Stabilising and Visualising Devices of the Gastrointestinal Tract

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Submitted for examination towards the award of Doctor of Philosophy in Biomedical Sciences

Trinity College
Trinity 2017

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Declaration of Authorship

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This thesis has not already been accepted, or is being concurrently submitted, by me or any other author, for any degree, diploma or other qualification in this University or elsewhere.

This thesis does not exceed 50 000 words, excluding bibliography, figure legends and appendices.

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Acknowledgements

As clinical lead, I must thank the various individuals that collaborated with me in this work;

Xing Li and Jeremy Van-Hill with the intestinal parameters assessment.
Anh Nguyen, Rahul Sathe, Gabe Greeley, Richard Yazbeck and Daniel Barrows with the engineering support.
Dennis Daniels and Laurence Lefebvre for the regulatory and validation support.
Dr. Hisashi Hara, Dr. Kota Momose, Andrew Harvey and Dr. Takahiro Hiratsuka with the pre-clinical model work. Yuko Tonohiro for cartoon production.
Dr. Reem Sharaiha, Dr. Toyooki Sonoda, Dr. James White and Dr. Art Sedrakyan for help and guidance in designing and executing the clinical trial.
Professor Kiyokazu Nakajima for his generous animal study support.

I want to reserve *heartfelt gratitude* towards,

The many wonderful teachers I've had on this journey so far including;

the late Dr. Spiros Comis, Dr. Evan Stein, Mr. Robin Hatter, Mr. Richard Miller and Kevin Byrne,

Professor Hermann Steller,

Professor Yaron Fuchs,

Professor Jeffrey Milsom,

Professor Alison Simmons,

Jeff and Susie,

Rahul, Neetu and Arha

Mum and Dad.

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Abstract

Flexible endoscopic systems have revolutionised both diagnostic and therapeutic standards of care for a variety of health conditions. Extending the capacity and safety of these devices, could enable broad deployment of endolumenal therapeutic actions, preventing unnecessary surgery. Although previous biocompatible inflatable balloon systems for *in-vivo* use have demonstrated some utility in small-bowel locomotion, little is known about the potential for double balloon systems to facilitate surgeries within the gastrointestinal tract. While considerable advances have been demonstrated in other clinical specialties due to innovative technology, these have been historically absent in gastrointestinal therapy, where reliance on formal surgery as the primary treatment modality for benign and malignant disease has persisted. Such innovations seen in other fields have shifted diagnosis and treatment to an earlier stage with minimally invasive approaches.

In this thesis, I present my DPhil work that shows evidence of the design and operation of a double-balloon oversheath for flexible endoscope stabilisation and visualisation through the development of a lumenal inter-balloon zone. The device delivered an increased visible mucosal surface area and improved tumour removal strategies through immersion and retraction capabilities in the lower gastrointestinal tract of large animals. Following this, I go onto consolidate this pre-clinical work in a clinical context with an emphasis on safety as well as some of the challenges encountered during this process.

Taken together, these data indicate that such devices could provide endolumenal surgical capabilities to the next generation of flexible endoscopic systems for the gastrointestinal tract.

Abbreviations

AP	Adenomatous Polyps
BMI	Body Mass Index
CAD	Computer aided design
CRC	Colorectal Cancer
eTAMIS	Endoscopic trans-anal minimally invasive surgery
EVAR	Endovascular Aneurysm Repair
FE	Flexible endoscopy
FIM	First-in-man
FOB	Faecal occult blood
GI	Gastrointestinal
GIT	Gastrointestinal Tract
ISO	International Organisation for Standardisation
KK	Kyoto-Kagaku model
SVDE	Stabilising and Visualisation Platform for Endoscopes
NAP	Neoplastic adenomatous polyps
NBI	Narrow-band-imaging
NYPH	New York Presbyterian Hospital
PU	Polyurethane
PTFE	Polytetrafluoroethylene
TPU	Thermoplastic polyurethane
TZ	Therapeutic Zone
WCMC	Weill Cornell Medical College

1. Introduction

1.1 Gastro-intestinal tract

The human gastrointestinal tract (GIT) can be thought of as a continuous tube from mouth to anus with distinct specialised regions related to functional significance. Broadly, the GIT consists of the oesophagus, stomach, and intestines, and is divided into upper and lower sections. Its main functions are that of extracting energy and the excretion of waste. The tract may also be divided into foregut, midgut, and hindgut, reflecting the embryological origin of each segment. For the purposes of my DPhil work I will focus on the lower GI tract (colon).

1.2 Clinical significance of the GI tract

Diseases may manifest anywhere along the GIT and are specific to the functional region and mechanisms involved, which can be congenital or acquired in origin. Broadly speaking, infectious, inflammatory and carcinomatous maladies have a preponderance for the GI tract postulated to be as a result of environmental antigens exposure and rapid cellular turnover. For the purposes of my work, I will focus on colorectal cancer and its precursor adenomatous polyps.

1.3 Colorectal cancer

Colorectal cancer (CRC) is a common and fatal disease. Approximately 150,000 new cases of CRC are annually diagnosed in the United States, including approximately 95,000 colon and 40,000 rectal cancers[1]. CRC claims 50,000 Americans lives annually. The incidence and mortality rates from CRC have been declining at a rate of up to 3 percent per year since the 90's, however, it remains the second most common cause of cancer death in men and the third in women[2].

In an opposite trend to the observed decline is the rather worrying recent observation that CRC incidence is increasing in the young. The rates of CRC have been steadily increasing at a rate of 2 percent per year from 1992 to 2012 in those aged less than 50[3]. The majority of individuals diagnosed with CRC at age 50 or less are symptomatic, which is associated with more advanced disease stage and poorer outcomes[4]. Looking to the future, the global incidence of CRC is expected to increase by 60% in the coming decade[5]. Such projected increases are not isolated to CRC, most cancer types are expected to follow this trend. If such projections come to pass it is unlikely that current diagnostic and treatment methods will suffice and innovative solutions for cancer prevention and early detection should be pursued globally[6].

The three predominant methods of CRC diagnosis are (1) after symptoms onset, (2) faecal occult blood (FOB) or faecal immuno histochemistry testing (FIT) and (3) screening colonoscopy. Screening detects early-stage malignancy, improves survival and is advocated by major societies and preventive care organizations[7]. Despite the benefits and endorsements, screening penetrance remains relatively low for those eligible[8]. One of the main aims of screening is to discover the precursor of CRC - adenomatous polyps - and to facilitate polyp removal whilst in the precancerous phase, or early-stage disease.

1.4 Adenomatous polyps of the intestine

The lower intestine (colon) has 3 layers, an outer muscle layer, and inner mucosal layer and between them a submucosal layer, which is a potential space (see figure 1). The intestinal mucosa is uniform in appearance and any protrusion into the lumen, arising from the mucosa, is termed a polyp. Intestinal polyps are classified as non-neoplastic, hamartomatous, neoplastic (adenomas and carcinomas), serrated (which can be neoplastic or non-neoplastic), and submucosal (which can be neoplastic or non-neoplastic).

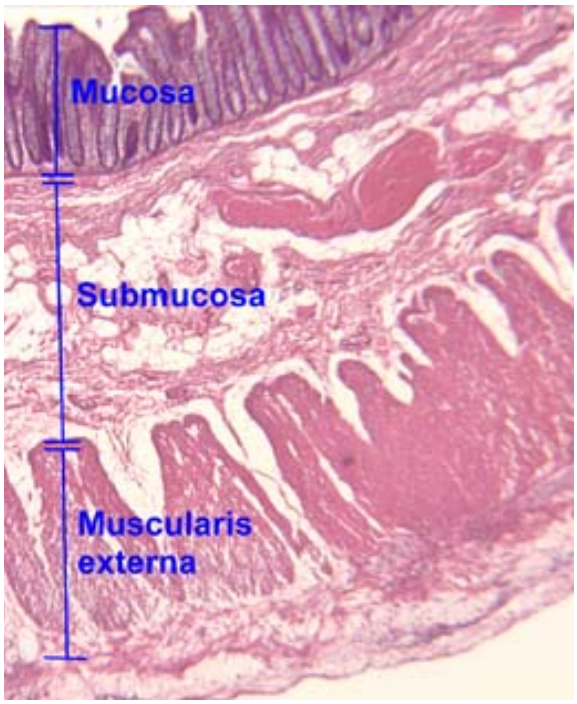


Figure 1: Layers of the intestine (courtesy of Dr. Gulwani[9])

The majority of CRC develops from Adenomatous Polyps (AP), many of which grow in size, and progress to dysplasia and cancer, this is termed the "Adenoma-carcinoma sequence"[10]. These changes generally arise from a predisposing genetic background with acquired effects[11].

The purported progression from adenoma to carcinoma has classically been described as 10 years[12]. In contrast to the polypoid protuberances that project into the intestinal lumen, a subset of CRC develops from flat or depressed adenomas. The non-polypoidal types account for nearly 40% of identified adenomas[13-15] and are more likely to harbour dysplastic changes or cancer malignancy than similar size polypoidal lesions. These lesions also present a diagnostic challenge as they are difficult to detect visually and are sometimes visible only through methodological mucosal analysis (which is time-consuming) and/or the use of surface staining with dyes such as indigo carmine or methylene blue[14].

Two-thirds of polyps are adenomas. Hyperplastic polyps account for most of the remaining one-third. Adenomas are found in up to 30% of the population, and prevalence increases with age[16, 17]. CRC risk increases with adenoma size, number present, and histological outcome[18, 19]. Once a patient has been found to harbour a polyp, the risk of forming another is increased and so evaluation should be scheduled at physician-led intervals depending on the histological type found. Interestingly, individuals who move from low- to high-risk CRC regions acquire that regions higher risk for the rest of their life – this suggest an environmental component[20].

Recently published work outlines how the rates of surgical colectomy for benign polyps are increasing in the United States, and not without significant morbidity and mortality[21, 22]. As my clinical background is that of colorectal surgery, I postulated that this observed trend was possibly due to the lack of relevant technology to assist removal and so for the purposes of my DPhil work, I will focus on Neoplastic Adenomatous Polyps (NAP) of the lower intestine due to the progression to CRC and its amenability to endolumenal treatment methods due to mucosal lesion location.

1.5 Neoplastic adenomatous polyps

2 main types of NAPs exist: (1) serrated polyps and (2) adenomatous polyps.

Serrated polyps are a heterogeneous group of polyps with variable malignant potential. They include hyperplastic polyps, traditional serrated adenomas, and sessile serrated polyps (also known as sessile serrated adenomas)[23].

Adenomatous polyps are dysplastic and so have malignant potential. Advanced age is a major risk factor for the development of intestinal adenomas. Screening studies indicate that adenomas prevalence is up to 30% at 50 years old[24-27]. By 70 years old, the rate increases to 50%[28]. Advancing Body Mass Index (BMI) and sedentary lifestyle are also risk factors[29, 30].

1.6 Adenomatous polyp classification

NAPs are further classified through visual/endoscopic examination as:

Sessile –where the base adjoins the surrounding mucosa in a contiguous fashion.
Pedunculated – where a mucosal stalk is present.
Flat – level or slightly raised surface in comparison to the surrounding mucosa.
Depressed – at a lower situation to the surrounding mucosa. These lesions are at a higher risk of harbouring high-grade dysplasia or malignancy[31].

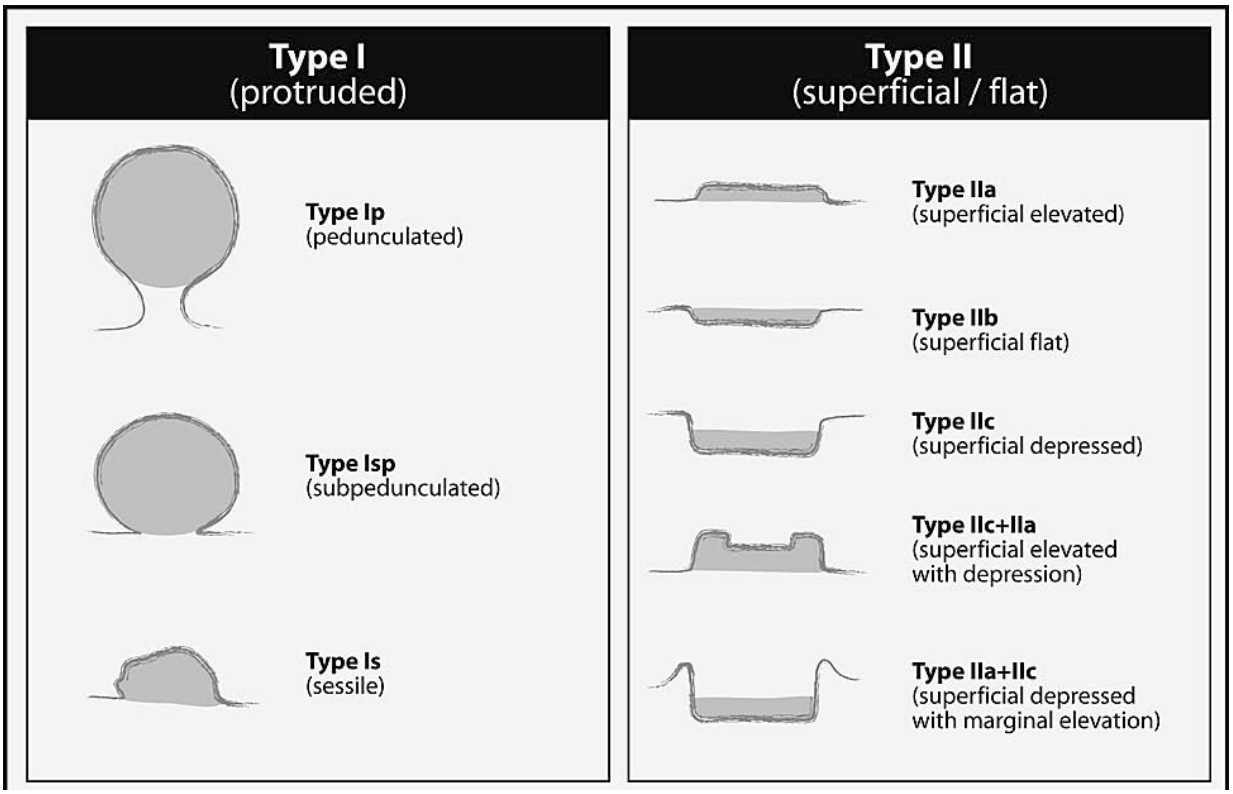


Figure 2: Paris classification of polyps (reproduced from Blanco et al[32])

The Paris classification of superficial neoplastic lesions categorises polypoid lesions of the GI tract (see figure 2)[33]. This method has been employed to allow the standardised global communication of polyp morphology. Emphasis is given to the type II lesions as they are associated with a high incidence of invasive cancer. Further endoscopic technological enhancements have been shown to improve the real-time characterisation of detected lesions. Magnifying endoscopy was introduced for the diagnosis of gastrointestinal diseases with magnified observations. Endoscopists can now visualise the fine details of mucosal surface and vascular patterns. The development of endoscopic technology with high magnification lenses, narrow-band-imaging (NBI) and chromoendoscopy has enabled operators to distinguish the superficial pit pattern of the mucosa[34, 35].

Kudo et al[36] developed the first method to classify polyps according to the pit pattern via magnifying endoscopy. Classification proceeded according to pit appearance, structure and

staining patterns (see figure 3). Type I and II are considered benign (e.g., normal, hyperplastic, inflammatory polyps), whereas classes III-V show neoplastic and malignant changes.

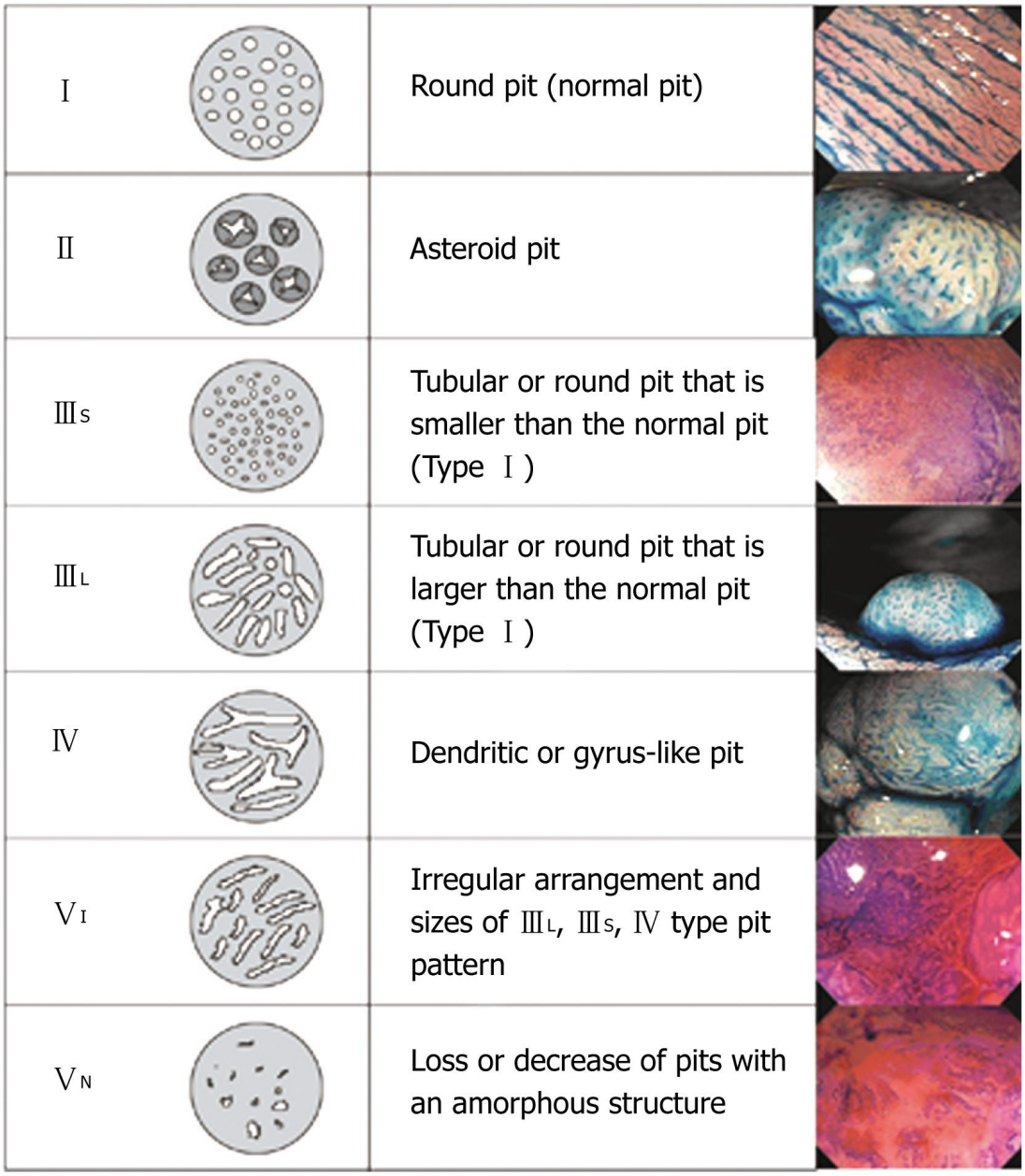


Figure 3: Kudo pit pattern (reproduced from Tanaka et al[37])

Note that the classification frameworks described above are focused on visualisation of the mucosa through the application of flexible endoscopy (FE), which will be described in detail later.

1.7 CRC surveillance

Removal of adenomatous polyps prevents cancer. In those patients that had the removal of one or more polyps during surveillance colonoscopy the incidence of colon cancer was 90 percent lower than patients with no polyps removed[38]. Screening colonoscopy is also safe[39]. Multiple studies have demonstrated a low complication rate from screening colonoscopy, and this risk is offset by the high number of potentially fatal tumours realised.

CRC incidence and mortality rates have been decreasing recently[40, 41]. Death rates from CRC have been decreasing at almost 3% per year for the past 11 years[42]. Mathematical modelling predicts that much of the observed reduction in CRC mortality has been a result of population-based screening methods[43]. There has also been a shift in the location of CRC towards the right-colon worldwide[44-48]. This shift may be due to the increased removal of polyps on the left but the evidence is still mixed[48, 49]. Colonoscopy is generally considered to be better at diagnosing left than right-sided CRC[50, 51], the main reason for this could be the endoscopic technical challenges that generally increase on the right side of the colon.

1.8 Polyp treatment options

Most polyps are amenable to endoscopic removal with simple endoscopic polypectomy, however some polyps are difficult to remove for a variety of reasons: large size (>2 cm), broad-based lesions, location in tortuous colonic segments, or location in haustral folds[52, 53]. Such polyps present a challenge to even advanced endoscopic practitioners using advanced

polypectomy methods. These polyps are termed complex polyps. Often, patients with complex polyps are then referred for oncologic surgical resection due to the small underlying risk of malignancy within the polyp. However, on histopathological analysis after surgery most of these polyps are found to be benign on final pathology[54]. The continued reliance on surgical methods to manage benign disease may further add to the evidence that the appropriate technology does not yet exist for the effective and efficient performance of endolumenal surgery – the performance of advanced procedures within the lumen of the intestine.

Traditional endoscopically mediated polypectomy methods are:

- Cold biopsy (no electrosurgery)
- Hot biopsy (monopolar electrosurgery)
- Cold snare excision
- Hot snare excision (monopolar electrosurgery)
- Fulguration, including with argon plasma coagulation
- Endoscopic Mucosal Resection (EMR)
- Endoscopic Submucosal Dissection (ESD)

Small polyps (<5 mm) are generally removed via biopsy forceps or by snare polypectomy. Those polyps sized >5 to 10 mm are also amenable to snare polypectomy. The use of cold snare biopsy is sometimes advocated in the right side of the intestine and caecum due to perforation risk with electrosurgical use[55].

Incomplete resection rates are higher for complex polyps. The rate of incomplete resection is reported to be significantly higher for larger polyps (>20 mm) compared to smaller polyps (less than 9 mm, 17 versus 7 percent) and for sessile serrated polyps as compared

with conventional adenomas (31 versus 7 percent)[56]. Larger sessile lesion polypectomy warrants intensive follow-up as nearly 30% recur or persist, and up to 20% develop into carcinoma despite visually clear margins[57].

For the purposes of my DPhil work I will only refer to those polyps that are complex in definition and require advanced endoscopic procedures such as EMR and ESD.

1.9 EMR and ESD

EMR (see figure 4) - Complex polyp EMR requires the injection of a submucosal agent, saline with dye or otherwise, and likely piecemeal resection via hot or cold snare of the polyp until all residual tumour has been removed visually[58].

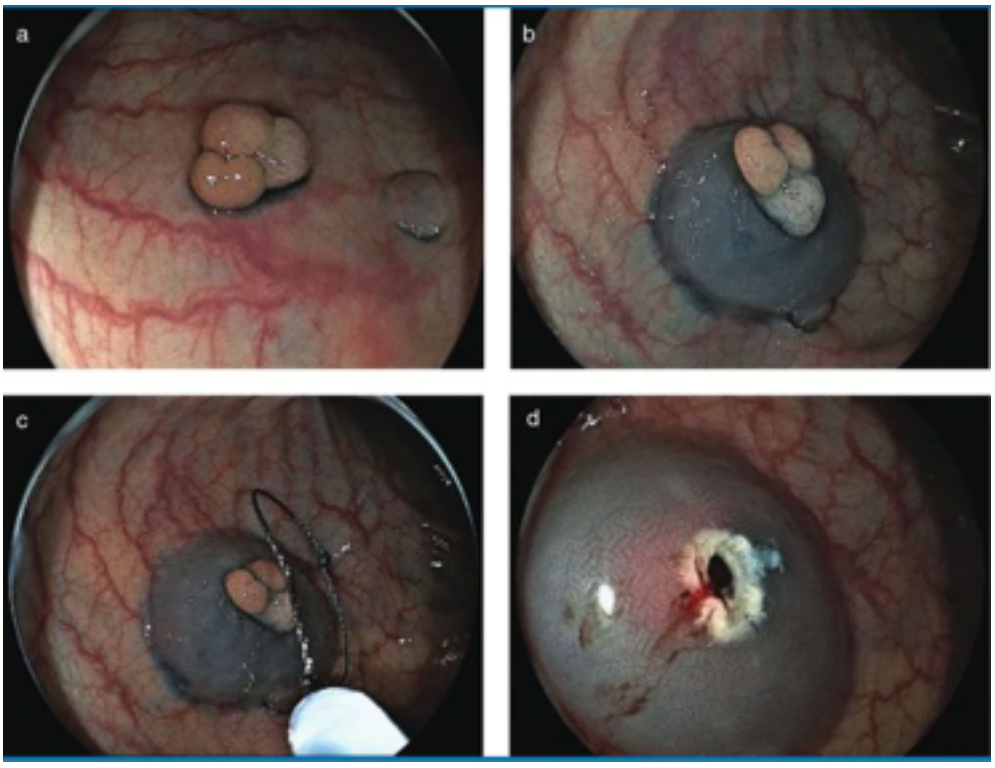


Figure 4: EMR procedure, a, polyp identification; b, submucosal injection; c, snare positioning; d, removal of polyp (reproduced from Yoshida et al[59]).

The EMR technique has a reported success rate of over 95% with a significant proportion of patients requiring multiple treatments of the same polyp. Reported colonic EMR recurrence rates are up to 50%[60-64]. Reported main procedural complications for EMR are bleeding and perforation (penetration of the muscle layer of the intestine – see figure 1). Bleeding rates following colonic EMR range up to 11 percent[64-66]. Perforation following EMR is rare (up to 1 percent)[67, 68].

ESD (see figure 5) – This technique facilitates *en-bloc* polyp resection allowing for improved histopathological specimen assessment. ESD was initially developed in Japan for the resection of early gastric cancer[69] and has subsequently been adapted to the lower intestine. It was only until recently that these techniques were adopted in the West.

Published literature has demonstrated high rates of R0 resection (microscopically margin-negative resection, in which no gross or microscopic tumour remains in the primary tumour bed[70]) and subsequent low recurrence rates of ESD (0 to 2%)[62, 71-73],compared with piecemeal EMR. Successful R0 resection following ESD was found in 85%[74]. However, the technique is technically challenging and so exhibits long procedure duration (up to 290 minutes have been reported)[72] and higher complication rates. The bleeding rate after ESD has been reported to be less than 2%[75]. ESD is also associated with higher perforation rates compared to EMR (6% vs 1%). However, over 90% of these perforations are managed endoscopically or with medical (observation and antibiotics) treatment only[62].

Hybrid technique - This technique involves a circumferential submucosal incision followed by the attempt of an *en-bloc* EMR of the lesion. It has been shown to improve *en-bloc* resection rates whilst decreasing procedure time and technical difficulty[76]. In humans, *en-*

bloc resection was achieved in 55% of the lesions attempted with the hybrid technique and was associated with a complication rate of 13%[77].

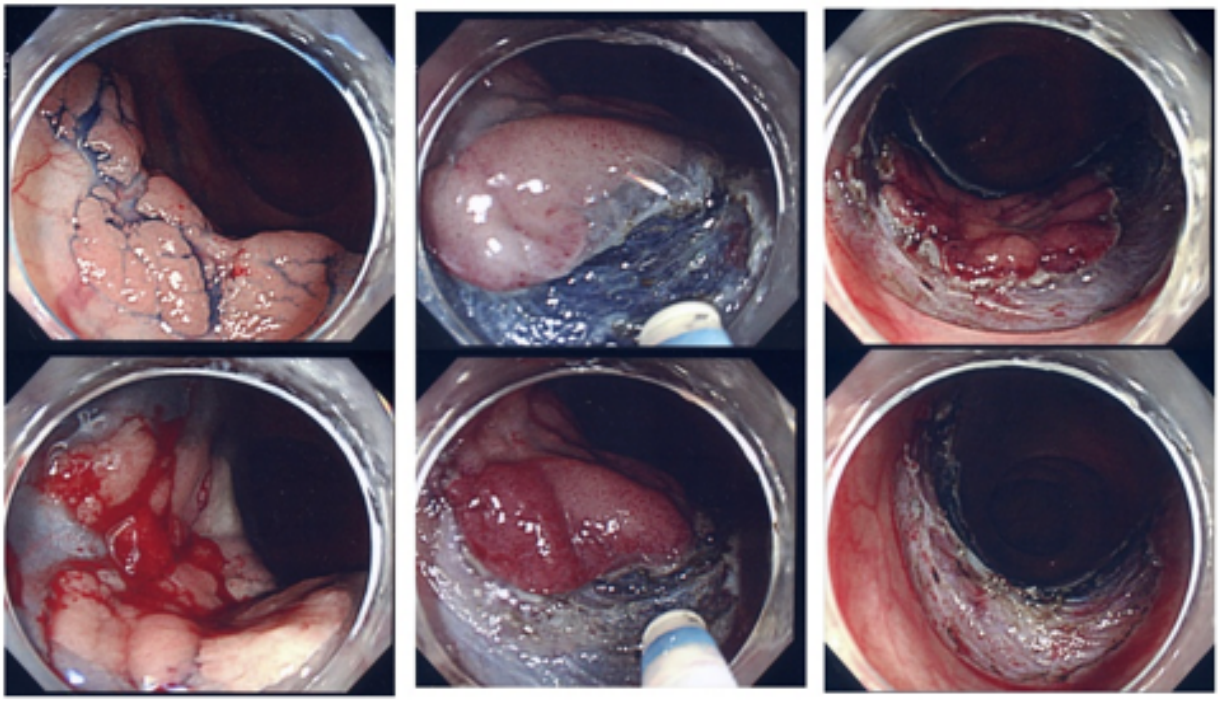


Figure 5: ESD procedure, from upper left panel – visualisation of sessile polyp, lower left panel – submucosal injection, upper middle panel – mucosal incision, lower middle panel – submucosal dissection, upper right panel – circumferential incision with submucosal dissection, lower right panel – lesion removed with resulting mucosal defect, (reproduced from Shida et al[78])

1.10 Challenges of advanced endolumenal procedures

Despite the ESD technique having favourable patient outcomes the uptake penetration in the West has been slow[79]. ESD is a complex, technically challenging procedure that requires extensive experience (and skill)[80]. Previous studies have shown that widespread technical difficulties primarily relate to sub-mucosal dissection and bleeding control[81]. In Japan, ESD is performed in the majority of colonic polyp cases through an extensive nationwide network of capable institutions[82]. Japanese endoscopists follow a regimented training scheme with mentorship, beginning with gastric ESD adeptness, where there is a larger safety margin, before moving onto the colon[83]. The colon is considered more

technically challenging due to its non-fixed nature and relative wall thinness, increasing perforation risk.

To gain proficiency in the West where the case volume is not readily apparent as well as ready access to mentors, models have played an important training role. A European panel of experts recommended that Western endoscopists should observe 15 live ESD cases, followed by *ex-vivo* experiments and finally *in-vivo* animal practicing prior to attempting human ESD. In addition, case selection with regards to the polyp anatomical site was also recommended starting with gastric and rectal lesions before moving proximally in a step-wise fashion once proficiency in each area is achieved[84]. This training approach however, is not feasible for many Western advanced endoscopic practitioners.

1.11 Tissue traction

Another main factor with regards to the long procedure times and technical difficulty associated with advanced endoscopic procedures such as ESD is the lack of robust and effective tissue traction. Tissue traction increases the tension of tissues to facilitate efficient dissection. Multiple endolumenal tissue traction methods have been attempted with varying degrees of success. Traction not only aids in tissue dissection, it also improves submucosal layer visualisation, through lifting away the mucosal flap from the field of view. This increases safety through anatomical layer and submucosal vessel identification. Traction is the most promising avenue to reduce endolumenal procedure times and complications. Several methods have been attempted to date, broadly, these are:

Internal traction - uses rings or springs that are clipped to one edge of the incised mucosa and then clipped to the opposite facing mucosa[85-87]. This method provides continuous traction but cannot generally be repositioned.

Suture and haemostatic clip placement - uses a 3-0 silk suture tied to a haemostatic clip. Once a mucosal flap has been developed the clip with the suture attached is deployed on the lesion edge. The free end of the suture outside the patient, is pulled towards the endoscope tip[88] thereby providing tissue traction towards the operator.

Clip-and-snare pulling - this method uses a haemostatic clip and a snare. After circumferential incision, the endoscope is externally looped into a snare. The scope and snare are reinserted into the patient. A working channel introduced haemostatic clip grasps the incised mucosal flap. The snare is pressed up to the clip. After tightening the snare to grasp the clip it is deployed providing traction towards the operator[89].

External forceps – using an accessory working channel – an external channel placed outside the FE - a second grasping forceps is delivered, grasping the lesion edge. Traction direction can be either towards or away from the endoscope tip. This method has been reported to increase the risk of mucosal injury upon insertion[90].

Double-scope method - a smaller-calibre endoscope is inserted alongside the main scope. Using grasping forceps, the smaller calibre scope grasps the incised mucosa whilst the main scope dissects (see figure 6). The need for two operators in this method is not always feasible[91].

There are multiple challenges associated with these methods. Most are technically difficult, require 2 operators in the case of the double endoscope method and pull the tissue towards the scope tip which is not ideal in the case of tissue dissection. The ideal position is traction away from the perspective of the operator. In addition, most studies reporting traction methods are for gastric lesions.

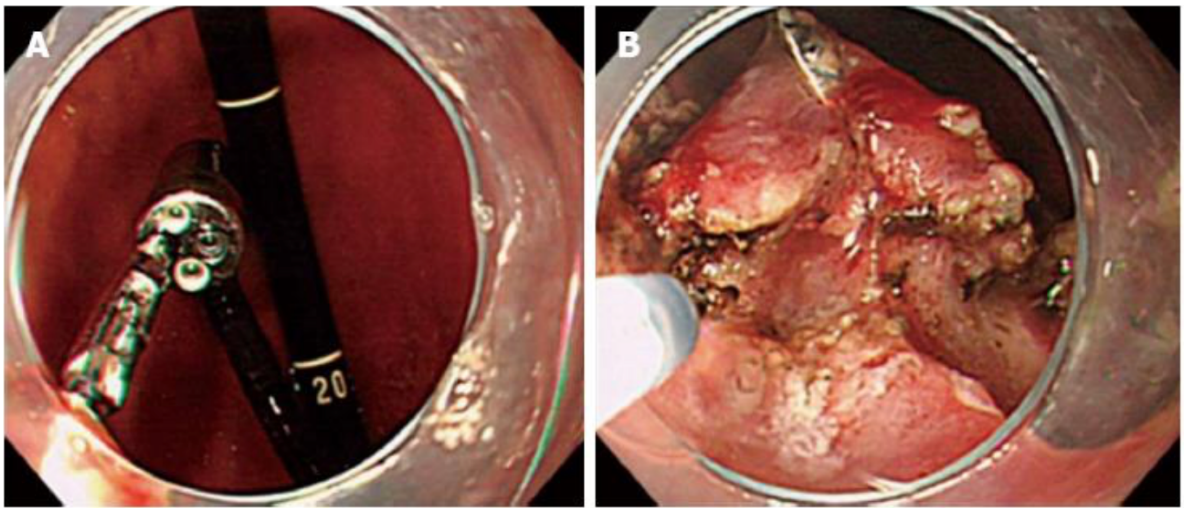


Figure 6: Double-endoscope ESD. A: Lesion grasped and lifted with one scope; B submucosal dissection performed through main scope (reproduced from Imaeda et al[92])

1.12 Surgery and complications

Where endoscopic removal is not possible, surgery is the only modality for treatment and still remains the most common treatment method for benign complex colonic polyps in the United States (Prof. J. Milsom). To provide an oncologically sound procedure in case of polyp carcinoma involves complete tumour removal, along with the vasculature and lymphatics. Segmental resection and wedge resection of the intestine are other options that may be performed according to the surgeons preference[93].

Regardless of the surgical procedure undertaken, there are significant complication risks. Many of these will vary according to various factors (see figure 7).

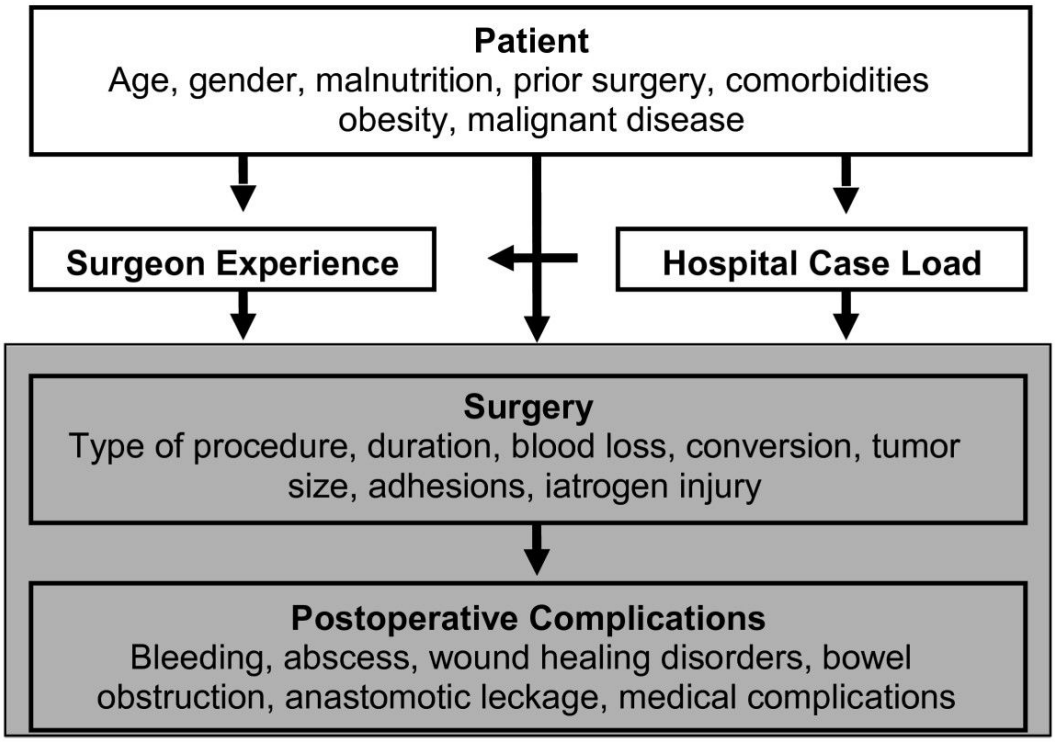


Figure 7: Risk factors for patient complications following CRC surgery (reproduced from Kirchoff et al[94]).

1.13 Major to minimally-invasive and organ preserving surgery shift in non-GI specialties

The breast and cardio-vascular surgical specialities move to a minimally invasive approach serves as recent examples of the shift to organ preservation surgery for early disease. To date, this change has been well documented with excellent results. This shift was facilitated in both specialties through the ability of the operator to have robust visualisation and tissue sampling capabilities.

For at least a century, mastectomy, the complete removal of the breast, was the main treatment for breast carcinoma[95]. Due to increasing population awareness and application of novel diagnostic innovations as well as wide-spread mammographic screening services, breast cancer shifted to diagnosis at an earlier stage[96]. Consequently, the introduction of breast conserving operations such as wide local excision, gave rise to improved cosmesis and less patient morbidity. Subsequent randomised clinical trials confirmed that the minimally invasive breast conservation mode of treatment was an appropriate method of primary therapy for the majority of women with early stage breast cancer[97]. More recent studies have advocated this approach as being preferable because of providing survival rates equivalent to those of total mastectomy and axillary dissection[98].

Both in cardiac and vascular surgery, the increasing use of less invasive methods has shifted the landscape away from open surgery towards the interventional techniques already dominated by other specialties (interventional radiology for example). The introduction of percutaneous coronary interventions, using a catheter based approach, has led to a clear reduction in coronary artery bypass operation volume, itself associated with significant morbidity and mortality[99]. As innovation has progressed, heart valve replacement in select patient groups are currently being performed percutaneously under radiological guidance[100]. The same trend can be seen in the shift of abdominal aortic aneurysm treatment, traditionally managed by graft placement surgery through an abdominal incision, to now endovascular arterial graft replacement (EVAR) using similar percutaneous catheter based approaches[101, 102].

1.14 Flexible endoscopy design stagnation and current limitations

In comparison to the innovation-fuelled progress seen in some specialities, the GI speciality has been historically neglected leading to relative stagnation. FE design and standard

procedures, considered the gold-standard for GI disease diagnosis, have not changed significantly during recent decades[103]. The FE tip can be articulated vertically and horizontally by steering wheels via cables. Manual insertion and retraction can be combined with rotation through torque of the entire endoscope. Light is transmitted from a light source to the endoscope tip from where a camera sensor returns its signal to an image processor connected to a monitor. Channels allow insufflation of the GI lumen with air or CO^2, aspiration of fluid content, and rinsing of the lens. A larger instrumentation channel accommodates various diagnostic and therapeutic tools. FE combines accurate mucosal visualisation, diagnosis and therapy compared to radiological imaging techniques and wireless capsule endoscopy. FE primarily has 1 forward facing camera with up to 180 degrees of viewing angle with a sub-centimetre focus. Within the shaft are 1 or 2 working channels less than 4mm in diameter. In the most basic sense, FE current design is still that of a relatively passive instrument, designed primarily for visualisation and diagnostic sampling. One might say that a similar level of technological investment to produce innovations have not been seen in the GI space as they have in the cardio-vascular space.

1.15 Models for GIT experimentation

Numerous GI models exist for the pre-clinical evaluation of devices and related technology. All have associated positive and negative aspects that must be taken into account when selecting the appropriate model.

In-vitro

1. Symbionix® trainer – primarily as a virtual reality trainer to condition the trainee to the endoscope controls and accessory tool use[104].

2. Kyoto-Kagaku® trainer – silicone colon in plastic 'abdomen' – bench top trainer utilising actual endoscopic equipment for a realistic experience.

Ex-vivo

1. Mounted animal tissue – real-time use of endoscopic equipment and related technology for realistic tissue response and skills acquisition.
2. Human cadaver – appropriate tissue response with incorporation of accurate human anatomical considerations

In-vivo

1. Canine model – similar to human intestine
2. Porcine model – rectum similar to human, larger size and ability to test systems in extreme configurations e.g. spiral colon

1.16 Endoscopic Full Thickness Resection

Endoscopic Full Thickness Resection (eFTR) could be thought of as the next step in endolumenal surgical evolution, after EMR and ESD. This is facilitated through full-thickness lesion excision (all layers of the intestine, see figure 1) as opposed to dissection at the sub-mucosal level. eFTR has been used to treat gastric lesions for some time, however its use is relatively nascent in colorectal lesion treatment.

Following the review of 28 studies (Sharma et al, unpublished - see appendix) that met specific inclusion criteria all (human studies only and reported above 10 patients), 24 gastric and 4 colonic reports were sourced between 1999-2015. These reports were all retrospective in nature and included a total of 828 patients. Of these, 100 patients underwent colonic eFTR (12%). When reported, the mean polyp size in the colonic group was 2.5cm. Reported clinical success was defined as complete lesion resection as per

histological confirmation and was observed in 100% of patients in the gastric group and 91% in the colonic group. Overall, a similar proportion of patients in the colonic eFTR group experienced post-procedural complications, local peritonitis and bleeding, compared to the gastric group (4%). Procedurally, an eFTR operation can be separated into 2 components (1) resection method and (2) defect closure.

In these reports, 8 different resection methods of gastric eFTR were described; Combined Endoscopic Laparoscopic Surgical (CELS)-type rendezvous procedures, grasp and snare techniques, Over The Scope Clip (OTSC) technique, suturing techniques, full-thickness ESD techniques, APC dissection, stapling and endoloops. In the colonic group 4 different methods of eFTR were described; lift and snare, dissection and active perforation, OTSC and EMR.

In the colonic eFTR group 4 different methods of defect closure were used, (t-tag closure, endoscopic haemostatic clipping, OTSC clip and a novel clip design). 6 different gastric eFTR defect closure techniques were described; suturing (both intra and extra lumenally), OTSC, stapling, haemostatic clips, omental patches and endoloops. In the gastric group, the mean time of procedure completion was significantly shorter (72.7 mins,10-480) than the colonic group (113 mins, 50-267, $p<0.05$).

In performing this literature review, it was evident that eFTR actually described a heterogeneous group of procedures, with differing methods and defect closure techniques across disciplines. This indicated that there was a clear need for bespoke technology facilitating such procedures in a pure endolumenal methodology.

1.17 Medical device development pathway

The U.S. Food and Drug Administration (FDA) defines a medical device as one that[105]:

- diagnoses, cures, lessens, treats, or prevents disease
- affects the function or structure of the body
- does not achieve primary intended purposes through chemical action

The FDA Centre for Devices and Radiological Health (CDRH) outlines a medical device total product life cycle as one that occupies product development from initial concept to product launch (see figure 8)[106]. The pathway for device development was once thought of as a linear one, however in reality it is cyclical and iterative. Ideas for healthcare innovations are first prototyped, evaluated, enhanced, re-tested, and optimised with a clear focus on patient safety. The device development pathway is a process with cycles and subsequent device modifications. Although often depicted as a grouped method with discrete parts – such as pre-clinical and clinical – these parts often overlap and portions may need to be repeated often as the device approaches its final design. These distinctions are useful for the relevant governmental body regulatory decision (FDA in the USA).

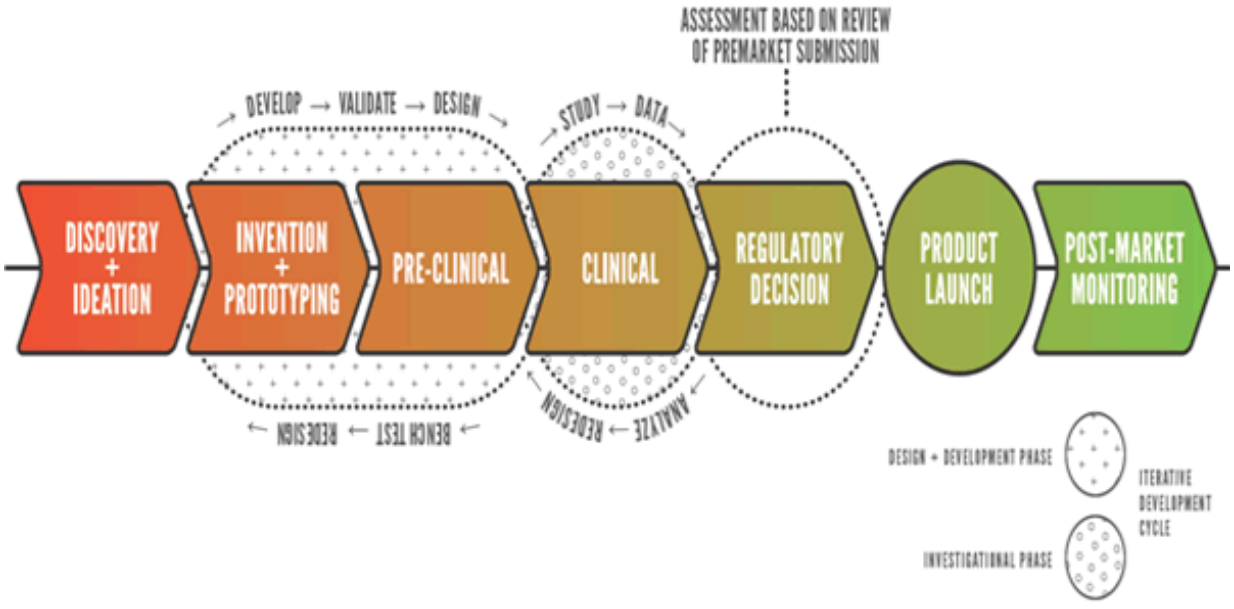


Figure 8: Medical device product life cycle (reproduced from CDRH[106])

1.18 Device biocompatibility and material selection

A biomedical device must preserve its set functions within the human body. Device materials will encounter the body. The International Organisation for Standardisation (ISO) has published guidance on device types (see table 1), classified according to the nature of evaluation involved and the body anatomical area it is used[107]. This framework dictates the biological testing required in the FDA approval process. The requirements can be classified into four main categories, including the device packaging chemical, mechanical, electrical, and thermal characteristics[108].

Most modern medical device packaging consists of synthetic polymers. Various synthetic and natural polymers are used in medical devices and some natural polymers may have additional benefits, such as biodegradability but also may exhibit allergy characteristics such as in the case of latex[109].

For the purposes of my work, I will discuss commercially available synthetic polymers, as they are abundant, cost-effective and do not exhibit the same allergic profile as natural polymers.

Device Categories			Biological Effect										
Body Contact		**Contact Duration** A = Limited (≤24 Hours) B = Prolonged (24 Hours – 30 Days) C = Permanent (>30 Days)		Cytotoxicity	Sensitization	Irritation/Intracutaneous	Acute Systemic Toxicity	Subchronic Toxicity (Subacute toxicity)	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity
Surface Devices	Skin	A		x	x	x							
		B		x	x	x							
		C		x	x	x							
	Mucosal Membrane	A		x	x	x							
		B		x	x	x	o	o		o			
		C		x	x	x	o	x	x	o		o	
	Breached or Compromised Surfaces	A		x	x	x	o						
		B		x	x	x	o	o		o			
		C		x	x	x	o	x	x	o		o	
Externally Communicating Devices	Blood Path, Indirect	A		x	x	x	x				x		
		B		x	x	x	x	o			x		
		C		x	x	o	x	x	x	o	x	o	o
	Tissue/Bone/ Dentin[1]	A		x	x	x	o						
		B		x	x	x	x	x	x	x			
		C		x	x	x	x	x	x	x			
	Circulating Blood	A		x	x	x	x		o[2]		x		
		B		x	x	x	x	x	x	x	x		
		C		x	x	x	x	x	x	x	x	o	o
Implant Devices	Tissue/Bone	A		x	x	x	o						
		B		x	x	x	x	x	x	x			
		C		x	x	x	x	x	x	x		o	o
	Blood	A		x	x	x	x	x		x	x		
		B		x	x	x	x	x	x	x	x		
		C		x	x	x	x	x	x	x	x	o	o

Table 1: FDA guidance on biological evaluation of medical devices, x denotes testing required, o indicates additional testing required (adapted from FDA[110])

From a biological perspective, medical device materials should be bioinert and biocompatible[111]. However, this characteristic depends on the type of material used. Biocompatibility is defined as, "the ability of a biomaterial to perform its desired function…, without eliciting any undesirable local or systemic effects in the recipient, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically relevant performance of that therapy"[112].

One challenge in the selection of materials for use in medical devices is the consideration of the anatomical area in which the device will be used. Different biological systems exhibit different mechanical parameters as well as inherent biological processes e.g. low pH in the stomach. Material selection must take these parameters into consideration to be specific for the intended purpose. Ceramics, metals, polymers, and polymer composites make up most of the materials used for device manufacture[113]. For the purposes of my DPhil work, I will focus on polymer materials.

1.19 Polymers

Polymers are extremely flexible biomaterials with a long history of use. They are available in an expansive array of structures, properties and forms that can be fashioned into any shape complexity, with specific advantages and disadvantages (see table 2). Polymers exhibit fluid absorption features, which may result in the structure increasing in size, and subsequently leach by-products into the surrounding tissue. Polymer and polymer composites are also non-magnetic and are radio opaque for radiological and magnetic resonance imaging studies[114].

1.20 Polymer sterilisation

Device sterilisation is a process which is employed to eliminate viruses, bacteria, fungi and spores[115]. Different methods of sterilisation exist such as ethylene oxide, gamma radiation, steam, electron beam, and dry heat with specific advantages and limitations[116]. In the case of polymers, damage can result from specific methods. For example, dry heat sterilisation methods could cause material deformation and further damage such as colour changes to the material itself[117, 118].

1.21 Polymer types

Polytetrafluoroethylene (PTFE) - PTFE (Teflon™, Dupont®) is a fluorocarbon with low friction and non-adherent properties, to date it has been used in a wide-variety of biomedical applications[113]. PTFE- coated catheters are commonly used as surgical drains[119]. PTFE devices can also be used to deliver drugs tissue targets within the body[120]. Modifications of stents with PTFE have also been shown to be able to modulate tumour effects *in-vivo*[121].

Polyurethane (PU) - PU is a polymer comprised of organic units joined by carbamic acid derivatives. PU has historically been used in a wide-range of biomedical applications[122]. PU can be tuned to allow tissue in-growth through *in-vivo* material degredation[123]. Post implantation it is stable over long periods[124, 125]. Due to its fabrication flexibility, different morphologies of PU can be used to suit the clinical application, e.g. PU foam as a packing material after mucosal trauma[126]. The properties of PU can also be modified to suit different biological applications[127].

Thermoplastic PU (TPU) is a relatively new material which has alternating hard and soft co-polymer blocks. This modification enables a diverse array of elastic and colour features that also provide improved mechanical and biocompatible properties[128]. The addition of silver atoms to TPU polymer blocks was found to have a reduced lag phase of bioactivity compared to normal PU composites[129]. Looking to the future, TPU has been combined with iron nanoparticles to display magnetic characteristics[130].

	Advantages	Disadvantages
Polyurethane[123, 131]	Durability Toughness Good biocompatibility Good biostability Low coefficient of friction	Environmental stress Cracking Degradation of the material in vivo
Polytetraftuaroethylene[132]	Inert Mechanically strong Insulator Hydrophobic	Stiff Insulation microdefects
Polyimide[133]	Chemical resistance, High tensile strength Flexible Temperature stable Heat resistance, High light transmittance	Fluid absorption

Table 2: Advantages and disadvantages of commonly used polymer materials

Polyimide (PI) – PI is an imide monomer block polymer. Numerous polyimides groups exist based on their polymer chains, hydrocarbon residue types, and functional groups. Due to this, PIs have varied physical properties and possible applications. PIs have demonstrated long term survivability *in-vitro* and no decrease in tensile properties in almost 2 years of implantation[134]. A differentiating use of PI compared to other polymers is in optoelectronic devices, meditated by its ability for wide range wavelengths transmission of light[135]. Polyimide sensors have also been used in neurological implants as well as for glaucoma pressure sensors[136].

Numerous other polymer classes exist[114], a comprehensive list and explanation of all these types would be beyond the scope of this thesis, as such, I have focussed on the most important types to my work.

1.22 Clinical studies for medical devices

Once a medical device has been fabricated, manufactured according to specific criteria and approved for clinical use by an appropriate regulatory body it is ready for clinical use. The Idea, Development, Exploration, Assessment and Long-term study (IDEAL) methodology is a useful framework for medical device innovations evaluation (see table 3)[137]. This framework was developed in conjunction with and subsequently endorsed by the FDA[138]. Despite the rapid expansion of medical device usage in the past decades the overall number of randomised controlled trials and systematic reviews in these innovations remains small compared with the number of studies evaluating drug treatments. Reported trials also fail to grasp the success characteristics of the intervention that significantly relies on operator skill and judgment[139].

IDEAL framework				
Stage 1: Idea	**Stage 2a: Development**	**Stage 2b: Exploration**	**Stage 3: Assessment**	**Stage 4: Long term study**
Question				
Can the procedure or device achieve a specific physical or physiological goal?	What is the optimal technique or design, and for which patients does it work best?	What are the outcomes of more widespread use? Can consensus equipoise be reached on a trial question?	How well does the procedure work compared with current standards of care?	What are the long term effects and outcomes of the procedure?
Aim				
Proof of concept	Safety, efficacy	Efficacy	Comparative effectiveness	Quality assurance
Patient base				
Single to few	10s	100s	100s+	100s+
Optimal study design(s)				
First-in-man study; structured case report	Prospective development study	Prospective collaborative observational study (Phase IIS) or feasibility randomised controlled trial (or both)	Randomised controlled trial	Observational study or randomised trial nested within a comprehensive disease based registry

Table 3: IDEAL framework stages (reproduced from McCulloch et al[137])

Idea (IDEAL stage 1) - Prior to clinical use of a medical device, all first-in-man (FIM) interventions should be included in an open access registry recording device key details. A literature review should first be performed[140]. Independent clinical governance review should be performed locally such as Institutional Review Board (IRB) oversight. Consent for new procedures is important: patients contemplating whether to undergo such procedures must fully understand their experimental nature, and the uncertainty that therefore surrounds any estimates of risk.

A key feature of this stage is the need to formally record unsuccessful interventions, to avoid unnecessary repetition by peers, as well as the successful ones, in a case-by-case description.

Development (IDEAL stage 2a) - This stage begins once doctors plan a case series using the new device. There are generally rapid iterative changes due to cumulative experience by the principal investigator on a case-by-case basis. Experience often makes the need for modification obvious after a few repetitions. Historically these modifications have been poorly reported i.e. reporting the final approach as opposed to the journey to get to that point. This method deprives the reader the opportunity to learn from the development process, and can provide a misleading picture of the use of a device.

The pressure to innovate and improve current treatments is such that all stakeholders including funders, patients, and clinical colleagues expect to be updated on progress as rapidly as possible, to make decisions about funding, treatment, or use. If such decisions are to be made regardless (which seems a reasonable assumption barring a radical change in how health provision is organised internationally), they should at least be made using the

most complete and accurate information available. The key principle in the IDEAL method is transparency

At the IDEAL 2a stage there should be prospective rather than retrospective studies, with sequential reporting of all cases and outcomes without omissions, and with clear explanations of when and how technique, design, or indications were changed. Sequential presentation of results might also reveal the effects of operator learning curves, which have an even more important role in the next stage of exploration. The FDA, which has been re-evaluating the regulatory framework for implantable devices since the Institute of Medicine report has put forward proposals for early studies of innovative devices that closely follow this model[141].

Prospective development study (PDS) key elements are a prior protocol, clearly defined objective outcomes, and transparent sequential reporting of cases, showing when changes in indication or technique are made. Data from this type of study will be more reliable and valid than information obtained from retrospective series.

The remaining IDEAL stages, exploration, assessment and long-term study are critical to the success of a medical device but are beyond the scope of my DPhil work.

1.23 My work

Published literature and future projections all point to a cancer disease burden that is global, pervasive and increasing alarmingly in the young. Key recommendations have expressed the unlikelihood of current methods to meet future needs and so the pursuit of alternative, novel approaches have been recommended.

Such methodological transformations have been seen in other specialties, changing from formal surgery to a more minimally invasive approach through device innovation, which has been historically stagnant in the GI space. Despite this, recent GI tumour removal strategies have surfaced such as ESD but remain technically challenging and poor uptake has persisted despite superior clinical outcomes.

This knowledge led me to investigate the practical use of a biocompatible medical device to stabilise the FE in the GIT as well as increase the visible mucosal field, to facilitate advanced endolumenal procedures such as ESD. In my DPhil work I will chart the development of a Stabilising and Visualisation Device for Endoscopes (SVDE) from a simple sketch to the completion of the first clinical trial following the preclinical and clinical frameworks outlined by the FDA and IDEAL.

My work will be divided into three sections (1) preclinical safety considerations, (2) preclinical functional characterisation and (3) clinical safety. I will also chart the multiple challenges that needed to be overcome in order to develop a safe, clinically relevant medical device.

2: Materials and methods

Introduction

As described in the introduction, there are important governmental and professional body frameworks to give guidelines to develop a safe device. Safety considerations are individualised to the type of medical device as well as the anatomical area being explored. This chapter outlines the discovery of the parameters followed to characterise the first SVDE prototype, including the important safety considerations to prevent serious patient injury. I go onto outlining the fabrication method for SVDE. I finally will prescribe the various *in-vitro*, *ex-vivo* and *in-vivo* preclinical experimental procedures used in the next chapter for reference.

2.1 Intestinal safety parameters identification

Firstly, I performed a literature review to identify human colonic basic parameters of interest with a focus on safety considerations. This is an important first step in the development of a medical device, particularly for engineering considerations. Sources are referenced with each parameter. I will attempt to consider and explain studies which deal with similar topics together, explain the significance of the results and whether they agree, and show the relevance to the proposed work.

Literature review methods

I performed a non-systematic review of the literature based on data from Medline (PubMed), Google Scholar and Science Direct. The research was done on articles in English, published prior to the 31st of December 2013. The research was based on the following Mesh headings (Medical Subject Headings): “geometry” OR “anatomy” AND “colon” OR “intestine”. Animal and human data was included. Based on these criteria, this

type of non-systematic review is called a mapping literature review i.e. a review that attempts to categorise existing literature on a certain topic. There are however, weaknesses with using this approach namely 1) Mapping literature non-systematic reviews lack a comprehensive quality assessment as this exercise mostly categorises literature by their study design and not on other elements and 2) the analysis of the found literature is mostly on a broad descriptive level which might oversimplify the drawn conclusions and masks variation between the results of the individual studies[142, 143].

Human

Basic Intestinal Geometry (Length and Diameter)

As a result of the search, 7 sources were identified. A summary of the findings are described below:

1) Burch 2008: The colon is generally 1.5m in length with a diameter of 7cm at the caecum, reducing to 2.5cm at the sigmoid. The caecum if a blind ended pouch, about 6cm in length. The ascending colon is approximately 13cm in length. The transverse colon is 50cm in length. The descending colon is 25cm in length. The sigmoid colon is 40cm in length. The rectum is 17-20cm in length. The anal canal is 3cm in length.

2) Moore 2010: The cecum is 10cm long with the widest diameter being 7.5cm. From the cecum the ascending colon extends 12-20cm. The transverse colon spans 40-50cm. Descending colon spans 25-30cm. Sigmoid colon 35-40cm in length. The rectum is defined as the last 12cm above the anal verge.

3) Gray 2001: The large intestine is 1.5 metres long. on an average it may be said to be 6.25 cm. in length and 7.5 in breadth. The sigmoid colon is 40cm in length. The rectum is 12cm long. The anal canal measures 2.5-4cm in length.

4) Einhorn 1904: The large intestine measures 5-6ft in length. At the cecum its diameter is 28.5cm, 20.5cm at the ascending and 14.5cm at the descending.

5) Sadahiro (1992): Length, diameter and surface area of each of 6 segments of the large intestine were determined and calculated in 920 Japanese patients who underwent barium

enema. Surface area of the cecum, ascending, transverse, descending, sigmoid and rectum were 62, 242, 513, 189, 374 and 202 cm^2 respectively.

6) Jones (1969): Radiographic analysis of colon diameter in United Kingdom normal patients (n=100), colitic (n=31) and those with megacolon (n=15). Normal patients had an ascending colon mean diameter of 5-6cm, the transverse 3.9-4.9cm and descending 3-3.5cm (air contrast versus plain radiographic film measurement).

7) Huebner (2007): Magnetic Resonance Images of 2 groups of nulliparous females. 30 years and younger (n=32) and 50 years and older (n=32). Older females had a 33 percent thicker internal anal sphincter (younger vs. older: 4.5 ± 0.7 vs. 5.9 ± 1 mm; $P < 0.001$), a 20 percent larger inner diameter (7.1 ± 1.3 vs. 8.5 ± 1.8 mm; $P = 0.001$), and a 27 percent larger outer diameter (16 ± 2.1 vs. 20.3 ± 3.3 mm; $P < 0.001$) than younger females.

Biases: Clear biases exist in the sources selected, particularly with regards to patient population; gender specific results such as in the case of Huebner et al and ethnic differences in the case of Sadahiro and Jones.

Summary of results

Anatomical Feature	**Measurement (cm)**
Length of Colon[144, 145]	123-200
Length of Caecum[144, 145]	6-10
Length of Ascending Colon[144, 145]	12-20
Length of Transverse Colon[144, 145]	45 - 50
Length of Descending Colon[144, 145]	22-30
Length of Sigmoid Colon[142]	25 - 46
Length of Rectum[144, 146]	17-20

Length of Anal Canal[144, 146]	2.5-4
Circumference of Caecum[147]	23.5-28.5
Circumference of Ascending[147]	20.5
Circumference of Descending[147]	14.5
Circumference of Sigmoid[145]	7.85
Diameter of caecum[148]	4
Diameter of Ascending[148, 149]	5-6
Diameter of transverse[148, 149]	4-5
Diameter of descending[148, 149]	3-3.5
Diameter of sigmoid[148]	3-4
Diameter of rectum[148]	4
Diameter of internal anal sphincter[150]	4.5-5.9
Surface area of caecum[148]	62cm^2
Surface area of Ascending[148]	242 cm^2
Surface area of transverse[148]	513 cm^2
Surface area of descending[148]	189 cm^2
Surface area of sigmoid[148]	374 cm^2
Surface area of rectum[148]	202 cm^2

Intestine flexure radii geometry

1 source was identified for flexure radii geometry, 3 D Computer Aided Design (CAD) data was reviewed, measured, and extrapolated. The results were as follows:

Anatomical Feature	Measurement
Hepatic flexure radius[151]	2 cm
Hepatic flexure degrees[151]	85 degrees
Splenic flexure radius[151]	2 cm
Splenic flexure degrees[151]	140 degrees

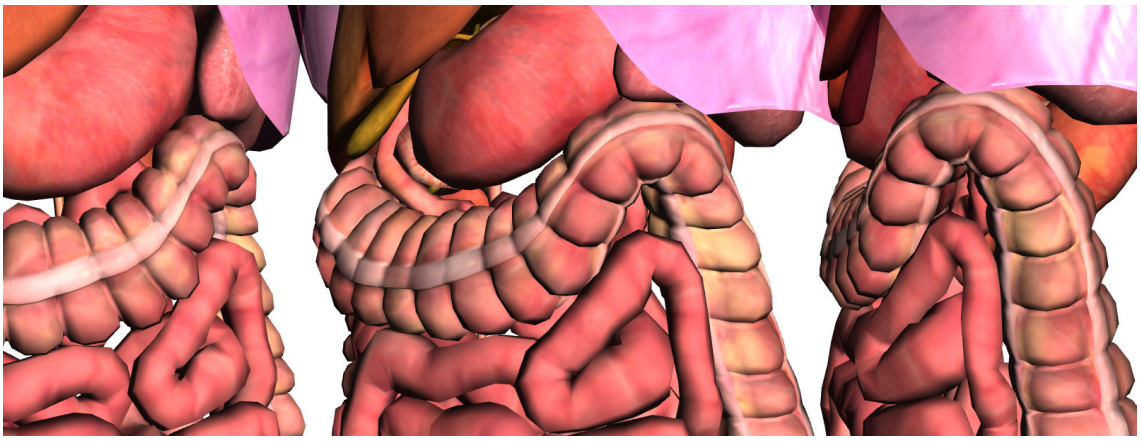


Figure 9: Splenic flexure 3-D model[151]

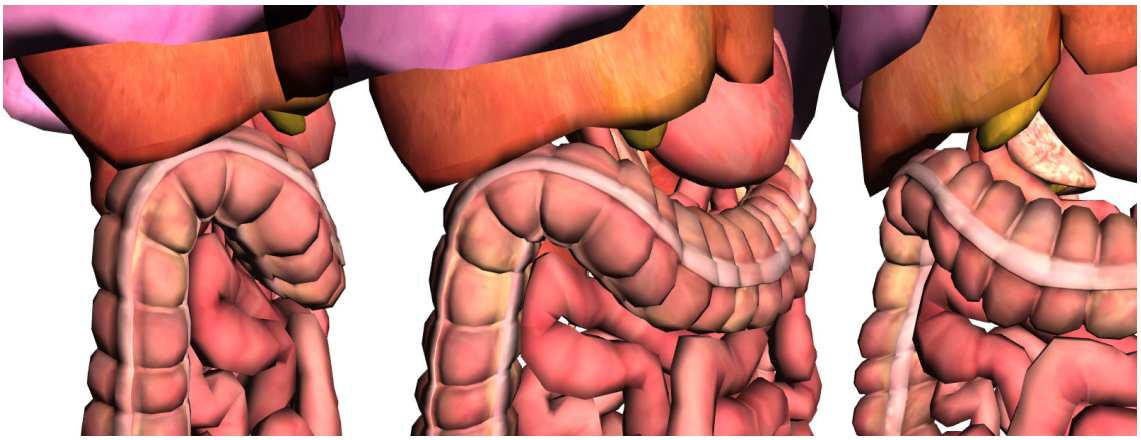


Figure 10: Hepatic flexure 3-D model[151]

Biases: Only one source was identified for this parameter.

Intra-abdominal pressure

One source was identified for intra-abdominal pressure (Kovac et al 2007). The results of this were as follows. The use of one source introduces significant bias.

Anatomical Feature	**Measurement**
Intra Abdominal Pressure[152]	6.5 mm Hg (range 2-16.2 mm Hg)

Intestinal tissue thickness

Since the bowel is characterized by spastic activity, colonic wall thickness varies with degrees of distension[153]. As a result of the search, 2 sources were identified. A summary of the findings are described below:

Wiesner et al (2002): 100 USA patients. Colonic wall thickness on computed tomography was measured. The normal colonic wall thickness ranged from 0 to 2 mm in colonic segments with a diameter of ≥4–6 cm, from 0.2 to 2.5 mm in colonic segments with a diameter of 3–4 cm, from 0.3 to 4 mm in colonic segments with a diameter of 2–3 cm, and from 0.5 to 5 mm in colonic segments with a diameter of 1–2 cm. Maximal colonic wall thickness ranged up to 6 and 8 mm in the proximal and distal colon, respectively, if the measured colonic segment showed a luminal width of <1 cm according to contraction.

Fisher (1982): 84 USA patients CT images were examined. None of the measured thicknesses exceeded 3mm.

Diameter (mm)	From (mm)	To (mm)
<10 mm	0.5	8
10 – 20 mm	0.5	5
20 – 30 mm	0.3	4
30 – 40 mm	0.2	2.5
40 – 60 mm	0	2

Table 4: Aggregate intestinal thickness measurements[153, 154]

Bias: Using 2 sources introduces a certain amount of bias. The United States population could be considered a heterogeneous population however, no specifics of the patient demographics were available from the reports.

Colon tissue mechanics

As a result of the search, 3 sources were identified. A summary of the findings are described below. These sources were particularly relevant to future work due to the device key feature of balloons. Inflation of balloons within the lumen on the large intestine increased the risk of intestinal stretching and potential bursting. These studies were performed on cadaveric or surgical specimens.

Egorov et al (2002): Using human tissue this study constructed stress-strain curves to failure (figures 11 and 12)[155]. These data are extremely important as they indicate the failure modes of the anatomy of interest. The tensile properties of 150 Russian origin cadaver transverse colons (6.5cm long by 1cm wide) were tested. The mean thickness of a specimen was equal to 1.95±0.85, and 0.910±0.37mm for cadaveric, surgically removed tissue and for cadaveric large bowel, respectively. The values of maximal stress and destructive strain were 0.9MPa and 180% for the large intestine.

Longitudinal specimens exhibit 2 stress points maxima: first point approximately coincides with muscular layer destruction and the second point the destruction of the submucosal layer. Haustral longitudinal specimen presents only one stress maximum, the muscular layer ruptures along the linear increase towards the maximum, with the submucosal layer rupturing at the fall of the maximum.

Why 150 cases were studied is unknown and unable to be gleaned from the publication. According to the paper, previous work by Yamada et al (1972) showed that various organs of animals and human beings placed in a physiological saline solution and stored overnight at 4°C had constant strength values for different postmortem times before testing. Despite this, it is unknown how the tissue was harvested and maintained in each regard only that the

cadavers were kept at 4C. This study indicated that the mechanical strength of the colon is determined by the muscular and submucosal layers, whereas the serosa and mucosa have no significant strength characteristics or contributions.

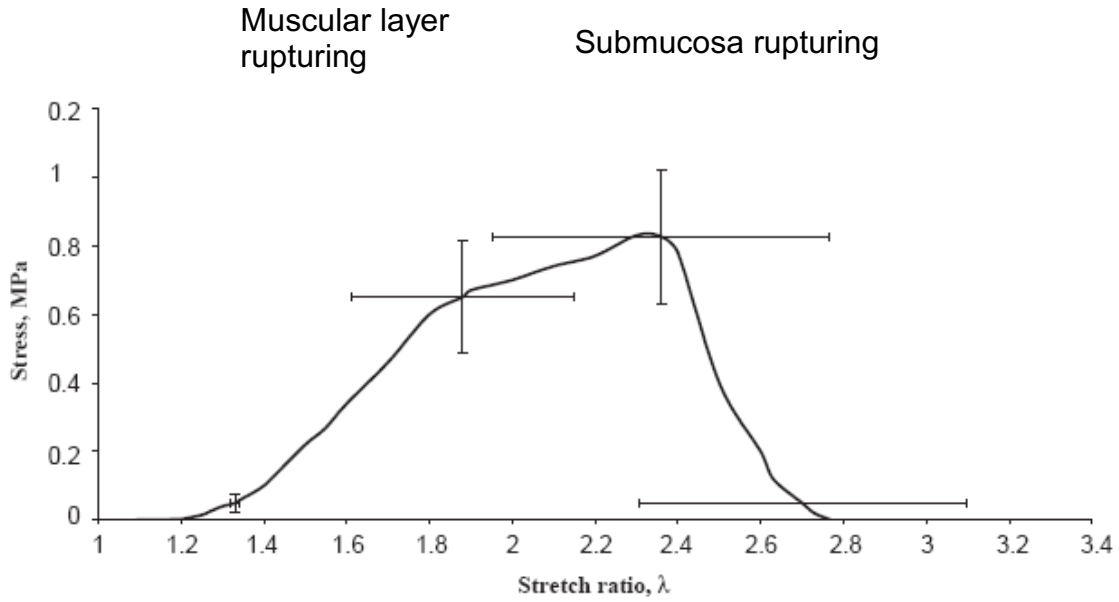


Figure 11: Overall stress-strain curve for tissue (reproduced from Egorov et al[155])

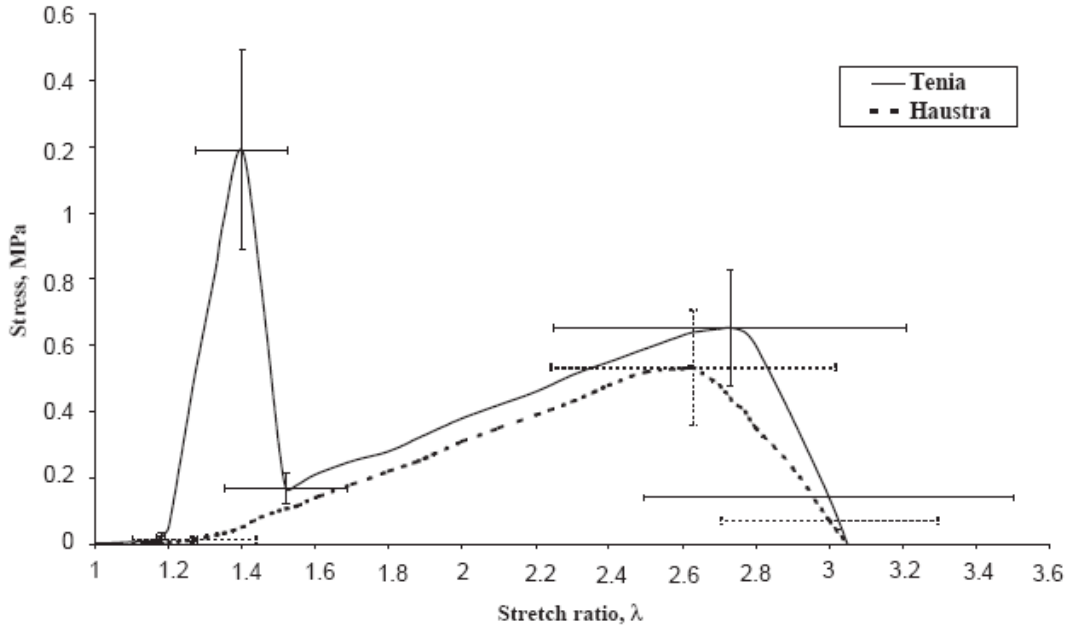


Figure 12: Overall stress-strain curve for tissue (reproduced from Egorov et al[155])

Parameter	ε_{beg} (%)	ε_{fin} (%)	σ_{r1} (MPa)	ε_{r1} (%)	σ_{r2} (Mpa)	ε_{r2} (%)
Value	33.29±13.0	176.66±39.48	0.645±0.165	87.85±27.0	0.826±0.197	135.98±40.58

Table 5
Cadaveric large bowel stress–strain parameters, longitudinal specimens

	ε_{beg} (%)	ε_{fin} (%)	σ_r (Mpa)	ε_r (%)	σ_a (MPa)	ε_a (%)	σ_b (Mpa)	ε_b (%)
Tenia	18.42±12.09	205.49±50.4	1.188±0.302	40.94±12.5	0.168±0.045	52.43±16.72	0.652±0.174	173.45±47.85
Haustra	27.12±16.8	205.65±29.48					0.533±0.173	162.78±38.75
Level of significance	<0.005	>0.5					<0.001	>0.2

Strain (%) = (stretch ratio – 1) * 100

Reminder stretch ratio = l/ lo

Hence strain = Δl / lo *100

Failure strain

First stress maximum

Strain level corresponding to first stress maximum

Second stress maximum

Strain level corresponding to second stress maximum

Table 5: Intestine stress-strain parameters (adapted from Egorov et al[155])

Watters et al (1984): Examination of the large intestines of 32 UK cadavers kept at 4C and 20 African cadavers. When any material is strained and the strain is held constant, the stress induced in the wall of that material decreases over time. Widths of different sections of intestine at burst were analysed with the percentage elongation from the original length noted[156]. Width at burst differed between the two groups, ranging from 70-99mm for the UK group to 104-129mm for the African group.

		Ascending colon	*Transverse colon*	*Descending colon*	*Sigmoid colon*
Burst strength (g)	Edinburgh	1378±822	1223±701	1242±657	1266±646
	Kampala	1799±648	1687±585	1638±499	1618±663
Cross-sectional area (mm^2)	Edinburgh	14·7±6·5	14·1±6·2	14·7±7·4	19·0±9·3
	Kampala	14·3±4·2	13·1±4·2	14·8±5·7	16·6±5·9
Tensile strength (g/mm^2)	Edinburgh	104±65	98±57	104±61	81±49
	Kampala	134±56	139±57	127±65	110±51
Internal diameter (mm)	Edinburgh	36±20	30±15	23±12	23±13
	Kampala	49±22	43±22	35±15	36±16
Width at burst (mm)	Edinburgh	99±48	90±39	70±31	71±30
	Kampala	129±46	108±41	111±36	104±33
Elongation (%)	Edinburgh	206±179	221±187	222±125	253±185
	Kampala	182±99	171±122	192±143	235±148
Stress relaxation	Edinburgh	0·179±0·028	0·189±0·029	0·185±0·020	0·188±0·024
	Kampala	0·162±0·025	0·171±0·020	0·181±0·017	0·178±0·019

Table 6: Width of colon at burst and % elongation (adapted from Watters et al[156])

Rosenburg et al (1972): In this investigation, a length of sigmoid colon was surgically removed in 15 patients. The segment was inflated with compressed air (70psi) at increasing pressures. The results demonstrated an average bursting pressure of 5.9 psi (standard deviation 0.59 psi)[159].

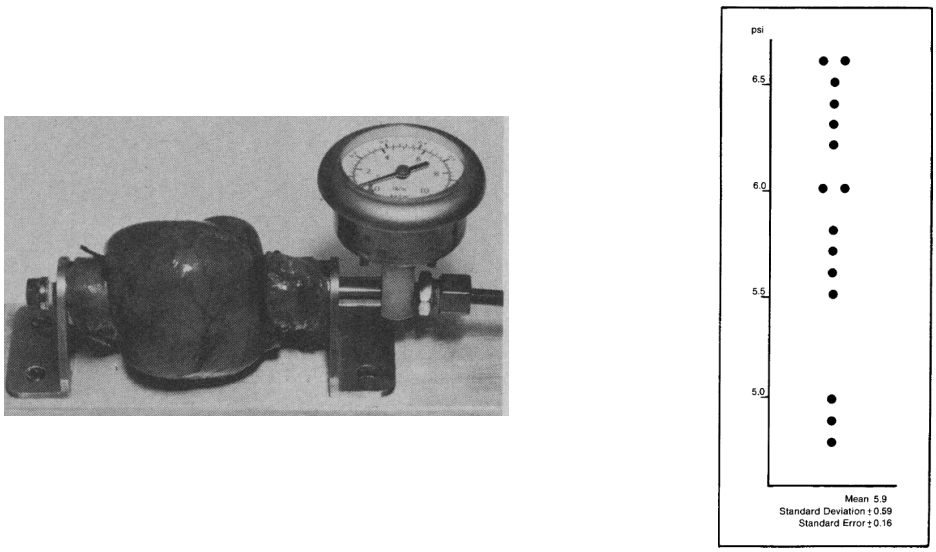


Figure 15: Left - experimental set-up and right - burst pressure results (reproduced from Rosenburg et al[159])

In contrast to the extreme tissue dynamics demonstrated by the above studies, I found 2 studies that attempted to describe the maximum tolerable pressures in-vivo.

Bharucha et al (2001): This study was particularly interesting as it charted colon compliance using the inflation of a balloon in 16 healthy subjects (8 male and 8 female). This was performed to identify the human intestine response to distension and was particularly pertinent to my work as it used balloons to provide the distension. The balloon was inflated to 44 mmHg and then deflated to 0 mmHg in 4-mmHg steps at 10, 30, and 60 ml/min, allowing volume fluctuations to stabilize at each pressure increment. Results of colon compliance testing in the descending colon with balloon barostatic distension[157]. This work demonstrated that balloons could be inflated in the colon up to 300ml in volume up to a pressure of 44mmHg with no overt clinical consequences.

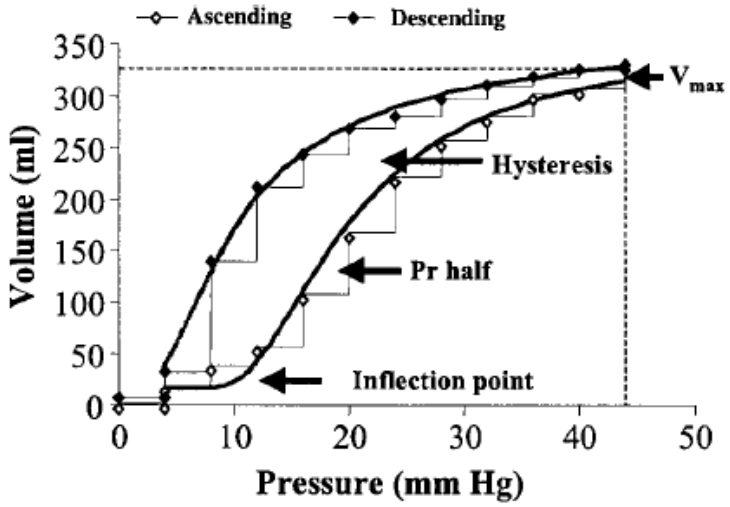


Figure 13: Step-wise (increment of 4 mmHg) inflation of the colon from 0 to 44 mmHg, pausing between the pressures for the volume to reach equilibrium (quasi-static equilibrium); step-wise deflation of the colon from 44 to 0 mmHg (reproduced from Bharucha et al[157])

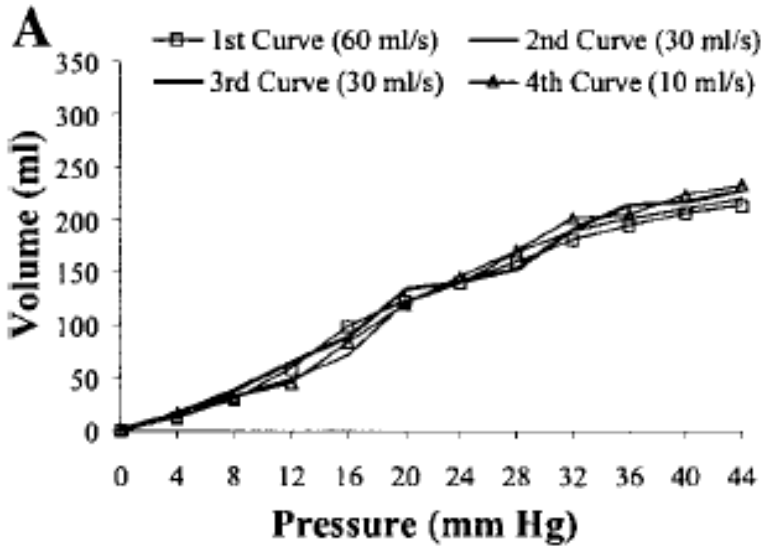


Figure 14: Effect of flow rate (10 ml/s to 60 ml/s) on P-V relationships during inflation Flow rate no effect on compliance in 13/16 individuals (reproduced from Bharucha et al[157])

Bretthauer et al (2003) extended Baruchas work above by incorporating Intra-colonic gas volume insufflated as a potential correlation with patient discomfort/pain[158]. Gas volume insufflated during colonoscopy was measured in 218 patients (both air or CO^2). A mean of 8.3 L of carbon dioxide (range 1.2-19.8 L) and 8.2 L of air (range 1.8-18 L) were insufflated. Mean volumes per minute were estimated to be 0.26 L/min for CO2 and 0.24 L/min for air.

Following this, intracolonic distension was measured using a barostat to evaluate discomfort/pain during inflation in the descending colon of 9 Inflammatory Bowel Syndrome (IBS) patients and 6 healthy controls. 2 air inflation methods were attempted; (1) step-wise distension in increments of 50 ml every 5 minutes (without deflating balloon in between), or (2) intermittent distension in increments of 50 ml every 5 minutes (preceded by completely deflating the balloon every time). Volume insufflated was from 0 ml to 450 ml or pain threshold volume. This work corroborated Baruchas work in that the maximal insufflated gas in the colon was up to 400ml in volume at which point there was patient discomfort.

Patients	**Step-wise (ml)**	**Intermittent (ml)**	**P-value**
IBS discomfort	172 +/- 76 161 +/- 74	167 +/- 43 150 +/- 56	NS NS
IBS pain	250 +/- 25 233 +/- 50	211 +/- 22 206 +/- 46	P< 0.01 P< 0.02
Control discomfort	200 (1), 250 (1), 400 (1)	200 (2), 350 (1), 400 (1)	
Control pain	300 (1)	350 (1)	

Table 7: Volume of gas insufflated before discomfort or pain occurs in humans

Biases: In selecting 3 reports for the cadaveric analysis and 2 reports for the in-vivo analyses, other pertinent reports could have been missed, giving misleading parameters, particularly in the context of the limited numbers in each study.

2.2 Device Requirement Specifications

This is the list of requirements for the SVDE. These requirements were based on clinical data as well as the parameters described in the section 2.1. It provides the full set of requirements against which the SVDE will be verified and validated pre-clinically.

Specific functional requirements

Number	Requirement
1.1	The device should increase the visible surface area of the colon wall by greater than 30% when viewed within the Therapeutic Zone. *(Needs to enhance visualisation)*
1.2	The device should be capable of flattening the inner surface of the colon wall. *(Enables enhanced visualisation of polyps in challenging locations, such as behind folds)*
1.3	The device should improve visualisation of the colon wall at flexures.
1.4	The device shall be capable of creating an isolated **Therapeutic Zone** within the colon that can expand and be maintained with the use of insufflation.
1.5	The device shall be capable of creating a **Therapeutic Zone** of at least 25 cm in length.
1.6	The device shall be able to axially extend the **fore balloon** so that the proximal end of the **fore balloon** is greater than 3cm and no more than 6 cm beyond the distal tip of the colonoscope.
1.7	With the **aft balloon** inflated to maximum allowable specification, the device should grip the colonic mucosa to support the colonoscope held only by the handle. *(Device must stabilise the colonoscope relative to target location within colon when aft balloon is inflated. This allows clinician to perform specific tasks without the colonoscope slipping inside the colon.*
1.8	With the fore balloon inflated to maximum allowable specification, the device shall be able to retract and extend the colonic mucosa. *(The device must be able to fold back or pull back colon wall for a better view or access of polyps when the TZ is created)*

Number	Requirement
1.9	The device shall enable the user to twist the endoscope by gripping the colonoscope through the sleeve *(Device should not prevent torqueing the colonoscope)*
1.10	The device should move axially less than (1 cm) relative to the colonoscope during a colonoscopy procedure. *(Device should not slide relative to colonoscope)*
1.11	The device shall not allow liquid to leak between the device base and the colonoscope during the course of a colonoscopy procedure.

User requirements

Number	Requirement
2.1	The device should be set up in less than 5 minutes by a single user who has received training.
2.2	The device shall be able to be set up by no more than two users.
2.3	The device shall allow the clinician to extend the fore balloon.
2.4	The device shall allow the nurse or technician to select which balloon is inflating and deflating independently of the other.
2.5	The device shall provide feedback for balloon inflation for both Fore and Aft balloons to the nurse or technician.
2.6	The device shall allow the extension mechanism position to be locked and unlocked.
2.7	The fore balloon shall be able to be recaptured into its original position in less than 15 seconds.
2.8	The device shall be able to inflate the fore and aft balloons in less than 15 seconds.
2.9	The device shall be able to deflate the fore and aft balloons in less than 15 seconds.
2.10	The device should be removed from the colonoscope in less than 2 minutes.

Interface requirements

Number	Requirement
3.1	The device shall attach to any commercially available colonoscope.
3.2	The device shall not impair use of cauterisation tools, forceps, snares, baskets and biopsy needles via the colonoscope working channel(s).
3.3	The device shall not significantly impair navigation of the colonoscope to a target location within the colon.
3.4	The device shall not significantly impair articulation of the colonoscope.
3.5	The device shall not significantly impair retroflex of the colonoscope when the Therapeutic Zone is created.
3.6	The device shall not block the suction port, lights, camera, working channel, or irrigation orifice of the colonoscope.

Physical Properties

Number	Requirement
4.1	The device external surface shall have smooth contours to facilitate colonoscope insertion into the patient. *(Minimize patient discomfort and prevent mucosal abrasion)*
4.2	The device, when attached to the colonoscope, should not increase the cross-sectional area by more than 10% when the balloons are not inflated. *(Minimize patient discomfort)*
4.3	The device mass should be no more than 1 kg. *(Minimize clinician fatigue – specification is based on anthropometric human factors data for sustained hold of object)*

Safety requirements

This list defined the major safety issues identified clinically.

Number	Requirement
5.1	The device must not cause clinically significant harm to the colon wall
5.2	The device shall not cause tear of the colon wall when used as instructed.
5.3	The device shall not cause perforation of the colon wall when used as instructed.
5.4	The device shall not contain rough surfaces, sharp corners or edges that could result in unacceptable harm to the patient or user.

2.3 Brainstorm and sketches

Following generation of the user requirements specifications, sketches of possible solutions to the problem were generated following clinical input. Below are the two most feasible design sketches after a process of clinical down-selection.

Inverted Balloon (Low Profile) Concept

This concept embodied a balloon profile that was folded in on itself so as to reside within a catheter. The material used would be very thin as to allow the balloon material to be easily accommodated within a narrow catheter lumen as well as having sufficient expansive capabilities. The user would push out the inner member as to remove the balloon material from the catheter where it could be inflated. After inflation, the balloon could be deflated and the member retracted returning the configuration to its collapsed state. The potential benefits of such a design was that it reduced the packed profile to less than 4-5mm. It would be able to be retracted and extended according to clinician preference which could be seen as desirable. However, multiple challenges were foreseen with this design particularly around the assembly and adhesion of the balloon material to the member. Due to the tight constraints of the balloon material within the catheter, there was a significant balloon material tearing risk. In addition, the small diameter catheters needed for such a design may cause problems with inflation and deflation of the balloon.

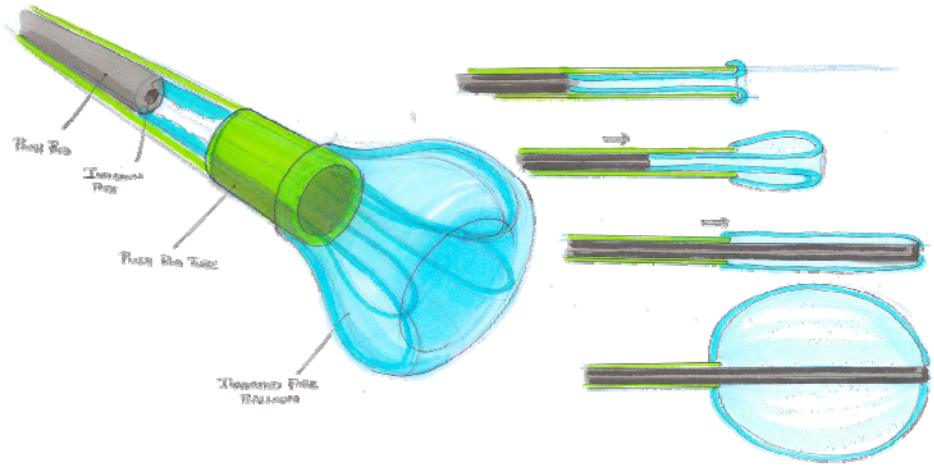


Figure 16: Sketch of inverted balloon (low profile) concept

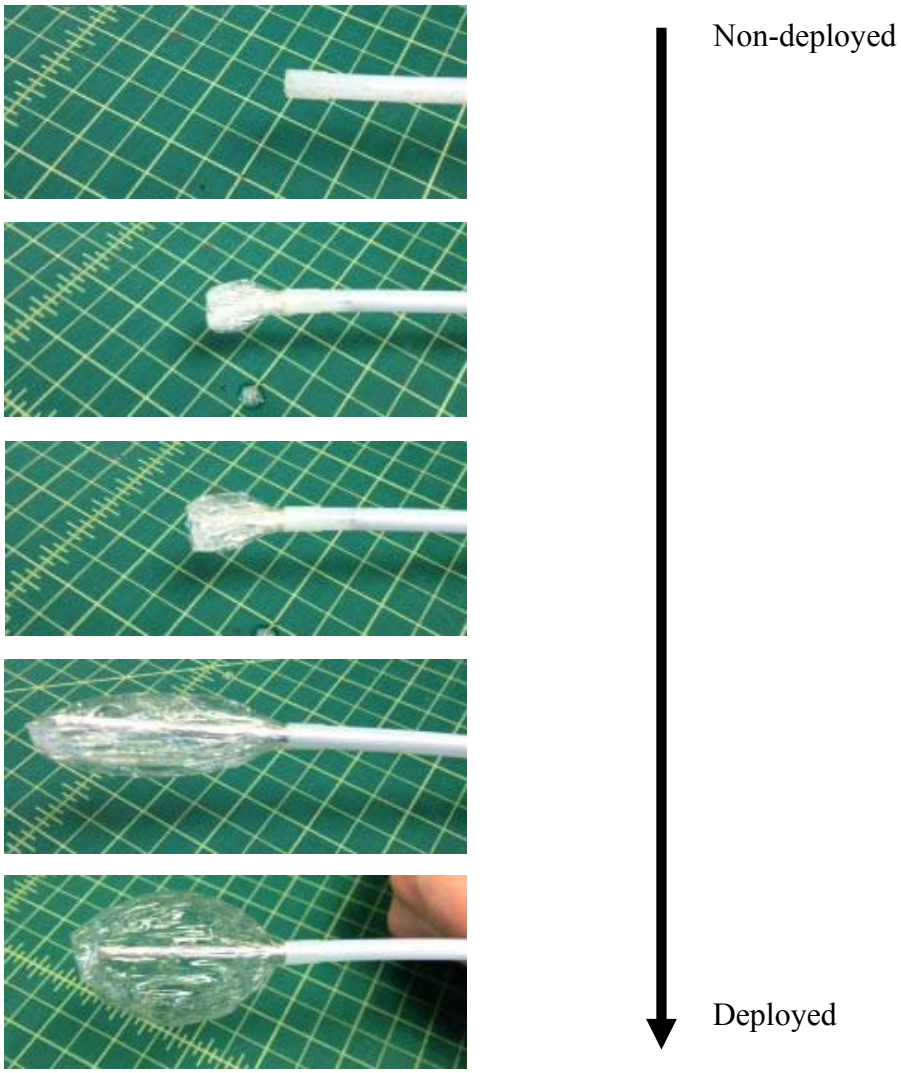


Figure 17: Inverted balloon (low profile) concept prototype

Dual Balloon Push Rod Concept

This concept involved 2 balloons. One balloon which resided behind the endoscope tip in a fixed position and another balloon that could be extended out in front from the endoscope tip as needed by the clinician. Both balloons would be independently controlled, as would be the distance between the two balloons. The benefits of such a design would be that no "balloon protection" would be needed as a thicker material could be used. There could be excellent control and recapture of fore balloon and such a design could have potential novelty. There were however clear challenges to this potential design primarily sound the higher cost associated with 2 balloons as well as the intricate design of the foreballoon. Two pushrods would be needed in this design also adding cost and there was a potential for the fore balloon to behave in a rolling fashion when deployed.

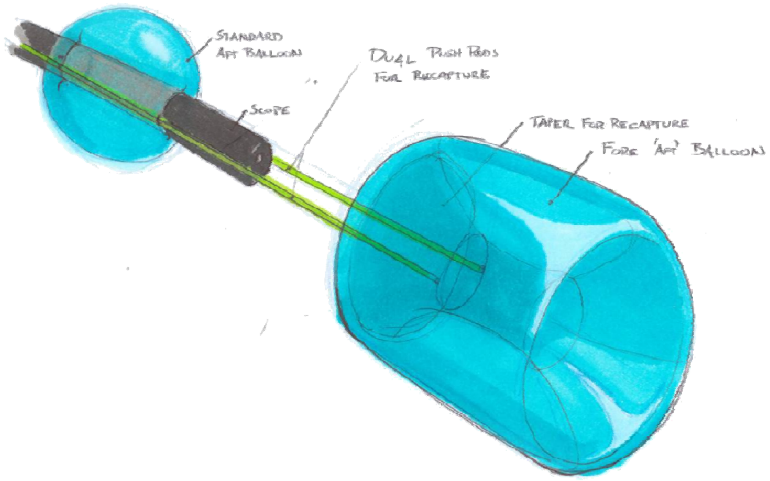


Figure 18: Sketch of dual balloon push rod concept

2.4 Balloon Pressure Dynamics

Clinically, we determined that balloons would be the best option to (1) meet the user requirements and (2) develop a suitable device. Key specifications were outstanding from the device requirements (section 2.1) such as balloon pressure, size and material. This needed to be analysed accordingly and a strategy developed to ensure a safe device.

Central to the SVDE concept was achieving creation of a therapeutic zone (TZ) – an inter balloon zone when both balloons are inflated (see figure 19). The creation of the TZ is in fact a balance of various factors such as the ability to grip the colon wall and stabilize the scope as well as achieving a high degree of patient safety. Prior to fabrication this analysis was necessary to establish parameters that allowed the SVDE balloons to meet key safety and functional requirements including: creation of a TZ, stabilising the endoscope mid-procedure, enabling insufflation and irrigation of the therapeutic zone, and improving visualisation and manipulation of the colon wall.

Following the literature review of colon biomechanics parameters along with relevant papers (see earlier), a balloon parameter analysis was developed and performed.



Figure 19: Therapeutic zone: area between two balloons (red arrow)

Definitions used in this analysis (see figure 20)

Current Balloon Radius (r): This is the measured radius of the balloon at any given state.

Initial Balloon Radius (R): The radius at which a balloon is moulded. This is the largest radius that the balloon can be filled to with no internal gauge pressure. After that point, the pressure in the balloon will increase due to physical deformation of its walls.

Source Pressure (PS): The regulated pressure to which the balloon is inflated. This is also the maximum pressure that the balloon can exert on the colon wall, in the event that the balloon is constrained below its initial diameter.

Internal Balloon Pressure (PBI): Internal pressure of the balloon – this will lag source pressure slightly during filling (transiently). In steady state, internal balloon pressure approaches source pressure.

Reflexive Balloon Pressure (PBR): This is the reactive pressure the balloon wall places on the internal gas due to elasticity of balloon material. It is a calculable pressure that can be subtracted from the balloon's regulated inflation pressure in order to determine the applied pressure on the colon.

Applied Colon Pressure (PBE): When the colon's initial radius is smaller than the balloon radius (r), the colon's elastin, collagen, and muscle tissue will apply a reactive tissue pressure to the balloon. Mathematically, this is the difference between the internal balloon pressure and the reflexive balloon pressure.

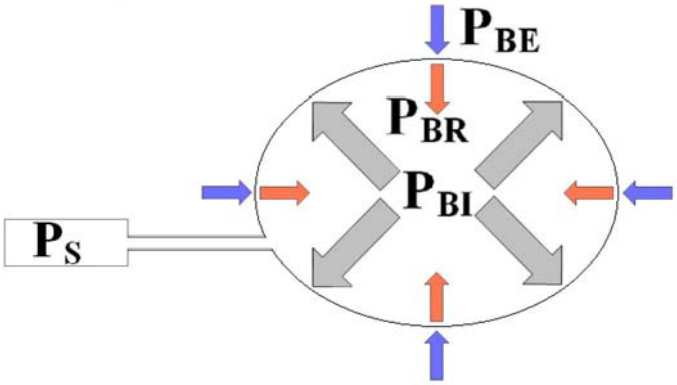


Figure 20: Diagram of internal and external balloon pressures. PS is source pressure, the pressure to which the inflation source is regulated. PBI is the internal balloon pressure, the pressure that the balloon is inflated to. PBI approaches PS at steady state. PBR is the reflexive balloon pressure, which is the pressure that the balloon wall applies on the gas inside the balloon. PBE is the External pressure on the balloon, which is equal to the pressure that the balloon applies to the colon. In open air, PBR is equal to PBI, because there is not an external pressure from the colon. PBE can be calculated by subtracting PBR from PBI.

Stress (σ): Force, within the balloon wall, per cross-sectional area, usually measured in Pascals (N/m^2).

Strain (Σ): Elongation of the balloon or colon wall as a fraction of original length, usually expressed in m/m or as a percentage.

Modulus of Elasticity (E): The rigidity of a material, equivalent to stress divided by the strain of the same material, usually measured in Pascals (N/m^2). Higher moduli correspond to more rigid materials.

Balloon Mechanics

Balloon mechanics are governed primarily by four parameters: internal pressure, initial balloon diameter, wall thickness, and modulus of elasticity. Though balloon wall thickness and modulus of elasticity effect balloon mechanics in the same fashion, they are important to consider separately because of material choice.

Balloon safety is contingent on the pressure that a balloon applies on various diameters of colon. In general, larger diameter colons bear substantially less pressure than colons of smaller diameter. To mitigate colon tearing risk, the balloon initial diameter and inflation pressure need to be controlled.

Balloon and device functionality rely on the balloons' ability to grip and seal against the colon wall. The balloons need to reach a certain size and pressure to achieve colon grip for a broad demographic.

A key device requirement is "The device shall not cause harm to the colon wall" (section 2.2, user requirement 5.1). In this analysis, harm to the colon wall, was studied in terms of colon burst and colon tear, this data was also readily available following my review of the literature (section 2.1). Colon burst is considered to be the point at which a portion of both the muscle tissue and the mucosa will tear completely through, creating a serious complication that would require formal surgery.

Assumptions and Limitations to the following analysis

The following analysis was predicated on specific studies of biomechanical data (detailed in section 2.1) and several assumptions that needed to be made. : First, we assumed that the stress and strain data from large populations was to be normally distributed. There were no large enough clinical reports that could give a reliable indicator of such a distribution. In assuming a normal distribution we were likely to result in a conservative outcome, due to improbability of extreme outliers. If we used 3 standard deviations, in some cases this would correspond to negative colon diameters. Overall it was assumed that separate biomechanical parameters were not correlated., however, colon wall thickness and colon diameter were the exception. In addition, failure stress and strain were also correlated as shown by the previous data. Incorporated into this analysis were the results of 2 UK based studies (Jones and Rosenburg) therefore we had to assume that the UK population was representative of the population for which the SVDE is intended. This was feasible as the UK population probably represented wide range of colons. The larger colon morphologies seen were most influential on maximum safe inflation pressures.

As described in previous literature outlined in section 2.1, burst pressure was determined to be mean burst pressure of 5.9 PSI (305.1 mmHg) and a standard deviation of 0.59 PSI (30.5 mmHg). Three standard deviations below the mean burst pressure is 213.6 mmHg[159] (Figure 14, page 45)**.** Maintaining a balloon inflation pressure below 213 mmHg, will ensure that colon damage, even in the event of a ruptured balloon, will be unlikely. The SVDE will be intended to function with inflation pressures significantly lower than 213mmHg.

As colon wall pressure is applied, the muscular layer begins to tear significantly earlier than the mucosal layer (section 2.1, see Figure 10-11, pages 41-42). In this analysis "colon tearing" refers to the point at which the muscle layer begins to tear. The SVDE must be designed to prevent the initiation of colon tears through a combination of designing the correct balloon diameter selection and inflation pressure regulation. Previous research has also given clear information on the mechanical characteristics that will come to bear on the way that the SVDE expands the colon[149].

According to previous investigations, muscle tear appears from stresses of 0.5-0.8 MPa and stretch ratios of 1.6-2.2. Mucosal tear occurs after muscular tear, from stresses of 0.6-1.0 MPa and stretch ratios of 1.9-2.8[155].

For this analysis, the 5th through 95th percentile (representing two standard deviations (+/- 2σ) from mean colon diameter), thicknesses and strengths have been chosen as reasonable "worst-case" of patient population. In addition a 100% factor of safety will be left above chosen inflation pressures.

Once deviations of colon biomechanical parameters are defined, the values of the parameters as well as the relationship between colon diameter and applied pressure can be established. A common equation for the increase in radius of a pressure vessel, $\delta=Pr^2/Et$, can be adapted for something that will stretch, a colon, or a balloon. Because rigid pressure vessels do not stretch enough for the increased surface area to affect the strain in the metal, the following equation can be used: $\delta=PrR/Et$, where R is a constant representing the initial radius of the colon, and r is the radius of the colon as a function of pressure. This allows the model of the colon to account for increasing surface area due to enlarged diameter. The

following analysis outlines the derivation of colon diameter with respect to applied pressure.

$$\sigma = \frac{Pr}{t} \qquad \textbf{Eqn. 1}$$

$$\varepsilon = \frac{Pr}{Et}$$

$$\delta = \frac{Pr\,R}{Et} \qquad \textbf{Eqn. 2}$$

$$r = R + \delta$$

$$r = R + \frac{Pr\,R}{Et} \qquad \textbf{Eqn. 3}$$

$$r(Et - PR) = REt$$

$$r = \frac{REt}{(Et - PR)}$$

$$D = \frac{2REt}{(Et - PR)} \qquad \textbf{Eqn. 4}$$

Legend of Symbols

o	Stress (Pa)
P	Pressure (Pa)
r	Current Balloon Radius (m)
R	Initial Balloon Radius (m)
t	Balloon Thickness (m)
Σ	Strain (m/m)
δ	Change in Radius (m)
E	Modulus of Elasticity (Pa)
D	Balloon Diameter (m)

The pressure applied by a balloon can be calculated by subtracting the reflexive pressure of the balloon from its internal pressure. The internal pressure of the balloon is a controllable parameter, and the reflexive pressure is a function of initial diameter, current diameter, balloon wall thickness, and balloon modulus of elasticity. Choosing these parameters allows the reflexive pressure to be calculated and subtracted from the regulated pressure. Calculating the applied balloon pressure, as a function of radius, can be done in the following way:

$$r = R + \frac{Pr\,R}{Et} \qquad \textbf{Eqn. 3}$$

$$PrR = (r - R)Et$$

$$P = \frac{(r - R)Et}{rR} \qquad \textbf{Eqn. 5}$$

Using the equations four and five, the diameter and applied pressure that the balloon and colon ultimately reach can be calculated. Additionally, plotting both the colon diameter as a function of applied pressure and the applied pressure from the balloon as a function of diameter allows the intersection to be displayed for a number of colon and balloon parameters.

Figure 21 depicts a plot of applied balloon pressure with respect to diameter of the nominal range of balloon parameters (45-50 mmHg pressure, 55-60 mm initial diameter, a thickness of 0.02 mm, and an elastic modulus of 50 MPa). A 60 mm diameter balloon regulated to 45 mmHg is shown in dark blue. A 55 mm diameter balloon regulated to 50 mmHg is shown in light blue. Both curves are superimposed on a plot of colon diameter with respect to applied pressure (plotted in black, green, yellow and red).

Each curve represents the diameter-pressure relationship for colons with differing biomechanical properties.

Black portions of the plot represent applied colon pressures and diameters that are unlikely to achieve colon grip.

Green portions represent pressures that are likely to achieve grip without colon tear.

Yellow portions begin at 50% of the stress or strain that cause tearing (in order to allow for a 100% factor of safety) and end at a stress or strain that causes colon tear.

Red portions represent the 95th percentile pressures that result in stresses or strains that result in colon tear and higher.

The intersection of the balloon diameter – applied pressure plot and each colon pressure – diameter curve represents the applied pressure and diameter that a colon with specific biomechanical data and a balloon with specific parameters would reach steady state at.

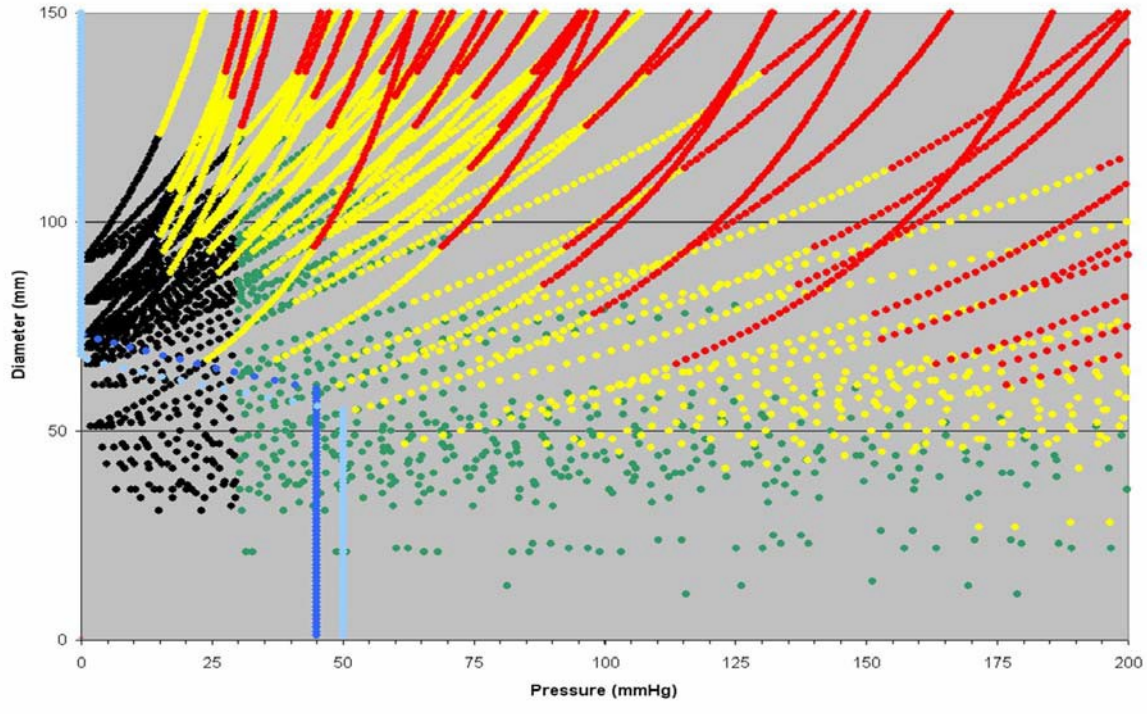


Figure 21: Plot of nominal balloon pressure behaviour relative to colon mechanics
The design parameters of pressure, initial diameter, thickness, and elastic modulus can be changed to vary the balloon's inflation behaviour and its interaction with colon mechanics.

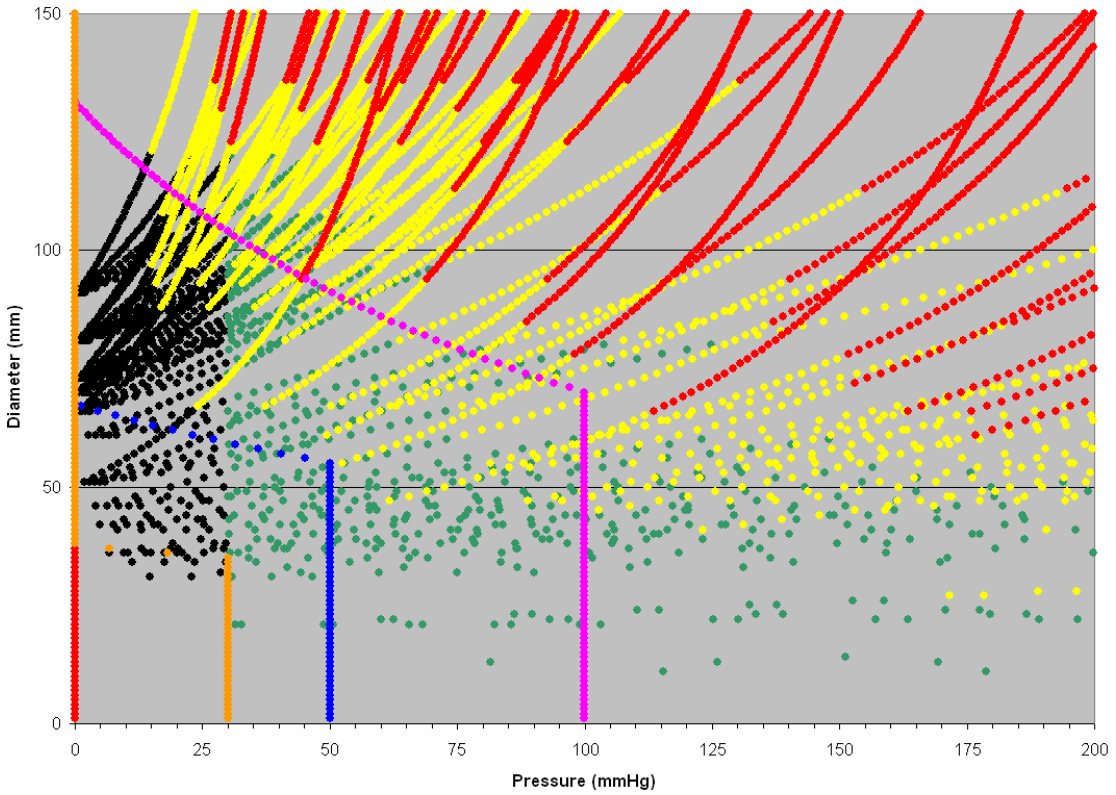


Figure 22: Plot of various balloon pressure behaviour relative to colon mechanics
Figure 6 depicts similar data as Figure 5, as well as examples of balloon behaviour curves of different diameter and pressure to demonstrate the sensitivity of mechanical parameters to colon biomechanics. The pink curve represents a large diameter balloon (70 mm) with high inflation pressure (100 mmHg), while the orange curve represents a small diameter balloon (35 mm) with low inflation pressure (30 mmHg). The blue curve represents a nominal balloon (55 mm diameter, 50 mmHg pressure).

(see figure 22) A large diameter, high inflation balloon has an inflation curve (pink) that has a small potential of tearing colon tissue, as demonstrated by the inflation curve passing through yellow portions of colon biomechanics curves, bordering on red portions (95th percentile of mechanics). Such a balloon may cause tissue damage in a small percentage of colon diameters. A small diameter, low inflation balloon has an inflation curve (orange) that has effectively no potential to tear colon tissue, but will only seal or grip a small percentage of colons, and hence has low efficacy. The blue curve represents the nominal balloon, and has at least a 100% safety factor on the 95th percentile of "worst-case" colon biomechanics.

Design considerations

Balloon Length and Shape

The balloon should be shaped to generate a seal against the colon wall as well as positive alignment with the lumen of the colon. The final length of the balloon will be informed by its ability to manipulate and align with the colon. A longer balloon will provide more axial force, for manipulation. A shorter fore balloon allows the aft balloon to be closer to the end of the scope, allowing the therapeutic zone to be smaller. Currently a length of 60-80 mm is recommended to maximize grip and manipulation of the colon while avoiding an unnecessarily cumbersome device.

Material

Polyurethane is the leading material choice for SVDE balloons (see section 1.21). Polyurethane has high elasticity, and its mechanical properties can be optimised via a wide range of durometers. Polyurethane also bonds well to itself or similar polymers. Nylon elastomer was another option for balloon material, but requires greater thickness to achieve similar mechanical properties to Polyurethane. Rigid materials are unlikely to enable a single size of balloon to function in a wide range of colon diameters. Hence, while rigid polymers such as PET (Polyethelene Terapthalate) are often used in vascular balloon applications for precise diameter control, such materials are not as desirable for SVDE.

Fabrication

Balloons manufactured by blow moulding typically can have an un-inflated diameter of 10 times the diameter of the tube that they are blown from. This manufacturing constraint intertwines the design of the pushrod, fore balloon, and their respective manufacturing techniques. Smaller balloons, about 20-25 mm initial diameter will not present a challenge to bond to the pushrod. However, balloons with larger initial diameters (40 to 60 mm)

require greater process control resolution or special adaptation in order to bond to the pushrod. Balloon material and thickness can affect the way that the balloon needs to be bonded to the pushrod, packed, covered and lubricated. The low density polyurethane intend for use for the SVDE should be bondable to a wide variety of materials, packed and protected normally. If it is necessary for the pushrod to be made of PTFE, or have a lubricious coating on the outside, accommodations may have to be made to fix the balloon to the pushrod.

Balloon parameter analysis conclusions

Based on this analysis, it was concluded that nominal balloon pressure (define specifically which pressure) should be 45-60 mmHg for a nominal moulded diameter of 55-70 mm. Elastic modulus was determined to be 50 MPa, and thickness of the material would likely range between 0.02 and 0.05 mm. These design parameters were chosen to allow a 100 % factor of safety for even the 95th percentile worst-case colon diameter, thickness, and strength, based on literature from a patient population from the UK, India, and Japan.

The preferred balloon material was decided to be low density polyurethane. The length and shape will likely be between a sphere and an ellipsoid to ensure appropriate alignment within the colon lumen. The likely length was to be between 60 and 80 mm.

Balloon pressure should range between 45 and 60 mmHg, and nominally between 45 and 55 mmHg. A pressure of 55 mmHg provides a 100% safety factor below the “worst case” colon tear threshold.

Inter and intra-patient colon diameter variation is too large for fixed diameter (rigid) balloon. Multiple balloon sizes (and knowledge of colon diameter in advance) would be

necessary if balloon diameter was the driving parameter for balloon geometry. Balloon volume is dependent on diameter, length, and shape.

This analysis led to informing the balloon design parameters specific to the SVDE and its conclusions were used as specific inputs to prototype development. The conclusions from this analysis served as inputs into the Product Requirement Specification (see section 2.5).

2.5 Updated device requirements (balloon)

Following the conclusions from the balloon parameter analysis (section 2.4), updated device requirements were generated to incorporate these findings.

Balloon physical properties

Number	Requirement
6.1	The nominal inflated diameter of the **aft balloon** should be no more than 60 mm and no less than 55 mm at maximum allowable pressure
6.2	The nominal inflated pressure of the **aft balloon** should be no more than 60 mmHg and no less than 30 mmHg. *(Ideal pressure is between 45 to 60 mmHg)*
6.3	The nominal inflated diameter of the **fore balloon** should be no more than 60 mm and no less than 55 mm at maximum allowable pressure.
6.4	The nominal inflated pressure of the **fore balloon** should be no more than 60 mmHg and no less than 30 mmHg. *(Ideal pressure is between 45 to 55 mmHg)*
6.5	The device balloons shall be comprised of polyurethane.
6.6	The device **fore balloon** burst pressure shall be greater than 300 mmHg. *(Ensures the balloon material is robust for inflation pressures of 30 to 60 mmHg with a 6 to 10X safety factor for material strength)*
6.7	The device **aft balloon** burst pressure shall be greater than 300 mmHg. *(Ensures the balloon material is robust for inflation pressures of 30 to 60 mmHg with a 6 to 10X safety factor for material strength)*
6.8	The device shall prevent the user from exceeding balloon pressure of 55 mmHg. *(Likely via a safety pressure release valve)*

2.6 Design and synthesis of SVDE

Summary

The SVDE consists of a sleeve made of thermoplastic polyurethane with incorporated lubricant[160], being translucent in colour to facilitate FE distance marking visualisation (see figure 23). This material combination provided low enough friction to allow FE insertion, whilst maintaining adequate ability to manoeuvre the FE, particularly through torque. In the GI tract, fluids surround the sleeve and functional torque must be maintained to allow user guided FE passage. Parallel with, and bonded to the sleeve was a balloon inflation lumen constructed from polyester-block-amide coextruded with a polytetramethylene glycol based thermoplastic polyurethane elastomer, which connected to the aft balloon (AB)[161]. Also parallel to the sleeve were two extension rods (pushrods) constructed from thermoplastic polyurethane resin travelling within coextruded perfluoroalkoxy alkane- thermoplastic polyurethane elastomer lumens[162].

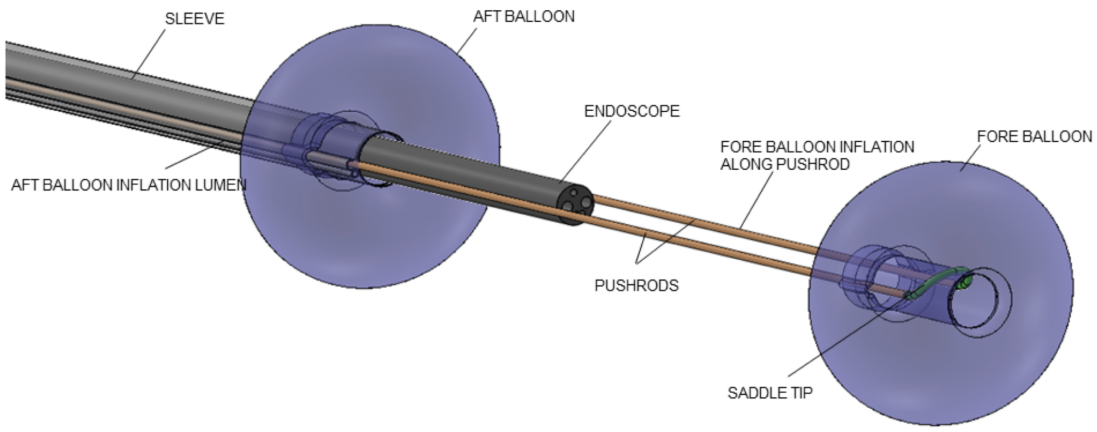


Figure 23: Final SVDE design

In order to provide an air supply to the FB, an extension rod also functioned as an inflation lumen. As the FE tip flexes up to 160 degrees in most cases, we chose this combination of materials for their ability to conform to the FE articulating tip without deformation whilst maintaining column strength during push-pull manoeuvres. Following the conclusions of the balloon pressure dynamics analysis (see section 2.4), both balloons were constructed from compliant, low durometer polyurethane, ensuring balloon-mucosal contact in varying diameters locations within the GI tract. Both balloons had a diameter of 60mm at 55mmHg. The fore-balloon (FB) was designed with a central channel permitting docking of the balloon onto the FE articulating tip (see figure 22) and multiple uses in one procedure. To prevent FB torsional configurations when inflated (e.g. in non-straight intestinal geometry), both pushrods bonded within the FB were connected with a higher durometer bridge, facilitating FB docking on the FE tip, positional maintenance, as well as providing an atraumatic tip for the pushrods to prevent damage to the GI tract.

To accommodate the varying outer diameters of FE systems (for adult and paediatric uses), a variable diameter base was fashioned with an adjustable silicone ring with concentric tightening action, ensuring an air and water tight seal. This also enabled the FE shaft to be fixed in position relative to the dual pushrods. Within the base was a sliding mechanism with incorporated lock, enabling variable distance of the FB relative to the AB and the ability to actively fix extension at a user determined distance, whilst the aft balloon (AB) remained fixed in position relative to the FE.

Manual controls were utilised both in the base handle and within an inflation control which features a manual inflation bulb. The inflation control featured the ability to inflate and deflate each balloon independently through a simple, single knob user interface. Each balloon was connected to a valve set to 55mmHg permitting balloon pressure exhausting to

ambient e.g. during intestinal contractions, and ensuring consistent inflation pressure during use, this corresponded to the balloon parameter investigations. The inflation control mechanism consisted of a series of floating plates, gaskets, and check valves. When rotated, the plates and gaskets formed pathways between a single inflation bulb (pump) and the balloons to allow for inflation and deflation of each balloon independent of the other. The check valves ensured air flowed in the correct direction through the pneumatic circuit (see figure 24).

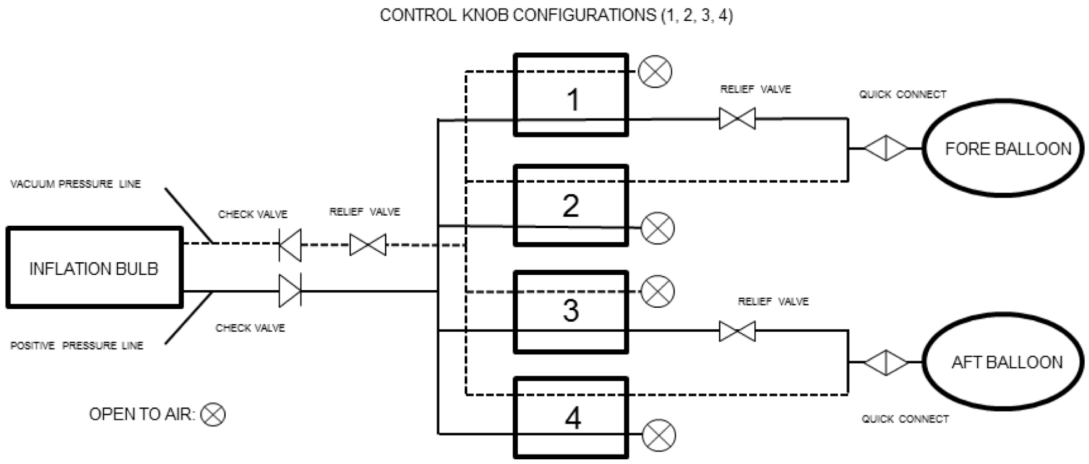


Figure 24: SVDE inflation circuit diagram

Device Assembly

The following section outlines how the SVDE was assembled in the laboratory. It was envisaged that eventually this procedure would be modified for manufacturing procedures.

Hardware and Fixtures

- Binder clips
- Heat sealing guide
- Heat sealer – ULINE H-87 Impulse Foot Sealer
- Mandrel
- Permanent marker
- Plastic syringe 50 ml
- Razor blades
- Scissors
- Scotch tape
- Soft-jaw vice
- Straight edge
- X-acto blades

Consumables

- 70/30 isopropyl alcohol
- Cyanoacrylate
- Lint-free wipes
- Silicone Lubricant – Dow Corning® 360 Medical Fluid

Procedure

Preparing the Sleeve

1. Lay down six feet of 0.5mm plastic sheet on the workbench and tape in place to hold it flat.

2. Adhere two six-foot strips of 3M® Adhesive Transfer Tape 950 side-by-side on the plastic sheet and press flat.

3. Use a razor blade to cut through the plastic along the outer edges of the tape. Discard the trimmed material.



4. Fold in half lengthwise, so the fold is between the two strips of tape, with the backing on the inside.

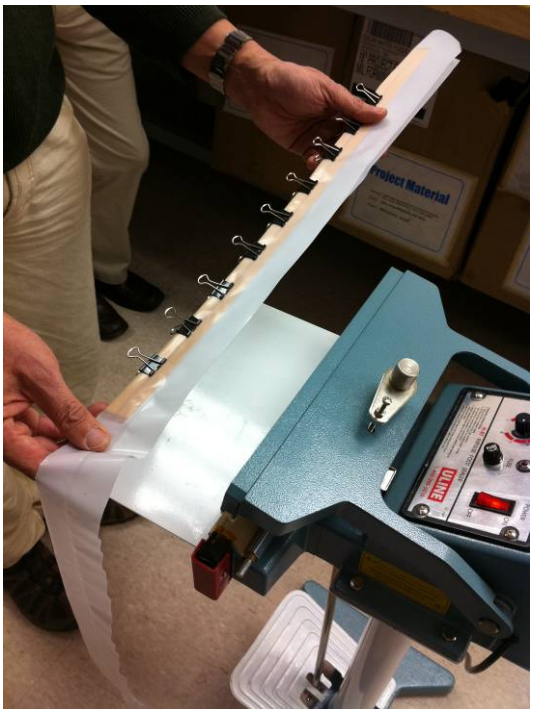
5. Use a razor blade to cut along the fold and separate the two strips of the prepared 3M® Adhesive Transfer Tape 950 tape assembly.

6. Cut a 10cm-wide, 180cm- long piece of 5mm thick LDPE and fold in half lengthwise over the heat sealing guide, using binder clips to hold in place.

7. Heat seal along the guide on both sides for at 140cm to create a sleeve with a seam.

8. Use the heat sealer to create a lead-in. Trim excess length beyond the lead-in, so that the shoulder of the end piece fits snugly into the remaining portion of the lead in.

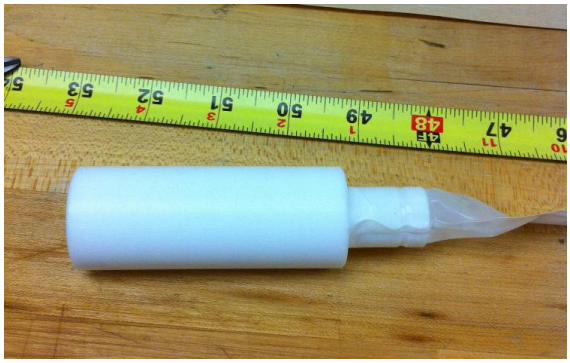
- Set the heat sealing timer to “6”





9. Use scissors to trim the excess material to approximately 1.5mm outside of the heat sealed area. Discard the trimmed material.

10. Insert the cylindrical end piece into the end of the heat sealed tube with the lead in, so the centre of the flat on the end piece is oriented to the seam of the sleeve. Continue insertion until the sleeve is adjacent to the shoulder of the end piece.



11. Use a length of 20kg fishing line to tie the sleeve to the end piece. Use the groove of the end piece as the guide for the line. Tie a clove hitch to encircle the end piece with a figure of eight knot in the end.

12. Cut 5mm–10mm from the end of the sleeve between the end piece shoulder and the fishing line to expose a section of the end piece.

13. Use a 10cm length of the prepared 3M Adhesive Transfer Tape 950 tape assembly to secure the sleeve to the end piece so it does not twist.

14. Insert the mandrel through end piece and the entire length of the sleeve; ensure the assembly is straight and taut.

15. Use a lint-free wipe and 70/30 isopropyl alcohol to clean the entire outside of the sleeve to remove oils and other contaminants from the surface. Allow the surface to dry.

16. Use a length of 3M Double Coated Tape 9500 to tape over the entire seam along the length of the sleeve, folding the seam down towards one side. Cut the tape to length so it is even with the end of the sleeve. Leave the backing on the tape.

17. Mark the backer of the 3M Double Coated Tape 9500 at 140cm away from the shoulder of the end piece.

18. Temporarily remove the mandrel and use scissors to trim the sleeve at the mark.

19. Peel the backing at the distal end of the sleeve about one inch to expose the adhesive.

20. Cut a 7cm piece of 3M Adhesive Transfer Tape 950 in half lengthwise and wrap around the distal end of the sleeve, covering the previously exposed adhesive.

21. Expose the adhesive from the outside of the piece that was just wrapped around the distal end.

22. Prepare a sheet of 2mm thick Teflon 7cm wide and 20cm in length by placing a piece of 3M Adhesive Transfer Tape 950 along one long edge. Leave the backing on.

23. Tightly wrap the Teflon around the mandrel so that it overlaps the exposed ring of adhesive.

24. Peel the backing from the adhesive on the edge of the Teflon and adhere the other side of the sheet to the adhesive.

25. Use a razor blade to remove the excess Teflon from the seam.

Assembling the Aft Balloon

1. Deflate the aft balloon by opening the valve and squeezing the air out of it.

2. It may be necessary to use a tool to open up the large center channel through the aft balloon. This channel will be where the device is located (the “sleeve channel”).

3. Slide the aft balloon over the sleeve until it is located 140cm from the end piece. Align balloon so the tube lines up with the sleeve seam.



4. Use two 7cm lengths of the prepared 3M Adhesive Transfer Tape 950 tape assembly to secure the aft balloon to the sleeve at both ends.

Preparing the Tubing

1. Lay out 360cm feet of tubing for each of the 4 tubing types (guide wire tubing, retraction cable tubing, extension cable tubing, and ripcord tubing) and tape in place to hold it down.



2. Mark guide wire tubing approximately 5mm from distal end.

3. Scrape around the inside of the guide wire tubing at tip with an X-acto blade or countersink tool to taper the inner diameter and remove any burrs.

4. Insert a dowel rod into guide wire tubing at tip to hold stiffness.

5. Apply a small amount of cyanoacrylate around the tip of the guide wire tubing on the outside of the tube.

6. Attach the black, polyimide tube around the end of the guide wire tubing until the ¼” marking on the distal end. Wipe any excess adhesive and allow to dry for 30 minutes.

7. Press the pulley pin into the pulley component using a vice. File down the pin if it sticks out.

8. Use a razor blade to cut a notch half way through the guide wire tube, just to the proximal side of the joint with the black polyimide tube to create a hole for the pull line.



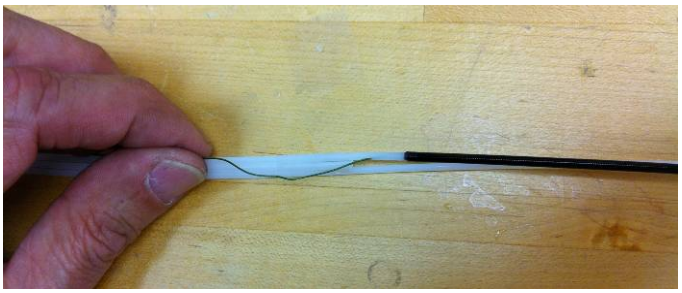
9. Use Scotch tape to attach the retraction tube to the guide wire tube so the tip is just below the hole and the tube is aligned with the hole. Wrap the tape around the tubing approximately 1.5 times.

10. Use the cyanoacrylate to tack the tubes together below the tape. Wipe off any excess adhesive.

11. Insert the black polyimide tube into one side of the pulley assembly. Insert the extension tube into the other side of the pulley assembly. Tack in place with a drop of cyanoacrylate. Tape the assembly down to hold in place. The pulley may only be assembled in one orientation.

12. Feed pull wire through hole in guide wire tube, through the black polyimide tube towards the pulley. After pull line emerges from pulley, feed the pull wire down the length

of the extension tube, making sure the line goes around the pulley pin and leaving some slack at the pulley pin. Leave 3 feet of pull line exposed at the end of the extension tube.



13. Feed the other end of the pull wire, where it emerges from the hole in the guide wire tube, down the length of the retraction tube until 90cm of pull line is exposed beyond the end of the retraction tube. Leave slack in the pull wire at the pulley end.

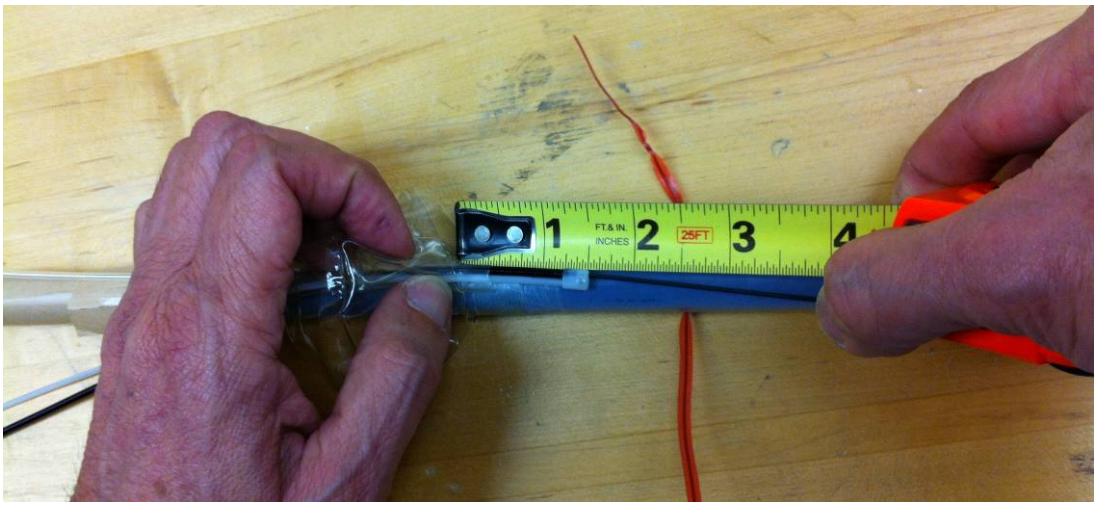
14. Place the tubing in a vice to hold steady.

15. Use 5kg line to tie the nitinol tube to the retract end of the pull line approximately 5mm-10mm from end of tube using clove hitch and lashing (x10) and ending with a double figure-8 knot. Trim the ends of the knot with a razor blade.

16. Put a dab of cyanoacrylate over the tied line and wipe away excess. Allow 30 minutes for glue to dry completely before continuing.

17. Pull 20kg line at proximal end until nitinol tube is inserted into pulley.

18. Insert the extend tube and the polyimide tube, with the nitinol tube inside if it, through the aft balloon tubing channel from the proximal end until the distal end of the pulley is 5cm in front of the aft balloon, keeping tubing along the sleeve seam.



Assembling the Fore Balloon

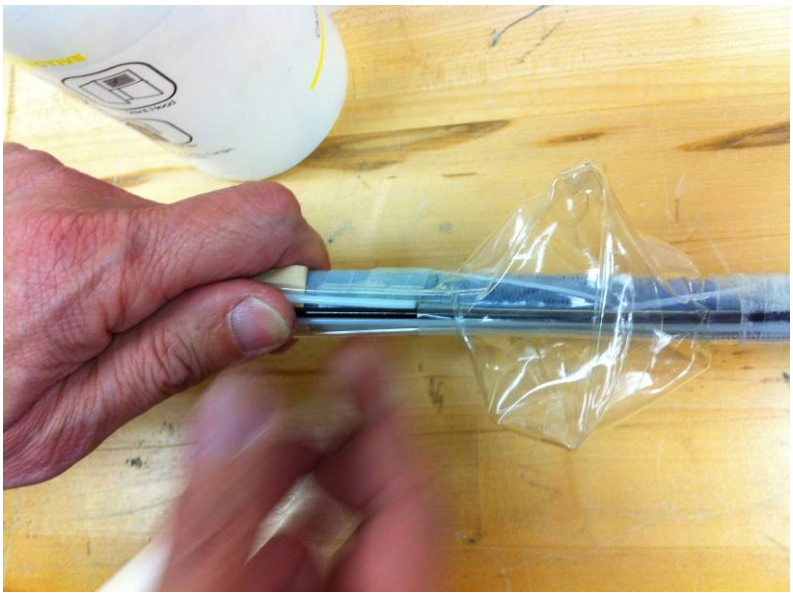
1. Cut the valve off of the fore balloon and collapse it.

2. Feed the Bowden cable on the fore balloon through the aft balloon tubing channel so the proximal side of the fore balloon is 10" from the distal side of the aft balloon. Align the fore balloon so that the Bowden cable does not twist about the sleeve.

3. Use 10cm of the prepared 3M Adhesive Transfer Tape 950 tape assembly and wrap it around the device on the distal side of the aft balloon to secure pulley and Bowden cable to sleeve. Trim the excess adhesive.

4. Use 10cm of the prepared 3M Adhesive Transfer Tape 950 tape assembly to secure ripcord tube so that it ends just before the proximal end of the aft balloon.

5. Pull off the backing of the 3M Double Coated Tape 9500 on the sleeve seam slowly, pressing down the tubes over the exposed tape. Do not allow the tubes to kink or twist.



6. Use a length of prepared 3M Adhesive Transfer Tape 950 tape assembly around the tubes, sleeve, and end piece together at the end piece shoulder.

7. Wrap a length of the prepared tape around the large diameter of the end piece to secure the tubes in the notch, leaving room to secure the braided tubing at the proximal end.

8. Cover up the tubing fully from aft balloon to end piece with 2 lengths of the prepared 3M Adhesive Transfer Tape 950 tape assembly. (Two pieces are required to cover the width of the tubes.)

9. Dab a small amount of cyanoacrylate near the tip of the nitinol tube, being sure not to cover the hole at the end of the tube. Continue to the next step immediately, before glue begins to cure.

10. Feed the nitinol tube quickly through the fore balloon channel and stick the end into the rubber tip.

11. Dab a small amount of cyanoacrylate inside the proximal end of the fore balloon channel to further secure to nitinol tube. Wipe off any excess adhesive.

12. Tie the proximal end of the fore balloon to the nitinol tube using 5kg line, making 5 clove hitches in a line and ending with a double figure-8 knot.

13. Dab a small amount of cyanoacrylate over the knot.

14. Test the pull-pull cables for binding.

15. Retract the fore balloon fully by pulling on the retract cable from the proximal end.

16. Label the cable lines at the proximal end for the fore and aft balloons, extend and retract cables, guide wire, and ripcord.

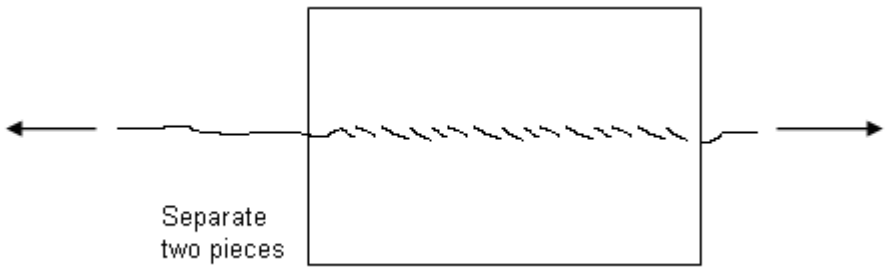
Assembling the Sheath

1. Trim the end of the ripcord tubing near the end piece, on the proximal side.

2. Lay two 5cm wide by 10cm long pieces of 1mm thick Teflon sheet directly on top of on each other.

3. Sew a long side of the ripcord sheath subassembly together:

4. Pull stitching on ripcord sheath tight from both ends, then unwrap the sheath so it lays flat.



5. Thread the ripcord through the ripcord tubing and out the proximal end, pulling the end until the ripcord sleeve is over both balloons.

6. Use syringes with valves to pull a vacuum on both balloons to completely collapse them so they will lay flat. Hold the balloons in the flattened state.

7. Take up all the slack in the ripcord.

8. Lay the sheath seam over the balloons and wrap the sheath around the balloons.

9. Pull the sheath as tight as possible and wrap strips of prepared 3M Adhesive Transfer Tape 950 tape assembly around sheath to hold it closed (Do not wrap strips over

ripcord sewed seam). While wrapping, orient Bowden cable to avoid tangling or wrapping it around the balloons.



10. Cover the length of the seam with the prepared 3M Adhesive Transfer Tape 950 tape assembly.

11. Tie a knot and loop in the ripcord.

2.7 SVDE use

Setting up the Therapeutic Zone (TZ) - The SVDE was inserted onto the endoscope using water as a lubricant. Upon insertion into the intestine and at an appropriate section, the Aft Balloon (AB) inflation selector was selected via the inflation handle control knob. The inflation/deflation bulb was squeezed until the desired pressure was reached (indicated by a constant green indicator). Upon confirmation of scope stability using longitudinal movements on the scope shaft, the FB was extended beyond the endoscope tip using the FB slider located on the handle of the device. Upon extension to the desired distance the FB inflation position was selected and the inflation bulb was again squeezed to inflate the FB, the degree of which was confirmed using the green indicator as well as visual representation on the endoscopic view. After confirmation of mucosal gripping, the FB was further extended using the handle knob to provide mucosal traction. Following the procedure, the reverse of the balloon inflation was performed and the FB redocked onto the endoscope tip.

2.8 Colon in-vitro, ex-vivo and in-vivo models

This section refers to the different models that will be employed to test the SVDE. The outline covers geometry of lower intestine, as well as other relevant medical data for the porcine colon.

In-vitro Models

Kyoto-Kagaku model with silicone colons.

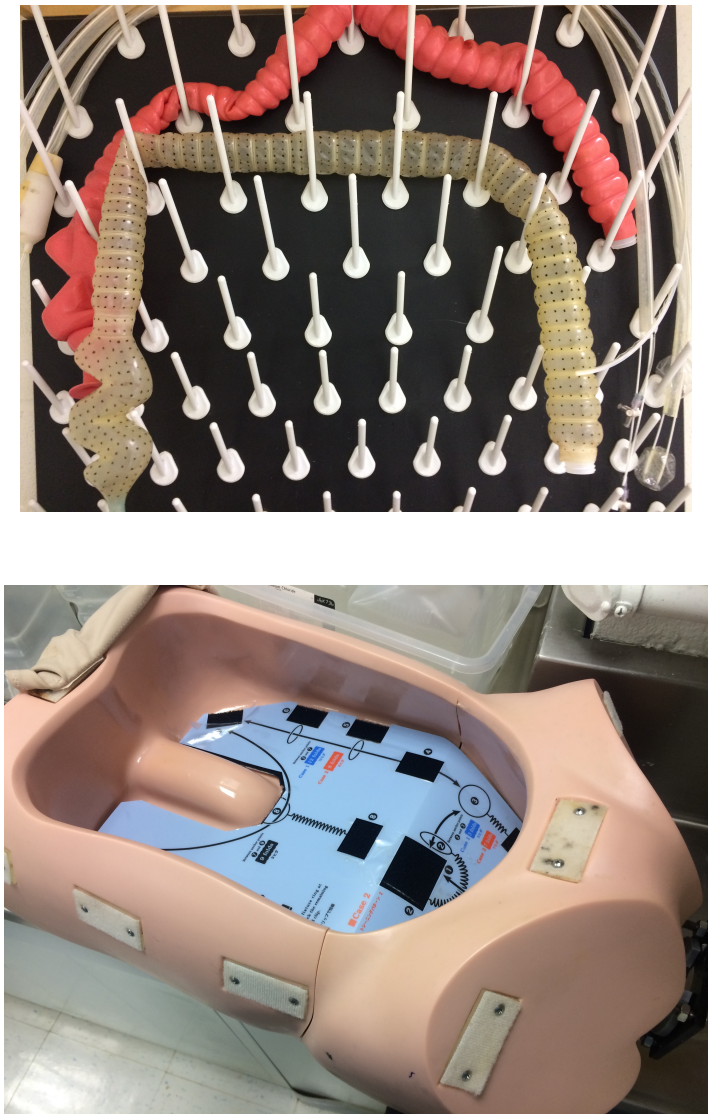


Figure 25: Kyoto-Kagaku® endoscopic trainer. Silicone colons (upper panel) mounted in abdomen model (lower panel).

Ex-vivo Models

This model was adapted from the ESD trainer shown to me by Ken Yamatani to train doctors in ESD methods (see figure 26). I adapted the model to include electrosurgery demarcated polyps. The reason I chose this was to ensure reproducibility in size and margin so post procedure analysis would be standardised. My earlier attempts with inks and dyes were abandoned due to imprecise demarcations.

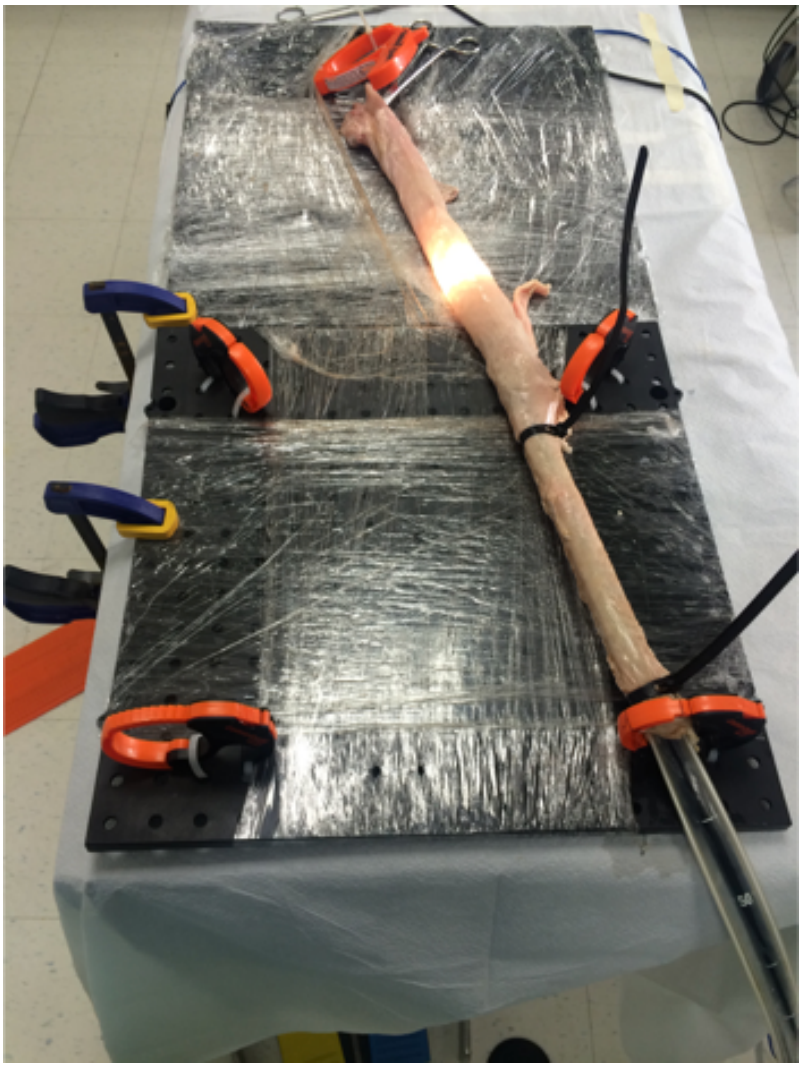


Figure 26: ESD ex-vivo model trainer

Using fresh ex-vivo porcine rectum, 4 cm “polyps” (with 5mm margin) were created using electrosurgery (see figure 27), a Bovie pen connected to an ERBE Vio200S generator was used. The porcine colon was prolapsed and measurements made from the anal verge.

This was mounted and positioned within the ESD model (see figure 26) using cable clamps and ties. All materials used in this model except the *ex-vivo* tissue was sourced from a local home improvement store.

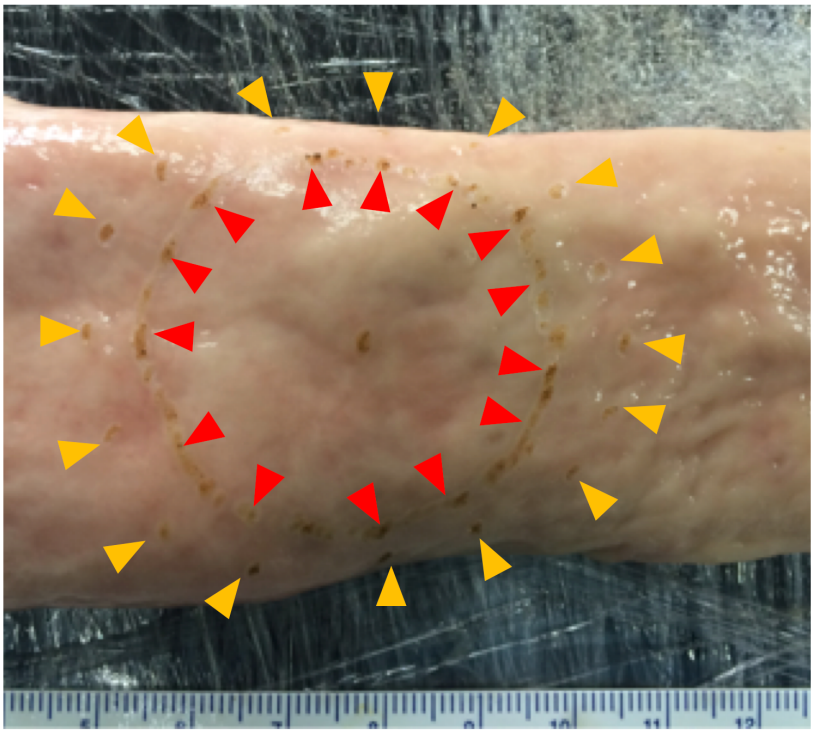


Figure 27: Everted ex-vivo porcine rectum with 4cm ‘polyp’ (red arrows)with 5mm margin (yellow arrows) demarcated with electrosurgery

In-vivo study

All animals studies were sanctioned according to the Japanese IACUC guidelines and Osaka University Animal Research Committee (Osaka, Japan) or CBSET IACUC guidelines (Massachusetts, USA).

In vivo Preparation

Circa 55kg pigs were prepped in advance of the procedure by animal facility staff with a 72 hr, 48 hr, and 24 hr all-liquid diet, with Miralax laxative 24 hrs in advance, with an enema to flush the colon 30 minutes prior to procedure. I would inspect and irrigate the colon with approximately 0.5 L of warm saline using an irrigation tube, immediately prior to the procedure to remove any residual residue.

Following this I inspected the intestine using a High Definition scope CF-H180AL and irrigation was performed if needed. Any abrasions or other abnormalities were noted and photographed at this point.

The pigs were anesthetized with 5% isoflurane and monitored throughout. Simulated intestinal polyps were created by using marking dots with an ESD electrosurgical knife with 1cm markings to 40 mm in diameter (see figure 28).

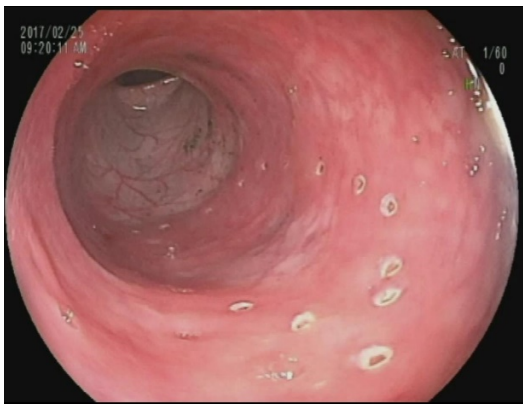


Figure 28: in-vivo porcine rectum with 4cm ‘polyp’ demarcated with electrosurgery

FB-clip retraction: Haemostatic clips (Long Clip, HX-610-090L; Olympus Medical Systems Corp., Tokyo, Japan) were placed in 2-3 places connecting the developed leading mucosal edge to the specially designed shelf of the FB (see figure23). Upon extending out the FB using the FB slider, the leading edge of the polyp was retracted in the opposite direction of the endoscope tip providing an unobstructed view with significant traction.

FB specimen retrieval: Post FB-clip retraction, the specimen was directly attached to the FB, following this, the free edge of the lesion was grasped and placed into the FB central channel using any available endoscopic tool. If necessary the FB was inflated slightly to close the lumen and facilitate removal.

Equipment used

Traditional cap-assisted ESD method (Olympus® cap D-201-12704) were performed using a paediatric colonoscope (Olympus® PCF-H180AL). Monopolar electrosurgery using ERBE electrosurgical generator with Olympus® Dualknife™ (KD-650U) and IT nano™ (KD-612U), 80w Cut 40w Coagulation. Submucosal injection was used in all cases (0.04% methylene blue, normal saline solution) through a Boston Scientific® 25G endoscopic needle injector.

Procedural times were recorded. Time to perform the circumferential incision and submucosal dissection were recorded. Occurrence of perforations was recorded. The maximal diameter of the specimen was determined after resection. Video and photo were taken of all procedures.

Definition of outcomes

The primary outcome measurement of this study was total procedure time and dissection time. Secondary outcome measurements included occurrence of adverse events such as perforation.

SVDE imaging. Animal protocol related to this study was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). Standard colonoscopic measurements were performed using a Kyoto-Kagaku Intestinal model (Kagaku, Japan). A silicone colon with $1cm^2$ interval markings was used for surface area measurements. Endoscopy system used; Olympus H180AL.

Balloon inflation duration histological evaluation. Mucosa in contact with the inflated balloons were collected 24 h after balloon inflation. The colon was trimmed at up to three areas of treatment. Two cross sections of each treatment zone were collected. Additionally, untreated control sections of the colon were obtained. Specimens were paraffin processed and stained with H&E for histomorphologic assessment. Light microscopy was used to determine scoring of parameters that reflected the degree and extent of the associated host response/repair process. Histomorphologic parameters were scored as described in the table below. Unless otherwise stated in the pathology data, all findings were graded as described below.

Score	Microscopic Changes Scoring Matrix
0	No observable change
1	Minimal - a nearly imperceptible feature/change in the tissue
2	Mild/moderate - an easily identifiable and/or notable feature/change in the tissue
3	Marked/severe - prominent to overwhelming feature/change in the tissue

Table 8: Histopathological scoring matrix

Tumour removal surgery. 45-55kg Yorkshire pigs were anaesthetized with 2.5% isoflurane. Animals were prepped and draped in sterile fashion. For the FE group a standard FE system (Olympus 180 or above) was used with an endoscope tip cap. After surgery, all animals were euthanized. Body weights were monitored before the surgery. For SVDE assisted retraction standard haemostatic clips were used (Olympus EZ clip)

Solution immersion technique. With both balloons inflated, normal saline solution was irrigated into the inter-balloon space through the FE irrigation channel. After 100mls of instillation, irrigation ceased and the height within the intestine measured over time.

Statistical analysis. Data are expressed as mean ± range where $n \geq 5$ and plotted or tabulated as individual data points where $n < 5$. Sample sizes were chosen to ensure adequate power (>85%, at significance of 0.05) to detect predicted effect sizes, which were estimated on the basis of either preliminary data or previous experiences with similar experiments. Differences between groups were assessed using unpaired, two-sided Student's t-tests for the calculation of P values. Prism for OSX (GraphPad Prism™ (GPSoftware Inc, UKR®),) was used for data analysis.

3. Pre-clinical safety characterisation

Introduction

Following the determination of basic safety parameters as well as the fabrication of the first prototype, the first step towards clinical use was an initial safety characterisation in appropriate pre-clinical models. This chapter outlines the work undertaken to determine the pre-clinical safety characteristics of SVDE.

3.1 SVDE does not encumber articulation of the endoscope and can take the shape of tortuous anatomy

The device must not affect the normal functions of the scope significantly (see user requirements, section 2.2). This can be defined as the ability to reach the caecum and traverse complex intestinal geometry as one would encounter in the general population. In addition, a key feature of the device is the ability to extend and retract the FB within the colon. The porcine colon, has a spiral shape, representing the extreme case *in-vivo* that the device would need to function within. The spiral porcine colon requires the endoscope to bend throughout its length. In the human colon, the device FB will be extended around a curve (flexure), while the tip of the endoscope may remain in a relatively straight section of the colon distally. In the porcine colon, the FB will need to be extended whilst the endoscope tip and FB are in the spiral curve configuration.

To increase the likelihood of success in eventual animal studies the device needed to be tested in many and varied bends, both along the length of the endoscope, and articulation in the tip of the endoscope to determine sheath conformity. The location, degree, and type of

bending, as well as the total number of bends, all need to be tested to see how these variables might affect the fore balloon extension.

Bending

Throughout the remainder of this work, bending will be used to refer to curves created along the length of the scope, but not at the articulation section of the scope (at the 10 cm mark or lower). For reference, the centre of the aft balloon of the SVDE device is located around the 20 cm mark.

Single Bend

First an experiment was conducted using a single bend along the length of the scope. The variables for a single bend include the degree of bending, the radius of bending, the location of the bend, and the location of the tubes throughout the bend. Bends can be between 90° to 360°, with the bend location measured from the centre of the bend (shown in figure 29). Depending on the bend degree and radius, the location of the bend cannot be closer to the tip of the scope than the 20 or 30 cm mark in order to prevent the full range of the bend from encroaching on the scope tip (10 cm mark or lower). None of the bend locations can occur past the 160cm mark, as it would begin to approach the endoscope handle.

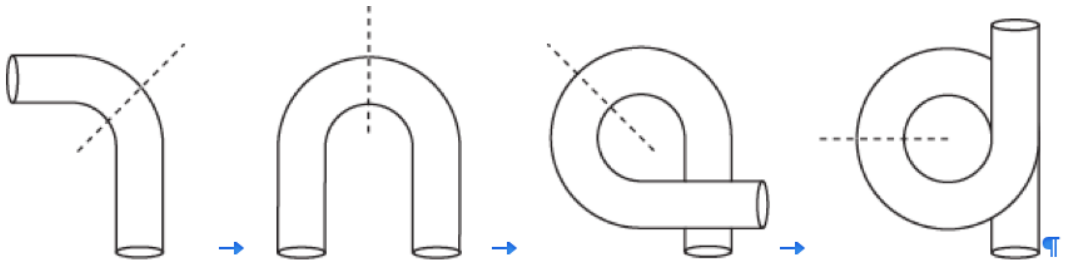
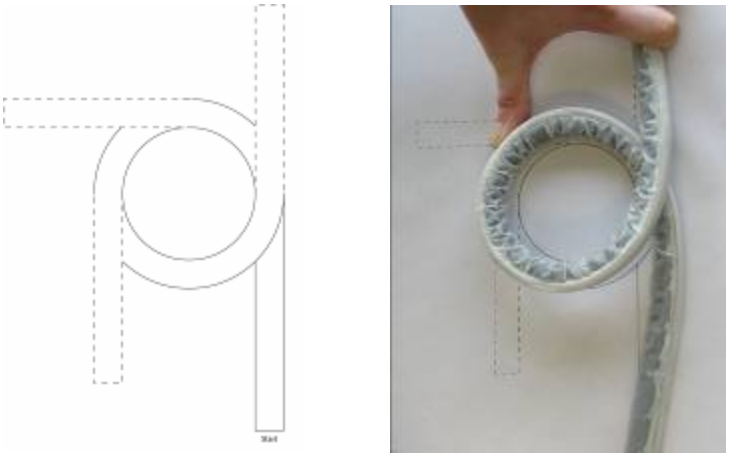


Figure 29: Bend location measurement marked with dotted line

For the initial experiment, the degree of bending was limited to 90°, 180°, 270°, and 360°, with priority on the higher degrees of bending (270° and 360°) under the assumption that these bends would require a higher force to extend the FB.

These experiments were first conducted at the 80cm mark (middle of the scope) and then at the 30 cm mark (near camera tip end of the scope) to assess the effect of bend location on balloon extension. Throughout the initial experiments, bends were limited to a single radius of 4.25 cm, the minimum possible radius. Consistency of the bend radius was ensured using a scope outline (see figure 30).

Figure 30: Bend outline Bend outline in practice



Multiple Bends

It is technically possible that a single bend alone will not result in failure for balloon extension. As a baseline, the scope was bent in 3 consecutive 360° bends with a radius of approximately 7 cm (shown in figure 31 below). This bend configuration was intended to represent the basic geometry of the spiral porcine colon.

Figure 31: Porcine Bend Configuration



Articulation

While bending describes curves along the length of the scope occurring entirely above the 10 cm mark, articulation describes curves created using the dials on the endoscope to turn the tip of the endoscope (below the 10 cm mark). Articulation can be tested by turning both the Up/Down dial and the Left/Right dials to different degrees at the endoscope handle.

Because most of the tip articulation occurs beyond the location of the retracted fore balloon, the articulation will always be conducted towards the location of the fore balloon to create the most stringent test. Turning of the two endoscope dials should always be conducted in a way to maximize interference with the fore balloon. Maximum rotation of the endoscope control wheels in contrary directions (e.g. maximal ‘up’ and ‘right’) can result in the most extreme flexion possible. (see Figure 32).

Articulation factors are also dependent on how far the sleeve is pulled up the scope. Initial testing will be conducted with the sleeve as close to the tip of the scope as possible, placing the fore balloon near the articulation pivot point. The articulation pivot point can be seen in figure 32.

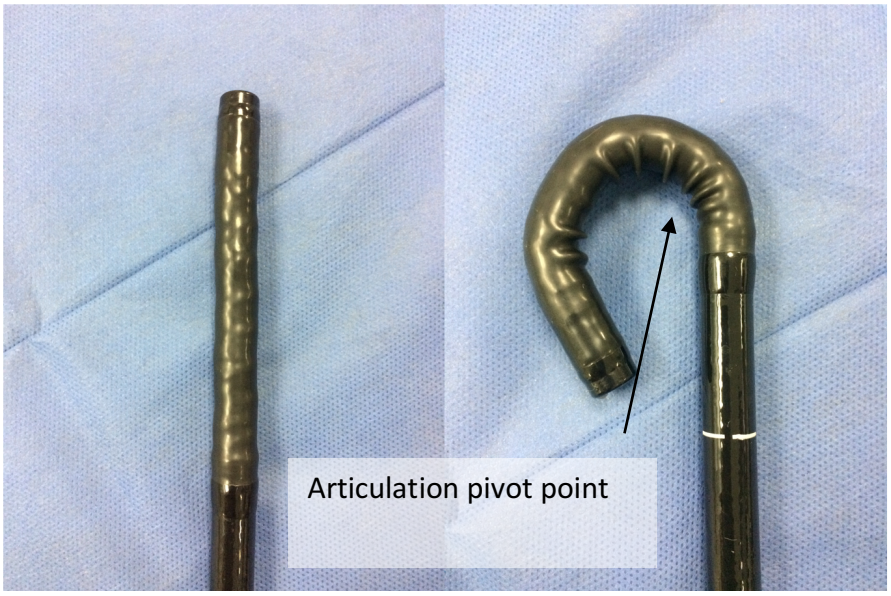


Figure 32: Articulation (maximum bending toward fore balloon) with pivot point illustrated (black arrow)

Results

Single Bend

The results from preliminary single bend testing are in table 9 below. For reference, the force required to extend the balloon on a straight scope was 4.4 N (N = 18).

Table 9: Preliminary single bend test results (n=3)

	Push rods inside		**Push rods outside**
Bend Degree:	**270°**	**360°**	**360°**
Bend Location			
30 cm	17.8 N	17.8 N	15.9 N
80 cm	7.5 N	6.3 N	7.3 N

Some kinking of the push rods were observed when the push rods were located on the inside of the curve. This result became important later in the clinical study results (see section 5.6). This was the cause for the difference in repeats from straight (n=18) to bend (n=3) as testing in the bent configuration irreversibly damaged the prototypes.

Multiple Bends

The average result from the porcine bend configuration (figure 31) test across 4 trials was 24.0 N.

Articulation

The results from the preliminary articulation testing are in table 10 below. The numbers listed in this table denote average results from 3 or more trials, unless otherwise noted.

	Articulation	
Left/Right Dial:	**0° Rotation**	**150° Rotation**
Up/Down Dial		
0° Rotation	(straight)	7.7 N
150° Rotation	*4.4 N	11.2 N

Table 10 Preliminary articulation test results (n=3)

Summary

Bending

What was found during these experiments was that bending the scope at 80 cm (mid-point) had a negligible effect on increasing the force required to extend the balloon compare to a straight scope. However, bending the scope at the 30 cm location, near the scope tip and SVDE balloons, increases the force required to extend the balloon almost 3X the extension force of a straight scope, from an average of 6 N to about 17 N.

Based on this preliminary bend experiment, having the tubes on the inside of the bend was at least as stringent if not more stringent than having the tubes on the outside. The average results between tubes on the inside and tubes on the outside was not significantly different and therefore should not make a difference in the force overall. However, tubes were

sometimes observed to kink and lead to higher forces on the extension cable if the tubes were on the inside of the bend.

Results of the porcine bend configuration test seem to indicate a compound effect from multiple bends in the system, with a force of 24.0 N for 3 x 360° bends, compared to 17.8 N for a single 360° bend near the tip of the scope, and 4.4 N for a straight scope.

Articulation

Articulation experiments revealed that worst-case articulation can yield a slight difference in force – 11.2 N on average, compared to an average of 4.4 N for a completely straight scope with no articulation. However, it is difficult to articulate the scope in such a way as to consistently interfere with the extension of the fore balloon. Intentional articulation of the scope in this manner requires a clear visual of the articulation pivot point, which is not available during normal use. At this point is was postulated that this type of worst-case articulation was unlikely to occur naturally in a normal use scenario, but may be possible in rare cases. (see clinical studies and discussion)

Conclusions

Extending the FB within complex geometry proved to be a challenge but was possible with reasonable forces. Central to achieving this is the balance of various conflicting requirements such as achieving low clinician input force while navigating through tortuous anatomy and high frictional forces.

3.2 SVDE functionality can be demonstrated *in-vitro*

Following the validation that the FB could be extended in complex geometry, I set out to determine if the overall system could function in an *in-vitro* model. The aim of this was to determine if the current design met the specific functional requirements in aiding colonoscopy procedures, including: creation of a therapeutic zone via reduced extension friction, stabilizing the endoscope mid-procedure insufflation and irrigation of the therapeutic zone, and improving visualization of the colon wall (see section 2.2).

The SVDE was tested against the criteria set out in the user needs specification (see section 2.2). One in-vitro test configuration was used – the human configuration in the Kyoto Kagaku model. 2 clinicians (including myself) performed the following experiment (see table 11). All test steps were performed once (n=1), with each clinician performing a step sequentially.

Test Order	Summary of Requirement	Test Steps	Result	Pass / Fail / Inconclusive
1	Not encumber scope or tool use - bend	Pre-lubricate device and sheath Insert wet guidewire Articulate scope tip with device, check sheath for damage	Sheath pre-lubed with ~ 5ml of colon lubricant Guidewire tube pre-wet with ~ 5 ml water and inserted from back of device Articulation works well: Dials turned fully Up, Down, Left, Right before insertion with no damage or inhibition of scope articulation	Pass
2	Not encumber scope or tool use - articulation	Insert scope and observe sheath and oversheath Ensure scope navigates anatomy with device	Insertion worked well: No damage or kinking to sheath and oversheath Navigation to caecum worked well with sleeve and sheath, scope "feels similar to regulator scope"	Pass
3	Activate sheath reliably and quickly	Capture image Balloon inflation / deflation to pop sheath - record pressure Pull sheath cable 15cm slowly and uniformly Confirm sheath activation and out of TZ Deflate fore and aft balloons	Pressure to pop sheath ranged from 60 mm Hg to 80 mm Hg for both Fore and Aft balloons Sheath activated successfully on all 6 pushrod devices by 2 different users. Pulling sheath with string is "easy" and pull tool worked relatively smoothly (required steadily increasing force to overcome static friction)	Pass
4	Fore balloon extension distance = 20cm	Capture Image Extend guidewire Capture Image Extend fore balloon to target length Capture image Seek feedback on "feel" from clinician	Extension worked in human configuration (90deg bend 4cm radius) multiple times with force similar to existing endoscope tools. Previous testing showed extension force ranged from 3 N to 8 N. Clinicians stated "Feels good, feels smooth", "feels safe when curving around bends” Extension worked in porcine configuration (3x360 deg bend18cm" radius) multiple times with force similar to existing endoscope tools. Previous testing showed extension force ranged from 4 N to 10 N. In two cases, porcine configuration was increased in rigor to 4 full loops, resulting still in full extension, though clinicians “felt a little more force.” Bowden cable can snag on aft balloon if inflated, preventing initial extension. However, when aft balloon is deflated after popping sheath, extension works reliably.	Pass
5	Aft balloon pressure	Inflate aft balloon and confirm remains inflated Measure balloon pressure (max TBD mmHg)	Aft balloon pressure reached after 10 to 15 seconds of low flow inflation. Inflation pressure varied between 60 mm Hg and 130 mm Hg,.	Pass

6	Stabilize scope with aft balloon	Capture before image Pull back on the scope 8cm, confirm stability Capture after image	For all devices and all test configurations, the aft balloon stabilizes the scope well. Clinicians can pull on the scope and the scope image remained relatively stationary.	Pass
7	Fore balloon pressure	Inflate fore balloon and confirm remains inflated Measure balloon pressure (max TBD mmHg)	Fore balloon pressure reached after 10 to 15 seconds of low flow inflation. Inflation pressure varied between 60 mm Hg and 130 mm Hg	Pass
8	Stabilize scope with both balloons	Capture before image Pull back on the scope 8cm, confirm stability Capture after image	For all devices and all test configurations, the aft balloon stabilizes the scope well. Clinicians can pull on the scope and the scope image remained relatively stationary.	Pass
9	Enhance visualization - increase visible surface area	Capture before image of visible colon wall (with both balloons deflated) Capture image of visible colon wall with insufflation Capture image of visible colon wall with SVDE and insufflation Use colon grid to approximate visible surface area	In a 90 degree flexure (5cm radius) silicone colon section, the directly visible surface area increased approximately 70% with SVDE In a straight silicone colon section, the directly visible surface area increased approximately 30% with ESP Measurements depend on the depth of field that is included - larger sample sizes of multiple configurations should be assessed in the future	Pass
10	Fold back colon wall	Pull back fore balloon approximately 5cm and verify colon wall folds before slipping	Once created, Therapeutic Zone can be manipulated to change morphology using insufflation, suction, elongation, and pulling back on folds	Pass
11	Maintain extension distance	Assess need for locking feature - Confirm target length can be maintained without extra operator or hand Pull back fore balloon 5cm, and elongate colon and observe w/o locking feature	Depending on location and morphology of in vitro colon, a locking mechanism may not be needed However, the in vitro colon model is different from natural colon tissue, and in vivo evaluation will help determine need for locking feature	Inconclusive – in vitro colon material not representative of natural colon

12	TZ remains insufflated	Insufflate and confirm TZ integrity after 30 seconds Measure TZ pressure with manometer	Fore and aft balloons allow slight air leakage due to prototype balloon seams on sealing surface, but colon still insufflated. Base pressure = 0s; 0.34 KPa - 5s; 0.30 KPa - 20s; 0.27 KPa - 30s	Pass
13	Not encumber scope or tool use - articulation	Retroflex scope with device in colon	SVDE allows scope to retroflex, and enable visualization behind a fold and an inflated aft balloon enables stabilization of the scope – tools were inserted into the working channel and could target the back of a fold.	Pass
14	Not encumber scope or tool use - compatible with tools	Capture image Introduce tools (snare, needle injection) down working channel near colon wall fold Capture image of tools Evaluate working space in TZ and ability to target a specific location with stabilized scope	Inflated balloons and Therapeutic Zone enable repeatable and accurate tool positioning relative to a target location.	Pass
15	Therapeutic Zone (TZ) liquid leak rate	Create shorter TZ - Flood and confirm TZ integrity after 10 seconds	Fore and aft balloons allows liquid leakage due to balloon seams on sealing surface, but colon still filled with liquid. Depending on the size of the TZ, flooding can take multiple minutes. Clinicians may not practically use this during a procedure on a frequent basis	Pass
16	Drain TZ with scope suction	After flooding TZ, use scope to suction	SVDE does not interfere with normal scope suction function.	Pass
17	Act as a brake - resistance to pullout	Deflate fore balloon Partially deflate aft balloon (measure pressure) Withdraw scope to act as a brake	Likely in vivo - in vitro colon not appropriate model for this test	Inconclusive

18	Not encumber scope or tool use - slide relative to scope	With both balloons deflated, advance / withdraw scope one arm stroke and observe device slip relative to scope	Sleeve slips / stretches 5mm to 10mm inch beyond scope during attachment to scope. However, when sized correctly and placed on scope, there is negligible axial slip	Pass
19	Not encumber scope or tool use - twist relative to scope	With both balloons deflated, twist scope 180 deg and observe device twist relative to scope	Scope with SVDE has similar torque handling compared to bare scope. The sleeve slips roughly 10 to 15 degrees for 180 degree scope twist when the interface is relatively dry. When wet, the sleeve could potentially slip more. Both clinicians stated “torquing feels good, no issues” "The taped tubes might enable better scope control during twisting, but also might irritate patient” – consideration for design activity	Pass
20	Straighten flexure - from/to angle	Start with 90 deg flexure, straighten to < 30 deg (need to mimic tissue behavior appropriately)	This is challenging to measure in vitro due to fixture constraints, and can be measured via fluoroscopy in vivo	Inconclusive

Conclusions

Conclusions of this study, measuring the increase in the directly visible colon surface with the balloons inflated. The method of measuring this is not explained. I was able to perform the fundamental features of the SVDE *in-vitro*, including: creation of a therapeutic zone via reduced extension friction, stabilising the endoscope mid-procedure insufflation and irrigation of the therapeutic zone, and improved visualisation of the colon wall.

The fore balloon was able to extend fully with low force, and was retracted and extended multiple times reliably during the experiment. The fore balloon navigated around 90 degree flexures and 180 degree bends in both models.

What became evident during this experiment was that SVDE might have the potential to improve visualisation within the colon through the manipulation of colon tissue to expose greater surface area during therapeutic applications. Following the experiments, through analysis of the images captured, I counted the visible 'dots' on the silicone colon used. I was able to show a 30% increase in directly-visible colon surface in a straight section of colon (35cm^2 versus 45 cm^2) and up to a 70% increase at a flexure (35 cm^2 versus 60 cm^2, see images). At this point I decided to test this further in future experiments (see section 4.1) .

There were several limitations of this study, including the small number of experimental repeats performed (n=1). In light of this, no definitive conclusions were able to be made.

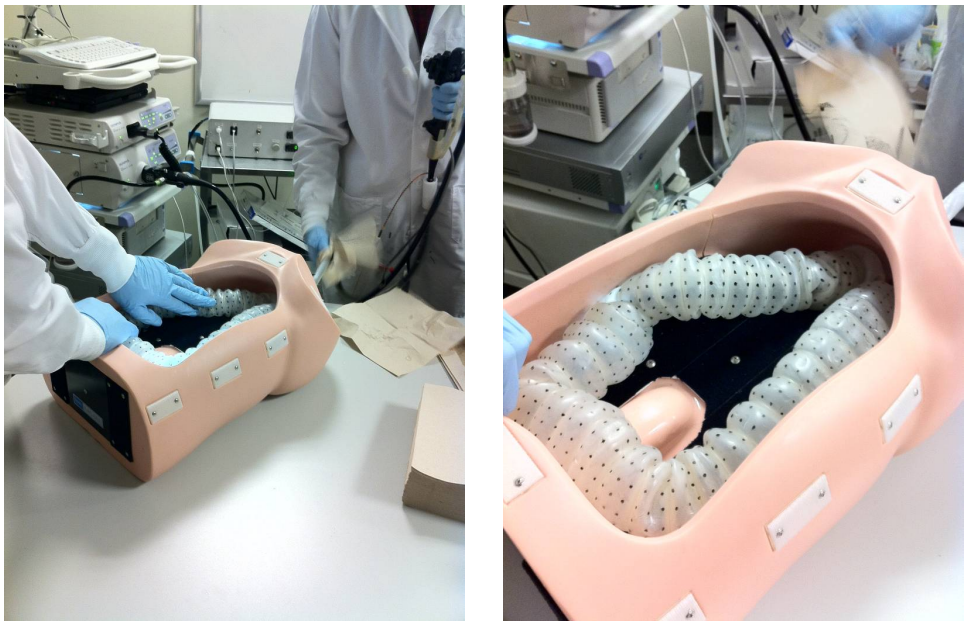


Figure 33: In Vitro Testing – Kyoto Kagaku Human Model with Dot Matrix Colon

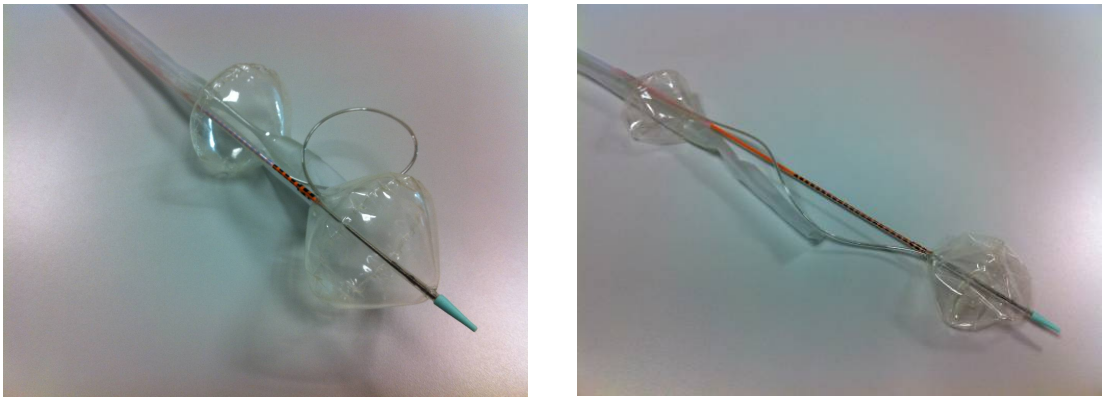
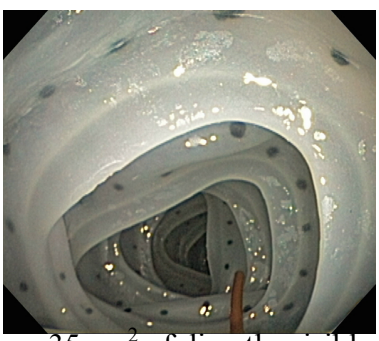
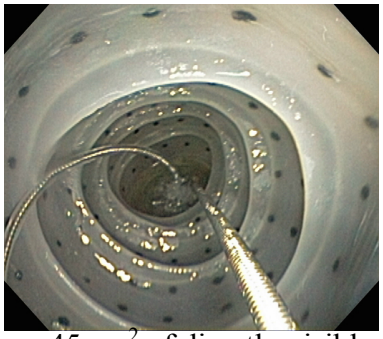


Figure 34: SVDE prototypes

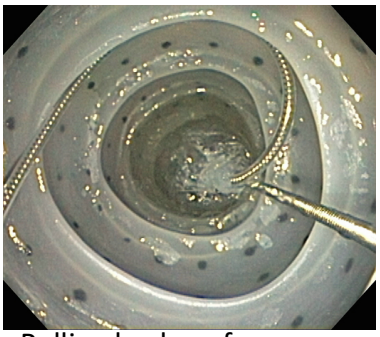
Figure 35: In a straight silicone colon section, the directly visible surface area increased approximately 30% with SVDE. The measurement depends on the depth of field that is included.



~ 35 cm^2 of directly visible surface area in straight colon prior to creating Therapeutic Zone

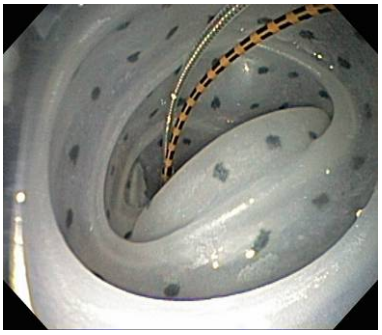


~ 45 cm^2 of directly visible surface area in straight colon prior to creating Therapeutic Zone



Pulling back on fore balloon exposes greater surface area near folds

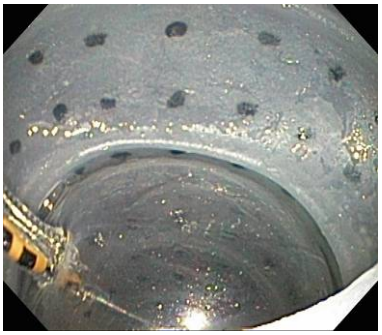
Figure 36: In a 90 degree bend (2 inch radius) silicone colon section, the directly visible surface area increased approximately 70% with SVDE. The measurement depends on the depth of field that is included.



~ 35 cm^2 of directly visible surface area in 90 deg bend prior to creating Therapeutic Zone

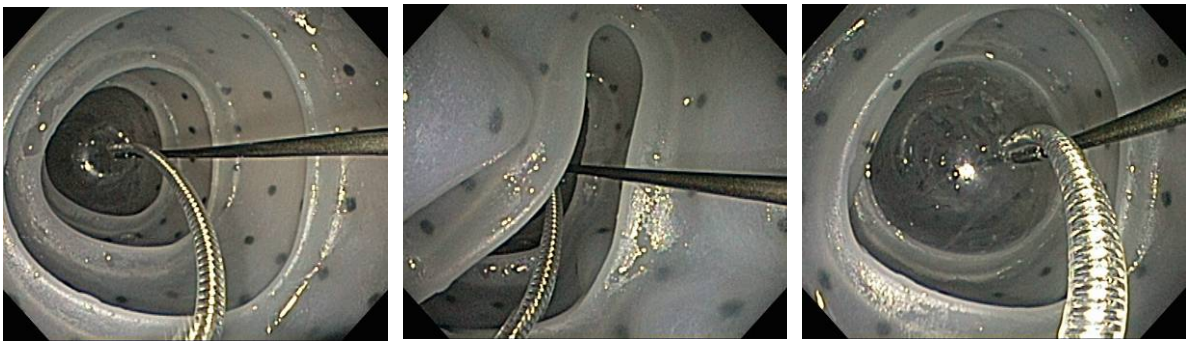


~ 60 cm^2 of directly visible surface area after creating Therapeutic Zone



Pulling back on fore balloon exposes greater surface area near folds

Figure 37: Once created, Therapeutic Zone can be manipulated to change morphology using insufflation, suction, elongation, and pulling back on folds.

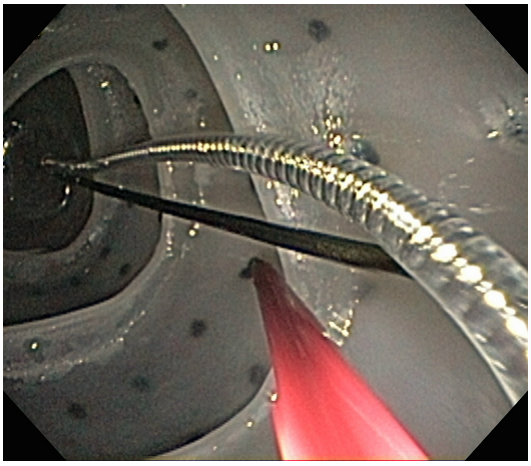


Therapeutic Zone with insufflation

Therapeutic Zone with suction

Therapeutic Zone – Pulling back folds

Figure 38: Inflated balloons and Therapeutic Zone enable repeatable and accurate tool positioning relative to a target location



3.3 SVDE safety evaluation *in-vivo*

After determining that the system met basic functionality *in-vitro*, I moved onto determining whether the system demonstrated safety characteristics *in-vivo*. The main purpose of this evaluation was to characterize the impact of SVDE on colon tissue. The highest risk to the patient from the SVDE was hypothesized to be excessive balloon pressure / diameter causing local trauma to colon tissue (see section 2.2). Following the preliminary analysis (see section 2.4 and 2.5) the current SVDE prototype balloons were 70 mm diameter, while porcine colon diameter for 45 kg pigs ranges from 30 to 45 mm.

It was therefore feasible that excessive balloon pressures and diameters could cause tissue damage and this exploratory study was conducted to characterize pressure / diameter / tissue damage relationship. The primary outcome for these experiments was macro and micro histological observations.

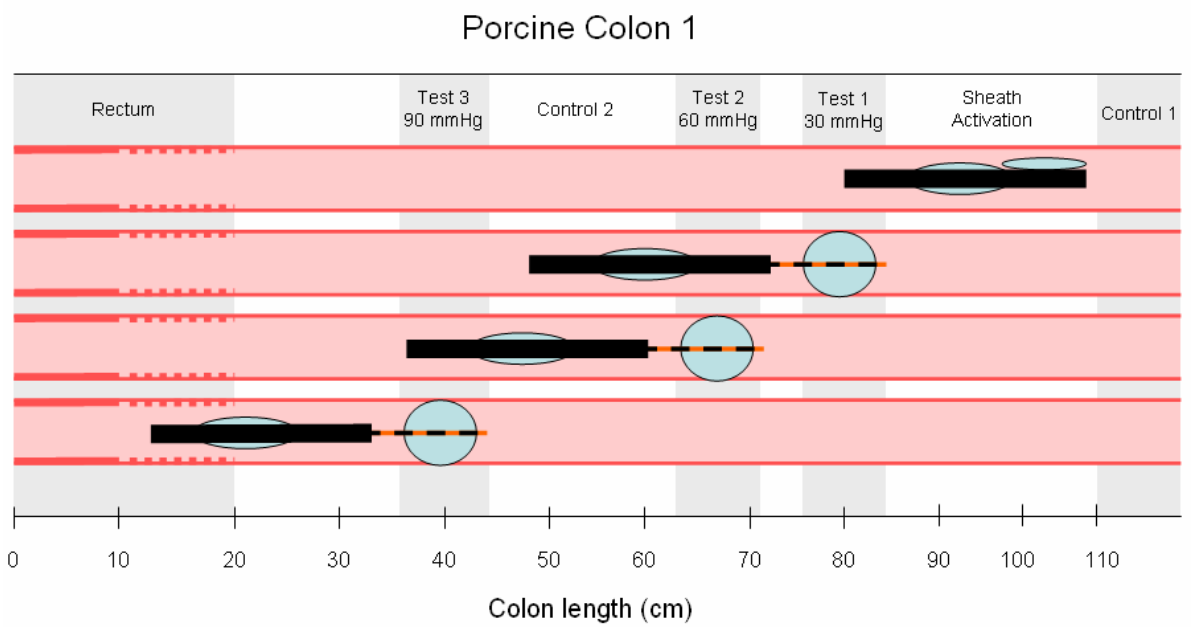
For each pig, the colon mucosal test area allocation was critical to ensure robust evaluation of balloon pressure and impact to tissue. There were three test locations and two control sections in each colon, as depicted in Table 12 below and Figure 39. Pressure testing was conducted in 10 mmHg increments. Each pressure reading was sustained for 2 minutes, colon diameter was measured externally, scope camera and external fluoroscopy images were taken, and the fore balloon was tested for colon gripping one minute after reaching the defined pressure.

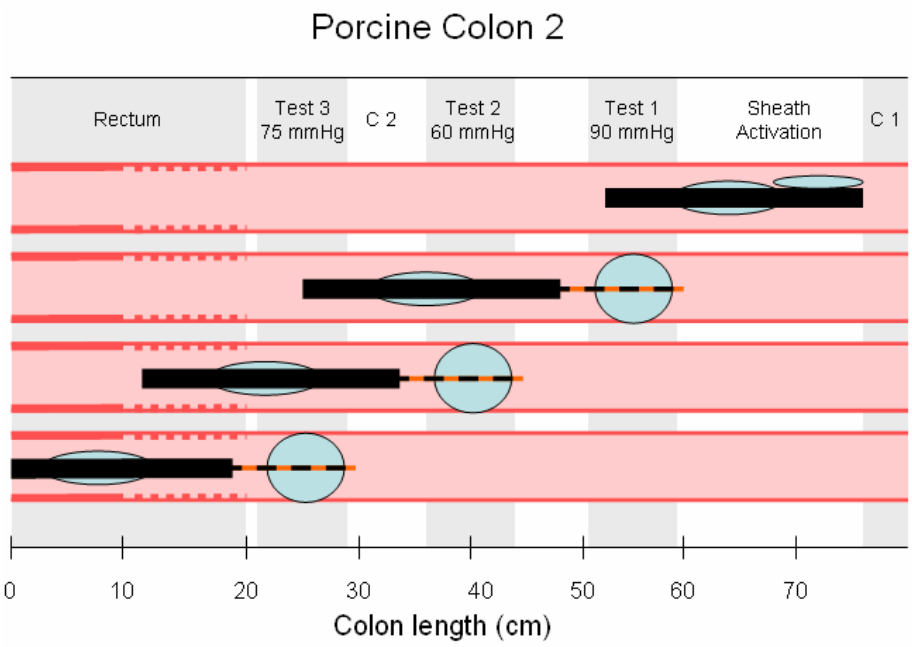
Table 12: Test Sections in Porcine Colon

Test Section	Pig 1	Pig 2
Test 1 – Pressure – Diameter testing	0 to 30 mmHg; 80 cm	0 to 90 mmHg; 55 cm
Test 2 - Pressure – Diameter testing	0 to 60 mmHg; 66 cm	0 to 60 mmHg; 40 cm
Test 3 - Pressure – Diameter testing	0 to 90 mmHg; 40 cm	0 to 75 mmHg; 25 cm
Control 1 (C1) – tissue untouched by scope or SVDE balloons	Distal of 110 cm	Distal of 75 cm
Control 2 (C2) – tissue untouched by SVDE balloons (but contacted by scope)	44 to 62 cm zone	30 to 35 cm zone

I placed superficial stitches at the bounds of each test location on the external surface of the colon to identify the test section for histology. The entire colon length was excised after the experiment and provided to the pathologists for histological analysis.

Figure 39: Test Sections in Porcine Colon (Pig 1 – upper panel vs. Pig 2 – lower panel)





Results

Inter-animal variation in rectum diameter

There was significant intra-animal and inter-animal variation with respect to colon diameter, colon diameter on the first pig (Pig 1) ranged from 40 mm to 50 mm depending on location, while the second pig (Pig 2) ranged from 27 mm to 40 mm. The rectum extended approximately 20 cm from the anus with relatively straight lumen and muscular colon wall. From a distance of 20 cm onwards, the colon wall tissue is thinner than the rectum, but relatively homogenous in thickness. The test area within Pig 1 was 110 cm, while Pig 2 was 70 cm, with each colon having adhesions beginning at 40 cm.
Both pigs were laporotomised to gain access to the intestinal organs. I removed colon adhesions using electro-surgical tools to the full length of the test area to free the colon and allow for farther scope travel. The distal end of colon was ligated to bound test area.

Based on limited sample size testing (n = 6 test locations in two pigs), an operational range of pressure for the fore balloon exists from approximately 40 mmHg to 80 mmHg that enables colon gripping with likely low risk of major tissue damage, but minor tissue damage may be possible. Balloons demonstrated ability to grip colon tissue at low pressure (20 to 40 mmHg), while acute macroscopic damage occurred at high pressure (over 80 mmHg), a reasonable safety factor for functionality for these specific prototype balloons. I performed the macroscopic evaluation on testing with further histological investigation from the pathologist obtained later. For this experiment I classified, “major” tissue damage to include a mucosal tear, perforation, or bleeding, while “minor” tissue damage was localized capillary damage (petechiae) or “colon blanching” (temporary blocking of capillary flow due to applied pressure).

Figure 40: Balloon Diameter vs Pressure

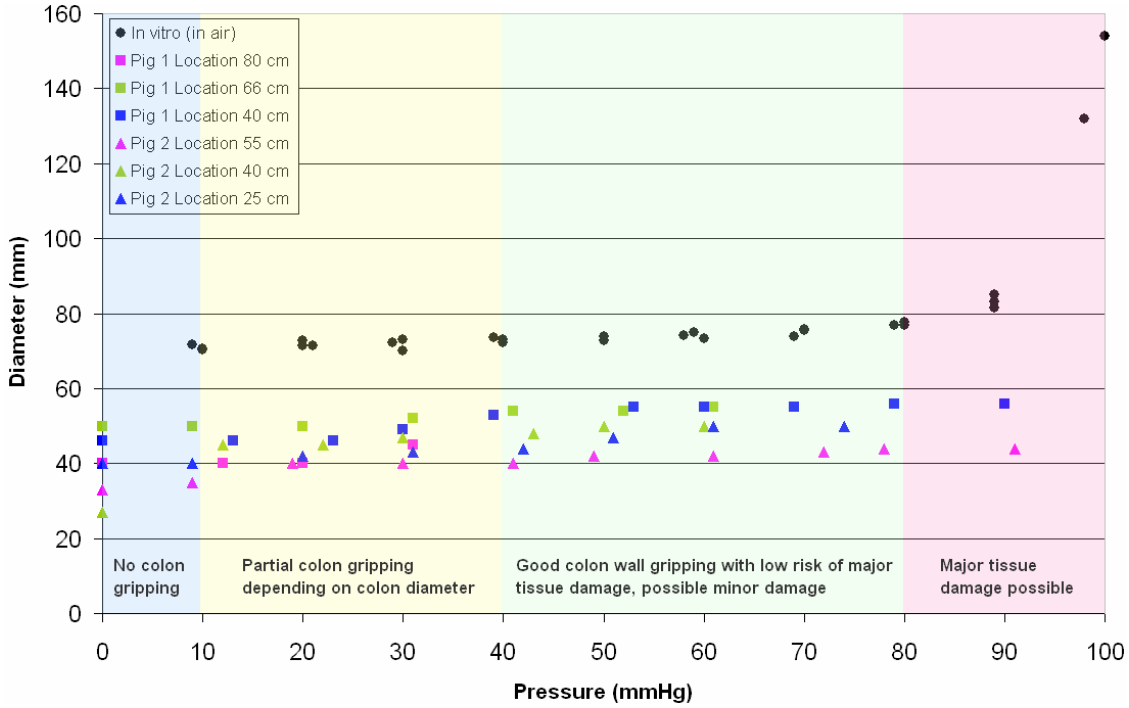


Figure 40, depicts the diameter – pressure relationship of the fore balloon in porcine colon with respect to colon grip and macroscopic evaluation of tissue damage.

Partial colon gripping can occur from 10 mmHg to 40 mmHg depending on initial colon diameter. Major tissue damage was observed at 90 mmHg on Pig 1, Test 3, resulting in a small mucosal tear, while local petechiae was observed at 80 mmHg. On Pig 2, Test 1, local petechiae was observed at relatively low pressure (20 mmHg). However, the initial colon diameter was 33 mm, and petechiae was observed when the colon diameter was distended by approximately 20%, similar to the degree of distension in Pig 1, Test 3.

Figure 39 also depicts the diameter-pressure relationship of a balloon in air for comparison of balloon mechanics. The material of the prototype balloons is polyurethane, a relatively rigid polymer. Hence, the full volume of the balloon was achieved at relatively low pressure (approximately 10 mmHg), and as pressure increases to approximately 80 mmHg, the diameter increases marginally, as this is the “elastic” regime of the balloon material behavior. At pressures above 80 mmHg, the balloon material began to plastically deform, as the material stretches thin, the balloon increases

substantially in volume and diameter. This data revealed that the balloons should be limited in pressure to approximately 80 mmHg to prevent plastic deformation.

Based on this preliminary safety evaluation daa in Figure 40, it is possible that functional testing with balloon pressure of 90 to 120 mmHg caused tissue damage.

Histopathology

Following the experiment, tissue samples were sent to histopathology for evaluation and scoring. Regardless of the pressures applied acutely with the SVDE, the overall effect on the colonic wall was minimal, though the presence and/or severity of the changes observed (eg, haemorrhage, oedema, ulceration) were pressure dependent. Both the low (70 mmHg) and medium (85 mmHg) pressures resulted in generally benign changes including minimal mural oedema and/or haemorrhage. However, the high (115mmHg) pressure balloon, in addition to relatively increased mural oedema and haemorrhage, also resulted in multifocal areas of minimal mucosal discontinuity/ulceration, an unfavorable observation relative to that observed with the low and medium pressure balloons. Although the exact cause of the mucosal discontinuities was not apparent, they were interpreted to be likely related to overstretching of the mucosa (i.e, “tearing”). Regardless, due to the limited (i.e, mucosa only) and minute nature of the change and the plasticity of the mucosa, the focally minimal areas of mucosal discontinuity were interpreted as transient with any clinical significance uncertain but doubtful

Conclusions

These data show that the SVDE has an operational range of balloon pressure that enables colon gripping with a low risk of major tissue damage, though minor acute tissue damage may be possible at high pressures, consistent with the balloon parameter analysis results. These conclusions should be tempered with the fact that each experiment was conducted over 2 minutes due to times constraints. This duration differs significantly from the expected actual balloon inflation duration in clinical situations (up to 60 minutes). In addition, the range of pressures used where short term tissue damage occurred was well above the planned range of use pressures (55 versus 115 mmHg). Therefore, these results could therefore be considered unrealistic or not relevant to real life situations in addition to being biased, i.e. high pressures over a short duration giving a false sense of safety.

In addition to these limitations was the small number of repeats used due to only 2 pigs used primarily due to cost reasons. The observed heterogeneity in results noted between both pigs suggests that ideally more experiments should have been performed in further pigs. As a result, the results obtained may be unrepresentative given the limited data acquired. This clearly has implications for my ability to say with certainty what the real effects of balloon inflation are.

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Balloon Diameter Pressure Data

Table 13: Pig 1; Push Rod 15; Test 1 (0 to 30 mmHg; balloon centre at 80 cm)

Pressure Target (mmHg)	Actual Pressure (mmHg)	Colon Diameter (mm)	Colon Grip	Colon Lumen Macroscopic Damage
0	0	40	No	None
10	12	40	Slight grip - can pull but not push	None
20	20	40	Slight grip - can pull but not push	None
30	31	45	Yes - feels snug, could be tighter	None

Table 14: Pig 1; Push Rod 15; Test 2 (0 to 60 mmHg; balloon center at 66 cm)

Pressure Target (mmHg)	Actual Pressure (mmHg)	Colon Diameter (mm)	Colon Grip	Colon Lumen Macroscopic Damage
0	0	50	No	None
10	9	50	No	None
20	20	50	Slight grip - can pull but not push	None
30	31	52	Yes, slight slip	None
40	41	54	Yes - good grip	None
50	52	54	Yes - good grip	None
60	61	55	Yes - colon rigid	None

Table 15: Pig 1; Push Rod 15; Test 3 (0 to 90 mmHg; balloon centre at 40 cm)

Pressure Target (mmHg)	Actual Pressure (mmHg)	Colon Diameter (mm)	Colon Grip	Colon Lumen Macroscopic Damage
0	0	46	No	None
10	13	46	No	None
20	23	46	Slight grip - can pull but not push	None
30	30	49	Slight grip - can pull but not push	None
40	39	53	Yes - good grip	None
50	53	55	Yes - good grip	None
60	60	55	Yes - good grip	None
70	69	55	Yes - good grip	None
80	79	56	Yes - "external colon feels tight"	Localized capillary damage (petechiae)
90	90	56	Yes - "external colon feels tight"	Small tear in mucosa

Table 16: Pig 2; Push Rod 16; Test 1 (0 to 90 mmHg; balloon centre at 55 cm)

Pressure Target (mmHg)	Actual Pressure (mmHg)	Colon Diameter (mm)	Colon Grip	Colon Lumen Macroscopic Damage
0	0	33	No	None
10	9	35	Slight slip	None due to Balloons (distal to inflation zone possible mucosal tear)
20	19	40	Slight slip	Localized capillary damage (petechial)
30	30	40	Yes - good grip	Nothing new
40	41	40	Yes - good grip	Nothing new
50	49	42	Yes - good grip	Nothing new
60	61	42	Yes - good grip	Nothing new
70	72	43	Yes - good grip	Nothing n
80	78	44	Yes - colon rigid, balloon stuck	Nothing
90	91	44	Yes - colon rigid, balloon stuck	Nothing new

Table 17: Pig 2; Push Rod 16; Test 2 (0 to 60 mmHg; balloon centre at 40 cm)

Pressure Target (mmHg)	Actual Pressure (mmHg)	Colon Diameter (mm)	Colon Grip	Colon Lumen Macroscopic Damage
0	0	27	No	None
10	12	45	Yes - good grip	None
20	22	45	Yes - good grip	None
30	30	47	Yes - good grip	None
40	43	48	Yes - colon rigid, balloon stuck	None
50	50	50	Yes - colon rigid, balloon stuck	None
60	60	50	Yes - colon rigid, balloon stuck	None

Table 18: Pig 2; Push Rod 16; Test 3 (0 to 75 mmHg; balloon centre at 25 cm)

Pressure Target (mmHg)	Actual Pressure (mmHg)	Colon Diameter (mm)	Colon Grip	Colon Lumen Macroscopic Damage
0	0	40	No	None
10	9	40	No	None
20	20	42	No	None
30	31	43	No	None
40	42	44	Yes - good grip	None
50	51	47	Yes - good grip	None
60	61	50	Yes - good grip	None
75	74	50	Yes - good grip	Yes - capillary blanching present

Experiment images

Image 1: Abrasion of colon tissue caused by irrigation during colon preparation

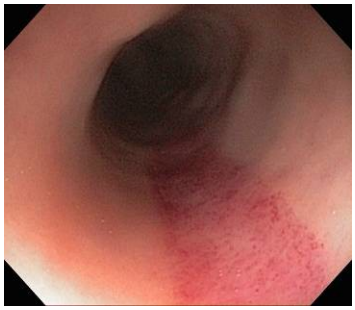


Image 2: Petechiae of colon wall after balloon inflation

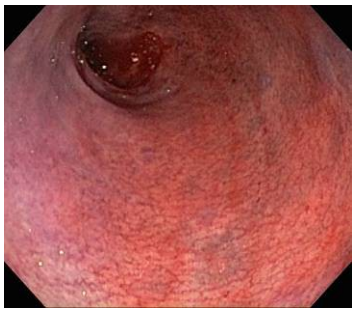
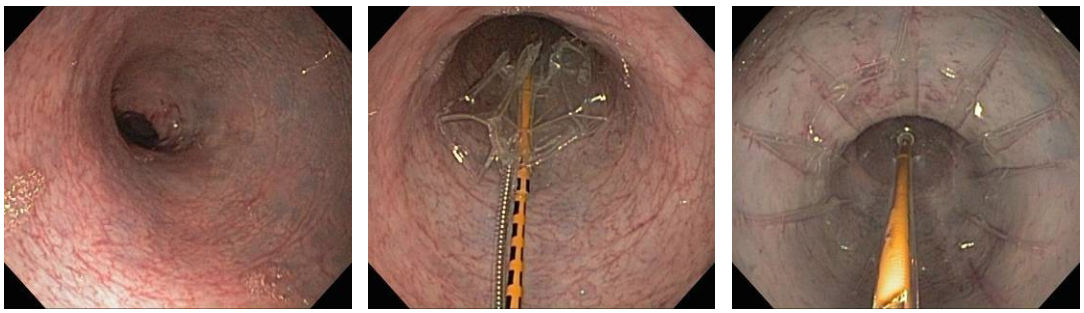
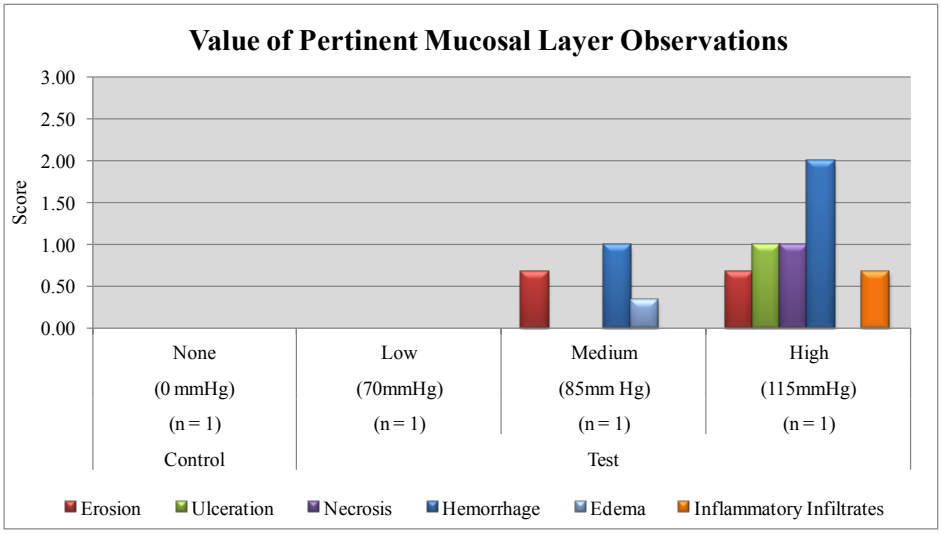
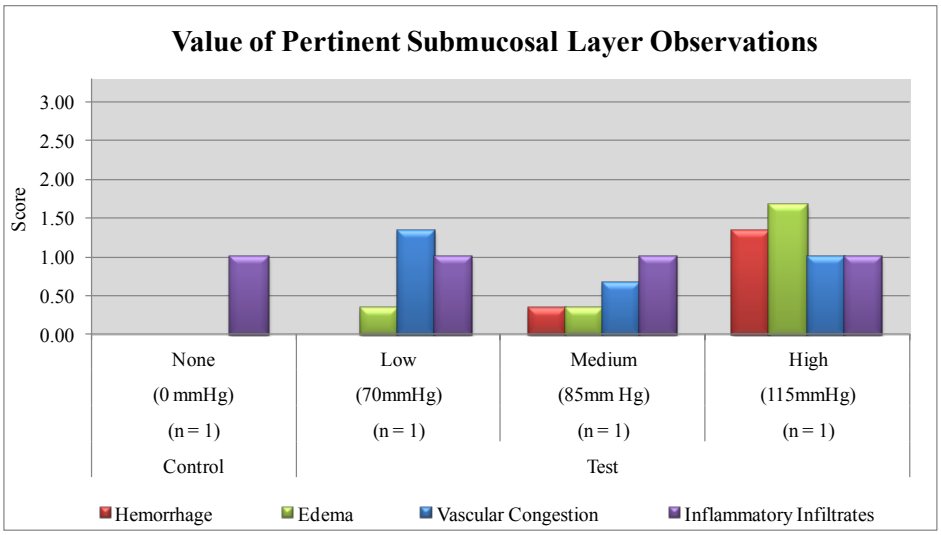


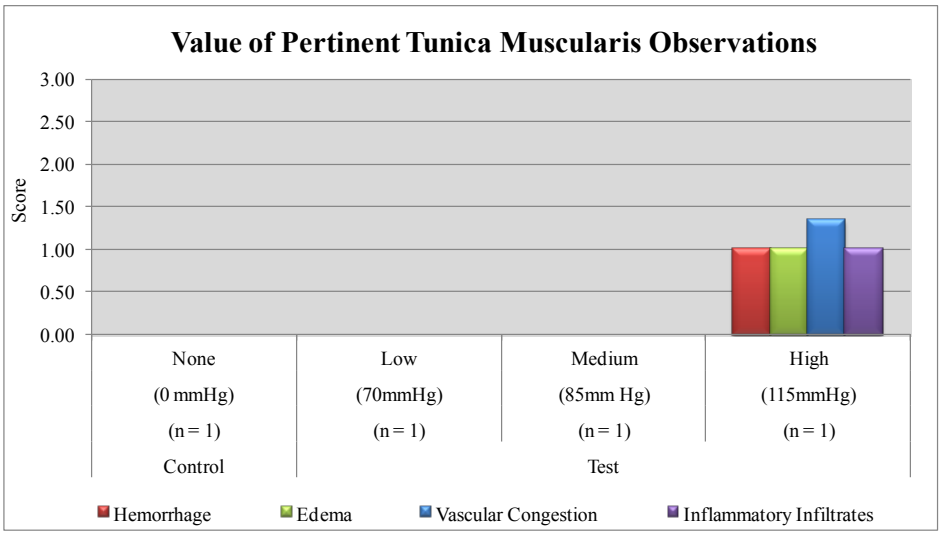
Image 3: Blanching of colon wall (far right image)

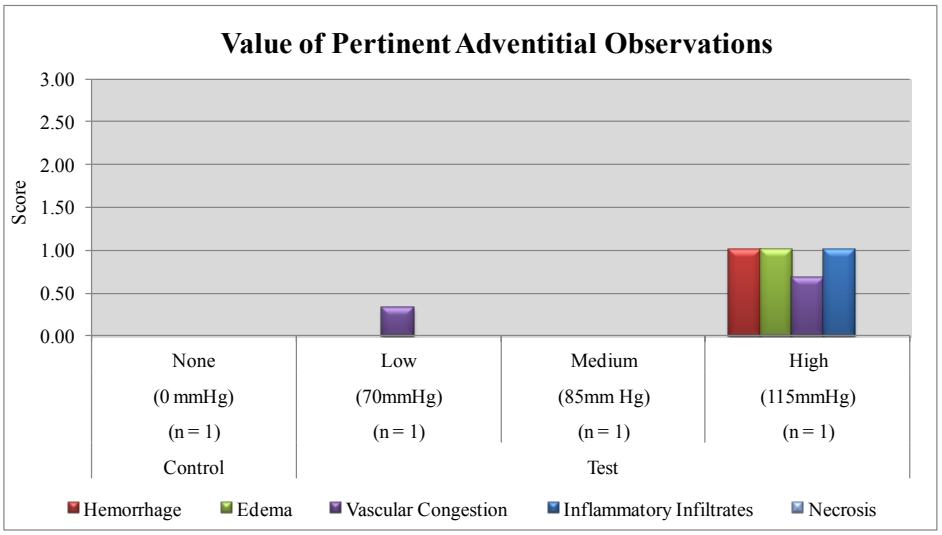


Histopathological results






Value of Pertinent Tunica Muscularis Observations
Score
3.00
2.50
2.00
1.50
1.00
0.50
0.00
None (0 mmHg) (n = 1) Control
Low (70mmHg) (n = 1)
Medium (85mm Hg) (n = 1)
High (115mmHg) (n = 1)
Test
Hemorrhage
Edema
Vascular Congestion
Inflammatory Infiltrates


Value of Pertinent Adventitial Observations
Score
3.00
2.50
2.00
1.50
1.00
0.50
0.00
None (0 mmHg) (n = 1) Control
Low (70mmHg) (n = 1)
Medium (85mm Hg) (n = 1)
High (115mmHg) (n = 1)
Test
Hemorrhage
Edema
Vascular Congestion
Inflammatory Infiltrates
Necrosis

3.4 Balloon inflation duration affects transmural intestinal damage

To evaluate the effect of balloon duration on the mucosal surface a triple balloon fixture with independent inflation control was fabricated i.e. 3 fore-balloons placed sequentially on pushrods with independent inflation controls. I selected 3 time points to represent procedural duration range of current complex endolumenal therapeutic procedures such as ESD, with particular focus on the upper limit (see section 1.9). The triple balloon fixture was placed according to the configuration shown in figure 41 and inflated to 55mmHg, the upper limit being 6 hours.

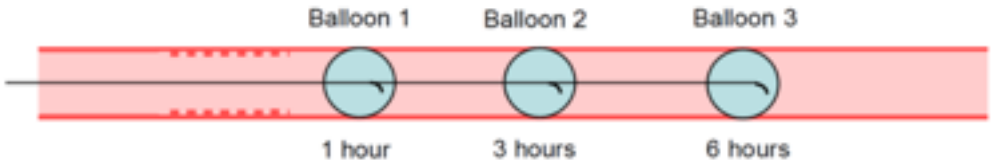


Figure 41: Diagram exhibiting experimental balloon placement

Following this the animals were sacrificed and OCT sections taken for H+E staining. FE mucosal imaging 6 h after balloon inflation showed the most significant changes. The other time points showed less to no change macro-histologically.

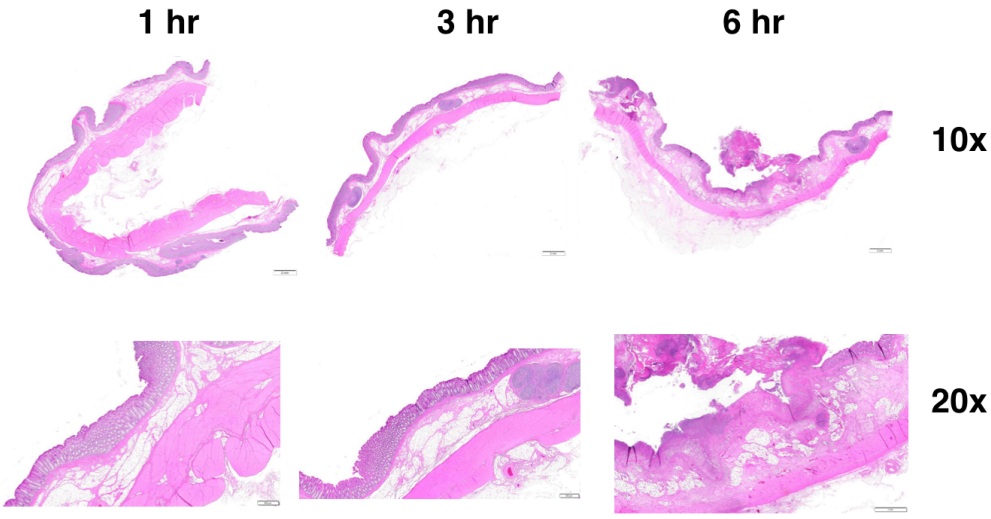


Figure 42: Histological changes at various time points, high and low magnification

Consistent with macro-histological findings, H+E stained slides showed significant neutrophils, haemorrhage, necrosis, oedema and ulceration at 6h (see figures 42 and 43). SVDE inflation characteristics at durations less than 1h offered no discernible transmural intestinal changes.

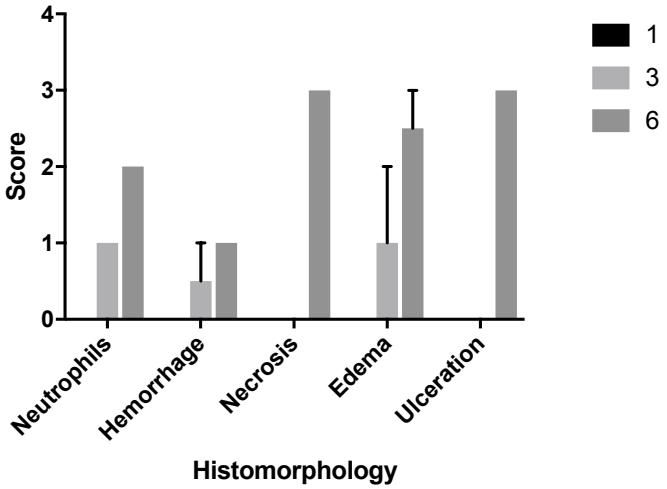


Figure 43: Histopathological scoring at time points

To remedy some of the limitations of the previous balloon pressure study, the durations spanned a more likely clinical range (1-6 hours) at the expected device balloon pressure of 55mmHg.

Similar to the previous study was the small number of repeats used due to only 2 pigs used again due to cost reasons. Ideally more experiments should have been performed in further pigs at possibly further time points. As a result, the results obtained may be unrepresentative given the limited data acquired. Whereas this experiment gives positive indications regarding the operating range of the final balloon, definitive conclusions are still unable to be made.

3.5 SVDE functionality can be demonstrated *in-vivo*

Following the safety characterisation of the balloon pressure and gripping experiments as well as the balloon-pressure duration study. The next step was to repeat the functionality experiment as performed *in-vitro* in an *in-vivo* setting. The purpose of this experiment was to demonstrate that the SVDE functionality was reproducible in an *in-vivo* setting, a secondary goal was to evaluate any major safety considerations following its use in the porcine colon. The same test method was used as in the *in-vitro* studies outlined in section 3.2.

Results

The test matrix begins on the next page.

Test Order	Need	Requirement	Test		Results
1			Inspect colon with different scope.	X	inserted to 90cm for inspection (up to spiral location) ~20cm some irritation present 20-40 some specks @35 some abrasion from prep t=3:35 for device install
			Attach device to scope. Lubricate inner lumen of fore balloon before pulling balloon onto scope.	X	
			Connect Inflation system. Lubricate device / scope prior to insertion.	X	
2	Not encumber scope or tool use	Not encumber scope or tool use - articulation	Insert scope into model	X	Tp = 1:21 45cm @ straight section
			Ensure scope navigates anatomy with device - go to straight section of colon	X	
3	Create Therapeutic Zone (TZ)	Aft balloon leak rate	Capture image / fluoro	X	P0aftballoon = 55; P5 = 49 Note: scope location unchanged
			Inflate aft balloon to 55 mm Hg and confirm remains inflated for a duration of 5 minutes, capture image	X	

Test Order	Need	Requirement	Test		Results
			Measure Aft balloon pressure	X	
4	Stabilize scope	Stabilize scope - move less than some distance under axial load	Capture image / fluoro (if necessary)	X	
			Pull back on the scope 3 inches, confirm stability	X	
			Capture image / fluoro	X	
5	Create Therapeutic Zone (TZ)	Fore balloon extension distance	Capture image / fluoro (if necessary)	X	Note" Moved back to straight section (deflated aft balloon) easy
			Extend fore balloon to 19 cm	X	
			Capture image / fluoro	X	
			Seek feedback on "feel" from clinician	X	

Test Order	Need	Requirement	Test		Results
6	Create Therapeutic Zone (TZ)	Fore balloon leak rate	Inflate fore balloon to 55 mm Hg and confirm remains inflated for a duration of 5 minutes	X	P1=56mmHg P2=50mmHg
			Measure Fore balloon pressure	X	
7	Enhance visualization - straight section	Enhance visualization - increase visible surface area	Capture before image of visible colon wall (with no insufflation) Suction air out of colon if necessary.	X	T=7s to TZ insufflation
			Insufflate and measure time to visual field deemed appropriate by clinician.	X	
			Capture image of visible colon wall with insufflation		
8	Enhance visualization - straight section	Fold back colon wall	Measure Fore balloon pressure	X	P=59mmHg -> p = 56mmHg Note: use clips for point of interest. Pulled back scope w/
			Capture image / fluoro	X	

Test Order	Need	Requirement	Test		Results
			Pull back fore balloon approximately 2 inches and verify colon wall folds before slipping.	X	aft balloon deflated to get scope away from clip. Note: Spend much time @ this location
			Capture image / fluoro	X	
9	Enhance visualization - straight section	Extend colon wall	Extend fore balloon approximately 2 inches and verify colon extends. Capture image / fluoro	X	
10	Create Therapeutic Zone (TZ)	Recapture Fore Balloon - Straight section	Deflate Fore Balloon, Capture image / fluoro	X	T1=20s (slow for images) T2=5s T3=4s T4=4s "Very easy"
			Recapture Fore Balloon, Capture multiple images / fluoro	X	
			Record time for recapture. Seek clinician feedback.	X	

Test Order	Need	Requirement	Test		Results
11	Enhance visualization - flexure	Enhance visualization - increase visible surface area	Deflate Aft Balloon and advance to flexure region	X	Note: Use air for Fluoro image Note: Spending > 45mins to locate good image T ~ 8s Deploying fore balloon was difficult
			Capture image / fluoro of flexure	X	
			Create TZ (inflate Aft Balloon, extend Fore balloon around flexure, inflate Fore Balloon).	X	
			Insufflate and measure time to visual field deemed appropriate by clinician.	X	
			Capture image of visible colon wall with insufflation	X	

Test Order	Need	Requirement	Test		Results
12	Create Therapeutic Zone (TZ)	TZ air leak rate and time to insufflation	Insufflate and confirm TZ integrity after 30 seconds. Use Manometer to measure intra-TZ pressure. Deflate Fore Balloon and observe pressure drop.		Over 3 hours into testing and image gathering, the Fore Balloon developed a small leak
13	Not encumber scope or tool use	Not encumber scope or tool use - compatible with tools	Capture image / fluoro		skip
			Introduce tools (snare, needle injection) down working channel near colon wall fold		
			Capture image of tools		
			Evaluate working space in TZ and ability to target a specific location with stabilized scope		

Test Order	Need	Requirement	Test		Results
14	Create Therapeutic Zone (TZ)	Recapture Fore Balloon - Flexure	Deflate Fore Balloon, Capture image / fluoro		
			Recapture Fore Balloon, Capture multiple images / fluoro		
			Record time for recapture. Seek clinician feedback.		
15	Not encumber scope or tool use	Not encumber scope or tool use - slide relative to scope	Deflate Aft Balloon.		
			Advance / withdraw scope one arm stroke and observe device slip relative to scope		
16	Not encumber scope or tool use	Not encumber scope or tool use - twist relative to scope	With both balloons deflated, twist scope 180 deg and observe device twist relative to camera orientation		

Table 19: SVDE *in-vivo* test matrix

Image 4: Extension of Fore balloon, balloon inflation, and pull-back of colon tissue to improve visualization of fold

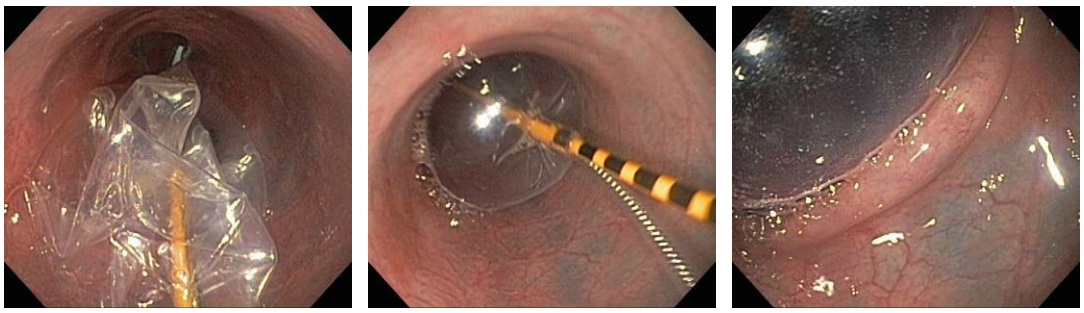


Image 5: Manipulation of colon tissue to improve visualization of fold



Image 6: Manipulation of colon tissue paired with use of inflated Fore balloon

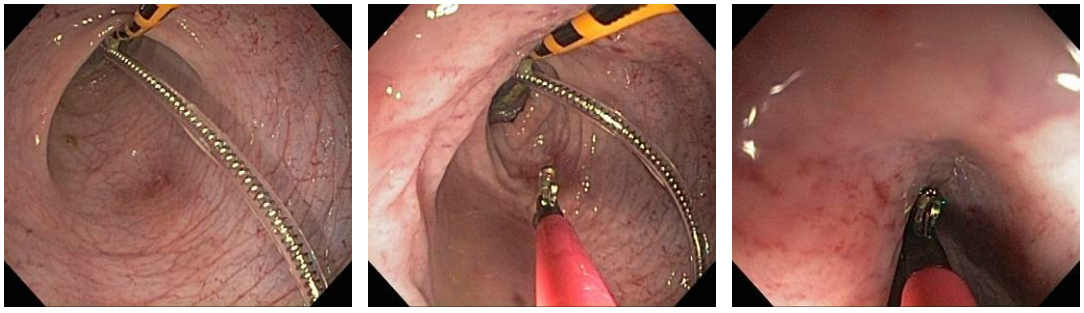
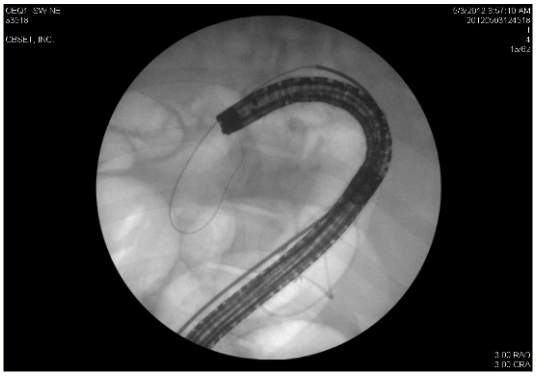


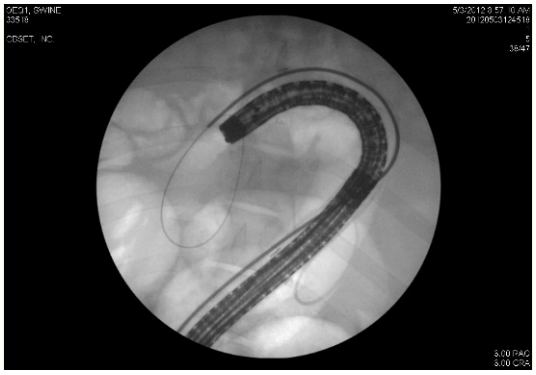
Image 7: Sequence of Fore Balloon extension via fluoroscopy (8 images total)



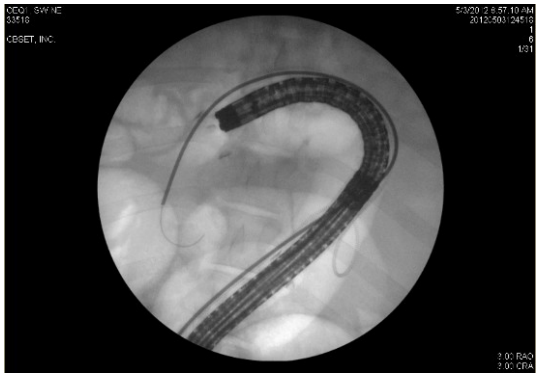
Fore balloon in initial position



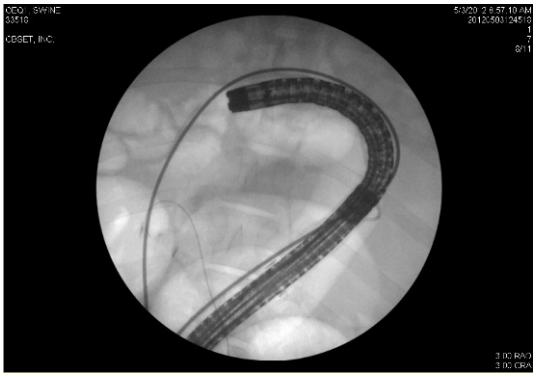
Guidewire advanced into lumen



Pushrod instrument advanced ~5 cm



Pushrod instrument advanced ~10 cm



Full Pushrod instrument extension



Aft balloon inflated

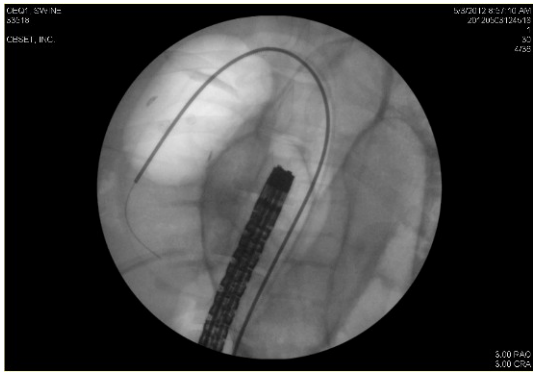


Fore balloon inflated (along with aft) Zone



Insufflation to create Therapeutic

Image 8: Full Fore Balloon extension around 180 degree flexure (5 to 6 cm radius)



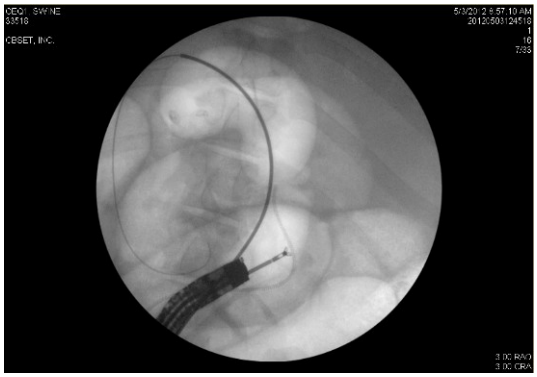
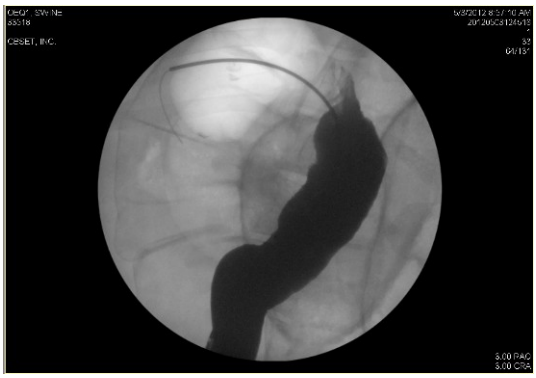
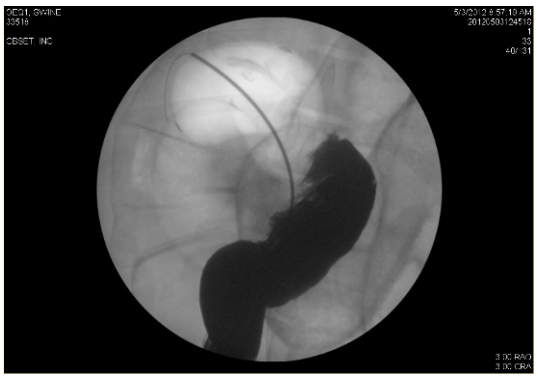


Image 9: Full Fore Balloon extension around 90 degree flexure, with tool use to target side of colon wall

Image 10: Therapeutic Zone demonstrated via contrast agent – Fore Balloon sealed against colon wall preventing leakage (aft balloon not shown, but is inflated and retaining contrast agent)



TZ created and filled with contrast agent balloon



TZ shortened by pulling on fore

Conclusions

This experiment was intended as an in-vivo repeat of one previously described in section 3.2 and on the positive side demonstrated successful FB extension *in-vivo*. SVDE also stabilised the endoscope mid-procedure, created a Therapeutic Zone (TZ) in tortuous colon anatomy, enabled insufflation and irrigation of the TZ, and showed potential for improving visualisation of the of the colon wall via manipulation of colon tissue. The fore balloon was able to be extended fully with low force in tortuous anatomy, and can be retracted and extended multiple times reliably during a procedure. However, a balloon leak caused cancellation of some of the test procedures and due to no further prototypes being available for testing we were unable to continue. This is a clear limitation of this experiment and ideally would need to be repeated prior to clinical use.

Of note, the porcine colon was perforated near the transition of the rectum and distal colon tissue (roughly 20 to 25 cm from anus), away from device activity (balloon extension, inflation, TZ creation). After review, I concluded the perforation was likely caused by excessive force transmitted tangentially during scope navigation, and was likely unrelated to balloon extension. Porcine colon tissue is typically thinner than human colon, and this must be taken into account moving forward. However, this observation was clearly of concern and needed to be taken into account moving forward. In our opinion the explanation of tangential force during colonoscopy (a recognised complication of standard colonoscopy <1%) was the highest in our suspicions, however the possible trauma during the passage of the device was also possible. There is also the potential of increased torque required by the user on the

scope whilst using the device. Such considerations must be taken into account moving forward.

4. Pre-clinical functional development

Introduction

Following the demonstration of SVDE safety regarding (1) the overall device as well as the ability to conform to various intestinal geometry, (2) balloon diameter and inflation pressure and (3) balloon pressure inflation duration, I set out to determine whether SVDE could be functionally deployed and of benefit clinically. I also set out to determine additional procedures or features that might be desirable to the clinician in performing endolumenal surgery.

4.1 SVDE achieves broad stabilisation and visualisation capability

The first step was to determine whether SVDE could function appropriately within typical colonic morphology. *In-vitro* studies of navigation, stability and visualisation were commenced. Using the Kyoto-Kagaku model and silicone colon, caecal intubation completion and times were measured. The importance of caecal intubation was as a proxy evaluation to demonstrate appropriate SVDE flexibility characteristics and conformity to the FE.

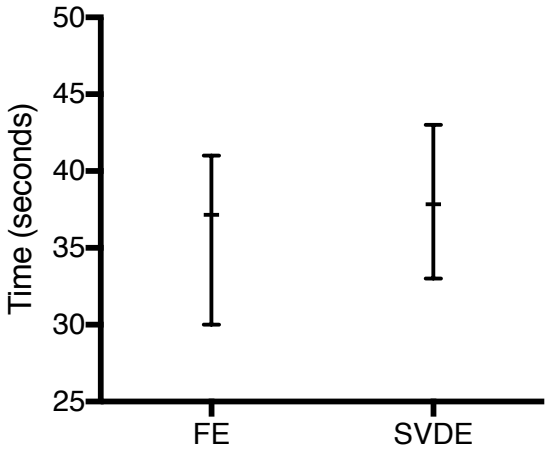


Figure 44: Time taken to reach caecum *in-vitro* (FE versus SVDE) (n=11)

No significant difference in time to reach caecum was measured between SVDE and FE indicating that there was no effect to scope functionality using SVDE (see figure 44).

SVDE provided broad stability once within the intestine and therapeutic zone deployed demonstrated through non-migration (see figure 45) when a 10N longitudinal force was applied to the scope outside the model.

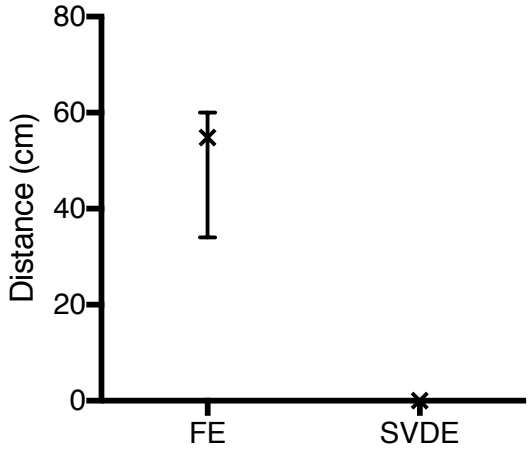


Figure 45: Distance travelled upon 10N external force application *in-vitro* (n=11)

In previous experiments, an indication had been made that the visible surface area increased with use of SVDE in both straight and flexure sections of the intestine (see section 3.2, figures 34-35). With the same configurations, I compared visible mucosal surface area with and without the device, in both anatomical configurations. A significantly increased visible mucosal field was observed with SVDE (see figure 46).

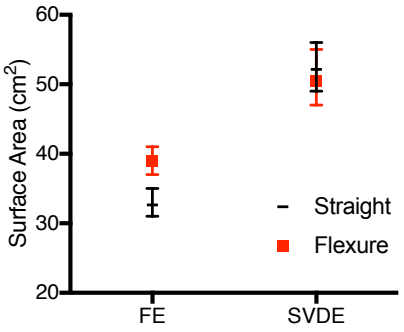


Figure 46: Visible mucosal surface area at intestinal flexure (red) and straight sections (black) *in-vitro*. (n=6)

In addition, time to reach maximal visualisation was significantly reduced with both balloons inflated and gas insufflation provided (see Fig 47). Reduced volumes of gas were used to reach a clinically acceptable level of visibility, this could also be thought of possibly reducing the chance of patient discomfort (see section 2.1, pressure data)

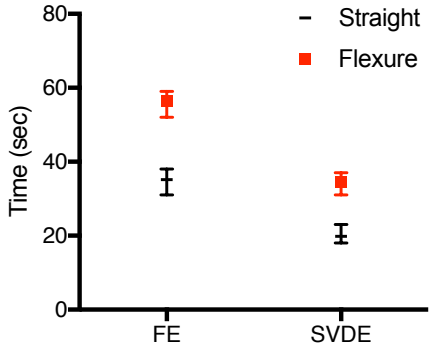


Figure 47: Time taken to reach clinically acceptable level of visibility at intestinal flexure (red) and straight sections (black) *in-vitro* (n=6)

A limitation of these experiments is the lack of a suitable learning curve given the small number of repeats. Ideally, more repeats would have been performed (up to 30), over a defined period of time with multiple operators, charting the difficulties encountered and the techniques used to overcome those challenges.

4.2 SVDE mediated intestinal tumour removal is feasible

Once the stability and visualisation characteristics had been determined of SVDE as well as the ability to navigate inside the intestine appropriately, the next step was to determine if SVDE could perform complex polypectomy i.e. ESD.

Using the technique described in the materials and methods section, I first of all conducted a feasibility assessment of the ability to perform an ESD using the SVDE. In the manner described in section 2.6, I set up the TZ proximal and distal to the polyp and used the FB gripping characteristics to provide additional tension to the mucosa.

Following this, I performed a comparison to the conventional method of performing ESD, the cap technique, versus SVDE (see figure 48).

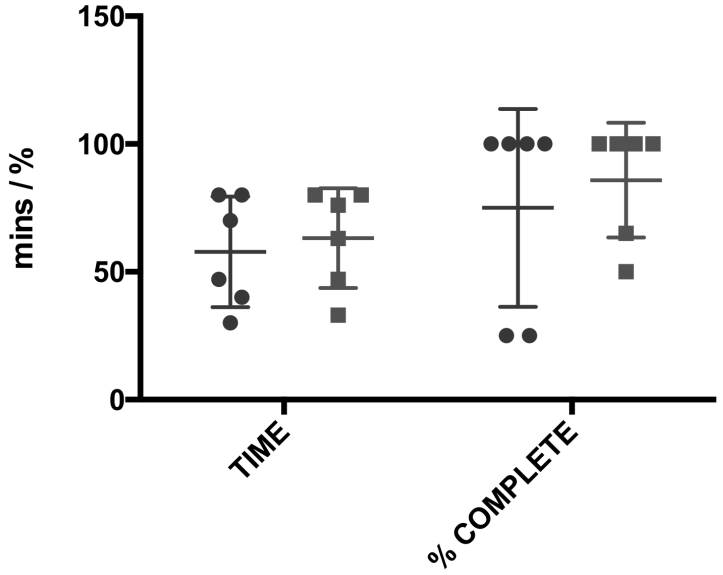


Figure 48: Time taken and percentage completion, cap (circle) versus SVDE (square) (n=24, 6 in each group)

On closer examination of the outcomes by variable attempt, by the sixth attempt the times taken for both the cap-assisted ESD and the SVDE assisted ESD were approximately the same (see figure 49).

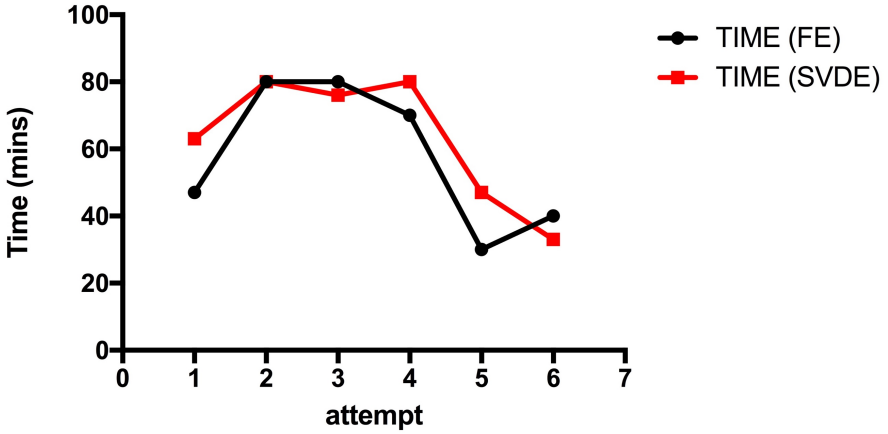


Figure 49: Time taken by attempt, FE (black) versus SVDE(red). (n=12, 6 in each group)

This confirmed that the technique was feasible and in fact did not affect the functionality of performing complex endolumenal procedures such as ESD. I noted during these experiments that the FE appeared much more stable, in keeping with the *in-vitro* stability work described in the previous sections. In addition, entry into the submucosal plane was much easier, using the inflated FB grip and applying longitudinal force appeared to provide mucosal traction. With this knowledge, I set about determining a method to improve tumour removal endolumenally using SVDE.

4.3 SVDE improves tumour removal through tissue traction

Mucosal traction is critical to the effective removal of tumours. During my previous experiments, it became evident that the FB provided a surface contact gripping tension that aided in entry into the submucosal plane. After further consideration in light of these observation, I concluded that it also represented an appropriate target onto which I could attach the mucosal edge or any tissue in general. After rudimentary experimentation with various rings and sutures attached to the FB and pushrods, I established a procedural intervention utilising haemostatic clipping of the incised mucosal edge to the proximal edge of the FB (see figure 50).

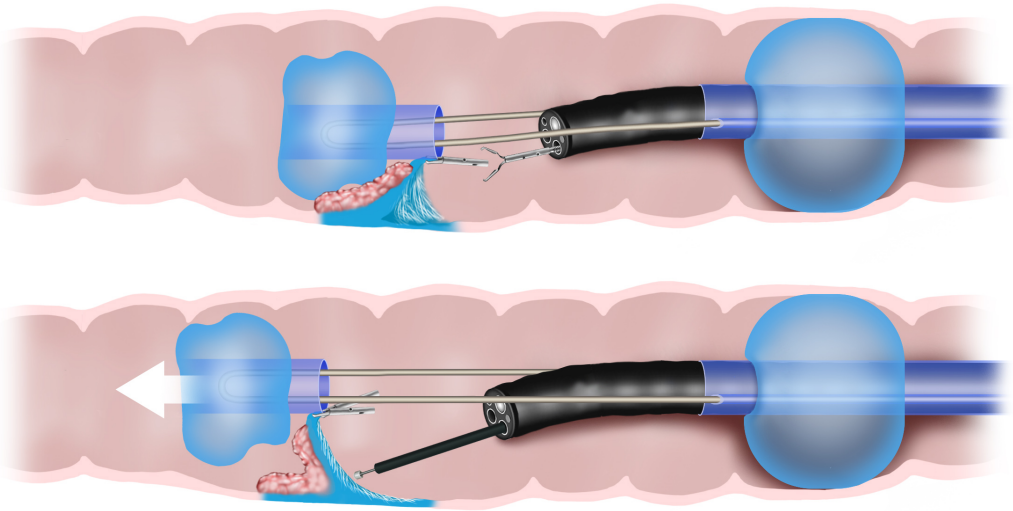


Figure 50: Cartoon of balloon assisted retraction. Upper panel – the balloon shelf is positioned over the incised mucosal edge and clipped. Lower panel – the FB is extended relative to the endoscope tip providing tissue traction.

The SVDE was mounted onto a colonoscope (Olympus PCF-H180AL; Olympus Corporation, Japan). Upon insertion into the model and at an appropriate section related to the lesion, the Aft-Balloon (AB) inflation selector was selected via the inflation handle control knob. The inflation/deflation bulb was depressed until the desired pressure was reached (indicated by the indicator turning green). Upon confirmation of scope stability using slight longitudinal movements on the scope shaft, the Fore-Balloon (FB) was extended beyond the endoscope tip using the FB slider located on the handle of the device. Upon extension to the desired distance the FB inflation position was selected and the inflation bulb was again squeezed to inflate the FB, the degree of which was confirmed using the indicator as well as visual representation on the endoscopic view. After confirmation of mucosal gripping, the FB was further extended using the handle knob to provide mucosal traction.

A circumferential mucosal incision was made at the lesion margin with the Olympus electrosurgical Dualknife . Following this, the balloons were deployed behind and in front of the lesion. Once the FB balloon shelf (yellow arrows on figure 51) was appropriately positioned adjacent to the incised mucosal edge, 3 haemostatic clips were placed connecting the mucosal edge to the FB shelf. The FB could therefore be moved and the attached mucosal edge be retracted back according to the operators needs. Dissection was then completed using the Olympus IT-nano electrosurgical knife. Total procedure time, dissection time, perforation and specimen margin were recorded.

After multiple procedural iterations *ex-vivo*, a technically feasible procedure was established (see figure 51 and section 2.7). I noted that the view of the submucosal plane improved considerably.

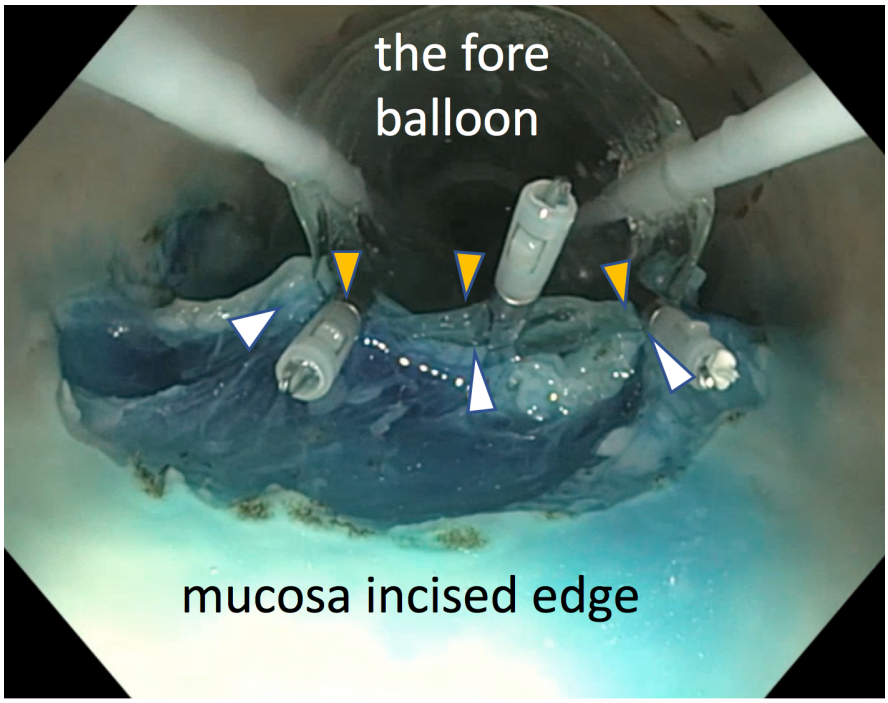


Figure 51: Endoscopic view of balloon assisted retraction technique *ex-vivo*. The balloon shelf (yellow arrows) are clipped to the free incised mucosal edge (white arrows).

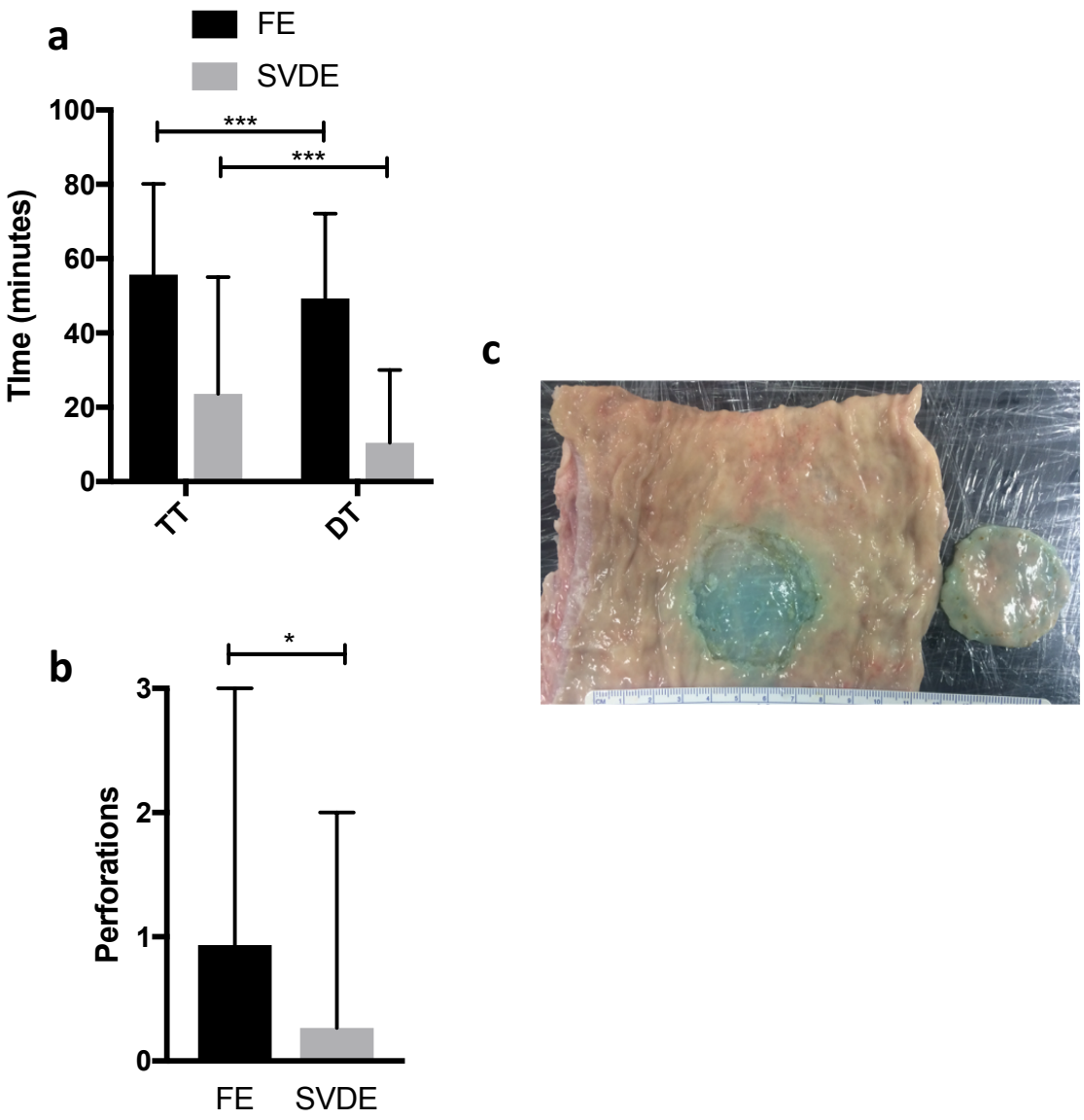


Figure 52: SVDE FB traction assisted ESD versus FE alone; a, total time (TT) and dissection time (DT); b, perforation average; c, macro-histological specimen post-procedure (n=12, 6 in each group)

The next step was to determine if this could reduce technical complexity as well as improve safety. Upon analysis of my experiments, I found that complex polypectomy under the assistance of SVDE FB traction was completed significantly shorter time, decreased transmural perforations and greater stability (see figure 52, a and b).

Residual tumour could not be detected at this stage through visual inspection (see figure 52, c).

Following confirmation of this technique *ex-vivo*, I transferred this procedure *in-vivo* to determine applicability as well as assessment of technical factors un-available *ex-vivo* e.g. bleeding. I was only able to perform this in one case (n=1)

In-vivo experiments showed that the technique was feasible and reproducible. The steps are shown in figure 53

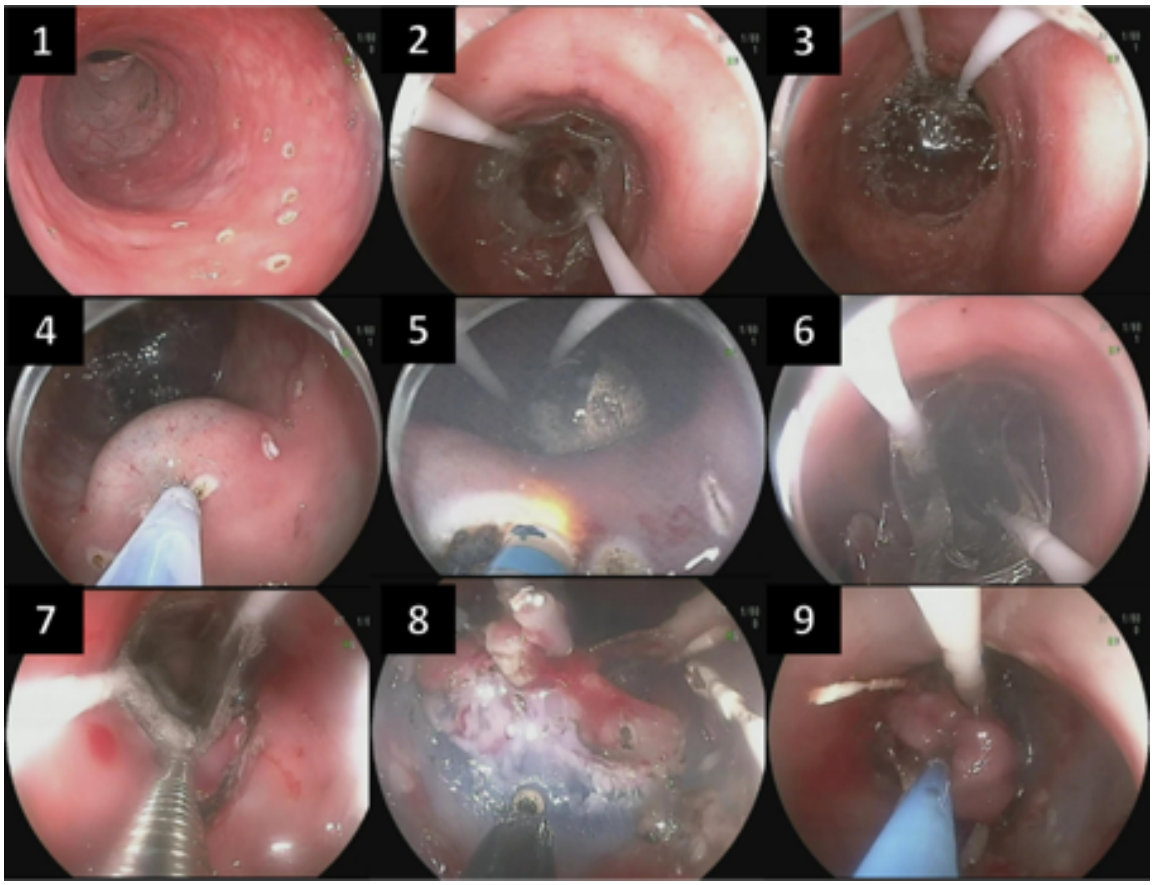


Figure 53: In-vivo SVDE FB assisted retraction ESD; 1, polyp demarcation; 2, FB extension; 3, FB inflation; 4, submucosal injection; 5, circumferential incision; 6, FB positioning over mucosal edge; 7, clipping of mucosal edge to FB; 8, submucosal dissection under traction; 9, specimen retrieval using FB channel.

During this experiment, I discovered a method for specimen retrieval by using the FB channel as a housing. By placing the removed specimen into the FB channel in turn prevented non-affected mucosal contamination (see Fig 53, panel 9) which could potentially be useful in clinical situations, acting as a retrieval pouch.

SVDE potentially resulted in improved visualization, stability and retraction, improving resection time, reducing transmural perforation and demonstrating improved tumour removal capabilities. However, these results should be considered in light of the small number of repeats, particularly in the case of the in-vivo experiment, where only 1 attempt was made, as such no definitive conclusions could be made.

4.4 SVDE facilitates underwater immersion screening of tumours

The major difficulty with performing advanced endolumenal procedures is the presence of electrosurgical mist and smoke from the electrosurgical knife. The enclosed intestinal space leads to rapid accumulation of smoke that requires suctioning out regularly. Through literature review a underwater immersion technique had been described[163] that used solution immersion of the tumour to provide some benefits namely (1) improved magnification due to the water interface, (2) reduced smoke and (3) hydro dissection and buoyancy. Despite this techniques benefits, it is difficult to execute as water levels are difficult to maintain in the intestine. I hypothesized that instilling solution into the TZ would facilitate underwater techniques such as ESD (see figure 54).

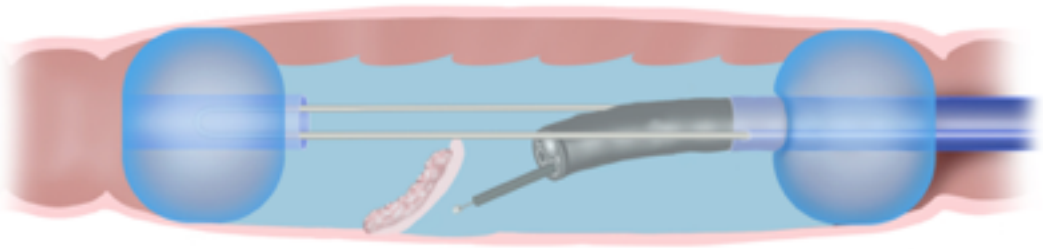


Figure 54: Water instillation within the therapeutic zone.

I first set out to determine if water levels could be maintained in the intestine in the *in-vitro* model due to the ability to see through the material to measure the fluid height (see figure 55)

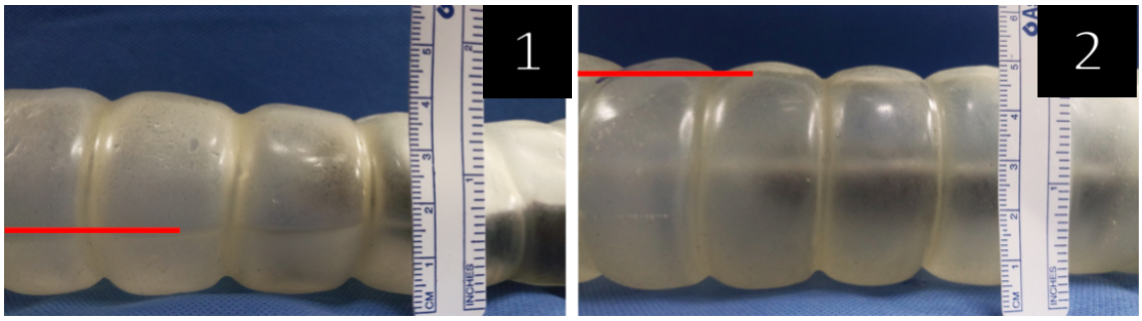


Figure 55: Intestinal solution level (red line) after 1 hr (1), FE (2), SVDE, therapeutic zone activated.

I then went onto to measure the fluid height over an hour. SVDE provided a significant maintenance of height compared to using the FE alone (see figure 56).

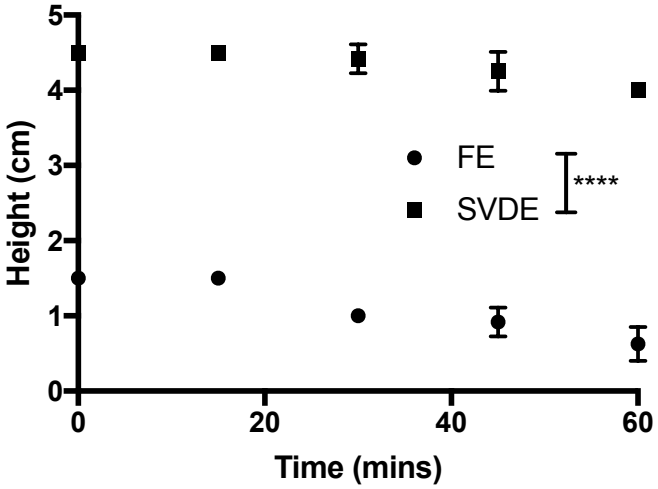


Figure 56: Intestinal solution height maintenance, SVDE versus FE (n=6, 3 in each group)

Now that I concluded that the fluid was maintained in the intestine, I moved onto determine whether this would assist in an underwater ESD experiment. SVDE was used

to evaluate tumour visibility and removal following solution immersion within the inter-balloon space.

It was evident from the beginning that electrosurgical activation within the saline filled inter-balloon space showed significantly improved visualisation (see figure 57)

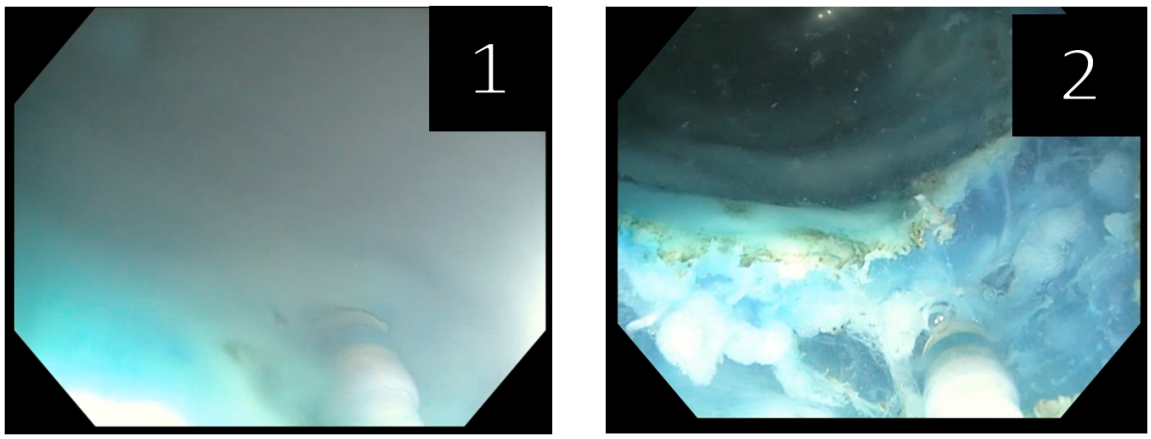


Figure 57: Tumour removal visibility with electrosurgery activation, (1) without and (2) with SVDE.

SVDE also resulted in a shorter procedure time duration, primarily due to the retraction capabilities and not improved visibility.

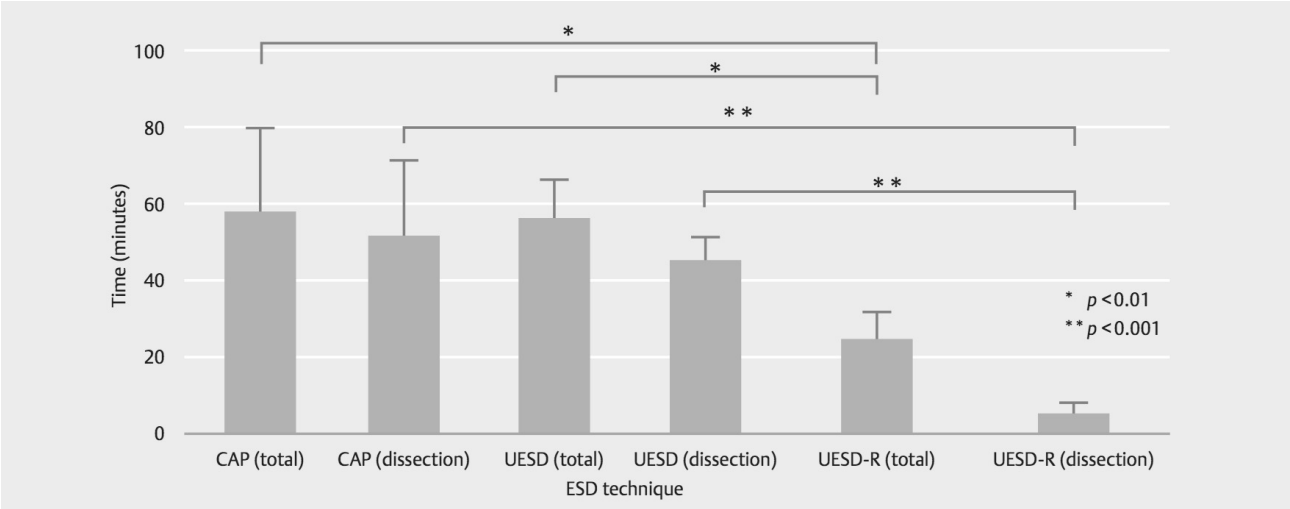


Figure 58: SVDE showed significantly improved immersion-assisted tumour removal time. For CAP group n = 6; for UESD group n = 6; UESD-R group n=6; *P < 0.01, **P < 0.001.

SVDE use underwater offers a simple facilitator of improved visualization and tumour removal. The dissection time reduction was due to the retraction provided and not the facilitation of prolonged fluid volume. As figure 57 suggests vision was qualitatively much improved under water. A limitation of this experiment was that no objective or semi-objective measurements of this improvement were pursued. One method of attempting to do this in the future would be to take various pictures of the procedure in 2 groups, underwater versus standard, and at random ask multiple endoscopists to rate the visibility of the photos in a blinded manner.

4.5 Radiographical parameter derived 3D printed abdominal model provides improved accuracy

At this point I had realised that the conventional *in-vitro* and *ex-vivo* models that I had been using in my experiments were convenient but had significant limitations namely the models accuracy. So I set about building a new *ex-vivo* GI model to enable improved evaluation of techniques and methods, not just with SVDE but any further innovations moving forward.

Method

Using sagittal section computed tomography (CT) Digital Imaging and Communications in Medicine (DICOM) images of a female and male pelvis (obtained from J. Milsom,

figure 59), the measured distance parameters pertaining to the abdomino-pelvic cavity. Both images were selected as to be at the general extremes of anatomical variation.



Figure 59: CT images; left, tall male; right, short female.

	From the xiphisternum to the pubic lower border(cm)	From splenic flexure to the height of the pubic rim(cm)	From hepatic flexure to the height of the pubic rim(cm)
patient A	32.63	29.13	25.21
patient B	38.78	30.84	27.73
average	35.705	29.985	26.47

Table 20: Dimensions derived from patient CT images

Using a standard pelvic model template the resulting patient dimensions (outlined in table 20) were inputted into 3-Dimensional modelling software – Auto-CAD (figure 60) and printed (figure 61). The aim was to have a model that could be flat-packed, easy to clean and light so as to aid in its travel for training purposes.

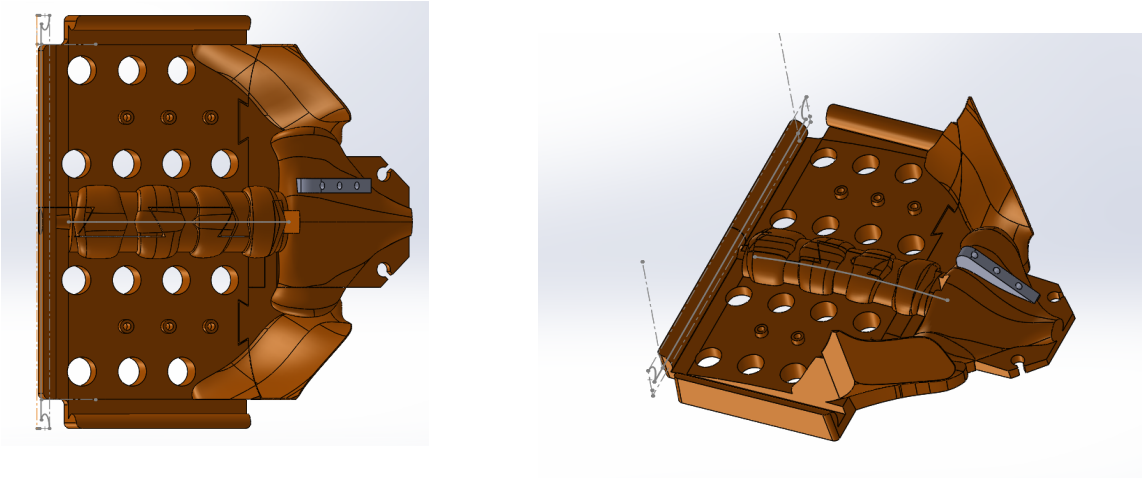


Figure 60: 3-D model of abdomino-pelvic model, left top down view and right oblique view

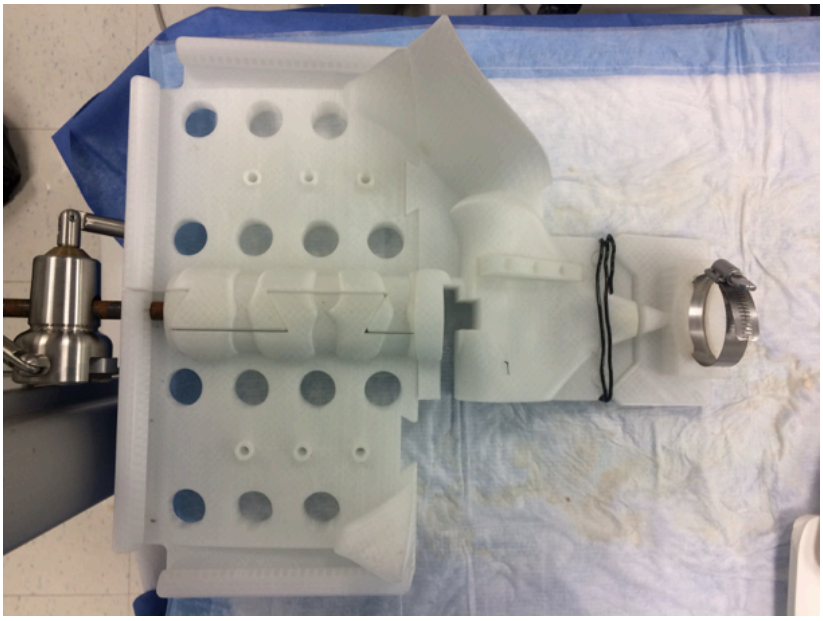


Figure 61: 3-D printed abdomino-pelvic shell

Once the shell was printed, flexible medical grade silicone borders were added to provide realistic abdomino-pelvic borders. Fresh *ex-vivo* porcine tissue was then mounted onto the rigid shell with paper sheets and metals fasteners to simulate human anatomical tethering (figure 62) and leaving the sigmoid free as in real-life.

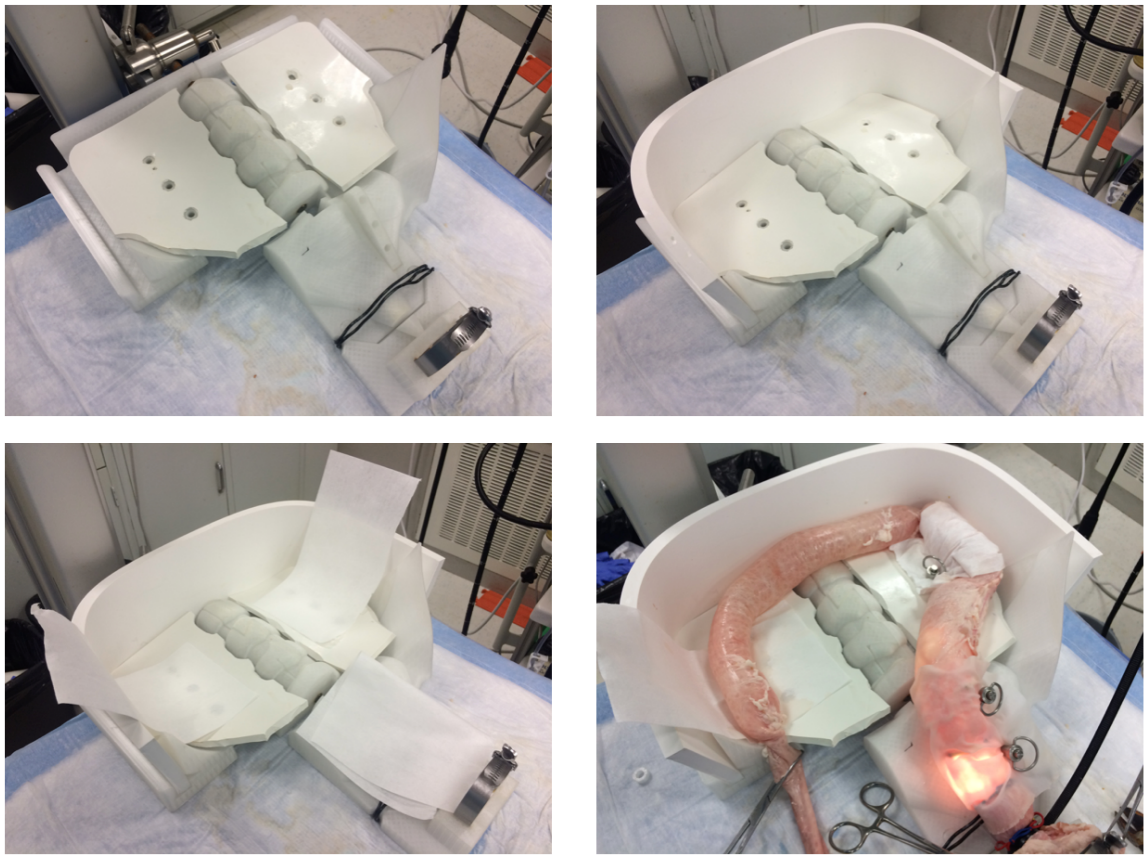


Figure 62: Step-wise placement of silicone borders - abdomino-pelvic shell with silicone inserts and *ex-vivo* porcine intestine mounted

I then went onto developing rectal valves by imbricating the rectal serosa with elastic bands. These were placed at specific intervals with the superior valve placed at 13cm from the anal verge (figure 63).

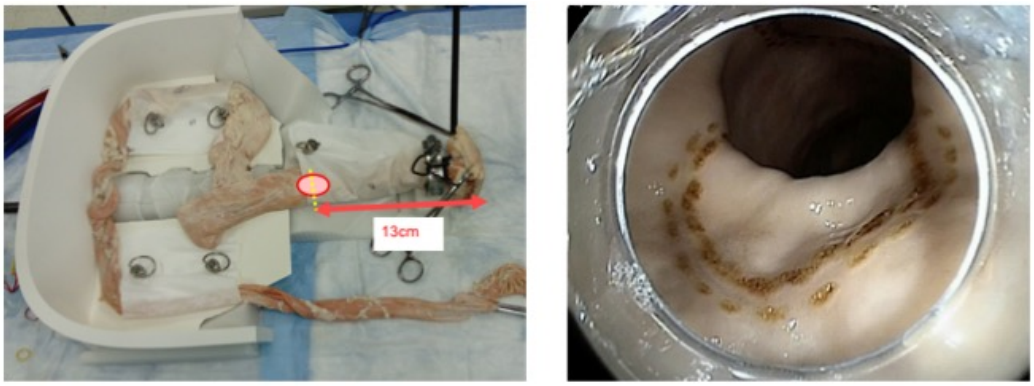


Figure 63: Left, mounting of the rectal valve bands with the superior rectal valve placed at 13cm from the anal verge. Right, endoscopic view of the superior rectal valve demonstrating accuracy.

The result was an accurate model with realistic colonoscopic simulation especially of common issues such as sigmoid looping as well as anatomical considerations such as rectal valves. The lack of tethering of the sigmoid intestine accurately reproduced sigmoid looping which is a common difficulty in standard colonoscopy, compare this to the standard silicone model which does not simulate looping. In addition, the use of fresh porcine tissue, simulated human endoscopic view and the ability of the model user to perform therapeutic actions, all of which are not commensurate with the standard silicone model.

4.6 Shorter length SVDE improves rectal eTAMIS

The original SVDE was designed to fit 168cm length colonoscopes, however it became evident that certain clinical applications would benefit from a shorter length SVDE such as rectal ESD. For this purpose, a shorter version of the SVDE was developed (103cm), this enabled shorter scope lengths to be used as well as gastroscopes (scopes for upper GI use) if needed.

Using the 3-D printed model described in the previous section with rectal folds, I set about determining whether SVDE would facilitate complex rectal ESD on a fold. This is typically considered a challenging procedure.

	ESD technique		
	FE	**SVDE**	**p value**
n=	5	5	
time to complete ESD (mins)	41(±26)	35(±16)	0.7
Set up time (mins)	19(±8)	22(±12)	0.4
Dissection time (mins)	23(±18)	13(±4)	0.8
Perforation	0	0	NS
Clear Margins	5	5	NS

Table 21: Outcomes following short SVDE use for Rectal fold ESD versus FE (n=10, 5 for each group)

In this preliminary evaluation, I could not find any significant differences in the parameters between the two techniques (see table 21). There was a slightly reduced mean completion and dissection times but these did not approach statistical significance.

Ideally further repeats of this experiment should have been performed to evaluate the learning curve however these were not performed for reasons of cost and time pressures. Therefore, the reasons non-inferiority and clear advantage for using SVDE in simulated rectal lesions remains unknown. SVDE traction instigation in the rectal model also required a different deployment technique to the methods previously described. Whereas in the standard fashion, the AB and FB would be deployed across a lesion, in this situation, I had to advance the scope farther into the model, past the lesion and deploy the FB 20cm upstream of the lesion. Following the deployment, I would then retract the scope and device outside the model positioning the FB adjacent to the mucosal edge. At this point the AB would be inflated stabilising the position. Often the aft balloon would be located outside the model. In addition, the shorter device added new features such as the ability to slide the scope within the SVDE sheath; whilst the sheath was fixed in place through balloon inflation. This was an interesting observation only available with the shorter device, as the length of scope not enclosed by the device was far greater than that of the standard 168cm device version. This enabled the scope tip to move within the TZ whilst the device remained stationary. Future experiments will focus on developing this technique further.

4.7 SVDE achieves clinician validation

Following the determination that SVDE provided enhanced tumour removal capability strategies, the last step prior to FDA submission and subsequent clinical use was clinician validation. This was performed under simulated conditions. The purpose of the validation was to ensure that the device met the specification/functional requirements, intended use, and user needs. 6 participants were used for validation. All participants were experienced attending Gastroenterologists or Colorectal Surgeons who had no prior involvement or practice with the device. 4 of the 6 participants performed the protocol 4 times, the remaining 2 performed the protocol 3 times, giving an n of 22 for each measured variable.

I led the testing that was performed in the laboratory using the Kyoto Kagaku Colonoscope Training Model. We used the Kyoto model and not the 3D printed model described earlier, due the need for expert endoscopists to use a validated colonoscopic trainer they would all be familiar with. The 3-D printed model was a prototype and not validated as well as being unused outside of myself and a colleague. The testing strategy built on the previous *ex-vivo and in-vivo* testing protocols and measured the time required by users to set up the device (remove the device from its box, inflate and deflate the balloons), attach it to the endoscope (using water lubrication insert the scope into the device and lock in place), navigate to the caecum (advance the scope as normal to the caecum), deploy the therapeutic zone (inflate the aft balloon, advance the foreballoon and inflate) and recapture the fore balloon into its original position (deflate the foreballoon and retract onto the endoscope tip. The testing also evaluated:

- Clinician control of the fore balloon – the clinician was able to locate the foreballoon control and slide the mechanism (rated out of 5, 1=poor, 2=below average, 3=average, 4=above average, 5= excellent)
- Tactile feedback provided during device navigation – feel of the device and scope when passing intestinal flexures (rated out of 3, 1=poor, 2=normal, 3=excellent)
- Ability of endoscopic tools to exit the working channel into the field of view – clinician used a standard biopsy forceps in the working channel of the endoscope and confirmed whether or not able to see the tool exit into the endoscope view (yes or no)
- Adequacy of device articulation – the movement of the endoscope dials in navigation to the caecum is in keeping with normal scope function (yes or no)
- Whether the device blocks the various endoscope accessories – the clinician is asked to activate the suction button, lens wash and irrigation function of the scope to ensure the device does not affect the scopes function (yes or no)
- Clinician ability to torque the endoscope with the device attached to it – the clinician gives feedback after reaching the cecum about his or hers ability to torque the scope with the device attached (yes or no)
- Flexibility of the patient-contacting components – the clinician ran his or her hand along the surface of the device to ensure no sharpness or traumatic surfaces (yes or no)

Results

Item	Test Description	Specification/ Acceptance Criteria	N	Results
1.	Setup Time	The device shall be set up in less than 15 minutes by no more than two users who have received training. (Set up includes removal from packaging and attachment to an endoscope.)	22	Average: 04:55 (4.91) Minimum: 03:10 (3.16) Maximum: 07:33 (7.55) Pass/Fail: Pass
2.	Device Attachment	Sliding and attaching the device on the endoscope shall take less than 5 minutes.	22	Average: 01:29 (1.48) Minimum: 01:05 (1.08) Maximum: 04:40 (4.66) Pass/Fail: Pass
3.	Fore Balloon Control	The device shall locate the fore balloon mechanism close to the endoscope control handle to allow the clinician to extend the fore balloon.	22	Average: 3.44 Minimum: 2 Maximum: 5 Pass/Fail: Pass
4.	Device Navigation	As the device is navigated through bends, tactile feedback shall be provided when intestinal tortuosity is encountered.	22	Average: 2.91 (out of 3) Minimum: 2 Maximum: 3 Pass/Fail: Pass
5.	Fore Balloon Recapture	The fore balloon shall be able to be recaptured into its original position in less than 2 minutes.	22	Average: 01:31 (1.51) Minimum: 00:14 (0.24) Maximum: 10:32 (10.54) Pass/Fail: Fail

Item	Test Description	Specification/ Acceptance Criteria	N	Results
6.	Tool Usage	The device shall not prevent endoscopic tools from exiting the working channel into the field of view.	22	Number Passed: 22 Number Failed: 0 Pass/Fail: Pass
7.	Navigation Time	The time to reach caecum shall not be more than 15 minutes.	22	Average: 01:27 (1.45) Minimum: 00:39 (0.65) Maximum: 02:58 (2.96) Pass/Fail: Pass
8.	Articulation Test	The device must not cause excessive torque to achieve the articulation necessary to navigate to the caecum with the fore balloon docked and deflated. This will be the pass/fail criteria to assess that the torque is acceptable.	22	Number Passed: 22 Number Failed: 0 Pass/Fail: Pass
9.	Endoscope Accessories	The device shall not block the suction port, lights, camera, working channel, or irrigation orifice of the endoscope.	22	Number Passed: 22 Number Failed: 0 Pass/Fail: Pass
10.	Torque Test	The device shall not impede the user's torqueing the scope.	22	Number Passed: 22 Number Failed: 0 Pass/Fail: Pass
11.	Atraumatic Device Test	The components that are in contact with the patient shall be comprised of a flexible material.	22	Number Passed: 22 Number Failed: 0 Pass/Fail: Pass

Foreballoon recapture trial details

Trial	Total Time Taken	Recaptured?	Pass/Fail
1	4:13.20	No	Fail
2	11:32.25	No	Fail
3	0:44.26	Yes	Pass
4	1:17.3	Yes	Pass
5	0:42.62	Yes	Pass
6	1:42.96	Yes	Pass
7	3:02.77	Yes	Fail
8	0:31.32	Yes	Pass
9	3:48.22	Yes	Fail
10	0:17.40	Yes	Pass
11	0:25.14	Yes	Pass
12	0:32.00	Yes*	Pass
13	0:35.45	Yes	Pass
14	0:43.28	Yes	Pass
15	0:28.95	Yes	Pass
16	0:51.08	Yes	Pass
17	0:30.35	Yes	Pass
18	0:38.47	Yes	Pass
19	0:14.65	Yes	Pass
20	1:01.53	Yes	Pass
21	0:18.88	Yes	Pass
22	0:17.18	Yes	Pass

Conclusions

The SVDE Validation successfully demonstrated the device's ability to be safely and properly used for the intended purpose by medical professionals who had no prior experience with the device. The only failing results were in the time elapsed in recapturing the Fore Balloon, where 4 of 22 re-docking tests exceeded the acceptance threshold of two minutes. Nevertheless, the results were deemed acceptable based on a conclusion that the causes of these failures could be mitigated through improved technique, training, and labelling, and that taking longer to re-dock the Fore Balloon does not generate any risk to the patient as the device could be removed from the patient with the FB undocked under direct vision.

5. Clinical safety

Introduction

In December 2016, FDA approval for SVDE was granted. FDA approval was obtained in under the 510K pathway rules in which essential equivalence is deemed the measure of safety and requires no clinical evidence. This pathway has given rise to some serious medical device controversies, primarily related to implantable devices such as vaginal meshes and orthopaedic implants. There were concerns regarding the use of SVDE in humans with little animal data or experience until this point. Ideally, we would have completed more animal studies prior to this to ethically confirm the safety characteristics of SVDE.

I will now set out to determine the safety characteristics of the device in human-use. This chapter outlines the clinical safety study that was conducted at Weill Cornell Medical College, New York Presbyterian Hospital. For the clinical study, I decided to follow the IDEAL principles as outlined in the introduction section (see section 1.22), the purpose of this was to encourage the open reporting of the challenges encountered in the clinical study.

The key principle in the IDEAL method is transparency with recommendations for structured reporting of first-in-human experience and early clinical usage (IDEAL stages 1- 2a) in a format termed the Prospective Development Study (PDS). There is a need to formally record unsuccessful interventions, so as to avoid unnecessary repetition by peers. Subsequent developmental stage (IDEAL 2a) should be prospective with reporting

of all cases and outcomes without omissions, and, with clear explanations of when and how technique, design, or indications were changed.

5.1 Doctor training

I provided the participants approximately 30 minutes of training prior to beginning the clinical study at a time convenient for the team. The training consisted of a short video introduction, device demonstration, reviewing the Instructions for Use (IFU), and hands-on introduction using the pre-clinical models. It is unknown if this training was adequate for the clinicians formally. Over a confirmation by the clinician to myself that he or she was happy to use the device we did not use a formal test to see if competency was gained. Ideally, this would have included comparisons to previous data to assess comparative outcomes such as time to cecum etc. It may have included a short live animal lab, or if a formal learning curve was able to be performed, the clinician could be assessed against such criteria.

5.2 SVDE clinical use preparation

Preparation and prior experience

The gasteroenteroIogical and colorectal surgical team at WCMC / NYPH, New York, began using the SVDE in April 2017, after appropriate Institutional Review Board approval (see appendix for documentation). The study was also registered with clinicaltrials.gov. Two doctors (Dr. Reem Sharaiha and Dr. Toyooki Sonoda) developed their familiarity with the platform in the porcine intestine by performing basic and advanced procedures in the laboratory mirroring the experiments I had performed and outlined in the previous chapter. Both doctors had previous experience of advanced endoscopic techniques. The WCMC / NYPH unit performs around 100 advanced endoscopic procedures a year (EMR and ESD). Table 22 defines the terminology used to denote the different approaches used during the series.

Procedure name	Abbreviation	Description
Colonoscopy	COL	Colonoscopy with no treatment
Endoscopic Submucosal Dissection	ESD	COL + En-bloc resection of polyp
Endoscopic Mucosal Resection	EMR	COL + Piecemeal resection of polyp
Hybrid	HYB	COL + Combination of EMR and ESD

Table 22: Procedure list used in the clinical study

Planning and protocol

This was an observational registry study of 30 patients to assess safety and feasibility. IRB approval was granted by Cornell (Number: 1610017641) and clinicaltrials.gov

registered (NCT03113578). Prior to the study, the DEIP had never been used in a human colon.

This was a PDS to determine (1) whether a colonoscope equipped with the DEIP could be advanced to the cecum successfully (primary endpoint) and (2) have its two balloon system deployed successfully in both the right and left colon to create TZ (secondary endpoint). Consecutive patients who were judged suitable for routine surveillance colonoscopy or advanced polypectomy without contraindications were eligible for the study. No restrictions were imposed on BMI or age. Patients with previous history of diverticulitis, strictures or previous abdominal surgery were excluded from the study. The initial procedural planning algorithm was therefore as shown in Figure 64.

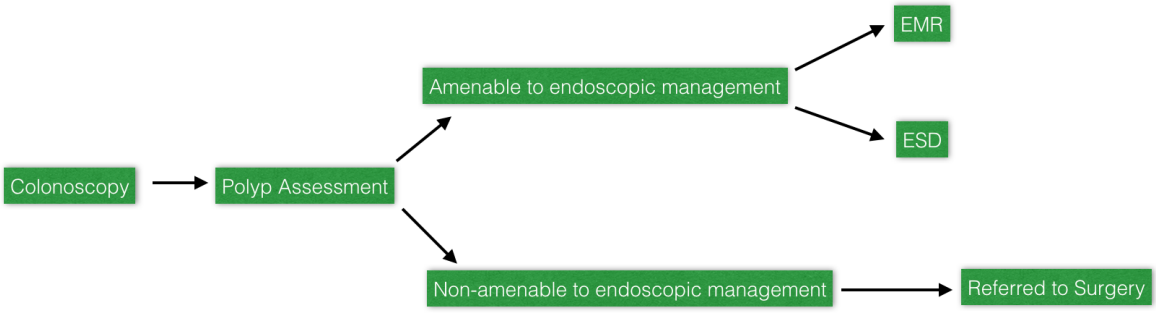


Figure 64: SVDE clinical study initial procedural planning algorithm

Prospective development study design - annotating changes

Following the IDEAL Recommendations, we documented sequentially all patients included in the study from the first case performed using the device and the principal

outcomes of interest in each case. When we made changes to the procedural technique or indications, we annotated the point in the series where this occurred. For the patients undergoing the procedure, we documented procedural time, occurrence of any complications and any additional procedures performed.

Technical details

Briefly, this is mentioned here to serve as the clinical starting point as any changes to the procedure following IDEAL recommendations should be related to this description.

The patient was positioned in lithotomy (operating room only) or in left lateral orientation. After per rectum examination, the SVDE was mounted on the FE and both inserted into the anus after lubrication. The sigmoid colon was generously irrigated with water to traverse its generally smaller calibre through lubrication. The colonoscopy was completed as usual and upon reaching the cecum, appropriate pictures were taken and the terminal ileum intubated. After this the FE and device were retracted slowly towards the anus carefully noting the mucosal surface for any abnormalities e.g. polyps. During withdrawal, at both the ascending and sigmoid colon, both the AB and FB were inflated and deflated after TZ set-up (see figure 2). After this, the sequence was reversed and the FB re-docked onto the endoscope tip. When lesions e.g. polyps were encountered, the clinician would manage them in the normal fashion. Any difficulties in endoscopic navigation e.g. looping were managed in the typical fashion i.e. abdominal pressure and patient position change. After completing the procedure, the SVDE and FE were removed from the patient and the SVDE discarded (device is single-use).

5.3 SVDE Clinical Function

First patient use occurred on the 26th April 2017. On initial observations, SVDE functioned in accordance with the pre-clinical work.

IDEAL Stage 1: First case procedure report

*Date:*26th April 2017
Location: Endoscopy department, New York Presbyterian Hospital.
Clinician: Dr. R. Sharaiha (gastroenterologist)

Patient details: 41-year-old female, previous benign polyps, no other relevant medical history, scheduled for routine outpatient colonoscopy. No contraindications to being selected for study.
Exam type: Routine colonoscopy
Indications: Previous history of benign polyps
Medications: Propofol sedation
Complications: No immediate complications

Procedure:
Anaesthesia: ASA Grade Assessment: I – A normal healthy patient.

SVDE mounting on endoscope: The device was removed from the packaging and placed on a sterile drape covered table. The endoscope was inserted into the device whilst irrigation fluid applied and advanced so that the endoscope tip was 1cm proud of the FB edge. At this point the device lock was applied. After, the balloons were inflated sequentially, ensuring there were no leakages. Following this both balloons were deflated. After this the outside of the device was lubricated with standard gel based lubrication and was ready for use.

Colonoscopy: After per rectum examination, the scope and SVDE were passed under direct vision, introduced through the anus and advanced to the caecum identified by the appendiceal orifice and ileocaecal valve. The scope was withdrawn from the cecum 10cm and the therapeutic zone set-up. First the aft-balloon was inflated, fore-balloon extended and inflated and then the reverse was performed. Then, the scope and device were withdrawn to 25cm from the anus. The therapeutic zone set-up procedure was repeated at this level. The colonoscopy and therapeutic zone set-up were performed without difficulty. The patient tolerated the procedure well. The quality of the bowel preparation was good.

Differences noted with SVDE: Slightly reduced tactile feedback through sheath but within normal limits. Device functions could be performed with no difficulties. Push rod kink was noted on extension of the fore-balloon.

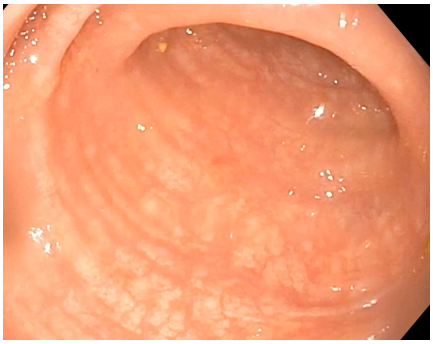
Findings: One small polyp found in the ascending colon. Biopsied.

Impression: One small polyp in the ascending colon. Otherwise, the examination was normal.

Device appearance after procedure
Push rod kink was observed in both push rods. No other abnormalities were noted.

Patient was discharged after procedure.

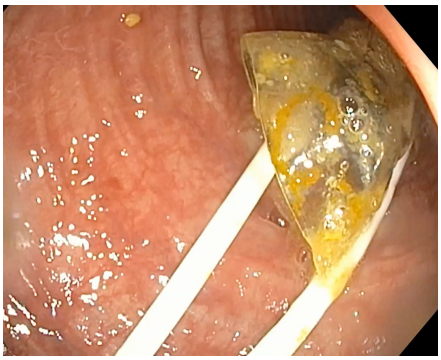
First human case – endoscopic view



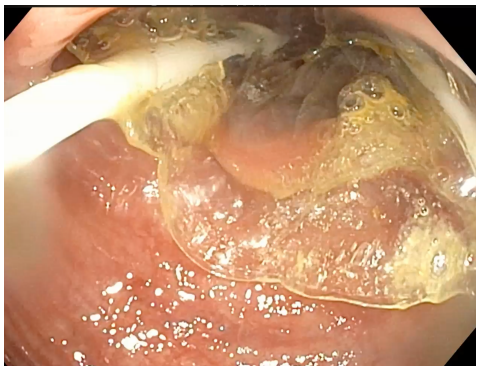
Pre-deployment lumenal view



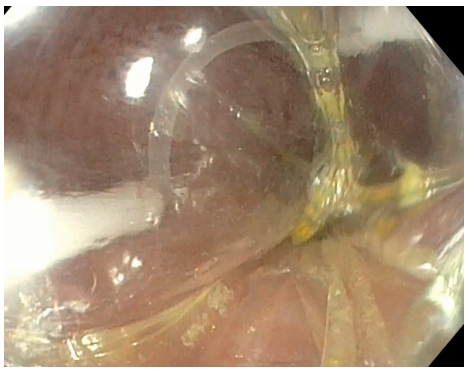
Deployment of FB



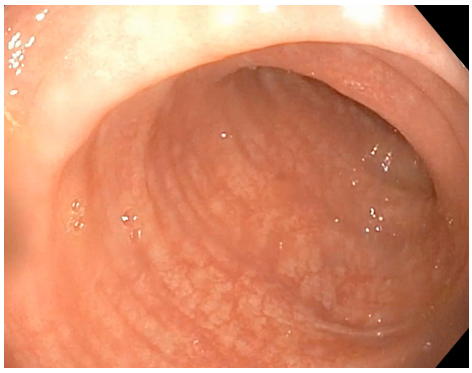
Full extension of FB past flexure



Inflation of FB demonstrating grip



Redocking of FB onto FE tip



Post TZ deployment lumenal view

Figure 65: First human case FB deployment characteristics

5.4 SVDE Clinical Results

There were 11 men and 19 women included in this study, with age ranging from 35 to 83 years (mean 63.6 years +/- 12 standard deviation). All cases were completed within a 6 month time period (April to September 2017) (see table 1). Two patients were excluded from the analysis due to protocol deviations (safety concern due to diverticular disease precluded fufillment of protocol-patient 13, previous abdominal surgery – patient 26).

Primary endpoint - Reaching Cecum

Cecum was successfully reached in 25 of the 28 (89%) patients (Intention to treat (ITT) group = 83%). Average time to reach cecum was 13.5 minutes, this was the same as the ITT group (Range: 3-48).

The reasons for inability to reach the cecum in three patients were as follows:

1) FE without DEIP could not reach cecum due to tortuosity and long length of colon (patient 6).

2) A long tortuous colon caused device malfunction (patient 16).

3) A long tortuous colon led to device removal (patient 28).

Additional procedures: Eight patients received additional interventions with DEIP due to findings observed during the procedure. These interventions were primarily previous site biopsies. One patient required polypectomy (EMR) which was successful.

Secondary endpoint – Therapeutic Zone creation (see figure 3)

In the Per protocol population, therapeutic zone creation was successful in 89% of patients where the device reached the right side of the intestine and 100% in those that reached the sigmoid.

There were no perforations, instances of bleeding post procedure, or deaths. Non-clinically significant mucosal abrasions were noted in five patients (17%). All patients were discharged on the same day of the procedure.

Case Number	Time to Cecum (min)	Therapeutic Zone Right Side?	Therapeutic Zone Left Side?	Lesion(s)	Intervention with DiLumen?	Comments
1	8	Yes	Yes	1 x biopsy - Ascending colon	Yes	Push rod malfunction (kink)
2	10	Yes	Yes	1 x biopsy - Splenic Flexure	Yes	Push rod malfunction (break)
3	12	Yes	Yes			Push rod malfunction (kink), . mucosal abrasions.
4	45	Yes	Yes			Push rod malfunction (kink), . mucosal abrasions.
5	20	Yes	Yes			Push rod malfunction (kink)
6	DNR	NE	NE			Push rod malfunction (kink)
7	12	Yes	Yes			
8	4	Yes	Yes			
9	8	Yes	Yes			
10	12	No				Push rod malfunction (break).
11	13	Yes	Yes			
12	4	Yes	Yes			
13	NE	NE	NE			
14	48	Yes	Yes			Mucosal Abrasions

15	26	Yes	Yes	3 x biopsy - Hepatic Flexure	Yes	
16	DNR	NR	NR			Push rod malfunction (break).
17	5	Yes	Yes			
18	5	Yes	Yes	2 x biopsy - Sigmoid	Yes	
19	10	Yes	Yes			
20	15	Yes	Yes			
21	10	Yes	Yes			
22	6	Yes	Yes			
23	15	Yes	Yes	1 x biopsy ascending colon and transverse colon	Yes	Mucosal Abrasions
24	15	Yes	Yes	1 x biopsy cecum-and transverse colon	Yes	
25	17	Yes	Yes			
26	DNR	NE	NE	2 x biopsy ascending colon	Yes	
27	8	Yes	Yes	4 x biopsy and 1 polypectomy	Yes	
28	DNR	NE	NE			
29	6	Yes	Yes			
30	3	Yes	Yes			Mucosal Abrasions

*NR = Not recorded DNR = Did not reach cecum NE = Not expected due to balloon inflation not attempted.

Table 23: SVDE Results: IDEAL format (Intention to Treat population)

5.5 Evolution of procedure strategy

During the whole series we made 5 changes to our procedural policy through the IDEAL methodology (see Figure 66). These were:

1. At patient 2, we adjusted the position of the patient to left lateral as opposed to lithotomy with leg stirrups, this allowed greater flexibility in patient positioning whilst performing the procedure.

2. At patient 6, we altered our loading position of the SVDE on the FE to placing the SVDE device handle back to the endoscope handle hilt. This was due to kinking of the push rods observed due to maximal retroflexion of the FE whilst traversing the sigmoid colon.

3. The loading position change was stopped after one case due to increased mucosal abrasions observed (case 7) and reverted to the original position (endoscope tip 1cm proud of the FB).

4. From patient 12 onwards, we adopted the use of lubrication as a device mounting method (applying the usual water based surgical lubricant onto the endoscope) allowing the device to behave more as an overtube whilst maintaining endoscope functions.

5. From patient 12 onwards, we advocated the use of a primary endoscope prior to device use in order to assess intestinal anatomy, straighten out sigmoid colon and plan treatment if necessary. This method was supported by literature[164].

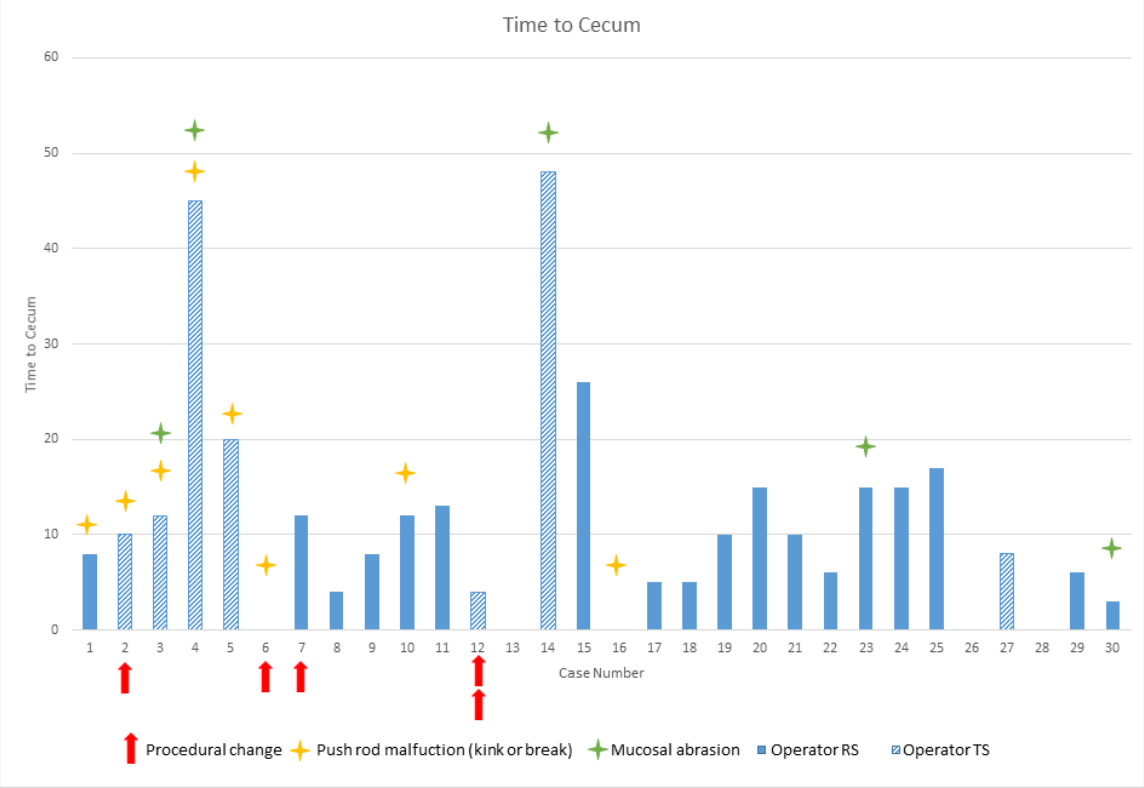
Change result:

Prior to last change (patient 12), push rod kinking and breakage occurred in 7 out of 11 patients. After change was implemented, 1 push rod kinking and breakage was observed in 19 patients (P=0.01).

Additional subjective clinician observations:

The clinician reported the balloons to be easily inflated and deflated in the ascending and sigmoid colon. Clinicians also reported increased stability of the FE tip upon balloon inflation and improved mucosal visualisation in the TZ.

Figure 66: Time to cecum with identification of complications with procedural change (Intention to Treat population)



Conclusions

Through systematic implementation of five procedural changes we found that these modifications resulted in increased device stability and performance:

1. Use of the DEIP over a standard adult or paediatric colonoscope appeared safe in traversing the entire colon.
2. In both the right and left side of the colon the FB can be deployed off the tip of the endoscope and a TZ established.
3. Mounting position of the device on the FE is critical.
4. The device has value in allowing improved stability and visualization.
5. The position of the patient should be kept flexible as in conventional colonoscopy, both in the endo suite and OR.
6. The use of lubrication as a mounting medium (compared to water) may add favourable movement characteristics to the endoscope.
7. The use of a primary endoscope prior to device use reduced kinking of the pushrods and difficulty traversing the sigmoid colon.

There are several limitations with this study. This was a single centre study in a tertiary referral centre with two clinicians of significant experience. Whereas training was provided, clinicians may have still been on their respective device learning curve. The number of patients included in the study are small and although these results do add confidence regarding the overall safety of the device, this evaluation is still on-going.

5.6 Analysing SVDE issues following clinical experience

The main device issue that was raised during the clinical study was the appearance of push-rod kinking (see figure 66 below). This affected the ability to deploy the FB, especially on the right side of the colon. Following this identification, I set out to perform a root-cause analysis of the cause of the kinking in the laboratory.

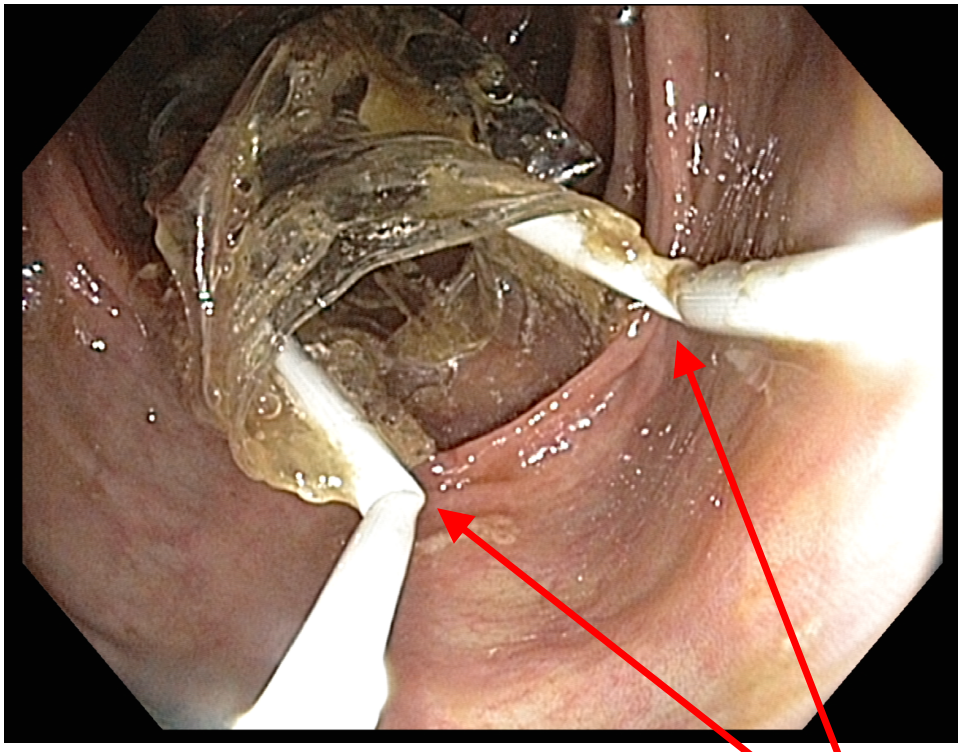


Figure 66a: Push rod kinking in human use

Method

My aim was to recapitulate as close as possible the clinical conditions in the laboratory. I used an SVDE and a paediatric colonoscope this also closely simulated what equipment had been used clinically.

I performed full endoscope tip retroflexion in both directions and observation of SVDE balloons and pushrods – inside and outside the Kyoto Kagaku model.

I used the KK model to simulate an acute sigmoid turn and scope impact against abdominal wall.

Results:

Figure 67: SVDE positioned on scope to maximise TZ distance



1) Retroflexed away from saddle – no kink



2) Retroflexed towards saddle – kink



3) Retroflexed away from saddle in KK model to simulate traversing sigmoid colon – no kink



4) Retroflexed towards saddle in KK model and pushed against wall to simulate traversing sigmoid colon – kink more acute (than photo 2)

Figure 68: SVDE positioned on scope to minimize TZ distance (SVDE pulled back to hilt of scope)



1) Retroflexed away from saddle – no kink



2) Retroflexed towards saddle – no kink

Conclusions

I identified the push rod kink to be due to movement of the articulating portion of the FE in the 'up' position against the saddle bridge connecting the two pushrods. In addition the pushrod kinking worsened on pushing against stiffer surface such as the abdominal wall. These findings correlated with the observations I had recorded clinically.

Chapter 6: Discussion

During my DPhil work I undertook the *in-vitro*, *ex-vivo* and *in vivo* characterisation of a double-balloon flexible endoscopic oversheath constructed from inexpensive biocompatible materials, in which the balloons can be controlled independently. I demonstrated a novel balloon design with redocking capability that allows multiple region use within the GIT, and using this design developed a single-use device with the capacity for endoscope stability and mucosal visualisation from within a large animal model. Combining the device with a flexible endoscope system allowed the platform to experimentally provide enhanced complex therapeutic capabilities e.g. ESD, even in challenging tumour positions.

The SVDE fabricated could be rapidly implemented for the evaluation and therapy of GI tumours in differential positions within the lumenal clock, facilitating, or not, gravity assistance. A recent study evaluating data collected from 147 patients found that those benign tumours removed through endolumenal capabilities greater than 3cm were deemed very difficult for removal, required extended procedural time and were hence likely to be referred for formal surgery through resection of the corresponding intestinal segment[165]. Hence, increased stabilisation, visualisation and retraction systems may provide significant clinical benefit, particularly within an organ-saving approach. I also demonstrated that underwater immersion tumour removal capabilities may provide better outcomes procedurally and functionally, such that this method could be more widely implemented using SVDE[163] through lumenal fluid volume maintenance.

The anatomical area was limited by the fixed length of sheath to FE optimised to the colon and not to upper GI lengths. Nevertheless, the total sheath length can be optimised for such uses. Assuming the extreme case of gastroscope usage (diameter 6mm, length 100cm), the sheath length and handle lock can be modified for this use. Looking ahead, we would expect that a custom designed system would be able to target tumours throughout the GI anatomy. Early investigations into a shorter SVDE version were explored here particularly with regard to rectal lesions treated by ESD and early feasibility results did not demonstrate inferiority, although further work in this area is needed.

By targeting 2 specific therapeutic procedures – underwater immersion and retraction capabilities for ESD, SVDE has shown broad tumour removal specificity in various porcine tumour models. The specific retraction-countertraction capability allowed real-time, FE-guided endolumenal surgery of intestinal tumours, which significantly improved accuracy in the macro-pathological validation of tumour margins. Controllable tumour retraction is an ideal prerequisite for tumour resection, in-keeping with the current move toward organ-preservation therapy. This is particularly useful in the visualisation of lesions at an intestinal haustra and flexures that were indeed detected by our studies and able to be manipulated using SVDE.

Following my pre-clinical work, I was encouraged that SVDE would be particularly helpful in performing diagnostic and therapeutic actions in the lower GI tract through improving the stability and visualisation capacity of FE clinically. After completion of the human, clinical feasibility and safety study, users noted the extra stability afforded

whilst the balloons were activated in forming the therapeutic zone. The balloons could be inflated and deflated in the ascending and sigmoid colon and there to be no safety issues. Subjectively those with long redundant sigmoid colons could be a challenge, and this was also the case on the few occasions the sigmoid was short.

As a result of the stepwise analysis of each procedure and reflection according to the IDEAL framework, I reached the following clinically relevant conclusions:

1. The mounting position of the SVDE on the FE was critical.
2. The device has clear advantages facilitating increased stability and improved visualisation.
3. The position of the patient should be kept flexible as in conventional colonoscopy, particularly in the environment used e.g. endoscopy suite versus operating room
4. The use of water-based lubrication as a mounting medium (compared to water) may have added favourable movement characteristics to the FE
5. The use of a primary endoscope prior to device use, reduced kinking of the pushrods and difficulty traversing the sigmoid colon

My work also highlighted the development process as bring integral to the identification of potential problems that may not fully establish themselves until once in clinical situations. Clear examples of this was the pushrod kinking and reduced rate of balloon grip on the right-side observed clinically. Both issues were discovered in the preclinical work but were deemed unlikely to happen, however they did happen with significant frequency. This was an example of identifying the issue as a specific technical problem rather than envisage the clinical ramifications at a very early stage.

From the outset there were significant weaknesses in the methodology which can be outlined as being the following. In choosing to perform a non-systematic review of the literature to determine the intestinal parameters at the beginning of the process I introduced a number of biases and from the outset. This could have been diminished by performing a systematic review with the appropriate relevant criteria. In relying on a set of general parameter assumptions and limitations from the outset also incorporated a second set of biases from then such as the reliance on two particular papers based from a UK population which may not be applicable to the rest of the world or the US population where the SVDE was first used. Within the preclinical characterisation, I would say that a small number of experimental repetitions were generally used due to time and resource constraints. Fresh porcine tissue was needed for these experiments not only due to the similarity to human colon but also the less than 24hr harvesting time period allows the minimal amount of decomposition and the maintenance of the submucosal space. Tissue used for a longer duration than this breaks down and thins. The cheapest supplier of such tissue at the time of writing this thesis cost $50 per intestine segment, each segment yielded 2-4 experiments. These constraints prevented me from making definite conclusions regarding the data, and there are clear implications of this approach in developing a device suitable for use in humans. In the case of the in-vivo experiments cost and time constraints resulted in an even smaller number of repetitions leading to limited data accrual. Each animal study cost in the region of $100,000. In some cases, and in hindsight, unrealistic or non-clinically relevant test parameters were used, such as in the histopathological experiment looking at 2 minutes only with very high balloon pressures. In retrospect, this test should have been performed for a clinically relevant

time period giving more realistic results. Histopathology on 2 pigs was not ideal, whereas the findings were reassuring, no meaningful conclusions related to safety can be made. The finding of perforation should have been pause for further testing, including further in-vivo testing which was not done. There was also a lack of learning curve data which could have greatly assisted in the training of clinicians. Qualitative observations in some cases pertaining to benefits such as the improved vision with underwater, but no quantitative data for confirmation lead to inconclusive results. I was unable to also perform validation experiments on the 3D model due to time constraints, this may have expanded its use, particularly in the device validation exercise. Overall, this model could have been expanded to explore the device applicability in differing areas of the intestine, however as a result limited data were gained and inconclusive with regards to the rectum. Finally, there were significant limitations in the number of in-vivo studies done despite an ethical imperative to do so.

In retrospect the evidence for the properties of the device could have been strengthened by a number of factors. Cost played a significant role in the completion of this work. Time and availability of other team members at key times such as during the in-vivo work could have been arranged in light of these challenges. Early bias incorporation could have been diminished by performing a systematic review with the appropriate criteria. An increased number of repetitions, by fixing the number of repetitions at 12 for the preclinical characterisation and performing a learning curve analysis on 30 attempts would have increased the confidence in the experimental outcome. Ideally the same procedures would be performed in-vivo to assess reproducibility and to appropriately demonstrate safety. I would have used clinically relevant test parameters, yielding a

suitable number of histopathological results to gain a suitable conclusion. Ideally I would have had time to develop quantitative test models to test some seen benefits such as underwater ESD smoke reduction. The 3D model would have been validated on clinicians of varying skill, I am currently in the process of doing this with 3 clinicians however the process in slow due to the clinicians time constraints.. Ideally, we would have moved onto demonstrating benefit or not of using the device in different anatomical areas such as the rectum, cecum and sigmoid. Whereas a training program was given by myself modelled on similar training given by other devices manufacturers in the field, a formal analysis should have been undertaken regarding the appropriate training to be given according to this type of device used and an appropriate way of measuring that the clinician had gained the appropriate knowledge. Considering the previous admissions to the ideal assessment of ex-vivo and in-vivo characteristics in addition to a robust learning curve, one could envisage measuring the training clinician against the results of those tests e.g. time to cecum, ESD times with and without retraction. Only after an attainment of the necessary parameter value, then the clinician would be deemed competent to use the device. This whole process could also be incorporated into the IDEAL framework and give the opportunity to evaluate if this training approach could decrease complications in clinical cases.

The next consideration is if I adequately demonstrated that SVDE was safe to use? Within the constraints of time and resources, we were unable to conclusively demonstrate that SVDE was safe to use. Given the limitations outlined previously, this was largely in part due to non clinically relevant test parameters used in the pressure mucosal injury experiment and the small number of repetitions in the in-vivo

experiments used for the pressure duration analysis. In addition, serious outcomes such as the mucosal perforation seen warranted further in-vivo testing.

Over the course of my work, the feasibility and usability within the constraints of the preclinical model setup were shown, including resection improvement using retraction and lumenal water level maintenance. I was also able to show that a group of clinicians previously untrained in using the device, were able to satisfactorily execute the functions of the device albeit within an experimental setting. I believe I have demonstrated initial safety and effectiveness of SVDE in its primary functions clinically. I have also outlined the initial problems encountered in device use and the remedies taken at both a methodological and research and development standpoint to solve such issues in a concise manner. My conclusion in this regard is that the technology has achieved stability and improved performance and is now ready for use with larger number of clinicians.

Though sufficient for our animal and human studies, one limitation of this device is the increased weight added to the FE. Without a clear picture of the expected ergonomic limits at the outset, achieving further weight loss as part of this study would have been difficult. Given the measured results, and with further development of the fabrication process—for example, changes to the handle geometry and materials—the design could potentially be reduced to between one-third and one-fifth of its present weight.

One further limitation is the reduced tactile feedback through the sheath. Our focus was on providing appropriate feedback to allow traversing of the intestinal anatomy, something that was demonstrated in animal and human studies. However, future work should include efforts to improve the tactile feedback through the sheath; for example, by integrating alternate additives or modifying the sheath material durometer. Another important direction of future research will be the development of systems that can be safely activated in the GI tract over longer periods (>1hr), thereby enabling longer balloon inflation times without the need for periodic deflation. At the time of writing this thesis, the device has been used in over 300 patients with no significant injury.

I was unable to explore the learning curve within the duration of my DPhil. The three clinicians that performed the majority of the clinical procedures to date, reported qualitatively, ease of using the device after 6 attempts, although definitive clinical data would be ideal in this scenario. In the therapeutic setting, the heterogeneity of polyp morphology has caused difficulties in how to categorise the procedures which requires further thought moving forward.

Moving forward the logical aims of a 2b study would aim to deal with issues such as the learning curves and give a consensus on indications where the device appears to have superiority. In addition clearer patient selection criteria and patient/clinician willingness to participate would form more robust guidelines. Ultimately, this would allow facilitated progression to an RCT.

Conclusions and future work

Research in endolumenal devices continues to push the boundaries of what is currently possible within the GIT, and it has already provided a range of options for local, organ sparing, tumour removal. Examples include clip appliers, suture methods and confocal technology[166, 167]. Such systems could allow the removal of transmural lesions in the lower GI tract, especially below the peritoneal reflection where perforation risk is minimised[168].

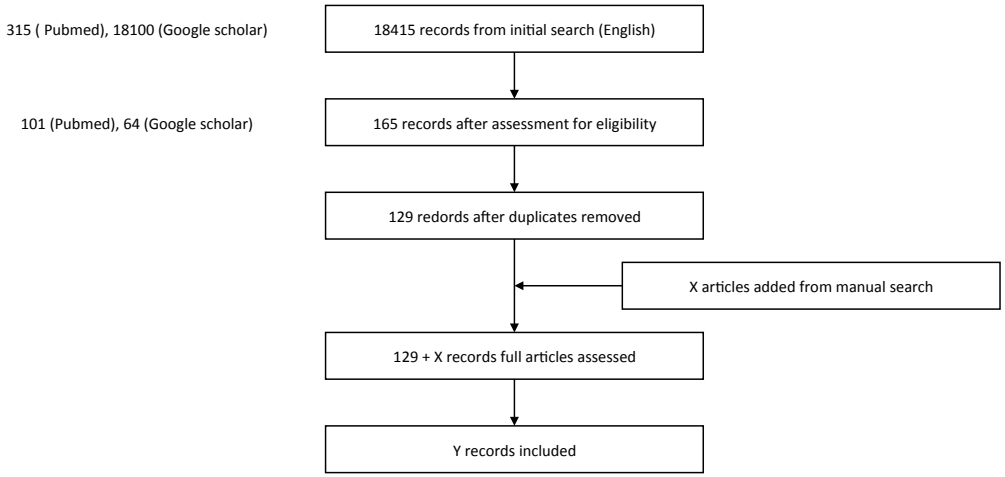
Potential challenges that may limit universal applicability of the device in the clinics include a lack of advanced FE therapeutic skills availability within institutions. Nevertheless, we anticipate that this visibility and stabilisation paradigm will deliver broad impact in tumour detection, removal and will be used to facilitate more complex procedures such as ESD in a timely manner through retraction and immersion capabilities.

Moving forward, I see no reason why devices such as this would not facilitate the next generation of full thickness excisions of the human intestine and open the field of endolumenal based treatments. The aim being that this method becomes the primary mode of CRC management. This data are too early to sensibly estimate the clinical therapeutic advantages of using the device, such as its utility in advanced endoscopic procedures such as ESD. However, the preclinical data are promising and the therapeutic clinical study is due to start in the month of this thesis submission.

At the time of writing this thesis, the next generation SVDE device is currently being worked upon. It builds on the current design with the addition of two 6mm channels permitting the use of additional tools. My goal moving forward is to incorporate the many things that I have learnt during my DPhil into their development.

Appendix

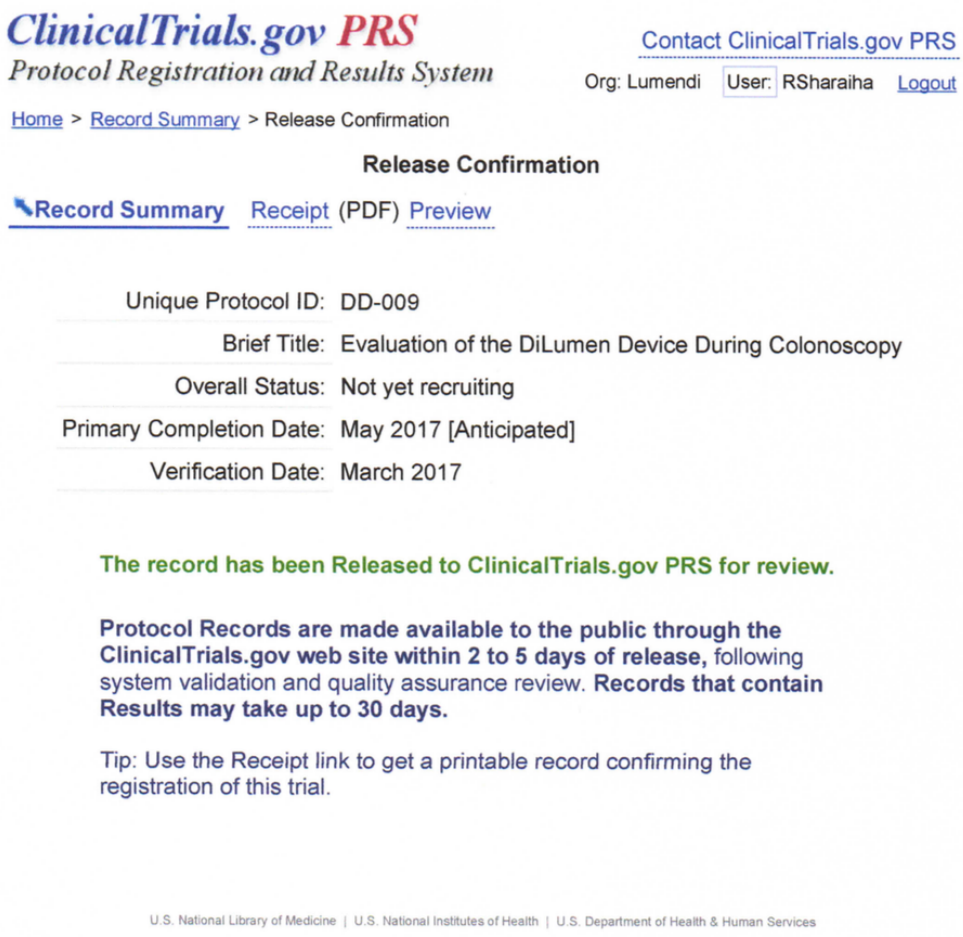
I – eFTR data



PMID	Paper title	Year	Report type	n=	Laparoscopy	Procedure time (mins)
25026878	Laparoscopy-assisted endoscopic full-thickness resection with basin lymphadenectomy based on sentinel lymph nodes for early gastric cancer	2014	Case Series	12	yes	138
10094748	Transgastrostomal endoscopic surgery for early gastric carcinoma and submucosal tumor	1999	case series or case report	13	yes	148
23254401	EndoResect study: endoscopic full-thickness resection of gastric subepithelial tumors	2013	prospective	14	yes	
25469264	Establishment of the hybrid endoscopic full-thickness resection of gastric gastrointestinal stromal tumors	2015	Case Series	16	yes	480
25221859	Endoscopic full-thickness resection for gastrointestinal lesions using the over-the-scope clip system: a case series	2015	Case Series	17	no	
12072999	Laparoscopic-endoscopic rendezvous resection of gastric tumors	2002	case series or case report	22	yes	
22098836	Endoscopic mucosal resection, endoscopic submucosal dissection, and beyond: full-layer resection for gastric cancer with nonexposure technique (CLEAN-NET)	2012	case series	24	yes	
21424195	Endoscopic full-thickness resection without laparoscopic assistance for gastric submucosal tumors originated from the muscularis propria	2011	retrospective	26	no	105
25380509	Endoscopic full-thickness resection of gastric subepithelial tumors: a single-center series	2015	Case Series	31	no	60
23823814	Endoscopic full-thickness resection of gastric stromal tumor arising from the muscularis propria	2013	Case Series	42	yes	95
	Endolumenal Endoscopic Full-Thickness Resection of Muscularis Propria–Originating Gastric Submucosal Tumors	2014	Case Series	48	no	59
24555874	Endolumenal endoscopic full-thickness resection of muscularis propria-originating gastric submucosal tumors	2014	Case Series	48	no	59
20589511	Full-thickness endoscopic resection of nonintracavitary gastric stromal tumors: a novel approach	2011	retrospective	66	compare	53.6
26021500	Clinical Control Study of Endoscopic Full-thickness Resection and Laparoscopic Surgery in the Treatment of Gastric Tumors Arising from the Muscularis Propria	2015	cohort study	92	no	85
16437279	Endoscopic full-thickness resection of the stomach: an experimental approach	2006	case series or case report	3	yes	
22807618	Endoscopic therapy for gastric stromal tumors originating from the muscularis propria	2012	retrospective	13	no	
	Hybrid natural orifice transluminal endoscopic surgery: endoscopic full-thickness resection of early gastric cancer and laparoscopic regional lymph node dissection--14 human cases	2011	prospective	14	yes for LN	143
23468195	Complete closure of large gastric defects after endoscopic full-thickness resection, using endoloop and metallic clip interrupted suture	2013	Case Series	20	no	10
	Complete closure of large gastric defects after endoscopic full-thickness resection, using endoloop and metallic clip interrupted suture	2012	retrospective	20	no	10
25320536	Endoscopic full-thickness resection for gastric submucosal tumors arising from the muscularis propria layer	2014	Case Series	35	no	90
25894443	Factors associated with endoscopic full-thickness resection of gastric submucosal tumors	2015	Case Series	41	no	78
24619327	Endoscopic full-thickness resection with defect closure using clips and an endoloop for gastric subepithelial tumors arising from the muscularis propria	2014	Case Series	51	no	52
25009400	Endoscopic full-thickness resection and laparoscopic surgery for treatment of gastric stromal tumors	2014	Case Series	60	yes	80
				728		102

PMID	Paper title	Year	Report type	n=	Laparoscopy	Procedure time (mins)
20438900	Endoscopic mucosal resection with full-thickness closure for difficult polyps: a prospective clinical trial	2010	prospective	16	yes	70
23897399	Endoscopic full-thickness resection of colonic submucosal tumors originating from the muscularis propria: an evolving therapeutic strategy	2013	Case Series	19	no	67
25763833	Endoscopic full-thickness resection in the colorectum with a novel over-the-scope device: first experience	2015	cohort study	25	no	50
25040930	Utility of a new reusable clip device for endoscopic treatment	2015	cohort study	40	no	267
				100		113.5

II – Clinical trials registration documentation



ClinicalTrials.gov PRS
Protocol Registration and Results System

Contact ClinicalTrials.gov PRS
Org: Lumendi User: RSharaiha Logout

Home > Record Summary > Release Confirmation

Release Confirmation

Record Summary Receipt (PDF) Preview

Unique Protocol ID:	DD-009
Brief Title:	Evaluation of the DiLumen Device During Colonoscopy
Overall Status:	Not yet recruiting
Primary Completion Date:	May 2017 [Anticipated]
Verification Date:	March 2017

The record has been Released to ClinicalTrials.gov PRS for review.

Protocol Records are made available to the public through the ClinicalTrials.gov web site within 2 to 5 days of release, following system validation and quality assurance review. **Records that contain Results may take up to 30 days.**

Tip: Use the Receipt link to get a printable record confirming the registration of this trial.

U.S. National Library of Medicine | U.S. National Institutes of Health | U.S. Department of Health & Human Services

III – IRB approval letter

Weill Cornell Medicine

Institutional Review Board
Mailing Address:
1300 York Avenue Box 89
New York, NY 10065

Telephone: 646-962-8200
E-mail: irb@med.cornell.edu

April 20, 2017

Reem Z. Sharaiha, MD

Submission Type:	Expedited New Response to Issues
Protocol Number:	1610017641
Risk Level:	Minimal Risk
Protocol Title:	First in human, single center, evaluation of the Dilumen device in routine colonoscopy
Expedited Review Category:	1

Dear Dr. Sharaiha:

The Institutional Review Board (IRB) has conducted an expedited review and approved the abovementioned protocol via expedited review procedures as per 45CFR46.110, including the following:

- CSEC Approval Letter – 2/9/2017
- Protocol – 3/9/2017
- Informed Consent and HIPAA Authorization for Clinical Study Investigation – 4/9/2017
- Clinical Trials Summary
- FDA 510(k) Letter – 12/6/2016

The protocol and its relevant documents stand approved for the following period:

Approved: 4/19/2017 **Expires:** 4/18/2018

Please do not hesitate to contact the IRB office staff if you have any questions or need assistance in complying with the terms of this approval.

Sincerely,

Alavy Sos, M.S.
Director, Institutional Review Board

Please note the following important information about this approval:

- No investigators on this study, who also serve as members of the Weill Cornell Medicine IRB, participated in the review, discussion or vote of this submission.
- Billing Compliance: This approval is contingent upon continued adherence with institutional billing compliance policies.
- Immediate Reporting: Investigators must follow the Immediate Reporting Policy at http://weill.cornell.edu/research/research_integrity/institutional_review_board/irb_adv.html. Failure to comply with IRB

IV – Consent form approval from IRB

WCMC IRB
Approval Date: 4/19/2017
Expiration Date: 4/18/2018

WEILL CORNELL MEDICAL COLLEGE

Informed Consent and HIPAA Authorization for Clinical Study Investigation

Project Title: First-in-Human, Single Center Evaluation of the DiLumen Device in Routine Colonoscopy

Research Project #: 1610017641

Principal Investigator: Reem Sharaiha, MD

Subject number: _____

INSTITUTION: Weill Cornell Medical College

INTRODUCTION

You are invited to consider participating in a registry study. You were selected as a possible participant in this study because you are undergoing a routine screening colonoscopy.

Please take your time to make your decision. It is important that you read and understand several general principles that apply to all who take part in our studies:

(a) Taking part in the study is entirely voluntary.

(b) Personal benefit to you may or may not result from taking part in the study, but knowledge gained from your participation may benefit others;

(c) You may decide not to participate in the study or you may decide to stop participating in the study at any time without loss of any benefits to which you are entitled.

The purpose and nature of the study, possible benefits, risks, and discomforts, other options, your rights as a participant, and other information about the study are discussed below. Any new information discovered which might affect your decision to participate or remain in the study will be provided to you while you are a participant in this study. You are urged to ask any questions you have about this study with members of the research team. You should take whatever time you need to discuss the study with your physician and family. The decision to participate or not to participate is yours. If you decide to participate, please sign and date where indicated at the end of this form.

The research study is being initiated by Weill-Cornell Medicine in conjunction with the device manufacturer, Lumendi, LLC. Lumendi is providing the device for this study at no cost to you or the institution. Dr. Reem Sharaiha is the primary investigator. Dr. Toyooki Sonoda is a co- investigator for the study.

V – Human study Case report form

	FIH Study Procedure Case Report Form	
Date: ____/_____/_____ dd mmm yyyy	Subject ID# _____	Subject Initials: _____

Attending Physician: Shariaha ……. Sonoda …… (tick which applies)_
Demographics:

Year of birth:……..

Age: _____ years Gender: ☐ Male ☐ Female

Race (Check only ONE box):
- ☐ White
- ☐ Black or African American
- ☐ Asian
- ☐ Hispanic
- ☐ Other:_____

Baseline/Pre-Procedure:

Date Informed Consent Signed __ __ /__ __ __ / __ __ __ __
dd mmm yyyy

Does patient meet inclusion/exclusion criteria? ☐ Yes ☐No

Relevant Comorbidities:
- ☐ Previous Colon Polyp
- ☐ History of Diverticulitis/Diverticulosis
- ☐ Hemorrhoids
- ☐ Anemia
- ☐ Other: _____
  _____

Procedural Data

Where is procedure being performed? ☐ OR ☐ Endo Suite

Please start video recording of loading device? ☐

Loading device on colonoscope was: ☐ Easy ☐ Somewhat Easy
☐ Somewhat difficult ☐ Difficult

Colonoscope used: ☐ Adult ☐ Pediatric

Brand: ☐ Olympus ☐ Fujinon ☐ Pentax ☐ Other: _____
Model #: _____ Serial #: _____

Time Colonoscope/ SVDE inserted: __ __:__ __
hh min
Was level of cecum attained: ☐ Yes ☐ No Time cecum was reached: __ __:__ __
hh min
Was TZ created in right colon? ☐ Yes ☐ No If Yes, time taken: __ __ __ min
Picture and video of TZ post inflation? ☐

If not, explanation: ☐ Balloons too big ☐ Balloons too small
☐ Problem with balloon inflation ☐ Unable to advance fore-balloon
☐ Other: _____

Able to deflate the balloons in right colon and re-dock the fore-balloon? ☐ Yes ☐ No

Able to create TZ in sigmoid colon? ☐ Yes ☐No If Yes, time taken: __ __ __min
Picture and video of TZ post inflation? ☐

If not, explanation: ☐ Balloons too big ☐ Balloons too small
☐ Problem with balloon inflation ☐ Unable to advance fore-balloon
☐ Other: _____
_____

Able to deflate the balloons in sigmoid colon and re-dock the fore-balloon? ☐ Yes ☐ No

Time Colonoscope/ SVDE removed from subject: __ __:__ __
hh min
Was pathology noted during colonoscopy? ☐ Yes ☐ No
If Yes: ☐ Polyp ☐ Tumor ☐ Other: _____

Location and number of lesion(s): ☐ Sigmoid…. ☐ Left Colon…. ☐ Right Colon…. ☐ Cecum….

Procedure: Was a polypectomy/biopsy done during the colonoscopy? ☐ Yes ☐ No
If Yes: Was SVDE used to facilitate the intervention ☐ Yes ☐ No
If Yes: Time taken to perform intervention from establishment of TZ to time balloons were deflated at end of intervention: __ __ __ min

Intervention performed: ☐ Biopsy ☐ Polypectomy

Size of lesion: ☐ <1cm ☐ 1-2cm ☐ 3cm ☐ 4cm ☐ >4cm
Type of lesion: ☐ Flat ☐ Sessile ☐ Other: _____

	Location	Procedure	DL used	Pro Time	Size of lesion	Type of lesion	comps
1							
2							
3							
4							

Safety

Were there any safety issues associated with the device or procedure? ☐ Yes ☐ No
If Yes: ☐ Perforation ☐ Bleeding ☐ Tissue Damage

☐ Other: _____

If Yes, please complete Adverse Event CRF

Bleeding: ☐ Minimal ☐ Moderate ☐ Severe

Tissue Damage: ☐ None ☐ Minimal ☐ Moderate ☐ Severe

Intervention for Perforation: ☐ None ☐ Clips ☐ Surgery
☐ Other: _____

Post-Procedure (Recovery)

Blood Pressure: _____/_____mmHg Pulse: _____bpm

If done, Hgb: _____ Hct: _____

Time of Discharge: __ __:__ __
hh min

_____ _____ _____
Investigator's Name (please print) Signature Date

References

1. Siegel, R., Desantis, C. & Jemal, A. Colorectal cancer statistics, 2014. *CA: a cancer journal for clinicians* **64**, 104-117 (2014).
2. Jemal, A. et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. *Journal of the National Cancer Institute* **109** (2017).
3. Miller, K.D. et al. Cancer treatment and survivorship statistics, 2016. *CA: a cancer journal for clinicians* **66**, 271-289 (2016).
4. Dozois, E.J. et al. Young-onset colorectal cancer in patients with no known genetic predisposition: can we increase early recognition and improve outcome? *Medicine* **87**, 259-263 (2008).
5. Arnold, M. et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*, gutjnl-2015-310912 (2016).
6. Bernard, W. & Christopher, P. World cancer report 2014. international agency for research on cancer. *World Health Organization, Lyon, France* (2014).
7. CDC, Vol. 2017 (
8. Joseph, D.A. et al. Colorectal cancer screening: Estimated future colonoscopy need and current volume and capacity. *Cancer* **122**, 2479-2486 (2016).
9. Gulwani, H. (2016).
10. Hill, M., Morson, B. & Bussey, H. Aetiology of adenoma—carcinoma sequence in large bowel. *The Lancet* **311**, 245-247 (1978).
11. Fearon, E.R. & Vogelstein, B. A genetic model for colorectal tumorigenesis. *Cell* **61**, 759-767 (1990).
12. Winawer, S.J. et al. Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* **112**, 594-642 (1997).
13. Saitoh, Y. et al. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. *Gastroenterology* **120**, 1657-1665 (2001).
14. Rembacken, B.J. et al. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. *Lancet (London, England)* **355**, 1211-1214 (2000).
15. Soetikno, R.M. et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. *Jama* **299**, 1027-1035 (2008).
16. Ferlitsch, M. et al. Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing screening colonoscopy. *Jama* **306**, 1352-1358 (2011).
17. Corley, D.A. et al. Adenoma detection rate and risk of colorectal cancer and death. *The New England journal of medicine* **370**, 1298-1306 (2014).
18. Winawer, S.J. et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *CA: a cancer journal for clinicians* **56**, 143-159; quiz 184-145 (2006).

19. Laiyemo, A.O. et al. Postpolypectomy colonoscopy surveillance guidelines: predictive accuracy for advanced adenoma at 4 years. *Annals of internal medicine* **148**, 419-426 (2008).
20. Flood, D.M. et al. Colorectal cancer incidence in Asian migrants to the United States and their descendants. *Cancer causes & control : CCC* **11**, 403-411 (2000).
21. Peery, A.F. et al. Increasing Rates of Surgery for Patients With Non-Malignant Colorectal Polyps in the United States. *Gastroenterology* (2018).
22. Peery, A.F. et al. Morbidity and mortality after surgery for nonmalignant colorectal polyps. *Gastrointestinal endoscopy* **87**, 243-250. e242 (2018).
23. Rex, D.K. et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. *The American journal of gastroenterology* **107**, 1315-1329; quiz 1314, 1330 (2012).
24. Heitman, S.J. et al. Prevalence of adenomas and colorectal cancer in average risk individuals: a systematic review and meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* **7**, 1272-1278 (2009).
25. Rex, D.K., Lehman, G.A., Hawes, R.H., Ulbright, T.M. & Smith, J.J. Screening colonoscopy in asymptomatic average-risk persons with negative fecal occult blood tests. *Gastroenterology* **100**, 64-67 (1991).
26. Rex, D.K. et al. Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. *The American journal of gastroenterology* **88**, 825-831 (1993).
27. Pendergrass, C.J. et al. Occurrence of colorectal adenomas in younger adults: an epidemiologic necropsy study. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* **6**, 1011-1015 (2008).
28. Williams, A.R., Balasooriya, B.A. & Day, D.W. Polyps and cancer of the large bowel: a necropsy study in Liverpool. *Gut* **23**, 835-842 (1982).
29. Ben, Q. et al. Body mass index increases risk for colorectal adenomas based on meta-analysis. *Gastroenterology* **142**, 762-772 (2012).
30. Wolin, K.Y., Yan, Y. & Colditz, G.A. Physical activity and risk of colon adenoma: a meta-analysis. *British journal of cancer* **104**, 882-885 (2011).
31. Watanabe, T. et al. Malignant potential in flat elevations. *Diseases of the colon and rectum* **36**, 548-553 (1993).
32. Parra-Blanco, A. et al. Risk for high-grade dysplasia or invasive carcinoma in colorectal flat adenomas in a Spanish population. *Gastroenterología y hepatología* **29**, 602-609 (2006).
33. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* **58**, S3-43 (2003).
34. Hewett, D.G. et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. *Gastroenterology* **143**, 599-607.e591 (2012).

35. Aihara, H., Saito, S. & Tajiri, H. Rationale for and clinical benefits of colonoscopy with narrow band imaging: pathological prediction and colorectal screening. *International journal of colorectal disease* **28**, 1-7 (2013).
36. Kudo, S. et al. Colorectal tumours and pit pattern. *Journal of Clinical Pathology* **47**, 880-885 (1994).
37. Tanaka, S., Kaltenbach, T., Chayama, K. & Soetikno, R. High-magnification colonoscopy (with videos). *Gastrointestinal endoscopy* **64**, 604-613 (2006).
38. Winawer, S.J. et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *The New England journal of medicine* **329**, 1977-1981 (1993).
39. Xirasagar, S., Hurley, T.G., Sros, L. & Hebert, J.R. Quality and Safety of Screening Colonoscopies Performed by Primary Care Physicians With Standby Specialist Support. *Medical care* **48**, 703-709 (2010).
40. Vital signs: Colorectal cancer screening, incidence, and mortality--United States, 2002-2010. *MMWR. Morbidity and mortality weekly report* **60**, 884-889 (2011).
41. Yang, D.X., Gross, C.P., Soulos, P.R. & Yu, J.B. Estimating the magnitude of colorectal cancers prevented during the era of screening: 1976 to 2009. *Cancer* **120**, 2893-2901 (2014).
42. SEER Stat Fact Sheet; colon and rectum. National Cancer Institute.
43. Edwards, B.K. et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* **116**, 544-573 (2010).
44. Troisi, R.J., Freedman, A.N. & Devesa, S.S. Incidence of colorectal carcinoma in the U.S.: an update of trends by gender, race, age, subsite, and stage, 1975-1994. *Cancer* **85**, 1670-1676 (1999).
45. Jessup, J.M., McGinnis, L.S., Steele, G.D., Jr., Menck, H.R. & Winchester, D.P. The National Cancer Data Base. Report on colon cancer. *Cancer* **78**, 918-926 (1996).
46. Cheng, L., Eng, C., Nieman, L.Z., Kapadia, A.S. & Du, X.L. Trends in colorectal cancer incidence by anatomic site and disease stage in the United States from 1976 to 2005. *American journal of clinical oncology* **34**, 573-580 (2011).
47. Thorn, M. et al. Trends in colorectal cancer incidence in Sweden 1959-93 by gender, localization, time period, and birth cohort. *Cancer causes & control : CCC* **9**, 145-152 (1998).
48. Stewart, R.J., Stewart, A.W., Turnbull, P.R. & Isbister, W.H. Sex differences in subsite incidence of large-bowel cancer. *Diseases of the colon and rectum* **26**, 658-660 (1983).
49. Schub, R. & Steinheber, F.U. Rightward shift of colon cancer. A feature of the aging gut. *Journal of clinical gastroenterology* **8**, 630-634 (1986).
50. Brenner, H. et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *Journal of the National Cancer Institute* **102**, 89-95 (2010).

51. Brenner, H., Chang-Claude, J., Seiler, C.M., Rickert, A. & Hoffmeister, M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Annals of internal medicine* **154**, 22-30 (2011).
52. Nivatvongs, S. Complications in colonoscopic polypectomy. An experience with 1,555 polypectomies. *Diseases of the colon and rectum* **29**, 825-830 (1986).
53. Gallegos-Orozco, J.F. & Gurudu, S.R. Complex colon polypectomy. *Gastroenterology & hepatology* **6**, 375-382 (2010).
54. Bertelson, N.L. et al. Colectomy for endoscopically unresectable polyps: how often is it cancer? *Diseases of the colon and rectum* **55**, 1111-1116 (2012).
55. Weston, A.P. & Campbell, D.R. Diminutive colonic polyps: histopathology, spatial distribution, concomitant significant lesions, and treatment complications. *The American journal of gastroenterology* **90**, 24-28 (1995).
56. Pohl, H. et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. *Gastroenterology* **144**, 74-80.e71 (2013).
57. Walsh, R.M., Ackroyd, F.W. & Shellito, P.C. Endoscopic resection of large sessile colorectal polyps. *Gastrointest Endosc* **38**, 303-309 (1992).
58. Soune, P.A. et al. Large endoscopic mucosal resection for colorectal tumors exceeding 4 cm. *World Journal of Gastroenterology : WJG* **16**, 588-595 (2010).
59. Yoshida, N. et al. Endoscopic mucosal resection with 0.13% hyaluronic acid solution for colorectal polyps less than 20 mm: a randomized controlled trial. *Journal of gastroenterology and hepatology* **27**, 1377-1383 (2012).
60. Hurlstone, D.P. et al. Colonoscopic resection of lateral spreading tumours: a prospective analysis of endoscopic mucosal resection. *Gut* **53**, 1334-1339 (2004).
61. Swan, M.P., Bourke, M.J., Alexander, S., Moss, A. & Williams, S.J. Large refractory colonic polyps: is it time to change our practice? A prospective study of the clinical and economic impact of a tertiary referral colonic mucosal resection and polypectomy service (with videos). *Gastrointest Endosc* **70**, 1128-1136 (2009).
62. Saito, Y. et al. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. *Surg Endosc* **24**, 343-352 (2010).
63. Khashab, M., Eid, E., Rusche, M. & Rex, D.K. Incidence and predictors of "late" recurrences after endoscopic piecemeal resection of large sessile adenomas. *Gastrointest Endosc* **70**, 344-349 (2009).
64. Conio, M. et al. EMR of large sessile colorectal polyps. *Gastrointest Endosc* **60**, 234-241 (2004).
65. Burgess, N.G. et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* **12**, 651-661.e651-653 (2014).

66. Zlatanic, J., Waye, J.D., Kim, P.S., Baiocco, P.J. & Gleim, G.W. Large sessile colonic adenomas: use of argon plasma coagulator to supplement piecemeal snare polypectomy. *Gastrointest Endosc* **49**, 731-735 (1999).
67. Luigiano, C. et al. Endoscopic mucosal resection for large and giant sessile and flat colorectal polyps: a single-center experience with long-term follow-up. *Endoscopy* **41**, 829-835 (2009).
68. Iishi, H. et al. Endoscopic piecemeal resection with submucosal saline injection of large sessile colorectal polyps. *Gastrointest Endosc* **51**, 697-700 (2000).
69. Takeuchi, Y. et al. Endoscopic submucosal dissection with insulated-tip knife for large mucosal early gastric cancer: a feasibility study (with videos). *Gastrointest Endosc* **66**, 186-193 (2007).
70. Hermanek, P. & Wittekind, C. The pathologist and the residual tumor (R) classification. *Pathology, research and practice* **190**, 115-123 (1994).
71. Tamegai, Y. et al. Endoscopic submucosal dissection: a safe technique for colorectal tumors. *Endoscopy* **39**, 418-422 (2007).
72. Fujiya, M. et al. Efficacy and adverse events of EMR and endoscopic submucosal dissection for the treatment of colon neoplasms: a meta-analysis of studies comparing EMR and endoscopic submucosal dissection. *Gastrointest Endosc* **81**, 583-595 (2015).
73. Oka, S. et al. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. *The American journal of gastroenterology* **110**, 697-707 (2015).
74. Puli, S.R. et al. Successful complete cure en-bloc resection of large nonpedunculated colonic polyps by endoscopic submucosal dissection: a meta-analysis and systematic review. *Annals of surgical oncology* **16**, 2147-2151 (2009).
75. Huang, C., Huang, R.X., Xiang, P. & Qiu, Z.J. Current research status of endoscopic submucosal dissection for colorectal neoplasms. *Clinical and investigative medicine. Medecine clinique et experimentale* **35**, E158-164 (2012).
76. Moss, A. et al. Lesion isolation by circumferential submucosal incision prior to endoscopic mucosal resection (CSI-EMR) substantially improves en bloc resection rates for 40-mm colonic lesions. *Endoscopy* **42**, 400-404 (2010).
77. Repici, A. et al. Insulated-tip knife endoscopic mucosal resection of large colorectal polyps unsuitable for standard polypectomy. *The American journal of gastroenterology* **102**, 1617 (2007).
78. Shida, T. Endoscopic Submucosal Dissection for Colorectal Lesions. (2011).
79. Othman, M.O. & Wallace, M.B. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) in 2011, a Western perspective. *Clinics and research in hepatology and gastroenterology* **35**, 288-294 (2011).
80. Tanaka, S. et al. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. *Gastrointestinal endoscopy* **66**, 100-107 (2007).
81. Yamamoto, S. et al. Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve. *Endoscopy* **41**, 923-928 (2009).

82. Tanaka, S. et al. Multicenter questionnaire survey on the current situation of colorectal endoscopic submucosal dissection in Japan. *Digestive Endoscopy* **22** (2010).
83. Gotoda, T., Friedland, S., Hamanaka, H. & Soetikno, R. A learning curve for advanced endoscopic resection. *Gastrointestinal endoscopy* **62**, 866-867 (2005).
84. Deprez, P.H. et al. Current practice with endoscopic submucosal dissection in Europe: position statement from a panel of experts. *Endoscopy* **42**, 853-858 (2010).
85. Matsumoto, K. et al. A new traction device for facilitating endoscopic submucosal dissection (ESD) for early gastric cancer: the “medical ring”. *Endoscopy* **43**, E67-E68 (2011).
86. Parra-Blanco, A. et al. Gastric endoscopic submucosal dissection assisted by a new traction method: the clip-band technique. A feasibility study in a porcine model (with video). *Gastrointestinal endoscopy* **74**, 1137-1141 (2011).
87. Chen, P.-J., Chu, H.-C., Chang, W.-K., Hsieh, T.-Y. & Chao, Y.-C. Endoscopic submucosal dissection with internal traction for early gastric cancer (with video). *Gastrointestinal endoscopy* **67**, 128-132 (2008).
88. Oyama, T. Counter traction makes endoscopic submucosal dissection easier. *Clinical endoscopy* **45**, 375 (2012).
89. Yasuda, M., Naito, Y., Kokura, S., Yoshida, N. & Yoshikawa, T. Sa1687 Newly-Developed ESD (CSL-ESD) for Early Gastric Cancer Using Convenient and Low-Cost Lifting Method (Lifting Method Using Clips and Snares) for Lesions is Clinically Useful. *Gastrointestinal Endoscopy* **75**, AB244 (2012).
90. Imaeda, H. et al. Novel technique of endoscopic submucosal dissection using an external grasping forceps for superficial gastric neoplasia. *Digestive Endoscopy* **21**, 122-127 (2009).
91. Higuchi, K. et al. Double-endoscope endoscopic submucosal dissection for the treatment of early gastric cancer accompanied by an ulcer scar (with video). *Gastrointestinal endoscopy* **78**, 266-273 (2013).
92. Imaeda, H. et al. Advanced endoscopic submucosal dissection with traction. *World journal of gastrointestinal endoscopy* **6**, 286 (2014).
93. Nelson, H. et al. Guidelines 2000 for colon and rectal cancer surgery. *Journal of the National Cancer Institute* **93**, 583-596 (2001).
94. Kirchhoff, P., Clavien, P.-A. & Hahnloser, D. Complications in colorectal surgery: risk factors and preventive strategies. *Patient Safety in Surgery* **4**, 5 (2010).
95. Keynes, G. Conservative treatment of breast cancer. *Br Med J* **2**, 643-647 (1937).
96. Veronesi, U. et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *New England Journal of Medicine* **347**, 1227-1232 (2002).
97. Lazovich, D., White, E., Thomas, D.B. & Moe, R.E. Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer. *Jama* **266**, 3433-3438 (1991).

98. Blichert-Toft, M. et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta oncologica* **47**, 672-681 (2008).
99. Epstein, A.J., Polsky, D., Yang, F., Yang, L. & Groeneveld, P.W. Coronary Revascularization Trends in the United States: 2001–2008. *Jama* **305**, 1769-1776 (2011).
100. Leon, M.B. et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *New England Journal of Medicine* **363**, 1597-1607 (2010).
101. Drury, D., Michaels, J.A., Jones, L. & Ayiku, L. Systematic review of recent evidence for the safety and efficacy of elective endovascular repair in the management of infrarenal abdominal aortic aneurysm. *The British journal of surgery* **92**, 937-946 (2005).
102. Eisenack, M., Umscheid, T., Tessarek, J., Torsello, G.F. & Torsello, G.B. Percutaneous endovascular aortic aneurysm repair: a prospective evaluation of safety, efficiency, and risk factors. *Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists* **16**, 708-713 (2009).
103. Hirschowitz, B. Demonstration of a new gastroscope, the" fiber-scope". *Gastroenterology* **35**, 50-53 (1938).
104. Cohen, J. et al. Multicenter, randomized, controlled trial of virtual-reality simulator training in acquisition of competency in colonoscopy. *Gastrointestinal endoscopy* **64**, 361-368 (2006).
105. FDA (
106. CDRH Medical Device Innovation Initiative White Paper. (2011).
107. Standardization, I.O.f. ISO 10993. Biological Evaluation of Medical Devices. (1995).
108. Lu, D.W., C Materials for Advanced Packaging. (Springer, 2009).
109. Asti, A. & Gioglio, L. Natural and synthetic biodegradable polymers: different scaffolds for cell expansion and tissue formation. *The International journal of artificial organs* **37**, 187-205 (2014).
110. FDA Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". (2016).
111. Kammula, R.G., Morris, J. M. Considerations for the biocompatibility evaluation of medical devices. *Med Device Diagn Ind* **23**, 82-92 (2001).
112. Williams, D.F. On the mechanisms of biocompatibility. *Biomaterials* **29**, 2941-2953 (2008).
113. Ramakrishna, S., Mayer, J., Wintermantel, E. & Leong, K.W. Biomedical applications of polymer-composite materials: a review. *Composites science and technology* **61**, 1189-1224 (2001).
114. Mark, J.E. Polymer data handbook. (Oxford university press, 2009).

115. Lerouge, S. 1—Introduction to sterilization: definitions and challenges. *Sterilisation of biomaterials and medical devices, Woodhead Publishing Series in Biomaterials*, 1-19 (2012).
116. Organization, W.H. The international pharmacopoeia, Vol. 1. (World Health Organization, 2006).
117. Villetti, M. et al. Thermal degradation of natural polymers. *Journal of thermal analysis and calorimetry* **67**, 295-303 (2002).
118. Park J.B., L.R.S. Polymeric Implant Materials. (Springer, Boston, MA; 1992).
119. Spelta, C., Tan, R., Picard, J. & Gummow, B. A comparison of bacterial colonisation between Teflon and polyurethane short term intravenous catheters. *Journal of Veterinary Internal Medicine* **26**, 743-743 (2012).
120. Heran, M.K., Pham, T.H., Butterworth, S. & Robinson, A. Use of a microporous polytetrafluoroethylene catheter balloon to treat refractory esophageal stricture: a novel technique for delivery of mitomycin C. *Journal of pediatric surgery* **46**, 776-779 (2011).
121. Na, H.K. et al. How to design the optimal self-expandable oesophageal metallic stents: 22 years of experience in 645 patients with malignant strictures. *European radiology* **23**, 786-796 (2013).
122. Davis, F.J. & Mitchell, G.R. Polyurethane based materials with applications in medical devices. *Biomater Prototyping Appl Med* **3**, 27-48 (2008).
123. Rahimi, A. & Mashak, A. Review on rubbers in medicine: natural, silicone and polyurethane rubbers. *Plastics, Rubber and Composites* **42**, 223-230 (2013).
124. Georgeu, G.A., Frame, J.D. & Frame, J.D. Conical polyurethane implants: an uplifting augmentation. *Aesthetic surgery journal* **33**, 1116-1128 (2013).
125. de la Pena-Salcedo, J.A., Soto-Miranda, M.A. & Lopez-Salguero, J.F. Back to the future: a 15-year experience with polyurethane foam-covered breast implants using the partial-subfascial technique. *Aesthetic plastic surgery* **36**, 331-338 (2012).
126. Hachem, R.A., Perez, E., Bueno, I., Van De Water, T.R. & Angeli, S.I. Comparison of Packing Material in Middle Ear Mucosal Trauma. *Otolaryngology—Head and Neck Surgery* **147**, P83-P84 (2012).
127. Dumas, J.E. et al. Synthesis, characterization, and remodeling of weight-bearing allograft bone/polyurethane composites in the rabbit. *Acta Biomaterialia* **6**, 2394-2406 (2010).
128. Pergal, M.V. et al. Structure and properties of thermoplastic polyurethanes based on poly (dimethylsiloxane): Assessment of biocompatibility. *Journal of Biomedical Materials Research Part A* **102**, 3951-3964 (2014).
129. Sowa-Söhle, E.N. et al. Antimicrobial efficacy, cytotoxicity, and ion release of mixed metal (Ag, Cu, Zn, Mg) nanoparticle polymer composite implant material. *BioNanoMaterials* **14**, 217-227 (2013).
130. Das, B., Mandal, M., Upadhyay, A., Chattopadhyay, P. & Karak, N. Bio-based hyperbranched polyurethane/Fe3O4 nanocomposites: smart antibacterial biomaterials for biomedical devices and implants. *Biomedical Materials* **8**, 035003 (2013).

131. Lamba, N.M., Woodhouse, K.A. & Cooper, S.L. Polyurethanes in biomedical applications. (CRC press, 1997).
132. Modjarrad, K. & Ebnesajjad, S. Handbook of polymer applications in medicine and medical devices. (Elsevier, 2013).
133. Meyer, J.-U., Stieglitz, T., Scholz, O., Haberer, W. & Beutel, H. High density interconnects and flexible hybrid assemblies for active biomedical implants. *IEEE Transactions on Advanced Packaging* **24**, 366-374 (2001).
134. Rubehn, B. & Stieglitz, T. In vitro evaluation of the long-term stability of polyimide as a material for neural implants. *Biomaterials* **31**, 3449-3458 (2010).
135. Kwon, K.Y., Sirowatka, B., Weber, A. & Li, W. Opto-µECoG array: A hybrid neural interface with transparent µECoG electrode array and integrated LEDs for optogenetics. *IEEE transactions on biomedical circuits and systems* **7**, 593-600 (2013).
136. Ren, T.-L. et al. in Electron Devices and Solid-State Circuits (EDSSC), 2010 IEEE International Conference of 1-6 (IEEE, 2010).
137. McCulloch, P., Cook, J.A., Altman, D.G., Heneghan, C. & Diener, M.K. IDEAL framework for surgical innovation 1: the idea and development stages. *BMJ* **346**, f3012 (2013).
138. FDA (2017).
139. Wente, M.N., Seiler, C.M., Uhl, W. & Büchler, M.W. Perspectives of evidence-based surgery. *Digestive surgery* **20**, 263-269 (2003).
140. Clarke, M., Hopewell, S. & Chalmers, L. Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report. *Journal of the Royal Society of Medicine* **100**, 187-190 (2007).
141. Challoner, D.R. & Senate, U. Medical Devices and the Public's Health: The FDA 510 (k) Clearance Process at 35 Years. *Written Statement before the Committee on Health, Education, Labor, and Pensions US Senate, Institute of Medicine of the National Academics, Washington* (2011).
142. Grant, M.J. & Booth, A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Information & Libraries Journal* **26**, 91-108 (2009).
143. Wickremasinghe, D., Kuruvilla, S., Mays, N. & Avan, B.I. Taking knowledge users' knowledge needs into account in health: an evidence synthesis framework. *Health policy and planning* **31**, 527-537 (2015).
144. Burch, J. Stoma care. (John Wiley & Sons, 2008).
145. Moore, S. Anatomic basis of tumor surgery. (Springer Science & Business Media, 2010).
146. Gray, H. (2001).
147. Einhorn, M. Diseases of the Intestines. (W. Wood, 1904).
148. 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. *Surgical and Radiologic Anatomy* **14**, 251-257 (1992).
149. Jones, J.H. & Chapman, M. Definition of megacolon in colitis. *Gut* **10**, 562 (1969).

150. Huebner, M. et al. Age effects on internal anal sphincter thickness and diameter in nulliparous females. *Diseases of the Colon & Rectum* **50**, 1405-1411 (2007).
151. Science, -.D. (
152. Kovač, N., Širanović, M. & Mazul-Sunko, B. Clinical significance of intraabdominal pressure and abdominal perfusion pressure in patients with acute abdominal syndrome. *Signa vitae* **2**, 14-17 (2007).
153. Wiesner, W., Mortelé, K.J., Ji, H. & Ros, P.R. Normal colonic wall thickness at CT and its relation to colonic distension. *Journal of computer assisted tomography* **26**, 102-106 (2002).
154. Fisher, J. Normal colon wall thickness on CT. *Radiology* **145**, 415-418 (1982).
155. Egorov, V.I., Schastlivtsev, I.V., Prut, E.V., Baranov, A.O. & Turusov, R.A. Mechanical properties of the human gastrointestinal tract. *Journal of biomechanics* **35**, 1417-1425 (2002).
156. Watters, D. et al. Mechanical properties of the colon: comparison of the features of the African and European colon in vitro. *Gut* **26**, 384-392 (1985).
157. Bharucha, A.E., Hubmayr, R.D., Ferber, I.J. & Zinsmeister, A.R. Viscoelastic properties of the human colon. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **281**, G459-G466 (2001).
158. Bretthauer, M., Hoff, G.S., Thiis-Evensen, E., Huppertz-Hauss, G. & Skovlund, E. Air and carbon dioxide volumes insufflated during colonoscopy. *Gastrointestinal endoscopy* **58**, 203-206 (2003).
159. Rosenburg, I.L. Inflation Injury to the Bowel. *Arch Surg* **105** (1972).
160. Lu, G., Kalyon, D.M., Yilgör, I. & Yilgör, E. Rheology and extrusion of medical-grade thermoplastic polyurethane. *Polymer Engineering & Science* **43**, 1863-1877 (2003).
161. Liaw, D.J. The relative physical and thermal properties of polyurethane elastomers: effect of chain extenders of bisphenols, diisocyanate, and polyol structures. *Journal of applied polymer science* **66**, 1251-1265 (1997).
162. Cardarelli, F. Polymers and elastomers. *Materials Handbook: A Concise Desktop Reference*, 691-750 (2008).
163. Binmoeller, K.F., Weilert, F., Shah, J., Bhat, Y. & Kane, S. “Underwater” EMR without submucosal injection for large sessile colorectal polyps (with video). *Gastrointestinal endoscopy* **75**, 1086-1091 (2012).
164. Han, S., Bhattacharya, K. & Cave, D.R. Preliminary colonoscopy facilitates retrograde double-balloon enteroscopy. *Endoscopy international open* **2**, E241-E243 (2014).
165. Sato, K. et al. Factors affecting the technical difficulty and clinical outcome of endoscopic submucosal dissection for colorectal tumors. *Surgical endoscopy* **28**, 2959-2965 (2014).
166. Yoshida, N., Doyama, H., Ota, R. & Tsuji, K. The clip-and-snare method with a pre-looping technique during gastric endoscopic submucosal dissection. *Endoscopy* **46**, E611-E612 (2014).
167. Kiesslich, R. et al. Confocal laser endoscopy for diagnosing intraepithelial neoplasias and colorectal cancer in vivo. *Gastroenterology* **127**, 706-713 (2004).

168. Noura, S., Ohue, M., Miyoshi, N. & Yasui, M. Significance of defect closure following transanal local full‐thickness excision of rectal malignant tumors. *Molecular and clinical oncology* **5**, 449-454 (2016).