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An evaluation of an early stage innovation for full-thickness excision of benign colonic polyps using the IDEAL framework

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Abstract

Aims: Colectomy is the current approach for patients with endoscopically unresectable benign polyps but risks considerable morbidity. Full-thickness laparoendoscopic excision(FLEX) is a novel, specifically developed procedure which could reduce this treatment burden and improve outcomes. However, traditional evaluations of surgical innovations have lacked methodological rigour. This study reports the development and feasibility of the FLEX procedure in selected patients.

Methods: A prospective IDEAL development study was undertaken by one surgeon of the FLEX procedure in selected patients with endoscopically unresectable benign colonic polyps. 3D-CT colonography reconstructions were used to preoperatively rehearse patient-specific, critical manoeuvres. Targetted, full-thickness excision was performed: after circumferential endoscopic argon plasma coagulation marking, transmural endoscopic sutures everted the bowel and resection undertaken by laparoscopic linear stapling. Feasibility outcomes (establishing 'local success') included evidence of complete polyp resection without adverse events (especially safe closure of the excision site).

Results: Ten patients with polyp median diameters of 35 mm (IQR 30 to 41) were referred for and consented to receive the FLEX procedure (median(IQR) age:74(59-78)yrs). During the same time frame no patient underwent colectomy for benign polyps. One further patient with presumed malignancy received FLEX for local excision because severe co-morbidity prohibited standard procedures. The FLEX procedure was locally successfully performed, with complete resection of the polyp and safe closure of the excision site, in eight patients. Three non-completed procedures were converted to laparoscopic segmental colectomy under the same anaesthetic because of endoscopic inaccessibility (2) and transcolonic suture failure (1).

Conclusions: The FLEX procedure is still under development. Early data demonstrate its safe used for excision of selected benign polyps. Modifications to transcolonic suture delivery are now required and there is a need for wider adoption before more definitive evaluation can be performed.

What does this paper add to the literature?

This study has shown, through an examination of the feasibility of the FLEX procedure for resection of complex, benign colonic polyps in clinical practice, that incorporating the IDEAL framework guidance can enhance transparency and reduce information bias.

Introduction

Widespread use of diagnostic and screening colonoscopy has resulted in increasing numbers of complex colonic polyps being identified[1, 2]. Many can be successfully removed with an endoscopic procedure alone, however, some require an alternative approach to avoid colectomy. Such an alternative may also have a role in frail patients wanting to avoid major surgery which, even when carried out laparoscopically, is associated with substantial morbidity and mortality[3-6]. Major colonic resection can produce negative impacts on bowel function and quality of life in a limited proportion of patients, particularly if there are postoperative complications[7-9]. To avoid colectomy, combined laparoendoscopic procedures to excise colonic polyps have been described in preclinical work, human case reports, small case series[10-29] and a small single centre randomized trial comparing the technique to laparoscopic colectomy[30]. Preclinical work in a porcine model demonstrated that precisely targetted full-thickness laparoendoscopic excision (FLEX) can provide 5cm diameter, full-thickness colonic wall specimens, and could address concerns of incomplete endoscopic excision[31]. The previously reported clinical studies have demonstrated feasibility of such combined approaches although these reports have methodological deficiencies including incomplete reporting of outcomes, a lack of clarity regarding patient selection and informed consent for the novel procedure, and a failure to document the whole patient population with complex colonic polyps[32]. These methodological limitations may be overcome by using the IDEAL (Idea-Development-Evaluation-Assessment-Longterm)[33] framework for the evaluation of innovative surgical techniques. IDEAL early phase reporting guidance[29] requires reporting details of the whole population treated during the same time frame to understand patient selection and uptake of the novel procedure, also reporting of modifications to the technique and the rationale for the changes made, so that the process of innovation is more transparent. This is to allow other clinicians and patients to benefit from the

experience. IDEAL also recommends that ethical approvals are gained to ensure that patients have full informed consent to undergo the novel technique. Despite the benefits of the IDEAL framework it has not been extensively investigated in prospective evaluations of novel surgical techniques.

This study aimed to prospectively describe the technical success and safety of FLEX for benign colonic polyps using the IDEAL framework.

Methods

Study procedures

The FLEX technique was intended to be performed as in figure 1 and was authorised by the New Procedures Committee of London North West Healthcare (LNWH) National Health Service (NHS) Trust to be used as part of standard NHS care. The study protocol was reviewed and a favourable proportionate ethics opinion provided by the Oxford A National Research Ethics Service Committee (13/SC/0654).

Eligibility

All patients with complex colonic polyps discussed at the St Mark's Hospital Polyp Meeting referred for FLEX or standard treatment were documented during the study period. Patients were considered eligible when they had a benign polyp less than 5cm in diameter, they would otherwise have needed to undergo segmental colectomy for polyp resection, and they gave informed consent to undergo the FLEX procedure and to collection of their data according to the study protocol. Patients under 18 years of age or who were pregnant were excluded from the study.

The need for colectomy was considered by the multidisciplinary St Mark's Polyp Meeting which is run by the senior therapeutic endoscopists[34]. The meeting considered lesions to be complex colonic polyps according to the British Society of Gastrenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI) guidelines[35]: either more than 40mm in diameter, located near the appendix orifice or the ileocaecal valve, within a segment of diverticulosis, following previous unsuccessful attempts at resection, or following endoscopist concern about location (e.g. behind a colonic fold or flexure). The specialist endoscopists at St Mark's Hospital are capable of providing endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) throughout the colon. The two predominant

providers of ESD had a life-time experience of around 200 procedures each at the commencement of the study. Lesions were considered endoscopically unresectable if they had been identified as such by one of these two senior endoscopists. Patients referred from other institutions were discussed at the Polyp Meeting and needed to be considered endoscopically unresectable by the senior endoscopists to be eligible for FLEX.

Preoperative lesion characterisation

Patients were reviewed using endoscopy and the Paris Classification[36] of the polyp recorded. All patients considered for FLEX underwent a CT colonography (CTC) to define the polyp location, mesenteric relationship and proportion of bowel circumference involvement, as previously described[37]. The CTC images were then reviewed using the overview, endoluminal, and cross-sectional views in order to plan and rehearse the surgery (Figure 1). The surgeon, endoscopist and radiologist undertook this together preoperatively at the CTC workstation.

Consent

Informed consent was obtained by the leader author (surgical consultant) from all the patients. The consent process included provision of information regarding the experimental nature of FLEX. Risks discussed included an approximate 10% chance of cancer in the polyp, the need for follow-up endoscopic surveillance, the potential need for laparoscopic repair of the bowel wall or a bowel resection if closure was not secure or the FLEX procedure not possible, and the potential need for surgical resection at a later date if cancer was found in the polyp. Patients were also informed that it was possible that some complications which were unexpected may occur because of the novelty of the approach. The potential benefit of avoiding a circumferential bowel anastomosis was discussed and patients were also offered standard laparoscopic colectomy. At the beginning of the study, patients were

considered for FLEX if they had a small early stage cancer if they had severe comorbidities precluding colectomy.

Patient preparation

Patients received bowel preparation (either Moviprep or Picolax) as guided by renal function. Patients were normally admitted to hospital on the day of surgery as per our hospital protocol.

Surgical Technique

Context

All procedures took place within an Olympus combined laparoendoscopic theatre in which both laparoscopic and endoscopic equipment are permanently fitted on pendants to facilitate this surgery (Figure 2).

Concept

At the time of surgery, laparoscopy was performed and, if required the colonic mesentery was mobilised with, or without, adhesiolysis. All study patients were scheduled to undergo the FLEX procedure using the concept illustrated in Figure 3. There were some modifications from the experimental technique previously described for FLEX. In the porcine model, eversion and fixation of the everted fold was achieved using BraceBars (Olympus Corporation, Tokyo, Japan) – 2 T-Tags joined by a nylon suture which were deployed endoscopically via a bespoke injection needle and were tightened down with an endoscopic pusher tube[31]. These are not available for clinical use. Consequently, the FLEX technique had to be modified to replicate this equipment.

Laparoscopic bowel clamps (45mm length, CEV567, MicroFrance, Saint Aubin le Monial, France) were placed across the terminal ileum to prevent small bowel

distension. Using carbon dioxide insufflation, an endoscope was passed to the site of the polyp.

The circumferential borders of the planned excision specimen were marked endoscopically from within the bowel lumen using an argon plasma coagulator (APC) (ERBE ICC 200, power settings: 40W and gas flow 2L; Erbe, Tuebingen, Germany) (Figure 3, step A). A 1cm margin from the polyp periphery was marked in order to ensure complete excision (indicated by A's on the diagram). The endoscopist protruded a catheter against the bowel wall 1cm from the lateral margin and similarly at the medial margin, in order to identify these sites and enable the surgeon to mark them by placing sutures there laparoscopically (Figure 4 pictures B and C).

Using an endoscope, a 230cm 19G endoscopic needle with a 5.5mm tip (1-ject XS; Medical Innovation Group, Shoeburyness, United Kingdom) was protruded through the bowel wall at the site of the argon mark and a suture pushed through the needle. The suture was clipped (Figure 3, step B) by the surgeon extraluminally and the needle withdrawn back into the bowel lumen. It was then placed through the bowel wall on the other side of the polyp at the argon mark (Figure 3, step C) and the thread was clipped externally/laparoscopically without tightening (Figure 3, step D). A second and a third suture were then placed repeating steps B-D. The sutures were tightened by pulling to evert the fold with the polyp inside at the apex of the inversion (Figure 3, step E). Further clips were then applied while the suture was pulled to secure this fold.

A laparoscopic linear stapler (ENDOPATH ETS-45; Ethicon Endo-surgery, Cincinnati, Ohio, USA) was placed below the clips on the outside of the bowel fold and deployed to excise the specimen, simultaneously stapling the colonic defect closed and preventing spillage of cells or contaminating material from the bowel (Figure 3, step F). Having the clips visible superficial to the stapler is important, ensuring complete excision of the lesion if the everting sutures have been placed in the correct sites.

After removal of the pecimen, the closed defect was tested for security by intraluminal air insufflation with laparoscopic observation of the closure site under fluid, when possible.

Carbon dioxide was extracted from the colon, the pneumoperitoneum deflated and the laparoscopic port sites closed, all as per standard care[38].

If the FLEX procedure could not be successfully completed, as described above, a standard laparoscopic colectomy performed using a medial-to-lateral dissection[38], under the same anaesthetic was performed. No specific criteria for conversion were prospectively defined, rather it was undertaken if safety and progress was felt to be compromised

Modifications and adaptions

Using the IDEAL framework criteria, all patients referred for the FLEX procedure were documented sequentially. When changes were made to the FLEX technique, this was annotated at the point where the change occurred and the type of adaptation was described.

Team and personnel experience

The surgeon and lead author of the study has a personal experience of greater than 2000 laparoscopic colorectal resections[39-46]. He also had experience of around 50 preclinical cases of the FLEX technique, live animal and porcine bowel models[31, 47-49].

The endoscopists involved in the clinical study (NS/STG) have both undertaken >10,000 colonoscopies, undertake EMR and ESD, and are UK Bowel Cancer Screening Programme (BCSP) screening colonoscopists working in a national referral centre for advanced therapeutic endoscopy

Outcomes

The focus of this study was the technical efficacy, 'local success', of the FLEX procedure. The primary intention was to evaluate the complete excision of the polyp with secure closure of the excision site, with the FLEX procedure being completed as planned. Other assessments included the proportion of patients undergoing FLEX from all those approached during the study period and the proportion of operations converted from FLEX to laparoscopic segmental colectomy. Adverse events were recorded including the in-hospital and and post-discharge complications/adverse events, the need for reoperation or readmission and length of hospital stay. Treatment outcomes included the size of the resection specimen and the histopathological assessment of the resected polyp.

Outcome assessment

Postoperative hospital stay was recorded from the day of operation until the day of discharge. Complications were recorded prospectively using the Clavien-Dindo classification[50]. Conversion was defined as a decision by surgeon to convert the FLEX procedure to segmental colectomy at any point after starting the laparoscopy. All outcomes were assessed by the surgeons participating in the study.

The excised sample was analysed by a pathologist as part of standard care and in accordance with the Royal College of Pathologists guidance on assessment of local excision specimens[51]. Intraoperative frozen section analysis of the resected specimen was not undertaken.

Statistical analysis

The entire cohort of eligible patients with whom FLEX was discussed were accounted for (consistent with IDEAL reporting guidance[33]). The outcomes collected for the

study are reported descriptively using summary statistics and in tables with each row

showing data for an individual participant.

Results

Patients

118 patients with presumed colonic polyps were discussed at the St Mark's Complex Polyp MDT between March 2014 and March 2016. Ten were referred for and offered the FLEX procedure and all consented to the procedure, understanding that it was a novel technique and not standard care. One patient with a 3cm ascending colon tumour with endoscopic appearances highly suggestive of cancer, but with biopsies showing high grade dysplasia who was considered too high risk for colectomy was offered and consented to the FLEX procedure. The median(IQR) patient age was 74(59-78) yrs. During the study, no planned colectomies were performed for benign, endoscopically unresectable polyps at our institution. Eight of the ten benign lesions were proximal to the splenic flexure (6 caecal and two transverse colon) with the remaining two in the descending colon. The clinical FLEX procedures were undertaken from April 2014 (Figure 4).

Technical achievements

All patients approached regarding FLEX elected to receive the intervention instead of colectomy. In the eleven patients in whom the FLEX procedure was attempted it was completed in eight (

Table 1. Patient characteristics and perioperative outcomes for the FLEX procedure

), with 3 conversions to laparoscopic colectomy under the same anaesthetic. The eight successfully completed FLEX procedures achieved complete resection and secure closure of the excision site (the primary outcome) without intraoperative consequences.

In one converted patient, endoscopic access to the polyp was not stable due to severe pan-colonic diverticular disease. In the second converted procedure the proximal descending colonic lesion occupied 60% of the colonic circumference – this had not been apparent on the preoperative CTC assessment and excision would have caused stenosis. In the third conversion, the linear stapling was unsatisfactory resulting in a staple line that was longitudinal rather than transverse.

Adverse events

Of the eight patients who had a successfully completed FLEX procedure, four were discharged uneventfully within 72 hours One patient developed an abdominal wall haematoma related to a laparoscopic port insertion, which was conservatively managed (length of stay 5 days). A further FLEX recipient developed a chest infection. The third patient with a complication was readmitted with an infected intra-abdominal haematoma after an apparently uncomplicated primary admission. The patient had been on ticagrelor (a novel antiplatelet agent), aspirin and clopidogrel for recurrent myocardial infarction following coronary stenting, prior to the procedure. The haematoma was drained under radiological guidance without problem. The patient with a lesion which was highly suggestive of malignancy died from a myocardial infarction on day 2 postoperatively. He had significant pre-existing cardiac disease (previous myocardial infarction, coronary artery bypass grafting and further coronary stenting) in additional to poorly controlled diabetes. He underwent a post-mortem examination

which confirmed myocardial infarction and showed the colonic excision site to be healed with no evidence of contamination or ischaemia.

Of the patients undergoing conversion from FLEX to a segmental colectomy one underwent a CT scan on day 2 which showed gas around the anastomosis due to local ischaemia. At reoperation the anastomosis was taken down and a temporary end ileostomy was formed, which was reversed 4 months later.

Treatment outcomes

The median(IQR) polyp diameter in the benign polyps was 35(30-40) mm. The median specimen diameter for completed FLEX procedures was 53mm (IQR: 48.5 – 60mm) (Table 2) (Figure 5). Pathological assessment revealed clear resection margins for all eleven patients. The resection margins were at least 5mm for the eight patients in whom FLEX was completed. The patient with a likely ascending colon cancer was confirmed as a T1 stage ascending colon cancer on histopathology. Two patients with presumed benign polyps had an unexpected cancer found in the excised specimen. One patient had a 2mm T1sm2 cancer: this was adjacent to the 35mm adenoma being resected and had not been endoscopically identified preoperatively. The other patient had a T2 cancer, with no lymphovascular invasion. Both patients were counselled regarding the risk of residual disease and offered the option of segmental colectomy and both opted for a surveillance strategy. At follow-up, they remain well with no adverse events.

Modifications

During the study, there were various modifications to the operative strategy as a result of the experiences gained during study delivery:

After patient 2, the 3/0 prolene suture which was protruded through the endoscopic needle was replaced by a 1000mm 2/0 prolene suture in order to avoid the suture being divided by the clip. We also once (?) used a shorter colonoscope in this procedure, rather than the standard 230cm version, but found it was difficult to reach the lesion, thus this was not repeated. Although the shorter colonoscope had originally been considered adequate, abdominal pressure and position changes to facilitate endoscopy cannot be used during laparoscopy.

Deployment of the suture from the endoscopic needle in the first two patients involved hydrostatic pressure from a fluid-filled syringe. After patient 2, a 1400mm endoscopic ultrasound needle guidewire (EZ Shot 2; Olympus Keymed, Southend-on-Sea, United Kingdom) was placed down the endoscopic needle to advance the suture out of the needle and hydrostatic pressure discontinued as it was unreliable. The 1400mm needle guidewire then overlapped the 1000 mm suture, which was inserted backwards up the needle lumen from the tip. Insertion of the guidewire resulted in protrusion of the suture by approximately 100mm.

The type of clip applied to the suture was changed from a titanium (Ligaclip) to a broader, locking clip (Hem-o-lock, (Weck Surgical Instruments, Teleflex Medical, Durham, NC, USA)) in an attempt to avoid cutting through the suture.

Prior to patient 3, transluminal sutures to mark the medial and lateral extent of the resection were placed laparoendoscopically and clipped. From patient 3 onwards, these were replaced by a silk suture stitched laparoscopically on the serosa of the bowel at the medial and lateral ends of the polyp, guided by the endoscopist (Figure 4c). This was faster and the stitches allowed the surgeon to apply traction facilitating stapler placement.

After patient 4, air testing with water irrigation over the suture line was abandoned because the stapled closure line could not usually be completely submerged under water.

Additionally, in patient 4, the endoscopist recognised that following eversion of the bowel, prior to clipping the tightened sutures, the lesion was not completely everted, suggesting it was not all incorporated within the everted segment and would have been incompletely excised. The relevant sutures were replaced in order to avoid incomplete excision.

In patient 10 the polyp was too large to evert the bowel with the polyp inside the everted segment. The polyp was therefore snared and removed endoscopically under laparoscopic oversight. The bowel wall was then everted in the standard fashion in order to excise the base and ensure complete histological assessment.

After the experience with death of the patient who preoperatively was felt likely to have a cancer, the decision was made not to offer the FLEX procedure to patients with similar lesions, as this would result in a profoundly morbid population, and particularly poor outcomes.

Discussion

This study has described the feasibility of the FLEX procedure for benign, complex polyps that would otherwise have required colectomy. Most of the attempted FLEX procedures were locally successful. This study also used the IDEAL framework in its design, delivery and reporting and it is one of the first detailed reports using the guidance, applied prospectively, during the surgical innovation. We have documented that the FLEX technique was continuing to be modified throughout the study and that while some progress was made, further technological adaptations are required to improve the delivery of the technique. This approach is in contrast to the usual method of presenting surgical innovation through retrospective case series (which may omit reporting selected patients), and failing to describe the whole parent population with complex colonic polyps. This study has importantly recorded details of all consecutive new patients that fulfiled the predetermined inclusion and exclusion criteria. The FLEX procedure now needs further modifications and wider adoption before a more advanced evaluation in a phase 2/3 study can be undertaken.

Some major technical challenges encountered and addressed in this feasibility study relate to the reciprocal operating situation between the endoscopist and laparoscopic surgeon. Each team had to orientate themselves in the same three-dimensional space and excellent collaboration and communication were required to facilitate the correct marking of margins and placement of sutures. This was aided by conceptualising and rehearsing the procedure using the CTC views, particularly the endoluminal and shell overviews. Another challenge was that the laparoscopic and endoscopic light sources would obscure the other operator's field of vision and that it was necessary to turn these away or down at times in order to maintain vision. A further issue was the necessity to look at both operating screens simultaneously, although this was mitigated by the integrated laparo-endoscopic theatre as both screens could be placed side by side in the optimum position. Some significant technical challenges remain, such as

the suture delivery through the colonic wall: this is feasible with endoscopic needles, but a longer needle shaft would improve suture deployment. Having placed the suture through the bowel wall and clipped it once makes the second deployment of the needle extremely difficult and time consuming, as the suture protruding through the needle renders the sharp bevel of the needle ineffective when puncturing the wall for the second time. A modification of the equipment is underway in order to improve this issue and considerably reduce operative complexity and duration. Some aspects of the technique appear stable, such as the specimen excision using the laparoscopic stapler.

Other reports examining laparoendoscopic approaches to colonic polyps have not used the IDEAL framework approach[32], limiting the learning that can be achieved. Within a recent systematic review, three studies utilised more than one laparoendoscopic technique to undertake polyp resection[22, 52, 53] and if the IDEAL framework had been followed, the surgical community might have gained more understanding of the relative merits of differing techniques. Additionally, there are further technical differences between the FLEX procedure and other laparoendoscopic techniques that require investigation. Most of the procedures reported have been a form of laparoscopically-monitored colonoscopic polypectomy. Lascarides and colleagues have recently shown in a randomised trial that laparoscopically-monitored colonoscopic polypectomy for endoscopically unresectable polyps resulted in a shorter length of stay compared to laparoscopic colectomy. Whilst this is likely, the concern with endoscopic polyp resection, even with laparoscopic assistance, is that it risks leaving residual polyp disease[54]. In addition, in early carcinomas, histopathological information is missing that might prevent the need for further resection, by comparison to the information obtained after full-thickness resection. The other predominant technique reported is an endoscopically-assisted laparoscopic colon wall excision, by simply excising a disc of colon without securely preventing spillage of contents as in

FLEX. While reports document the feasibility of full-thickness resection (and luminal opening) followed sequentially by colonic wall closure[14], animal studies have demonstrated bacterial contamination resulting in localised sepsis[55] and, theoretically, spillage of malignant cells risks potential upstaging of any unsuspected cancer. In addition, if the lesion is not precisely marked as in FLEX, incomplete excision is more likely.

Two patients in our cohort had an unexpected cancer within the resection specimen. The rate of unexpected malignancy in endoscopically unresectable colonic polyps undergoing segmental colectomy is around 10%[56-58], with a similar rate found in a review of laparoendoscopic colonic polyp surgery[32]. Some of the laparoendoscopic studies used intra-operative frozen section analysis, which did allow some patients to undergo standard oncological resection under the same anaesthetic, however, it was associated with failure to diagnose cancer in one case. Determining malignant features within a polyp can be difficult histologically[59, 60]. Features such as pseudoinvasion present specific difficulties requiring careful assessment of multiple polyp sections[61, 62]. In addition, a proportion of polyp cancers will be adequately resected using local excisional approaches, but again this requires careful pathological analysis of multiple sections and is not possible within frozen section analysis. For this reason frozen section analysis was not undertaken in this study. As the risk of malignancy is around 10% in complex polyps that require surgery the consent process must be robust and discuss the implications for future treatment if malignancy is detected. Furthermore, the current experience with delivering the FLEX procedure suggests selecting a morbid population with small colonic cancers, who would be unlikely to tolerate colectomy, may result in poor outcomes.

This study has some limitations: in particular, the small sample size. In addition, the study has not had the opportunity to address many lesions on the mesenteric surface of the colon. These lesions will produce specific technical challenges due to proximity

of the blood supply and may require specific technical modifications as further experience is gained. However, by using the IDEAL framework recommendations, this study has allowed the maximal amount of learning to be generated from the involvement of each study participant and continuing this approach will allow greater understanding of the potential and limitations of the FLEX technique.

Conclusion

This study has shown, through an examination of the feasibility of the FLEX procedure for resection of complex, benign colonic polyps in clinical practice, that incorporating the IDEAL framework guidance can enhance transparency and reduce information bias. This is particularly important for an early-stage surgical innovation, such a FLEX, where comparison against a control group is not yet appropriate because the intervention is not stable. This process has allowed the safe and efficient transition of a technique from the animal model into clinical practice.

Table 1. Patient characteristics and perioperative outcomes for the FLEX procedure

Patient	Age (years)	Reason endoscopically unresectable	Mesenteric location	Colon location	Paris classification	Operative duration (mins)	Operation undertaken	Complications (C-D grade)	Hospital stay (days)
1	53	Appendiceal location	A	Caecum	1sp	170	FLEX	-	2
2	79	Malignant	A	Ascending	1s	120	FLEX	Mortality (5)	2
3	62	Unstable access - severe diverticulosis	M	Hepatic flexure	1sp	150	Segmental right colectomy	Anastomotic leak (3b)	19
4	74	Appendiceal location	M	Caecum	LST-G	140	FLEX	-	3
5	67	Size and flexure location	M	Descending	1sp	210	Segmental left colectomy	-	4
6	83	SMF - previous EMR in caecum	A	Caecum	LST-G	150	FLEX	Abdominal wall haematoma (1)	5
7	82	Pain on lifting injection	A	Transverse	IIa+IIc	163	FLEX	-	3
8	56	Appendiceal location	A	Caecum	1sp	113	FLEX	Intra-abdominal haematoma (2)	2
9	83	Appendiceal location	M	Caecum	1s	296	Ileo-caecal resection	Atrial fibrillation (1)	8
10	42	Size	M	Descending	Ip	180	FLEX	-	3
11	73	Appendiceal location	A	Caecum	Is	120	FLEX	Chest infection (1)	8

Key: A – anti-mesenteric; M – mesenteric; EMR – endoscopic mucosal resection. SMF – submucosal fibrosis. Hospital stay – primary admission from day of surgery

Table 2. Histopathological outcomes of patients receiving the FLEX procedure

Patient	Maximum diameter of polyp (mm)	Maximum diameter specimen (mm)	Minimum excision margin (mm)	Lesion pathology diagnosis	Comment
1	35	60	25	TVA LGD	2mm sm2 cancer adjacent to benign polyp
2	30	53	8	T1 sm2 adenocarcinoma	
3	41	Colectomy	120	TVA LGD	
4	35	45	10	TVA LGD	
5	43	Colectomy	110	TVA LGD	
6	40	52	4	TVA LGD	
7	17	53	21	TVA HGD	
8	24	42	8	TA LGD	
9	35	Colectomy	-	TVA LGD	
10	39	60	15	Leiomyoma	
11	25	65	14	HGD	T2, mod diff adenoca, no LVI

Key: TVA – tubulovillous adenoma; TA – tubular adenoma; LGD – low grade dysplasia, LVI - lymphovascular
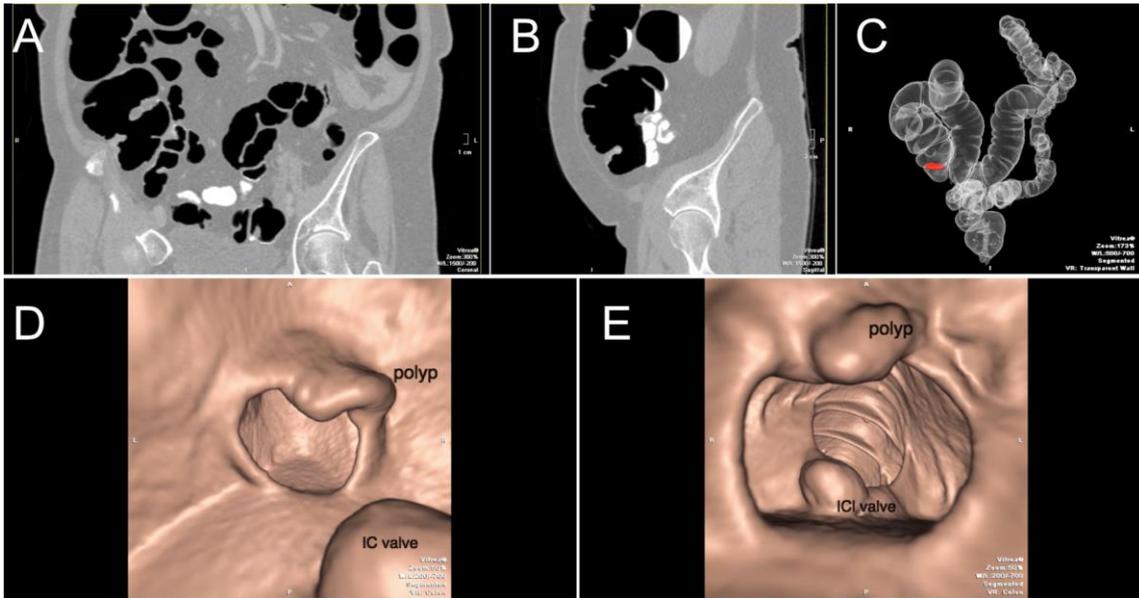
invasion.

Figure 1. CT colonography assessments for patients undergoing FLEX

A) Coronal CT image showing 35mm polyp opposite the ileo-caecal fold

B) Sagittal image of the caecal polyp

C) 3d reconstruction 'shell' view showing the polyp in red

D) Retrograde view of endoluminal reconstruction showing relationship of polyp to the ileocaecal fold

E) Prograde view of endoluminal reconstruction showing relationship of polyp to the ileocaecal fold

Figure 2. Combined laparoendoscopic theatre demonstrating use of boom mounted screens to allow collaborative and simultaneous visualisation of the endoscopic and laparoscopic images by both laparoscopic surgeon and endoscopist (Imaging taken with preoperative patient consent)
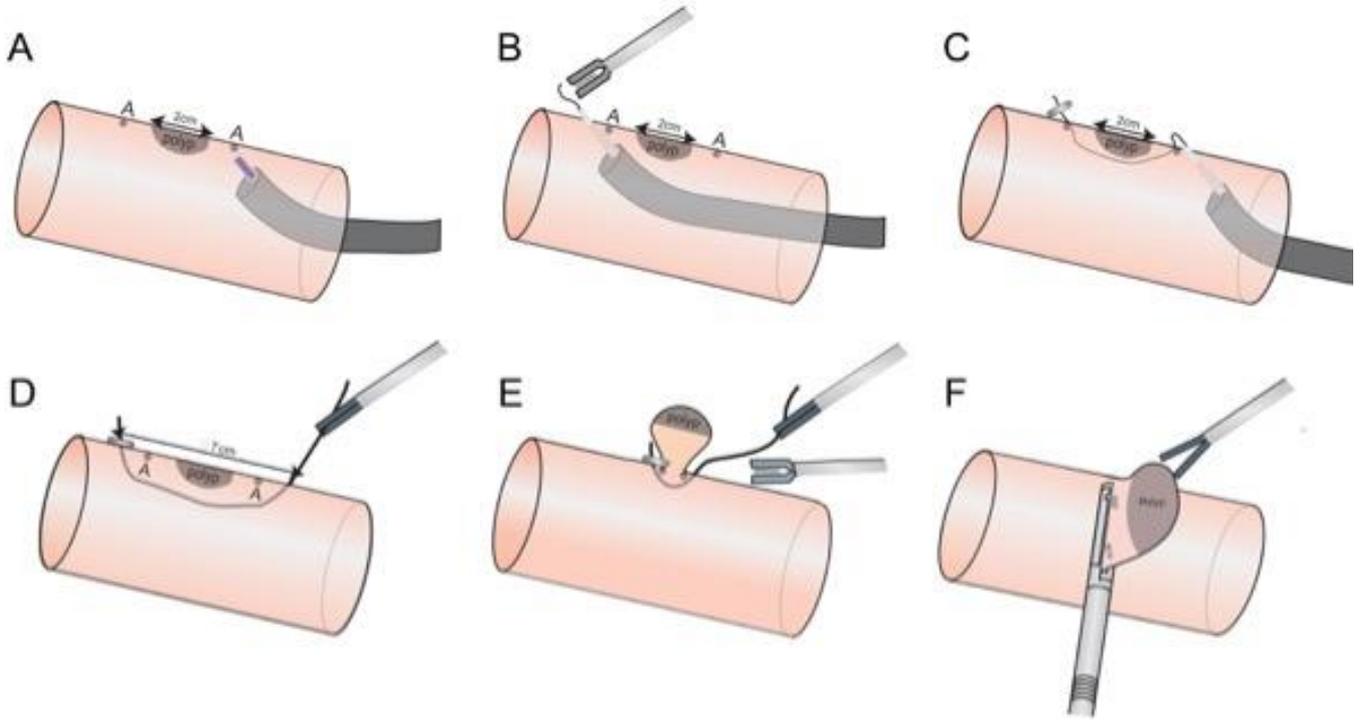
Figure 3. Schematic of the FLEX procedure modified for the human population
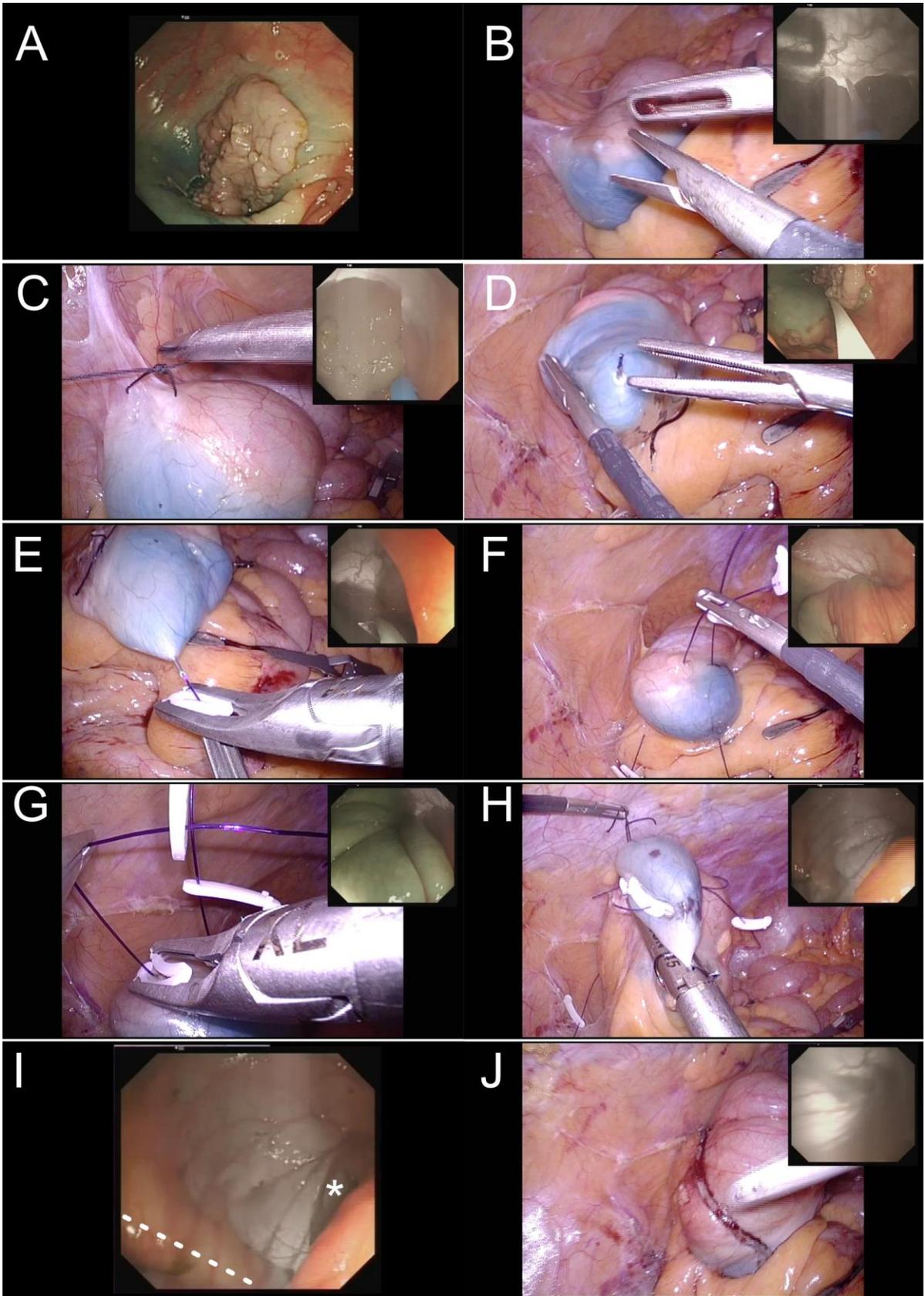
Figure 2. Operative components of the FLEX procedure

Operative steps:

A) Endoscopic view of 50mm caecal polyp (Paris classification: LST) with a 1cm circumferential argon plasma coagulator (APC) margin marked around the polyp in order to ensure complete excision. An attempt had been made to snare resect this polyp prior to FLEX but was abandoned because of submucosal fibrosis from previous resection attempts.

B) Identification of margins around polyp from internal and external views by endoscopic-laparoscopic co-operation using the APC catheter protruding against the luminal surface of the colon.

C) External laparoscopically placed sutures, guided by the endoscopist, to identify lateral border of excision. A further suture will be placed at the opposite, medial, extent

D) A needle is placed through the bowel wall endoscopically through which an endoscopic suture is protruded

E) Placement of Hem-o-lok™ clip around suture

F) Two sutures have now been placed and Hem-o-lok™ clips applied without pulling the sutures tight in order to avoid distortion of the endoscopic view.

G) The sutures are tightened to evert a fold of bowel which is further secured using hem-o-lok™ clips.

H) Laparoscopic stapled excision of the plicated, everted bowel, preventing spillage of cells or contaminating material from the bowel, with endoscopic oversight of stapler placement to ensure complete excision (small image overlay on right).

I) Endoscopic view following stapled excision showing endoluminal view of stapled margin (dotted line) and non-obstructed ileocaecal valve (*).

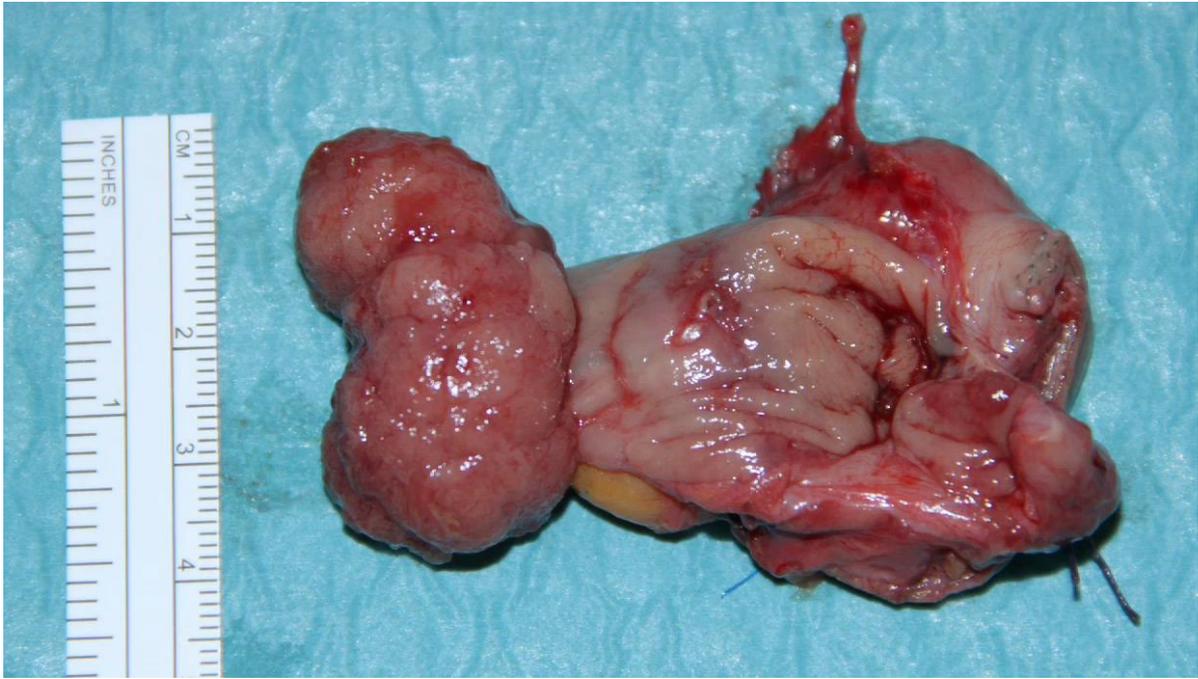J) The completed staple-line excision in the colon.

Figure 5. Macroscopic histopathology specimen from a FLEX procedure: Patient 1 who had a 35mm caecal polyp.

Bibliography

1.   Atkin W, Wooldrage K, Brenner A, Martin J, Shah U, Perera S, et al. Adenoma surveillance and colorectal cancer incidence: a retrospective, multicentre, cohort study. *The lancet oncology* 2017; **18:** 823-34.
2.   Atkin W, Wooldrage K, Parkin DM, Kralj-Hans I, MacRae E, Shah U, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet* 2017; **389:** 1299-311.
3.   Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). *Annals of surgery* 2011; **254:** 868-75.
4.   Askari A, Nachiappan S, Currie A, Bottle A, Athanasiou T, Faiz O. Selection for laparoscopic resection confers a survival benefit in colorectal cancer surgery in England. *Surgical endoscopy* 2016; **30:** 3839-47.
5.   Sood A, Meyer CP, Abdollah F, Sammon JD, Sun M, Lipsitz SR, et al. Minimally invasive surgery and its impact on 30-day postoperative complications, unplanned readmissions and mortality. *The British journal of surgery* 2017; **104:** 1372-81.
6.   Keller DS, Delaney CP, Hashemi L, Haas EM. A national evaluation of clinical and economic outcomes in open versus laparoscopic colorectal surgery. *Surgical endoscopy* 2016; **30:** 4220-8.
7.   Brigic A, Sakuma S, Lovegrove RE, Bassett P, Faiz O, Clark SK, et al. A prospective case control study of functional outcomes and related quality of life after colectomy for neoplasia. *Int J Colorectal Dis* 2017; **32:** 777-87.
8.   Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. *Annals of surgery* 2014; **259:** 916-23.
9.   Magdeburg J, Glatz N, Post S, Kienle P, Rickert A. Long-term functional outcome of colonic resections: how much does faecal impairment influence quality of life? *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2016; **18:** O405-O13.
10.   Agrawal D, Chak A, Champagne BJ, Marks JM, Delaney CP. Endoscopic mucosal resection with full-thickness closure for difficult polyps: a prospective clinical trial. *Gastrointest Endosc* 2010; **71:** 1082-8.
11.   Beck DE, Karulf RE. Laparoscopic-assisted full-thickness endoscopic polypectomy. *Diseases of the colon and rectum* 1993; **36:** 693-5.
12.   Cruz RA, Ragupathi M, Pedraza R, Pickron TB, Le AT, Haas EM. Minimally invasive approaches for the management of "difficult" colonic polyps. *Diagnostic and therapeutic endoscopy* 2011; **2011:** 682793.
13.   Franklin ME, Jr., Portillo G. Laparoscopic monitored colonoscopic polypectomy: long-term follow-up. *World journal of surgery* 2009; **33:** 1306-9.
14.   Fukunaga Y, Tamegai Y, Chino A, Ueno M, Nagayama S, Fujimoto Y, et al. New technique of en bloc resection of colorectal tumor using laparoscopy and endoscopy cooperatively (laparoscopy and endoscopy cooperative surgery - colorectal). *Diseases of the colon and rectum* 2014; **57:** 267-71.
15.   Goh C, Burke JP, McNamara DA, Cahill RA, Deasy J. Endolaparoscopic removal of colonic polyps. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2014; **16:** 271-5.
16.   Grunhagen DJ, van Ierland MC, Doornebosch PG, Bruijninckx MM, Winograd R, de Graaf EJ. Laparoscopic-monitored colonoscopic polypectomy: a multimodality method to avoid segmental colon resection. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2011; **13:** 1280-4.
17.   Hensman C, Luck AJ, Hewett PJ. Laparoscopic-assisted colonoscopic polypectomy: technique and preliminary experience. *Surgical endoscopy* 1999; **13:** 231-2.

18. Lee MK, Chen F, Esrailian E, Russell MM, Sack J, Lin AY, et al. Combined endoscopic and laparoscopic surgery may be an alternative to bowel resection for the management of colon polyps not removable by standard colonoscopy. *Surgical endoscopy* 2013

19. Lee SW, Garrett KA, Shin JH, Trencheva K, Sonoda T, Milsom JW. Dynamic Article: Long-term Outcomes of Patients Undergoing Combined Endolaparoscopic Surgery for Benign Colon Polyps. *Diseases of the colon and rectum* 2013; **56:** 869-73.

20. Prohm P, Weber J, Bonner C. Laparoscopic-assisted coloscopic polypectomy. *Diseases of the colon and rectum* 2001; **44:** 746-8.

21. Smedh K, Skullman S, Kald A, Anderberg B, Nystrom P. Laparoscopic bowel mobilization combined with intraoperative colonoscopic polypectomy in patients with an inaccessible polyp of the colon. *Surgical endoscopy* 1997; **11:** 643-4.

22. Wilhelm D, von Delius S, Weber L, Meining A, Schneider A, Friess H, et al. Combined laparoscopic-endoscopic resections of colorectal polyps: 10-year experience and follow-up. *Surgical endoscopy* 2009; **23:** 688-93.

23. Winter H, Lang RA, Spelsberg FW, Jauch KW, Huttl TP. Laparoscopic colonoscopic rendezvous procedures for the treatment of polyps and early stage carcinomas of the colon. *Int J Colorectal Dis* 2007; **22:** 1377-81.

24. Wood JJ, Lord AC, Wheeler JM, Borley NR. Laparo-endoscopic resection for extensive and inaccessible colorectal polyps: a feasible and safe procedure. *Ann R Coll Surg Engl* 2011; **93:** 241-5.

25. Leicher LW, de Vos Tot Nederveen Cappel WH, van Westreenen HL. Limited Endoscopic-Assisted Wedge Resection for Excision of Colon Polyps. *Diseases of the colon and rectum* 2017; **60:** 299-302.

26. Gorgun E, Benlice C. En Bloc Resection of a 5-cm Flat Ascending Colonic Lesion with Endoscopic Submucosal Dissection Combined with Laparoscopy. *Diseases of the colon and rectum* 2016; **59:** 1230.

27. Lin AY, O'Mahoney PR, Milsom JW, Lee SW. Dynamic Article: Full-Thickness Excision for Benign Colon Polyps Using Combined Endoscopic Laparoscopic Surgery. *Diseases of the colon and rectum* 2016; **59:** 16-21.

28. Crawford AB, Yang I, Wu RC, Moloo H, Boushey RP. Dynamic article: combined endoscopic-laparoscopic surgery for complex colonic polyps: postoperative outcomes and video demonstration of 3 key operative techniques. *Diseases of the colon and rectum* 2015; **58:** 363-9.

29. Quyn AJ, Vujovic Z, Ziyaie D, Steele RJ, Campbell KL. Laparoscopic-assisted colonoscopy: results and follow-up endoscopic success. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2016; **18:** O376-O9.

30. Lascarides C, Buscaglia JM, Denoya PI, Nagula S, Bucobo JC, Bergamaschi R. Laparoscopic right colectomy vs laparoscopic-assisted colonoscopic polypectomy for endoscopically unresectable polyps: a randomized controlled trial. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2016; **18:** 1050-6.

31. Brigic A, Southgate A, Sibbons P, Clark SK, Fraser C, Kennedy RH. Full-thickness laparoendoscopic colonic excision in an experimental model. *The British journal of surgery* 2013; **100:** 1649-54.

32. Currie A, Brigic A, Blencowe NS, Potter S, Faiz OD, Kennedy RH, et al. Systematic review of surgical innovation reporting in laparoendoscopic colonic polyp resection. *The British journal of surgery* 2015; **102:** e108-16.

33. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* 2009; **374:** 1105-12.

34. Tsiamoulos ZP, Rajaratnam R, Wawszczak A, Thomas-Gibson S, Suzuki N, Latchford A, et al. Su1547 A Multi-Disciplinary Team (Mdt) Approach for Complex Benign

Colorectal Polyps: First Results in a Tertiary Referral Centre. *Gastrointestinal Endoscopy*; **81:** AB323.

35. Rutter MD, Chattree A, Barbour JA, Thomas-Gibson S, Bhandari P, Saunders BP, et al. British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps. *Gut* 2015; **64:** 1847-73.

36. Endoscopic Classification Review G. Update on the paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy* 2005; **37:** 570-8.

37. Currie AC, Burling D, Mainta E, Ilangovan R, Moorghen M, Lung P, et al. An analysis of the accuracy of computed tomography colonography when defining anatomy for novel full-thickness colonic excision techniques in early colonic neoplasia. *Colorectal Disease* 2016; **18:** 983-8.

38. St Mark's Hospital Academic Institute (2017) St Mark's Hospital Academic Institute Laparoscopy video archive. **Vol. 2017**.

39. Buchanan GN, Malik A, Parvaiz A, Sheffield JP, Kennedy RH. Laparoscopic resection for colorectal cancer. *The British journal of surgery* 2008; **95:** 893-902.

40. Faiz O, Brown T, Colucci G, Kennedy RH. A cohort study of results following elective colonic and rectal resection within an enhanced recovery programme. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2009; **11:** 366-72.

41. Currie AC, White I, Malietzis G, Moorghen M, Jenkins JT, Kennedy RH. Outcomes following laparoscopic rectal cancer resection by supervised trainees. *The British journal of surgery* 2016; **103:** 1076-83.

42. Jenkins JT, Currie A, Sala S, Kennedy RH. A multi-modal approach to training in laparoscopic colorectal surgery accelerates proficiency gain. *Surgical endoscopy* 2016; **30:** 3007-13.

43. West NP, Kennedy RH, Magro T, Luglio G, Sala S, Jenkins JT, et al. Morphometric analysis and lymph node yield in laparoscopic complete mesocolic excision performed by supervised trainees. *The British journal of surgery* 2014; **101:** 1460-7.

44. White I, Jenkins JT, Coomber R, Clark SK, Phillips RK, Kennedy RH. Outcomes of laparoscopic and open restorative proctocolectomy. *The British journal of surgery* 2014; **101:** 1160-5.

45. McNicol FJ, Kennedy RH, Phillips RK, Clark SK. Laparoscopic total colectomy and ileorectal anastomosis (IRA), supported by an enhanced recovery programme in cases of familial adenomatous polyposis. *Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland* 2012; **14:** 458-62.

46. Mirza MS, Longman RJ, Farrokhyar F, Sheffield JP, Kennedy RH. Long-term outcomes for laparoscopic versus open resection of nonmetastatic colorectal cancer. *J Laparoendosc Adv Surg Tech A* 2008; **18:** 679-85.

47. Kennedy RH, Cahill RA, Brigic A, Sibbons P, Fraser C. Full-thickness laparoendoscopic excision in the stomach: the FLEx technique. *Surgical innovation* 2012; **19:** 93-8.

48. Kennedy RH, Cahill RA, Sibbons P, Fraser C. The "FLEX" procedure: a new technique for full-thickness laparo-endoscopic excision in the colon. *Endoscopy* 2011; **43:** 223-9.

49. Brigic A, Southgate A, Sibbons PD, Clark SK, Fraser C, Kennedy RH. Full-thickness laparoendoscopic stapled excision of colonic lesion in a porcine ex vivo model. *Endoscopy* 2013; **45 Suppl 2 UCTN:** E167-8.

50. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery* 2004; **240:** 205-13.

51. Williams GT, Quirke P, Shepherd NA (2007) *Appendix D.* Proforma for Local Excision Specimens. In: *Dataset for Colorectal Cancer, 2nd Edition* Royal College of Pathologists, London.

52. Franklin ME, Jr., Portillo G. Laparoscopic monitored colonoscopic polypectomy: long-term follow-up. *World journal of surgery* 2009; **33:** 1306-9.

53. Grunhagen DJ, van Ierland MC, Doornebosch PG, Bruijninckx MM, Winograd R, de Graaf EJ. Laparoscopic-monitored colonoscopic polypectomy: a multimodality method to avoid segmental colon resection. *Colorectal Disease* 2011; **13:** 1280-4.

54. Gill MD, Rutter MD, Holtham SJ. Management and short-term outcome of malignant colorectal polyps in the north of England(1). *Colorectal Disease* 2013; **15:** 169-76.

55. Raju GS, Malhotra A, Ahmed I. Colonoscopic full-thickness resection of the colon in a porcine model as a prelude to endoscopic surgery of difficult colon polyps: a novel technique (with videos). *Gastrointest Endosc* 2009; **70:** 159-65.

56. Bertelson NL, Kalkbrenner KA, Merchea A, Dozois EJ, Landmann RG, De Petris G, et al. Colectomy for endoscopically unresectable polyps: how often is it cancer? *Diseases of the colon and rectum* 2012; **55:** 1111-6.

57. Jang JH, Balik E, Kirchoff D, Tromp W, Kumar A, Grieco M, et al. Oncologic colorectal resection, not advanced endoscopic polypectomy, is the best treatment for large dysplastic adenomas. *Journal of Gastrointestinal Surgery* 2012; **16:** 165-71.

58. Pokala N, Delaney CP, Kiran RP, Brady K, Senagore AJ. Outcome of laparoscopic colectomy for polyps not suitable for endoscopic resection. *Surgical endoscopy* 2007; **21:** 400-3.

59. Komuta K, Batts K, Jessurun J, Snover D, Garcia-Aguilar J, Rothenberger D, et al. Interobserver variability in the pathological assessment of malignant colorectal polyps. *The British journal of surgery* 2004; **91:** 1479-84.

60. van Putten PG, Hol L, van Dekken H, Han van Krieken J, van Ballegooijen M, Kuipers EJ, et al. Inter-observer variation in the histological diagnosis of polyps in colorectal cancer screening. *Histopathology* 2011; **58:** 974-81.

61. Tanizawa T, Seki T, Nakano M, Kamiyama R. Pseudoinvasion of the colorectal polypoid tumors: serial section study of problematic cases. *Pathology international* 2003; **53:** 584-90.

62. Muto T, Bussey HJ, Morson BC. Pseudo-carcinomatous invasion in adenomatous polyps of the colon and rectum. *Journal of clinical pathology* 1973; **26:** 25-31.