth at DBE was considered to have been reached when enteroscope insertion was no longer possible despite manoeuvres for managing deep looping [168]. Estimated SB insertion depth was calculated using the method described by May et al. [51;61]. Procedure duration and other related details were recorded in real-time on a specially designed proforma by 1 of 3 other designated endoscopy research fellows. Start and end of procedures were defined by entry or exit of the enteroscope into/from the patient's mouth respectively with exclusion of time spent applying

endotherapy (all endotherapy was applied only during DBE procedures). As per standard practice for deep enteroscopy in our unit, fluoroscopy was not used for any of the procedures.

Figure 48: *The 'Cantero' manoeuvre. Looping within the stomach (**A**) is reduced by a combination of gentle traction (red arrow) and clockwise rotation (green arrow) of the overtube (**B**) (Images courtesy of Spirus Medical, LLC, MA, USA)*



8.3.3 Collected data

Data collected included: demographics (age and gender), indications for deep enteroscopy, history of abdominal or pelvic surgery, estimated insertion depth, time to reach maximal insertion depth, time to reach the tattoo placed during the preceding procedure; total procedure duration, limitations encountered, estimation of procedure difficulty using a 10cm visual analogue scale (VAS) (where 0=very easy and 10=very difficult). Enteroscopic findings, including evidence of procedure-related mucosal

trauma, which was graded according to the 6 point trauma score described by Buscaglia et al [264] and immediate complications, were also recorded.

8.3.4 Statistical analysis

The study was powered to detect a difference in insertion depth between the two methods. Based on experience, the within-subject standard deviations were considered to be 0.75m. A difference of 0.5m in insertion depth between methods was arbitrarily considered to be of clinical importance. Although it was initially calculated that 24 patients were required to achieve a 5% significance level and 90% power, analysis of the results from the first 15 patients (30 procedures) at 13 months, demonstrated highly statistically significant differences between SE and DBE procedures; it was therefore considered ethically justified to conclude the study at that point.

Data were collated into a computer database (Microsoft Office® 2010, Microsoft Corporation, WA, USA) and analysed using GraphPad® InStat, version 3.0 (GraphPad software Inc., CA, USA) software. Descriptive statistics were used to examine patient demographics. Two-sided non-parametric testing (Mann-Whitney U test) was used to examine for differences in SB insertion depths and procedure duration. VAS scores for procedure difficulty were examined using a two-sided *t* test. Binomial statistics were used to assess for differences in diagnostic yields. Results are presented as means ± standard deviation (SD) and medians (with 95% confidence intervals (CI)) and ranges. Selected box-plots illustrating medians and interquartile ranges are also presented.

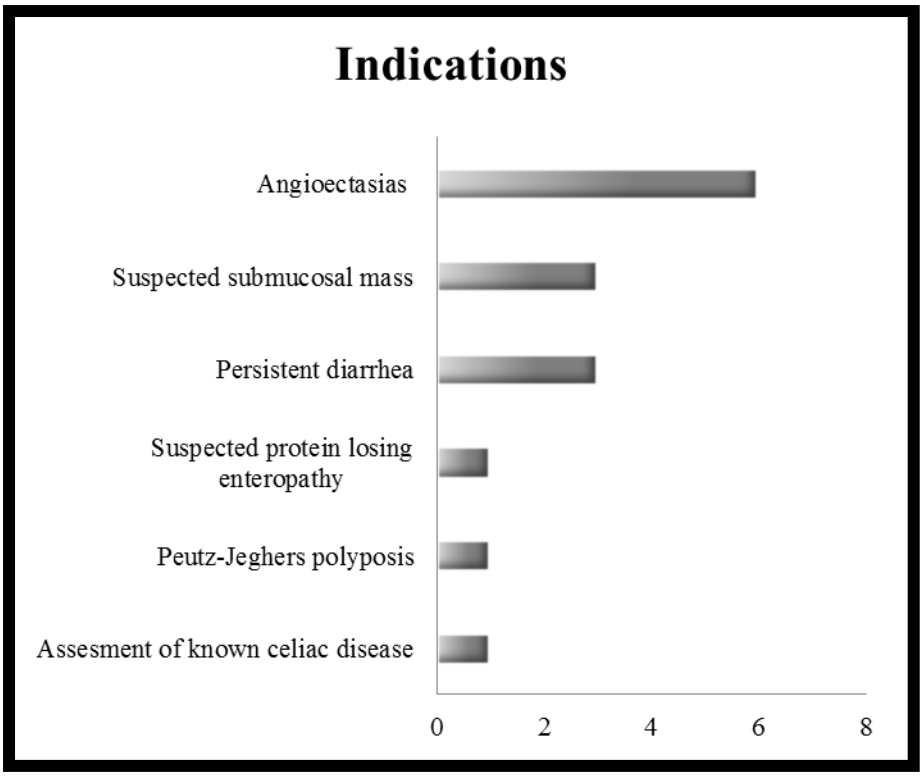
8.4 Results

Fifteen patients (10 women, 5 men; mean age 51.4 ±15.4, range 24-74 years), only 4 of whom had a history of abdominal or pelvic surgery, were recruited (**Table 18**). The indications for deep enteroscopy are described (**Figure 49**).

Table 18: *Patient characteristics*

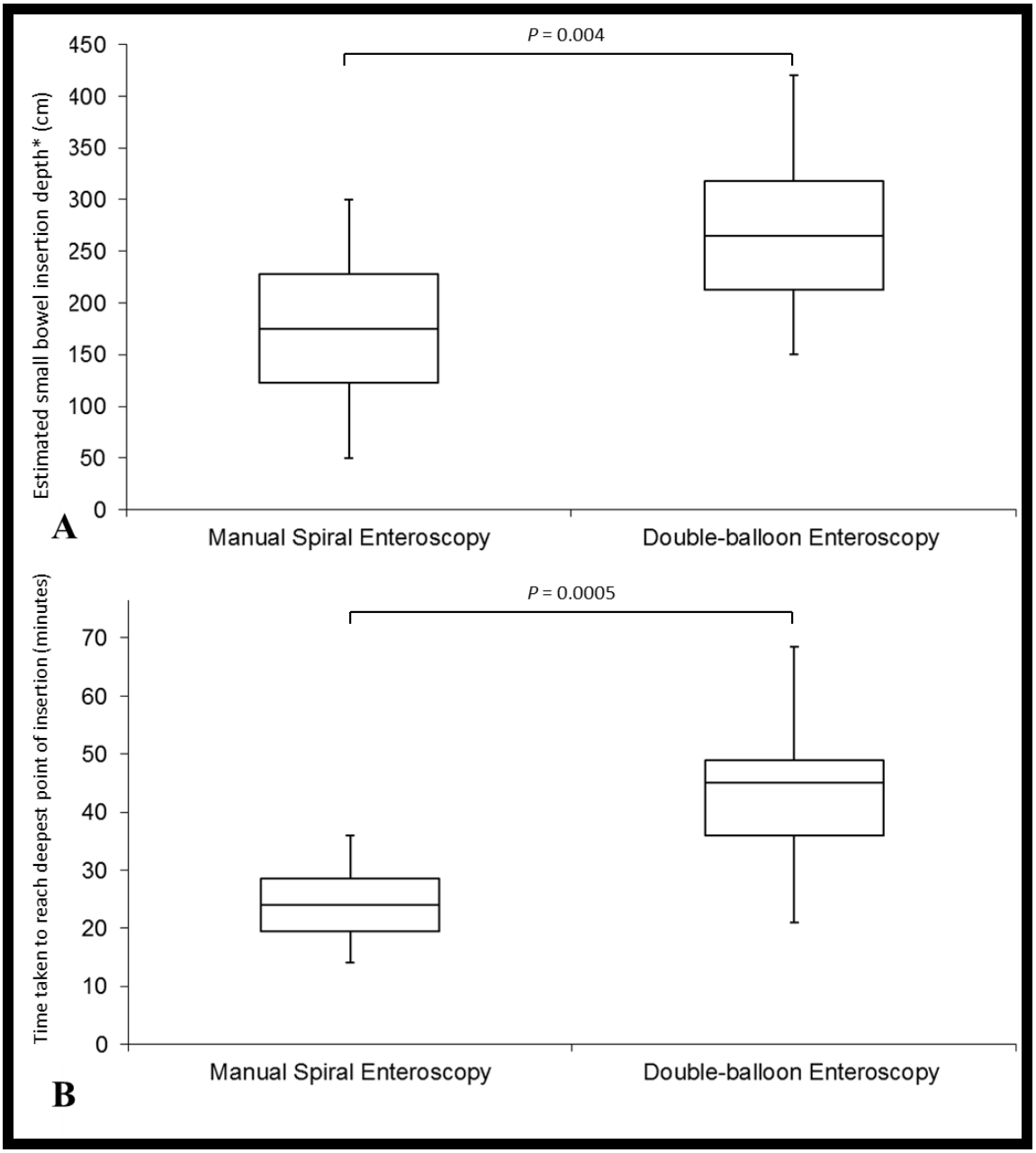
Patient number	Age (years)	Gender	History of abdominal/pelvic surgery
1	61	F	No
2	38	F	Yes
3	72	M	Yes
4	50	F	No
5	54	F	Yes
6	51	F	No
7	39	F	No
8	24	M	No
9	45	F	No
10	49	F	No
11	27	M	No
12	59	M	No
13	74	M	No
14	74	F	No
15	54	F	Yes

Figure 49: *Indications for deep enteroscopy procedures*



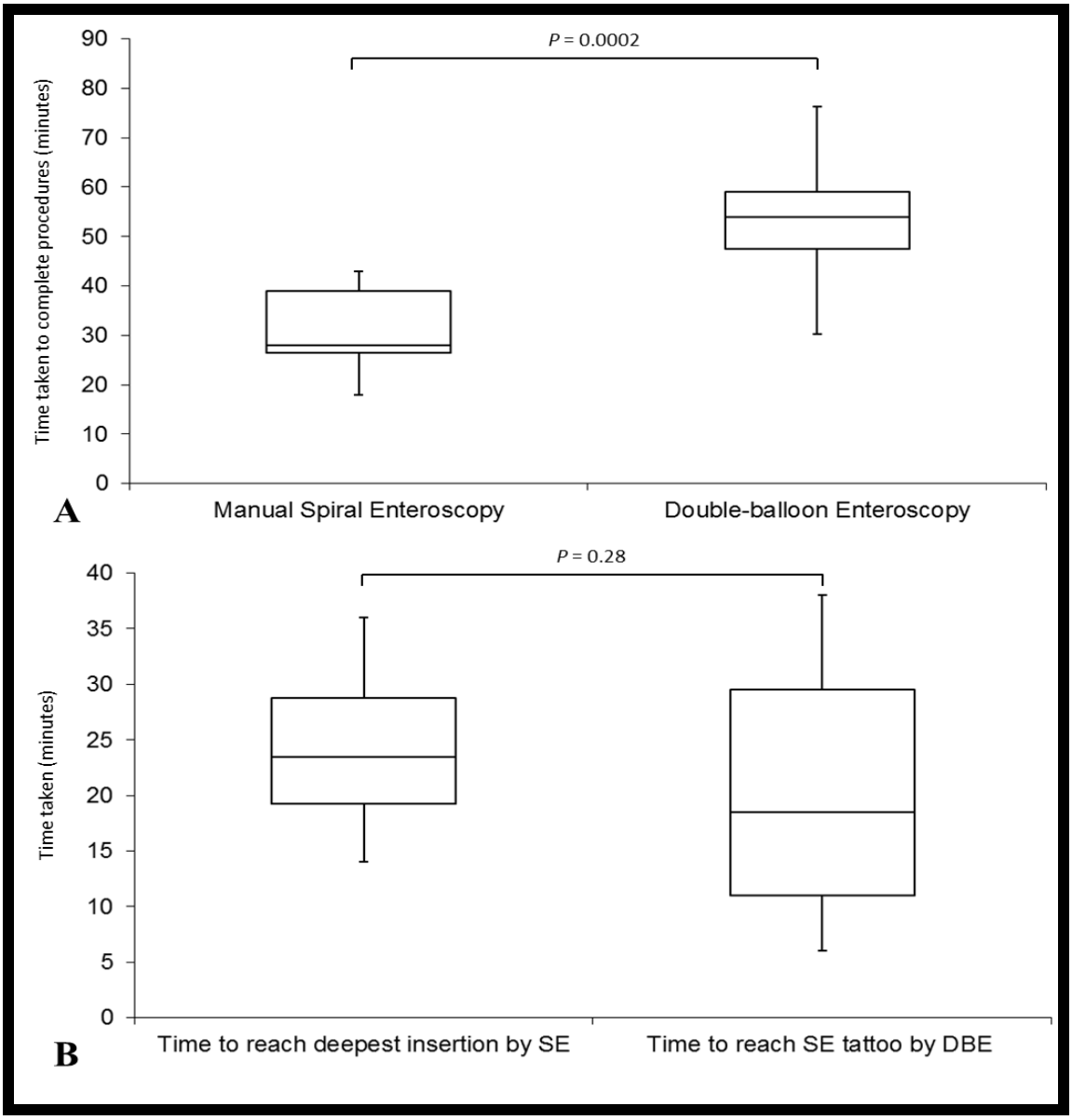
The tattoo placed at SE was visualised and passed by DBE in 14 patients. In patient 11, the sub-mucosal tattoo placed during SE could not be reached by DBE after an estimated final SB insertion depth of 160cm. Analysis after exclusion of patient 11, found significantly deeper SB insertion for DBE as compared with SE; median (95% CI) insertion depths for DBE vs. SE were 265 (227-324) cm vs. 175 (132-212) cm, respectively, representing an increase in median SB insertion depth of 51% for DBE, *P*=0.004 (**Figure 50A**). Conversely, the median time taken to reach the deepest point of insertion was significantly shorter for SE as compared with that for DBE procedures; median (95% CI) times for SE vs. DBE were 24 (20-28) minutes vs. 45 (35-53) minutes respectively, *P*=0.0005 (**Figure 50B**).

Figure 50: *Estimated small bowel insertion depth (**A**) and time taken to reach the deepest point of insertion (**B**) for manual spiral enteroscopy and double-balloon enteroscopy procedures. Two-sided Mann-Whitney U test, values are expressed as medians (horizontal lines) and the 25th and 75th percentiles of the interquartile range (boxes). The whiskers are set at 1.5x the 25th and 75th percentiles respectively. *Insertion depths were estimated at DBE using the method described by May et al. [51].*



The median total-duration of deep enteroscopy procedures (excluding time taken to apply endotherapy at DBE) was also significantly shorter for SE (median (95% CI) duration of SE vs. DBE was 28 (27-36) minutes vs. 54 (45-62) minutes respectively, *P*=0.0002 (**Figure 51A**). In the 14 patients where the comparison was possible, the median time taken by SE to reach maximal depth of insertion was not significantly different to the time taken by DBE to reach the submucosal tattoo placed at SE (median (95% CI) times for SE vs. DBE were 24 (20-28) minutes vs. 19 (14-26) minutes respectively, *P*=0.28) (**Figure 51B**).

Figure 51: *Time taken to complete manual spiral enteroscopy (SE) and double-balloon enteroscopy (DBE) procedures (**A**) and time taken to reach the deepest point of insertion by SE as compared with time taken to reach SE tattoo by DBE (**B**). Two-sided Mann-Whitney U test, values are expressed as medians (horizontal lines) and the 25th and 75th percentiles of the interquartile range (boxes). The whiskers are set at 1.5x the 25th and 75th percentiles respectively.*



There were no significant differences between the mean VAS procedure difficulty scores for the 2 types of enteroscopy (the mean VAS ±SD (95% CI) procedure difficulty score for SE vs. DBE was 5.3 ±2.3 (4.0-6.6) vs. 5.2 ±2.4 (3.9-6.5) respectively, *P*=0.86). Endoscopists reported that the main limiting factors which prevented deeper SB insertion during SE procedures were 'lack of SB engagement' and 'SB tethering' which occurred in 73% and 27% of SE respectively. The main factors which prevented deeper insertion at DBE were 'unfavourable looping' (tight angulations and deep looping which hindered deeper insertion) and 'SB tethering' (a fixed and immobile SB) which occurred in 53% and 20% of DBE procedures respectively. 'SB tethering' which was presumed to arise from underlying post-surgical adhesional disease occurred in all procedures relating to patients who had undergone previous abdominal or pelvic surgery.

Although this was not one of the study end-points, we also made a comparison of diagnostic yields and found that these were similar for both procedures (diagnostic yield SE vs. DBE, 46.7% vs. 53.3% respectively, *P*=0.4). However, in 1 case, deeper SB insertion at DBE (median SB insertion at DBE vs. SE, 270cm vs. 150cm respectively) led to the identification of the suspect SB lesion seen at preceding SBCE (a SB lipoma) which had not been reached by SE.

Mild SE-related mucosal trauma was observed in 9 patients (60%). The observed mucosal trauma was all located in the oesophagus and at the ligament of Treitz and consisted of grade 1 (oedema/erythema) or grade 2 (superficial hematoma/erosion) lesions [264] in 7 and 2 patients respectively. No additional complications [151] were observed with any of the DBE procedures.

8.5 Discussion

Since the introduction of SE in 2008 [57], while several reports have suggested that this technology allows deep enteroscopy procedures to be performed more rapidly [57-59;62;264-266], only two studies (both from Germany) [60;61] have prospectively compared SE and DBE performance.

The first of these 2 studies, performed by Frieling et al. [60] was a non-randomised study performed in a cohort of 35 patients assigned to either SE (n=18) or DBE (n=17) which showed no difference between the 2 modalities for procedure duration or depth of SB insertion. The second study was a cross-over study performed by the Wiesbaden group [61] in a cohort of 10 patients which showed that although procedure duration was significantly shorter for SE, significantly deeper SB insertion was achieved by DBE. The use of different methodologies for the estimation of SB insertion depth achieved during SE and DBE procedures however potentially confounds the results these 2 studies and a conclusive answer to the question of whether SE and DBE enable similar insertion SB depths has been lacking.

In order to try to avoid this confounding factor, we performed a prospective, back-to-back comparative study of SE and DBE performance, using the same method of SB insertion depth estimation. In our study, SB insertion depth was estimated during DBE procedures using the method described by May et al. [51], since its step-wise estimation of advancement of the enteroscope into the SB appears to be less susceptible to bias [61] than the method described for SE procedures [57]. Our preliminary experience has suggested that DBE was more likely to facilitate deeper SB insertion than SE [59], we therefore elected not to randomise the order in which deep enteroscopy procedures were performed and in all cases SE procedures preceded DBE. This rationale was used with

the aim of facilitating the use of the same methodology [51] for SB insertion depth estimation.

8.5.1 Estimated SB insertion depth

Our study demonstrates that DBE facilitates deeper SB intubation than SE overall. In 14/15 patients enrolled, the DBE procedure, not only enabled visualisation of the sub-mucosal tattoo placed at SE but also facilitated significantly deeper enteroscopy, with an overall increase in estimated median SB insertion depth of 51% for DBE as compared with SE. In the 10th patient, unfavourable SB looping hindered the DBE procedure despite the use of alternative ancillary techniques [168] and the tattoo placed at SE could not be reached at an estimated final SB insertion depth of 160cm (during DBE). Since we were unable to estimate the SB insertion depth achieved during SE, no comparison with that attained during DBE could be performed in this particular case.

Our results here, support the findings of the Wiesbaden group [61] whose study of 10 patients showed that in all cases where SE procedures were performed first (n=4), subsequent DBE allowed deeper SB insertion than the submucosal tattoo placed at SE (increase in estimated depth of SB insertion: median 100cm, range 40-80cm). In the other 6/10 patients enrolled in the Wiesbaden study [61], SE either failed to reach the tattoo placed at a previous DBE (n=3) or allowed tattoo visualisation but was unable to facilitate deeper SB insertion (n=3).

8.5.2 Deep enteroscopy procedure duration

The median time taken to reach maximal SB insertion depth (defined as the point when no further enteroscope advancement into the SB could be made despite the use of

ancillary measures [57-59;168;264] was significantly shorter for SE as compared with DBE. Although these findings are also similar to results of the Wiesbaden [61] study where the investigators reported significantly shorter insertion times for SE procedures as compared with DBE, our study design, also allowed for a comparison of the time taken to achieve maximal insertion depth at SE with the time taken for DBE procedures to reach the sub-mucosal tattoo placed at SE. In the 14/15 patients where this comparison was possible, we found that the median times taken were similar for both procedures, suggesting that the two technologies afford a comparable rate ('speed') of advancement into the SB.

The non-randomised study by Frieling et al. [60], did not report details of the time taken to reach maximal SB insertion depth but showed a similar total-duration for SE and DBE procedures. Our findings in relation to total procedure duration in contrast, were similar to those reported by the Wiesbaden group [61] and showed that SE procedures were completed in a shorter time as compared with DBE. When considering our finding that SE and DBE procedures appear to facilitate a similar 'speed' of enteroscope advancement into the SB, the longer duration of DBE procedures is therefore likely to relate to the time taken to achieve deeper SB insertion by this technology.

8.5.3 Factors identified by the endoscopists as having a negative effect on SB insertion depth

No significant differences were detected between the difficulty scores of the 2 enteroscopy techniques. 'Lack of SB engagement' and 'SB tethering', were identified as the main limiting factors to deeper SB insertion at SE. Although efforts to counteract these limiting factors were undertaken using the 'Cantero manoeuvre' [57;58;264], the 'over-the-scope manoeuvre' [57;58;264] and abdominal counter-pressure [59], these

factors eventually prevented further enteroscope insertion at SE. These factors which limited deeper SB insertion at SE have also been reported by others [60;264]. Deeper SB insertion during DBE was limited by 'unfavourable looping' and 'tethering' of the SB, two phenomena which are also well recognised and as shown in our experience and that of others [123;156]. Although these limiting factors are often encountered in the setting of a past history of abdomino-pelvic surgery, our study was not designed to detect significant differences in this regard.

8.5.4 Diagnostic yield

Although our study was also not sufficiently powered to detect differences in diagnostic yields, our findings here are similar to those of the other 2 comparative studies from Germany [60;61] which found no differences in diagnostic yield (although it is likely that these 2 studies were also underpowered and therefore confounded by a type II error in this regard). However, our 1 case (patient 6) where the suspected SB lesion was detected by DBE only on deeper SB insertion than SE, supports the findings of our preliminary experience [59] and the notion that deeper enteroscopy may influence yield [61]. Studies designed specifically to detect differences in diagnostic yields may therefore be worthwhile.

8.5.5 SE related tissue trauma

Although no clinically significant immediate post-procedure complications [151] such as bleeding, perforation or pancreatitis were observed in any of our patients, SE-related mild mucosal trauma of the oesophagus and at the ligament of Treitz was observed in a total of 9 cases. As has also been shown by others [57;264], mucosal trauma is a

recognised potential complication of SE. In most cases, this manifests itself as mild, mucosal oedema/erythema or as superficial haematomata/erosions but deeper injury such as lacerations [264] and perforations (up to 0.34%) [58] have also been reported. Tissue trauma during SE may be chiefly related to the wide plastic helical projection (5.5mm profile) [58;60] and the relatively stiff design of the plastic overtube; however, a recent laparoscopic evaluation of DBE and SE in a small study of live porcine models [267], has suggested that the SE technique itself may also contribute to this trauma. The animal model study by Soria et al. [267] showed that unlike DBE, SE may lead to 'twisting' of vessels at the root of the SB mesentery with resultant transient disturbances of the vascular supply, ecchymosis and small peritoneal tears. These findings suggest that the SE technique itself may induce more iatrogenic injury than originally indicated by Akerman et al. [57] who described that SB pleating during SE occurs without apparent twisting of the SB and its mesentery.

8.5.6 Limitations of the study

This was a small prospective study conducted in a tertiary referral centre for advanced endoscopy where operators had more experience with DBE than with SE. However, the investigators had undertaken multiple dedicated training sessions in SE [59] and as shown by Buscaglia et al. [264] in their report on the SE training initiative, this procedure is considered easy to learn and proficiency can be achieved after the performance of about five supervised-training enteroscopies. Although the order of procedures was not randomised in order to facilitate the use of a single method for the estimation of SB insertion depth [51], we recognise that this may have led to intrinsic bias and therefore constitutes another limitation of the study. It may also be argued that the investigators may have achieved greater SB insertion depths at DBE by pursuing

DBE procedures for a longer period of time. In this study, insertion duration at enteroscopy was however governed by insertion progress and the point of 'failure-to-progress' was achieved sooner with SE (despite the use of dedicated ancillary manoeuvres) than with DBE; our results here are also similar to the findings of May et al. [61]. Although the highly significant differences detected at interim analysis were deemed to provide ethical justification to conclude the study at that point, we also recognise that early closure of the study may represent another limitation by 'swinging' the data towards bias.

8.5.7 Conclusion

Our study showed that DBE achieved significantly deeper SB insertion than SE procedures. Although the maximal insertion depth was achieved sooner with SE procedures, in the majority of cases (14/15), the time taken to reach the same SB insertion depth was not significantly different for the two procedures, suggesting that the actual speed of SE insertion (in its current, manual form) may be similar to that achieved at DBE. It remains uncertain as to whether this may translate into improved diagnostic yields and improved outcomes in routine clinical practice and further larger studies which are adequately powered to address these questions are required.

9 Comparison of double-balloon colonoscopy (DBC) and conventional colonoscopy (CC) performance in pre-defined technically difficult (TD) cases

9.1 Background

Colonoscopy is considered the gold-standard procedure for the diagnosis, management and prevention of colorectal disease [268-270]. However, failure to reach the caecum is reported to occur in up to 10% of attempted cases [63;64;66;117]. This often results in the need for further investigation, additional risks, inconvenience for patients and cost [66]. A technically difficult (TD) colon with characteristics that are typically unfavourable to colonoscopy (e.g. the presence of tight sigmoid angulations or dolichocolon), not only increases the risk of failure [66] but may also result in a prolonged and painful procedure [69;71;73;74;77;85]. TD colonoscopy may result in failure to reach the caecum despite the use of good colonoscopy technique and the use of ancillary equipment such as magnetic endoscopic imaging (MEI), a paediatric colonoscope, an upper GI endoscope, and/or a plastic cap attached to the tip of the chosen endoscopic instrument [66;113]. In recent years, endoscopists have therefore turned their attention to balloon assisted colonoscopy, double-balloon colonoscopy (DBC) in particular, as potential alternatives technology for the intubation of a TD colon [66;92-97;100;122;271].

DBC is a technology which is directly derived from DBE and uses a similar system of two latex balloons and a stabilising overtube for insertion and withdrawal of a dedicated, slim colonoscope. Although several series on the use of DBC for TD colonoscopy have been published, only one randomised study has prospectively compared its performance with conventional colonoscopy (CC) for this indication to date [113]. This study from Japan showed a faster and higher caecal intubation rate for DBC but the definition of a TD case was subjectively defined by time taken to achieve caecal intubation (>30 minutes) during previous colonoscopy [113].

In order to circumvent this potential confounding factor, our prospective, randomised comparative study of DBC with CC for TD cases used a set of pre-determined, evidence-based, minimal criteria for patient recruitment. These minimal criteria were in turn determined by an original, evidence-based scoring system designed at our unit, specifically for this purpose.

9.1.1 Development and validation of an original, evidence-based scoring-system for TD colonoscopy

Several studies have identified a number of patient-related factors which may be associated with TD colonoscopy. These factors include: female gender [63;65;67;68;70-74;76;77;80-85], increasing age (>60 years) [68-72;74;83], a history of abdominal/pelvic surgery [63;65;69;72;73;77;80;83;84] chronic constipation [71;77](often in the setting of a dolichocolon [65;66;75;76;84;86-91]), small body habitus (BMI<22 or W/H ratio <1) [67-70;72;73] and previously failed colonoscopy [65;66;84;92-100]. In an attempt to pre-define TD cases, we proposed an original scoring-system, incorporating these factors which have been shown to be associated with TD colonoscopy (**Table 20**).

In this proposed cumulative scoring-system, the total-score is calculated by simple addition of individual patient-related factors. Since the scoring-system also takes into account the association of female gender with TD colonoscopy [63;65;67;68;70-74;76;77;80-85], the total-score range for a given patient would be: 1-8 in the case of a woman and 0-7 in the case of a man (**Table 19**). While female gender, age >60 years, small body habitus and a history of previous abdominal/pelvic surgery were each given a score of 1, a history of chronic constipation (as defined by the Rome III criteria [272]) and failed colonoscopy (defined as a failed colonoscopy by a consultant gastroenterologist), were arbitrarily each given a score of 2.

Table 19: *A proposed original, evidence-based cumulative scoring-system incorporating factors which have been shown to be associated with TD colonoscopy. The total-score is calculated by simple addition of individual patient-related factors (i.e. the total score range for a given patient would be: 1-8 in the case of a woman and 0-7 in the case of a man). [*]As defined by the 'Rome III criteria' [272]; [†]Failed colonoscopy by a consultant gastroenterologist*

Patient-related factor	Score
Female gender	1
Age ≥ 60 years	1
Small body habitus (BMI <22 or W/H ratio <1)	1
Previous abdominal/pelvic surgery	1
Chronic constipation[*]	2
History of failed colonoscopy[†]	2

9.1.2 Prospective pilot study to assess the correlation of the proposed scoring-system for TD colonoscopy with the time taken for colonic intubation by experienced colonoscopists

9.1.2.1 Aims

In the absence of a universally accepted measure of technical difficulty at colonoscopy, the time taken for colonic intubation (time taken to reach the caecum) is often used as a surrogate marker for this [67;68;70-77;79]; we therefore assessed the correlation of our proposed scoring-system for TD colonoscopy with the time taken to reach the caecum at colonoscopy. This pilot study was conducted with the significant help and collaboration of two of the author's research fellow colleagues, namely Dr Masanao Nakamura and Dr Alberto Murino.

9.1.2.2 Methods

The prospective pilot study was performed in a cohort of 30 patients (all-comers), who were referred to our unit for a colonoscopy. Prior to colonoscopy, patients received bowel preparation in the form of 13g of senna granules and a total of 3 sachets of magnesium citrate (Citromag, Bioglan Laboratories, Hertfordshire, UK), 2 sachets given on the day before and 1 given on the morning of the procedure. Carbon dioxide (CO_2), (CO_2Efficient^{TM} systems, E-Z-EM Inc., NY, USA) was used for colonic insufflation and all procedures were performed by 1 of 5 experienced colonoscopists. Although all 5 colonoscopists had performed >1000 colonoscopies each, it must be stated that colonoscopists 1 and 2 were considerably more experienced and had performed >3000 and >7000 cases, respectively. The colonoscopists' relative experience and their respective contribution to the pilot study are shown (**Table 20**). Colonoscopy procedures

were performed using our unit's standard (12.2mm external diameter) variable-stiffness adult colonoscope (EVIS Lucera™ CF-Q260, Olympus, Tokyo, Japan).

Table 20: Respective experience and relative contribution of colonoscopists involved in the pilot study

Colonoscopist	Respective experience (colonoscopies previously performed (n))	Relative contribution to pilot study (colonoscopies performed(n))
1	>3000	16
2	>7000	2
3	>1000	7
4	>1000	3
5	>1000	2

The colonoscopist was allowed to switch to the use of ancillary equipment in the form of a MEI (ScopeGuide® UPD, Olympus, Tokyo, Japan) and/or a paediatric colonoscope (EVIS Lucera™ PCF-Q260, Olympus, Tokyo, Japan) when failing to progress with the standard colonoscope. The use (and respective doses) of sedation (midazolam and pethidine) and smooth muscle relaxant (hyoscine-N-butylbromide, Buscopan®, Boehringer, Ingelheim Gmbh, Germany) was left to the colonoscopists' clinical judgement (not standardised) and no formal comparisons relating to drugs/doses used, were made. Data on patient characteristics relating to our proposed scoring-system (i.e. gender, age, BMI, W/H ratio, history of abdominal/pelvic surgery, chronic constipation, dolichocolon and previously failed colonoscopy) were collected pre-procedure and the patient's TD score was calculated; the colonoscopist performing the procedure was blinded to the patient's TD score. The time taken for colonic intubation (excluding any time taken for endotherapy) use of ancillary equipment, and adequacy of bowel

preparation (adequate or inadequate, as subjectively judged by the endoscopist), were also recorded. Data were collated into a computer database (Microsoft Office® 2010, Microsoft Corporation, WA, USA) and analysed using GraphPad® InStat, version 3.0 (GraphPad software Inc., CA, USA) software. Correlation between time taken for colonic intubation and the magnitude of the proposed TD score was examined non-parametrically using Spearman's rank correlation coefficient (r_s); a P value of <0.05 was regarded to be statistically significant.

9.1.2.3 Results

Thirty patients (18 women, 12 men; mean age 58 ±16, range 21-86 years) were enrolled. One patient had to be excluded from the pilot study since the colonoscopy had to be stopped due to the presence of a colonic stricture; the results of the other 29 patients were analysed as planned. The median TD score was 3 (range 0-6) (**Figure 52**) while the median time taken for colonic intubation to the caecum was 9 minutes (range 3-23 minutes). A switch to ancillary equipment (a paediatric colonoscope) was required in three cases. The TD scores in these three cases were 3, 4 and 6 and the switch to a paediatric colonoscope was made at 4, 8 and 6 minutes respectively. The overall time taken for colonic intubation to the caecum was in turn 8 minutes for the first of these 3 cases and 14 minutes for the other 2. Examination of the overall time taken for colonic intubation (to the caecum) vs. TD score magnitude for the pilot cohort using Spearman's rank correlation coefficient, showed a significant positive correlation between the two variables (r_s=0.6; 95% CI 0.29-0.80, P=0.0006) (**Figure 53**). In order to assess the impact of colonoscopist experience on caecal intubation time, a comparison of the caecal intubation times of the more experienced colonoscopists (i.e. those who had performed >3000 cases (n=2)) and the less experienced colonoscopists (i.e. those who had

performed <3000 cases (n=3)) was also made. This comparison showed no differences in median (95% CI) time taken for caecal intubation between the 2 groups, 9 (8.1-13.5) vs. 8 (5.0-8.2) minutes respectively, P= 0.34. The median (95% CI) doses for midazolam and pethidine were 1.25 (0.5-1.1) and 0 (4.8-14.2) mg, respectively. The median (95% CI) dose of hyoscine-N-butylbromide (Buscopan®, Boehringer, Ingelheim Gmbh, Germany) used was 20 (16.3-19.5) mg. All but 3 patients were considered to have adequate bowel preparation; no further analysis relating to this was possible.

Figure 52: *Range of distribution of the proposed TD score magnitude for patients enrolled in the pilot study. *Since none of the enrolled patients had a TD score of 7 or 8, these two values were omitted from the figure.*

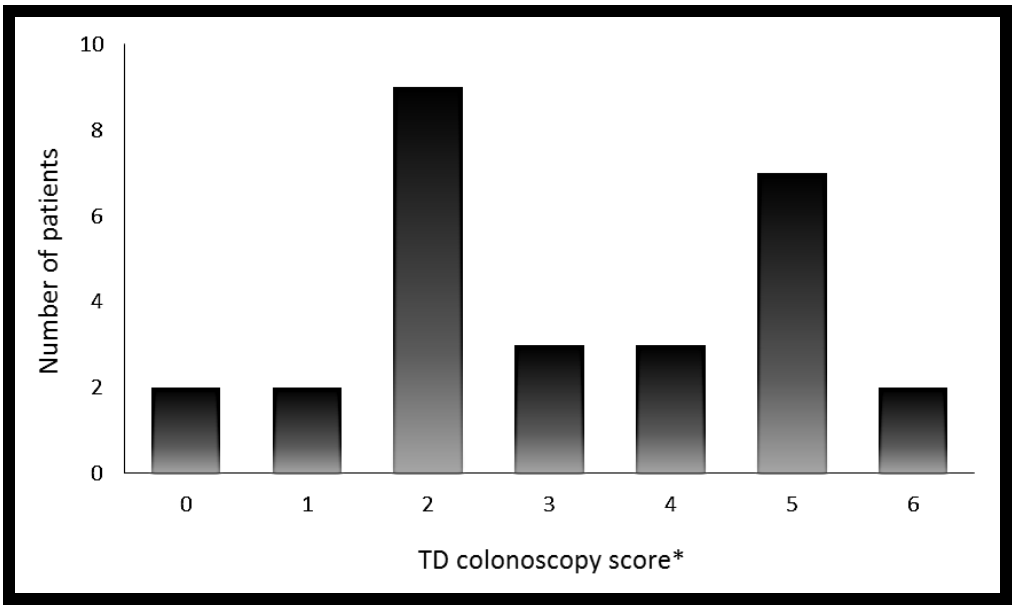
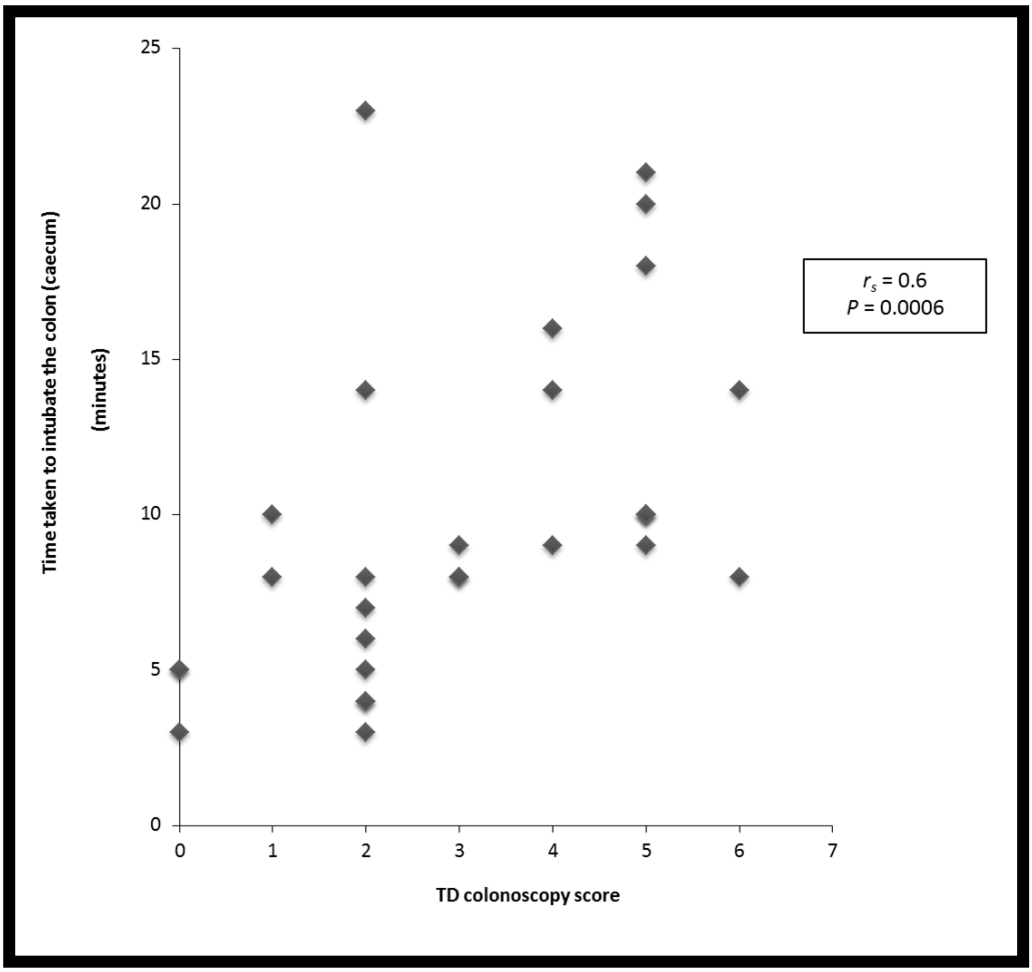


Figure 53: *Scatter plot of the time taken to intubate the colon (caecum) at colonoscopy vs. TD score magnitude; r_s, Spearman's rank correlation coefficient (non-parametric testing was used since the distribution of TD scores was non-Gaussian)*



9.1.2.4 Discussion

This pilot study demonstrated a significant positive correlation between our proposed scoring-system for TD colonoscopy and our surrogate marker of technical difficulty (time taken to reach the caecum).

One potential limiting factor of this pilot study aimed at assessing the construct-validity of our proposed scoring-system for TD colonoscopy, was that the study used an arbitrarily chosen 'marker' for technical difficulty. However, in our experience and that of others [67;68;70-77;79], the time taken for colonic intubation to the caecum is fairly reflective of the technical difficulty of procedures. We also recognise that the validation pilot study was also potentially confounded by non-standardisation of sedation and smooth muscle relaxant administration, the adequacy (or inadequacy) of bowel preparation and the heterogeneous group of colonoscopists with varying experience. It is likely however that relative experience may not have had such a confounding impact, since the comparison of caecal intubation times for colonoscopists with greater (having performed >3000 colonoscopies) experience was similar to that of those who were considered less experienced (having performed <3000 colonoscopies).

Bearing these limitations in mind, in the absence of any other evidence-based, objective predictive scores of TD colonoscopy, we proceeded to use this proposed scoring-system for the purpose of selection of appropriate patients for our prospective randomised study comparing DBC to CC in patients with TD colonoscopy.

9.2 Prospective, randomised study comparing DBC to CC in TD colonoscopy

9.2.1 Aims

The main study pursued a prospective comparison of the performance of DBC with CC for TD cases. The primary objective was to determine whether any of the two types of colonoscopy (i.e. DBC vs. CC) would enable faster colonic intubation (to the caecum) in patients who were deemed to have TD colons. The secondary objectives were to determine whether any of the two types of colonoscopy (i.e. DBC vs. CC) would: i) enable a higher caecal intubation rate and ii) facilitate a more comfortable procedure in patients with TD colons.

9.2.2 Methods

9.2.2.1 Patients

During the period of study, request-forms of patients (both genders, ≥18 years of age) who were referred to St Mark's Hospital for a routine (diagnostic) colonoscopy were 'screened' for parameters predictive of TD colonoscopy using our original scoring-system (**Table 20**), once every 4-6 weeks. TD colonoscopy was considered more likely to occur in patients with a TD score ≥3. Patients who fulfilled this criterion were then contacted by telephone for confirmation of their calculated TD colonoscopy score. Potential participants with confirmed TD scores score ≥3 were then provisionally invited (pending exact BMI and W/H ratio measurements) to take part in the study. The exclusion criteria were unwillingness to undergo colonoscopy or to participate in the

study, lack of capacity, a history of colonic resection and contraindications to colonoscopy or conscious sedation.

All patients fulfilling the study entry criteria gave their written informed consent to participate. The research protocol and conduct of the study was approved by the regional research ethics committee and by the institution's research and development review board (Outer West London REC Ref. 10/H0709/12; RD 10/003) and registered with the International Standard Randomised Controlled Trial Number Register (ISRCTN77510548). The study was carried out in accordance with the World Medical Association Declaration of Helsinki, 1964 (incorporating all later amendments) [129].

9.2.2.2 Study design

This was a prospective, randomized, comparative study (of parallel design). Participating patients were randomized 1:1 using opaque sealed envelopes, to either a DBC or a CC procedure by our endoscopy unit's research administrator.

9.2.2.3 Colonoscopy procedures and equipment

Prior to colonoscopy, patients received bowel preparation in the form of 13g of senna granules and three sachets of magnesium citrate (Citromag, Bioglan Laboratories, Hertfordshire, UK), two sachets on the day before and one on the morning of the procedure. CO_2 (CO_2Efficient^{TM} systems, E-Z-EM Inc., NY, USA) was used as an insufflating agent and all colonoscopies were performed by one of two experienced endoscopists (CF and EJD) each of whom had performed >1000 colonoscopies. Both endoscopists were also proficient in the double-balloon technique (having performed

>200 double-balloon endoscopies each). Caecal intubation was defined as passage of the tip of the colonoscope into the caecal pole; this was photo and video documented.

As per approved study protocol, patients agreed to commence their procedure without sedation and sedation was administered during the procedure, on demand, as necessary, in the form of low dose generic intravenous midazolam and pethidine. Supplemental oxygen was used routinely. An antispasmodic agent in the form of intravenous hyoscine-N-butylbromide (Buscopan®, Boehringer Ingelheim Gmbh; Germany) was also used, unless contra-indicated. Anti-foaming agent (bubble-breaker) in the form of 1% simethicone suspension (Infacol®, Forest Laboratories, Dartford, UK) was sprayed down the colonoscope working channel to improve endoscopic view quality as required.

CC procedures were commenced with the patients in the left lateral decubitus position, while DBC procedures were begun with the patient in a supine position (as per standard unit practice); during colonoscopy, the study protocol allowed the endoscopist to change patient position as necessary. CC procedures were performed using our unit's standard (12.2mm external diameter) variable-stiffness adult colonoscope (EVIS Lucera™ CF-Q260, Olympus; Tokyo, Japan). DBC procedures were performed with the EC-450BI5 (9.4mm external diameter, 152cm working length) double-balloon colonoscope (Fujifilm, Saitama, Japan) equipped with dedicated overtube and 2 latex balloons, using the standard double-balloon technique [20;123] as described in Chapter 1 (**Figure 7B**). Colonoscopists were allowed to switch to the use of ancillary equipment in the form a MEI (ScopeGuide® UPD, Olympus, Tokyo, Japan) and/or a paediatric colonoscope (EVIS Lucera™ PCF-Q260, Olympus, Tokyo, Japan) in the event of failing to progress with the designated colonoscope. Fluoroscopy was not used.

9.2.2.4 Collected data

Data collected included: patient demographics (age and gender), indications for colonoscopy and TD score (including BMI and W/H ratio measurements). The time taken to intubate the colon (from rectal insertion to caecal intubation) and to complete colonoscopy (from rectal insertion of the colonoscope to its withdrawal from the patient's body) was recorded. Any time taken for endotherapy was excluded from the record and details relating to the use of ancillary equipment were also recorded. Doses of any sedative or antispasmodic drugs used during the procedure were documented.

At the end of the colonoscopy, patients were assessed on their tolerance to the procedure by marking a 10cm VAS (0, non-existent; 10, unbearable) to quantify overall discomfort and pain. Similar VAS's for perceived overall patient discomfort and pain were completed by the endoscopist and the attending nurse.

Measurements of patient vital parameters (lowest and highest systolic blood pressure (SBP), lowest and highest pulse rates and lowest oxygen saturations) taken by attending nurses during the endoscopy were recorded. Patient recovery was defined objectively using the modified Aldrete scoring system [273-275] (**Table 20**); recovery duration (from withdrawal of the colonoscope from the patient's body to the time when the patient achieved a modified Aldrete score ≥9 [273-275]) and any immediate complications [151] were also recorded.

Patient satisfaction with the procedure was recorded on a 5-point Likert scale (5=very satisfied, 4=satisfied, 3=neutral, 2=dissatisfied or 1=very dissatisfied) and patients were asked whether or not they would opt to undergo the same type of colonoscopy again should this be required in the future. Technical ease was evaluated by the endoscopist at the end of the procedure using a 10cm VAS (0, very easy; 10, very challenging).

Table 21: The *modified Aldrete Recovery Scoring System [273-275]; patient recovery is confirmed by a total score of ≥9*

Modified Aldrete Recovery Scoring System*	
Respiration	**Score**
Able to breathe deeply and cough freely	2
Dyspnoea, shallow or limited breathing	1
Apnoea	0
Oxygen saturation	
Saturation > 92%	2
Needs supplemental oxygen to maintain saturation >90%	1
Saturation <90% with oxygen	0
Circulation	
Systolic blood pressure within 20mm Hg of pre-operative level	2
Systolic blood pressure within 20-50mm Hg of pre-operative level	1
Systolic blood pressure +/- 50mm Hg of pre-operative level	0
Consciousness	
Fully awake	2
Arousable on calling	1
Unresponsive	0
Activity: able to move voluntarily or on command	
Four extremities	2
Two extremities	1
No extremities	0
*Recovery is confirmed when the patient achieves a total score of ≥9	

9.2.3 Statistical analysis

The power calculation and statistical analyses were performed with the assistance of a nominated consultant medical statistician. The main objective measure of the study was to detect a difference in colonic intubation time between the two types of colonoscopy. Considering an estimated SD of 10 minutes, a total of 44 patients (i.e. 22 patients in each group), was required for the study to have 90% power to detect a difference of 10 minutes between groups. A *P* value of <0.05 was regarded to be statistically significant.

Data were collated into a computer database (Microsoft Office® 2010, Microsoft Corporation, WA, USA) and analysed using GraphPad® InStat, version 3.0 (GraphPad software Inc., CA, USA) software. The unpaired t test (two sided) and Fisher's exact test

were used to examine patient demographics. Two-sided non-parametric testing (Mann-Whitney) was used to examine for differences in TD scores, procedure duration and VAS scores and satisfaction scores between the two groups; Fisher's exact test was used to examine for differences caecal intubation rates and patient's future choice of procedure. Results are presented as means ± SD and medians (with 95% confidence intervals (CI)) or ranges. Selected box-plots illustrating medians and interquartile ranges are also presented.

9.2.4 Results

The study was performed between May 2010 and November 2011; over this 18 month period, of a total number of 2249 patient referrals assessed for eligibility, 2205 were excluded since their TD scores were ≤3. The remaining 44 patients were prospectively recruited and randomised (DBC, n=22; CC, n=22) as shown in the CONSORT [132] study flowchart (**Figure 54**). Patient demographics and indications for colonoscopy are described (**Table 22**); there were no significant demographic differences among the patients in the 2 study groups. There was no difference in the total number or type of colonoscopies performed by each endoscopist: CF (number of colonoscopies), n=25 vs. EJD (number of colonoscopies), n=19, *P*=0.58 and CF (DBC) n=12 vs. EJD (DBC) 10, *P*=1.0.

Figure 54: *DBC vs. CC for technically difficult (TD) colonoscopy study flow diagram (CONSORT [132])*

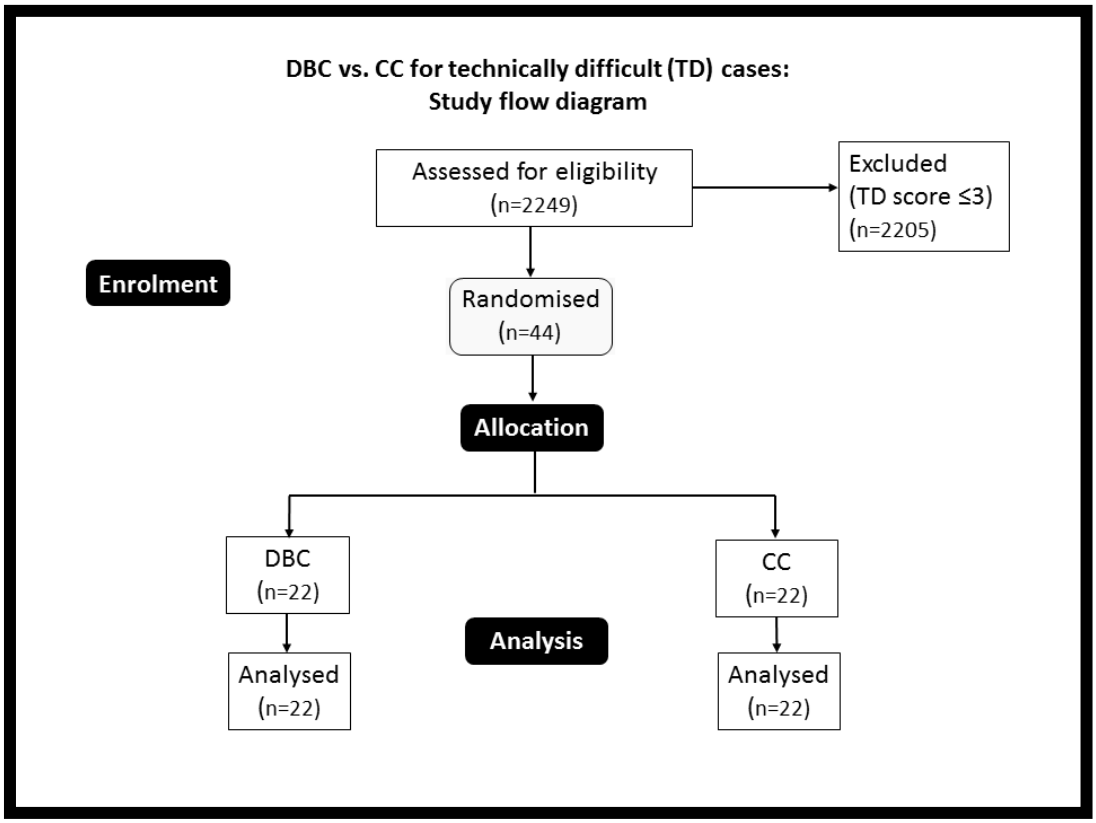
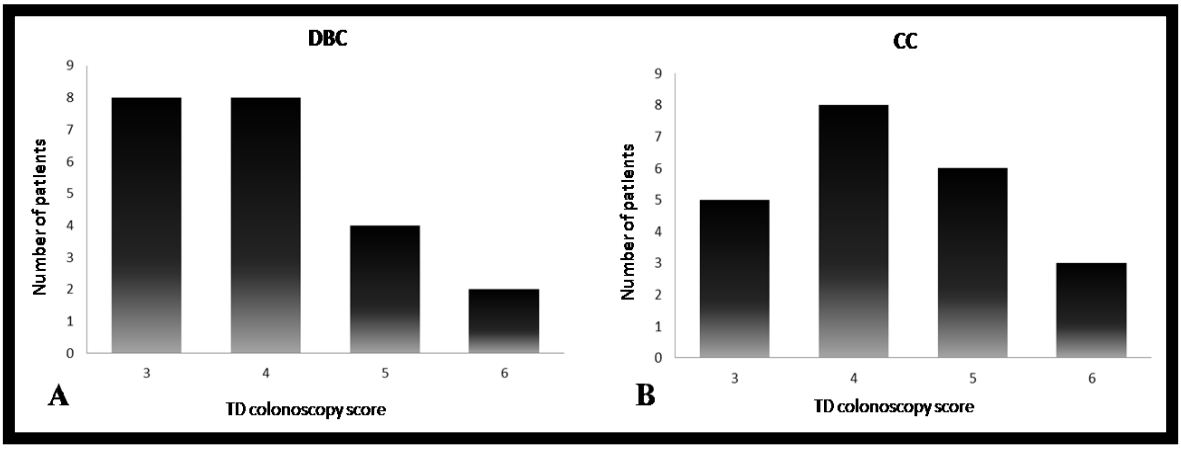


Table 22: *Patient demographics and indications for colonoscopy *unpaired t test; **Fisher's exact test; no significant differences in demographic variables were detected between the 2 study groups*

Patient demographics and indications for colonoscopy			
	DBC	**CC**	
Patients (n)	22	22	
Age (mean ± SD)(years)	68 ± 10	65 ± 12	P=0.29*
Gender (men/women)	7/15	12/10	P=0.22**
Indications (n)			
Polyp follow-up	11	2	
Family history of colorectal cancer	4	4	
Iron deficiency anaemia	2	3	
Rectal bleeding	3	7	
Ulcerative colitis (surveillance)	1	3	
Diarrhoea	1	2	

The median calculated pre-procedure TD scores were the same for both groups; median (95% CI) for DBC vs. CC was 4.0 (3.6-4.4) vs. 4.0 (3.9-4.8) *P*=0.27; the distribution of scores for the two study groups is shown (**Figure 55**). The number of patients with a history of previously failed colonoscopy was also similar in both groups; DBC vs. CC: 13/22 (59.1%) vs. 12/22 (54.5%), respectively, *P*=1.0.

Figure 55: *Range of distribution of TD scores for patients randomised to the DBC group (A) and CC group (B)*

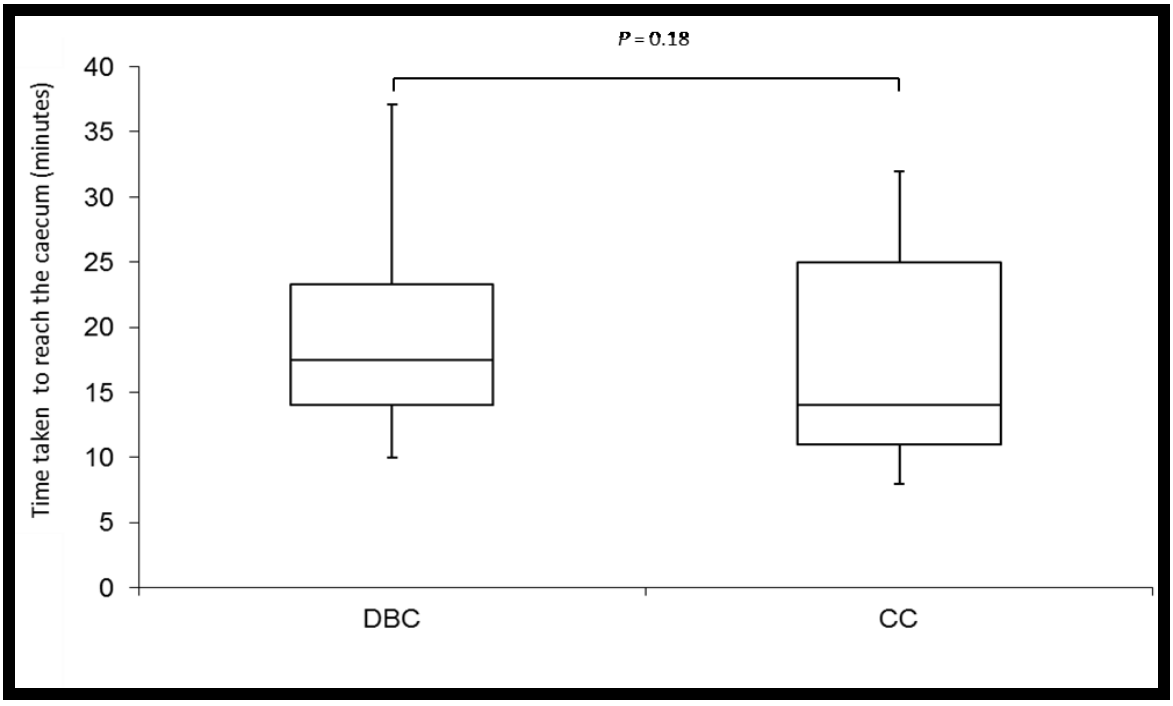


9.2.4.1 Time taken to achieve caecal intubation respective caecal intubation rates

While DBC facilitated total colonoscopy in all 22 cases without requiring the use of ancillary equipment, within the CC group, the use of additional equipment (MEI and/or paediatric colonoscope) was required in 9 cases (41%), after a median time of 12 (range: 7-22) minutes of failing to progress. In 3 of these CC cases, caecal intubation failed to be achieved (after a median time of 38 minutes of failing to progress) despite the use of a MEI and a switch to a paediatric colonoscope.

Analysis of the time taken for caecal intubation to be achieved during the 22 DBC cases as compared with that for the remaining 19 completed CC cases, did not reveal a statistically significant difference between the two procedures: median time (95% CI) taken for caecal intubation at DBC vs. CC: 17.5 (16.0-23.7) vs. 14.0 (13.0-20.1) minutes respectively, P=0.18 (**Figure 56**). The median time (95% CI) taken for colonoscopy completion was longer for DBC, although this difference did not reach statistical significance: DBC vs. CC: 31.3 (28.8-36.6) vs. 23.0 (22.7-32.9) minutes respectively, P=0.08.

Figure 56: *Comparison of time taken to achieve caecal intubation at DBC vs. CC. Two-sided Mann-Whitney U test; values are expressed as medians (horizontal lines) and the 25th and 75th percentiles of the interquartile range (boxes). The whiskers are set at 1.5x the 25th and 75th percentiles respectively.*



Examination of the unassisted caecal intubation rates (where no ancillary equipment was used to facilitate caecal intubation) showed that this was significantly higher for DBC than that achieved during CC: 22/22 (100%) vs. 13/22 (59%), respectively, *P*=0.019. The median (95% CI) TD score for the 9 CC cases where ancillary equipment was required was significantly higher than that for the remaining 13 CC cases where no ancillary equipment was required: 5 (4.5-5.5) vs. 4 (3.3-4.4), respectively, *P*=0.006. In 5 of these cases, the endoscopist identified "tight angulation of the sigmoid colon" as the main limiting factor to successful progress; in the remaining 4 cases "excessive looping" appeared to be the major limiting factor. In the 3 CC cases where caecal intubation failed despite the use of a MEI and a switch to a paediatric colonoscope, 2 of the cases had a

TD score of 6 while the remaining case had a TD score of 5; in all these 3 cases, "tight angulation" was identified as the main limiting factor.

9.2.4.2 Patient comfort, sedation requirements, recovery duration, vital parameters and adverse events

Median (95% CI) patient discomfort and pain scores were significantly lower for DBC as compared with CC, 2.3 (1.9-3.3.2) vs. 5.5 (3.5-6.1), P=0.01 and 2.0 (1.5-3.2) vs. 5.9 (3.6-6.2), P=0.005 respectively (**Figure 57**). These results were mirrored by significant differences in median VAS scores for patient discomfort and pain as perceived by the attending nurse and the endoscopist. The median (95% CI) VAS scores for DBC vs. CC as recorded by the attending nurse for perceived patient discomfort and pain were: 1.6 (1.3-2.5) vs. 4.5 (2.8-5.3), P=0.013 for patient discomfort and 1.5 (1.2-2.5) vs. 5.0 (3.0-5.7), *P*=0.014 for patient pain (**Figure 58**). The median (95% CI) VAS scores for DBC vs. CC as recorded by the endoscopist for perceived patient discomfort and pain were: 1.4 (1.3-2.5) vs. 6.3 (4.6 -6.6), $P < 0.0001$ and 1.4 (1.3-2.8) vs. 6.1 (4.6-6.6), $P < 0.0001$, respectively (**Figure 59**).

Figure 57: *Comparisons of patient VAS scores at DBC vs. CC for patient discomfort (**A**) and pain (**B**). Two-sided Mann-Whitney U test; values are expressed as medians (horizontal lines) and the 25th and 75th percentiles of the interquartile range (boxes). The whiskers are set at 1.5x the 25th and 75th percentiles respectively.*

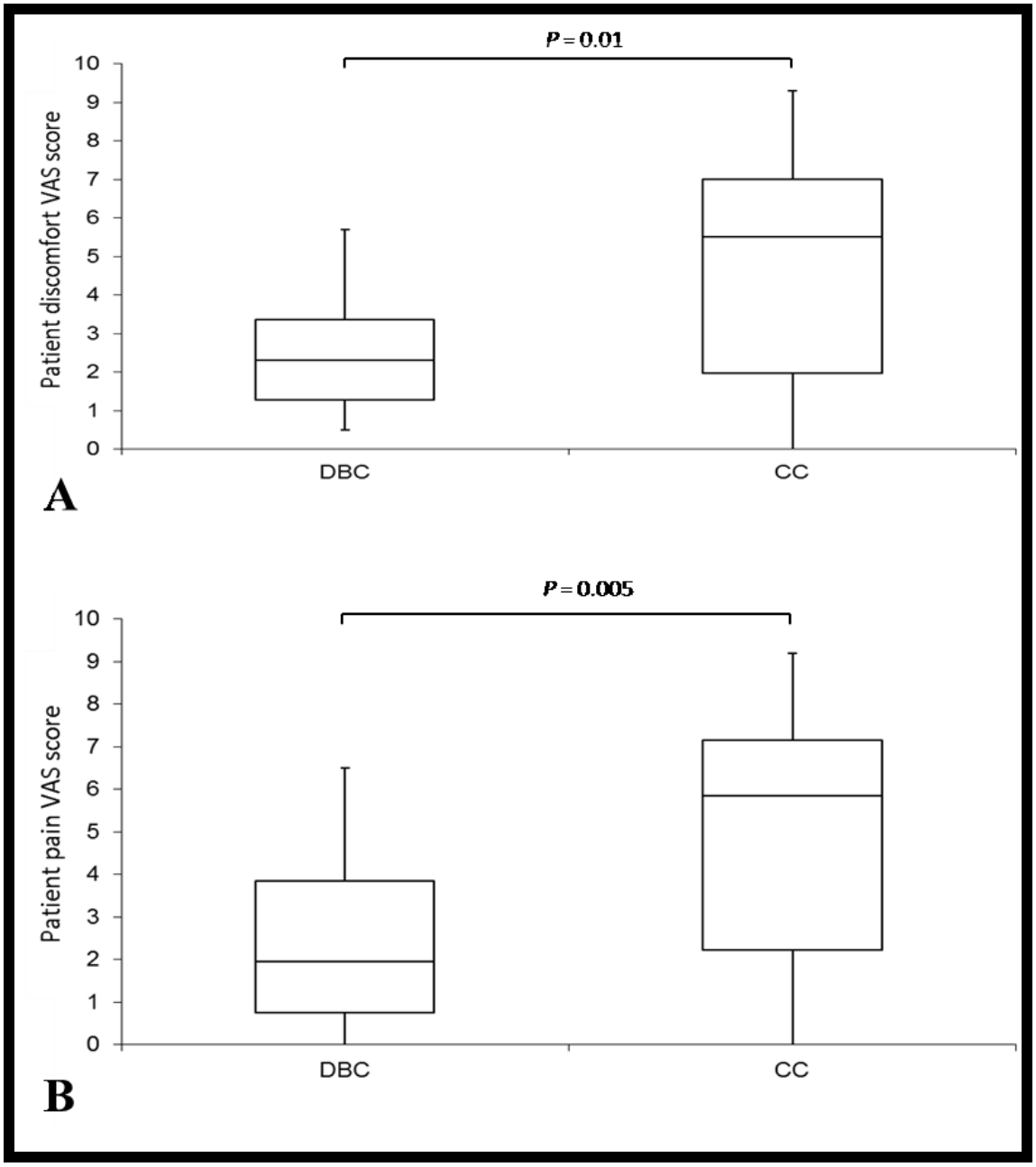


Figure 58: *Comparisons of VAS scores at DBC vs. CC for patient discomfort (**A**) and patient pain (**B**) as perceived by the attending nurse. Two-sided Mann-Whitney U test; values are expressed as medians (horizontal lines) and the 25th and 75th percentiles of the interquartile range (boxes). The whiskers are set at 1.5x the 25th and 75th percentiles respectively.*

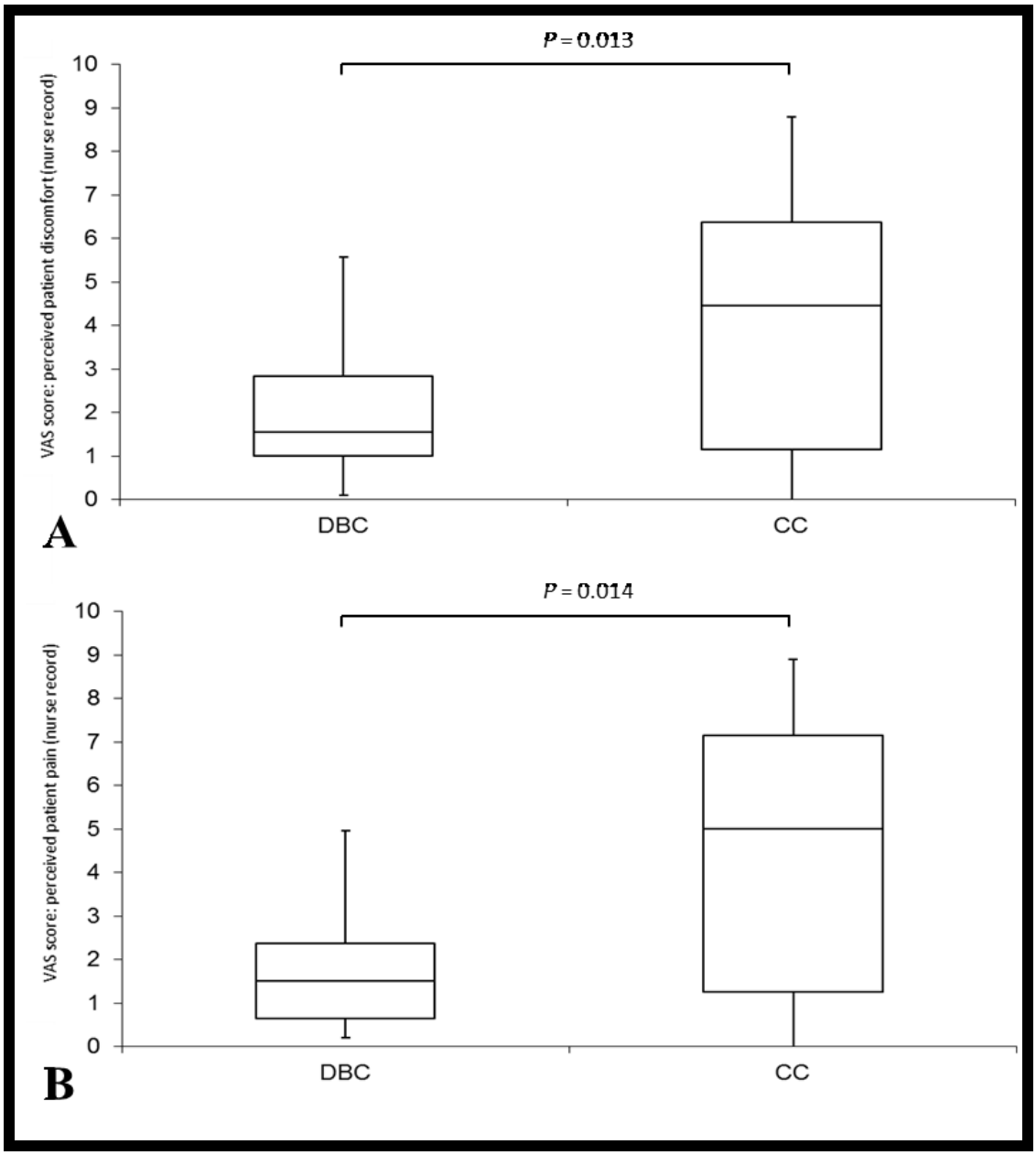
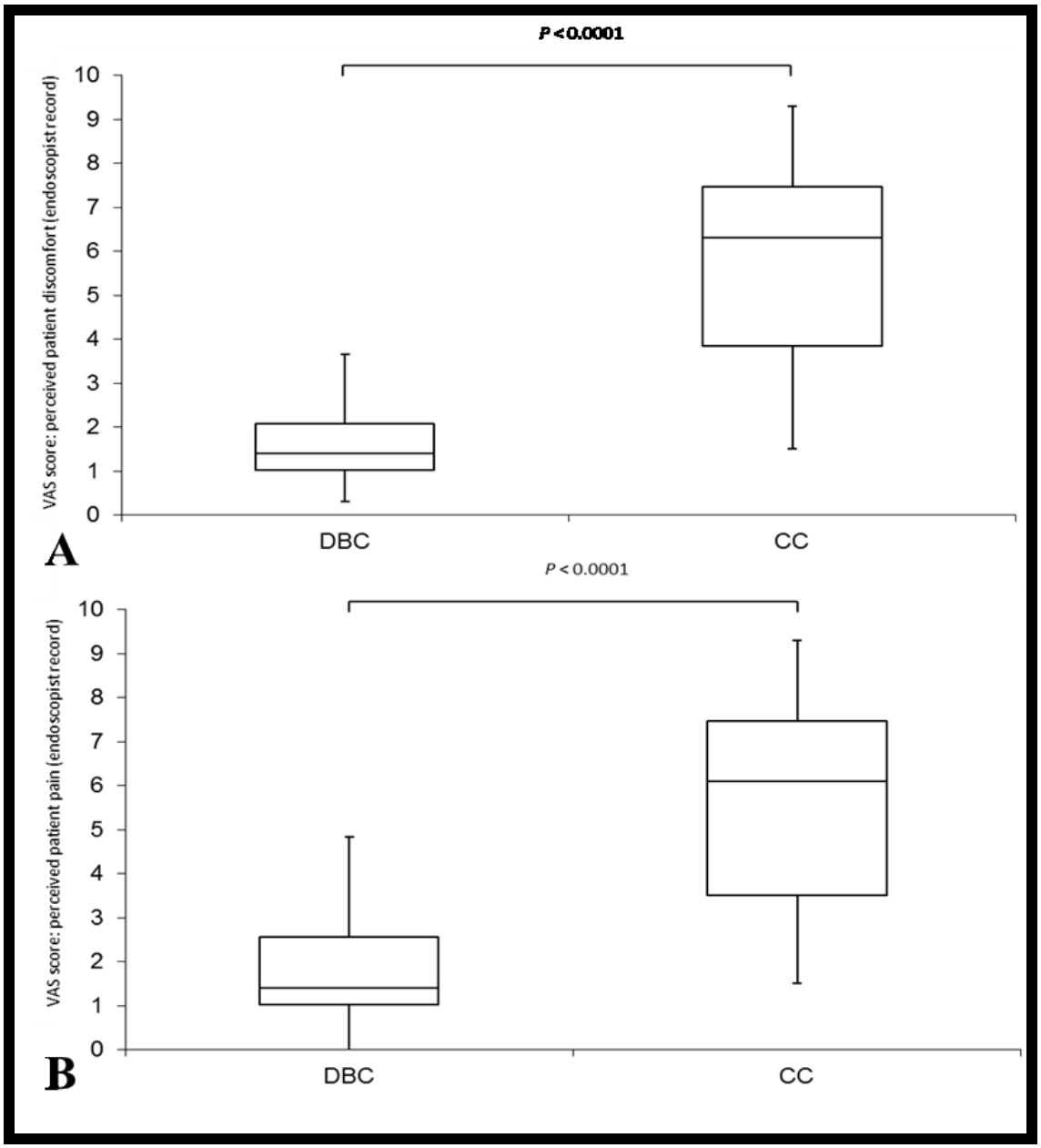


Figure 59: *Comparisons of VAS scores at DBC vs. CC for patient discomfort (A) and patient pain (B) as perceived by the endoscopist. Two-sided Mann-Whitney U test; values are expressed as medians (horizontal lines) and the 25th and 75th percentiles of the interquartile range (boxes). The whiskers are set at 1.5x the 25th and 75th percentiles respectively.*



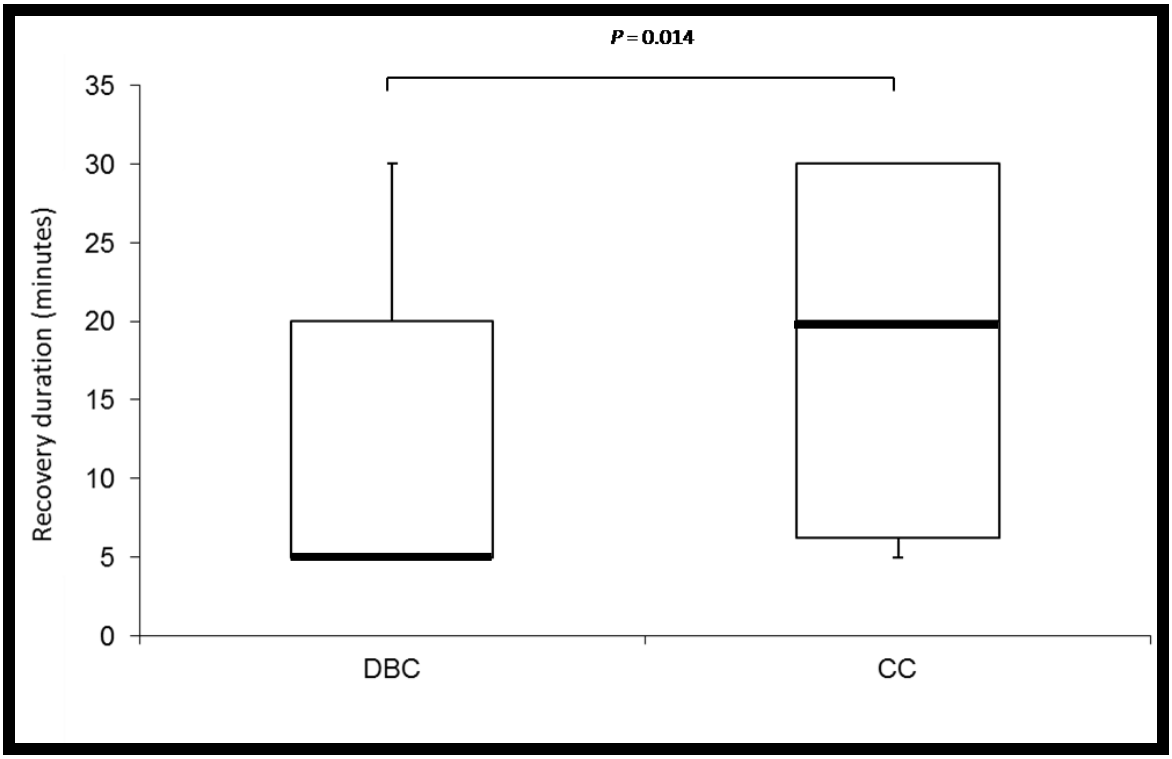
The dose of antispasmodic in the form of hyoscine-N-butylbromide (Buscopan®, Boehringer Ingelheim Gmbh; Germany) was the same for both groups: median dose (95% CI) for DBC vs. CC: 20 (19.2-24.4) vs. 20 (19.2-23.4) mg, respectively, *P*=0.98. However, the median doses of sedative drugs used were significantly lower for DBC than for CC procedures. The median (95% CI) midazolam dose for DBC vs. CC was 0 (0.2-1.1) vs. 1.25 (0.9-2.1) mg, *P*=0.023 while that for pethidine was 0 (5.7-20.4) vs. 25 (19.4-39.6) mg *P*=0.014, respectively.

Patient recovery time was also significantly shorter for DBC procedures; median (95% CI) recovery time for DBC vs. CC: 5 (7.4-14.4) vs. 20 (13.8-23.5) minutes, P=0.014, respectively (**Figure 60**). No differences in patient vital parameters i.e. median levels of oxygen saturation, SBP or pulse rate readings were detected between the two groups (**Table 22**) and none of the procedures was associated with any adverse events [151].

Table 23: *Patient vital parameters for DBC vs. CC procedures; *Mann-Whitney U test (two-sided), bpm, beats per minute*

Patient vital parameters			
	DBC	**CC**	***P****
Oxygen saturation: median (95% CI), %	97 (95.9-97.4)	98 (95.7-98.3)	0.21
Highest SBP: median (95% CI), mmHg	146 (140.4-160.4)	140.5 (132.1-154.2)	0.23
Lowest SBP: median (95% CI), mmHg	77 (74.1-83.8)	74 (71.4-82.6)	0.48
Highest pulse rate: median (95% CI), bpm	99 (92.6-106.2)	92.5 (89.3-100.3)	0.44
Lowest pulse rate: median (95% CI), bpm	77 (74.1-83.8)	74 (71.4-82.6)	0.48

Figure 60: *Comparisons of patient recovery duration: DBC vs. CC Two-sided Mann-Whitney U test; values are expressed as medians (bold horizontal lines) and the 25th and 75th percentiles of the interquartile range (boxes). The whiskers are set at 1.5x the 25th and 75th percentiles respectively.*



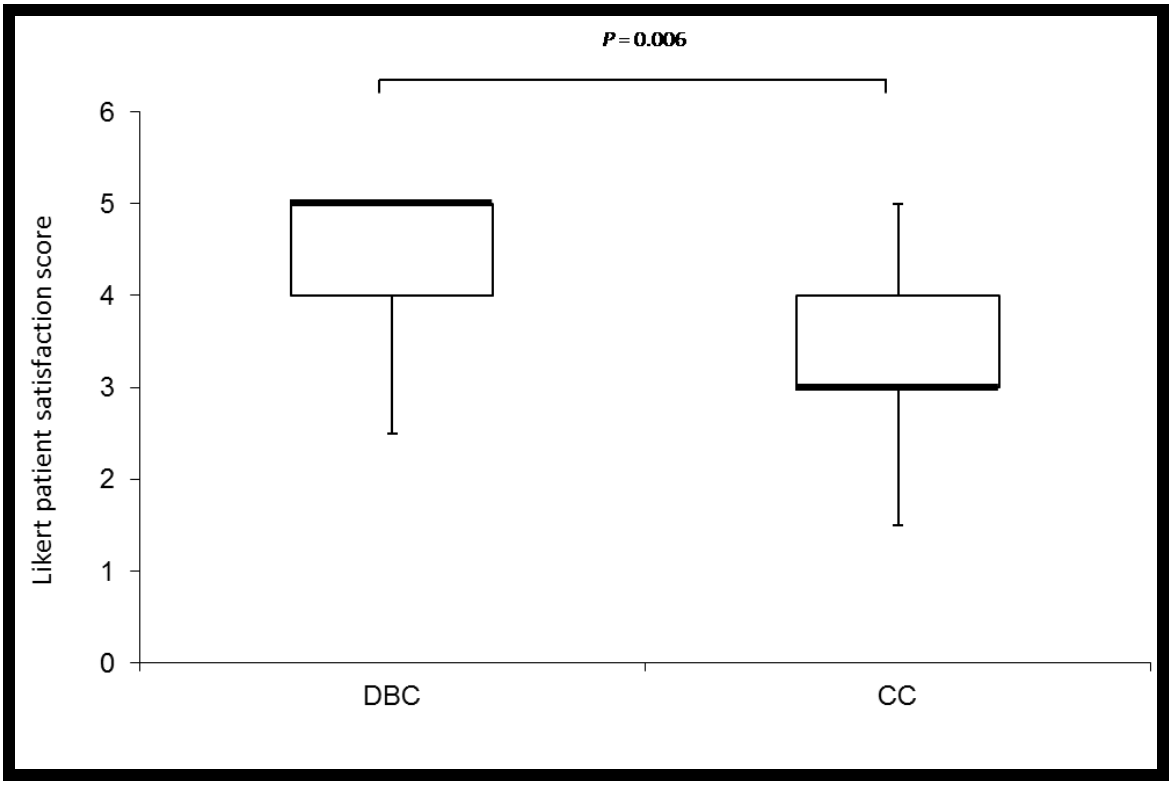
9.2.2 Patient satisfaction and technical ease of procedure performance

Examination of the 5-point Likert satisfaction scores (5=very satisfied, 4=satisfied, 3=neutral, 2=dissatisfied or 1=very dissatisfied), showed that patients from the DBC group expressed significantly higher levels of satisfaction than patients from the CC group; DBC vs. CC median (95% CI) satisfaction score: 5.0 (3.6-4.8) vs. 3.0 (2.7-3.8), P=0.006, respectively (**Figure 61**).

When asked about whether or not they would opt to have the same type of colonoscopy again or consider an alternative option in the future, all patients in the DBC group said that would have a DBC again, while 9 patients (41%) in the CC group said that they

would consider an alternative procedure in the future if they were given a choice, $P < 0.0001$.

Figure 61: *Comparisons of patient satisfaction 5-point Likert scores* (5=very satisfied, 4=satisfied, 3=neutral, 2=dissatisfied or 1=very dissatisfied) *for DBC vs. CC. Two-sided Mann-Whitney U test; values are expressed as medians (bold horizontal lines) and the 25th and 75th percentiles of the interquartile range (boxes). The whiskers are set at 1.5x the 25th and 75th percentiles respectively.*



Examination of the endoscopist's VAS score for perceived procedure difficulty (0, very easy and 10, very challenging) showed that DBC procedures were found to be significantly easier to perform than CC procedures; median (95% CI) technical difficulty VAS score (where a ↑score represents ↑difficulty) for DBC vs. CC: 3.6 (3.5-5.2) vs. 6.6 (6.1-7.7), respectively, $P = 0.0005$.

9.2.5 Discussion

Since the introduction of DBC, although several series have reported on the utility of the technology for achieving caecal intubation in previously incomplete or TD colonoscopy [66;96;117-120;122;123] only one study [113] has prospectively compared DBC with CC date. This study by Suzuki et al. [113] which was performed in a cohort of 94 patients with a history of TD colonoscopy who were randomly assigned to DBC (n=47) or CC (assisted by MEI + transparent cap) (n=47), demonstrated that caecal intubation was achieved in a shorter time and at a higher rate in the DBC group. The definition of TD colonoscopy used by this Japanese study was however based on the time taken to achieve caecal intubation (>30 minutes) at previous colonoscopy.

In our prospective, randomised comparative study of DBC vs. CC for TD cases we attempted to objectively define TD colonoscopy according to a proposed original; evidence based a cumulative scoring system incorporating the various factors which have been shown to be associated with a TD procedure (female gender, ↑age, small body habitus and a history abdominal/pelvic surgery, chronic constipation and previous failed colonoscopy) [63;65-68;70-77;80-100] (**Table 20**).

In order to assess the construct validity of our proposed scoring system, we performed a pilot study in a cohort of 29 patients, in order to examine the correlation of our proposed TD score with the time taken to achieve caecal intubation (a frequently used surrogate marker of technical difficulty [67;68;70-77;79]). Accepting the limitations, examination of the data from our pilot study showed a significant positive correlation (r_s=0.6, P=0.0006) between the TD score magnitude and the time taken to achieve caecal intubation. Although we recognise the limitations and potentially confounding factors (heterogeneity of colonoscopist experience, adequacy/inadequacy of bowel preparation, and non-standardised administration of sedative and antispasmodic agents) of this pilot

study, preliminary validation of our original TD colonoscopy score enabled us to objectively recruit patients for the main study as initially intended. More formal validation of the scoring system for TD colonoscopy (which will also address all other potentially confounding factors) may also facilitate its use as a 'predictive' risk-stratification tool for TD cases in clinical practice; potentially allowing clinicians to strategically plan endoscopy lists by allocating extended time-slots and preparing dedicated equipment for patients with a high TD score.

9.2.5.1 Time taken to achieve caecal intubation and respective caecal intubation rates

Examination of the time taken to achieve caecal intubation (the main objective measure of the study) was only possible in 19/22 (86%) of CC cases vs. 22/22 (100%) of DBC cases, since caecal intubation was unsuccessful in 3 CC cases, despite the use of ancillary equipment. Unlike the findings of the study by Suzuki et al. [113] who showed a shorter caecal intubation time for DBC, our comparison of the time taken to achieve caecal intubation in the remaining cases where total colonoscopy was successful showed no significant difference between the 2 groups.

Since the availability of ancillary equipment (such as a MEI) for CC may not be routinely available in clinical practice, we elected to commence all procedures unassisted; ancillary equipment was therefore only used on demand in the setting of failure to progress at colonic intubation. A comparison of the unassisted caecal intubation rates (i.e. where no ancillary equipment was required) showed that this was significantly higher for DBC (22/22, 100%) as compared with CC (13/22, 59%) and caecal intubation at CC failed, despite the use of ancillary assistance in 3 cases. The

findings of the Suzuki et al. for this outcome [113] also showed a significantly higher caecal intubation rate for DBC, even though the Japanese investigators used ancillary assistance with a MEI + transparent cap for all their CC cases from the start. In our study, a higher TD score (≥5) was associated with a requirement for ancillary assistance in CC. Also in keeping with the findings of Suzuki et al. [113], the main factors which appeared to have a negative effect on colonic intubation in the 9 CC cases where ancillary equipment was required were "tight angulation of the sigmoid colon" (which affected 5 of these cases, including the 3 cases where CC remained incomplete despite ancillary assistance) and "excessive looping" (which affected the remaining 4 cases). These findings, which are also similar to those reported in another case series [122] suggest that the slimmer DBC colonoscope coupled with the stability and gentle-traction provided by its overtube and balloons may facilitate successful negotiation of tight angulations and improved control of looping, potentially accounting for the higher caecal intubation rate achieved by DBC.

9.2.5.2 Patient comfort, sedation requirements, recovery duration, vital parameters and immediate adverse events

Patient discomfort and pain VAS scores were significantly lower for DBC as compared with CC procedures. This outcome was also mirrored by significantly lower VAS scores for perceived patient pain and discomfort as recorded by the attending nurse and endoscopist. Sedation requirements were significantly lower for DBC and this was associated with a shorter recover period after DBC procedures. Both procedures appeared to be equally safe; no significant differences in patient vital parameters or immediate adverse events were observed. Our findings here also support the results of Suzuki et al. [113] who reported that DBC was associated with lower VAS scores for

pain and lower sedation requirements; similarly, no adverse events were reported in the Japanese study.

9.2.5.3 Patient satisfaction and technical ease of procedure performance

Our analysis of patient satisfaction with the colonoscopy they had just undertaken showed significantly higher levels of satisfaction in the DBC group. Also, while all the patients in DBC group said that they were ready to undergo the same type of procedure again, 41% of patients in the CC group said that they would consider an alternative option, should they require a further colonoscopy in the future. These findings parallel the outcomes relating to the VAS scores for discomfort and which suggested that overall, patients found DBC to be the more comfortable of the 2 procedures. Examination of the VAS scores for technical performance also showed that the endoscopists found DBC easier to perform than CC procedures.

9.2.5.4 Limitations of the study

This was a small prospective study, performed in a single tertiary referral centre. Other limitations of the study include the use of subjective scores (VAS and Likert scores) to measure some of the outcomes and the absence of longer term (30 day) complication data. We also recognise that comfort-score data from patients who have received sedation may have been potentially confounded by the amnesic effects of the sedatives used.

9.2.5.5 Conclusion

Our study is the first study relating to TD colonoscopy, where 'technical difficulty' was defined by the use of an evidenced based, cumulative scoring system, incorporating patient characteristics which have been shown to be associated with a TD procedure. The construct validity of our proposed scoring system for TD colonoscopy was confirmed by a pilot study, allowing us to use it to recruit patients for the main study according to their TD score. More formal evaluation (which is planned) of our original scoring system may permit its use in routine clinical practice, potentially allowing endoscopists to pre-plan their lists according to the TD score of patients. Our randomised comparative study of DBC vs. CC for TD cases generally confirms the findings of others [92;113;117;122] and suggests that DBC may be a superior instrument for achieving successful caecal intubation in technically difficult cases compared to unassisted CC. DBC is also associated with a better patient experience during colonoscopy performed in this setting. Larger multicentre studies are required to confirm our findings.

10 Discussion

10.1 Summary of findings and potential impact on current clinical practice

The unifying concept underpinning this body of work, relates to the application of recent advances in flexible endoscopic technology for the benefit of minimally invasive patient care. This work tested the principle of 'advancing minimally invasive aspects of flexible gastrointestinal endoscopy' by evaluating the role of examples of such technologies in the three key divisions of the luminal digestive system, namely the upper GI tract, SB and the colon, within a UK clinical setting. Measures of patient comfort, diagnostic ability and new therapeutic indications were evaluated; the overall hypothesis being that these technological advancements can provide an alternative minimally invasive option of care which is safe, at least as effective and better tolerated by patients.

10.1.2 Upper GI endoscopy

The study described in Chapter 2, is the first prospective, randomised, comparison to evaluate the role of unsedated transnasal OGD (T-OGD) as an alternative to per-oral conventional OGD (C-OGD) in the UK. This comparison of latest available UT endoscopes with the most commonly available conventional gastroscope is also one of the most comprehensive. Aside from a general comparison of T-OGD with C-OGD in terms of patient tolerance (from multiple perspectives i.e. patient, nurse and endoscopist), T-OGD feasibility (procedure preparation, duration and recovery times),

safety and diagnostic performance (endoscopic view and biopsy quality); the study also compared the performance of 2 different sized UT endoscopes used via both the transnasal and oral route.

The findings for the general appraisal of C-OGD1 (OGD using 9.0mm endoscopes) as compared with T-OGD are similar to those of studies performed in other countries and show that T-OGD is significantly better tolerated than C-OGD1 performed with or without low dose sedation [8;9;11-13;133;134]. The comparative evaluation of the use of UT endoscopes for OGD performed via the transnasal vs. the oral route suggested that improved patient experience during OGD is more dependent upon the route used for the procedure than the endoscope calibre itself, echoing reports from other groups [2;12;13;16;135].

My comparisons of endoscopic view quality, diagnostic yield (including biopsy quality) and technical feasibility showed that the performance of UT endoscopes is comparable to that of the wider calibre conventional endoscope used in the study. The failure rate for passage of the UT endoscope through the transnasal route was low (6%) and within the same range reported elsewhere (3-8%) [2;10;13;144]. As regards to preparation and procedure duration, I found that it took longer to prepare for and to perform T-OGD; however, this was offset by a significantly shorter recovery time for T-OGD. The enhanced recovery associated with T-OGD has been shown to potentially facilitate savings in personnel and facility costs in the order of 20-36% [145;146].

My comparison of patient experience and overall performance with the 2 UT endoscopes showed that the slimmer, 4.9mm endoscope did not offer any significant advantages over the 5.9mm UT endoscope; in fact views of the duodenum were deemed to be inferior and handling of the thinner endoscope more difficult.

The first prospective study to compare T-OGD using the latest available UT 5.9mm and 4.9mm endoscopes with C-OGD in the UK, has confirmed that unsedated transnasal endoscopy is associated with significantly higher levels of patient tolerance and satisfaction as compared with C-OGD. The study also confirmed that even within a UK clinical setting, T-OGD is a highly feasible and safe alternative to C-OGD and affords similar diagnostic quality. The use of UT endoscopes via the oral but more so the transnasal route is confirmed to be associated with improved patient tolerance as compared with C-OGD.

Although this study was performed in a tertiary referral institute of academic endoscopy, its findings are universally applicable to other endoscopy centres within the country. In my experience and that of others [276], T-OGD is not a difficult procedure to learn and after a short session of mentoring, one only requires a few cases to gain proficiency. The key to success relies on adequate patient preparation with topical anaesthesia and 'generous' lubrication of the endoscope shaft, in order to ensure ease of insertion and patient comfort. The procedure's safety and tolerability lends itself well to endoscopy nurse-led services. In our institution, for example, the senior nurse endoscopist who took part in our study took initiative to train other nurses in the technique in order to be able to provide a sedation free, 'pure' T-OGD list in the near future. It is also likely, that the advantages associated with T-OGD may be amplified further in the setting of a district general or community hospital or specialised GP practice where investigation of upper GI symptoms could be performed more cost effectively while avoiding the need for additional staff and sedation associated risks and expense. The findings of the study may help to generate more awareness of the success and tolerability of T-OGD and its general applicability to UK clinical practice. Furthermore, new indications which take advantage of the favourable characteristics of UT endoscopes such as single-step naso-jejunal tube

placement and high resolution direct cholangioscopy [276-280] demonstrate that the place of these advanced instruments in the endoscopy unit is not limited to T-OGD.

10.1.3 Small bowel endoscopy (Enteroscopy)

The advances in endoscopic technology seen over the last few years have revolutionised the practice of flexible endoscopy of the SB. As a result of this breakthrough, brought about by the introduction of device assisted enteroscopy, DBE in particular, endoscopists are no longer confined by the intrinsic limitations of push enteroscopy (PE) or the invasiveness of intra-operative enteroscopy (IOE) and instead, are able to effectively 'delve into the depths of the SB' without the need for major operative surgery.

As a reflection of this impressive leap forward, much of this thesis has involved studies examining minimally invasive aspects of flexible endoscopy as applied to the SB. These studies included an evaluation of the current overall performance, limitations and safety of DBE practised in UK hospitals with an interest in deep enteroscopy, the application of DBE to the provision of minimally invasive endotherapy and a comparison of DBE with the more recently developed SB technology, known as spiral enteroscopy (SE).

My evaluation of the performance, limitations and safety of DBE practice in the UK is described in Chapter 3. The overall diagnostic yield of positive findings of the first 1000 DBE cases performed in the UK was 57.8%; a result that is comparable to the overall pooled detection rate of 68.1%, as reported [148] in a recent international systematic review including 45 studies with a total of 5615 patients. Similar to the findings of a German database [39], the diagnostic yield of the UK cases was (at least in part), dependent on indication and suggests that careful patient selection before consideration

for DBE may impact procedure outcome. Perhaps not surprisingly, the diagnostic yield was higher for patients, in whom pan-enteroscopy was achieved, supporting the view that although challenging, particularly in patients with a history of laparotomy, an attempt at achieving pan-enteroscopy in selected patients can be worthwhile [155].

DBE procedures performed in patients with a history of abdominal or pelvic surgery were associated with a significantly lower median SB insertion depth as compared with procedures performed in surgically naïve patients. SB tethering and unfavourable looping occurred significantly more often in patients with a history of surgery and were considered to be the major limitations to DBE insertion. The UK experience and that of others [27;152;156;157] highlights how post-surgical changes to SB anatomy may challenge successful intubation during DBE procedures by leading to a reduction in insertion depth. Adhesive disease is also likely to be a contributing factor to the UK pan-enteroscopy outcome of 17.7%, while similar to the pan-enteroscopy rate of 21%, reported by the (prospective) German database [39], is at the lower end of the range of pan-enteroscopy rates (8-66%) described by other European series [30;155;158].

I found that the median depth of SB insertion during DBE appears to be affected by the route of approach and type of gas used for insufflation. The anterograde route was found to be associated with deeper SB insertion as compared with the retrograde route and supports the notion that the latter approach is more technically challenging [152;153]. The results also supported the findings of Domagk et al. [154] who showed that the use of CO_2 as an insufflating agent was also associated with deeper SB insertion.

In the UK, the overall immediate complication rate of 1% is similar to that (0.72-1.2%) reported by others [27;30;38;39;148]. Also similar to the findings of other reports [27;30;38;39;148], most immediate adverse events (9/10) were related to the use of endotherapy (such as polypectomy and dilatation of SB strictures). In the UK

experience, post-DBE pancreatitis was also rare entity and only occurred during 1 anterograde case (0.1% of all DBE procedures, 0.l5% of anterograde DBEs); a result which compares favourably to those reported by others (0.2%-0.49%) [27;30;38;39;148]. Although none of the UK complications was associated with any mortality, it must be stressed that our series lacked formal 30 day complication data and it is therefore possible that serious longer-term complications may have been missed.

Despite the study's limitations (related to retrospective analysis, heterogeneity of experience among DBE users and lack of 30 day complication data), this first report of the performance, limitations and safety of DBE performed in the UK provides reassurance of the safety and effectiveness of DBE, particularly in a UK setting. Careful consideration to the limitations of DBE as highlighted in the report may help endoscopists to improve the success of future procedures. The use of the two published [167;168] original, alternative techniques for DBE insertion, described in chapter 4 may also help endoscopists to overcome some of the technical limitations reported by the UK DBE experience.

The application of specific types of minimally invasive DBE facilitated endotherapy with the deep SB is described in chapters 5, 6 and 7, respectively.

Chapter 5 describes one of the first published series [188] to demonstrate the effectiveness of DBE enabled endoscopic balloon dilatation of SB strictures, related to Crohn's disease (CD). The results of this cohort study (which were drawn upon by an international OMED-ECCO committee for the formulation of consensus statements on the use of SB endoscopy in patients with inflammatory bowel disease (IBD) [171]),

showed that DBE facilitated SB stricture dilatation in CD is feasible and effective. In this study of 11 patients, stricture dilatation was feasible in 9 patients (in the other 2 patients, the strictures could not be reached, due to limited insertion depth within the post-surgical abdomen). In 8 of these 9 patients, stricture dilatation was uncomplicated and at a mean follow-up period of 20.5 months, although 2 patients required repeat dilatation, all 8 patients remained surgery-free, with significant improvement of their VAS scores for obstructive symptoms. In this study, 1 patient (with actively inflamed CD strictures) unfortunately developed a delayed perforation requiring a temporary jejunostomy. This case highlights the fact that although endoscopic balloon dilatation of strictures is considered a relatively safe procedure, the risk of perforation in certain cases may be as high as 11% [186;187]. SB strictures that are long (>5cm), severely inflamed and ulcerated should therefore be considered high-risk and a potential contraindication to DBE assisted balloon dilatation [42].

The study demonstrated that the technique of DBE facilitated SB stricture dilatation offers a minimally invasive, effective alternative to surgical resection or stricturoplasty for selected patients with fibrostenotic CD of the SB. Since the publication of this study [188], a further study from Japan [189] has confirmed these findings and showed that DBE facilitated endoscopic balloon dilatation was successful in 18 of 25 cases. Two patients in the Japanese cohort suffered complications in the form of bleeding and pancreatitis but the cumulative surgery-free rates for all subjects were 83% and 72% at 6 and 12 months respectively [189].

The results add to the growing evidence in support of this minimally invasive approach to the management of selected patients with CD SB strictures and its incorporation into daily clinical practice as proposed by the original, published algorithm (**Figure 39)** [281;282] .

In chapter 6, the largest study to date on DBE facilitated polypectomy of SB polyps in patients with PJS is described. In this cohort of 36 patients (24 adults and 12 children), DBE facilitated polypectomy was shown to be an effective alternative to laparotomy and IOE for selected adult and paediatric patients with PJS and significant SB polyposis. DBE (with or without laparoscopic assistance) facilitated significant polyp clearance in 74% of patients and these remained symptom and intervention free at a median follow-up of 2 years. This study also confirmed that a past history of surgery and resultant formation of adhesive disease limits the depth of SB insertion achievable at DBE and led to incomplete procedures in several cases. Interestingly, SB tethering with tight angulations and irreducible looping, resulting in inadequate depth of insertion were encountered solely in adults but none of the children, most likely to be reflective of underlying post-surgical SB adhesive disease, since 92% of adults had a history of previous, often multiple laparotomies, as compared with just 25% of children. The outcome here suggests that removal of significant SB polyps for selected patients with PJS by DBE is likely to be most successful when offered to patients earlier-on in life, before exposure to multiple major abdominal surgeries. The study also evaluated the use of laparoscopic assistance [216] for high risk, sessile polyps. Although more invasive than DBE alone, lap-DBE is still less invasive than laparotomy with IOE and was successful in 3 of 4 patients undergoing this procedure.

Considering these limitations (26% of patients in the cohort ultimately required surgery) as well as the natural history of PJS, it is clear, that laparotomy with IOE will continue to have a major role in the therapeutic management of PJS SB polyposis. The study also underlines the importance of ensuring that these procedures are performed with expert surgical back-up to hand. One of the patients in this cohort suffered an acute post-polypectomy perforation during an emergency DBE for intussusception and a successful

outcome was ensured by the immediate conversion of the procedure to a laparotomy and IOE through the defect by the attending surgeon and endoscopist.

The ideal management of patients affected by this condition will continue to demand a dedicated, multi-disciplinary approach that is tailor-made according to the needs of each patient. Nonetheless, this largest combined series of adult and paediatric patients with PJS to be reported to date, demonstrates that DBE facilitated polypectomy provides an effective therapeutic alternative to laparotomy with IOE [207-210;212]. The introduction of a DBE-based approach to therapy earlier-on in life may improve polyp clearance success rates if small bowel surgery and therefore adhesional disease can be avoided. If successfully achieved, the outcomes of this minimally invasive approach, like more traditional methods, have the potential to alter the course of the disease process in patients with PJS SB polyposis.

Chapter 7 describes the first prospective published series to focus on the feasibility and technique of DBE assisted DPEJ [238]. This series demonstrated the success and safety of an adaptation of the original PE method described by Shike et al. [232], using DBE to facilitate ‘a stable platform’ for DPEJ insertion within a suitably accessible, superficial loop of jejunum. In this cohort, the intrinsic characteristics of controlled endoscopic insertion with minimal of SB looping and stretching [20;45;54;152] facilitated safe and successful DPEJ placement in 9 of the 10 patients in whom it was attempted. This result compares favourably to the outcomes relating to the PE based technique, where failure rates may be as high as 32% [231].

This small cohort was the first published study [238] to demonstrate the feasibility and safety of DBE assisted DPEJ placement as a safe and successful alternative technique to

PE facilitated insertion. Although no adverse events occurred in this series, it is likely that the overall complication rate (of up to 10%) associated with DPEJ placement by PE [231], may still apply to the DBE facilitated technique and this should be borne in mind when considering this type of enteral access in routine clinical practice.

The prospective comparative study of spiral enteroscopy (SE) and DBE described in chapter 8 is the first back-to-back study to be performed within the same cohort of patients, using the same method of SB insertion depth estimation for both SE and DBE. Since initial experience suggested that this technology may facilitate relatively faster deep enteroscopy [57-59;62;264-266], the introduction of SE was met with much interest. However, 2 dedicated prospective studies [60;61] which compared SE with DBE, used different methodologies to assess SB insertion depth achieved during SE and DBE procedures and it therefore remained unclear as to whether these 2 procedures facilitated the achievement of similar SB insertion depths. In order to try to provide a definitive conclusion, a prospective, back-to-back comparative study of SE and DBE performance, using the same method of SB insertion depth estimation was performed.

In this study, SB insertion depth was estimated during DBE procedures, only using the method described by May et al. [51]. The results showed that DBE facilitated deeper SB intubation than SE most often and in 14/15 patients enrolled, DBE not only enabled visualisation of the sub-mucosal tattoo placed at SE but also facilitated significantly deeper enteroscopy, as compared with SE. Similar to the results of the Wiesbaden study [61], the median time taken to reach maximal SB insertion depth was significantly shorter for SE as compared with DBE. However, in the 14/15 patients where the comparison was possible, our study showed that the median times taken to reach the same the same depth were similar for both procedures, suggesting that both had a similar

a rate of advancement into the SB. Although I accept that this study has limitations relating to potential intrinsic bias (non-randomised order of procedures and early conclusion), it is the first study to compare the performance of SE with DBE using the same method for estimating SB insertion depth, showed that in its current (manual) form, SE appears to be inferior to DBE in terms of its ability to achieve deep SB insertion and similar to DBE in terms of SB insertion speed. While larger studies are required to confirm these results, the findings suggest that DBE remains the 'gold standard' deep enteroscopy technology and that the performance of manual SE does not appear to be equivalent.

The main outcome measure of this study related to a comparison of SB insertion depth. Although this is often used as a surrogate marker for clinical performance of these respective technologies, one must bear in mind that we remain uncertain as to whether or not this translates into improved clinical outcomes. Possibly, a more clinically useful comparison may be obtained by using diagnostic yield or detection/treatment of SB pathology as the main outcome measure. Since it is likely that such a comparative study would need to enrol much larger numbers of patients than those included in our study and the studies by Frieling and May [60;61], a multi-centre, possibly international set-up is likely to be required.

The remarkable technological developments witnessed over the last decade have revolutionised the investigation and management of SB disease. In parallel to the introduction of the breakthrough endoscopic technologies of SBCE and deep enteroscopy, there has also been significant progress in dedicated SB cross-sectional imaging technologies in the form of CT and MR enterography/enteroclysis [283-292]. These radiological technologies complement their endoscopic 'counterparts' in that they

are also able to provide detail about mural and extramural pathology/anatomy while also providing further information regarding the vascularity of lesions and the degree of active inflammation. State-of-the-art dedicated SB cross-sectional imaging also has a role to play in the pre-assessment of patients being considered for deep enteroscopy, particularly in the presence of suspected SB strictures which have precluded (or complicated) the use of SBCE. The SB endoscopic technologies on the other hand, are able to provide a detailed visual assessment of SB mucosal pathology. SBCE and deep enteroscopy technologies are also non-competitive modalities which complement each other. SBCE, being the least invasive 'arm' of SB endoscopy is used as a first-line 'scout' in patients with suspected SB disease. Deep enteroscopy is then employed in patients who require further evaluation or treatment of pathology identified by other means, since it is generally considered to represent the 'therapeutic arm' of SB endoscopy.

Although all these relatively new technologies require dedicated training to gain proficiency, deep enteroscopy is particularly labour-intensive and requires prolonged, focused commitment. While some reports on DBE training have suggested that performance may improve after about 20 to 35 procedures [152;159], as reported by Gross et al.[160], expertise in the procedure requires significantly more experience to be achieved (>100 – 150 procedures); this is particularly relevant to the more challenging retrograde (rectal route) approach. These data on training strongly suggests that expertise in DBE (and related deep enteroscopy technologies such as single-balloon and spiral enteroscopy) would best be achieved through dedicated, lengthy advanced endoscopy fellowships in specialist centres. Measures of competency in deep enteroscopy should in the future be assessed by validated competency assessment tools, similar to those used for colonoscopy and polypectomy [161-165]. Key performance indicators could include measures of lesion recognition, diagnostic yield, depth of SB insertion, success of deep

SB intubation via the retrograde route, success of deep SB intubation in technically challenging cases (such as procedures performed in patients with a history of abdominal/pelvic surgery), success of therapy in cases with a therapeutic indication and peri-procedure and 30 day complication rates. Given the labour intensive and challenging nature of these procedures, it is likely that in order to achieve long-term, high quality safe and successful outcomes deep enteroscopy services will only be provided by a few tertiary referral centres across the country. Apart from enhancing outcomes for patients, this model of care in dedicated SB endoscopy centres would also enable the efficient use of scarce and expensive resources (such as anaesthetic support and case-specific lists) within our healthcare system.

10.1.4 Colonoscopy

Chapter 9 describes a prospective, randomised comparative study of DBC vs. CC for TD cases. This is only the second study to perform such a comparison and the first to use an objective, evidence based [63;65-68;70-77;80-100], cumulative scoring system (**Table 20**) to define TD colonoscopy. The construct validity of the scoring system was assessed by means of a pilot study which demonstrated significant positive correlation between the magnitude of the proposed TD score and the time taken to achieve caecal intubation (a frequently used surrogate marker of technical difficulty [67;68;70-77;79]). The comparative study of DBC vs. CC for TD cases showed that the unassisted caecal intubation rate (i.e. where no ancillary equipment was required) was significantly higher for DBC. These findings are similar to those of Suzuki et al. [113] who also showed a significantly higher caecal intubation rate for DBC, even though the Japanese investigators used ancillary assistance with magnetic endoscopic imaging (MEI) + transparent cap for all their CC cases from the start of each procedure. Unlike the

findings of the Japanese study, the results of our study did not show a significant difference in the time taken to complete either of the 2 types of colonoscopy. However, our findings showed that patient discomfort and pain VAS scores were significantly lower for DBC as compared with CC procedures. Sedation requirements were also significantly lower for DBC and this was reflected by a shorter recover period after DBC procedures. My findings support the results of Suzuki et al. [113] who reported that DBC was associated with lower pain VAS scores and sedation requirements. Analysis of patient satisfaction showed significantly higher levels of satisfaction in the DBC group and while all the patients in DBC group said that they were ready to undergo the same type of procedure again, 41% of patients in the CC group said that they would consider an alternative option in the future. Finally, evaluation of the technical performance VAS scores showed that endoscopists found DBC easier to perform than CC procedures.

'Technical difficulty' was defined by the use of an evidenced based, cumulative scoring system, incorporating patient characteristics which have been shown to be associated with a TD procedure. This scoring system (which was provisionally validated by a pilot study), may lend itself to routine clinical practice, potentially allowing endoscopists to pre-plan their lists according to the TD score of patients, which is calculated prior to colonoscopy. This randomised comparative study of DBC vs. CC for TD colonoscopy suggests that DBC is a useful instrument for achieving successful caecal intubation and is associated with an improved patient experience. The findings favour the incorporation of DBC into the armamentarium of the endoscopy unit.

DBC complements other alternative technologies such as computed tomographic colonography (CTC) [293-304] and colon capsule endoscopy (CCE) (Pillcam Colon2, Given Imaging, Yoqneam, Israel) [305-309] in the investigation of suspected colonic pathology in cases of TD colonoscopy. CTC, which is the more established and readily

available of these 2 alternative technologies, can be performed using minimal bowel preparation (incorporating faecal tagging with simple radio-opaque contrast media (such as barium) with subsequent electronic 'subtraction' of the luminal contents, also known as 'electronic cleansing') [295;296;300-304], also allows for the detection of extra-luminal pathology and has diagnostic sensitivities and specificities which are similar to colonoscopy [295-297;299-303]. Its main disadvantage comes from radiation-exposure related risks [293]. Second generation CCE is an emerging technology which employs the use of a 'dual-headed' wireless capsule endoscope (**Figure 62**) with a capacity to vary its image capture frame-rate (from 4 to 35 frames per second), depending on the speed of colonic transit. This technology's main advantages relate to its minimally invasive and radiation-free nature. Although recent data have reported a diagnostic sensitivity and specificity of 89% [310;311], which approaches that of colonoscopy, these outcomes are dependent on a rigorous bowel preparation regimen which at present may reduce this modality's appeal and clinical applicability [310;311].

Figure 62: *The Pillcam Colon2 second generation wireless colon capsule endoscope (Image courtesy of Given Imaging, Yoqneam, Israel)*



It is therefore likely that in the day-to-day clinical setting of TD or failed conventional colonoscopy, patients will be referred for a CTC or possibly a CCE in the first instance and if these initial investigations were to reveal colonic pathology, warranting further colonoscopic evaluation or intervention, DBC could be considered next since this may facilitate success.

10.2 Conclusion and future directions

In conclusion, this thesis has examined the role and usefulness of a selection of advanced flexible GI endoscopic technologies for the enhancement of minimally invasive patient care. The first evaluation of transnasal upper GI endoscopy performed in the UK, confirmed that transnasal endoscopy using ultrathin endoscopes, is a feasible, effective and acceptable alternative to conventional oral upper GI endoscopy and may help to broaden its clinical appeal in this country.

The series of studies which followed were dedicated to device assisted enteroscopy (DBE in particular); these studies showed that DBE is capable of providing a safe and effective, minimally invasive alternative to surgery in selected patients with particular clinical conditions. A comparison of spiral enteroscopy as an alternative to DBE, showed that spiral enteroscopy (in its current, manual form), appears to be inferior to DBE in its ability to facilitate deep enteroscopy. Further work is required in order to establish whether or not this translates to improved outcomes in routine clinical practice. It is also important to note that deep enteroscopy requires intensive dedicated training which may best be obtained through advanced fellowships at specialised tertiary centres. Given the set-up and training required, it is also likely that deep enteroscopy services are likely to continue to be delivered at dedicated centres.

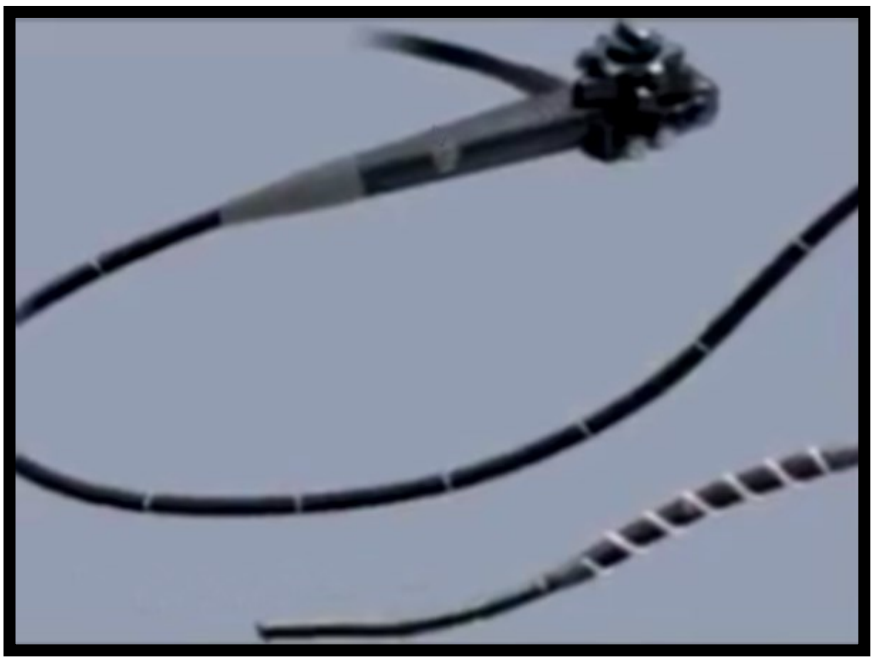
The work evaluating technically difficult colonoscopy has i) enabled the development and preliminary validation of a score for technical difficulty which after further work, has the potential to be applied to routine clinical practice in the future and ii) established the usefulness of DBC as a more effective tool (as compared to conventional colonoscopy without ancillary assistance) in technically difficult cases where caecal intubation is required. In day-to-day clinical practice, DBC may complement alternative technologies such as CTC and CCE for the investigation and management of cases of TD colonoscopy.

In the future, further technical developments may continue to enhance the performance of ultrathin upper GI endoscopes by the integration of higher definition CCD and brighter, more efficient illumination using advanced light emitting diode (LED) technology. The incorporation of a wider calibre instrument channel may also expand the therapeutic applications of these endoscopes. Such improvements may also continue to broaden the application of ultrathin instruments to other fields of GI endoscopy (such as one-step naso-jejunal tube placement, direct cholangioscopy and as auxiliary instruments for endoscopic resection of large polyps).

Another technology which may have an impact on deep enteroscopy practice is the concept of 'motor-powered' spiral enteroscopy [312]. This technology (which still awaits FDA and CE approval), involves the use of a motor-powered, single-operator; foot-pedal controlled spiral incorporated into a dedicated 160cm enteroscope (**Figure 63**). A pilot study performed by Akerman et al. in 27 patients [312] using the latest version of the prototype, showed that the motor-powered spiral enteroscopy was able to facilitate visualisation of the entire GI tract (using a combination of anterograde and retrograde approaches) within approximately 60 minutes. Although this appears to be

promising, it is likely that some of the limitations relating to manual spiral enteroscopy (such as tissue trauma and concern about its use in the post-surgical abdomen) would still apply to the motor-powered version and that specific measures to mitigate these limitations (possibly including the use of a retractable spiral) may need to be developed.

Figure 63: *The 'Endeavour®' motorised-spiral enteroscope prototype (Spirus Medical, LLC, MA, USA) incorporating a removable, motor-controlled plastic spiral. (Image courtesy of Spirus Medical, LLC, MA, USA)*



Other ground-breaking advances in the field of flexible GI endoscopy also include the award winning '*i*-Snake', developed by a multidisciplinary team from the Departments of Computing and Surgery and the Institute of Biomedical Engineering at this university (Imperial College London) [313;314]. The '*i*-Snake' aims to become the 'intelligent endoscopic platform of the future', with integration of state of the art imaging technology, specially designed articulated 'joints' and sensor-assisted control (**Figure**

64) [313;314]. This cutting-edge platform is intended to augment the precision and success of minimally invasive flexible endoscopy and endo-surgery and associated benefits to patient care.

Figure 64: *Computer generated model of the 'i-Snake' illustrating the head of the instrument and specially designed robotic 'joints' and sensors (Image courtesy of Imperial College London)*



11 Bibliography

1 Froehlich F, Gonvers JJ, Fried M: Conscious sedation, clinically relevant complications and monitoring of endoscopy: results of a nationwide survey in Switzerland. Endoscopy 1994;26:231-234.

2 Preiss C, Charton JP, Schumacher B, Neuhaus H: A randomized trial of unsedated transnasal small-caliber esophagogastroduodenoscopy (EGD) versus peroral small-caliber EGD versus conventional EGD. Endoscopy 2003;35:641-646.

3 Quine MA, Bell GD, McCloy RF, Charlton JE, Devlin HB, Hopkins A: Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods. Gut 1995;36:462-467.

4 Shaker R: Unsedated trans-nasal pharyngoesophagogastroduodenoscopy (T-EGD): technique. Gastrointest Endosc 1994;40:346-348.

5 Rozen P, Fireman Z, Gilat T: Arterial oxygen tension changes in elderly patients undergoing upper gastrointestinal endoscopy. II. Influence of the narcotic premedication and endoscope diameter. Scand J Gastroenterol 1981;16:299-303.

6 Rozen P, Fireman Z, Gilat T: The causes of hypoxemia in elderly patients during endoscopy. Gastrointest Endosc 1982;28:243-246.

7 Classen M, Phillip J: Electronic endoscopy of the gastrointestinal tract. Initial experience with a new type of endoscope that has no fiberoptic bundle for imaging. Endoscopy 1984;16:16-19.

8 Campo R, Montserrat A, Brullet E: Transnasal gastroscopy compared to conventional gastroscopy: a randomized study of feasibility, safety, and tolerance. Endoscopy 1998;30:448-452.

9 Dean R, Dua K, Massey B, Berger W, Hogan WJ, Shaker R: A comparative study of unsedated transnasal esophagogastroduodenoscopy and conventional EGD. Gastrointest Endosc 1996;44:422-424.

10 Dumortier J, Napoleon B, Hedelius F, Pellissier PE, Leprince E, Pujol B, Ponchon T: Unsedated transnasal EGD in daily practice: results with 1100 consecutive patients. Gastrointest Endosc 2003;57:198-204.

11 Stroppa I, Grasso E, Paoluzi OA, Razzini C, Tosti C, Andrei F, Biancone L, Palmieri G, Romeo F, Pallone F: Unsedated transnasal versus transoral sedated upper gastrointestinal endoscopy: a one-series prospective study on safety and patient acceptability. Dig Liver Dis 2008;40:767-775.

12 Thota PN, Zuccaro G, Jr., Vargo JJ, Conwell DL, Dumot JA, Xu M: A randomized prospective trial comparing unsedated esophagoscopy via transnasal and transoral routes using a 4-mm video endoscope with conventional endoscopy with sedation. Endoscopy 2005;37:559-565.

13 Trevisani L, Cifala V, Sartori S, Gilli G, Matarese G, Abbasciano V: Unsedated ultrathin upper endoscopy is better than conventional endoscopy in routine outpatient gastroenterology practice: a randomized trial. World J Gastroenterol 2007;13:906-911.

14 Dumonceau JM, Dumortier J, Deviere J, Kahaleh M, Ponchon T, Maffei M, Costamagna G: Transnasal OGD: practice survey and impact of a live video retransmission. Dig Liver Dis 2008;40:776-783.

15 Lee SY, Kawai T: Transnasal route: new approach to endoscopy. Gut Liver 2008;2:155-165.

16 Maffei M, Dumonceau JM: Transnasal esogastroduodenoscopy (EGD): comparison with conventional EGD and new applications. Swiss Med Wkly 2008;138:658-664.

17 Tatsumi Y, Harada A, Matsumoto T, Tani T, Nishida H: Current status and evaluation of transnasal esophagogastroduodenoscopy. Dig Endosc 2009;21:141-146.

18 Hosseinpour M, Behdad A: Evaluation of small bowel measurement in alive patients. Surg Radiol Anat 2008;30:653-655.

19 Sinnatamby CS: Abdomen: The Gastrointestinal Tract; in Sinnatamby CS, (ed): Last's Anatomy. Regional and Applied. Philadelphia, Elsevier/Churchill Livingstone, 2011, pp 233-252.

20 Yamamoto H, Sekine Y, Sato Y, Higashizawa T, Miyata T, Iino S, Ido K, Sugano K: Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc 2001;53:216-220.

21 Leighton JA: The role of endoscopic imaging of the small bowel in clinical practice. Am J Gastroenterol 2011;106:27-36.

22 Pasha SF, Leighton JA: Enteroscopy in the diagnosis and management of Crohn disease. Gastrointest Endosc Clin N Am 2009;19:427-444.

23 Iddan G, Meron G, Glukhovsky A, Swain P: Wireless capsule endoscopy. Nature 2000;405:417.

24 Cazzato IA, Cammarota G, Nista EC, Cesaro P, Sparano L, Bonomo V, Gasbarrini GB, Gasbarrini A: Diagnostic and therapeutic impact of double-balloon enteroscopy (DBE) in a series of 100 patients with suspected small bowel diseases. Dig Liver Dis 2007;39:483-487.

25 Ell C, May A, Nachbar L, Cellier C, Landi B, Di CS, Gasbarrini A: Push-and-pull enteroscopy in the small bowel using the double-balloon technique: results of a prospective European multicenter study. Endoscopy 2005;37:613-616.

26 Gerson LB: Double-balloon enteroscopy: the new gold standard for small-bowel imaging? Gastrointest Endosc 2005;62:71-75.

27 Gerson LB, Tokar J, Chiorean M, Lo S, Decker GA, Cave D, Bouhaidar D, Mishkin D, Dye C, Haluszka O, Leighton JA, Zfass A, Semrad C: Complications associated with

double balloon enteroscopy at nine US centers. Clin Gastroenterol Hepatol 2009;7:1177-82, 1182.

28 Gerson LB, Batenic MA, Ross A, Semrad C: Long-Term Outcomes after Double Balloon Enteroscopy for Obscure Gastrointestinal Bleeding. Clin Gastroenterol Hepatol 2009;7:664-669 .

29 Lo SK, Mehdizadeh S: Therapeutic uses of double-balloon enteroscopy. Gastrointest Endosc Clin N Am 2006;16:363-376.

30 Mensink PB, Haringsma J, Kucharzik T, Cellier C, Perez-Cuadrado E, Monkemuller K, Gasbarrini A, Kaffes AJ, Nakamura K, Yen HH, Yamamoto H: Complications of double balloon enteroscopy: a multicenter survey. Endoscopy 2007;39:613-615.

31 Mensink PB, Groenen MJ, van Buuren HR, Kuipers EJ, van der Woude CJ: Double-balloon enteroscopy in Crohn's disease patients suspected of small bowel activity: findings and clinical impact. J Gastroenterol 2009;44:271-276.

32 Mensink PB, Aktas H, Zelinkova Z, West RL, Kuipers EJ, van der Woude CJ: Impact of double-balloon enteroscopy findings on the management of Crohn's disease. Scand J Gastroenterol 2010;45:483-489.

33 Monkemuller K, Weigt J, Treiber G, Kolfenbach S, Kahl S, Rocken C, Ebert M, Fry LC, Malfertheiner P: Diagnostic and therapeutic impact of double-balloon enteroscopy. Endoscopy 2006;38:67-72.

34 Monkemuller K, Fry LC, Neumann H, Rickes S, Malfertheiner P: [Diagnostic and therapeutic utility of double balloon endoscopy: experience with 225 procedures]. Acta Gastroenterol Latinoam 2007;37:216-223.

35 Monkemuller K, Fry LC, Malfertheiner P: Double-balloon enteroscopy: beyond feasibility, what do we do now? Endoscopy 2007;39:229-231.

36 Monkemuller K, Fry LC, Ebert M, Bellutti M, Venerito M, Knippig C, Rickes S, Muschke P, Rocken C, Malfertheiner P: Feasibility of double-balloon enteroscopy-assisted chromoendoscopy of the small bowel in patients with familial adenomatous polyposis. Endoscopy 2007;39:52-57.

37 Monkemuller K, Bellutti M, Fry LC, Malfertheiner P: Enteroscopy. Best Pract Res Clin Gastroenterol 2008;22:789-811.

38 Moschler O, May AD, Muller MK, Ell C: [Complications in double-balloon-enteroscopy: results of the German DBE register]. Z Gastroenterol 2008;46:266-270.

39 Moschler O, May A, Muller MK, Ell C: Complications in and performance of double-balloon enteroscopy (DBE): results from a large prospective DBE database in Germany. Endoscopy 2011;43:484-489.

40 Murphy SJ, Kornbluth A: Double balloon enteroscopy in Crohn's disease: where are we now and where should we go? Inflamm Bowel Dis 2011;17:485-490.

41 Neumann H, Fry LC, Rickes S, Jurczok C, Malfertheiner P, Monkemuller K: A 'double-balloon enteroscopy worth the money': endoscopic removal of a coin lodged in the small bowel. Dig Dis 2008;26:388-389.

42 Pohl J, May A, Nachbar L, Ell C: Diagnostic and therapeutic yield of push-and-pull enteroscopy for symptomatic small bowel Crohn's disease strictures. Eur J Gastroenterol Hepatol 2007;19:529-534.

43 Pohl J, May A, Aschmoneit I, Ell C: Double-balloon endoscopy for retrograde cholangiography in patients with choledochojejunostomy and Roux-en-Y reconstruction. Z Gastroenterol 2009;47:215-219.

44 Thomson M, Venkatesh K, Elmalik K, van d, V, Jaacobs M: Double balloon enteroscopy in children: diagnosis, treatment, and safety. World J Gastroenterol 2010;16:56-62.

45 Yamamoto H, Yano T, Kita H, Sunada K, Ido K, Sugano K: New system of double-balloon enteroscopy for diagnosis and treatment of small intestinal disorders. Gastroenterology 2003;125:1556-1557.

46 Yamazaki R, Mori T, Nakazato T, Aisa Y, Imaeda H, Hisamatsu T, Hibi T, Okamoto S: Non-tuberculous mycobacterial infection localized in small intestine developing after allogeneic bone marrow transplantation. Intern Med 2010;49:1191-1193.

47 Yan KK, Kelly MI, Samuel DS: Direct endoscopic percutaneous jejunostomy placement with double balloon enteroscopy. Endoscopy 2010;42 Suppl 2:E43.

48 Yang CW, Chen YY, Yen HH, Soon MS: Successful double balloon enteroscopy treatment for bleeding jejunal diverticulum: a case report and review of the literature. J Laparoendosc Adv Surg Tech A 2009;19:637-640.

49 Yano T, Yamamoto H, Sunada K, Miura Y, Taguchi H, Arashiro M, Yoshizawa M, Hayashi Y, Miyata T, Tanaka H, Kobayashi E, Sugano K: New technique for direct percutaneous endoscopic jejunostomy using double-balloon endoscopy and magnetic anchors in a porcine model. Dig Endosc 2011;23:206.

50 May A, Nachbar L, Ell C: Double-balloon enteroscopy (push-and-pull enteroscopy) of the small bowel: feasibility and diagnostic and therapeutic yield in patients with suspected small bowel disease. Gastrointest Endosc 2005;62:62-70.

51 May A, Nachbar L, Schneider M, Neumann M, Ell C: Push-and-pull enteroscopy using the double-balloon technique: method of assessing depth of insertion and training of the enteroscopy technique using the Erlangen Endo-Trainer. Endoscopy 2005;37:66-70.

52 May A, Ell C: Push-and-pull enteroscopy using the double-balloon technique/double-balloon enteroscopy. Dig Liver Dis 2006;38:932-938.

53 May A, Ell C: European experiences with push-and-pull enteroscopy in double-balloon technique (double-balloon enteroscopy). Gastrointest Endosc Clin N Am 2006;16:377-382.

54 Yamamoto H, Sugano K: A new method of enteroscopy--the double-balloon method. Can J Gastroenterol 2003;17:273-274.

55 Hartmann D, Eickhoff A, Tamm R, Riemann JF: Balloon-assisted enteroscopy using a single-balloon technique. Endoscopy 2007;39 Suppl 1:E276.

56 Tsujikawa T, Saitoh Y, Andoh A, Imaeda H, Hata K, Minematsu H, Senoh K, Hayafuji K, Ogawa A, Nakahara T, Sasaki M, Fujiyama Y: Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: preliminary experiences. Endoscopy 2008;40:11-15.

57 Akerman PA, Agrawal D, Cantero D, Pangtay J: Spiral enteroscopy with the new DSB overtube: a novel technique for deep peroral small-bowel intubation. Endoscopy 2008;40:974-978.

58 Akerman PA, Cantero D: Spiral enteroscopy and push enteroscopy. Gastrointest Endosc Clin N Am 2009;19:357-369.

59 Despott EJ, Hughes S, Marden P, Fraser C: First cases of spiral enteroscopy in the UK: let's "torque" about it! Endoscopy 2010;42:517.

60 Frieling T, Heise J, Sassenrath W, Hulsdonk A, Kreysel C: Prospective comparison between double-balloon enteroscopy and spiral enteroscopy. Endoscopy 2010;42:885-888.

61 May A, Manner H, Aschmoneit I, Ell C: Prospective, cross-over, single-center trial comparing oral double-balloon enteroscopy and oral spiral enteroscopy in patients with suspected small-bowel vascular malformations. Endoscopy 2011;43:477-483.

62 Mensink PB: Spiral enteroscopy: from "new kid on the block" to established deep small-bowel enteroscopy tool. Endoscopy 2010;42:955-956.

63 Church JM: Complete colonoscopy: how often? And if not, why not? Am J Gastroenterol 1994;89:556-560.

64 Marshall JB, Barthel JS: The frequency of total colonoscopy and terminal ileal intubation in the 1990s. Gastrointest Endosc 1993;39:518-520.

65 Waye JD, Bashkoff E: Total colonoscopy: is it always possible? Gastrointest Endosc 1991;37:152-154.

66 Rex DK: Achieving cecal intubation in the very difficult colon. Gastrointest Endosc 2008;67:938-944.

67 Anderson JC, Gonzalez JD, Messina CR, Pollack BJ: Factors that predict incomplete colonoscopy: thinner is not always better. Am J Gastroenterol 2000;95:2784-2787.

68 Bernstein C, Thorn M, Monsees K, Spell R, O'Connor JB: A prospective study of factors that determine cecal intubation time at colonoscopy. Gastrointest Endosc 2005;61:72-75.

69 Chung YW, Han DS, Yoo KS, Park CK: Patient factors predictive of pain and difficulty during sedation-free colonoscopy: a prospective study in Korea. Dig Liver Dis 2007;39:872-876.

70 Hsieh YH, Kuo CS, Tseng KC, Lin HJ: Factors that predict cecal insertion time during sedated colonoscopy: the role of waist circumference. J Gastroenterol Hepatol 2008;23:215-217.

71 Kim WH, Cho YJ, Park JY, Min PK, Kang JK, Park IS: Factors affecting insertion time and patient discomfort during colonoscopy. Gastrointest Endosc 2000;52:600-605.

72 Oh SY, Sohn CI, Sung IK, Park DI, Kang MS, Yoo TW, Park JH, Kim HJ, Cho YK, Jeon WK, Kim BI: Factors affecting the technical difficulty of colonoscopy. Hepatogastroenterology 2007;54:1403-1406.

73 Park DI, Kim HJ, Park JH, Cho YK, Sohn CI, Jeon WK, Kim BI, Ryu SH, Sung IK: Factors affecting abdominal pain during colonoscopy. Eur J Gastroenterol Hepatol 2007;19:695-699.

74 Ristikankare M, Hartikainen J, Heikkinen M, Janatuinen E, Julkunen R: The effects of gender and age on the colonoscopic examination. J Clin Gastroenterol 2001;32:69-75.

75 Saunders BP, Halligan S, Jobling C, Fukumoto M, Moussa ME, Williams CB, Bartram CI: Can barium enema indicate when colonoscopy will be difficult? Clin Radiol 1995;50:318-321.

76 Saunders BP, Fukumoto M, Halligan S, Jobling C, Moussa ME, Bartram CI, Williams CB: Why is colonoscopy more difficult in women? Gastrointest Endosc 1996;43:124-126.

77 Takahashi Y, Tanaka H, Kinjo M, Sakumoto K: Prospective evaluation of factors predicting difficulty and pain during sedation-free colonoscopy. Dis Colon Rectum 2005;48:1295-1300.

78 Witte TN, Enns R: The difficult colonoscopy. Can J Gastroenterol 2007;21:487-490.

79 Yoshikawa I, Honda H, Nagata K, Kanda K, Yamasaki T, Kume K, Tabaru A, Otsuki M: Variable stiffness colonoscopes are associated with less pain during colonoscopy in unsedated patients. Am J Gastroenterol 2002;97:3052-3055.

80 Cirocco WC, Rusin LC: Factors that predict incomplete colonoscopy. Dis Colon Rectum 1995;38:964-968.

81 Hull T, Church JM: Colonoscopy--how difficult, how painful? Surg Endosc 1994;8:784-787.

82 Sadahiro S, Ohmura T, Yamada Y, Saito T, Taki Y: Analysis of length and surface area of each segment of the large intestine according to age, sex and physique. Surg Radiol Anat 1992;14:251-257.

83 Shah HA, Paszat LF, Saskin R, Stukel TA, Rabeneck L: Factors associated with incomplete colonoscopy: a population-based study. Gastroenterology 2007;132:2297-2303.

84 Waye JD: Completing colonoscopy. Am J Gastroenterol 2000;95:2681-2682.

85 Elphick DA, Donnelly MT, Smith KS, Riley SA: Factors associated with abdominal discomfort during colonoscopy: a prospective analysis. Eur J Gastroenterol Hepatol 2009;21:1076-1082.

86 Gray EJ, Marteinsson BT: Dolichocolon: indications for operation. Am Surg 1971;37:509-511.

87 Hughes ES, McDermott FT, Johnson WR, Polglase AL: Surgery for constipation. Aust N Z J Surg 1981;51:144-148.

88 Kessler H, Hohenberger W: Laparoscopic total colectomy for slow-transit constipation. Dis Colon Rectum 2005;48:860-861.

89 Lennard-Jones JE: Constipation.; in Feldman M, Freidman LS, Sleisenger MH, (eds): Sleisenger and Fordtran's gastrointestinal and liver diseases. Philadelphia, Saunders, 2002, pp 181-210.

90 McMahon JM, Underwood ES, Kirby WE: Colonic spasm and pseudo-obstruction in an elongated colon secondary to physical exertion: diagnosis by stress barium enema. Am J Gastroenterol 1999;94:3362-3364.

91 Ripetti V, Caputo D, Greco S, Alloni R, Coppola R: Is total colectomy the right choice in intractable slow-transit constipation? Surgery 2006;140:435-440.

92 Hotta K, Katsuki S, Ohata K, Abe T, Endo M, Shimatani M, Nagaya T, Kusaka T, Matsuda T, Uraoka T, Yamaguchi Y, Murakami Y, Saito Y: A multicenter, prospective trial of total colonoscopy using a short double-balloon endoscope in patients with previous incomplete colonoscopy. Gastrointest Endosc 2012;75:813-818.

93 Jackson CS, Haq T, Olafsson S: Push enteroscopy has a 96% cecal intubation rate in colonoscopies that failed because of redundant colons. Gastrointest Endosc 2011;74:341-346.

94 Kaltenbach T, Soetikno R, Friedland S: Use of a double balloon enteroscope facilitates caecal intubation after incomplete colonoscopy with a standard colonoscope. Dig Liver Dis 2006;38:921-925.

95 Keswani RN: Single-balloon colonoscopy versus repeat standard colonoscopy for previous incomplete colonoscopy: a randomized, controlled trial. Gastrointest Endosc 2011;73:507-512.

96 Moreels TG, Pelckmans PA: Double-balloon endoscope for failed conventional colonoscopy. Clin Gastroenterol Hepatol 2008;6:259.

97 Okamoto R, Motomura Y, Akahoshi K, Kashiwabara Y, Endo S, Higucchi N, Oda M, Kubokawa M, Matsui N, Nakamura K, Takayanagi R: Is double-balloon colonoscopy a better aid to unskilled colonoscopists than conventional colonoscopy? Fukuoka Igaku Zasshi 2011;102:333-340.

98 Rex DK, Goodwine BW: Method of colonoscopy in 42 consecutive patients presenting after prior incomplete colonoscopy. Am J Gastroenterol 2002;97:1148-1151.

99 Rex DK, Chen SC, Overhiser AJ: Colonoscopy technique in consecutive patients referred for prior incomplete colonoscopy. Clin Gastroenterol Hepatol 2007;5:879-883.

100 Vemulapalli KC, Rex DK: Evolving techniques in colonoscopy. Curr Opin Gastroenterol 2011;27:430-438.

101 Ambardar S, Arnell TD, Whelan RL, Nihalani A, Forde KA: A preliminary prospective study of the usefulness of a magnetic endoscope locating device during colonoscopy. Surg Endosc 2005;19:897-901.

102 Dai J, Feng N, Lu H, Li XB, Yang CH, Ge ZZ: Transparent cap improves patients' tolerance of colonoscopy and shortens examination time by inexperienced endoscopists. J Dig Dis 2010;11:364-368.

103 Hoff G, Bretthauer M, Dahler S, Huppertz-Hauss G, Sauar J, Paulsen J, Seip B, Moritz V: Improvement in caecal intubation rate and pain reduction by using 3-dimensional magnetic imaging for unsedated colonoscopy: a randomized trial of patients referred for colonoscopy. Scand J Gastroenterol 2007;42:885-889.

104 Jess P, Bulut O, Almasi A, Waaddegaard P: The usefulness of a magnetic endoscope locating device in colonoscopy in daily practice: a prospective case-controlled study. Surg Endosc 2009;23:1353-1355.

105 Kozarek RA, Botoman VA, Patterson DJ: Prospective evaluation of a small caliber upper endoscope for colonoscopy after unsuccessful standard examination. Gastrointest Endosc 1989;35:333-335.

106 Lee YT, Hui AJ, Wong VW, Hung LC, Sung JJ: Improved colonoscopy success rate with a distally attached mucosectomy cap. Endoscopy 2006;38:739-742.

107 Lee YT, Lai LH, Hui AJ, Wong VW, Ching JY, Wong GL, Wu JC, Chan HL, Leung WK, Lau JY, Sung JJ, Chan FK: Efficacy of cap-assisted colonoscopy in comparison with regular colonoscopy: a randomized controlled trial. Am J Gastroenterol 2009;104:41-46.

108 Ness RM, Gottlieb K, Rex DK, Lehman GA: Difficult sigmoid colon intubation: guide wire exchange technique. Gastrointest Endosc 1996;44:99-101.

109 Shah SG, Brooker JC, Williams CB, Thapar C, Saunders BP: Effect of magnetic endoscope imaging on colonoscopy performance: a randomised controlled trial. Lancet 2000;356:1718-1722.

110 Shah SG, Saunders BP, Brooker JC, Williams CB: Magnetic imaging of colonoscopy: an audit of looping, accuracy and ancillary maneuvers. Gastrointest Endosc 2000;52:1-8.

111 Shah SG, Brooker JC, Thapar C, Williams CB, Saunders BP: Patient pain during colonoscopy: an analysis using real-time magnetic endoscope imaging. Endoscopy 2002;34:435-440.

112 Shah SG, Brooker JC, Thapar C, Suzuki N, Williams CB, Saunders BP: Effect of magnetic endoscope imaging on patient tolerance and sedation requirements during colonoscopy: a randomized controlled trial. Gastrointest Endosc 2002;55:832-837.

113 Suzuki T, Matsushima M, Tsukune Y, Fujisawa M, Yazaki T, Uchida T, Gocyo S, Okita I, Shirakura K, Sasao K, Saito T, Sakamoto I, Igarashi M, Koike J, Takagi A, Mine T: Double-balloon endoscopy versus magnet-imaging enhanced colonoscopy for difficult colonoscopies, a randomized study. Endoscopy 2012;44:38-42.

114 Waye JD: Imaging of the colonoscope: magnetic, fluoroscopic, or neither? Gastrointest Endosc 2000;52:131-133.

115 Waye JD: The best way to painless colonoscopy. Endoscopy 2002;34:489-491.

116 Westwood DA, Alexakis N, Connor SJ: Transparent cap-assisted colonoscopy versus standard adult colonoscopy: a systematic review and meta-analysis. Dis Colon Rectum 2012;55:218-225.

117 Gay G, Delvaux M: Double-balloon colonoscopy after failed conventional colonoscopy: a pilot series with a new instrument. Endoscopy 2007;39:788-792.

118 Matsushita M, Shimatani M, Tanaka T, Fukata N, Kawamata S, Okazaki K: Short double-balloon enteroscope for previously failed colonoscopy. Gastrointest Endosc 2011;73:854-855.

119 May A, Nachbar L, Ell C: Push-and-pull enteroscopy using a single-balloon technique for difficult colonoscopy. Endoscopy 2006;38:395-398.

120 Monkemuller K, Knippig C, Rickes S, Fry LC, Schulze A, Malfertheiner P: Usefulness of the double-balloon enteroscope in colonoscopies performed in patients with previously failed colonoscopy. Scand J Gastroenterol 2007;42:277-278.

121 Moreels TG, Macken EJ, Roth B, Van Outryve MJ, Pelckmans PA: Cecal intubation rate with the double-balloon endoscope after incomplete conventional colonoscopy: a study in 45 patients. J Gastroenterol Hepatol 2010;25:80-83.

122 Pasha SF, Harrison ME, Das A, Corrado CM, Arnell KN, Leighton JA: Utility of double-balloon colonoscopy for completion of colon examination after incomplete colonoscopy with conventional colonoscope. Gastrointest Endosc 2007;65:848-853.

123 Sugano K, Yamamoto H, Kita H: Double-balloon endoscopy: theory and practice. ed 1, Tokyo, Spinger, 2006.

124 Moreels TG, Macken EJ, Roth B, Van Outryve MJ, Pelckmans PA: Cecal intubation rate with the double-balloon endoscope after incomplete conventional colonoscopy: A study in 45 patients. J Gastroenterol Hepatol 2009;25:80-83.

125 Abraham NS, Fallone CA, Mayrand S, Huang J, Wieczorek P, Barkun AN: Sedation versus no sedation in the performance of diagnostic upper gastrointestinal endoscopy: a Canadian randomized controlled cost-outcome study. Am J Gastroenterol 2004;99:1692-1699.

126 Bell GD: Review article: premedication and intravenous sedation for upper gastrointestinal endoscopy. Aliment Pharmacol Ther 1990;4:103-122.

127 Mokhashi MS, Hawes RH: Struggling toward easier endoscopy. Gastrointest Endosc 1998;48:432-440.

128 Rimmer KP, Graham K, Whitelaw WA, Field SK: Mechanisms of hypoxemia during panendoscopy. J Clin Gastroenterol 1989;11:17-22.

129 WMA: World Medical Association Declaration of Helsinki; http://www.wma.net/en/30publications/10policies/b3/index.html; 2008.

130 Jensen MP, Karoly P, Braver S: The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27:117-126.

131 EDWARDS AL, KENNEY KC: A comparison of the Thurstone and Likert techniques of attitude scale construction. J Appl Psychol 1946;30:72-83.

132 Moher D, Schulz KF, Altman D: The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-1991.

133 Choe WH, Kim JH, Ko SY, Kwon SY, Kim BK, Rhee KH, Seo TH, Lee TY, Hong SN, Lee SY, Sung IK, Park HS, Shim CS: Comparison of transnasal small-caliber vs. peroral conventional esophagogastroduodenoscopy for evaluating varices in unsedated cirrhotic patients. Endoscopy 2011; 43:649-656.

134 Frieling T, Schindler P, Kuhlbusch-Zicklam R, Heise J, Hulsdonk A, Kreysel C: Krefeld CONTRA study: conventional peroral Esophago-Gastro-Duodenoscopy (EGD) vs. transnasal EGD--a prospective and randomised study with independent evaluation of conscious sedation, endoscope diameter, and access path. Z Gastroenterol 2010;48:818-824.

135 Dumortier J, Ponchon T, Scoazec JY, Moulinier B, Zarka F, Paliard P, Lambert R: Prospective evaluation of transnasal esophagogastroduodenoscopy: feasibility and study on performance and tolerance. Gastrointest Endosc 1999;49:285-291.

136 Dumortier J, Josso C, Roman S, Fumex F, Lepilliez V, Prost B, Lot M, Guillaud O, Petit-Laurent F, Lapalus MG, Ponchon T: Prospective evaluation of a new ultrathin one-plane bending videoendoscope for transnasal EGD: a comparative study on performance and tolerance. Gastrointest Endosc 2007;66:13-19.

137 Teague R: BSG guideline on safety and sedation during endoscopic procedures. 2003. http://www.bsg.org.uk/clinical-guidelines/endoscopy/guidelines-on-safety-and-sedation-during-endoscopic-procedures.html; 2003.

138 Seip B, Bretthauer M, Dahler S, Friestad J, Huppertz-Hauss G, Hoie O, Kittang E, Nyhus S, Pallenschat J, Sandvei P, Stallemo A, Svendsen MV, Hoff G: Patient satisfaction with on-demand sedation for outpatient colonoscopy. Endoscopy 2010;42:639-646.

139 Tatsumi Y, Harada A, Matsumoto T, Tani T, Nishida H: Feasibility and tolerance of 2-way and 4-way angulation videoscopes for unsedated patients undergoing transnasal EGD in GI cancer screening. Gastrointest Endosc 2008;67:1021-1027.

140 Walter T, Chesnay AL, Dumortier J, Mege-LeChevallier F, Hervieu V, Guillaud O, Lapalus MG, Lepilliez V, Fumex F, Ponchon T, Scoazec JY: Biopsy specimens obtained

with small-caliber endoscopes have comparable diagnostic performances than those obtained with conventional endoscopes: a prospective study on 1335 specimens. J Clin Gastroenterol 2010;44:12-17.

141 Rodriguez SA, Banerjee S, Desilets D, Diehl DL, Farraye FA, Kaul V, Kwon RS, Mamula P, Pedrosa MC, Varadarajulu S, Song LM, Tierney WM: Ultrathin endoscopes. Gastrointest Endosc 2010;71:893-898.

142 Cohen LB, Ladas SD, Vargo JJ, Paspatis GA, Bjorkman DJ, Van der Linden P, Axon AT, Axon AE, Bamias G, Despott E, Dinis-Ribeiro M, Fassoulaki A, Hofmann N, Karagiannis JA, Karamanolis D, Maurer W, O'Connor A, Paraskeva K, Schreiber F, Triantafyllou K, Viazis N, Vlachogiannakos J: Sedation in digestive endoscopy: the Athens international position statements. Aliment Pharmacol Ther 2010;32:425-442.

143 Despott EJ, Schreiber F: Advanced cardiac life support training. Digestion 2010;82:113-114.

144 Postma GN, Cohen JT, Belafsky PC, Halum SL, Gupta SK, Bach KK, Koufman JA: Transnasal esophagoscopy: revisited (over 700 consecutive cases). Laryngoscope 2005;115:321-323.

145 Garcia RT, Cello JP, Nguyen MH, Rogers SJ, Rodas A, Trinh HN, Stollman NH, Schlueck G, McQuaid KR: Unsedated ultrathin EGD is well accepted when compared with conventional sedated EGD: a multicenter randomized trial. Gastroenterology 2003;125:1606-1612.

146 Gorelick AB, Inadomi JM, Barnett JL: Unsedated small-caliber esophagogastroduodenoscopy (EGD): less expensive and less time-consuming than conventional EGD. J Clin Gastroenterol 2001;33:210-214.

147 Ross AS: A decade of double-balloon enteroscopy: what have we learned? Gastrointest Endosc 2011;74:571-572.

148 Xin L, Liao Z, Jiang YP, Li ZS: Indications, detectability, positive findings, total enteroscopy, and complications of diagnostic double-balloon endoscopy: a systematic review of data over the first decade of use. Gastrointest Endosc 2011;74:563-570.

149 Delvaux M, Gay G: International Conference on Capsule and Double-Balloon Endoscopy (ICCD). Paris, 27-28 August 2010. Endoscopy 2011;43:533-539.

150 Gay G, Delvaux M, Fassler I: Outcome of capsule endoscopy in determining indication and route for push-and-pull enteroscopy. Endoscopy 2006;38:49-58.

151 Cotton PB, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, Mergener K, Nemcek A, Jr., Petersen BT, Petrini JL, Pike IM, Rabeneck L, Romagnuolo J, Vargo JJ: A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71:446-454.

152 Mehdizadeh S, Ross A, Gerson L, Leighton J, Chen A, Schembre D, Chen G, Semrad C, Kamal A, Harrison EM, Binmoeller K, Waxman I, Kozarek R, Lo SK: What is the learning curve associated with double-balloon enteroscopy? Technical details and early experience in 6 U.S. tertiary care centers. Gastrointest Endosc 2006;64:740-750.

153 Mehdizadeh S, Han NJ, Cheng DW, Chen GC, Lo SK: Success rate of retrograde double-balloon enteroscopy. Gastrointest Endosc 2007;65:633-639.

154 Domagk D, Bretthauer M, Lenz P, Aabakken L, Ullerich H, Maaser C, Domschke W, Kucharzik T: Carbon dioxide insufflation improves intubation depth in double-balloon enteroscopy: a randomized, controlled, double-blind trial. Endoscopy 2007;39:1064-1067.

155 May A, Farber M, Aschmoneit I, Pohl J, Manner H, Lotterer E, Moschler O, Kunz J, Gossner L, Monkemuller K, Ell C: Prospective multicenter trial comparing push-and-pull enteroscopy with the single- and double-balloon techniques in patients with small-bowel disorders. Am J Gastroenterol 2010;105:575-581.

156 Gerson LB, Flodin JT, Miyabayashi K: Balloon-assisted enteroscopy: technology and troubleshooting. Gastrointest Endosc 2008;68:1158-1167.

157 Mehdizadeh S, Lo SK: Treatment of small-bowel diaphragm disease by using double-balloon enteroscopy. Gastrointest Endosc 2006;64:1014-1017.

158 Heine GD, Hadithi M, Groenen MJ, Kuipers EJ, Jacobs MA, Mulder CJ: Double-balloon enteroscopy: indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease. Endoscopy 2006;38:42-48.

159 Tee HP, How SH, Kaffes AJ: Learning curve for double-balloon enteroscopy: Findings from an analysis of 282 procedures. World J Gastrointest Endosc 2012;4:368-372.

160 Gross SA, Stark ME: Initial experience with double-balloon enteroscopy at a U.S. center. Gastrointest Endosc 2008;67:890-897.

161 Gupta S, Anderson J, Bhandari P, McKaig B, Rupert P, Rembacken B, Riley S, Rutter M, Valori R, Vance M, van der Vleuten CP, Saunders BP, Thomas-Gibson S: Development and validation of a novel method for assessing competency in polypectomy: direct observation of polypectomy skills. Gastrointest Endosc 2011;73:1232-1239.

162 Gupta S, Bassett P, Man R, Suzuki N, Vance ME, Thomas-Gibson S: Validation of a novel method for assessing competency in polypectomy. Gastrointest Endosc 2012;75:568-575.

163 Haycock A, Koch AD, Familiari P, van DF, Dekker E, Petruzziello L, Haringsma J, Thomas-Gibson S: Training and transfer of colonoscopy skills: a multinational, randomized, blinded, controlled trial of simulator versus bedside training. Gastrointest Endosc 2010;71:298-307.

164 Haycock AV, Bassett P, Bladen J, Thomas-Gibson S: Validation of the second-generation Olympus colonoscopy simulator for skills assessment. Endoscopy 2009;41:952-958.

165 Haycock AV, Patel JH, Tekkis PP, Thomas-Gibson S: Evaluating changes in gastrointestinal endoscopy training over 5 years: closing the audit loop. Eur J Gastroenterol Hepatol 2010;22:368-373.

166 Ross AS, Waxman I, Semrad C, Dye C: Balloon-assisted intubation of the ileocecal valve to facilitate retrograde double-balloon enteroscopy. Gastrointest Endosc 2005;62:987-988.

167 Despott E, Fraser C: Achieving successful ileal intubation during retrograde double balloon enteroscopy: description of a novel, alternative technique (with video). Endoscopy 2009;41 Suppl 2:E309-E310.

168 Despott EJ, Murino A, Fraser C: Management of deep looping when failing to progress at double-balloon enteroscopy. Endoscopy 2011;43 Suppl 2 UCTN:E275-E276.

169 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG: Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases with Time, Based on Systematic Review. Gastroenterology 2011;42:46-54.

170 Cosnes J, Gower-Rousseau C, Seksik P, Cortot A: Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology 2011;140:1785-1794.

171 Bourreille A, Ignjatovic A, Aabakken L, Loftus EV, Jr., Eliakim R, Pennazio M, Bouhnik Y, Seidman E, Keuchel M, Albert JG, Ardizzone S, Bar-Meir S, Bisschops R, Despott EJ, Fortun PF, Heuschkel R, Kammermeier J, Leighton JA, Mantzaris GJ, Moussata D, Lo S, Paulsen V, Panes J, Radford-Smith G, Reinisch W, Rondonotti E, Sanders DS, Swoger JM, Yamamoto H, Travis S, Colombel JF, Van GA: Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. Endoscopy 2009;41:618-637.

172 Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J: Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. Gut 2001;49:777-782.

173 Van AG, Rutgeerts P: Medical management of postoperative recurrence in Crohn's disease. Gastroenterol Clin North Am 2004;33:347-60, x.

174 Gardiner KR, Dasari BV: Operative management of small bowel Crohn's disease. Surg Clin North Am 2007;87:587-610.

175 Greenstein AJ, Meyers S, Sher L, Heimann T, Aufses AH, Jr.: Surgery and its sequelae in Crohn's colitis and ileocolitis. Arch Surg 1981;116:285-288.

176 Lee EC, Papaioannou N: Minimal surgery for chronic obstruction in patients with extensive or universal Crohn's disease. Ann R Coll Surg Engl 1982;64:229-233.

177 Parker MC, Wilson MS, Menzies D, Sunderland G, Clark DN, Knight AD, Crowe AM: The SCAR-3 study: 5-year adhesion-related readmission risk following lower abdominal surgical procedures. Colorectal Dis 2005;7:551-558.

178 Kita H, Yamamoto H, Yano T, Miyata T, Iwamoto M, Sunada K, Arashiro M, Hayashi Y, Ido K, Sugano K: Double balloon endoscopy in two hundred fifty cases for the diagnosis and treatment of small intestinal disorders. Inflammopharmacology 2007;15:74-77.

179 May A, Nachbar L, Pohl J, Ell C: Endoscopic interventions in the small bowel using double balloon enteroscopy: feasibility and limitations. Am J Gastroenterol 2007;102:527-535.

180 Alexander-Williams J, Allan A, Morel P, Hawker PC, Dykes PW, O'Connor H: The therapeutic dilatation of enteric strictures due to Crohn's disease. Ann R Coll Surg Engl 1986;68:95-97.

181 Aston NO, Owen WJ, Irving JD: Endoscopic balloon dilatation of colonic anastomotic strictures. Br J Surg 1989;76:780-782.

182 Kelly SM, Hunter JO: Endoscopic balloon dilatation of duodenal strictures in Crohn's disease. Postgrad Med J 1995;71:623-624.

183 Williams AJ, Palmer KR: Endoscopic balloon dilatation as a therapeutic option in the management of intestinal strictures resulting from Crohn's disease. Br J Surg 1991;78:453-454.

184 Morini S, Hassan C, Lorenzetti R, Zullo A, Cerro P, Winn S, Giustini M, Taggi F: Long-term outcome of endoscopic pneumatic dilatation in Crohn's disease. Dig Liver Dis 2003;35:893-897.

185 Tichansky D, Cagir B, Yoo E, Marcus SM, Fry RD: Strictureplasty for Crohn's disease: meta-analysis. Dis Colon Rectum 2000;43:911-919.

186 Couckuyt H, Gevers AM, Coremans G, Hiele M, Rutgeerts P: Efficacy and safety of hydrostatic balloon dilatation of ileocolonic Crohn's strictures: a prospective longterm analysis. Gut 1995;36:577-580.

187 Thomas-Gibson S, Brooker JC, Hayward CM, Shah SG, Williams CB, Saunders BP: Colonoscopic balloon dilation of Crohn's strictures: a review of long-term outcomes. Eur J Gastroenterol Hepatol 2003;15:485-488.

188 Despott EJ, Gupta A, Burling D, Tripoli E, Konieczko K, Hart A, Fraser C: Effective dilation of small-bowel strictures by double-balloon enteroscopy in patients with symptomatic Crohn's disease (with video). Gastrointest Endosc 2009;70:1030-1036.

189 Hirai F, Beppu T, Sou S, Seki T, Yao K, Matsui T: Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. Dig Endosc 2010;22:200-204.

190 Aretz S, Stienen D, Uhlhaas S, Loff S, Back W, Pagenstecher C, McLeod DR, Graham GE, Mangold E, Santer R, Propping P, Friedl W: High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. Hum Mutat 2005;26:513-519.

191 Beggs AD, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, Bertario L, Blanco I, Bulow S, Burn J, Capella G, Colas C, Friedl W, Moller P, Hes FJ, Jarvinen H, Mecklin JP, Nagengast FM, Parc Y, Phillips RK, Hyer W, Ponz de LM, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen JT, Clark SK, Hodgson SV: Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut 2010;59:975-986.

192 Giardiello FM, Trimbath JD: Peutz-Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol 2006;4:408-415.

193 Utsunomiya J, Gocho H, Miyanaga T, Hamaguchi E, Kashimure A: Peutz-Jeghers syndrome: its natural course and management. Johns Hopkins Med J 1975;136:71-82.

194 Latchford AR, Neale K, Phillips RK, Clark SK: Peutz-Jeghers syndrome: intriguing suggestion of gastrointestinal cancer prevention from surveillance. Dis Colon Rectum 2011;54:1547-1551.

195 Latchford AR, Phillips RK: Gastrointestinal polyps and cancer in Peutz-Jeghers syndrome: clinical aspects. Fam Cancer 2011; 10:455-461.

196 van Lier MG, Mathus-Vliegen EM, Wagner A, van Leerdam ME, Kuipers EJ: High cumulative risk of intussusception in patients with Peutz-Jeghers syndrome: time to update surveillance guidelines? Am J Gastroenterol 2011;106:940-945.

197 van Lier MG, Westerman AM, Wagner A, Looman CW, Wilson JH, de Rooij FW, Lemmens VE, Kuipers EJ, Mathus-Vliegen EM, van Leerdam ME: High cancer risk and increased mortality in patients with Peutz-Jeghers syndrome. Gut 2011;60:141-147.

198 Hyer W: Polyposis syndromes: pediatric implications. Gastrointest Endosc Clin N Am 2001;11:659-vii.

199 Hyer W. Implications of Peutz-Jeghers Syndrome in Children and Adolescents. In: Riegert-Johnson DL, Boardman LA, Hefferon T, et al., editors. Cancer Syndromes [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2009- ebook. Available from: http://www.ncbi.nlm.nih.gov/books/NBK26374.

200 Will OC, Phillips RK, Hyer W, Clark SK: Symptomatic polyposis in a 4-year-old: the exception proves the rule. J Paediatr Child Health 2009;45:320-321.

201 Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, Booker SV, Krush AJ, Yardley JH, Luk GD: Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 1987;316:1511-1514.

202 Oncel M, Remzi FH, Church JM, Connor JT, Fazio VW: Benefits of 'clean sweep' in Peutz-Jeghers patients. Colorectal Dis 2004;6:332-335.

203 Spigelman AD, Thomson JP, Phillips RK: Towards decreasing the relaparotomy rate in the Peutz-Jeghers syndrome: the role of peroperative small bowel endoscopy. Br J Surg 1990;77:301-302.

204 Parker MC, Ellis H, Moran BJ, Thompson JN, Wilson MS, Menzies D, McGuire A, Lower AM, Hawthorn RJ, O'Briena F, Buchan S, Crowe AM: Postoperative adhesions: ten-year follow-up of 12,584 patients undergoing lower abdominal surgery. Dis Colon Rectum 2001;44:822-829.

205 Pennazio M, Rossini FP: Small bowel polyps in Peutz-Jeghers syndrome: management by combined push enteroscopy and intraoperative enteroscopy. Gastrointest Endosc 2000;51:304-308.

206 You YN, Wolff BG, Boardman LA, Riegert-Johnson DL, Qin R: Peutz-Jeghers syndrome: a study of long-term surgical morbidity and causes of mortality. Fam Cancer 2010;9:609-616.

207 Gao H, van Lier MG, Poley JW, Kuipers EJ, van Leerdam ME, Mensink PB: Endoscopic therapy of small-bowel polyps by double-balloon enteroscopy in patients with Peutz-Jeghers syndrome. Gastrointest Endosc 2010;71:768-773.

208 Kopacova M, Tacheci I, Rejchrt S, Bures J: Peutz-Jeghers syndrome: diagnostic and therapeutic approach. World J Gastroenterol 2009;15:5397-5408.

209 Chen TH, Lin WP, Su MY, Hsu CM, Chiu CT, Chen PC, Kong MS, Lai MW, Yeh TS: Balloon-assisted enteroscopy with prophylactic polypectomy for Peutz-Jeghers syndrome: experience in Taiwan. Dig Dis Sci 2011;56:1472-1475.

210 Ohmiya N, Taguchi A, Shirai K, Mabuchi N, Arakawa D, Kanazawa H, Ozeki M, Yamada M, Nakamura M, Itoh A, Hirooka Y, Niwa Y, Nagasaka T, Ito M, Ohashi S, Okamura S, Goto H: Endoscopic resection of Peutz-Jeghers polyps throughout the small intestine at double-balloon enteroscopy without laparotomy. Gastrointest Endosc 2005;61:140-147.

211 Ohmiya N, Nakamura M, Takenaka H, Morishima K, Yamamura T, Ishihara M, Miyahara R, Kawashima H, Itoh A, Hirooka Y, Watanabe O, Ando T, Goto H: Management of small-bowel polyps in Peutz-Jeghers syndrome by using enteroclysis, double-balloon enteroscopy, and videocapsule endoscopy. Gastrointest Endosc 2010;72:1209-1216.

212 Sakamoto H, Yamamoto H, Hayashi Y, Yano T, Miyata T, Nishimura N, Shinhata H, Sato H, Sunada K, Sugano K: Nonsurgical management of small-bowel polyps in Peutz-Jeghers syndrome with extensive polypectomy by using double-balloon endoscopy. Gastrointest Endosc 2011;74:328-333.

213 Aaltonen LA, Jarvinen H, Gruber SB, Billaud M, Jass JR: Tumours of the Small Intestine; in Hamilton SR, Aaltonen LA, (eds): World Health Organisation Classification of Tumours. Pathology and Genetics of Tumuors of the Digestive System. Lyon, IARC Press, 2000, pp 74-77.

214 Gupta A, Postgate AJ, Burling D, Ilangovan R, Marshall M, Phillips RK, Clark SK, Fraser CH: A prospective study of MR enterography versus capsule endoscopy for the surveillance of adult patients with Peutz-Jeghers syndrome. AJR Am J Roentgenol 2010;195:108-116.

215 von EE, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453-1457.

216 Ross AS, Dye C, Prachand VN: Laparoscopic-assisted double-balloon enteroscopy for small-bowel polyp surveillance and treatment in patients with Peutz-Jeghers syndrome. Gastrointest Endosc 2006;64:984-988.

217 DiSario JA, Baskin WN, Brown RD, Delegge MH, Fang JC, Ginsberg GG, McClave SA: Endoscopic approaches to enteral nutritional support. Gastrointest Endosc 2002;55:901-908.

218 Pearce CB, Duncan HD: Enteral feeding. Nasogastric, nasojejunal, percutaneous endoscopic gastrostomy, or jejunostomy: its indications and limitations. Postgrad Med J 2002;78:198-204.

219 Delegge MH: Small bowel endoscopic enteral access. Gastrointest Endosc Clin N Am 2007;17:663-686.

220 DiSario JA, Foutch PG, Sanowski RA: Poor results with percutaneous endoscopic jejunostomy. Gastrointest Endosc 1990;36:257-260.

221 Fan AC, Baron TH, Rumalla A, Harewood GC: Comparison of direct percutaneous endoscopic jejunostomy and PEG with jejunal extension. Gastrointest Endosc 2002;56:890-894.

222 Baskin W, Johanson JF: Trans-PEG ultra thin endoscopy for PEG/J Placement. Gastrointest Endosc 2003;57:146-147.

223 Delegge MH, Duckworth PF, Jr., McHenry L, Jr., Foxx-Orenstein A, Craig RM, Kirby DF: Percutaneous endoscopic gastrojejunostomy: a dual center safety and efficacy trial. JPEN J Parenter Enteral Nutr 1995;19:239-243.

224 Delegge MH, Patrick P, Gibbs R: Percutaneous endoscopic gastrojejunostomy with a tapered tip, nonweighted jejunal feeding tube: improved placement success. Am J Gastroenterol 1996;91:1130-1134.

225 Floch MH: Indications for percutaneous gastrostomy (jejunostomy) (PEG/J). Am J Gastroenterol 1990;85:1074-1075.

226 Oksuzoglu G, Kav T, Ates Y, Bagci S: A trick for performing PEG-J more quickly. Endoscopy 2008;40 Suppl 2:E184.

227 Ott L, Annis K, Hatton J, McClain M, Young B: Postpyloric enteral feeding costs for patients with severe head injury: blind placement, endoscopy, and PEG/J versus TPN. J Neurotrauma 1999;16:233-242.

228 Rumalla A, Baron TH: Results of direct percutaneous endoscopic jejunostomy, an alternative method for providing jejunal feeding. Mayo Clin Proc 2000;75:807-810.

229 Wolfsen HC, Kozarek RA, Ball TJ, Patterson DJ, Botoman VA: Tube dysfunction following percutaneous endoscopic gastrostomy and jejunostomy. Gastrointest Endosc 1990;36:261-263.

230 Baron TH: Double-balloon enteroscopy to facilitate retrograde PEG placement as access for therapeutic ERCP in patients with long-limb gastric bypass. Gastrointest Endosc 2006;64:973-974.

231 Maple JT, Petersen BT, Baron TH, Gostout CJ, Wong Kee Song LM, Buttar NS: Direct percutaneous endoscopic jejunostomy: outcomes in 307 consecutive attempts. Am J Gastroenterol 2005;100:2681-2688.

232 Shike M, Schroy P, Ritchie MA, Lightdale CJ, Morse R: Percutaneous endoscopic jejunostomy in cancer patients with previous gastric resection. Gastrointest Endosc 1987;33:372-374.

233 Panagiotakis PH, DiSario JA, Hilden K, Ogara M, Fang JC: DPEJ tube placement prevents aspiration pneumonia in high-risk patients. Nutr Clin Pract 2008;23:172-175.

234 Baron TH: Direct percutaneous endoscopic jejunostomy. Am J Gastroenterol 2006;101:1407-1409.

235 Orlando-Lopez R, Ross AS, Dye CE, Semrad CE: Double Baloon Enteroscopy Facilitates Direct Percutaneous Endoscopic Jejunostomy Placement. Gastrointest Endosc 2008;67:AB266.

236 Banerjee S, Shen B, Baron TH, Nelson DB, Anderson MA, Cash BD, Dominitz JA, Gan SI, Harrison ME, Ikenberry SO, Jagannath SB, Lichtenstein D, Fanelli RD, Lee K, Van GT, Stewart LE: Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc 2008;67:791-798.

237 Ponsky JL, Gauderer MW: Percutaneous endoscopic gastrostomy: a nonoperative technique for feeding gastrostomy. Gastrointest Endosc 1981;27:9-11.

238 Despott EJ, Gabe S, Tripoli E, Konieczko K, Fraser C: Enteral access by double-balloon enteroscopy: an alternative method of direct percutaneous endoscopic jejunostomy placement. Dig Dis Sci 2011;56:494-498.

239 May A, Nachbar L, Wardak A, Yamamoto H, Ell C: Double-balloon enteroscopy: preliminary experience in patients with obscure gastrointestinal bleeding or chronic abdominal pain. Endoscopy 2003;35:985-991.

240 May A, Nachbar L, Ell C: Extraction of entrapped capsules from the small bowel by means of push-and-pull enteroscopy with the double-balloon technique. Endoscopy 2005;37:591-593.

241 May A, Nachbar L, Schneider M, Ell C: Prospective comparison of push enteroscopy and push-and-pull enteroscopy in patients with suspected small-bowel bleeding. Am J Gastroenterol 2006;101:2016-2024.

242 May A: Current status of double balloon enteroscopy with focus on the Wiesbaden results. Gastrointest Endosc 2007;66:S12-S14.

243 May A, Manner H, Schneider M, Ipsen A, Ell C: Prospective multicenter trial of capsule endoscopy in patients with chronic abdominal pain, diarrhea and other signs and symptoms (CEDAP-Plus Study). Endoscopy 2007;39:606-612.

244 May A: How to approach the small bowel with flexible enteroscopy. Gastroenterol Clin North Am 2010;39:797-806.

245 May A, Friesing-Sosnik T, Manner H, Pohl J, Ell C: Long-term outcome after argon plasma coagulation of small-bowel lesions using double-balloon enteroscopy in patients with mid-gastrointestinal bleeding. Endoscopy 2011;43:759-765.

246 Monkemuller K, Neumann H, Meyer F, Kuhn R, Malfertheiner P, Fry LC: A retrospective analysis of emergency double-balloon enteroscopy for small-bowel bleeding. Endoscopy 2009;41:715-717.

247 Monkemuller K, Fry LC, Kuhn R, Rickes S: Massive obscure overt gastrointestinal bleeding secondary to an ileal carcinoid diagnosed and treated using double-balloon enteroscopy. Endoscopy 2011;43 Suppl 2:E160-E161.

248 Monkemuller K, Zabielski M, Poppen D, Fry LC: Endoscopic removal of an impacted root canal needle in the jejunum using double-balloon enteroscopy. Gastrointest Endosc 2011;73:844-846.

249 Moreels TG, Op de BB, Pelckmans PA: Double-balloon enteroscopy to remove a strangulated enteroclysis catheter from the small bowel. Case Rep Gastroenterol 2008;2:250-255.

250 Moreels TG, Hubens GJ, Ysebaert DK, Op de BB, Pelckmans PA: Diagnostic and therapeutic double-balloon enteroscopy after small bowel Roux-en-Y reconstructive surgery. Digestion 2009;80:141-147.

251 Nakamura M, Niwa Y, Ohmiya N, Goto H: Which route should we select when performing double-balloon enteroscopy? Gastrointest Endosc 2008;67:577-578.

252 Nakamura N, Matsushita M, Tahashi Y, Shimatani M, Aoi K, Yanagawa M, Okazaki K: Diagnostic yield of double-balloon enteroscopy with intestinal juice analysis for intestinal strongyloidiasis. Dig Endosc 2010;22:370-372.

253 Nakashima Y, Nakamura I, Miyatani H, Yoshida Y, Konishi F, Yamada S: Double-balloon enteroscopy for diagnosis of Meckel's diverticulum in a patient with gastrointestinal bleeding. Endoscopy 2007;39 Suppl 1:E140-E141.

254 Norimura D, Isomoto H, Niino D, Akazawa Y, Yamaguchi N, Ohnita K, Shikuwa S, Takeshima F, Nakao K: Intestinal mantle cell lymphoma observed by double-balloon endoscopy with Fuji Intelligent Chromo Endoscopy. Endoscopy 2011;43 Suppl 2:E26-E27.

255 Nosho K, Endo T, Yoda Y, Yoshida M, Goto A, Yamashita K, Yamamoto H, Yoshida Y, Arimura Y, Hirata K, Imai K: Diaphragm disease of small intestine diagnosed by double-balloon enteroscopy. Gastrointest Endosc 2005;62:187-189.

256 O'Kelly F, Lim KT, Ravi N, Mahmud N, Reynolds JV: The value of double balloon enteroscopy in diagnosing blue rubber bleb naevus syndrome: a case report. Cases J 2010;3:29.

257 Okabe Y, Kuwaki K, Kawano H, Kaji R, Sugiyama G, Ishida Y, Yasumoto M, Naito Y, Toyonaga A, Tsuruta O, Sata M: Direct cholangioscopy using a double-balloon enteroscope: choledochojejunostomy with intraductal biliary carcinoma. Dig Endosc 2010;22:319-321.

258 Oshitani N, Yukawa T, Yamagami H, Inagawa M, Kamata N, Watanabe K, Jinno Y, Fujiwara Y, Higuchi K, Arakawa T: Evaluation of deep small bowel involvement by double-balloon enteroscopy in Crohn's disease. Am J Gastroenterol 2006;101:1484-1489.

259 Perez-Cuadrado E, Mas P, Hallal H, Shanabo J, Munoz E, Ortega I, Lopez MA, Torrella E, Lopez HA, Martin A, Carballo F: Double-balloon enteroscopy: a descriptive study of 50 explorations. Rev Esp Enferm Dig 2006;98:73-81.

260 Ross A, Mehdizadeh S, Tokar J, Leighton JA, Kamal A, Chen A, Schembre D, Chen G, Binmoeller K, Kozarek R, Waxman I, Dye C, Gerson L, Harrison ME, Haluszka O, Lo S, Semrad C: Double balloon enteroscopy detects small bowel mass lesions missed by capsule endoscopy. Dig Dis Sci 2008;53:2140-2143.

261 Ross A: Push-and-pull enteroscopy: one balloon or two? Am J Gastroenterol 2010;105:582-584.

262 Domagk D, Mensink P, Aktas H, Lenz P, Meister T, Luegering A, Ullerich H, Aabakken L, Heinecke A, Domschke W, Kuipers E, Bretthauer M: Single- vs. double-balloon enteroscopy in small-bowel diagnostics: a randomized multicenter trial. Endoscopy 2011;43:472-476.

263 Takano N, Yamada A, Watabe H, Togo G, Yamaji Y, Yoshida H, Kawabe T, Omata M, Koike K: Single-balloon versus double-balloon endoscopy for achieving total enteroscopy: a randomized, controlled trial. Gastrointest Endosc 2011;73:734-739.

264 Buscaglia JM, Dunbar KB, Okolo PI, III, Judah J, Akerman PA, Cantero D, Draganov PV: The spiral enteroscopy training initiative: results of a prospective study evaluating the Discovery SB overtube device during small bowel enteroscopy (with video). Endoscopy 2009;41:194-199.

265 Judah JR, Draganov PV, Lam Y, Hou W, Buscaglia JM: Spiral enteroscopy is safe and effective for an elderly United States population of patients with numerous comorbidities. Clin Gastroenterol Hepatol 2010;8:572-576.

266 Drug VL, Balan G, Sangeap AM, Akbar Q, Mitrica D, Dimofte G: Spiral enteroscopy--a novel method for the management of small bowel diseases--case report and description of technique. Rev Med Chir Soc Med Nat Iasi 2011;115:101-104.

267 Soria F, Lopez-Albors O, Morcillo E, Sarria R, Carballo F, Perez-Cuadrado E, Sanchez F, Latorre R: Experimental laparoscopic evaluation of double balloon versus spiral enteroscopy in an animal model. Dig Endosc 2011;23:98.

268 Logan RF, Patnick J, Nickerson C, Coleman L, Rutter MD, von WC: Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut 2011; 61:1439-1446.

269 Pawa N, Arulampalam T, Norton JD: Screening for colorectal cancer: established and emerging modalities. Nat Rev Gastroenterol Hepatol 2011;8:711-722.

270 Qaseem A, Denberg TD, Hopkins RH, Jr., Humphrey LL, Levine J, Sweet DE, Shekelle P: Screening for Colorectal Cancer: A Guidance Statement From the American College of Physicians. Ann Intern Med 2012;156:378-386.

271 Schembre DB, Ross AS, Gluck MN, Brandabur JJ, McCormick SE, Lin OS: Spiral overtube-assisted colonoscopy after incomplete colonoscopy in the redundant colon. Gastrointest Endosc 2011;73:515-519.

272 Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC: Functional bowel disorders. Gastroenterology 2006;130:1480-1491.

273 Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth Analg 1970;49:924-934.

274 Aldrete JA: Modifications to the postanesthesia score for use in ambulatory surgery. J Perianesth Nurs 1998;13:148-155.

275 Aldrete JA: Post-anesthetic recovery score. J Am Coll Surg 2007;205:e3-e4.

276 Maffei M, Dumortier J, Dumonceau JM: Self-training in unsedated transnasal EGD by endoscopists competent in standard peroral EGD: prospective assessment of the learning curve. Gastrointest Endosc 2008;67:410-418.

277 Lee YN, Moon JH, Choi HJ, Kim DC, Chung JH, Lee TH, Cha SW, Cho YD, Park SH, Kim SJ: Direct biliary drainage using transnasal endoscopy for patients with severe-to-moderate acute cholangitis. J Gastroenterol Hepatol 2013;28:739-743.

278 Mori A, Sakai K, Ohashi N, Maruyama T, Tatebe H, Shibuya T, Inoue H, Okuno M: Electrohydraulic lithotripsy of the common bile duct stone under transnasal direct cholangioscopy. Endoscopy 2008;40 Suppl 2:E63.

279 Pohl J, Ell C: Direct transnasal cholangioscopy with ultraslim endoscopes: a one-step intraductal balloon-guided approach. Gastrointest Endosc 2011;74:309-316.

280 Seo MS, Moon JH, Choi HJ, Kim HK, Cheon YK, Cho YD, Lee MS: Bile-Duct Stone Removal under Direct Transnasal Cholangioscopy Using an Ultraslim Upper Endoscope. Gut Liver 2010;4:428-429.

281 Despott EJ, Fraser C: Small bowel endoscopy in inflammatory bowel disease. Best Pract Res Clin Gastroenterol 2012;26:279-291.

282 Despott EJ, Warusavitarne J, Fraser C: Stricturing Crohn's disease; in Hart AL, Ng SC, (eds): Inflammatory Bowel Disease: An Evidence-based Practical Guide. Shrewsbury, tfm Publishing Limited, 2012, pp 133-144.

283 Alliet P, Desimpelaere J, Hauser B, Janssens E, Khamis J, Lewin M, De GE, Smets F, Paquot I, Veereman G, Souverijns G: MR enterography in children with Crohn disease: results from the Belgian pediatric Crohn registry (Belcro). Acta Gastroenterol Belg 2013;76:45-48.

284 Arrive L, El MS: MR enterography versus MR enteroclysis. Radiology 2013;266:688.

285 Davis JS, Ryan ML, Fields JM, Neville HL, Perez EA, Sola JE: Use of CT enterography for the diagnosis of lower gastrointestinal bleeding in pediatric patients. J Pediatr Surg 2013;48:681-684.

286 Ghonge NP, Aggarwal B, Gothi R: CT enterography: state-of-the-art CT technique for small bowel imaging. Indian J Gastroenterol 2013;32:152-162.

287 Hammer MR, Podberesky DJ, Dillman JR: Multidetector computed tomographic and magnetic resonance enterography in children: state of the art. Radiol Clin North Am 2013;51:615-636.

288 Hashimoto S, Shimizu K, Shibata H, Kanayama S, Tanabe R, Onoda H, Matsunaga N, Sakaida I: Utility of computed tomographic enteroclysis/enterography for the assessment of mucosal healing in Crohn's disease. Gastroenterol Res Pract 2013;2013:984916.

289 Huprich JE, Barlow JM, Hansel SL, Alexander JA, Fidler JL: Multiphase CT Enterography Evaluation of Small-Bowel Vascular Lesions. AJR Am J Roentgenol 2013;201:65-72.

290 Masselli G, Casciani E, Polettini E, Laghi F, Gualdi G: Magnetic resonance imaging of small bowel neoplasms. Cancer Imaging 2013;13:92-99.

291 Raman SP, Horton KM, Fishman EK: Computed tomography of Crohn's disease: The role of three dimensional technique. World J Radiol 2013;5:193-201.

292 Wang Z, Chen JQ, Liu JL, Qin XG, Huang Y: CT enterography in obscure gastrointestinal bleeding: A systematic review and meta-analysis. J Med Imaging Radiat Oncol 2013;57:263-273.

293 Albert JM: Radiation Risk From CT: Implications for Cancer Screening. AJR Am J Roentgenol 2013;201:W81-W87.

294 Badiani S, Tomas-Hernandez S, Karandikar S, Roy-Choudhury S: Extracolonic findings (ECF) on CT colonography (CTC) in patients presenting with colorectal symptoms. Acta Radiol 2013.

295 Furlow B: Computed tomography colonography. Radiol Technol 2013;84:493CT-511CT.

296 Halligan S: CT colonography for investigation of patients with symptoms potentially suggestive of colorectal cancer: a review of the UK SIGGAR trials. Br J Radiol 2013;86:20130137.

297 Halligan S, Atkin WS: CT colonography for diagnosis of symptomatic colorectal cancer: The SIGGAR trials and their implication for service delivery. Clin Radiol 2013;68:643-645.

298 Hampshire T, Roth HR, Helbren E, Plumb A, Boone D, Slabaugh G, Halligan S, Hawkes DJ: Endoluminal surface registration for CT colonography using haustral fold matching. Med Image Anal 2013;17:946-958.

299 Hassan C, Pooler BD, Kim DH, Rinaldi A, Repici A, Pickhardt PJ: Computed tomographic colonography for colorectal cancer screening: Risk factors for the detection of advanced neoplasia. Cancer 2013;119:2549-2554.

300 Pullens HJ, van Leeuwen MS, Laheij RJ, Vleggaar FP, Siersema PD: CT-colonography after incomplete colonoscopy: what is the diagnostic yield? Dis Colon Rectum 2013;56:593-599.

301 Robbins JB, Kim DH: Computed tomographic colonography: evidence and techniques for screening. Semin Roentgenol 2013;48:264-272.

302 Saunders JH, Miskovic D, Bowman C, Panto P, Menon A: Colorectal cancer is reliably excluded in the frail and elderly population by minimal preparation CT. Tech Coloproctol 2013; [Epub ahead of print].

303 Stoker J: Diagnosis: CT colonography has finally arrived. Nat Rev Clin Oncol 2013;10:254-255.

304 van R, V, Boellaard T, van der Paardt M, Serlie I, de HM, Stoker J, van VL, Vos F: Electronic Cleansing for 24-hour Limited Bowel Preparation CT Colonography Using Principal Curvature Flow. IEEE Trans Biomed Eng 2013; [Epub ahead of print]..

305 Manes G, Ardizzone S, Cassinotti A: PillCam Colon and ulcerative colitis: what do physicians need to know? Endoscopy 2013;45:325.

306 Mateescu BR, Bengus A, Marinescu M, Staniceanu F, Micu G, Negreanu L: First Pillcam Colon 2 capsule images of Whipple's disease: Case report and review of the literature. World J Gastrointest Endosc 2012;4:575-578.

307 Ye CA, Gao YJ, Ge ZZ, Dai J, Li XB, Xue HB, Ran ZH, Zhao YJ: PillCam colon capsule endoscopy versus conventional colonoscopy for the detection of severity and extent of ulcerative colitis. J Dig Dis 2013;14:117-124.

308 Singeap AM, Trifan A, Cojocariu C, Stanciu C: Colon capsule endoscopy compared to colonoscopy for colorectal neoplasms diagnosis: an initial experience and a brief review of the literature. Rev Med Chir Soc Med Nat Iasi 2012;116:145-149.

309 Spada C, De VF, Cesaro P, Hassan C, Riccioni ME, Minelli GL, Bolivar S, Zurita A, Costamagna G: Accuracy and safety of second-generation PillCam COLON capsule for colorectal polyp detection. Therap Adv Gastroenterol 2012;5:173-178.

310 Spada C, De VF, Cesaro P, Hassan C, Riccioni ME, Minelli GL, Bolivar S, Zurita A, Costamagna G: Accuracy and safety of second-generation PillCam COLON capsule for colorectal polyp detection. Therap Adv Gastroenterol 2012;5:173-178.

311 Spada C, Hassan C, Munoz-Navas M, Neuhaus H, Deviere J, Fockens P, Coron E, Gay G, Toth E, Riccioni ME, Carretero C, Charton JP, Van GA, Wientjes CA, Sacher-Huvelin S, Delvaux M, Nemeth A, Petruzziello L, de Frias CP, Mayershofer R, Amininejad L, Dekker E, Galmiche JP, Frederic M, Johansson GW, Cesaro P, Costamagna G: Second-generation colon capsule endoscopy compared with colonoscopy. Gastrointest Endosc 2011;74:581-589.

312 Akerman PA, Haniff M: Spiral enteroscopy: Prime time or for the happy few? Best Pract Res Clin Gastroenterol 2012;26:293-301.

313 i-Snake Robot for Minimally Invasive Intervention http://www1.imperial.ac.uk/medicine/research/researchthemes/healthtechnologies/surgicaltechnologies/isnake/: 2011.

314 Robotics award for i-Snake team http://phys.org/news/2011-06-robotics-award-i-snake-team-video.html: 2011.

Appendix 1

Publications, presentations, invited lectures and awards relating to this work

A1.1 Original Articles and Papers

(Despott, Edward J. Sciverse Scopus Author ID 15759059900; h index: 5)

1. **Despott EJ,** Fraser C.
   Small Bowel Endoscopy in Inflammatory Bowel Disease
   Best Pract Clin Res Gastroenterol 2012 Jun;26(3):279-91.

2. Murino A, **Despott EJ,** Hansmann A, Heath P, Fraser C.
   A rare case of small bowel intussusception
   Endoscopy 2012 May;44 Suppl 2:E157-8. Epub 2012 May 23.

3. **Despott EJ**, O'Rourke A, Ankin V, Davison C, Panter S, Bromly J, Place J, Corbett M, Fraser C. **Tracheal aspiration of capsule endoscopes: detection, management and susceptibility**
   Dig Dis Sci 2012 Jul;57(7):1973-4. Epub 2012 May 23.

4. **Despott EJ**, Murino A, Hussain T, Goldstein D, Naji Y, O'Rourke A, Fraser C. **First report of a secondary aortojejunal fistula visualized by small bowel capsule endoscopy** *Dig Dis Sci* 2012 Jan; 57(1):256-7. Epub 2011 Aug 17.

5. **Despott EJ**, Murino A, Fraser C.
   Management of deep looping when failing to progress at double-balloon enteroscopy (DBE)
   Endoscopy 2011; 43: E275-6. Epub 2011 Sep 13.

6. **Despott EJ**, Tadrous PJ, Naresh K, Marshall M, Saunders BP.
   An unusual finding at screening colonoscopy: polypoid follicular lymphoma with marginal zone differentiation (with video)
   Endoscopy 2011; 43:E266-7. Epub 2011 Aug 12.

7. Cohen LB, Ladas SD, Vargo JJ, Paspatis GA, Bjorkman DJ, Van der Linden P, Axon AT, Axon AE, Bamias G, **Despott EJ,** Dinis-Ribeiro M, Fassoulaki A, Hoffman N, Karagiannis JA, Karamanolis D, Maurer W, O'Connor A, Paraskeva K, Schreiber F, Triantafyllou K, Viazis N, Vlachogiannakos J.
   The OMED/ESGE Athens consensus statement on sedation in digestive endoscopy
   Aliment Pharmacol Ther 2010 Aug; 32(3):425-42. Epub 2010 May 8.

8. **Despott E**, Gabe S, Tripoli E, Polecina A, Konieczko K, Fraser C.
   Enteral access by double balloon enteroscopy: an alternative method of direct percutaneous endoscopic jejunostomy placement
   Digest Dis Sci Feb;56(2):494-8. Epub 2010 Jun 29.

9. **Despott E**, Hughes S, Marden P, Fraser C.
   First cases of spiral enteroscopy in the UK: let's "torque" about it!
   Endoscopy 2010 Jun;42(6):517. Epub 2010 May 26.

10. **Despott E**, Schreiber F
    Advanced Cardiac Life Support (ACLS) training for sedation providers in digestive endoscopy
    Digestion 2010;82:113–114.

11. **Despott E**, Fraser C.
    Achieving successful ileal intubation during retrograde double balloon enteroscopy: description of a novel, alternative technique (with video)
    Endoscopy 2009;41:E309-10. Epub 2009 Nov 17.

12. **Despott E**, Tripoli E, Polecina A, Konieczko K, Fraser C
    Effective dilation of small bowel strictures by double balloon enteroscopy in patients with symptomatic Crohn's disease (with video)
    Gastrointest Endosc. 2009 Nov;70(5):1030-6. Epub 2009 Jul 28.

13. Bourreille A, Ignjatovic A, Aabakken L, Loftus Jr EV, Eliakim R, Pennazio M, Bouhnik Y, Seidman E, Keuchel M, Albert JG, Ardizzone S, Bar-Meir S, Bisschops R, **Despott EJ**, Fortun PF, Heuschkel R, Kammermeier J, Leighton J A, Mantzaris GJ, Lo S, Paulsen V, Radford-Smith G, Reinisch W, Rondonotti E, Sanders DS, Swoger J M, Yamamoto H, Travis S,. Colombel J-F, Van Gossum A **Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED–ECCO consensus** *Endoscopy* 2009; 41: 618–637.

14. Postgate A, **Despott E**, Talbot I, Phillips R, Aylwin A, Fraser C **An unusual cause of diarrhoea: diffuse intestinal nodular lymphoid hyperplasia in association with selective immunoglobulin A deficiency (with video)** *Gastrointest Endosc* 2009;70: 168-169

15. Postgate A, **Despott E**, Patch D, O'Beirne J, Fraser C **Significant small-bowel lesions detected by alternative diagnostic modalities after negative capsule endoscopy** *Gastrointest Endosc* 2008; 68: 1209-1214

A1.2 Oral presentation of abstracts to national & international Scientific Societies

1. **Digestive Diseases Federation (DDF) Meeting 2012, *Liverpool, June 2012***
   A prospective, back-to-back comparative study of spiral enteroscopy and double-balloon enteroscopy
   Despott E, Murino A, Bourikas LA, Nakamura M, Fraser C. *Gut* 2012; (Suppl I)A20

2. **BSG Annual Meeting 2010, *Liverpool, March 2010***
   The UK multicentre DBE registry
   Despott E, Hughes S, Deo A, Sanders DS, Sidhu R, Willert R, Plevris J, Trimble K, Jennings J , Fraser C. *Gut* 2010;59 (Suppl I)A11

3. **BSG Annual Meeting 2010, *Liverpool, March 2010***
   Final analysis of SCENT
   Despott E, Baulf M, Bromley J, Gupta S, Fraser C. *Gut* 2010;59 (Suppl I)A24

4. **BSG Annual Meeting 2010, *Liverpool, March 2010***
   Spinning forward down the small bowel
   Despott E, Hughes S, Marden P, Fraser C. *Gut* 2010;59 (Suppl I)A10

5. **BSG Annual Meeting 2010, *Liverpool, March 2010***
   Web-based learning in gastroenterology: real-life learning outcomes from a training and assessment module in lesion recognition at capsule endoscopy
   Haycock A, Postgate A, **Despott E**, Fraser C. *Gut* 2010;59(Suppl I)A9

6. **Gastro 2009 (World Congress of Gastroenterology and UEGW), *London, November 2009***
   Interim analysis of SCENT: The first UK prospective, randomised, head-to-head trial of transnasal versus oral upper GI endoscopy
   Despott E, Baulf M, Tripoli E, Konieczko K, Fraser C. *Endoscopy*2009; 41(Suppl I)A46

7. **Gastro 2009, *London, November 2009***
   Introducing spiral enteroscopy in the UK
   Despott E, Tripoli E, Konieczko K, Fraser C. *Endoscopy* 2009;41(Suppl I)A4

8. **International Society for Gastrointestinal Hereditary Tumours (InSiGHT) International Society Biennial Meeting 2009, *Dusseldorf, June 2009***
   Small bowel polypectomy by double balloon enteroscopy: novel therapy for patients with Peutz-Jeghers syndrome
   Despott E, Phillips R, Clark S, Tripoli E, Konieczko K, Fraser C. *Familial Cancer* 2009;8(Suppl 1)

9. **ECCO 2009, *Hamburg, February 2009***
   Double balloon enteroscopy: advancing the management of Crohn's disease small bowel strictures
   Despott E, Tripoli E, Polecina A, Konieczko K, Fraser C. Journal of Crohn's and Colitis 2009; 3: S71 *(Commended oral presentation with poster)*

10. **UEGW 2008, *Vienna, October 2008***
    Double Balloon Enteroscopy: An effective way of Direct Percutaneous Endoscopic Jejunostomy (DPEJ) Tube insertion
    Despott E, Gabe S, Tripoli E, Fraser C. *Endoscopy* 2008; 40(Suppl. 1)A32

11. **BSG Annual Meeting 2008, *Birmingham, March 2008***
    DBE: Reaching the depths of the small bowel
    Despott E, Tripoli E, Polecina A, Konieczko K, Fraser C. *Gut* 2008;57(Suppl I)A30

A1.3 Poster presentation of abstracts to national & international Scientific Societies

During the conduct of this work, I have also presented 25 posters at national and international meetings. The abstracts of these presentations have been published in supplements of *Endoscopy*, *Gastrointest Endosc* and *Gut*.

A1.4 Book chapter and other book contributions

1. **Despott EJ**, Warusavitarne J, Fraser C: The optimal management of stricturing Crohn's disease. In: Inflammatory Bowel Disease – An Evidence-based Clinical Guide. Edited by Hart AL, Ng SC. London: TFM Publishing; 2011

2. Surawicz CM: Infections and other non-inflammatory bowel disease colitides. In: Colonoscopy Principles and Practice (2nd edition). Edited by Waye JD, Rex DK, Williams CB. Oxford: Blackwell Publishing Limited; 2009: 659-674.
   (Despott EJ: Photographic contributions

A1.5 Invited talks and lectures

1. **2nd UK Capsule Endoscopy Symposium, Edinburgh, *April 2012***
   'Deep Enteroscopy'

2. **10th European Capsule Endoscopy Training Programme (BSG & ASGE endorsed) Combined Course, *London, April 2011***
   'SBCE reporting'

3. **10th European Capsule Endoscopy Training Programme (BSG & ASGE endorsed) Combined Course,** ***London, April 2011***
   'Device assisted deep enteroscopy'

4. **Imperial College Surgical MSc Course, St Mary's Hospital, Imperial College Healthcare,** ***London, Jane 2011***
   'Deep enteroscopy update'

5. **St Mark's Frontiers in Colorectal and Intestinal Diseases,** ***London, Dec 2010***
   'All colorectal bleeding can be managed without surgery: the endoscopist's perspective'

6. **St Mark's Deep Enteroscopy Masterclass,** ***London, November 2010***
   'Consultant's corner'; 'Enteroscopy case mix'; 'Hands-on training'

7. **The Inaugural UK Capsule Endoscopy Symposium,** ***Sheffield, June 2010***
   'Therapeutic enteroscopy'

8. **Scottish National for Endoscopy Study Day, St John's Hospital,** ***Livingstone, Scotland, December 2009***
   'Unsedated upper GI endoscopy: the transnasal route'

9. **Imperial College Surgical MSc Course, St Mary's Hospital,** ***London, November 2009***
   'Advanced small bowel endoscopy: the state of the art'

10. **South West (UK) Gastro Meeting 2009,** ***Torbay, May 2009***
    'Transnasal upper GI endoscopy in the UK'

11. **St Mark's Small Bowel Symposium,** ***London, April 2009***
    'Optimal management of obscure GI bleeding'

12. **OMED/ECCO Summit on small bowel endoscopy in inflammatory bowel disease,** ***Brussels, December 2008***
    'Small bowel capsule endoscopy and device assisted enteroscopy in established Crohn's disease'

13. **2nd St Mark's National DBE Workshop,** ***London, October 2008***
    'Double balloon enteroscopy: case mix'

14. **1st St Mark's National DBE Workshop,** ***London, February 2008***
    'Double balloon enteroscopy: the evidence base'

A1.6 Awards and grants

1. **BSG Travelling Fellowship to attend advanced endoscopy training at the National Cancer Centre (NCC) in Tokyo, Japan (£2000, Mar 2012)**
   Awarded one of the only three UK places at a highly competitive, pan-national selection process

2. **Shire Innovations Travel Grant**
   (£500, Oct 2011)
   UEGW 2011, Stockholm
   Awarded by an independent panel of UK experts for quality and clinical relevance of an abstract accepted for presentation at UEGW 2011

3. **ECCO Advanced Intensive Inflammatory Bowel Disease (IBD) Course**
   ECCO Annual Meeting, Prague, Czech Republic
   (Fully funded; Feb 2010)
   Awarded one of the only five UK places to attend this intensive IBD course

4. **Young Clinicians Programme (YCP) Bursary Gastro 2009**
   Gastro 2009 (The historic joint congress of the UEGF, the WGO and OMED), London
   (Fully funded; Nov 2009)
   Awarded one of the only 30 UK places to attend a fully funded seven day dedicated YCP, the Gastro 2009 postgraduate course and the Gastro 2009 congress

5. **ECCO Highly Commended Abstract**
   ECCO Annual Meeting, Hamburg, Germany
   (Feb 2009)
   Awarded for the quality of an abstract accepted for presentation

6. **Finalist (4th place) North East Thames Gastroenterology (London Deanery) Research Day**
   Royal Free Hospital, London
   (Dec 2008)
   Research day dedicated to the presentation of research abstracts from the North East Thames SpR training rotation (out of a total of 33 submitted abstracts)

7. **UEGW Travel Grant**
   UEGW, Vienna, Austria
   (€1,000; Oct 2008)
   Awarded for the quality of an abstract accepted for presentation

8. **British Society of Gastroenterology/Keymed-Olympus Travel Grant**
   DDW and Advanced Endoscopy Update, San Diego and South Carolina, USA
   ($1,500; May 2008)
   Awarded one of the only 10 UK places to attend DDW and the Advanced Endoscopy Update at Professor P. Cotton's Unit at the Medical University of South Carolina (MUSC)

A1.7 Organisation of courses and symposia

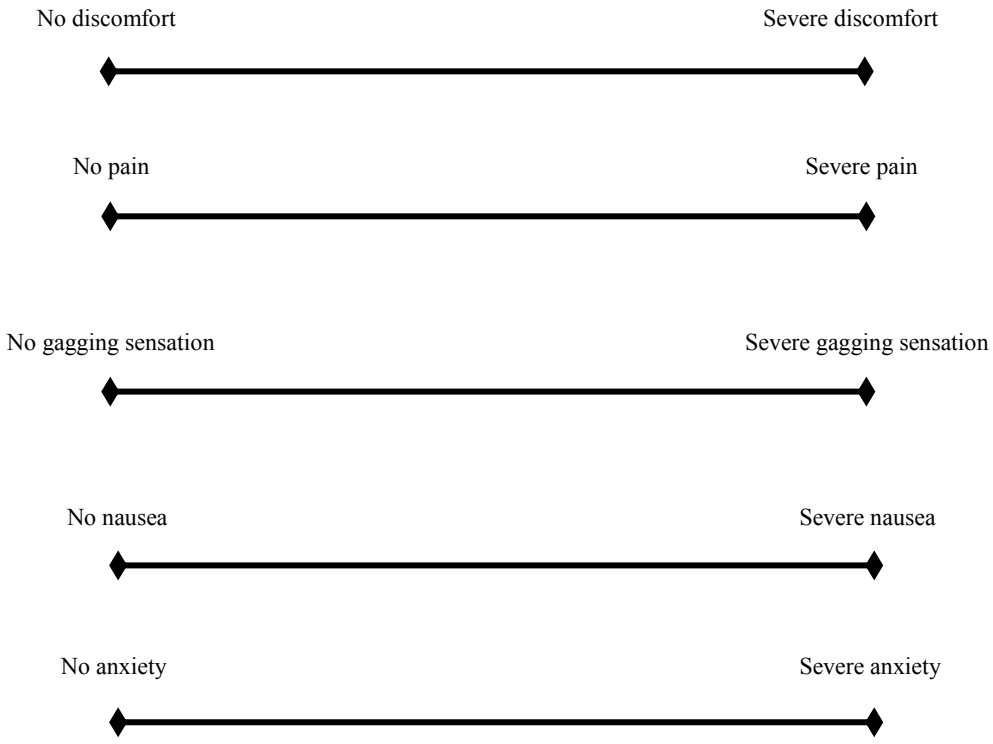
Throughout the course of my studies, I have also taken the opportunity to co-organise with Dr Fraser several symposia and courses relating to the advanced endoscopy technologies described in this thesis. These included the '*1st and 2nd UK double-balloon enteroscopy symposia*' and the '*1st European Deep Enteroscopy Masterclass*' which also included hands-on training on dedicated endoscopy animal training models.

Appendix 2

St Mark's Conventional Endoscopy versus trans-Nasal endoscopy sTudy (SCENT): data collection sheets

A2.1 Patient's own assessment: visual analogue scale (VAS)

Please place an **"X"** at the appropriate point on each line that best represents how you felt during the test you have just undergone:



A2.2 Patient's own assessment: Likert satisfaction score

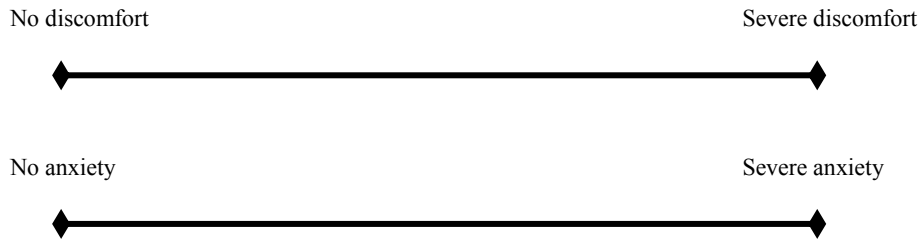
Overall, how satisfied are you with the test you have undergone?
(Please tick the appropriate box as shown: ☑)

very satisfied	*satisfied*	*neutral*	*dissatisfied*	*very dissatisfied*
□	□	□	□	□

Should you require another gastroscopy in the future, would you have the test done the same way next time?

Yes □ **No** □

A2.2 Nurse assessment: visual analogue scales (VAS) for perceived patient discomfort and anxiety; record of vital parameters and dose of sedative used



Lowest oxygen saturation during the procedure: ____

Lowest systolic blood pressure during the procedure: ____

Highest systolic blood pressure during the procedure: ____

Lowest pulse rate during the procedure: ____

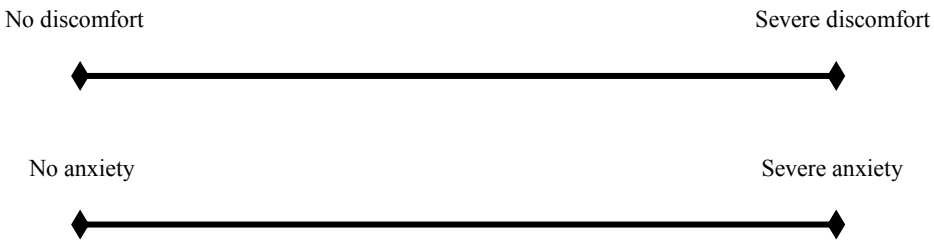
Highest pulse rate during the procedure: ____

Timing of the actual procedure (mins): ____

Dose of midazolam used: ____

Recovery time (mins): ____

A2.3 Endoscopist assessment: visual analogue scales (VAS) for perceived patient discomfort, anxiety and technical aspects



Technical Aspects

Ease of endoscope insertion



Endoscope handling, steerability



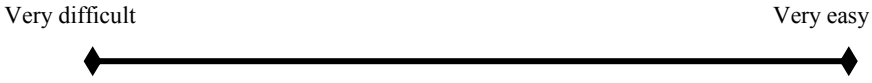
Ease of D2 intubation



Ease of taking random biopsies



Ease of taking targeted biopsies



Overall feasibility of procedure



A2.4 Endoscopist assessment: visual analogue scales (VAS) for endoscopic view quality

Views of the oesophagus

Very poor Very good



Views of the stomach (forward view)

Very poor Very good



Views of the stomach (retroflexed view)

Very poor Very good



Views of the first part of the duodenum (D1)

Very poor Very good



Views of the second part of the duodenum (D2)

Very poor Very good



Overall impression of diagnostic ability of the endoscope

Very poor Very good



A2.5 Views obtained through ultrathin and conventional upper GI endoscopes

Figure A2.5.1 *Views of the upper GI tract as obtained through an ultrathin endoscope (EG-530N, Fujifilm, Saitama, Japan); gastro-oesophageal junction (**A**); fundus and cardia (**B**); pyloric antrum (**C**) and second part of duodenum (**D**).*

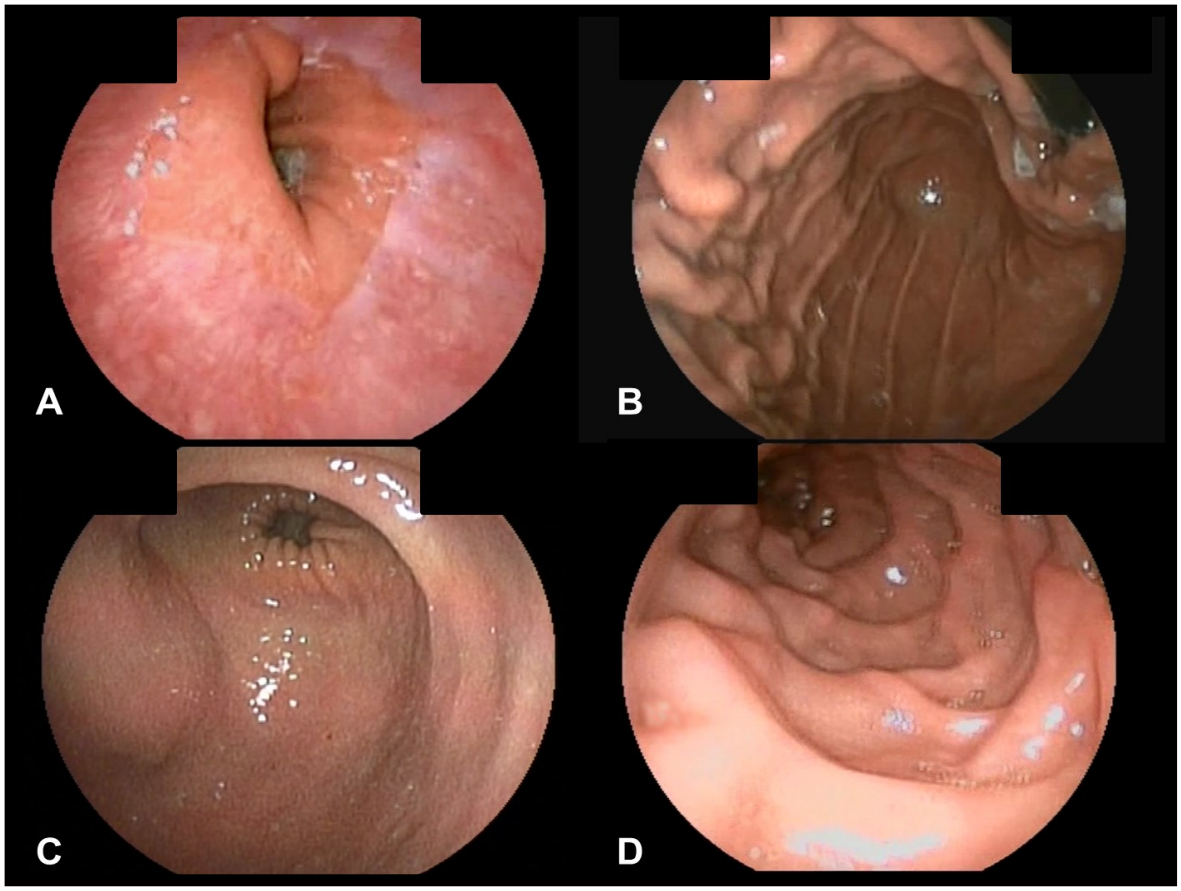
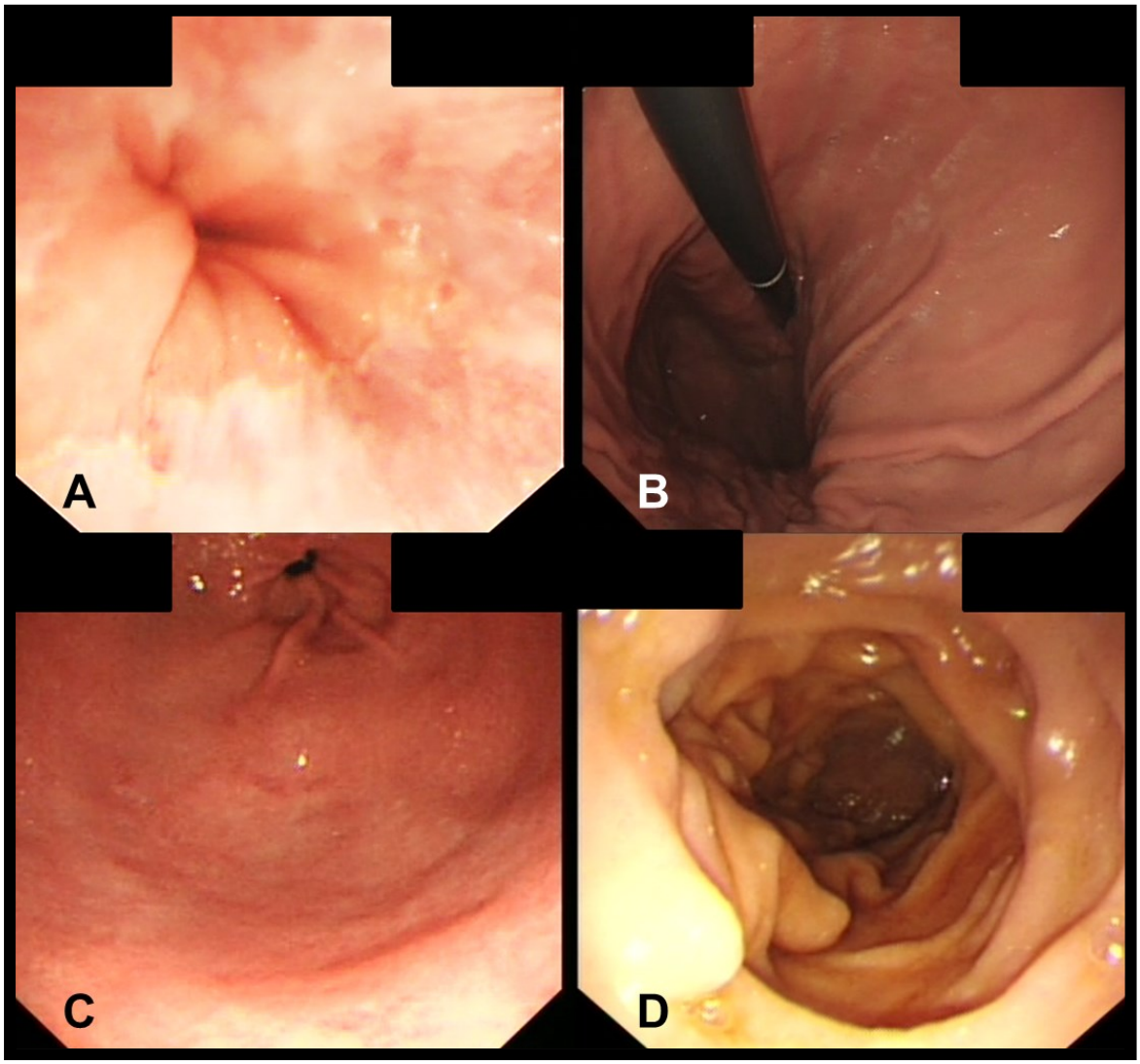


Figure A2.5.2 *Views of the upper GI tract as obtained by a conventional endoscope (GIF-XQ260, Olympus, Tokyo, Japan); gastro-oesophageal junction (**A**); fundus and cardia (**B**); pyloric antrum (**C**) and second part of duodenum (**D**).*



Appendix 3

SPiral Enteroscopy Comparative Study (SPECS): data collection sheets

A3.1 Patient demographics, indication for deep enteroscopy and past surgical history

Gender: M □ F□

Age: ____

Indication for deep enteroscopy procedure:

_____
_____

Past history of abdominal or pelvic surgery:

_____
_____
_____

Additional comments:

_____
_____

A3.2 Spiral enteroscopy (SE) data

Time taken to reach most distal point of insertion: _____ (min)

Time taken to complete the whole SE procedure: _____(min)

Estimated depth of insertion at SE: _____ (cm)

Findings at SE:

_____
_____
_____
_____
_____
_____

VAS: ease of SE procedure (estimated by endoscopist):

Very easy — Very difficult



Complications (if any):

_____
_____
_____
_____
_____
_____

A3.3 Double-balloon enteroscopy (DBE) data

Time taken to reach most distal point of insertion: _____ (min)

Time taken to complete the whole DBE procedure: _____(min)

Estimated depth of insertion at DBE: _____ (cm)

Findings at DBE:

_____
_____
_____
_____
_____
_____

VAS: ease of DBE procedure (estimated by endoscopist):

Very easy Very difficult



Complications (if any):

_____
_____
_____
_____
_____
_____

Appendix 4

Double-balloon colonoscopy vs. conventional colonoscopy: data collection sheets

A4.1 Patient's own assessment: visual analogue scale (VAS) and Likert satisfaction score

Please place an **"X"** at the appropriate point on each line which best represents how you felt during the test you have just undergone:

No discomfort — Severe discomfort



No pain — Severe pain



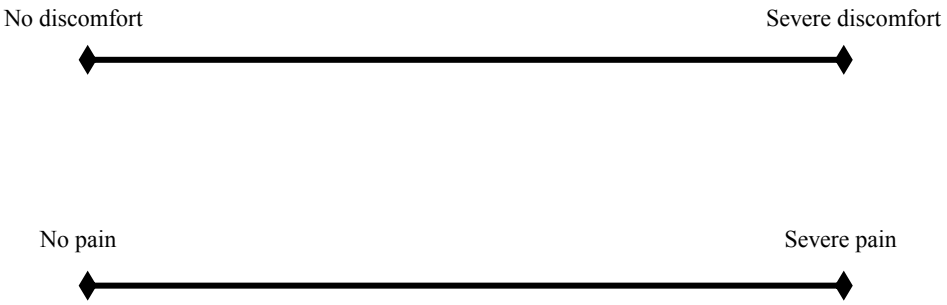
Overall, how satisfied are you with the test you have undergone?
(Please tick the appropriate box as shown: ☑)

very satisfied	*satisfied*	*neutral*	*dissatisfied*	*very dissatisfied*
□	□	□	□	□

Should you require another colonoscopy in the future, would you have the test done the same way next time?
Yes □ **No** □

A4.2 Nurse assessment: visual analogue scales (VAS) for perceived patient discomfort and pain; record of vital parameters and dose of sedative used

Perceived overall patient discomfort and pain during procedure



Lowest oxygen saturation during the procedure: ____

Lowest systolic blood pressure during the procedure: ____

Highest systolic blood pressure during the procedure: ____

Lowest pulse rate during the procedure: ____

Highest pulse rate during the procedure: ____

Timing of the actual procedure (mins): ____

Dose of midazolam used: ____

Dose of pethidine used: ____

Dose of propofol used: ____

Dose of Buscopan® used: ____

Dose of glucagon used: ____

Recovery time (mins): ____

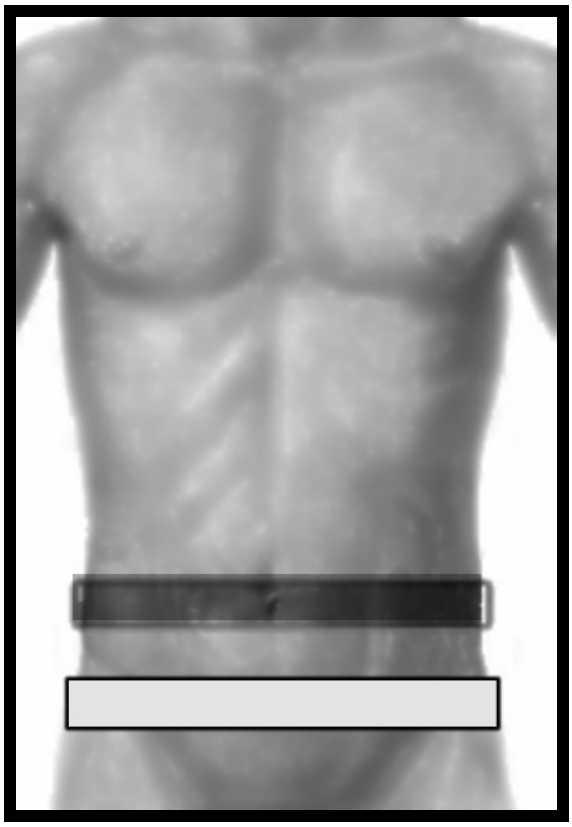
Time to caecal intubation (mins): ____

Time taken to complete the colonoscopy (mins): ____

A4.3 Waist, hip-girth, height and weight measurements and calculated BMI

Using a tape measure:

1) Please measure the patient's waist at the level of the umbilicus as shown by black rectangular mark on the diagram of the abdomen below
and
2) The patient's hip girth at the level of the iliac crests as shown by the white rectangular mark on the diagram of the abdomen below



Waist measurement (Black); Hip Measurement (White)

Waist measurement (cm):_____

Hip measurement (cm):_____

Weight (kg): _____

Height (m):_____

BMI (weight (kg)/ height^2 (m^2): _____

A4.4 Endoscopist assessment: visual analogue scales (VAS) for perceived patient discomfort and pain; technical ease of colonoscopy

Perceived overall patient discomfort and pain during procedure





Technical ease of colonoscopy procedure



A4.5 Patient recovery and discharge using the Modified Aldrete Recovery Scoring System

Please use the following scoring system to record the patient's recovery score at 5 minutes post-procedure and then at 10 minute intervals until a score ≥9 is reached.

Modified Aldrete Recovery Scoring System*	
Respiration	**Score**
Able to breathe deeply and cough freely	2
Dyspnoea, shallow or limited breathing	1
Apnoea	0
Oxygen saturation	
Saturation > 92%	2
Needs supplemental oxygen to maintain saturation >90%	1
Saturation <90% with oxygen	0
Circulation	
Systolic blood pressure within 20mm Hg of pre-operative level	2
Systolic blood pressure within 20-50mm Hg of pre-operative level	1
Systolic blood pressure +/- 50mm Hg of pre-operative level	0
Consciousness	
Fully awake	2
Arousable on calling	1
Unresponsive	0
Activity: able to move voluntarily or on command	
Four extremities	2
Two extremities	1
No extremities	0
*Recovery is confirmed when the total score ≥9	

Time post procedure (minutes)	5	10	20	30	40	50	60
Total Aldrete score (Max score=10)							

Full recovery has occurred (and the patient may be discharged) when the Aldrete score ≥9