# Development of a new, minimally invasive, full thickness excision technique for early colonic neoplasia

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# Declaration of Originality

This thesis represents original work that the author carried out at St. Mark's Hospital, North West London Hospitals Trust, and has not been presented in any other form to any other university. Work of others has been appropriately referenced.

The work presented here was carried out under the supervision of Professor Robin H. Kennedy (St. Mark's Hospital London and Imperial College, London), Professor Susan K. Clark (St. Mark's Hospital London and Imperial College, London) and Dr Chris Fraser (Wolfson Unit for Endoscopy, St. Mark's Hospital London and Imperial College, London).

# Copyright Declaration

# Abstract

Introduction of bowel cancer screening programmes internationally has resulted in a significant shift in diagnosis towards early stage disease. In addition, the number of patients diagnosed with complex benign colorectal polyps is increasing.

Advanced endoscopic techniques including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) as well as transanal endoscopic microsurgery (TEMS) are being increasingly utilised for excision of early rectal neoplasia. An equivalent surgical technique is currently not available for colonic lesions, and endoscopic techniques are associated with a high risk of complications such as bleeding, perforation and recurrence than in the rectum. Hemicolectomy with *en bloc* mesenteric excision remains the gold standard treatment for patients with early, node negative colon cancer and large colonic polyps. Even when performed laparoscopically within an enhanced recovery protocol, problems such as death, anastomotic leakage and other complications occurring in up to 40% of patients make colectomy a morbid intervention.

The introduction to this thesis reviews the literature on the development and staging of colorectal cancer as well as currently available endoscopic and surgical techniques. In order to improve our understanding of the morbidity associated with hemicolectomy for the treatment of benign colonic polyps, two studies examined short term outcomes after surgery. The results suggest similar 30-day outcomes to those after cancer resection. In addition, a two-part study was designed to assess bowel function and related quality of life in patients who underwent hemicolectomy for colonic neoplasia, a subject that is poorly documented in the literature. As an introduction to the laboratory work, a systematic review of endoscopic full thickness excision techniques is presented. The final three chapters of the thesis describe *ex-vivo* development and outcome data after a porcine survival study of a laparo-endoscopic excision technique for colonic lesions as a potential alternative to hemicolectomy.

**Dedicated to my family**

**without whom none of this**

**would have been possible**

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# Chapter 1 Introduction

## 1.1 Colorectal cancer

Colorectal cancer (CRC) is the third most common cancer in the UK with estimated lifetime risk of 1 in 15 for men and 1 in 19 for women[1]. It is the second most common cause of cancer death in England with over 30 000 new cases diagnosed each year and approximately 13 000 deaths[1]. Most of the tumours occur in the left side of the bowel with two-thirds of all cases in the colon.

### 1.1.1 Development of colorectal neoplasia

CRC is increasingly classified into specific phenotypes on the basis of molecular profiles[2] and at least three different pathogenic pathways have been implicated. The role of adenoma in CRC development was originally described by Vogelstein et al.[3] who demonstrated that a stepwise accumulation of genetic alterations accompanies the adenoma-carcinoma sequence in the colon. The accumulation of genetic alterations occurs concomitantly with morphological changes resulting in formation of a small adenomatous polyp. This is followed by progression from low-grade dysplasia to a larger lesion with high risk features (high grade dysplasia) and finally invasive cancer. The earliest molecular aberration in this pathway is the loss of adenomatous polyposis coli (APC) which is the tumour suppressor gene responsible for mucosal hyperproliferation. This occurs at an early stage of tumourigenesis[4]. Increased DNA replication leads to accumulation of genetic 'accidents' and mutations in a number of genes including KRAS[5] and P53[5, 6] in increasingly large adenomas and early cancer[3]. This pathway is thought to account for approximately 85% of all CRCs and it usually occurs over several years[2]. It also characterises familial adenomatous polyposis and is therefore often referred to as the APC pathway[7]. Alternatively, this pathway is also known as the chromosomal instability (CIN) pathway as tumours arising from it are characterised by gross chromosomal abnormalities including insertions, deletions and loss of heterozygosity[7].

The most prevalent familial colorectal cancer syndrome is Lynch syndrome (previously known was hereditary non-polyposis colorectal cancer, HNPCC), accounting for about 2% of all CRCs[8]. It is inherited in an autosomal dominant pattern and is characterised with germline mutations in one of several DNA mismatch repair genes, most commonly MLH1, MLH2 and MSH6[2, 7]. The loss of DNA mismatch repair function results in accumulation of mutations in microsatellite regions of the genome[9] and therefore microsatellite instability (MSI) and tendency to malignant progression[2, 7]. Abnormalities in mismatch repair are also identifiable in approximately 15% of sporadic CRCs and the MSI occurs when the promoter region in the mismatch repair system is silenced by hypermethylation of CpG islands[10]. These tumours are more likely to be proximally located, to present at a more advanced age, to occur in women and tend to be associated with a favourable prognosis[11].

CRCs arising via the 'serrated pathway' form a heterogeneous group with respect to molecular alterations, precursor lesions and biological behaviour[12, 13]. A proportion of 'serrated adenocarcinomas' are characterised by an activating mutation of the BRAF oncogene and defective DNA mismatch repair, resulting in microsatellite instability (MSI-high), MLH1 inactivation and high CpG island methylator phenotype[13]. BRAF-associated tumours tend to develop from sessile serrated lesions, occur in the proximal colon and have a relatively good prognosis[7, 12]. CRCs arising from pedunculated or traditional serrated lesions are believed to evolve via the KRAS mutation. Tumours in this pathway are characterised by microsatellite stable (MSS) or MSI-low phenotype, retained MLH1 expression and lower CpG island methylation than BRAF-associated lesions. The majority occur in the distal colon and are associated with rapid progression and poor prognosis[12, 14, 15].

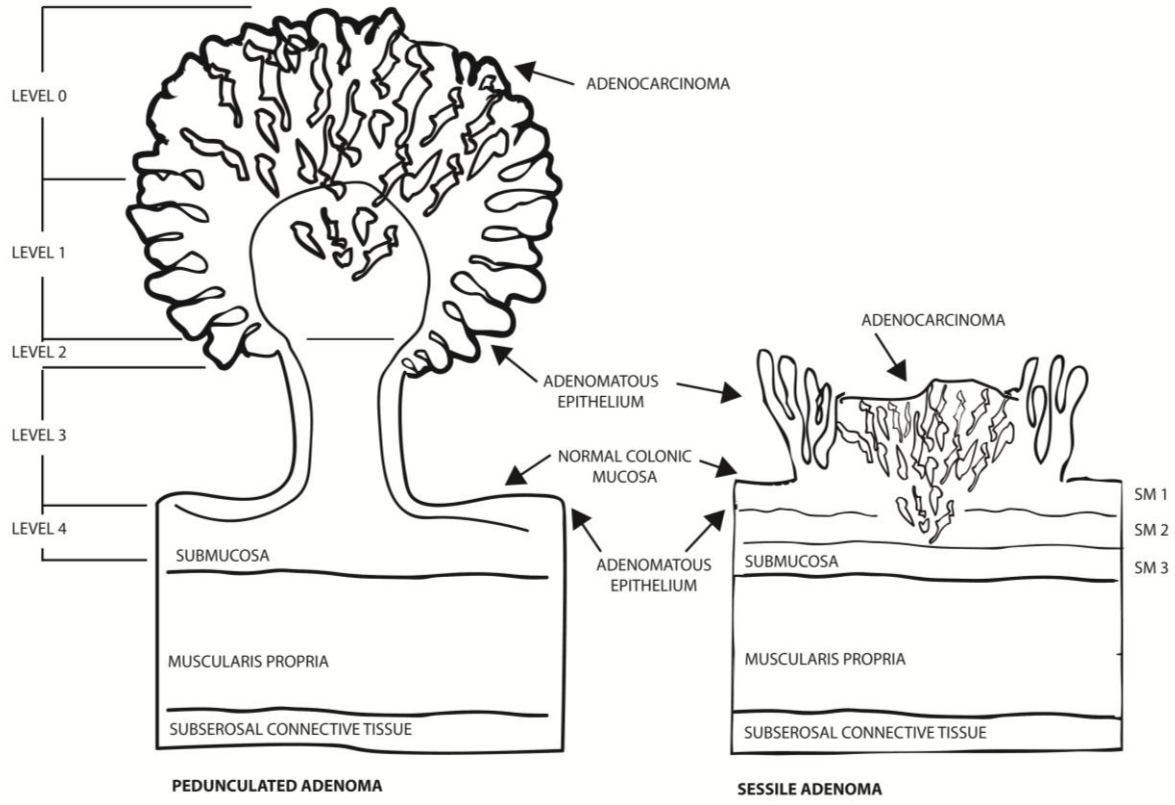
### 1.1.2 Precursor lesions

CRC arises primarily from adenomas and approximately 40% of patients over the age of 50 have at least one small colorectal adenoma[16]. These mucosal lesions, pedunculated or sessile, are by definition neoplastic and must show at least low grade dysplasia[17]. Morphologically, adenomatous polyps are classified according to their predominant architectural pattern into tubular, villous and tubulovillous adenomas[17]. The risk of malignancy is highly correlated with increasing polyp size[18, 19], villous or serrated morphology[12] and the presence of high grade dysplasia[12, 20]. Serrated polyp is a general term for lesions that show serrated (saw tooth) architecture of the epithelial compartment[21]. Unlike classical adenomas, serrated lesions are often sessile and relatively flat and are therefore more difficult to detect than conventional adenomatous polyps. They are thought to account for up to 17.5% of proximal tumours[15].

High-grade dysplasia is usually focal and limited to the superficial portion of the polyp. Endoscopic removal is sufficient provided that the specimen is removed *en bloc* and histological examination demonstrates intact muscularis mucosae or lamina propria[22]. If however, neoplastic cells invade through the muscularis mucosae into the submucosa, the term malignant polyp is used and management of such lesions is debated. pT1 tumours invade submucosa to varying degrees and they have been sub-staged according to their morphology by Haggitt[23] and Kikuchi[24]. Haggitt et al.[23] described a classification system for pedunculated polyps with levels of invasion ranging from 0 (mucosal high grade dysplasia) to 4 (infiltration of the bowel wall below the stalk). This system, however, is unsuitable for sessile lesions and Kikuchi et al.[24] described an alternative method whereby invasion of the submucosa is divided into thirds, ranging from superficial invasion (sm1) to deep invasion of the lower third (sm3) (Figure 1.1, adapted from Haggitt et al.[23]) The frequency of nodal disease increases with the depth of invasion being 2%, 8% and 23% respectively for sm1, sm3 and sm3 lesions[25]. In addition, poor differentiation, lymphovascular invasion and inadequate resection margin clearance (<2mm)[26] have also been associated with an

increased risk of residual intramural or nodal disease. The aim of pathological assessment is therefore to indicate the risk of residual disease and the need for subsequent surgical resection.

***Figure 1.1 Classification of polyps with invasive carcinoma***




***Adapted from:*** *Nivatvongs et al.[25], as per Haggitt et al.[23] and Kikuchi et al.[24]*

### 1.1.3 Spread of the disease

The routes of spread of the primary tumour are by direct, lymphatic or haematogenous spread, or by shedding of viable malignant cells from serosal surface into the peritoneal cavity. Direct spread occurs in all directions within the bowel wall and may lead to invasion of both intra- and retroperitoneal structures. The lymphatic spread of colonic cancer progresses from the involvement of submucosal vessels followed by extramural spread to paracolic lymph nodes closest to the primary tumour. In advanced disease, the tumour cells metastasise along the main colonic vessels eventually reaching para-aortic lymph nodes.

Rectal cancer spreads to the lymph nodes in the mesorectum with the subsequent involvement of the nodes associated with the superior haemorrhoidal and inferior mesenteric vessels. Extra-mesorectal nodes are most commonly found along the middle rectal artery; the internal iliac chain; and the obturator, median sacral, and, less commonly, external or common iliac nodes[27, 28]. The commonest site for haematogenous spread of colorectal cancer is the liver, occurring in approximately 50% of all patients[29]. In addition, 10% of patients develop lung metastases at some stage, and other reported sites include adrenal gland, bone, kidney and brain. Peritoneal spread is rare and is associated with poor prognosis[8].

### 1.1.4 Staging and prognosis

The prognosis is very much dependent on the stage of the CRC at the time of the diagnosis, with the depth of the wall invasion (T), presence of the lymph node (N) or distant metastases (M) being the major prognostic factors.

***Table 1.1 pTNM classification of colorectal tumours***

| Stage | T | N | M |
|---|---|---|---|
| **0** | Tis | No | M0 |
| **I** | T1, 2 | N0 | M0 |
| **II** | | | |
| **IIA** | T3 | N0 | M0 |
| **IIB** | T4 | N0 | M0 |
| **III*** | | | |
| **IIIA** | T1, T2 | N1 | M0 |
| **IIIB** | T3, T4 | N1 | M0 |
| **IIIC** | Any T | N2 | M0 |
| **IV** | Any T | Any N | M1 |

***Abbreviations:*** *N1 = there are tumour cells in up to three regional lymph nodes; N2 = there are tumour cells in four or more regional lymph nodes*

The TNM staging system was initially developed to predict cancer prognosis, but its function has expanded and is now used to determine treatment and patient eligibility for clinical trials[30]. At present, the Royal College of Pathologists recommends that the 5th edition of the

TNM staging system[31] is used for colorectal cancer reporting at a national level[32, 33] (Table 1.1). This version has been used in the most recent generation clinical trials and population studies[30]. Despite the advances in surgical techniques and adjuvant treatments however, the overall 5-year survival following a diagnosis of CRC in the UK is just over 50%[34]. As such, it is one of the lowest in Europe[35]. Worldwide introduction of screening programmes over the past decade however, is likely to change this in the near future.

## 1.2 Management of CRC

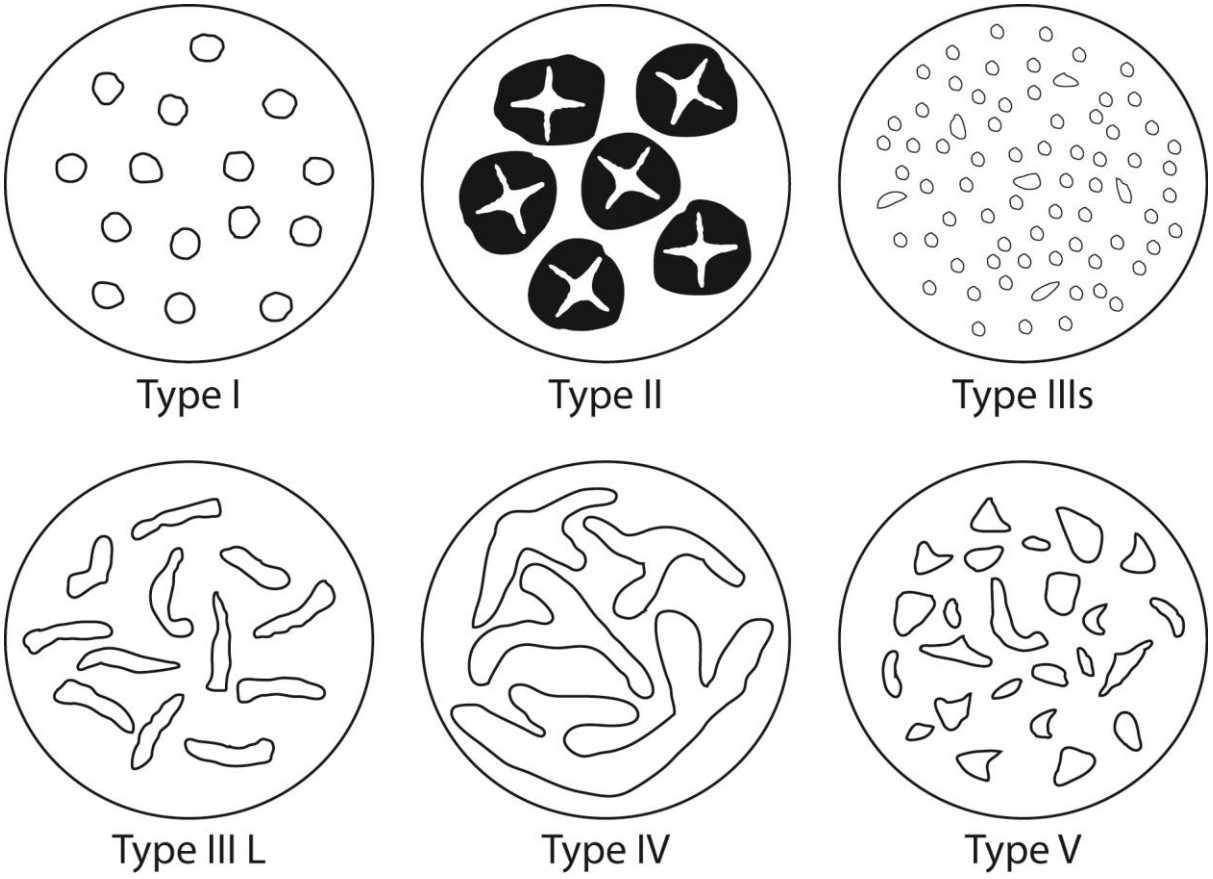
The advances in the management of CRC over the last two decades include introduction of colorectal screening, laparoscopic surgery and treatment planning through a multidisciplinary approach. Tumour stage is central to prognosis, operative approach, and the decision whether to administer neoadjuvant treatment. Accurate pre-operative staging is therefore essential for planning of optimal therapy.

### 1.2.1 Pre-operative staging

#### *1.2.1.1 Endoscopic assessment of the lesion*

Although mucosal biopsy and histological assessment are the 'gold standard' for differentiating neoplastic from non-neoplastic lesions, lesion characterisation during diagnostic colonoscopy forms an integral part of staging and treatment decision making process. Kudo et al.[36] developed a 'pit pattern' classification for polyps based on different morphological features using magnifying endoscopy and indigo carmine dyes. Pit patterns are categorized into five different groups which correlate with the final pathology (Figure 1.2, adapted from Kudo et al.[36]). The authors suggested that most lesions showing pattern types $III_S$, $III_L$ and IV are adenomas or intramucosal carcinomas and as such are suitable for endoscopic treatment. Lesions with type V pit pattern however are most likely to harbour invasive carcinoma and as such, should be treated surgically.

***Figure 1.2 Pit pattern classification***




***Adapted from:*** *Kudo et al.*[36]

***Type 1.*** *Normal roundish pits;* ***Type II.*** *Stella or papillary pits typical of hyperplastic polyps;* ***Type IIIs.*** *Small round or tubular pits (smaller than Type I);* ***Type IIIL.*** *Large round or tubular pits (larger than Type I);* ***Type IV.*** *Branch-like or sulcus-like pits typical of tubulovillous adenomas;* ***Type V.*** *Loss of architecture typical of invasion or high grade dysplasia*

Multiple studies published since have confirmed that pit pattern classification has high accuracy in polyp differentiation[37, 38] and good inter-observer and intra-observer reproducibility (mean kappa values 0.716 and 0.810 respectively)[39]. Although the classification is widely accepted, magnifying endoscopes are expensive, the examination process is time consuming and there is an appreciable learning curve requiring experience with approximately 200 lesions to overcome it[40]. The extra training and time required for magnifying chromoendoscopy have not made it popular in the West and the technique is therefore rarely utilised for lesion characterisation outside a research setting.

Narrow band imaging (NBI) is a new optical technique that highlights superficial vessels in the mucosa through the use of optical filters and allows a more detailed visualisation of the mucosal and vascular patterns. Using a system of vascular intensity, NBI has high sensitivity and specificity (92% and 86% respectively) in distinguishing neoplastic and non-neoplastic polyps[41]. The 'blue light' optical modality can be activated at the push of a button on the colonoscope head. As such, it is likely to overcome some of the issues encountered with chromoendoscopy and be more acceptable in a busy clinical setting.

#### *1.2.1.2 Computed Tomography (CT)*

Computed tomography (CT) is universally available, easily reproducible and therefore has been the principal investigation in the staging of CRC. It has a potential to visualise the tumour (site, size and infiltration into surrounding structures) in addition to detecting distant metastases. It also plays an important role in both assessing the response to treatment and post-operative disease surveillance.

The main value of pre-operative CT scan is to diagnose metastatic disease rather than accurately measure the depth of local invasion[42-44]. In a recently published meta-analysis examining the diagnostic precision of CT in local staging of colon cancer, the pooled sensitivity, specificity and diagnostic odds ratio (DOR) for differentiating between T1/T2 and T3/T4 tumours were 86% (95% CI 78 - 92%), 78% (95% CI 71 - 84%) and 22.4 (95% CI 11.9 - 42.4) respectively[45]. Identification of malignant lymph nodes also remains poor, with the overall sensitivity and specificity of 70% (95% CI 59 - 80%) and 78% (95% CI 66 - 86%), and DOR of 8.1 (95% CI 4.7 - 14.1)[45].

Generally, all patients with colonic malignancy undergo the same treatment regardless of the local stage of the disease, provided that they are fit for surgery, and any subsequent treatment is dependent on histological assessment of surgical specimen. Patients with rectal cancer, however, can be investigated with additional imaging modalities to increase accuracy of pre-operative staging and several treatment options are available.

### *1.2.1.3 Endoscopic Ultrasound (EUS)*

EUS is selectively used in pre-operative staging of rectal lesions[46-48]. It is usually performed to assess the depth of invasion (T stage), identify those suitable for local excision or even those in whom neo-adjuvant treatment is indicated. In a recent meta-analysis comparing EUS, CT and MRI in staging of rectal cancer, transrectal EUS had the highest sensitivity and specificity, 94% (95% CI 90 - 97%) and 86% (95% CI 80 - 90%) respectively, for assessment of invasion of muscularis propria[49]. Sensitivity and specificity values for nodal involvement however were comparably low for all three modalities 67% (95% CI 60 - 73%) and 55% (95% CI 43 - 67%); 66% (95% CI 54 - 76%) and 78% (95% CI 71 - 84%) and 74% (95% CI 67 - 80%) and 76 % (95% CI 59 - 87%) respectively[49].

In contrast, EUS has not gained widespread use for local staging of colonic lesions because until recently, accurate pre-operative local staging of colonic cancer had no therapeutic consequences. With advances in endoscopic techniques and success of the screening programmes however, accurate staging of colonic lesions has become more relevant. Several authors have reported varying degrees of success with using ultrathin mechanical radial scanning probes that can be passed through a 2.8mm endoscopic channel for assessment of early stage colonic tumours. Akahoshi et al.[50] used a 12 MHz scanning probe in patients with colonic cancer (n = 83) and reported accuracy of 88% for T1 tumours, 64% for T2, 95% for T3 and 100% for T4 colonic lesions respectively. Similar results were reported by Tseng et al.[51], Matsumoto et al.[52] and Stergiou et al.[53] with the overall accuracy for T stage being 85%, 91.4% and 94% respectively. Nodal assessment however remains suboptimal and reported overall accuracy is inconsistent ranging from 24%[52] to 84%[53].

Major limitations of the studies published to date, however, are the small number of patients involved and some authors including patients with rectal or even gastric cancer[50, 51, 54], limiting the validity of the data. The results are operator dependant and technical challenges encountered include limited depth of tissue penetration using high frequency transducers and unsatisfactory water immersion coupling for lesions located at flexures[51]. Although EUS

may have a role in assessment of the depth of the invasion of colonic lesions, at present, low accuracy for nodal assessment limits its role in routine practice even in expert hands. EUS however allows local evaluation of the depth of invasion of rectal lesions and enables identification of patients suitable for local excision.

#### *1.2.1.4 Magnetic Resonance Imaging (MRI)*

In patients with advanced rectal cancer, circumferential extent of the tumour through the rectal wall into the surrounding mesorectum is one of the most important features when considering suitability for total mesorectal excision (TME) or need for extended resection[55]. The relationship between the tumour and the circumferential resection margin (CRM) can be easily assessed with MRI in order to determine if surgery is adequate primary treatment or whether neo-adjuvant therapy should be considered. The largest study reported to date designed to examine the accuracy of MRI in predicting the presence or the absence of tumour at the surgical CRM in patients with rectal cancer is the MERCURY trial[56]. Over 400 participants were recruited prospectively from 12 colorectal units in four European countries. The authors demonstrated that MRI is highly accurate and reproducible in the multicentre setting with specificity of 92% (327/354, 95% CI 90 – 95) for prediction of clear CRM.

### 1.2.2 Principles of surgery for CRC

#### *1.2.2.1 Management of rectal cancer*

The anatomical position of the rectum deep within the pelvis surrounded by pelvic nerves and the associated anal sphincter complex makes surgical management particularly challenging. The factors governing the choice of procedure include local extent of the tumour, proximity to the sphincter, presence of distant metastases and patient co-morbidities. The mesorectal fascia encloses the mesorectum including its associated lymphatic drainage and vasculature, providing a natural boundary for the tumour. The objective of total mesorectal excision (TME), originally described by Heald et al.[57], is to remove the mesorectum and its fascia intact as an *en bloc* specimen containing the cancer

in the middle or lower rectum. This involves identification of the fascial plane followed by meticulous sharp dissection around it both circumferentially and distally. Adoption of this technique reduces the rate of local recurrence and cancer related death[29, 57, 58].

Acquisition of advanced laparoscopic skills and optimisation of surgical technique over the past decade have led to an interest in utilising this approach in patients with rectal cancer. Although laparoscopic procedures for excision of the rectum are regarded as technically demanding, several studies[59-62] have demonstrated short-term benefits of minimally invasive surgery. Despite growing enthusiasm however, laparoscopic proctectomy is not universally accepted due to the lack of good quality data and concerns regarding oncological safety. The UK Medical Research Council trial of conventional *vs.* Laparoscopic-Assisted Surgery in Colorectal Cancer (UK MRC CLASICC)[59] was the first multicentre, randomised controlled trial (RCT) for laparoscopic surgery including patients with rectal cancer and the long-term data were recently published[63, 64]. In the original study[59], the authors reported no difference in short term endpoints between the groups, with a shorter hospital stay observed in the laparoscopic group (median 10 days *vs.* 13 days). A trend towards higher CRM involvement in patients undergoing anterior resection laparoscopically (6% open *vs.* 12% laparoscopic group, p 0.19) raised the possibility that laparoscopic procedure may be associated with an increased risk of local recurrence. At 3-[63] and 5-year[64] follow-up however, this had not translated into an increased incidence of local recurrence and no difference was observed in the overall survival (OS), disease-free survival (DFS) and distant recurrence rates. Although similar findings were reported in a recently published meta-analysis[65], the verdict on laparoscopic rectal cancer surgery is expected upon completion of two large, multicentre RCTs in Europe (COLOR II)[66] and North America (ACOSOG-Z6051)[67] specifically designed to compare outcomes of laparoscopic-assisted and open surgery for rectal cancer.

#### *1.2.2.2 Management of early rectal cancer*

Although TME is the gold standard for treatment of rectal cancer, the benefits of radical surgery are offset by relatively high rate of complications[59], mortality[59] and poor functional

outcomes[68]. Endoluminal therapeutic options are greater in the rectum than in the colon due to easy access and as a result, localised excision (LE) techniques for rectal lesions were developed in parallel with the advent of TME. Parks[69] described a technique for transanal excision of rectal adenomas which has been increasingly used for treatment of selected early rectal cancers. You et al.[70] reported that the rate of LE increased from 26.6% to 43.7% and 5.8% to 16.8% for T1 and T2 cancers respectively in the United States between 1989 and 2003. In the same study, patients undergoing LE had a significantly lower 30-day morbidity when compared to radical surgery (RS) (5.6% *vs.* 14.6%, p <0.001). The major problem with this approach in treatment of rectal cancer however is non-radical resection. The mesorectum and its associated lymph nodes remain intact increasing the risk of understaging and under treatment of nodal disease, and therefore the likelihood of local recurrence and distant metastases.

***Table 1.2 Oncological outcomes of LE according to Parks vs. RS for early rectal cancer***

| Author, year | Type of study | LE *vs.* RS (n) | LR (5-yrs) | OS (5-yrs) |
|---|---|---|---|---|
| **Mellgren et al., 2000[71]** | Retrospective | T1 69 *vs.* 30<br>T2 39 *vs.* 123 | T1 18% *vs.* 0%‡<br>T2 47% *vs.* 10%‡ | T1 72% *vs.* 80%<br>T2 65% *vs.* 81%‡ |
| **Nascimbeni et al., 2004[72]** | Retrospective | T1 70 *vs.* 74 | T1 7% *vs.* 3% | T1 72% *vs.*90%‡ |
| **Ptok et al. 2007[73]** | Prospective | T1 105 *vs.* 312 | T1 6% *vs.* 2%‡ | T1 91% *vs.* 92% |
| **You et al. 2007[70]** | Retrospective | T1 601 *vs.* 493<br>T2 164 *vs.* 866 | T1 13% *vs.* 7%‡<br>T2 22% *vs.* 15%‡ | T1 77% *vs.* 82%<br>T2 68% *vs.* 77%‡ |

***Abbreviations:*** *LE = local excision; RS = radical surgery; LR = local recurrence; OS = overall survival*

*‡statistically significant (p <0.05)*

Local recurrence rates at 5-years reported by You et al.[70] were significantly higher following LE but the OS was comparable between the groups for patients with T1 cancer (Table 1.2). The risk of mortality in this series[70] was influenced by age, high tumour grade and comorbidities rather than the type of surgery. Although this is the largest series published to date, interpretation of the remaining literature is difficult due to the retrospective nature of the

studies reported, patient selection (high risk *vs.* low risk early cancers) and small study samples (Table 1.2).

Utilisation of transanal endoscopic microsurgery (TEMS) has been shown to result in lower recurrence rates compared to LE due to better access and exposure of rectal lesions[74]. During TEMS, the rectum is insufflated with carbon dioxide and special instruments are introduced through airtight ports for sharp dissection under direct vision. The procedure is suitable for lesions located throughout the rectum with the lower border of adenoma between 1cm and 15cm from the anal verge[75]. The margin of normal tissue should be 5mm from the macroscopic tumour edge for benign lesions and 10mm if malignancy is suspected[76]. Serious morbidity and mortality occur in less than 15% [77, 78] and 1.4%[77] respectively, and the reported median hospital stay of three days [78, 79] is significantly shorter than after RS. The 'ideal' rectal tumour for local excision is a small (T1) lesion with invasion confined to the superficial submucosa (sm1) in the absence of adverse histopathological features (poor differentiation, vascular, lymphatic or perineural invasion and tumour and/or budding)[80]. Several comparative series of TEMS *vs.* RS have been reported to date[78, 81] including one small randomised controlled trial[82]. Winde et al.[82] randomised 50 patients with T1 rectal cancer either to TEMS or RS and after a median follow-up of more than 40 months, the local recurrence rate after TEMS was 4.1% compared to 0% in the RS group. Other groups (Table 1.3), in addition to abundance of single or multi-institution case series published to date[77, 83, 84], have reported significantly higher local recurrence rates after TEMS.

The ability to avoid laparotomy and preserve the rectum however, is an attractive treatment option for a select group of patients despite the risk of local recurrence. With the reported incidence of nodal involvement for T1 and T2 lesions of 12.7% and 19% respectively[85], oncological compromise may be acceptable to those with concomitant comorbidity or unwilling to have a temporary or a permanent stoma. Although TEMS may be a definitive treatment for a significant proportion of patients with early disease, the procedure itself results in a large biopsy specimen. If post-TEMS pathology is unfavourable, treatment

options including completion surgery or adjuvant chemoradiotherapy can be carefully discussed.

***Table 1.3 Oncological outcomes of TEMS vs. RS for early rectal cancer***

| Author, year | Type of study | LE *vs.* RS (n) | LR (5-yrs) | OS (5-yrs) |
|---|---|---|---|---|
| **Winde et al. 1996**[82] | RCT | T1 24 *vs.* 26 | T1 4% *vs.* 0% | T1 96% *vs.* 96%‡ |
| **Lee et al. 2003**[81] | Prospective | T1 52 *vs.* 17<br>T2 22 *vs.* 83 | T1 4% *vs.* 0%<br>T2 20% *vs.* 9%‡ | T1100% *vs.*93%<br>T2 95% *vs.* 96% |
| **De Graaf et al. 2009**[78] | Prospective | T1 80 *vs.* 75 | T1 24% *vs.* 0%‡ | T1 75% *vs.* 77% |

***Abbreviations:*** *LE = local excision; RS = radical surgery; LR = local recurrence; OS = overall survival; NS = not specified*

*‡statistically significant (p <0.05)*

### *1.2.2.3 Surgical management of colonic cancer*

Optimal treatment for colonic cancer remains a hemicolectomy with *en bloc* removal of all regional lymph nodes to eliminate the disease and allow accurate staging. Over the past two decades there have been two major developments in elective colonic surgery: the introduction of laparoscopy and enhanced recovery after surgery (ERAS) protocol. The safety and advantages of laparoscopic colectomy for colon cancer have been demonstrated by several RCTs. In a recently published meta-analysis laparoscopic surgery was associated with lower morbidity, less pain, faster recovery and reduced hospital stay without compromising oncological clearance[86]. In addition, the equivalence of medium-term cancer outcomes following open or laparoscopic colonic resection has been demonstrated by several research groups[63, 64, 87, 88]. The long-term follow-up data from the MRC CLASICC trial[89] showed no difference in the OS (78.3% for open *vs.* 82.7% for laparoscopic approach, p 0.780) or DFS (89.5% *vs.* 77.0% respectively, p 0.589) between the two groups. However intraoperative conversion to open surgery was associated with worse outcomes (OS hazard ratio 2.28, p <0.001 and DFS hazard ratio 2.20, p 0.007)[89].

ERAS was pioneered by Henrik Kehlet[90, 91] and developed in parallel with laparoscopic surgery. This 'fast track' perioperative care pathway consists of a multidisciplinary approach involving clinicians, nurses, dieticians and anaesthetists with the aim to reduce surgical stress response and organ dysfunction by promoting faster post-operative recovery with fewer complications. The advantages of ERAS have been demonstrated in several randomised controlled trials[92-94]. The combination of laparoscopic surgery with enhanced recovery in the LAFA trial (LAparoscopy and/or Fast-track multimodal management *vs.* standard care) resulted in a significant reduction in hospital stay when compared to open surgery and standard care (median 5 days *vs.* 7 days, p <0.001)[94]. All treatment groups in this trial had similar morbidity, mortality, reoperation and readmission rates (Table 1.4).

***Table 1.4 Post-operative outcomes of laparoscopic and open colonic cancer surgery with or without ERAS care***

| | Laparoscopic surgery & ERAS | Open surgery & ERAS | Laparoscopic surgery & standard care | Open surgery & standard care |
|---|---|---|---|---|
| **Median (IQR) LOS, days** | 5 (4 – 8) | 7 (5 – 11) | 6 (4.5 – 9.5) | 7 (6 – 13)[‡] |
| **30-day morbidity** | 34.0% | 46.2% | 33.9% | 40.8% |
| **30-day reoperation** | 10.0% | 14.0% | 10.1% | 18.4% |
| **30-day readmission** | 6.0% | 7.5% | 6.4% | 2.0% |
| **Mortality** | 2.0% | 4.3% | 1.8% | 2.0% |

*Vlug et al. 2011*[94]

[‡]*statistically significant (p <0.05)*

Although the provision of laparoscopic service with ERAS programme is more expensive in comparison to standard care, these costs are likely to be counterbalanced by reduction in hospital stay[93, 94]. Provision of laparoscopic surgery for cancer resection in patients suitable for this approach was supported by NICE in 2006, provided that the procedures are undertaken by appropriately trained surgeons[95]. In order to facilitate introduction of laparoscopic colorectal surgery in England in a safe and structured way, the National Training Programme was set up in 2008[96]. This has resulted in a significant increase in the

number of colorectal procedures performed laparoscopically from only 5% in 2006 to 40% in 2012[97].

### 1.2.3 Adjuvant and neo-adjuvant treatment of CRC

#### *1.2.3.1 Radiotherapy in management of rectal cancer*

Treatment strategy for rectal cancer depends on pre-operative MRI assessment of the CRM[56]. Radiotherapy is employed in four main modalities: pre-operative short course neoadjuvant radiotherapy (SCRT) or long course usually with chemotherapy; post-operative regimen when directed by unfavourable histology and palliative treatment for symptom control[98]. A positive CRM is not sufficiently controlled with post-operative treatment[99] and pre-operative regimens are thought to offer several advantages. These include improved response of the target tissue which has not been rendered hypoxic by previous surgery, lower rate of early toxicity and potential downstaging of the tumour resulting in reduction of involved surgical margins and improved sphincter preservation rates[98].

Although the radiation techniques are similar between neoadjuvant SCRT and long course chemoradiotherapy (CRT), the fractionation and timing of surgery differ. Traditionally, the SCRT is delivered in 25Gy over 5 days followed by surgery within 10 days. Neoadjuvant CRT course delivers 45 to 54Gy of radiation over 5 weeks concurrently with chemotherapy (several regimens), followed by surgery 4 to 12 weeks later. These competing approaches have evolved in parallel; SCRT was developed in Northern Europe and long-course CRT in the United States and several European countries.

The Stockholm Colorectal Cancer Study Group (SCCG) conducted two randomised trials (Stockholm I and II)[100, 101] evaluating SCRT *vs.* surgery alone, demonstrating a significant decrease in the incidence of pelvic recurrence (12% *vs.* 25%, $p < 0.001$) and improvement in the OS (45% *vs.* 39%, $p < 0.03$). This trial was followed by the Dutch TME trial[102] where the same design was applied in addition to high quality standardised surgery. The results of this

trial demonstrated a further reduction of local recurrence rate (2.4% *vs.* 8.2%, p <0.001) with no effect on the OS.

Although SCRT is less expensive and more convenient, it offers less downsizing effect as the delay to surgery is short. Pre-operative CRT is indicated when CRM is thought to be threatened or involved on pre-operative imaging. This regimen is more effective at reducing the tumour bulk, making restorative surgery more feasible. The German Rectal Cancer Group[103] assessed the efficacy of pre-operative and post-operative CRT in a randomised study, reporting significantly lower local recurrence (6% *vs.* 13%, p 0.006), increased sphincter preservation rate (39% *vs.* 19%, p 0.004) and fewer acute and long-term side effects following the pre-operative regimen. In a randomised trial by Bujko et al.[104], neoadjuvant CRT resulted in a lower incidence of CRM involvement (4.4% *vs.* 12.9%, p 0.017) and higher rate of complete pathological response (16.1% *vs.* 0.7%) when compared to SCRT. This, however, had no effect on the local recurrence or the OS. The effect of treatment schedules on tumour response, resectability, complications and local recurrence rates are being investigated for both neo-adjuvant regimens[105, 106]. The preliminary results recently published on behalf of the Timing of Rectal Cancer Response to Chemoradiation Consortium suggest that neoadjuvant CRT followed by additional chemotherapy (mFOLFOX-6) and delay in surgery in patients with evidence of clinical response may result in an increase of pathological complete response rate[105].

Several studies[107] have reported complete tumour regression following neo-adjuvant CRT for distal rectal cancer defined as the absence of residual cancer cells in the definitive surgical specimen[108]. This outcome, however, requires a radical procedure associated with a significant risk of morbidity and mortality and its necessity is debated. Patients who exhibit such a profound response to neoadjuvant CRT may represent a distinct group with a particularly favourable outcome. In the absence of tumour on post-treatment endoscopic or MRI assessment, these patients are potential candidates to alternative treatment options such as TEMS or strict surveillance programme alone (watch-and-wait policy)[109] avoiding

surgery altogether. The safety and efficacy of this approach is currently being investigated[110].

### *1.2.3.2 Adjuvant treatment for CRC*

Surgery is the cornerstone of cure of CRC localised to the bowel wall. The benefits of adjuvant treatment with fluorouracil/leucovorin (5-FU/LV) in reducing the risk of relapse and prolonging survival of patients with node positive (Stage III) colon cancer are well established[111, 112]. The MOSAIC[113] study demonstrated that addition of oxaliplatin to 5-FU/LV results in an additional 7% increase in 3-year DFS for stage II and III disease, leading to a 4.2% increment in the OS at 6 years for patients with stage III disease[114].

Adjuvant therapy for patients with stage II disease remains controversial due to the lack of adequately powered RCTs. A subgroup analysis of the MOSAIC trial participants (n = 899) showed that patients with low-risk stage II colon cancer (n = 330) or those over the age 70 (n = 315) do not benefit from additional oxaliplatin[115]. High-risk stage II patients, defined as those with T4 staging, tumour perforation, bowel obstruction, poorly differentiated tumour, venous invasion, or fewer than 10 lymph nodes examined, however, had a significantly improved time to recurrence (hazard ratio 0.62; 95% CI, 0.41 – 0.93; p 0.02) although this did not translate into better OS and DFS rates. In contrast, the results of the QUASAR study[116] showed a small but significant OS gain of 3.6% with a similar benefit for both colon and rectal cancers. Therefore the risks of treatment toxicities need to be carefully weighed against the potential small benefit of adjuvant chemotherapy for patients with Stage II disease.

Although recombinant monoclonal antibodies to epidermal growth factor (cetuximab and panitumumab) and vascular endothelial growth factor (bevacizumab) are licensed for the treatment of metastatic disease, there is a growing interest in applying them in adjuvant and even neoadjuvant settings. Early results of the recently published FOxTROT trial[117] suggest that neoadjuvant therapy (oxaliplatin, 5-FU/LV with or without panitumumab) is associated

with significant downstaging (p 0.04), resulting in fewer incomplete resections (p 0.002) and reduced apical lymph node metastasis (p <0.0001) in patients with locally advanced (T3 and T4) resectable colonic tumours. Two patients in this trial had a complete pathological response and the long-term results are awaited. In addition, recruitment of patients with high-risk stage II and stage III disease for the QUASAR 2 study[118] is now completed. This multicentre RCT was designed to compare the effect of adjuvant capecitabine with bevacizumab *vs.* capecitabine alone at 3-year DFS and the results are currently awaited.

## 1.3 Recent developments

### 1.3.1 Screening for CRC

The lifetime risk for developing CRC in the Western world is approximately 5%. Almost 80% of cancers are thought to arise from benign adenomas and the slow transition from a polyp to a carcinoma makes it one of the most preventable cancers. The aim of CRC screening programmes is to prevent development of advanced disease through detection of adenomas and cancers confined to the bowel wall. Although several screening methods are available, guaiac-based faecal occult blood test (FOBT) is the most extensively studied. A Cochrane review[119] of several randomised trials has provided high quality evidence that when offered biennially, this non-invasive test has the potential to reduce CRC-related mortality by 16%. Colonoscopy, the current gold standard for detection of neoplastic lesions, is recommended if a certain number of test cards are positive. In conjunction with adequate bowel preparation, colonoscopy is safe, accurate and is well tolerated by patients. Polyps detected during the procedure are removed, thereby interrupting the adenoma carcinoma sequence. The further surveillance schedule is arranged depending on histological examination of the specimen[120].

Following the success of other screening programmes, the NHS Bowel Cancer Screening Programme (BCSP) was introduced in 2006 and over 1 million tests have been performed to

date[121]. The results of the pilot study suggested a substantial shift in the diagnosis towards early stage of the disease[122]. Logan et al.[121] subsequently reported that a significant proportion of the screened population are now diagnosed with Stage I and II disease (Table 1.5). In addition, small studies have reported a higher incidence of colonic polyps and adenomas within the BCSP when compared to symptomatic population (47% *vs.* 30% and 79% *vs.* 47% respectively, p <0.005)[123]. Polyps detected through screening are also likely to be larger when compared to symptomatic population[124] requiring more complex endoscopic intervention.

***Table 1.5 Dukes' staging of CRC detected after first investigation of the first million people screened in England***

| | **Males** | **Females** | **Total** | |
|---|---|---|---|---|
| **Polyp cancer** | 114 | 41 | 155 | 9.8% |
| **Dukes' A** | 349 | 154 | 503 | 32.0% |
| **Dukes' B** | 316 | 148 | 464 | 29.5% |
| **Dukes' C** | 272 | 133 | 405 | 25.7% |
| **Dukes' D** | 37 | 10 | 47 | 3.0% |
| **Total** | **1088** | **486** | **1574** | **100%** |

*Logan et al.[121]*

Almost 80% of cancers diagnosed through the NHS BCSP until 2011 were left-sided supporting the need for a national flexible sigmoidoscopy screening programme. Atkin et al.[125] recently published results of the once-only flexible sigmoidoscopy trial with 170,432 participants. The intention-to-treat analysis demonstrated that the incidence of CRC in the intervention group was reduced by 23% (hazard ratio 0.77, 95% CI 0.70 – 0.84) and mortality by 31% (hazard ratio 0.69, 0.59 – 0.82)[125] and similar findings have been reported by other research groups[126-128]. However, when adjusted for self-selection bias, the incidence in participants attending screening was further reduced by 33% and mortality by 43%. As a result, a one-off flexible sigmoidoscopy will incorporated into the national

screening programme in England from 2013 and will be offered to those aged between 55 and 64.

### 1.3.2 Advances in endoscopic techniques

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are advanced endoscopic techniques developed for minimally invasive removal of benign and early malignant lesions with preservation of gastrointestinal wall.

EMR is typically used for removal of flat lesions confined to the muscularis mucosa. The procedure involves injection of a mixture of normal saline, adrenaline and methylene blue dye into the submucosa in order to lift the mucosa (and the polyp) away from the muscle layer. This fluid filled 'safety cushion' facilitates the removal of a flat lesion, minimising the risk of mechanical or thermal damage to the thin colonic wall. The rate of EMR-associated adverse events is low and the most frequently encountered complications are bleeding (range 0.8% - 10.8%)[129, 130] and colonic perforation (range 0% - 3.1%)[129, 131]. The main disadvantage of this technique is that *en bloc* excision can only be performed for lesions smaller than 2cm in diameter (Table 1.6). Larger lesions are removed in a piecemeal fashion instead, compromising the quality of histopathological examination as accurate assessment of the lateral and vertical tumour clearance margins using multiple tissue samples is difficult. In addition, the risk of local recurrence is significantly increased with this approach (Table 1.7).

***Table 1.6 Efficacy of EMR and ESD***

| Author, year | Procedure | No. of polyps | Mean (SD) size of the lesion, mm | En-bloc excision | Completeness of excision |
|---|---|---|---|---|---|
| **Bories et al., 2006**[132] | EMR | 52 | 29.8 | 45% | 98% |
| **Lim et al., 2010**[130] | EMR | 239 | 19.6 (12.4) | 72% | 86% |
| **Yoshida et al., 2012**[133] | EMR | 614 | Median 8.3 (5 – 20) | 94% | 78% |
| **Nishiyama et al., 2010**[134] | ESD | 204 | Median 27.4 (10 – 75) | 87% | 78% |
| **Saito et al., 2010**[135] | ESD | 1111 | 35 (18.0) | 88% | 89% |
| **Saito et al., 2010**[131] | EMR *vs.* ESD | 228 *vs.* 145 | 28 (8.0)<br>37 (14.0) | 33% *vs.* 84%‡ | - |
| **Tajika et al., 2011**[136] | EMR *vs.* ESD | 104 *vs.* 85 | 25 (6.8)<br>31 (9.0) | 48% *vs.* 83%‡ | - |

‡*statistically significant (p <0.05)*

ESD technique was developed in Japan for treatment of early gastric lesions but over the recent years it has been found to be effective for treatment of large colorectal neoplasms. The margins of the lesion are usually marked by electrocautery and a deep submucosal lift is created with injection of a viscous solution such as hyaluronic acid which provides a longer lasting lift[133]. A circumferential incision into the submucosa is performed around the lesion using a specialised needle knife for dissection. Tissue retraction and view of the submucosa are maintained by a transparent cap that is attached to the tip of the endoscope. The effectiveness of this approach is therefore less limited by the size of the lesion or its configuration. Deeper excision results in a specimen of superior quality when compared to piecemeal EMR[114, 118], reducing the risk of local recurrence (15.4 *vs.* 2.0, p 0.002)[136] at the expense of higher complication rates (Table 1.7). In addition, intact specimen enables thorough histopathological evaluation of the depth of invasion as well as assessment of lateral margins.

***Table 1.7 Complications associated with EMR and ESD***

| Author, year | Procedure | Median (SD) duration of the procedure, min | Bleeding | Perforation | Recurrence |
|---|---|---|---|---|---|
| **Conio et al., 2004**[129] | EMR | - | 10.8% | 0% | 21.9% |
| **Bories et al., 2006**[132] | EMR | - | 5.8% | 2.0% | 15.0% |
| **Lim et al., 2010**[130] | EMR | - | 0.8% | 0.8% | 20.1% |
| **Yoshida et al., 2012**[133] | EMR | 2.1 (1.5) | 1.1% | 0% | - |
| **Nishiyama et al., 2010**[134] | ESD | - | 1.0% | 9.8% | 0% |
| **Saito et al., 2010**[135] | ESD | 116 (88.0) | 1.5% | 4.9% | - |
| **Saito et al., 2010**[131] | EMR *vs.* ESD | 29 (25.0) *vs.* 108 (71.0)‡ | 3.1% *vs.* 1.4% | 1.5% *vs.*% | 14.0% *vs.* 2.0%‡ |
| **Tajika et al., 2011**[136] | EMR *vs.* ESD | 29.4 (26.1) *vs.* 87.2 (49.7) | 2.9% *vs.* 2.4% | 0% *vs.* 5.9%‡ | 15.4% *vs.* 2.0% ‡ |

*‡statistically significant (p <0.05)*

Both procedures offer a less invasive, alternative treatment option when compared to standard surgery. Unlike TEMS, EMR and ESD require sedation only and are associated with fewer complications[137, 138]. To date, only one study comparing the effectiveness of ESD *vs.* laparoscopic resection of early colorectal cancer has been published. Kiriyama et al.[139] reported a retrospective review of 297 colorectal ESD procedures and 292 laparoscopic colorectal resections performed for treatment of T1 cancers. The tumour size in the ESD group was larger (37mm *vs.* 20mm, p <0.001) but the procedure time, hospital stay and complication rate were significantly lower when compared to laparoscopic surgery[139]. In addition, 3-year survival rates of 99.2% and 99.5% respectively were comparable. Although these results question the role of radical surgery in treatment of early CRC, the risk of residual disease (intramural or nodal) has to be considered. Gill et al.[140] recently published the outcomes of patients diagnosed with malignant colorectal polyps on behalf of the Northern Colorectal Cancer Audit Group. Of the 184 patients managed by polypectomy at

the initial procedure: 71 (38.6%) had subsequent surgery and residual tumour at the polypectomy site was found in nine (12.7%) patients, with four (5.6%) having positive lymph nodes alone.

### 1.3.3 Development of localised excision techniques for colonic lesions

The majority of the colonic polyps diagnosed during diagnostic colonoscopy are suitable for EMR or ESD. Both however, require good visualisation of the lesion and maintenance of a stable position throughout the polypectomy. Difficulties are encountered with large colonic adenomas or those located behind a mucosal fold, and although endoscopic intervention may still be viewed as an option, obtaining a good view to snare the polyp safely can be challenging. The perceived risk of uncontrollable bleeding, perforation and incomplete resection may prevent an attempt at polypectomy and traditionally, these patients are referred for hemicolectomy.

In parallel with the advances in laparoscopy, a number of published series have described laparo-endoscopic approaches for lesions with benign pre-operative histology. Several combinations of laparo-endoscopic 'rendezvous' procedures have been described including laparoscopically assisted endoscopic polypectomy (LAEP), endoscopically assisted wedge or transluminal resection (EAWR and EATR respectively) and endoscopically assisted segmental resection (EASR)[141-145]. LAEP is the least invasive procedure, indicated when the view of the lesion is limited either due to the tortuous colon or for lesions at acutely angulated locations. Laparoscopic mobilisation of flexures or adhesions facilitates the passage of the endoscope towards the previously inaccessible polyp. Furthermore, applying two points of fixation using laparoscopic graspers can facilitate straightening and rotation of the colonic segment[146], optimising intraluminal exposure of the polyp. Standard endoscopic polypectomy is performed using electrosurgical snare and the serosal surface inspected throughout the procedure for changes suggestive of thermal damage. In the event of an injury, the breach can be controlled laparoscopically either by placement of sutures or application of a linear stapling device.

In cases where LACP is not feasible, EAWR can be performed using a laparoscopic linear stapler. The lesion is visualised endoscopically to ensure complete excision and advancing the endoscope beyond the resection area protects the lumen during wedge resection. This is particularly relevant for caecal polyps where utilisation of endoscopy intra-operatively ensures that the ileo-caecal valve is protected during stapling[147]. Colonic lesions located near the mesentery, however, are not suitable for this approach and laparoscopic colotomy is performed instead with endoscopic guidance (EATR)[141]. The bowel segment is exteriorised though a mini-laparotomy and the colotomy site is closed either by laparoscopic sutures or application of laparoscopic stapling device. Endoscopic assistance is valuable for both approaches as it ensures completeness of excision and that the suture line does not leak[144]. EASR can also be used for lesions unsuitable for any of the aforementioned techniques, but endoscopic assistance was also utilised for lesion localisation prior to routine use of colonic tattooing. The term EASR is used interchangeably for a limited segmental resection and formal hemicolectomy with *en bloc* mesenteric resection.

Although these approaches are technically demanding, the advantages over standard surgical resection are obvious. The LACP maintains integrity of the colonic wall and mesenteric blood supply, potentially avoiding surgery in over 80% of patients (Table 1.8). However most benign polyps that require surgery do so because of their size and therefore carry a risk of containing a focus of malignancy[148]. Franklin et al.[143] performed frozen section on all LACP specimens so that definitive surgery could be performed during the same procedure in the presence of invasive malignancy. The authors recently published their long term outcomes concluding that LACP performed for 209 polyps is a safe and efficient procedure with short hospital stay and low recurrence rates[149]. Clinical applicability of EAWR and EATR however is yet to be demonstrated. Tangential excision during EAWR cannot guarantee adequate lateral tumour clearance margin even with endoscopic assistance, whereas the risk of seeding of malignant cells during EATR is a concern. These issues could potentially explain the low uptake of these procedures.

*Table 1.8 Results of laparo-endoscopic procedures for colonic lesions*

| Author, year | No. patients | No. polyps | Procedures | Surgery avoided | Median (range) LOS, days | Complications | Malignancy | Recurrence |
|---|---|---|---|---|---|---|---|---|
| **Feussner et al., 2003**[141] | 75 | 80 | 9 LAEP<br>28 EAWR<br>22 EATR<br>21 EASR | 56 (74%) | 6 (1-18) | 6 (8.0%) | 7 (9.3%) | - |
| **Winter et al., 2007**[142] | 38 | 38 | 8 LACP<br>23 EAWR<br>2 EATR<br>5 EASR | 33 (87%) | 4 (2 - 9)<br>8 (2 – 39) | 2 (5.3%) | 5 (13.2%)‡ | 2 metastatic disease |
| **Franklin et al., 2007**[143] | 110 | 149 | 130 LACP<br>1 EATR<br>18 EASR | 98 (89%) | LAPC average 1.14<br>EASR average 5 | 4 (3.6%) | 11 (10.0%) | - |
| **Wilhelm et al., 2009**[144] | 146 | 154 | 8LACP<br>72 EAWR<br>40 EATR<br>26 EASR | 121 (83%) | 8 (3 – 35) | 36 (24.7%) | 17 (12.0%) | 1 adenoma<br>2 metastatic disease |
| **Wood et al., 2011**[145] | 16 | 16 | 9 LACP<br>4 EASR | 12 (75%) | 2 | 2 (13.0%) | 1 (6.3%) | - |

‡*Advanced disease was diagnosed in two patients prior to surgery*

### 1.3.4 Feasibility of sentinel lymph node mapping in CRC

Standard surgical treatment for colon cancer remains hemicolectomy with *en bloc* mesenteric resection of the regional lymph nodes, as metastatic status of these nodes remains the most important factor for determining adjuvant treatment. This of course was appropriate when approximately 90% of patients diagnosed with CRC presented with symptomatic, locally advanced disease[122]. In the view of the recently published data from the screening programmes however, many have started to question whether radical resection is the 'best' treatment option for this group of patients and an appropriate use of healthcare resources. The reported incidence of nodal disease in patients with T1 and T2 colon cancer is 5% and 19% respectively[150] and therefore lymphadenectomy provides no additional therapeutic benefit for over 80% of patients with original diagnosis of Stage I disease. Provided that nodal negativity could be assured prior or during surgery, the operative extent of surgery could potentially be reduced considerably.

SLN mapping technique is based on the principle that the first possible sites of metastasis along the lymphatic drainage route from the primary lesion are known as sentinel lymph nodes (SLNs). The nodes can be identified using injection of dyes, radioisotopes or a combination of both. Following this, the nodes are evaluated by multilevel sectioning and immunohistochemistry for metastases that might have otherwise been missed by conventional methods. Evaluation of the SLNs can result in an accurate assessment of the nodal status in the entire lymphatic basin and as such enables identification of node-negative patients with melanoma, breast and more recently gastric cancer[151-154], sparing them the morbidity of lymphadenectomy. Its feasibility and diagnostic accuracy in patients with CRC however remains unclear mainly due to the high false negative rates (Table 1.9). In a recently published meta-analysis[155] including 52 studies, the overall sensitivity rates for both colonic and rectal cancer were low (86% and 82% respectively) regardless of T stage,

*Table 1.9 Feasibility of SLN mapping in CRC*

| Author, year | No. patients | Tumour location | Stage of the disease | | | | | Detection | Accuracy | Sensitivity | False negative |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Tis | T1 | T2 | T3 | T4 | | | | |
| **Wood et al., 2002**[145] | 100 | Colon 88%<br>Rectum 22% | 0 | 25 | 23 | 46 | 6 | 97% | 95% | 92% | 8% |
| **Kitagawa et al., 2002**[156] | 56 | Colon 21%<br>Rectum 79% | Data not provided | | | | | 91% | 92% | 82% | 18% |
| **Braat et al., 2004**[157] | 35 | Colon 100% | 0 | 6 | 20 | 51 | 23 | 94% | 97% | 91% | 9% |
| **Saha et al., 2006**[157] | 500 | Colon 82%<br>Rectum 18% | 15 | 11 | 16 | 52 | 5 | 98% | 96% | 90% | 10% |
| **Bilchik et al., 2006**[158] | 132 | Colon 72%<br>Rectum 28% | 0 | 17 | 15 | 65 | 3 | 100% | 95% | 88% | 12% |
| **Stojadinovic et al., 2007**[159] | 84 | Colon 100% | 6 | 7 | 20 | 65 | 2 | 98% | 90% | 69% | 31% |
| **Bembenek et al., 2007**[160] | 315 | Colon 100% | Data not provided | | | | | 85% | 86% | 54% | 46 |

tumour localisation or histological technique utilised. Others however have suggested that the outcomes are significantly affected by the study design, tumour stage and size, patient selection and variation in surgical experience[150, 161, 162]. Mapping agents utilised in the previous studies are not ideal. Blue dyes are difficult to localise in patients with a high body mass index (BMI), who unfortunately comprise a large proportion of our patient population, thus producing only limited (if any) visualisation of the afferent lymphatic vessels and SLN(s). Radioactive colloids require involvement of a nuclear medicine physician and lack the ability to visualise the nodes and lymphatic channels in real time. In addition, signal interference occurs if the SLN(s) is too close to the injection site. Some authors[150, 161] advocate that the procedure might be more effective in patients with early stage colonic cancer as in advanced disease nodes are replaced by tumour forcing lymphatic drainage to take alternative routes and therefore increasing the false negative rates. In order to address some of the aforementioned issues a number of researchers have utilised optical imaging using the near-infrared (NIR) fluorescence lymphatic tracer indocyanine green (ICG) that enables real-time intraoperative visualisation of lymphatic channels and SLNs with promising results[163-165].

Traditionally, the role of SLN mapping in CRC was not to minimise the operative extent, but to identify lymph nodes situated outside the standard operative field or metastases overlooked by traditional histopathological assessment. Adjuvant chemotherapy is not usually offered to patients with node-negative disease, however approximately 30% of all apparently pN0 CRC patients develop loco-regional and/or distant recurrence[166]. Utilisation of SLN mapping would enable application of ultra-sectioning techniques on a select group of lymph nodes most likely to harbour metastases with the potential to upstage approximately 15% of patients[155]. Although the prognostic impact of micrometastases and occult tumour cells (OTC) is still unclear, some studies have suggested that they may have a negative impact on the OS[167, 168]. Recruitment into the EnROUTE study[166] designed to delineate a

subset of pN0 patients with micrometastases ($pN0_{micro+}$) and evaluate the benefits from adjuvant chemotherapy is currently on-going.

## 1.4 Summary

Treatment of CRC is complex. At present, good pre-operative staging and minimally invasive treatment options are available for patients with large rectal polyps and early rectal cancer. Localised excision techniques for treatment of rectal lesions are associated with lower morbidity, mortality and hospital stay and are being increasingly utilised as definitive treatment for a select group of patients. The equivalent treatment options for patients with complex, early colonic lesions are limited and further developments in surgical techniques and technology as well as local staging are necessary to improve outcomes in this patient group.

# Chapter 2 Aims of work presented in this thesis

## 2.1 Clinical problem

Almost 50% of patients diagnosed through screening have Stage I CRC of which approximately 80% have node-negative disease. In addition, the screened population tends to present with higher number of complex benign polyps[123, 124].

The availability of minimally invasive therapeutic approaches such TEMS, EMR and ESD in addition to pre-operative chemoradiotherapy enable clinicians to present treatment options other than proctectomy to patients diagnosed with certain rectal lesions. Although the risk of invasion increases with the size of the polyp, localised excision can be a definitive treatment for a significant proportion of these patients without a considerable risk of morbidity, mortality and protracted recovery period[169].

Endoluminal treatment options for colonic lesions however are limited. Histological examination of the specimen following piecemeal EMR is challenging and the procedure is associated with relatively high polyp recurrence rates. ESD requires high level of expertise to correctly perform submucosal dissection and promptly control any procedure related complications[170]. In addition to the limited experience of Western endoscopists, the procedure is not adequately reimbursed at present time[171] making it difficult to assess its cost-effectiveness. For lesions unsuitable for endoscopic treatment, hemicolectomy with *en bloc* mesenteric excision is generally the only surgical treatment option available. Approximately 2 000 patients per year in England alone undergo surgery for benign colorectal polyps[172] and the number is likely to increase following implementation of the national one-off flexible sigmoidoscopy programme. In addition, data for short- and long-term outcomes following surgery are poorly documented and if similar to those following colonic cancer resections, the risks are quite significant. The need for a less invasive treatment

option for treatment of benign colonic lesions and node-negative colon cancer is becoming increasingly clear.

## 2.2 Hypothesis

The aim of the work in this dissertation was to examine the hypothesis that localised full thickness excision of colonic lesions is a feasible and safe alternative to hemicolectomy.

### 2.2.1 Clinical studies

The clinical studies began with the review of patients undergoing surgery for benign colonic polyps to determine their short-term outcomes when compared to patients with colon cancer (Chapter 3). This was a retrospective, case matched study from two institutions.

In the second study (Chapter 4), a retrospective analysis of the Health Episodes Statistics (HES) database was conducted with the aim to compare short-term outcomes following colorectal resection for benign polyps with those performed for CRC at a national level. Access to a large number of patients is likely to provide data that more accurately reflect current practice than data from single institutions.

The aim of the third study (Chapters 5) was to determine the effects of hemicolectomy on patients' bowel function and related quality of life in a prospective manner when compared to healthy controls. If the effect is significant, the results of the study would not only improve consent process for patients undergoing surgery, but it would also add impetus to the development of alternative treatment options for those with localised colonic disease.

### 2.2.2 Laboratory studies

The first chapter in the second part of this dissertation (Chapter 6) is a systematic review of localised full thickness resection techniques for colonic lesions described to date. This systematic review includes the inversion full thickness excision technique previously

described at St. Mark's Hospital and Northwick Park Institute for Medical Research (NPIMR)[173].

In Chapter 7, the laboratory experiments were set out to assess technical deficiencies in the previously described inversion technique in order to determine whether the procedure time and the size of the excised specimen could be improved in comparison to the original study. In chapter 8 of the thesis, further experiments aimed to describe *ex vivo* development of the inversion Full thickness Laparo-endoscopic EXcision (FLEX) technique to the eversion technique are presented. Finally, a survival study in porcine models is described in Chapter 9 with the aim to assess the feasibility and safety of the modified eversion FLEX technique *in vivo*.

# Chapter 3 Short-term outcomes after hemicolectomy for benign colonic polyps: a prospective case-matched study

## 3.1 Introduction

Colonoscopic polypectomy is a definitive treatment for the majority of colonic adenomas encountered in routine practice. It is associated with low morbidity and mortality, and is usually performed as an outpatient procedure. The effectiveness of this approach however may be limited for complex colonic lesions defined as: those exceeding 3cm in diameter, located at colonic flexures, crossing two haustral folds or two thirds of the circumference, or those with suspicious morphology. Increased risk of complications, incomplete resection and recurrence associated with polypectomy procedures must be carefully weighed against the disadvantages of surgery. Due to the risk of malignant transformation or the chance that the polyp may contain invasive malignancy even in the context of negative biopsy, a large proportion of these patients is referred for definitive surgery.

In parallel to developments in laparoscopy and advanced endoluminal therapies, several laparo-endoscopic hybrid procedures have been described[142-144] as potential alternatives to laparotomy. Their clinical application however is limited to few centres only, most likely due to the fact that the risk of incidental malignancy in such lesions is reported to be up to 18%[174-176]. Instead, laparoscopic hemicolectomy has become a treatment of choice for patients with colonic polyps unsuitable for endoscopic management. Routine use of endoscopic tattooing improves intraoperative localisation regardless of the size of the lesion whereas short- and long-term benefits of the laparoscopic approach over laparotomy for cancer resections are well documented[86, 89, 177]. Although several small studies have been published looking specifically at patients undergoing colectomy for unresectable polyps, their focus has mainly been on the feasibility of laparoscopic approach, tumour localisation and

incidence of invasive carcinoma[174-176, 178]. Short-term outcomes of these patients in comparison to those undergoing laparoscopic resections for malignancy have not been reported to date.

The study described in this chapter was designed to compare 30-day outcomes of patients undergoing hemicolectomy for the treatment of complex benign colonic polyps to those undergoing comparable cancer resections. The primary outcomes in this study were morbidity, mortality, reoperation, readmission rates and the length of stay (LOS). Other outcomes recorded were duration of the procedure, intra-operative blood loss, size of the excised specimen and the lesion following fixation in formalin.

## 3.2 Methods

### 3.2.1 Patient selection

Consecutive patients who underwent surgery for benign colonic polyps were identified from prospectively maintained surgical databases at two teaching hospitals, St. Mark's Hospital, London, England and Beaumont Hospital, Dublin, Ireland. The study was conducted following appropriate departmental approval in each hospital. Both centres are tertiary referral centres for endoscopy. Data from the hospital in Ireland were collected during a period between September 2010 and October 2012. The database in the English centre was commenced in March 2006 and patient details were recorded prospectively until October 2012. In order to identify missing patients in the hospital with the longest data collection period, the hospital clinical coding system was searched for surgical procedures using the Office of Population Consensus and Surveys Classification of Surgical Operations and Procedures fourth revision (OPCS-4)[169] in addition to the terms 'benign', 'elective', and consultant codes. Procedure categories and respective OPSC-4 codes were as follows: right hemicolectomy: H07; extended right and transverse colectomy: H06 and H08, respectively;

left hemicolectomy: H09; sigmoid colectomy: H10 and anterior resection: H33.2/H33.3/H33.4/H33.8/H33.9)[169].

### 3.2.2 Eligibility criteria and matching process

In order to evaluate clinical outcomes of patients with truly benign disease, only patients diagnosed with a benign colonic adenoma on histological evaluation of the surgical specimen were selected for the study. Patients with rectal lesions, synchronous lesions, inflammatory bowel disease or those with a polyposis syndrome were excluded from the study.

Once all suitable patients were identified, we attempted to match each patient undergoing surgery with two consecutive patients having resections for malignancy (IUCC Stage I to III) from prospectively maintained colorectal cancer databases in the respective institutions. Patients with disseminated disease or those undergoing palliative surgery were excluded. Matching criteria used were age (+/-5 years), sex, ASA grade, surgical procedure and resection type (laparoscopic/open/converted).

### 3.2.3 Data collection

Data were collected from case notes, endoscopy and pathology reports for all patients. Dataset included the following: gender, height and weight, endoscopic location/appearance of the polyp, pre-operative and post-operative histology, details of intra-and post-operative care, LOS, 30-day complications, readmission and reoperation details. Both the endoscopy report and case notes were consulted to establish the reason for surgery. Post-operative complications were classified using the Claiven-Dindo classification of surgical complications[179]. The complications are graded I to V and the risk and invasiveness of the therapy used to correct a specific complication is the cornerstone to rank the complication.

### 3.2.4 Statistical analysis

To account for the case matched design of the study, all analyses were performed using multilevel statistical methods with input from a medical statistician. Multilevel linear

regression was used to compare continuous variables between the groups and multilevel logistic regression was used for binary variables. Log transformation was performed for continuous variables with skewed distribution prior to analysis. All outcomes were adjusted for potentially confounding variables. Where possible, further analyses were performed to adjust for potential confounding demographic factors not accounted for during the matching process.

## 3.3 Results

### 3.3.1 Patient characteristics

A total of 57 patients met our inclusion criteria and 46 were successfully matched with one or two patients who underwent surgery for colonic cancer for all the matching criteria. Eleven patients were not eligible for the study for the following reasons: no suitable matching patients available (n = 6), colotomy or wedge excision performed (n = 2), surgery performed in a different hospital (n = 1), extensive surgery performed due to diverticular disease (n = 1) and case notes not available (n = 1). Patients were operated on by one open (PM) and two experienced laparoscopic surgeons at St. Mark's Hospital, London, RHK (n = 28) and JTJ (n = 5), and one surgeon in the Irish centre (RC, n = 12). A bowel cancer screening programme was available in the English centre only and 12/34 patients (35%) were detected through screening. Mean age of patients with benign colonic polyps was 63.7 years (SD 8.9) with five patients (11%) under the age of 60, 24 (52%) patients 60 to 70 years of age, 13 (28%) patients 70 to 80 years of age and three patients (7%) over 80 years of age. There was no significant difference between the groups for body mass index (BMI) or history of previous abdominal surgery (Table 3.1).

*Table 3.1 Pre-operative characteristics of patients in both groups*

| | Patients with benign colonic polyps (n = 46) | Patients with colonic cancer (n = 81) | P |
|---|---|---|---|
| **Gender** | | | |
| **Male** | 28 (61%) | 49 (60%) | (*) |
| **Female** | 18 (39%) | 32 (40%) | |
| **Mean (SD) age, years** | 67.3 (8.9) | 67.9 (8.4) | (*) |
| **Mean (SD) BMI** | 28.0 (4.9) | 27.0 (3.9) | 0.11 |
| **ASA** | | | |
| **I** | 16 (35%) | 24 (30%) | (*) |
| **II** | 25 (54%) | 47 (58%) | |
| **III** | 5 (11%) | 10 (12%) | |
| **Previous abdominal surgery** | 15 (33%) | 26 (32%) | 0.66 |

*(*) No formal statistical comparison made as part of the matching criteria*

### 3.3.2 Lesion characteristics

On pre-operative histological evaluation, five lesions (11%) were tubular adenomas, three (7%) were villous, 34 (74%) were tubulovillous, two (4%) were serrated and two (4%) were adenomas not specified. Of 46 patients, 10 (22%) had high-grade dysplasia, 11 (24%) had moderate and 20 (44%) had low-grade dysplasia. Histological features were similar in the final surgical specimen (Table 3.2). The majority of the polyps were sessile lesions located in the right side of the colon (61%). The size of the polyps was poorly documented in endoscopy reports and therefore the size of the lesion documented in histopathology reports was collected instead.

The median size of the lesion following fixation of the surgical specimen was 4cm (IQR 2.5, 5.4). Over 50% of patients referred for surgery had polyps exceeding 3.5cm in diameter and the most common indication for surgery were the size of the lesion (31%), difficult anatomical position (26%) and suspicious endoscopic or histological findings (26%). A small proportion of resections (15%) were performed for polyps smaller than 2.5cm in diameter, all of which were difficult to access and were therefore deemed unsuitable for endoscopic therapy.

*Table 3.2 Polyp characteristics*

| | Pre-operative | Post-operative |
|---|---|---|
| **Pre-operative histology** | | |
| **Tubulous adenoma** | 5 (11%) | 6 (13%) |
| **Villous adenoma** | 3 (7%) | 4 (9%) |
| **Tubulovilous adenoma** | 34 (74%) | 35 (76%) |
| **Serrated adenoma** | 2 (4%) | 1 (2%) |
| **Not available** | 2 (4%) | 0 (0%) |
| **Dysplasia** | | |
| **None** | 4 (9%) | 0 (0%) |
| **Low grade** | 20 (44%) | 13 (28%) |
| **Moderate** | 11 (30%) | 8 (17%) |
| **High/Severe** | 10 (22%) | 12 (26%) |
| **Not available** | 1 (2%) | 13 (28%) |

*Table 3.3 Pre-operative polyp characteristics*

| | Lesion n |
|---|---|
| **Endoscopic location** | |
| **Caecum** | 19 (41%) |
| **Ascending colon** | 6 (13%) |
| **Hepatic flexure** | 1 (2%) |
| **Transverse colon** | 3 (7%) |
| **Splenic flexure** | 3 (7%) |
| **Descending colon** | 4 (9%) |
| **Sigmoid** | 10 (22%) |
| **Morphology** | |
| **Sessile** | 34 (74%) |
| **Pedunculated** | 8 (17%) |
| **Not recorded** | 4 (9%) |
| **Indication for surgery** | |
| **Polyp size** | 14 (31%) |
| **Difficult anatomical position** | 12 (26%) |
| **Incomplete removal** | 4 (9%) |
| **Recurrent polyp** | 2 (4%) |
| **Suspicious +/- high grade dysplasia** | 12 (26%) |
| **Not clear** | 2 (4%) |
| **Polyp size (maximum dimension) on post-operative specimen** | |
| **<2.5cm** | 7 (15%) |
| **2.5 – 3.4cm** | 13 (28%) |
| **3.5 – 4.4cm** | 5 (11%) |
| **4.5 – 5.4cm** | 8 (17%) |
| **>5.5cm** | 11 (24%) |
| **Unavailable** | 2 (5%) |

### 3.3.3 Surgical outcomes

Right hemicolectomy was the most commonly performed surgical procedure (63%), followed by sigmoid colectomy (22%) and left hemicolectomy (15%). The majority of the procedures were laparoscopic (91%) and two cases (4%) were converted to open procedure due to either poor view of the splenic flexure or adhesions (Table 3.4). No intra-operative complications were encountered. Blood loss was slightly higher for patients undergoing cancer surgery (40ml *vs.* 25ml, p 0.01) however no difference was observed in the procedure duration between the two groups (p 0.67).

***Table 3.4 Operative details***

| | **Patients with benign colonic polyps (n = 46)** | **Patients with colonic cancer (n = 81)** | **P** |
|---|---|---|---|
| **Side of resection** | | | |
| **Right** | 29 (63%) | 52 (64%) | (*) |
| **Left** | 17 (37%) | 29 (36%) | |
| **Operation** | | | |
| **Laparoscopic** | 42 (92%) | 76 (94%) | |
| **Open¥** | 2 (4%) | 3 (4%) | (*) |
| **Converted** | 2 (4%) | 2 (2%) | |
| **Median (IQR) blood loss, ml** | 25 (0,80) | 40 (20, 90) | **0.01** |
| **Median (IQR) operation time, minutes** | 180 (125, 215) | 180 (140, 200) | 0.67 |
| **Median (IQR) length of excised specimen (right), cm** | 34 (17, 43) | 38 (22, 50) | **<0.001** |
| **Median (IQR) length of excised specimen (left), cm** | 29 (22, 40) | 26 (24, 39) | 0.42 |

*(*) No formal statistical comparison made as part of the matching criteria*

*(¥) One patient chose to have an open procedure and the second patient was operated on by a surgeon who only practices open surgery*

Surgical specimens were slightly longer in patients undergoing right sided resections for malignancy (38cm *vs.* 34cm, p <0.001) although no difference between the groups was observed for left-sided resections. Principles of ERAS were followed for all patients during the post-operative period[93].

In the unadjusted analysis the LOS was similar between the two groups with a median of 5.5 days (IQR 4, 8) for the benign group and 5 days (IQR 3, 6) for the colon cancer group (Table 3.5). Following multilevel linear regression with adjustment for confounding variables (blood loss, size of the excised specimen) however, hospital stay was significantly shorter following cancer surgery (ratio 1.25, 95% CI 1.02, 1.56, p 0.04). The overall rate of complications was 46% (21/46) and 31% (25/81) respectively and the difference between the groups was not statistically significant (OR 2.11, 95% CI 0.82, 5.41). Some patients developed more than one complication during the post-operative period and the majority were minor (Clavien Dindo[179] Grade II, 81% and 71% respectively) (Table 3.5). The most common complication was post-operative ileus (nine and eight patients respectively) followed by wound infection (five and four patients respectively) (Table 3.6).

***Table 3.5 Surgical outcomes***

| Outcome | n | Unadjusted(*) | | Adjusted(**) | |
|---|---|---|---|---|---|
| | | OR (95% CI) | P | OR (95% CI) | P |
| **Median (IQR) LOS, (days)(†)** | | | | | |
| **Cancer** | 5 (3, 6) | 1 | | 1 | |
| **Benign Polyps** | 5.5 (4, 8) | 1.17 (0.97, 1.42) | 0.10 | 1.26 (1.02, 1.56) | **0.04** |
| **Complications** | | | | | |
| **Cancer** | 25 (31%) | 1 | | 1 | |
| **Benign Polyps** | 21 (46%) | 1.89 (0.88, 4.08) | 0.10 | 2.11 (0.82, 5.41) | 0.12 |
| **Reoperations** | | | | | |
| **Cancer** | 1 (1%) | 1 | | | |
| **Benign Polyps** | 4 (9%) | 7.62 (0.83, 70.3) | 0.07 | (#) | |
| **Readmission** | | | | | |
| **Cancer** | 2 (2%) | 1 | | | |
| **Benign Polyps** | 3 (7%) | 2.76 (0.44, 17.1) | 0.28 | (#) | |

*(*) Analysis accounts for all matching variables (age, sex, ASA score, side & type of resection)*

*(**) Further adjusted for, blood loss and size of the excised specimen*

*(†) Differences in outcome between groups are presented as ratio (95% CI)*

*(#) Adjusted analysis not performed due to insufficient occurrences of outcome*

*Table 3.6 Post-operative complications*

| | Patients with benign colonic polyps (n = 21/46) | Patients with colonic cancer (n = 25/81) |
|---|---|---|
| **Clavien Dindo Classification** | | |
| **I** | 1 (4%) | 6 (21%) |
| **II** | 21 (81%) | 20 (71%) |
| **IIIb** | 4 (15%) | 1 (4%) |
| **IVa** | 0 (0%) | 1 (4%) |
| **Total** | **26 (100%)** | **28 (100%)** |
| **Complications*** | | |
| **Ileus** | 9 | 8 |
| **Wound infection** | 5 | 4 |
| **Anastomotic leak** | 4 | 1 |
| **Pneumonia** | 2 | 2 |
| **Unexplained fever/raised inflammatory markers (normal CT)** | 1<br>1 | 2<br>2 |
| **Atrial fibrillation** | 1 | 1 |
| **Adhesive small bowel obstruction** | 1 | 0 |
| **Acute coronary syndrome** | 1 | 0 |
| **Bleeding per rectum** | 1 | 0 |
| **Laryngeal ulcer** | 0 | 1 |
| **Urinary tract infection** | 0 | 1 |
| **Ischaemic stroke** | 0 | 1 |
| **Unexplained tachycardia** | 0 | 1 |
| **Bradycardia** | 0 | 1 |
| **Right bundle branch block** | 0 | 1 |
| **Port haematoma** | 0 | 1 |
| **Non-infectious diarrhoea** | 0 | 1 |
| **Anaemia requiring transfusion** | 0 | 1 |

*(*) Some patients had more than one complication*

***Table 3.7 Demographic details of patients with anastomotic leak***

| Patient | Histology | Age | ASA | BMI | Procedure | Reason for surgical referral | Pre-operative histology (benign patients) | Post-operative histology (benign patients) | Size of the lesion (benign patients) |
|---|---|---|---|---|---|---|---|---|---|
| **1** | Benign | 67 | 2 | 38.2 | Lap right hemicolectomy | Polyp in a difficult anatomical position | TVA with low-grade dysplasia | TVA with low-grade dysplasia | 5cm |
| **2** | Benign | 83 | 3 | 38.0 | Lap sigmoid colectomy | Suspicious polyp in a difficult anatomical position | TVA with high-grade dysplasia | TVA with high-grade dysplasia | 2cm |
| **3** | Benign | 66 | 1 | 28.0 | Lap sigmoid colectomy | Polyp in a difficult anatomical position | TVA with moderate dysplasia | TVA with moderate dysplasia | 10cm |
| **4** | Benign | 69 | 2 | 23.0 | Lap sigmoid colectomy | Incomplete excision of TVA with high grade dysplasia | TVA with high grade dysplasia | TVA with high grade dysplasia | 4cm |
| **5** | Cancer | 75 | 3 | 21.9 | Lap sigmoid colectomy | Carcinoma | NA | NA | NA |

***Abbreviations:*** *TVA = tubulovillous adenoma*

Anastomotic leakage occurred in four (9%) patients with benign pathology and one (1%) patient in the colonic cancer group (OR 7.62, 95% CI 0.83, 70.3, p 0.07) (Table 3.7). All patients had International Classification grade C leakage[180], defined as requiring a laparotomy. Three patients (7%) in the benign group were readmitted to hospital within 30 days of the initial surgery for: unexplained fever (normal CT scan, treated with empirical antibiotics); adhesive bowel obstruction (treated conservatively); anastomotic leak (surgery). Two patients (2%) in the colon cancer group were readmitted for adhesive bowel obstruction (treated conservatively) and anastomotic leakage (Hartmann's procedure). No deaths were observed in either group.

## 3.4 Discussion

With the improvements in technology and experience gained over the past decade, laparoscopic hemicolectomy performed within an enhanced recovery protocol has become the gold standard surgical treatment for complex colonic polyps. In the absence of a definitive diagnosis of cancer however, this might seem overly aggressive. To our knowledge, this is the first study designed to examine whether hemicolectomy for benign polyps is safer than for cancer and by aggregating the experience from two tertiary centres, we were able to review the outcomes of 46 patients from prospectively maintained databases. The results of this study suggest that the short term outcomes after this intervention are similar in patients with benign polyps and those undergoing potentially curative surgery for colonic malignancy. No statistically significant differences were observed between the groups for any of the primary outcomes other than a slight increase in hospital stay in the benign group following adjustment for potential confounders. This could be explained by the small study sample. A similar range of complications was observed between the two groups. In addition, the morbidity reported in this study is comparable to the outcomes of the recently published LAFA trial[94] in which complications occurred in 34%, readmission in 6% and anastomotic leakage of 7% of patients.

All polyps included in this series were deemed unsuitable for endoscopic treatment by expert endoscopists with advanced therapies, complex EMR and ESD, being routinely performed in both institutions. Although the commonest indication for surgery was the size of the polyp, over two thirds of the lesions were located in the right colon. Performing polypectomy in the right colon that is thin walled is challenging and the risk of perforation or bleeding is high[181]. The results of a recently published study suggest that delayed haemorrhage most commonly occurs following right sided polypectomy (OR 4.67, 95% CI 1.88, 11.61, p 0.001) and the risk of bleeding increases by 13% for every 1mm increase in polyp diameter (OR 1.13, 95% CI 1.05, 1.20, p<0.001)[182]. In addition, many argue that the risk of perforation in patients with a potentially malignant lesion is unacceptable, as peritoneal seeding has a potential to convert a Stage I cancer into potentially incurable disease. Although most of the studies looking specifically at patients undergoing colectomy for unresectable polyps have typically been small, Bertelson et al.[183] reported the outcomes of 750 patients, which is the largest described to date. The aim of their study was to determine the incidence of malignancy in surgically resected benign polyps and 17.7% (133/750) had invasive colonic carcinoma of which 23% (31/133) had nodal disease. If malignancy or even nodal disease have been accurately excluded pre- or intra-operatively, and a suitable full thickness excision performed instead, more than three quarter of the patients in this study would have been spared the attendant morbidity of hemicolectomy.

The strengths of this study include prospective data capture reducing the observation bias. Potential confounding factors were addressed during the matching process and by statistical analysis where possible. Our data collection occurred during a period when laparoscopic surgery within an ERAS protocol was standard treatment in both institutions and all procedures were performed by experienced laparoscopic surgeons. Despite both centres being tertiary referral hospitals, the small number of patients undergoing surgery reflects the endoscopic expertise. High rate of anastomotic leakage in the benign cohort is difficult to

explain as both groups were treated by experienced surgeons. Although this is likely to be due to the small number of patients in this study, a larger series is required to confirm this.

## 3.5 Conclusion

In conclusion, the results from this study represent a step forward towards understanding the risks associated with hemicolectomy in patients with benign colonic polyps with a study sample that is similar to the previously published single-institution series[178, 184, 185]. Despite a small study sample, our results suggest that laparoscopic hemicolectomy, even for benign disease, causes significant morbidity in at least one third of the patients. Undertaking hemicolectomy in this cohort therefore needs to be carefully considered.

# Chapter 4 Short term outcomes of surgical polypectomy: interrogation of the Hospital Episodes Statistics

## 4.1 Introduction

As discussed in the previous chapter, large studies reporting outcomes after surgery for benign colonic polyps are relatively uncommon, and to date have included small, retrospective series only[174, 176, 178, 186]. The results of the study described in Chapter 3 suggest that morbidity following laparoscopic hemicolectomy for treatment of complex colonic polyps is similar to that observed in patients undergoing potentially curative cancer resection. Despite collaboration between two tertiary centres however, our study sample was relatively small. The most reliable outcome data following colorectal resection published to date is derived from large randomized trials of laparoscopic *vs.* open surgery for cancer[59, 87, 94]. In order to find more meaningful differences between the two cohorts and establish the true risk of morbidity, a larger study sample is required.

The study presented in this chapter was designed to examine the short-term outcomes following colorectal resection for benign polyps with those performed for CRC using the Hospital Episodes Statistics (HES) database in England.

## 4.2 Methods

### 4.2.1 Health Episode Statistics

The HES database has been described in several publications[169, 187-189]. This record based system was established in 1987 and it collates the data for all patients admitted to English NHS Trusts using hospitals' Patient Administration System (PAS). The records contain information regarding geographic, demographic, diagnostic and procedural data for

individual patient attendance at an NHS hospital. Each episode contains one primary and up to 13 secondary diagnoses[189], categorized according to the International Classification of Disease 10th revision (ICD-10). In addition, up to 12 procedural fields are coded using the Office for Population Census and Surveys Classification of Surgical Operations and Procedures 4th revision (OPCS-4)[169, 189]. The Charlson comorbidity index derived from secondary diagnoses is a marker of comorbidity and greater scores are associated with worse outcomes[190]. In addition, the Carstairs index of deprivation is a composite socioeconomic deprivation score that is linked to HES according to patient postal code[169] and specifically uses four variables: unemployment, overcrowding, car ownership and social class[191].

### 4.2.2 Patient selection

All patients that underwent an elective primary colorectal procedure with a diagnosis of CRC or benign colorectal neoplasia between April 2000 and March 2007 in English NHS trusts were included in this study. This dataset was already available. Patients were selected using the relevant ICD-10 codes for benign colorectal polyps as well as those for CRC (Table 4.1). Benign and malignant neoplasms of the anus and anal canal were excluded. Procedure categories and respective OPCS-4 codes used for patient selection are also presented in the Table 4.2. Cases with missing data for operative procedures but with a diagnosis of CRC or benign colorectal polyp were excluded. Patients were categorised into five age cohorts for analysis: <50, 51 – 60; 61 – 70; 71 – 80 and >81 years.

*Table 4.1 ICD-10[192] codes used for data selection*

| ICD-10 Code | Description for benign lesions | ICD-10 Code | Description for malignant lesions |
|---|---|---|---|
| **D12.0** | Benign neoplasm of caecum | **C18.0** | Malignant neoplasm of caecum |
| **D12.2** | Benign neoplasm of ascending colon | **C18.2** | Malignant neoplasm of ascending colon |
| **D12.3** | Benign neoplasm of transverse colon (applicable to splenic and hepatic flexure) | **C18.3** | Malignant neoplasm of hepatic flexure |
| **D12.4** | Benign neoplasm of descending colon | **C18.4** | Malignant neoplasm of transverse colon |
| **D12.5** | Benign neoplasm of sigmoid colon | **C18.5** | Malignant neoplasm of splenic flexure |
| **D12.6** | Benign neoplasm of colon, unspecified | **C18.6** | Malignant neoplasm of descending colon |
| **D12.7** | Benign neoplasm of recto-sigmoid junction | **C18.7** | Malignant neoplasm of sigmoid colon |
| **D12.8** | Benign neoplasm of rectum | **C18.8** | Malignant neoplasm of overlapping sites of colon |
| | | **C18.9** | Malignant neoplasm of colon, unspecified |
| | | **C19** | Malignant neoplasm of recto-sigmoid junction |
| | | **C20** | Malignant neoplasm of rectum |

*Table 4.2 OPCS-4[193] codes used for data selection*

| OPCS-4 Code | Description for surgical procedures |
|---|---|
| **H07.1 to H07.4, H07.8, H07.9** | Right hemicolectomy |
| **H06.1 to H06.4, H06.8, H06.9** | Extended right hemicolectomy |
| **H08.1 to H08.5, H08.8, H08.9** | Transverse colectomy |
| **H09.1 to H09.5, H09.8, H09.9** | Left hemicolectomy |
| **H10.1 to H10.5, H10.8, H10.9** | Sigmoid colectomy |
| **H33.5, H33.6** | Hartmann's procedure; anterior resection and stoma formation |
| **H33.2 to H33.4, H33.8, H33.9** | Anterior resection |
| **H33.1** | Abdominoperineal resection (APER) |

### 4.2.3 Outcome measures

30-day in-hospital mortality (defined as death from all causes occurring within 30 days of admission), 28-day readmission rates and LOS were primary end-points. LOS describes the time (days) that a patient spent as an inpatient during their index admission whereas readmissions were considered as subsequent emergency admissions within 28-days of the date of discharge after their original procedure[169].

### 4.2.4 Ethical approval

The study was approved under Section 251 by the National Information Governance Board for Health and Social Care (formerly section 60 by the Patient Information Advisory Group), and by the South East Ethics Committee[187].

### 4.2.5 Statistical analysis

Categorical variables were assessed using $\chi^2$ test including age (recoded in age bands). Length of stay was analysed by log-normal transformation and independent *t* test with back exponentiation due to its non-normal distribution. Logistic regression models were constructed to evaluate 30-day mortality after adjustment for age, sex, comorbidity, social deprivation index, lesion location (rectum/colon) and diagnosis (benign/malignant). Co-variables with significance of $p \leq 0.100$ on univariable analysis were included in multifactorial regression analysis. SPSS version 20 for Windows (SPSS, Chicago, Illinois, USA) was used for the statistical analyses.

## 4.3 Results

A total of 8 659 patients were identified having undergone major colorectal resection for treatment of benign colorectal polyps between 1st April 2000 and 31st March 2007. Over the same period, 111 047 patients underwent surgery for CRC. Both groups had similar sex distribution but a significantly higher proportion of patients with benign diagnosis had colonic disease ($p < 0.001$) (Table 4.3). A similar proportion of right sided resections was noted in

each group (28.4% in the benign *vs.* 25.2% in the CRC group, p <0.001) (Figure 4.1). Co-morbidity scoring differed significantly between the two groups (p <0.001) with the benign group having fewer patients with high co-morbidity index (p <0.001) whereas patients diagnosed with CRC tended to be older (Figure 4.2). In addition, patients in the benign category were less likely to undergo a laparoscopic procedure (4.43% *vs.* 5.23%, p <0.001) although the observed numbers were very low in both groups.

***Table 4.3 Demographic data***

| | **Patients with benign colorectal polyps (n = 8 659)** | **Patients with CRC (n = 111 047)** | **P** |
|---|---|---|---|
| **Gender** | | | |
| **Male** | 4 466 (51.6%) | 63 681 (57.3%) | **<0.001** |
| **Female** | 4 193 (48.4%) | 47 366 (42.7%) | |
| **Location** | | | |
| **Colon** | 6 635 (76.6%) | 54 086 (48.7%) | **<0.001** |
| **Rectum** | 2 024 (23.4%) | 56 961 (51.3%) | |
| **Charlson score ≤2** | | | |
| **Colon** | 6 251 (97.7%) | 31 193 (57.7%) | **<0.001** |
| **Rectum** | 1 906 (97.7%) | 35 099 (61.6%) | |
| **Charlson score >2** | | | |
| **Colon** | 149 (2.3%) | 22 887 (42.3%) | **<0.001** |
| **Rectum** | 44 (2.3%) | 21 856 (38.4%) | |
| **Laparoscopy** | 384 (4.43%) | 5 809 (5.23%) | **<0.001** |

***Figure 4.1 Operative procedures for both groups***

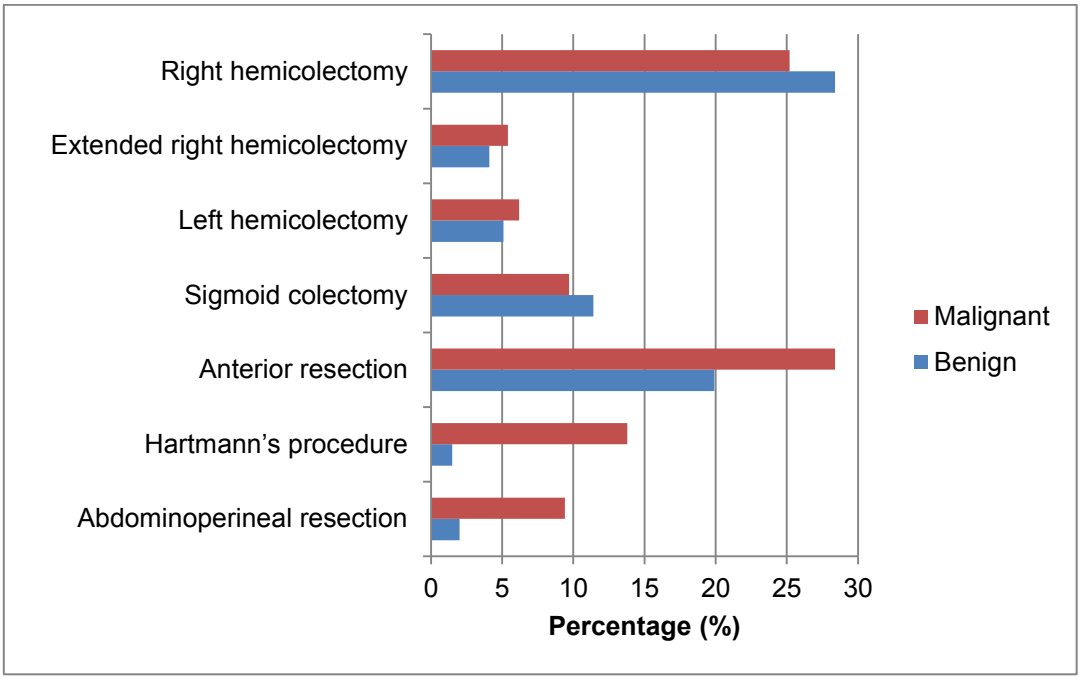
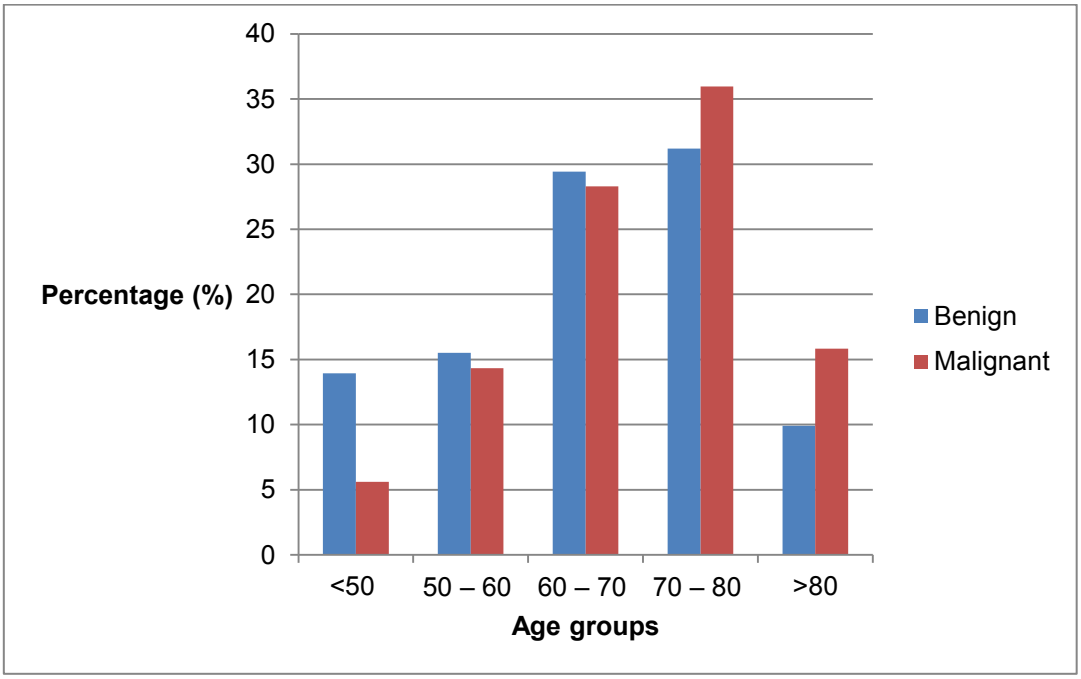



***Figure 4.2 Age distribution in each group***




The overall readmission rates were similar between the groups (8.9% for benign *vs.* 8.6% for CRC cohort; p 0.372) (Table 4.4). Higher 28-day readmission rate was noted following

colonic surgery in the benign cohort (8.7% *vs.* 7.2% respectively, p <0.001) however no difference between the groups was observed following rectal surgery. The risk of in-hospital death within 30-days of admission was lower for patients undergoing surgery for benign colonic and rectal polyps when compared to CRC patients (1.7% and 2.2% *vs.* 4.0 and 3.6% respectively, p <0.001). The risk of mortality, however, increased significantly with age for both groups irrespective of the lesion location (rectum or colon) (Figure 4.3), with the highest observed mortality for patients over the age of 81 in both groups, (4.88% for benign and 8.66% for CRC patients, p <0.001). Both groups had a long hospital stay for colonic and rectal resections (p <0.001) (Table 4.4).

***Table 4.4 Study end points***

| | **Patients with benign colorectal polyps (n = 8 659)** | **Patients with CRC (n = 111 047)** | **P** |
|---|---|---|---|
| **Readmission** | 772 (8.9%) | 9 592 (8.6%) | 0.372 |
| **Colon** | 580 / 6 635 (8.7%) | 3 918 / 54 086 (7.2%)* | |
| **Rectum** | 192 / 2 024 (9.5%) | 5 674 / 56 961 (10.0%) | |
| **Mortality** | 159 (1.8%) | 4 196 (3.8%) | **<0.001** |
| **Colon** | 114 / 6 635 (1.7%) | 2 160 / 54 086 (4.0%)* | |
| **Rectum** | 45 / 2 024 (2.2%) | 2 036 / 56 961 (3.6%)* | |
| **Mean (SD) LOS, days**[≠] | 10.5 (1.9) (0 - 279) | 12.7 (1.8) (1 - 468) | **<0.001**[¥] |
| **Colon** | 10.1 (1.9) (0 - 231) | 11.7 (1.7) (0 - 313)* | |
| **Rectum** | 12.2 (1.8) (0 - 279) | 13.9 (1.8) (0 - 468)* | |

*(*) The difference detected between the groups was significant*

*(≠) Derived from exponential logarithmic transformation*

*(¥) Independent t test*

Following case-mix adjustment for age, sex, social deprivation, co-morbidity, lesion location and cancer diagnosis, advanced age, complications and social deprivation scores were found to be associated with an independent increase in 30-day mortality risk (OR 14.84, 95% CI 10.94 – 20.14; p <0.001, OR 2.84, 95% CI 2.66 – 3.03; p <0.001 and OR 1.39, 95% CI 1.25 - 1.54; p <0.001 respectively) (Table 4.5). The additional mortality risk posed by a diagnosis of malignancy was not significant in the multifactorial logistical regression.

*Figure 4.3 Cumulative mortality by surgical procedure*

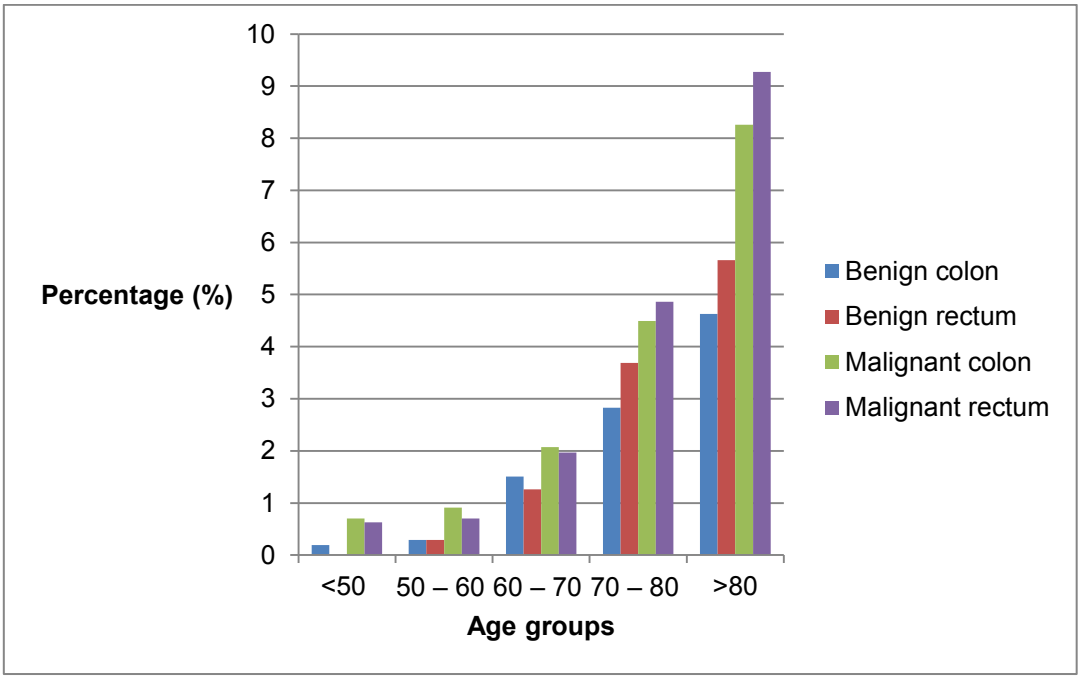



*Table 4.5 Multiple regression analysis*

| Outcome | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P | OR (95% CI) | P |
| **Sex** | 0.68 (0.63, 0.72) | **<0.001** | 0.65 (0.60, 0.68) | **<0.001** |
| **Age (years)** | | **<0.001** | | **<0.001** |
| **>50** | 1.00 | | 1.00 | |
| **51 – 60** | 1.38 (0.98, 1.95) | 0.064 | 1.31 (0.93, 1.84) | 0.129 |
| **61 - 70** | 3.42 (2.51, 4.66) | **<0.001** | 3.90 (2.27, 4.21 | **<0.001** |
| **71 – 80** | 8.21 (6.07, 11.12) | **<0.001** | 7.33 (5.41, 9.93) | **<0.001** |
| **>81** | 15.92 (11.75, 21.58) | **<0.001** | 14.84 (10.94, 20.14) | **<0.001** |
| **Carstairs score** | | **<0.001** | | **<0.001** |
| **1 (least deprived)** | 1.00 | | 1.00 | |
| **2** | 1.10 (0.99, 1.21) | 0.062 | 1.04 (0.94, 1.15) | 0.411 |
| **3** | 1.26 (1.14, 1.38) | **<0.001** | 1.16 (1.05, 1.28) | **0.003** |
| **4** | 1.32 (1.19, 1.46) | **<0.001** | 1.21 1.09, 1.28) | **<0.001** |
| **5** | 1.49 (1.35, 1.67) | **<0.001** | 1.39 (1.25, 1.54) | **<0.001** |
| **6 (most deprived)*** | 0.00 | 0.997 | 0.00 (0.00) | 0.996 |
| **Charlson score** | 3.12 (2.94, 3.33) | **<0.001** | 2.84 (2.66, 3.03) | **<0.001** |
| **Rectal** | 0.94 (0.89, 0.99) | **0.045** | 1.06 (0.99, 1.13) | 0.056 |
| **Malignant** | 0.47 (0.41, 0.56) | **<0.001** | 0.97 (0.83, 1.15) | 0.754 |

*(*) Sample size too small to perform formal analysis*

## 4.4 Discussion

Our review of 30-day outcomes following surgery for benign colorectal polyps from all English NHS hospitals is the largest series of this kind described to date. The results of this study support our findings presented in Chapter 3. Although the observed 30-day in-hospital mortality for the benign cohort was 50% lower when compared to that of patients undergoing cancer resections, at approximately 2% it remains considerable, with advanced age rather than diagnosis being an independent risk factor. The risk of mortality following surgery for patients with benign colorectal polyps aged 71 – 80 and >80 (3.0% and 4.9% respectively) reiterates the need for a careful balance of the risks associated with surgery and other treatment options. In addition, LOS in excess of 10 days and 28-day readmission rates approaching 9% are substantial, despite this cohort being younger with a lower co-morbidity score. Slight increase in hospital stay following colonic resections for benign polyps described in Chapter 3 (median 5.5, IQR 4, 8 *vs.* 5, IQR 3, 6) was not observed in this national cohort (median 10.5, IQR 7, 17 *vs.* 12.7, IQR 8, 14). The difference in the LOS between the two studies is likely to be due to the different data collection period and the fact that the majority of the procedures presented in Chapter 3 were performed laparoscopically within ERAS protocol.

Patient demographics suggest that rectal surgery was avoided when possible in the benign cohort, with significantly fewer patients undergoing rectal excision compared to the cancer group (23.4% *vs.* 51.3%). This could be explained by the increasing utilisation of advanced endoluminal therapies such as EMR, ESD and TEMS, as discussed in Chapter 1. However, due to the lack of a localised excision technique for colonic lesions equivalent to TEMS procedure, a significant proportion of patients diagnosed with colonic lesions are directly referred for surgery. More than a third of all resections in the benign cohort were performed for right sided lesions. Although the risk of complications associated with advanced polypectomy techniques is higher in the right colon[181], some studies suggest that a significant proportion of such patients can be managed by well-trained endoscopists[194-197].

Brooker et al.[196] compared the outcomes of large sessile polyps (>2cm) treated by specialist and non-specialist endoscopists in a single unit, reporting that specialists more frequently attempted endoscopic resection of polyps thought to be benign (93% *vs.* 75%), with 42% of the lesions located proximal to the splenic flexure. In this retrospective study, surgery was avoided in 76% of cases treated by specialists, compared to 40% treated by non-specialists. Similar findings were reported in a prospective series form Australia[197] in which 174 patients were referred to a specialist tertiary referral service. Over a 21 month period, surgery was avoided in 90% of the cases with only few complications which included post-polypectomy syndrome (6.4%) and significant delayed bleeding (3.7%). In addition, following an economic analysis comparing tertiary referral service and surgical intervention, the authors estimated a mean cost-saving of $6 900 and a reduction in the LOS of 6.7 days per patient.

Unfortunately, many patients referred for surgery do not get the benefit of an expert endoscopist performing their colonoscopy. Widespread introduction of CRC screening is likely to lead to an increase in the number of patients diagnosed with benign colorectal polyps[123, 124] and therefore it is not unreasonable to suggest that those with complex lesions warrant referral to a tertiary centre for management. Centres with high volume of difficult cases and expertise to offer advanced endoluminal therapies and TEMS service are likely to achieve results similar to those reported by Brooker et al.[196] and Swan et al.[197]. In addition, taking into account that approximately 18% of the polyps harbour a malignant focus[183], a careful pathological assessment is essential. Experienced and meticulous pathological examination of the specimen is essential when determining the adequacy of local excision and the risk of nodal involvement, as it will influence the need for definitive surgery.

This study has several shortcomings that should be noted. Data for patients undergoing surgery for benign colorectal polyps were only available for a period from April 2000 to March 2007. Introduction of the Laparoscopic National Training Programme[96, 97] has had a significant effect on elective colorectal surgery over the past five years as demonstrated in Chapter 3. The proportion of laparoscopic resections in this study was very small (4.43% in

the benign and 5.23% in CRC cohort) and therefore the impact of minimally invasive surgery on patient outcome cannot be assessed. Due to the nature of HES database, it is impossible to ascertain the reasons for surgery and a proportion of the patients may have been deemed unsuitable for endoscopic treatment by expert endoscopist. In addition, a specific OPCS code for TEMS procedure was not available during this period and therefore a proportion of the patients classed as having surgery for both benign and malignant rectal lesions may have indeed had a TEMS procedure.

## 4.5 Conclusion

This is the largest series to date reporting short-term outcomes of patients undergoing surgery for treatment of benign colorectal polyps using historical data. High post-operative morbidity, mortality and prolonged in-hospital stay emphasise the need to improve the way that these patients are managed. In addition, patients with advanced age diagnosed with complex colorectal polyps might benefit from a referral to a tertiary centre offering advanced endoluminal therapies and TEMS in order to minimise the risk of complications.

# Chapter 5 Functional outcomes and related quality of life after hemicolectomy: prospective case-controlled study

## 5.1 Introduction

The introduction of screening, earlier diagnosis of the disease and advances in surgical and adjuvant treatments are likely to improve the overall survival of patients with CRC. In addition to disease free survival and traditional clinical outcome measures such as morbidity and mortality, quality of life is an important outcome of CRC treatment[198, 199]. Although several studies have reported bowel, urinary and sexual dysfunction after rectal cancer treatment[200-202], the relationship between bowel function and QOL after colonic resection is scarcely reported in the literature. Most healthy individuals average one bowel movement per day[203] and the events that occur within the colon providing this regularity include absorption of water and electrolytes, coordinated propulsion of faecal mass from the right colon to the rectum, storage, and ultimately, expulsion[204]. Therefore, the unavoidable distortion of bowel anatomy after colonic resection may lead to a number of functional disturbances which may be of long-term importance to the patient.

Few studies published to date have focused on the outcomes following left sided resection (sigmoid and anterior resection) for the treatment of CRC[205-208] and diverticular disease[209, 210], suggesting that after surgery patients have an increase in stool frequency[206, 208]. These studies have made limited use of validated questionnaires designed to assess bowel function and related QOL. Instead, bowel function is usually reported as numeric data from self-constructed questionnaire surveys[205-208]. This makes it challenging to translate the scanty data that are available into clinically meaningful information for patients. To address the gap in our knowledge, we designed a prospective study to assess 'early' (≤12 months after surgery) and 'intermediate' (two to four years after surgery) bowel function in patients

undergoing hemicolectomy with *en bloc* mesenteric resection (open/laparoscopic) and its effect on the patients' QOL when compared to healthy controls. Our proposed hypothesis was that potentially curative hemicolectomy for invasive and non-invasive colonic neoplasia adversely affects patients' bowel function and QOL.

## 5.2 Methods

### 5.2.1 Recruitment process

#### *5.2.1.1 Pre-operative patient group recruited for assessment of 'early' bowel function*

Patients diagnosed with colonic neoplasia were identified during the weekly colorectal cancer MDT meetings in four centres (St. Mark's Hospital, London; Oxford Radcliffe Hospitals, Oxford; St. Mary's Hospital, London and The London Clinic, London). A research fellow (A.B., N.R.A.S.) or research assistant (S.S.) approached patients in the clinic to discuss the study in detail. A patient information sheet (PIS) was provided for patients to take away and consider whether they wished to participate. Potential participants were approached again during their pre-operative assessment or after surgery, and provided that they fulfilled study inclusion criteria (Table 5.1), their consent to participate was obtained.

#### *5.2.1.2 Post-operative patient group recruited for assessment of 'intermediate' bowel function*

Eligible patients who had colonic neoplasia resected two to four years previously were identified from prospectively maintained colorectal cancer databases in two teaching hospitals (St. Mark's Hospital, London and John Radcliffe Hospitals, Oxford) using criteria presented in (Table 5.1). Initially, a letter of invitation to participate in the study was posted to patients two weeks prior to their regular appointment. Patients were then approached in the clinic by the research fellow (A.B.) or research assistant (S.S.) to discuss the study further and answer questions. Consent was obtained from those willing to participate and study

questionnaires completed. Due to the slow recruitment observed during the first three months of the study, the protocol was amended to enable postal recruitment. An invitation letter and a reply slip were posted to potentially eligible patients with no follow-up appointment pending. Implied consent to take part in the study was assumed if the patients returned the reply slip agreeing to a telephone interview during which study questionnaires were completed and relevant sociodemographic data collected. All non-responders were contacted within two weeks after the invitation was mailed to ensure that the information was received and to encourage response.

#### *5.2.1.3 Controls*

The control group consisted of siblings, partners and spouses of patients diagnosed with colonic neoplasia who were approached to take part in the study for evaluation of 'early' bowel function. More than one member of each family was approached to compensate for subjects with no controls. Control subjects were recruited into the study at the same time as the patients, using the criteria presented in Table 5.2.

### 5.2.2 Data collection

Sociodemographic (sex, age, ethnicity, BMI, employment status, marital status) and clinical data including past medical, surgical and drug history were recorded for both patient groups. Particular care was taken to record the use of laxatives, analgesia (opiate based) or antibiotics within 4 weeks of recruitment, at 6 and 12 months after surgery for patients who had been recruited pre-operatively. The caecum, ascending and transverse colon were defined as the 'right' and descending and sigmoid colon as the 'left' colon. Clinical notes and pathology reports were reviewed to record the level of concomitant co-morbidity (ASA grade), intra- and post-operative data, stage of the disease and adjuvant treatment. The length of all resected colonic specimens was recorded after fixation. Post-operative complications with a potential to have an adverse effect on post-operative bowel function including anastomotic leakage, intra-abdominal abscess formation and further abdominal surgery were recorded.

### *Table 5.1 Inclusion and exclusion criteria for patients*

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Male or female aged 18 and above<br>• Able and willing to comply with study requirements<br>• For assessment of 'early' bowel function patients with a diagnosis of invasive or non-invasive neoplasm suitable for curative colonic resection (open/laparoscopic)<br>• For assessment of 'intermediate' bowel function patients who underwent curative colonic resection (open/laparoscopic) for treatment of invasive or non-invasive neoplasm<br>• Surgical procedures: right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid colectomy/high anterior resection*<br>• ASA grade I, II or III**<br>• IUCC stage I to III | • Poor cognitive ability or the inability to provide fully informed consent or complete study questionnaires<br>• Diagnosis of Crohn's disease, ulcerative colitis or coeliac disease<br>• Rectal neoplasm<br>• Previous pelvic radiation<br>• Previous bowel resection (colon, stomach or small bowel), bypass surgery or vagotomy<br>• Emergency colonic resection<br>• Previous stoma<br>• Localised recurrence of the disease during the study period<br>• Diagnosis of anal incontinence prior to surgery |

*(*) For lesions located above 15cm from the anal verge*

*(**) For 'intermediate' bowel function group, ASA grade at the time of surgery was recorded*

### *Table 5.2 Inclusion and exclusion criteria for controls*

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Siblings, partners or spouses of patients recruited for assessment of 'early' bowel function<br>• Male or female aged 18 and above<br>• Able and willing to comply with study requirements | • Poor cognitive ability or the inability to provide fully informed consent or complete study questionnaires<br>• Diagnosis of Crohn's disease, ulcerative colitis or coeliac disease<br>• Previous pelvic radiation<br>• Previous bowel resection (colon, stomach or small bowel), bypass surgery or vagotomy<br>• Diagnosis of anal incontinence |

### 5.2.3 Study questionnaires

#### *5.2.3.1 Memorial Sloan-Kettering Cancer Centre (MSKCC) bowel function questionnaire*

Study participants were provided with the Memorial Sloan-Kettering Cancer Centre (MSKCC) bowel function questionnaire designed to evaluate bowel function following rectal resection[211]. Despite extensive literature review, we were unable to identify a validated questionnaire developed specifically to evaluate bowel function following colonic resection. The questionnaires that have been rigorously developed are those to assess continence[212-214] and were therefore deemed not suitable for this study. The MSKCC questionnaire was designed to measure bowel function rather than quality of life[211, 215] and has been validated against the more established Faecal Incontinence Quality of Life Scale (FIQL) and the European Organisation of Research and Treatment of Cancer Quality of Life (EORTC) questionnaires: QLQ-C30 (core cancer module) and QLC-38 (colorectal cancer specific module)[211].

The questionnaire consists of 18 items (Table 5.3) that are grouped into three subscales: frequency, diet and urgency/soilage. In addition, four individual questions (Q) of clinical significance are also included: incomplete emptying after a bowel movement [Q4], having a second bowel movement within 15 minutes [Q6], knowing the difference between gas and bowel movement [Q7] and the ability to control the passage of wind [Q12]. The frequency subscale includes 6 questions (Q1, Q5, Q8, Q9, Q10, Q11) regarding the number of bowel movements per 24 hours (divided into quintiles), stool consistency and the ability to get to the toilet on time. Four questions (Q2, Q3, Q13, Q14) relating to the impact of certain food/drink items on bowel movements and avoidance of those items are included in the dietary subscale. The urgency/soilage subscale consists of four questions (Q15, Q16, Q17, Q18) concerning faecal leakage (day or night and use of pads) and the impact of bowel function on social activities. The responses are given on a 5-point Likert scale for all items

apart from the item asking for the number of bowel movement per 24 hours (categorised into quintiles).

***Table 5.3 The MSKCC questionnaire***

| | | | | | | |
|---|---|---|---|---|---|---|
| **1** | **Over the last 4 weeks, how many bowel movements do you generally have in 24 hours? *(please write down the number)*** | **_____ bowel movements/24 hours** | | | | |
| | **Over the last 4 weeks ……. (please tick most appropriate answer)** | **Always** | **Most of the time** | **Sometimes** | **Rarely** | **Never** |
| **2** | **Do certain solid foods increase the number of bowel movements in a day?** | 1 | 2 | 3 | 4 | 5 |
| **3** | **Do certain liquids that you drink increase the number of bowel movements in a day?** | 1 | 2 | 3 | 4 | 5 |
| **4** | **Do you feel like you have totally emptied your bowels after a bowel movement?** | 5 | 4 | 3 | 2 | 1 |
| **5** | **Do you get to the toilet on time?** | 5 | 4 | 3 | 2 | 1 |
| **6** | **Do you have another bowel movement within 15 minutes of your last bowel movement?** | 1 | 2 | 3 | 4 | 5 |
| **7** | **Do you know the difference between having to pass gas (air) and needing to have a bowel movement?** | 5 | 4 | 3 | 2 | 1 |
| **8** | **Have you used medicines to decrease the number of bowel movements (drugs like Imodium®, Lomotil®)?** | 1 | 2 | 3 | 4 | 5 |
| **9** | **Have you had diarrhea (no form, watery stool)?** | 1 | 2 | 3 | 4 | 5 |
| **10** | **Have you had loose stool (slight form, but mushy)?** | 1 | 2 | 3 | 4 | 5 |
| **11** | **Have you been able to wait 15 minutes to get to the toilet when you feel like you are going to have a bowel movement?** | 5 | 4 | 3 | 2 | 1 |
| **12** | **Have you been able to control the passage of gas (air)?** | 5 | 4 | 3 | 2 | 1 |
| **13** | **Have you limited the types of solid foods you eat to control your bowel movements?** | 1 | 2 | 3 | 4 | 5 |
| **14** | **Have you limited the types of liquids you drink to control you bowel movements?** | 1 | 2 | 3 | 4 | 5 |
| **15** | **Have you had soilage (leakage of stool) of your undergarments during the day?** | 1 | 2 | 3 | 4 | 5 |
| **16** | **Have you used a tissue, napkin, and/or pad in your undergarments during the day in case of stool leakage?** | 1 | 2 | 3 | 4 | 5 |
| **17** | **Have you had soilage (leakage of stool) of your undergarments when you go to bed?** | 1 | 2 | 3 | 4 | 5 |
| **18** | **Have you had to alter your activities because of your bowel function?** | 1 | 2 | 3 | 4 | 5 |

*Temple et al.*[211]

Within the three subscales, scores for diet and urgency/soilage range from 4 to 20 and frequency from 6 to 30. One total score is obtained by summing all 18 items ranging between 18 and 90. Higher scores indicate better function.

#### *5.2.3.2 EQ-5D Quality of Life questionnaire*

To evaluate participants' QOL, we chose the EuroQol EQ-5D questionnaire which consists of the index score representing the societal value of health state and has a scale ranging from 0 (no quality of life) to 100 (optimal quality of life). This is a descriptive system that measures health-related QOL on five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). It also contains a visual analogue scale, the EQ-VAS, representing the patient perspective. This scale also ranges from 0 (no quality of life) to 100 (optimal quality of life). This is a simple questionnaire and was deliberately chosen to optimise compliance with study requirements.

### 5.2.4 Assessment and follow-up

Patients recruited for assessment of 'early' bowel function were asked to complete questionnaires at three points during the study – at recruitment, and at 6 and 12 months after surgery. Patients who described a change in bowel habit prior to diagnosis of colonic neoplasm were provided with two sets of study questionnaires – one for documentation of their bowel habit and QOL at the time of recruitment and the second recording their bowel habit preceding the onset of bowel symptoms (historic data). Comparison of questionnaire variables between patients and controls was made at baseline, and then and 6 and 12 months follow-up. For the subgroup of patients who reported a change in bowel habit, the 'historic' data were used as the baseline values rather than the values obtained immediately prior to surgery.

In the assessment of 'intermediate' bowel function we assumed that a one-off measurement of bowel function and QOL was representative of patients' regular bowel habit at two to four years after surgery and study questionnaires were completed during the interview. Control

subjects were also required to complete one set of questionnaires and for the purposes of analysis, the 6 and 12 month values were assumed to be the same as those at the baseline.

### 5.2.5 Ethical approval

Ethical approval to conduct the study was obtained from the National Research Ethics Service (NRES) Committee London – Stanmore in May 2011 with a substantial amendment to allow postal recruitment ('intermediate' bowel function group) and postal follow-up ('early' bowel function group) in September 2011 (REC reference 11/LO/0294).

### 5.2.6 Power calculation

The MSKCC questionnaire was validated in 2005 and to date has been utilised in several small clinical studies[198, 216, 217]. To obtain meaningful results for patients undergoing segmental colectomy, we based our power calculation on the preliminary results from an on-going study conducted by the authors who developed the questionnaire. The study was designed to measure functional outcomes and QOL in patients undergoing surgery for rectal cancer[218] and preliminary data collected at six months after surgery suggest that bowel function was clinically worse when a drop of 5 points in the median total score was observed[218].

Extrapolating this data, we calculated that a sample size of 85 participants in each group would give 90% power to demonstrate a difference in the median total score of 5 between the patients and controls, assuming the α value of 0.05. To allow for a 10 to 15% loss of patients due to withdrawal from the study (5%), local (anastomotic/peritoneal) disease recurrence (5%) or death (1 - 2%), we aimed to recruit 98 patients in the 'early' bowel function group.

### 5.2.7 Statistical methods

Categorical variables were compared between the groups using the Fisher's exact test and normally distributed continuous variables using the unpaired *t* test. Continuous data with skewed distribution were examined using the Mann-Whitney test. Linear regression was

used to perform further analyses allowing adjustment for the differences in demographics between the two groups. Log transformation was performed for positively skewed data using linear regression, whereas bootstrapping methods alongside the regression methods were used to analyse negatively skewed outcomes. The results are presented as regression coefficients, which is the mean difference in the outcome between the groups reported as the value for the patient group minus the value for the control group. Therefore, a positive value suggests higher scores and better function for the patient group. The exception is the number of bowel movements per 24 hours which is reported as the ratio of the number of bowel movements in the patient group compared to that observed in the control group. The Spearman's rank correlation was performed to evaluate the relationship between the bowel function and QOL as well as the MSKCC items and the bowel length excised.

## 5.3 Results

### 5.3.1 Demographic data

For assessment of 'early' bowel function a total of 121 patients were recruited prior to surgery and data for 91 patients were included in the final analysis. In addition, 85 controls agreed to take part in the study. The majority of the patients were recruited from St. Mark's Hospital, London (n = 42) and Oxford Radcliffe Hospitals, Oxford (n = 57). Reasons for exclusion from the final analysis were: loss to follow-up (n = 15), stoma formation (n = 8), death during the study period (n = 5), emergency surgery (n = 1) and rectal cancer (n = 1). Although this data were not collected, we estimate that approximately 10 – 20% of patients approached in the clinic declined to take part.

A total of 106 patients who underwent surgery two to four years previously in two teaching hospitals (St. Mark's Hospital London; Oxford Radcliffe Hospitals, Oxford) were invited to take part, of which 85 agreed to participate. All patients approached in the clinics (n = 48) agreed to take part in the study with the exception of one. Fifty eight invitation letters and

reply slips were posted, of which 41 patients returned the reply slip (71% response rate) and 40 agreed to participate. Two of these patients however could not then be contacted and were not included. Six non-responders declined to take part and 11 could not be contacted.

***Table 5.4 Baseline demographics***

| | Control group (n = 85) | 'Early' bowel function group | | 'Intermediate' bowel function group | |
|---|---|---|---|---|---|
| | | (n = 91) | P | (n = 85) | P |
| **M:F** | 34:51 | 43:47 | 0.36 | 49:36 | **0.03** |
| **Mean (SD) age** | 58.2 (13.4) | 71.2 (10.5) | **<0.001*** | 69.0 (11.2) | **<0.001*** |
| **Ethnicity** | | | | | |
| **White** | 77 (92%) | 79 (87%) | 0.34 | 68 (81%) | 0.07 |
| **Other** | 7 (8%) | 11 (13%) | | 16 (19%) | |
| **Marital status** | | | | | |
| **Single** | 11 (13%) | 5 (5%) | | 13 (16%) | |
| **Married** | 66 (78%) | 64 (70%) | **0.001** | 52 (63%) | **0.007** |
| **Living with partner** | 7 (8%) | 6 (7%) | | 6 (7%) | |
| **Widowed** | 1 (1%) | 16 (18%) | | 12 (14%) | |
| **Employment** | | | | | |
| **Retired** | 37 (44%) | 70 (77%) | **<0.001** | 63 (75%) | **<0.001** |
| **Unemployed** | 5 (6%) | 8 (9%) | | 5 (6%) | |
| **Working** | 50 (51%) | 13 (14%) | | 16 (19%) | |
| **Laxatives** | | | | | |
| **Baseline** | 1 (1%) | 8 (9%) | **0.02** | | |
| **6-months** | 1 (1%) | 12 (14%) | **0.002** | 9 (11%) | **0.02** |
| **12 months** | 1 (1%) | 5 (6%) | 0.21 | | |
| **Antibiotics** | 1 (1%) | 0 (0%) | 0.48 | 5 (6%) | 0.21 |
| **Anti-diarrhoeal medication** | | | | | |
| **Baseline** | 1 (1%) | 0 (0%) | 0.48 | 5 (6%) | 0.21 |
| **6-months** | 1 (1%) | 11 (13%) | **0.005** | | |
| **12 months** | 1 (1%) | 5 (6%) | 0.21 | | |
| **Opiates** | | | | | |
| **Baseline** | 5 (6%) | 2 (2%) | 0.27 | | |
| **6-months** | 5 (6%) | 6 (7%) | 0.06 | 4 (5%) | 1.00 |
| **12 months** | 5 (6%) | 1 (1%) | 0.11 | | |
| **Diabetes** | 1 (1%) | 10 (11%) | **0.01** | 11 (13%) | **0.005** |
| **BMI** | 27.2 (4.8) | 26.1 (5.6) | 0.18* | 27.3 (25.0, 31.4) | 0.22** |

*(*) Unpaired t-test, data presented as mean (SD)*

*(**) Mann-Whitney test, data presented as median (IQR)*

Group comparison of demographic data is presented in Table 5.4 where several differences were observed: the control group were found to be younger, more likely to be married and to be working at recruitment compared to both patient groups. Patients were more likely to use laxatives and anti-diarrhoeal agents six months after surgery although this difference was not observed at 12 months. General demographics of patients recruited for assessment of 'intermediate' bowel function were similar to that of the patients recruited prior to surgery. This group were also more likely to use laxatives.

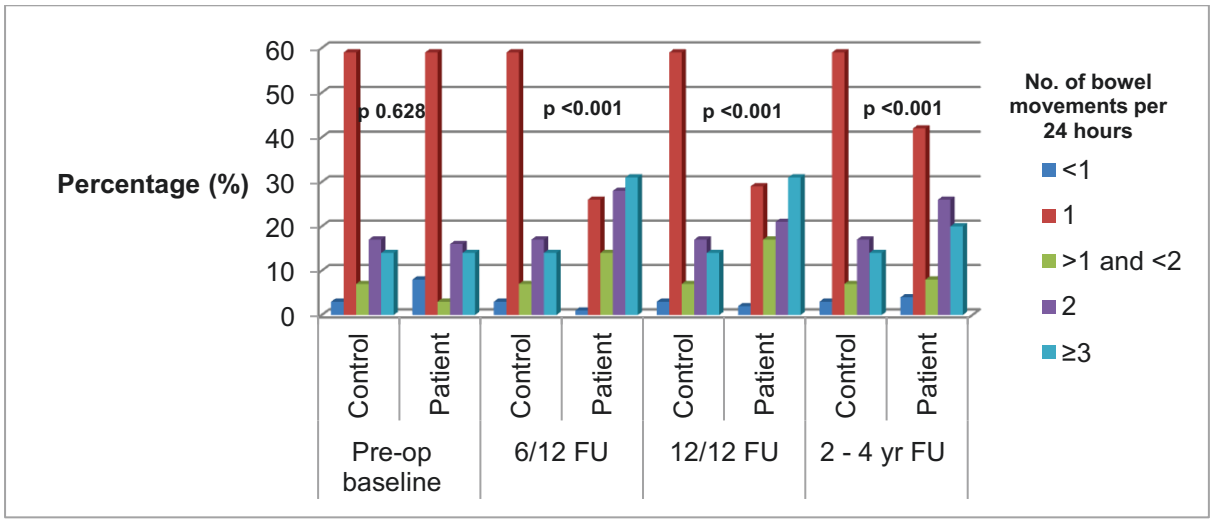
### 5.3.2 MSKCC questionnaire

For the purposes of this study we present the number of bowel movements per 24 hours independently and include the values in the MSKCC frequency score as instructed by the authors of the questionnaire (personal communication). The first analysis demonstrated a higher dietary score for patients at each time point, indicating better function when compared to controls (Table 5.5). Patients however appear to experience a significantly higher number of bowel movements per 24 hours (Figure 5.1 and Table 5.5). At 6 and 12 months after surgery approximately a third of patients experienced more than three motions per day, with an additional 20 to 30% experiencing two. Although the number of patients reporting three or more motions per day decreased to 20% in the intermediate group, the number is still significantly higher than the 10% of controls.

Lower scores, indicating worse function, were reported for the urgency item (p 0.008) and knowing the difference between gas and bowel movement [Q7] at 6 and 12 months after surgery (p 0.05 and <0.001 respectively). This appeared to persist at two to four years after surgery and the 'intermediate' bowel function group also reported difficulty in controlling the passage of wind [Q12] (Table 5.6). After adjusting for the differences in demographics, however, statistically significant differences remained for several items only. This includes: increase in the number of bowel movements at each time point [ratio 1.59, (95% CI 1.31,

1.92), p <0.001; 1.45, (95% CI 1.21, 1.75), p <0.001 and 1.44 (95% CI 1.20, 1.73), p <0.001 respectively]; knowing the difference between gas and bowel movement [Q7] at 12 months; and at two to four years after surgery, the ability to control the passage of wind [Q12] as well as a lower frequency score (Table 5.6 and Table 5.7). No association was observed between the bowel length excised and any of the MSKCC items.

***Figure 5.1 No. bowel movements split into quintiles at each time point***




We also examined the MSKCC scores over time for symptomatic patients, defined as those who developed change in bowel habit associated with cancer (Table 5.8). The results indicate that at 12 months after surgery these patients have a lower total MSKCC score than their baseline value (p 0.006) due to a decrease in frequency, dietary and urgency scores as well as the inability to discriminate between the gas and stool [Q7]. This suggests that patients who present with a change in bowel habit need longer than a year for their bowel function to stabilise and be similar to that prior to the onset of symptoms. When compared to controls using linear regression (including the differences between the groups) however, at 12 months after surgery patients only scored lower for the gas-stool differentiation question [Q7] (p 0.03) in addition to the increased number of bowel movements per day.

*Table 5.5 MSKCC questionnaire*

| | Median (IQR) score for patient group | Median (IQR) score for control group | P* |
|---|---|---|---|
| **Baseline 'early' bowel function group [n = 91]** | | | |
| **Bowel movements per 24 hours** | 1.0 (1.0, 2.0) | 1.0 (1.0, 2.0) | 0.40 |
| **Frequency score** | 26 (22, 28) | 26 (23, 27) | 0.45 |
| **Dietary score** | 19 (16, 20) | 16 (14, 18) | **<0.001** |
| **Urgency score** | 20 (20, 20) | 20 (20, 20) | 0.87 |
| **MSKCC Q4** | 4 (3, 5) | 4 (4, 4) | 0.90 |
| **MSKCC Q6** | 5 (4, 5) | 4 (4, 5) | 0.09 |
| **MSKCC Q7** | 5 (4, 5) | 5 (5, 5) | 0.16 |
| **MSKCC Q12** | 4 (4, 5) | 4 (4, 5) | 0.93 |
| **Total score** | 80 (76, 85) | 79 (74, 83) | 0.09 |
| **'Early' bowel function group at 6 months** | | | |
| **Bowel movements per 24 hours** | 2.0 (1.0, 3.0) | 1.0 (1.0, 2.0) | **<0.001** |
| **Frequency score** | 25 (22, 26) | 26 (23, 27) | 0.06 |
| **Dietary score** | 18 (15, 20) | 16 (14, 18) | **0.01** |
| **Urgency score** | 20 (18, 20) | 20 (20, 20) | **0.008** |
| **MSKCC Q4** | 4 (3, 4) | 4 (4, 4) | 0.12 |
| **MSKCC Q6** | 4 (3, 5) | 4 (4, 5) | 1.00 |
| **MSKCC Q7** | 5 (4, 5) | 5 (5, 5) | **0.05** |
| **MSKCC Q12** | 4 (4, 5) | 4 (4, 5) | 0.27 |
| **Total score** | 78 (72, 82) | 79 (74, 83) | 0.32 |
| **'Early' bowel function group at 12 months** | | | |
| **Bowel movements per 24 hours** | 2.0 (1.0, 2.5) | 1.0 (1.0, 2.0) | **<0.001** |
| **Frequency score** | 24 (22, 27) | 26 (23, 27) | 0.07 |
| **Dietary score** | 18 (16, 20) | 16 (14, 18) | **0.005** |
| **Urgency score** | 20 (18, 20) | 20 (20, 20) | **0.004** |
| **MSKCC Q4** | 4 (3, 4) | 4 (4, 4) | 0.65 |
| **MSKCC Q6** | 4 (3, 5) | 4 (4, 5) | 0.67 |
| **MSKCC Q7** | 5 (4, 5) | 5 (5, 5) | **<0.001** |
| **MSKCC Q12** | 4 (4, 5) | 4 (4, 5) | 0.43 |
| **Total score** | 79 (70, 84) | 79 (74, 83) | 0.33 |
| **'Intermediate' bowel function group [n = 85]** | | | |
| **Bowel movements per 24 hours** | 2.0 (1.0, 3.0) | 1.0 (1.0, 2.0) | **<0.001** |
| **Frequency score** | 24 (21, 26) | 26 (23, 27) | **0.03** |
| **Dietary score** | 18 (16, 20) | 16 (14, 18) | **0.009** |
| **Urgency score** | 20 (19, 20) | 20 (20, 20) | **0.04** |
| **MSKCC Q4** | 4 (3, 5) | 4 (4, 4) | 0.10 |
| **MSKCC Q6** | 4 (3, 5) | 4 (4, 5) | 0.95 |
| **MSKCC Q7** | 5 (4, 5) | 5 (5, 5) | **0.002** |
| **MSKCC Q12** | 4 (3, 4) | 4 (4, 5) | **<0.001** |
| **Total score** | 81 (73, 84) | 79 (74, 83) | 0.08 |

*(*) Mann-Whitney test*

*Table 5.6 MSKCC questionnaire linear regression analysis for 'early' bowel function group*

| | Mean (95% CI) group difference[§] | P |
|---|---|---|
| **Baseline 'early' bowel function group [n = 91]** | | |
| **Bowel movements per 24 hours[¥]** | 0.95 (0.78, 1.16) | 0.61 |
| **Frequency score** | 0.1 (-1.2, 1.4) | 0.92 |
| **Dietary score** | 1.1 (0.2, 2.1) | **0.02** |
| **Urgency score** | 0.3 (-0.3, 1.0) | 0.39 |
| **MSKCC Q4** | 0.1 (-0.3, 0.5) | 0.75 |
| **MSKCC Q6** | 0.2 (-0.1, 0.6) | 0.26 |
| **MSKCC Q7** | 0.0 (-0.3, 0.2) | 0.75 |
| **MSKCC Q12** | -0.1 (-0.4, 0.2) | 0.72 |
| **Total score** | 1.8 (-1.2, 4.2) | 0.19 |
| **'Early' bowel function group at 6 months**** | | |
| **Bowel movements per 24 hours[¥]** | 1.59 (1.31, 1.92) | **<0.001** |
| **Frequency score** | -0.3 (-1.6, 0.9) | 0.61 |
| **Dietary score** | 0.1 (-0.9, 1.2) | 0.90 |
| **Urgency score** | -0.6 (-1.5, 0.2) | 0.15 |
| **MSKCC Q4** | -0.1 (-0.5, 0.3) | 0.52 |
| **MSKCC Q6** | -0.1 (-0.6, 0.3) | 0.48 |
| **MSKCC Q7** | -0.1 (-0.4, 0.2) | 0.31 |
| **MSKCC Q12** | -0.1 (-0.4, 0.2) | 0.55 |
| **Total score** | -1.1 (-4.1, 2.1) | 0.51 |
| **'Early' bowel function group at 12 months***** | | |
| **Bowel movements per 24 hours¥** | 1.45 (1.21, 1.75) | **<0.001** |
| **Frequency score** | -1.2 (-2.7, 0.1) | 0.07 |
| **Dietary score** | 0.7 (-0.3, 1.6) | 0.16 |
| **Urgency score** | -0.5 (-1.4, 0.3) | 0.24 |
| **MSKCC Q4** | 0.1 (-0.3, 0.4) | 0.72 |
| **MSKCC Q6** | -0.1 (-0.6, 0.3) | 0.54 |
| **MSKCC Q7** | -0.4 (-0.7, -0.1) | **0.01** |
| **MSKCC Q12** | -0.4 (-0.8, 0.0) | 0.06 |
| **Total score** | -1.5 (-4.6, 1.6) | 0.36 |

*(§) Regression coefficient where a higher value indicates higher score and therefore better function for patients*

*(*) Adjusted for age, marital status, employment, laxatives at baseline, diabetes*

*(¥) Due to log transformation results are reported as the ratio of number of movements in the patient group*

*(**) Adjusted for age, marital status, employment, diabetes, laxatives & anti-diarrhoeal medication*

*(***) Adjusted for age, marital status, employment, diabetes*

### *Table 5.7 MSKCC questionnaire linear regression analysis for 'intermediate' bowel function group*

| | Mean (95% CI) group difference[§] | P |
|---|---|---|
| **'Intermediate' bowel function group [n = 85][≠]** | | |
| **Bowel movements per 24 hours[¥]** | 1.44 (1.20, 1.73) | **<0.001** |
| **Frequency score** | -1.5 (-3.0, 0.0) | **0.03** |
| **Dietary score** | 0.6 (-0.4, 1.6) | 0.23 |
| **Urgency score** | -0.6 (-1.5, 0.3) | 0.20 |
| **MSKCC Q4** | -0.1 (-0.5, 0.3) | 0.47 |
| **MSKCC Q6** | -0.1 (-0.5, 0.3) | 0.54 |
| **MSKCC Q7** | -0.2 (-0.5, 0.1) | 0.12 |
| **MSKCC Q12** | -0.6 (-1.0, -0.3) | **<0.001** |
| **Total score** | -2.7 (-36.0, 0.7) | 0.11 |

*(§) Regression coefficient where a higher value indicates higher score and therefore better function for patients*

*(≠) Adjusted for age, sex, marital status, employment, laxative use and diabetes*

*(¥) Due to log transformation results are reported as the ratio of number of movements in the patient group*

### *Table 5.8 MSKCC values for patients presenting with symptoms of change in bowel habit*

| | Median (IQR) historical score, [n = 35] | Immediate pre-operative values | | 6 month follow-up | | 12 month follow-up | |
|---|---|---|---|---|---|---|---|
| | | Median (IQR) | P | Median (IQR) | P | Median (IQR) | P |
| **Bowel movements per 24 hours** | 1.0 (1.0, 2.0) | 2.0 (1.0, 5.0) | **0.001** | 2.0 (1.0, 3.0) | **<0.001** | 2.0 (1, 2.1) | **<0.001** |
| **Frequency score** | 27 (24, 29) | 22 (19, 26) | **<0.001** | 24 (21, 26) | **0.004** | 24 (21, 28) | **0.003** |
| **Dietary score** | 20 (18, 20) | 18 (14, 20) | **0.001** | 18 (15, 20) | 0.05 | 18 (15, 20) | **0.02** |
| **Urgency score** | 20 (19, 20) | 19 (16, 20) | **0.001** | 20 (18, 20) | **0.01** | 20 (18, 20) | **0.02** |
| **MSKCC Q4** | 4 (4, 5) | 3 (2, 4) | **0.002** | 3 (3, 4) | **0.008** | 4 (3, 5) | 0.16 |
| **MSKCC Q6** | 4 (4, 5) | 3 (3, 5) | **0.03** | 5 (3, 5) | 0.62 | 4 (3, 5) | 0.27 |
| **MSKCC Q7** | 5 (5, 5) | 4 (3, 5) | **<0.001** | 5 (4, 5) | 0.07 | 4 (4, 5) | **0.03** |
| **MSKCC Q12** | 4 (4, 5) | 4 (3, 4) | **0.03** | 4 (4, 5) | 0.82 | 4 (4, 5) | 0.84 |
| **Total score** | 82 (78, 87) | 74 (61, 80) | **<0.001** | 79 (68, 82) | **0.001** | 80 (70, 84) | **0.005** |

### 5.3.3 EQ-5D questionnaire

No difference in the QOL between patients and controls was observed at any time point (Table 5.9). A weak positive correlation was observed between the EQ-VAS score and the ability to control the passage of wind [Q12] (rs 0.30, p 0.005), urgency score (rs 0.29, p 0.007) and the total MSKCC score (rs 0.31, p 0.006) at six months after surgery, indicating that patients able to control wind, those without symptoms of urgency and higher total MSKCC score have better QOL. A similar relationship between the EQ-VAS and the ability to fully evacuate bowels [Q4] was seen at 12 months (rs 0.34, p 0.01). In the 'intermediate' bowel function group, complete evacuation [Q4] was positively correlated with both EQ-5D variables (rs 0.29, p 0.007 and rs 0.25, p 0.02 respectively) whereas knowing the difference between gas and bowel movement [Q7] with EQ-5D-QOL only (p 0.02). The results indicate that for patients in the 'intermediate' bowel function group, full evacuation and the ability to differentiate between wind and solid stool were associated with a better QOL.

***Table 5.9 EQ-5D questionnaire linear regression analysis***

| | **Mean (95% CI) group difference[§]** | **P** |
|---|---|---|
| **Baseline 'early' bowel function group [n = 91]*** | | |
| **EQ-5D-QOL** | -0.01 (-0.07, 0.05) | 0.78 |
| **EQ-VAS** | -2.5 (-9.3, -3.9) | 0.45 |
| **'Early' bowel function group at 6 months**** | | |
| **EQ-5D-QOL** | -0.02 (-0.08, 0.04) | 0.52 |
| **EQ-VAS** | -3.9 (-9.6, 1.8) | 0.18 |
| **'Early' bowel function group at 12 months***** | | |
| **EQ-5D-QOL** | 0.00 (-0.06, 0.06) | 0.95 |
| **EQ-VAS** | -0.3 (-5.9, 6.1) | 0.93 |
| **'Intermediate' bowel function group [n = 85][≠]** | | |
| **EQ-5D-QOL** | -0.04 (-0.11, 0.04) | 0.31 |
| **EQ-VAS** | -2.1 (-7.8, 3.6) | 0.47 |

*(§) Regression coefficient where a higher value indicates higher score and therefore better function for patients*

*(*) Adjusted for age, marital status, employment, diabetes and laxatives*

*(**) Adjusted for age, marital status, employment, diabetes, laxatives and anti-diarrhoeal medication*

*(***) Adjusted for age, marital status, employment, diabetes*

*(≠) Adjusted for age, sex, marital status, employment, laxative use, diabetes*

### 5.3.4 Right sided versus left sided resections

Both patient cohorts undergoing right- or left-sided resections had similar demographic details and post-operative outcomes (Table 5.10 and Table 5.11). Principles of ERAS were followed for post-operative care of all patients and over 80% of procedures were laparoscopic. Anastomotic leakage occurred only in two patients following left-sided resections recruited for assessment of 'early' bowel function. Both were successfully treated with antibiotics only (International Classification grade A)[180].

No difference in QOL between the groups was observed at any time point after surgery. At six and 12 months follow-up, patients who underwent left-sided resections experienced a higher number of bowel movements [2.0 (1.5, 3.3) *vs.* 1.5 (1.0, 2.5), p 0.04 and 2.0 (1.5, 3.0) *vs.* 1.5 (1.0, 2.0), p 0.002 respectively] and slightly lower scores for Q6 (having a second bowel movement within 15 minutes) [4 (3, 5) *vs.* 5 (4, 5) at both time points, p 0.001 and 0.01 respectively]. Results from the intermediate group suggest that few years after surgery this appears to resolve, although this group of patients had a lower frequency score following right-sided resections, indicating worse function (Table 5.12).

*Table 5.10 Demographics details right- vs. left-sided colonic resections for patients recruited for assessment of 'early' bowel function*

| | Right-sided resection (n = 47) | Left sided-resection (n = 44) | P |
|---|---|---|---|
| **M:F** | 22 (47%) : 25 (53%) | 21 (49%) : 22 (51%) | 1.00 |
| **ASA grade** | | | |
| **I** | 7 (18%) | 9 (26%) | 0.22 |
| **II** | 20 (51%) | 21 (60%) | |
| **III** | 12 (31%) | 5 (14%) | |
| **Type of surgery** | | | |
| **Laparoscopic** | 41 (87%) | 37 (86%) | 0.09 |
| **Open** | 5 (11%) | 1 (2%) | |
| **Converted** | 1 (2%) | 5 (12%) | |
| **Median (IQR) LOS, days*** | 6 (4, 10) | 5 (4, 7) | 0.29 |
| **30-day complications** | 14 (30%) | 13 (30%) | 1.00 |
| **30-day readmission** | 0 (0%) | 5 (12%) | **0.02** |
| **30-day reoperation** | 0 (0%) | 0 (0%) | - |
| **Mean (SD) size of the excised specimen, cm**** | 29.4 (12.8) | 27.2 (9.1) | 0.36 |
| **IUCC stage** | | | |
| **I** | 9 (20%) | 11 (26%) | 0.19 |
| **II** | 18 (41%) | 14 (33%) | |
| **III** | 17 (39%) | 14 (33%) | |
| **benign** | 0 (0%) | 4 (9%) | |
| **Distant recurrence at 6 months** | 2 (5%) | 0 (0%) | 0.50 |
| **Distant recurrence at 12 months** | 2 (4%) | 1 (2%) | 1.00 |
| **Chemotherapy** | 19 (40%) | 16 (34%) | **<0.0001** |

*(*) Mann-Whitney test*

*(**) Unpaired t-test*

*Table 5.11 Demographic details right- vs. left-sided colonic resections for patients recruited for assessment of 'intermediate' bowel function*

| | Right-sided resections (n = 48) | Left-sided resections (n = 37) | P |
|---|---|---|---|
| **M:F** | 26 (54%) : 22 (46%) | 10 (27%) : 27 (73%) | 0.015 |
| **ASA grade** | | | 0.22 |
| **I** | 7 (15%) | 8 (22%) | |
| **II** | 33 (68%) | 26 (70%) | |
| **III** | 7 (15%) | 1 (3%) | |
| **not available** | 1 (2%) | 2 (5%) | |
| **Type of surgery** | | | 0.25 |
| **Laparoscopic** | 38 (79%) | 32 (87%) | |
| **Open** | 8 (16%) | 3 (8%) | |
| **Converted** | 2 (5%) | 2 (5%) | |
| **Median (IQR) LOS, days*** | 4 (3, 6) | 5 (4, 6) | 0.15 |
| **30-day complications** | 14 (29%) | 6 (16%) | **0.02** |
| **30-day readmission** | 4 (8%) | 1 (3%) | 0.30 |
| **30-day reoperation** | 1 (2%) | 1 (3%) | 0.68 |
| **Mean (SD) size of the excised specimen, cm**** | 29.4 (12.8) | 27.2 (9.1) | 0.36 |
| **IUCC stage** | | | 0.19 |
| **I** | 6 (12%) | 10 (27%) | |
| **II** | 23 (48%) | 12 (32%) | |
| **III** | 19 (40%) | 15 (41%) | |
| **Distant recurrence** | 1 (2%) | 2 (5%) | 0.50 |

*(*) Mann-Whitney test*

*Table 5.12 MSKCC outcomes right- vs. left-sided colonic resections*

| | Median (IQR) score for right-sided resections | Median (IQR) score for left-sided resections | P |
|---|---|---|---|
| **Baseline 'early' bowel function group [n = 91]** | | | |
| **Bowel movements per 24 hours** | 1.0 (1.0, 1.5) | 1.0 (1.0, 2.0) | 0.68 |
| **Frequency score** | 26 (22, 28) | 27 (23, 28) | 0.72 |
| **Dietary score** | 18 (16, 20) | 19 (17, 20) | 0.71 |
| **Urgency score** | 20 (20, 20) | 20 (20, 20) | 0.88 |
| **MSKCC Q4** | 4 (3, 5) | 4 (3, 5) | 0.53 |
| **MSKCC Q6** | 5 (4, 5) | 4 (4, 5) | 0.15 |
| **MSKCC Q7** | 5 (4, 5) | 5 (4, 5) | 0.77 |
| **MSKCC Q12** | 4 (4, 5) | 4 (4, 5) | 0.50 |
| **Total score** | 80 (75, 84) | 81 (77, 86) | 0.56 |
| **'Early' bowel function group at 6 months** | | | |
| **Bowel movements per 24 hours** | 1.5 (1.0, 2.5) | 2.0 (1.5, 3.3) | **0.04** |
| **Frequency score** | 25 (22, 28) | 25 (22, 26) | 0.27 |
| **Dietary score** | 18 (15, 20) | 18 (15, 20) | 0.73 |
| **Urgency score** | 20 (19, 20) | 20 (18, 20) | 0.96 |
| **MSKCC Q4** | 4 (3, 4) | 4 (3, 4) | 0.29 |
| **MSKCC Q6** | 5 (4, 5) | 4 (3, 5) | **0.001** |
| **MSKCC Q7** | 5 (4, 5) | 5 (4, 5) | 0.98 |
| **MSKCC Q12** | 4 (4, 5) | 4 (4, 5) | 0.43 |
| **Total score** | 80 (73, 84) | 77 (71, 81) | 0.20 |
| **'Early' bowel function group at 12 month** | | | |
| **Bowel movements per 24 hours** | 1.5 (1.0, 2.0) | 2.0 (1.5, 3.0) | **0.002** |
| **Frequency score** | 25 (22, 27) | 23 (21, 27) | 0.17 |
| **Dietary score** | 18 (15, 20) | 18 (16, 20) | 0.62 |
| **Urgency score** | 20 (18, 20) | 20 (18, 20) | 0.88 |
| **MSKCC Q4** | 4 (3, 4) | 4 (3, 5) | 0.73 |
| **MSKCC Q6** | 5 (4, 5) | 4 (3, 5) | **0.01** |
| **MSKCC Q7** | 5 (4, 5) | 4 (4, 5) | 0.50 |
| **MSKCC Q12** | 4 (4, 5) | 4 (3, 5) | 0.23 |
| **Total score** | 79 (70, 84) | 77 (70, 81) | 0.27 |
| **'Intermediate' bowel function group [n = 85]** | | | |
| **Bowel movements per 24 hours** | 2.0 (1.0, 2.5) | 2.0 (1.0, 2.5) | 0.87 |
| **Frequency score** | 24 (21, 26) | 25 (23, 27) | **0.03** |
| **Dietary score** | 18 (15, 20) | 18 (16, 20) | 0.31 |
| **Urgency score** | 20 (18, 20) | 20 (19, 20) | 0.17 |
| **MSKCC Q4** | 4 (3, 4.5) | 3 (3, 5) | 0.81 |
| **MSKCC Q6** | 4 (3, 5) | 5 (3, 5) | 0.86 |
| **MSKCC Q7** | 4.5 (4, 5) | 5 (4, 5) | 0.12 |
| **MSKCC Q12** | 4 (2.5, 4) | 4 (3, 4) | 0.67 |
| **Total score** | 78 (71, 82) | 79 (74, 83) | 0.27 |

## 5.4 Discussion

Almost 50% of patients undergoing surgery for colonic neoplasia have concerns about post-operative bowel function[219]. The colon plays a key physiological role in defecation and fluid balance and understandably patients seek counselling preoperatively. This study was motivated by the need to generate an estimate of bowel dysfunction after hemicolectomy and its effect on QOL as the literature on this subject is scarce. Assuming that the overall bowel function is represented by the total MSKCC score, the results of our study suggest that bowel function of patients undergoing hemicolectomy for neoplasia, as well as their QOL, are comparable to that of healthy controls as early as six months after surgery. However, we also observed that certain elements of the MSKCC questionnaire remain altered one to four years after surgery. At 12 months follow-up patients reported having difficulty discriminating between wind and solid stool whereas those recruited for assessment of 'intermediate' bowel function reported having difficulty controlling the passage of wind. In addition, both of our patient cohorts reported an increased number of bowel movements at each follow-up time point, with one in five patients having more than three motions per day two years after surgery. Although this was significantly higher than the values reported by our controls or previous reports[220, 221], patients do not seem to perceive this as an issue when assessed using the EQ-5D QOL and EQ-VAS scores. However, weak correlation between several items of the MSKCC and their QOL was observed. Patients with higher total MSKCC scores, no symptoms of urgency and those able to control win appear to have a better QOL during the first year after surgery. For patients in the 'intermediate' bowel function group, the ability to fully evacuate their bowel and differentiate between wind and solid stool, was also associated with a better QOL.

Although the number of studies reporting on this subject is small, similar findings have been published previously. Graf et al.[222] reported functional outcomes of patients who underwent anterior resection at least three years previously (n = 70) , comparing them to patients who had undergone hemicolectomy during the same period (n = 40). Although patients reported

a higher number of bowel movements following rectal surgery (16% *vs.* 8% respectively reporting >4 motions per day, p <0.001), no difference was observed between the groups for gas-stool discrimination and emptying difficulties. The majority (88%) of hemicolectomy patients in this cohort described their bowel function as excellent or good. Adachi et al.[208] compared late functional outcomes of patients who underwent anterior *vs.* sigmoid resection using a self-constructed questionnaire, and found that an increased length of resected specimen was associated with worse functional outcomes following sigmoid colectomy (p <0.05). The number of patients reporting poor bowel function however was relatively small (n = 16) which could explain why in our study we found no correlation between the length of the resected specimen and any of the MSKCC items and EQ5D in either patient group.

Although we found a weak correlation between several MSKCC items and the EQ-5D QOL and EQ-VAS scores, the overall QOL of patients in our study was comparable to that of slightly younger control group. Theodoropoulus et al.[221] recently reported the use of SF-36, EORTC QLQ-C30, QLQ-CR29 and GIQLI questionnaires to evaluate patients' QOL at one, six and 12 months after laparoscopic colectomy. These authors reported that at six and 12 months after surgery, almost all QOL scores were better than baseline and were comparable to the general population values. In addition, Ramsey et al.[202] reviewed QOL of long-term CRC survivors more than five years after their initial treatment and found that patients had a relatively high perceived QOL compared to age-matched, population based controls. Therefore, although we utilised a very simple QOL instrument, our findings are in keeping with the previously published studies.

The observed increase in bowel frequency however is not easy to explain taking into account that we found no association between the length of the bowel excised and any of the MSKCC items. In both groups of patients, the pelvic autonomic nerves were preserved. Sarli et al.[220, 223] have suggested that high ligation of inferior mesenteric artery (IMA) during left hemicolectomy can lead to damage of the lower mesenteric ganglion[219], the origin of thoracolumbar sympathetic nerves[224]. This damage, associated with the preservation of the

parasympathetic pelvic nerves, could be responsible for the increased motility of the residual colon and rectum and altered functioning of the internal anal sphincter as sphincter innervation by the thoracolumbar sympathetic nerves has been demonstrated[225, 226]. In addition, animal studies have shown that resection of the ganglion and plexus around the IMA causes contractile abnormalities in the distal colon with an increased number of bowel movements and diarrhoea[227]. Dobrowski et al.[228] recently published a study aimed to investigate functional results after sigmoid resection following ligation or preservation of the IMA origin. The authors reported that at 12 months after surgery increased bowel frequency and incomplete evacuation were more common after IMA ligation with an adverse effect on patients' QOL. However with a total of 43 patients recruited in the study, it is difficult to draw conclusions that are clinically relevant.

Wilson et al.[229] however reported increased incidence of diarrhoea during the early post-operative period following right hemicolectomy. This might be expected as resection of the ileo-caecal valve can result in bile acid malabsorption[230]. Failure of absorption of bile acids in the distal ileum results in bile acid overload in the colon leading to loose stools by various mechanisms including increased colonic motility, mucus secretion and stimulation of defecation[231]. In addition, the colon as an organ demonstrates regional differences. The proximal and distal segments have different embryological origins, and different function. The ascending colon demonstrates the greatest absorptive capability and the chime resides within this segment the longest, maximising its contact with mucosa. As a result the salvage of water and electrolytes is primarily accorded to the proximal colon[232, 233]. The absorption of water primarily follows a para-cellular pathway, although trans-cellular route via protein channels is also available for larger molecules[234]. In the event that a large amount of watery chime is delivered to the colon, the distal colon and rectum contribute to this task, although to a lesser extent[233]. As a result, diarrhoea is more likely to ensue after right, as opposed to a left hemicolectomy.

Despite the prospective nature of this adequately powered case-controlled study, utilising validated questionnaires, there are several potential limitations that may affect the generalizability of our conclusions to patients undergoing colonic surgery. A selection bias exists as only patients and controls willing and able to take part in the study were recruited. These patients and controls are potentially at a higher level of functioning than the average patient population. Recall bias is common in self-reported surveys and a large proportion of our patients presented with a change in bowel habit which may have had an effect on the baseline values for both questionnaires. Although loss to follow-up was relatively low (12%), these patients may have been embarrassed to talk about their bowel function after surgery due to the severity of their symptoms. In addition, having survived cancer may strengthen positive health perceptions in this relatively older patient population if they compare their present health to that at the time of cancer diagnosis. Although the reported QOL is very similar between patients and controls using a very simple QOL questionnaire, one could argue that similar results are likely to be obtained using more elaborate questionnaires such as those described by Theodoropoulus et al.[221] and Ramsey et al.[202].

The results of this study suggest that certain aspects of bowel function after hemicolectomy remain altered years after surgery and should be evaluated further. A study of a similar design presented in this chapter using the MSKCC questionnaire and perhaps more detailed QOL questionnaire could be conducted using our results for power calculation to estimate a more appropriate sample size. Longer follow up would clarify the discrepancy observed between the ‘early’ and ‘intermediate’ bowel function following different resections. In addition, semi-structured interviews may help identify issues that are specific for this patient group and could be used to design a questionnaire for assessment of bowel function following hemicolectomy.

## 5.5 Conclusion

Guided by the results of this study, we can draw several conclusions. These that can be used during pre-operative consultation of patients with colonic neoplasia scheduled to undergo elective hemicolectomy: 1) their overall bowel function and QOL are likely to be similar to that of general population as early as six months after surgery; 2) their bowel function is unlikely to be affected by certain food or drink items any more that it was before surgery or when compared to healthy population; 3) even few years after surgery one in five patients are likely to experience more than three bowel movements per day although this will not affect their QOL; 4) patients undergoing left-sided resections are more likely to experience an increased number of bowel movements during the first 12 months after surgery whereas two to four years after surgery, patients who underwent right sided resections are more likely to be affected; 5) despite the increase in the number of bowel movements per day, the patients should be able to 'hold on' for a reasonable length of time without having an accident or adverse effect on their social activities; 6) at times, they may find it difficult to differentiate between wind and solid stool.

# Chapter 6 Current status of endoscopic full thickness resection of colonic lesions: systematic review

## 6.1 Introduction

The literature published to date supports utilisation of TEMS as an alternative to radical surgery for treatment of a select group of patients with benign rectal polyps and early cancers[78, 79, 137, 235]. The procedure enables preservation of the rectum and results in a full thickness excision of the lesion with an adequate margin of healthy tissue. Interest in developing similar endoscopic full thickness resection techniques (EFTR) for colonic and gastric lesions has increased over the past decade as recently summarised by Kopelman et al[236]. If available, EFTR would obviate the need for radical surgery in a significant proportion of these patients and even replace piecemeal EMR as a procedure of preference. The procedure could minimise the risk of residual intramural disease and recurrence, enabling a more accurate assessment of resection margins and depth of invasion in the full thickness specimen. Several research groups have described surgical procedures as potential alternatives to hemicolectomy both in clinical and preclinical models[142-144, 237, 238].

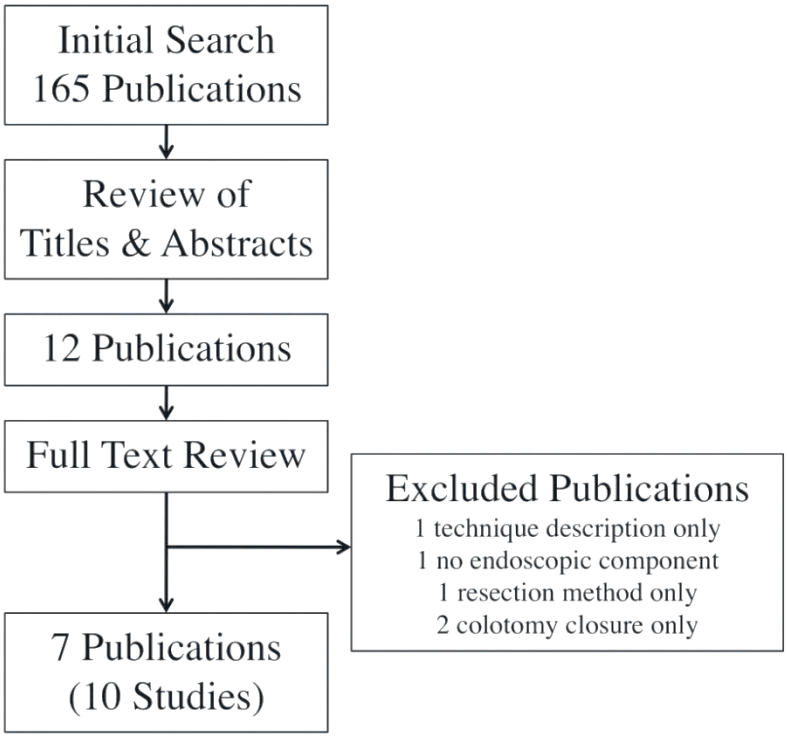
In addition, a description of a hybrid technique called the Full thickness Laparo-endoscopic EXcision (FLEX) recently technique[173] published from our institution. Although the procedure was successfully performed in both acute and survival animal models, technical issues encountered have prevented the development of a translational study. These are discussed in detail in Chapter 7. Prior to attempting to modify the original FLEX technique, we conducted a systematic review of the studies describing colonic EFTR, focusing on clinical outcomes and technical aspects, to assess the feasibility and safety of this approach.

## 6.2 Methods

### 6.2.1 Study selection

The published literature was searched using OVID SP for MEDLINE, EMBASE and PsychINFO databases for studies reporting EFTR of colonic lesions published between January 1990 and June 2012. Both animal and human studies were included. The search strategy is presented in Figure 6.1. Duplicate records were excluded and two reviewers (A.B. and N.R.A.S) independently screened titles and abstracts of the remaining citations in order to obtain full text articles of the potentially eligible studies. Reference lists of these articles were also searched for additional relevant publications.

***Figure 6.1 Literature search***




### 6.2.2 Study eligibility

All studies describing full thickness colonic resection and defect closure were eligible for inclusion in the review. Conference proceedings, abstracts and case reports were excluded as they lacked sufficient detail. Only articles published in English were included. Any

disagreement about eligibility was resolved by discussion with the third assessor (S.K.C.). Two authors (A.B. and N.R.A.S) extracted the data from included papers using a predefined protocol.

### 6.2.3 End points

The primary end point was successful *in vivo* completion of an endoscopic or a laparo-endoscopic full thickness colonic resection and subsequent closure of the resulting defect. Secondary end points were intraoperative complications, anastomotic bursting pressures, procedure duration, size and quality of the excised specimen, post-operative complications and post-mortem findings.

## 6.3 Results

### 6.3.1 Published studies

A total of seven publications[173, 237-242] published by five research groups were retrieved by the search strategy. These publications included 10 studies describing full thickness colonic resection and closure of the defect using acute and survival porcine models. The adult pig is accepted as a suitable model for studying gastrointestinal tract interventions due to the similarities to the human in anatomy, vascular supply of the rectum and sigmoid segment as well as the thickness of colonic wall[237]. Von Renteln et al. reported two different closure methods[238, 242] whereas Schurr et al.[237] described three separate studies in a single publication. For the purpose of this review, these are referred to as independent studies. Experimental work in human cadavers, an ex-vivo porcine model and an acute animal study were described by Rieder et al.[241], but EFTR procedure was performed in its entirety only in the latter study. Therefore, only the results of this complete procedure were included in the review (Table 6.1).

***Table 6.1 Summary of procedural methods***

| Study authors | Procedure | Approach | Study type | No. of animals |
|---|---|---|---|---|
| Schurr et al., 2001[237] | EFTR performed by conventional circular stapler | Laparotomy with endoscopic resection (pre-RCM) | A & S | 10 & 5 |
| | EFTR performed by endoscopic FTRD | Endoscopic only (pre-RCM) | S | 5 |
| | EFTR performed by endoscopic FTRD | Laparoscopically monitored endoscopic resection (pre-RCM) | A | 10 & 10 |
| Rajan et al., 2002[239] | EFTR performed by endoscopic FTRD | Endoscopic only (pre-RCM) | S | 8 |
| Raju et al., 2009[240] | EFTR performed using endoscopic knife/snare and interrupted TAS for defect closure | Endoscopic only (post-RCM) | S | 20 |
| Von Renteln et al., 2010[238] | Snare resection of the lesion followed by OTSC application using twin-grasper to approximate colotomy edges | Endoscopic only (post-RCM) | A | 10 |
| | Endoloop applied to the base of the pseudopolyp prior to snare resection; closure reinforced by application of OTSC over the endoloop | Endoscopic only (pre-RCM) | A | 4 |
| Rieder et al., 2010[241] | Tissue manipulated into an OTSC using TAS where the clip was applied prior to snare resection | Laparoscopically monitored endoscopic resection (pre-RCM) | A | 2 |
| Von Renteln et al., 2011[242] | Tissue manipulated into an OTSC using a grasper followed by snare resection above the clip | Endoscopic only (pre-RCM) | S | 8 |
| Kennedy et al., 2011[173] | Inversion of the bowel segment achieved using laparoscopic BBs placed on either side of the polyp; the inverted area is over-sewn laparoscopically and pseudopolyp resected endoscopically | Laparoscopically assisted endoscopic resection (pre-RCM) | A & S | 3 & 4 |
| **Total Row** | | | | **99** |

***Abbreviations:*** *EFTR = endoscopic full thickness resection; FTRD = full thickness resection device; pre-RCM = pre-resection closure method; post-RCM = post-resection closure method; A = acute study; S = survival study; OTSC = Over-The-(endo)Scope Clip; TAS = tissue apposition system; BB = brace bars*

Six out of seven publications[173, 238-242] reported details of ethical approval to conduct the research. There was a significant variation in weights of animals utilised in these studies, ranging from 20kg to 74.9kg. Details of pre-operative starvation protocols were described in three studies[173, 239, 240]. The distal colon was prepared using pre-operative oral bowel preparation[239], intraoperative colonic lavage[173, 238, 241, 242] or a combination of both[240]. Isoflurane was the most commonly used anaesthetic agent (5/9). A total of 113 procedures were performed in 99 animals, 50 of which were enrolled in survival studies.

### 6.3.2 Procedural methods

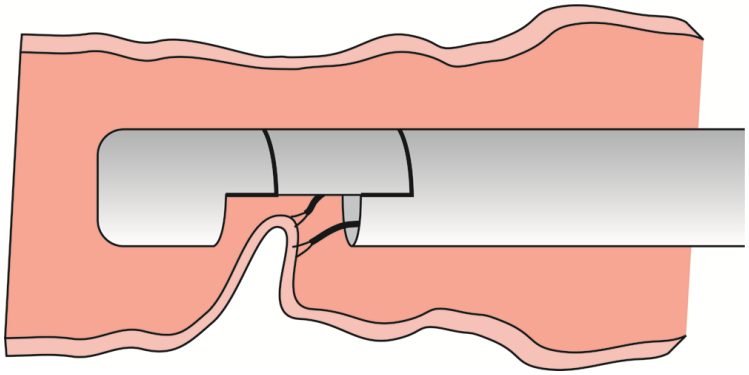
Studies included used either a 'pre-resection' closure method, in which the colonic wall was plicated and anastomosed prior to resection, or a 'post-resection' closure, where specimen resection preceded defect closure. Combined stapling/cutting devices were considered as pre-resection closure methods as the abdominal cavity was not exposed to endoluminal contents. The resection techniques and closure methods employed varied significantly between the studies and a brief summary is presented in Table 6.1.

#### *6.3.2.1 Full thickness resection device (FTRD)*

Schurr et al.[237] and Rajan et al.[239] described the use of a Full Thickness Resection Device (FTRD) consisting of a hollow flexible shaft with a resection head (Figure 6.2). An endoscope with an outer diameter of 9.8mm was introduced into the central channel alongside tissue manipulators in order to manoeuvre colonic tissue under direct endoscopic vision. The head of the device contained a resection chamber surrounded by a semi-circular stapler and a cutting blade. The device was available in a rectal (25cm) or colonic (50cm) version. In the first study reported by Schurr et al.[237] the FTRD was still under development and a conventional surgical stapler was used as a predicate device to imitate the procedure. In this study, following a midline laparotomy and mobilisation of the sigmoid colon, the circular stapler was inserted transanally. Both colon and its accompanying mesentery were manoeuvred into one side of the stapler and a semi-circular resection and anastomosis were

performed. The procedure was undertaken in 10 acute and five survival animals. Two studies reported in the same paper and an additional study published by Rajan et al.[239] were performed using the FTRD with the aim of assessing the feasibility and safety of EFTR. Both authors described placing coagulation marks on the colonic mucosa to simulate a target lesion of approximately 3cm in diameter. Following transanal insertion of FTRD, the lesion was manoeuvred into the resection chamber using either traction or suction. The device was deployed creating a stapled full thickness resection.

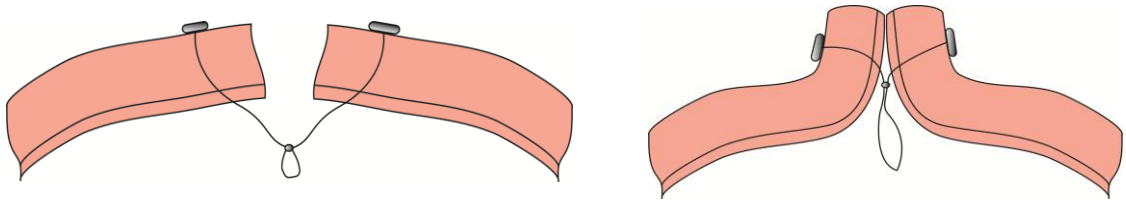
***Figure 6.2 Tissue manipulation into the head of the FTRD under endoscopic vision***



#### *6.3.2.2 Post-resection closure method using Tissue Apposition System (TAS)*

In the paper published by Raju et al.[240], EFTR was performed on the mesenteric (n = 10) and anti-mesenteric (n = 10) side of the colon. The authors created a colotomy using an insulated needle-knife and a snare for excision. The resulting defect was closed with a series of Tissue Apposition Systems (TAS) (Ethicon, Endo-Surgery Inc., Cincinnati, Ohio) (Figure 6.3). This was a single application system and it was reloaded as many times as necessary to close the defect.

***Figure 6.3 Step-by-step closure of the colonic wall defect using T-tags***



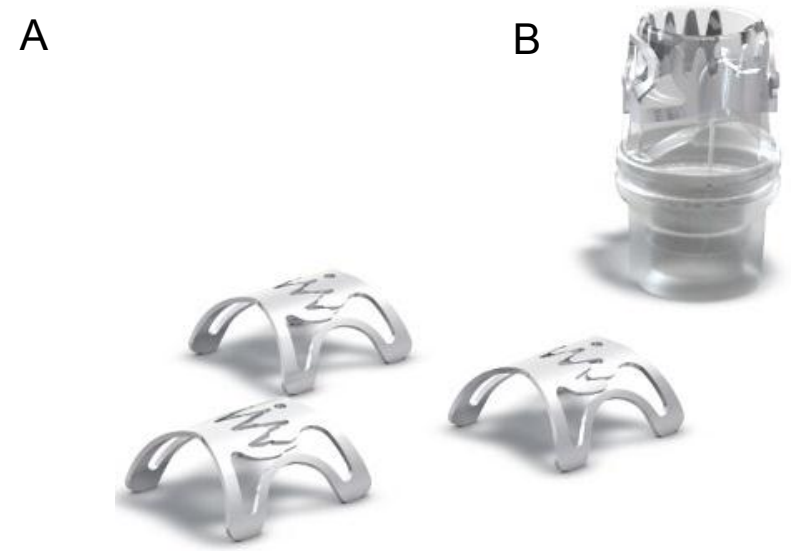
#### *6.3.2.3 Pre- and post-resection closure using Over-The-(endo)Scope-Clip device*

Several variations of a grasp and snare technique were described by Von Renteln et al.[238, 242] and Rieder et al.[241]. An Over-The-(endo)Scope-Clip (OTSC) (Ovesco Endoscopy, Tubingen Germany (Figure 6.4) was used for both pre- and post-resection closure methods described in the first paper published by Von Renteln et al.[238]. A tissue anchor (Ovesco Endoscopy, Tubingen, Germany), introduced through a double channel gastroscope (2T160, Olympus, Hamburg, Germany), deployed three needles at its tip in order to grasp the bowel wall creating a colonic fold. Eight procedures were performed in four animals in which the base of the colonic fold was ligated with an endoloop (HX-400U-30, Olympus) prior to snare resection (2.5cm snare, SD-990, Olympus). An OTSC was then loaded onto a transparent 14mm cap at the end of the endoscope and applied at the base of the endoloop. This group is referred to as the pre-resection closure group. A further 20 procedures were performed in 10 animals with defect closure subsequent to the resection (post-resection closure method). The edges of the resulting colotomy were manipulated into the cap using a twin grasper (Ovesco, Endoscopy) and one or more OTSCs were applied to close the defect.

In the subsequent paper published by the same research group[242], a modified pre-resection closure method was described. Following colonic lavage, mucosal diathermy marks were placed to simulate a 2cm polyp. In this series a single channel endoscope (EG-2940, Pentax, Hamburg, Germany) was fitted with a transparent cap preloaded with an OTSC and a snare. The delineated area of the colonic wall was manipulated is into the cap using

forceps (FG-42-L, Olympus, Hamburg, Germany) and OTSC deployed at the base inverting a full thickness of colonic wall. The specimen was resected with a snare taking the tissue superficial to the clip.

***Figure 6.4 Schematic illustration of the clip closure device described.***




***A.** Over-The-(endo) Scope Clip (OTSC); **B.** OTSC loaded onto a cap*

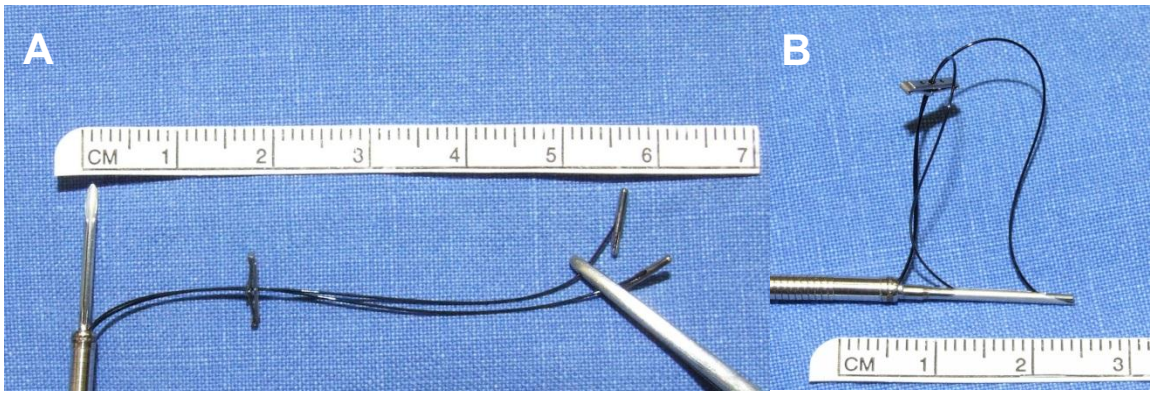
A pre-resection closure method using the same closure system (OTSC, Ovesco Endoscopy, Tubingen, Germany) mounted on a dual channel gastroscope (GIF-2T-160, Olympus) was also described by Rieder et al.[241]. In an attempt to improve excision accuracy, anchoring TAS were placed at a predetermined distance from a simulated lesion to draw colonic wall into the cap with the aid of suction. Subsequent to this, the OTSC was deployed at the base of the inverted fold and a standard snare (Boston, Scientific) was used to resect the tissue superficial to the clip. This procedure was performed with laparoscopic overview.

#### *6.3.2.4 Full thickness Laparo-endoscopic EXcision (FLEX) technique*

The technique developed in our institution[173] was also identified during the literature search. This hybrid laparo-endoscopic approach requires two operators (a surgeon and an

endoscopist), two working endoscopes (R-scope, Olympus, Keymed and GIF-Q240, Olympus Keymed) and a prototype double lumen anal sealing device. A simulated polyp was created by submucosal injection of black ink (Spot®) and circumferential argon plasma coagulator (APC) marks were placed 1cm away from the edge of the polyp. A laparoscopic bowel clamp was placed proximally to prevent proximal bowel insufflation. Three pairs of the prototype BraceBars™ (BBs) (Olympus Medical Systems, Olympus) were placed 1cm away from the mucosal APC marks, in order to invert the area of the colon bearing the polyp. The BraceBars™ system consisted of a bifurcating nylon thread with a small tag at each end and a tag-tightener (Figure 6.5). Each pair was preloaded into a needle catheter used to perforate the serosal surface of the colon laparoscopically (from the outside in).

***Figure 6.5 BraceBars™ System***




***A.*** *The thread that connects two BBs is secured in the needle;* ***B.*** *BBs preloaded into the needle catheter before the needle is retracted into the catheter with the tightener*

To ensure the correct placement of BBs, diathermy marks were placed on the serosal surface 1cm away from the endoluminal APC marks for guidance. This was achieved by endoscopic assistance by applying pressure to the colonic wall (from the inside out) using grasping forceps. Once the tags were deployed and approximated using the tightener, the excess suture was cut and the process repeated. The inversion site (approximately 6cm in length) was over-sewn laparoscopically in two layers. The endoluminal fold of the colon created during the inversion process was resected endoscopically using a hook or triangle

knife (Olympus, Keymed). One endoscope was used as a working platform for cutting (R-scope, Olympus, Keymed) while the second endoscope provided traction (GIF-Q240, Olympus Keymed). Mucosal APC marks and BBs visible endoluminally provided guidance during the resection process to ensure that adequate margin of clearance was achieved. Procedural steps of the technique are presented in the Figure 6.6.

### 6.3.3 Feasibility

#### *6.3.3.1 Complete resection and defect closure*

From the studies included in this review, the overall EFTR completion rate was 89% with a mortality rate of 4% (Table 6.2). Although excision of the lesion was achieved in all procedures regardless of the resection method, failure to close the defect in studies describing a post-resection closure method was a common problem[238, 240, 242]. Raju et al.[240] reported snapping of TAS sutures in 1/20 (5%) animals leaving a 3 to 4cm colonic wall defect. Post-resection defect closure using the OTSC system with the aid of twin graspers was successful in only 9/20 (45%) cases [238]. Von Rentlen et al.[238] however reported failure to close the defect in 11/20 (55%) animals, mainly in those with defects exceeding 2.9cm in diameter.

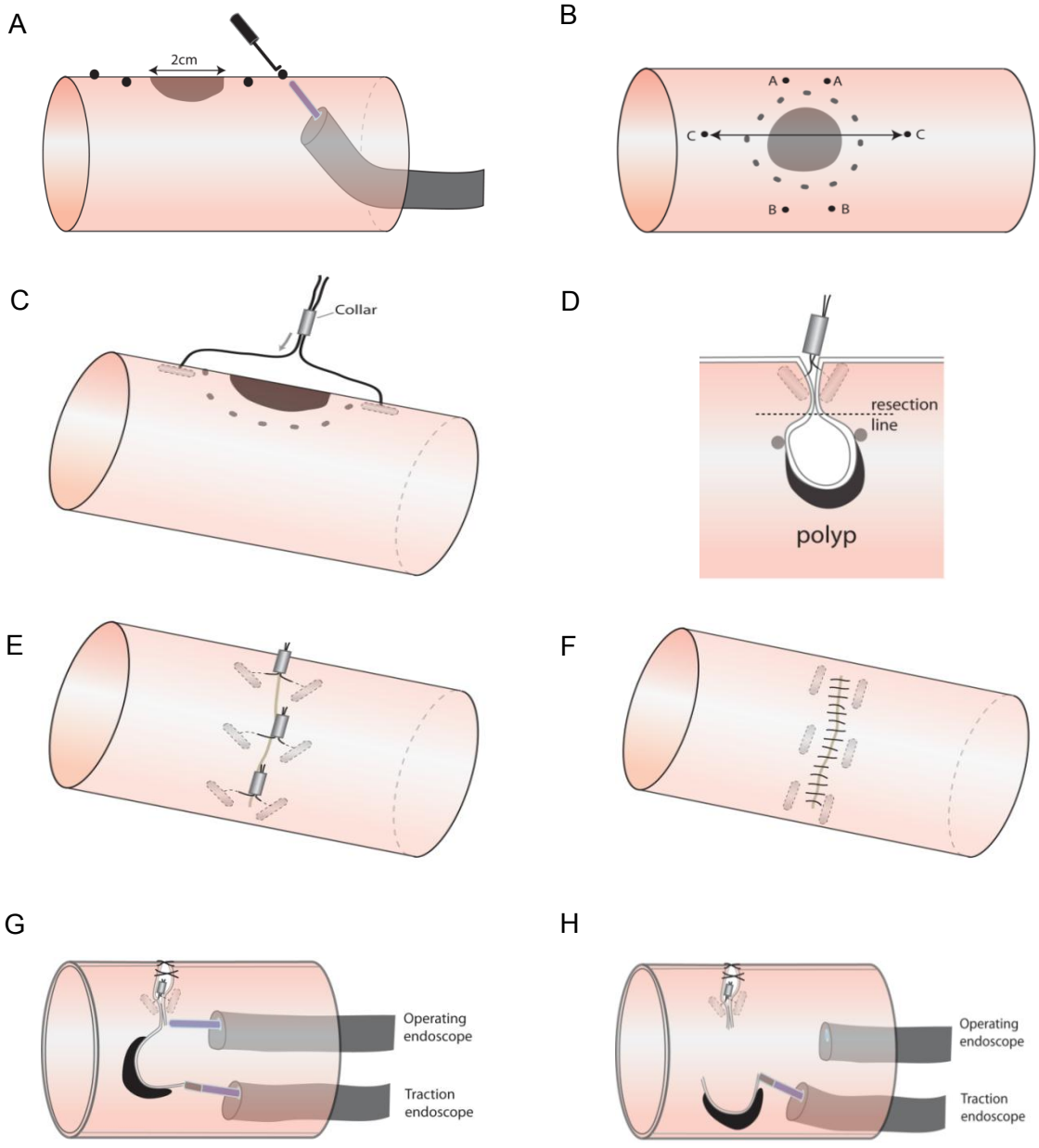
### 6.3.4 Safety

#### *6.3.4.1 Intraoperative complications*

In animals where EFTR was successfully completed, the overall procedural complication rate was 22%, ranging from 0% to 67% (Table 6.2). These complications included both clinical problems and equipment related issues. Rajan et al.[239] used 10 FTRD devices for eight procedures as failure to staple occurred in two animals due to the engagement of a safety 'lock-out' mechanism. Failed devices were replaced and procedures were completed successfully. Incomplete cutting of the tissue occurred in another animal leaving a narrow tag of tissue attached at the end of the resection line that was cut with electrosurgical snare. Rajan et al.[239] also reported transient bleeding at the resection site in one animal, in keeping

with findings reported by Schurr et al.[237] who observed small haematomas (range 2 – 20mm in diameter) close to the staple line in five acute animals treated with the FTRD.

***Figure 6.6 Schematic illustration of the FLEX technique as described originally***




***A.*** *Placement of endoluminal APC and serosal diathermy markings;* ***B.*** *Circumferential APC marks visible endoluminally delineate lateral clearance margin whereas serosal diathermy markings (A, B and C) indicate position of BBs;* ***C*** *&* ***D.*** *Laparoscopic placement of BBs including side-view of the colonic fold inverted into the lumen (clear resection line is visible between BBs and APC marks);* ***E*** *&* ***F.*** *Inversion site is over-sewn laparoscopically;* ***G*** *&* ***H****. Pseudopolyp is retracted and excised*

Von Renteln et al.[238] reported complications in 6/9 (67%) animals associated with the post-resection closure method using the OTSC system. In one case, the anchor pins were placed through the colonic wall into the adjacent small bowel wall resulting in small bowel perforation. Defect closure using OTSCs resulted in luminal obstruction at the site of anastomosis in three animals. In addition, OTSC closure was associated with incorporation of a loop of small bowel into the clip, resulting in bowel obstruction in two animals. Fewer complications (2/8 animals) were observed in the pre-resection closure arm of this study including lumen obstruction following OTSC application (n = 1) and cutting of the endoloop during snare resection (n = 1). The resulting defect was successfully closed with application of an OTSC. The same research group subsequently described a modified method of pre-resection closure in eight animals and concluded that this approach was more successful with complications occurring in only two animals[242]. The OTSC failed to deploy in one case leaving a large colonic defect. Although the defect was successfully closed with application of two clips this resulted in lumen obstruction and the animal was euthanized immediately. Incomplete closure was observed in one additional case that was rectified by the application of two clips, resulting in closure and a patent lumen.

Schurr et al.[237] described manipulating tissue into the FTRD using either suction or tissue graspers. Small bowel entrapment into the closure device occurred when suction was applied to aid tissue manipulation into the device. Similar findings were reported by another group investigating closure of colonic perforation using OTSC[243]. Accidental incorporation of adjacent organs was greatly reduced by the use of traction to manipulate colonic wall, rather than suction in both studies.

***Table 6.2 Intraoperative outcome measures***

| Study authors | Study type | Procedure method | Procedure completed | Intraoperative complications | Procedure duration, min | Median (range) size of the excised specimen, cm |
|---|---|---|---|---|---|---|
| **Schurr et al., 2001**[237] | A | Circular stapler | 10/10 (100%) | 5/10 (50%) | - | - |
| | S | Circular stapler | 5/5 (100%) | 0/5 (0%) | - | - |
| | S | Traction into the FTRD | 5/5 (100%) | 0/5 (0%) | - | Over 3 |
| | A | Suction (S) or traction (T) | 20/20 (100%) | (S) 3/10 (30%)<br>(T) 0/10 (0%) | - | - |
| **Rajan et al., 2002**[239] | S | Traction into the FTRD | 8/8 (100%) | 4/8 (50%) | Mean 30.2 | Mean 3.6 (1.5 – 5.2) |
| **Raju et al., 2009**[240] | S | Post-RCM using TAS | 19/20 (95%) | 0/19 (0%) | Marking: median 3 (1 – 7)<br>Resection: median 6 (2.5 – 35)<br>Closure: median 41 (21 – 125)<br>**Overall: median 50 (24.5 – 167)** | Median 1.7 (1 – 2.5) |
| **Von Renteln et al., 2010**[238] | A | Post-RCM using OTSC | 9/20 (45%) | 6/9 (67%) | Resection: mean 4 (2 – 10)<br>Closure: mean 10.8 (5 – 26)<br>**Overall: mean 14.8 (7 – 36)** | Mean 3.3 (2.4 – 5.5) |
| | A | Pre-RCM using endoloop | 8/8 (100%) | 2/8 (25%) | Resection: mean 27.9 (19 –36)<br>Closure: mean 3.6 (2 – 6)<br>**Overall: mean 31.5 (21 – 42)** | Mean 1.8 (1.2 – 2.2) |
| **Rieder et al., 2010**[241] | A | Pre-RCM using OTSC | 2/2 (100%) | 0/2 (0%) | Mean 33 +/- 4 | Mean 2.2 (0.1) |
| **Von Renteln et al., 2011**[242] | S | Pre-RCM using OTSC | 8/8 (88%) | 2/8 (25%) | Median 3 (2 – 12) | 7.6cm$^2$ (5.4 – 11cm$^2$) |
| **Kennedy et al., 2011**[173] | A | Laparo-endoscopic | 3/3 (100%) | 0/3 (0%) | - | Median 2.5 (2 – 3) |
| | S | Laparo-endoscopic | 4/4 (100%) | 0/4 (0%) | Median 233 (201 – 245) | Median 3.5 (3.5 – 4) |
| **Total** | | | **101/113 (89%)** | **22/101 (22%)** | | |

***Abbreviations:*** *A = acute study; S = survival study;FTRD = full thickness resection device; post-RCM = post-resection closure method; pre-RCM = pre-resection closure method; TAS = tissue apposition system; OTSC = Over-The-(endo)Scope Clip*

### 6.3.4.2 Bursting pressures

Five studies[173, 237, 238, 240] reported examining anastomotic integrity (Table 6.3). Raju et al.[240] used methylene blue dye only to detect a leak in the acute study. Two studies reported bursting pressures following acute[237, 238] and one after survival experiments[173]. Although Schurr et al.[237] reported pressures of >38mmHg for FTRD stapled anastomosis, values presented by von Renteln et al.[238] differed significantly between pre- and post-resection closure. The combination of an endoloop with the OTSC produced a higher mean pressure (Table 6.3). Kennedy et al.[173] were the only group to report bursting pressures following a survival study with a median pressure of 245mmHg following a laparoscopic hand-sewn, partial-circumferential anastomosis.

***Table 6.3 Colonic anastomosis bursting pressure***

| Study authors | Study type | Closure method | Testing method | Mean (SD) bursting pressure, mmHg |
|---|---|---|---|---|
| **Schurr et al., 2001[237]** | A | FTRD | Not clear | >38 |
| **Raju et al., 2009[240]** | S | Post-RCM using TAS | Blue dye | - |
| **Von Renteln et al., 2010[238]** | A | Post-RCM using OTSC | Inflation using sphygmomanometer under immersion | 29.2 (29.92) |
| | A | Pre-RCM using endoloop | Inflation using sphygmomanometer under immersion | 76.6 (31) |
| **Kennedy et al., 2011[173]** | S | Laparo-endoscopic | Inflation using sphygmomanometer under immersion | Median 245 [240 – 260] |

***Abbreviations:*** *A = acute study; S = survival study; FTRD = full thickness resection device; pre-RCM = pre-resection closure method; post-RCM = post-resection closure method; TAS = tissue apposition system, OTSC = Over-The-(endo)Scope Clip*

### 6.3.4.3 Duration of the procedure, size and quality of the excised specimen

Data on procedure duration was recorded in six studies[173, 238-242], however, significant heterogeneity in reporting was observed. Procedure duration ranged from 2 to 245 minutes with the mean or median ranging from 3 to 233 minutes (Table 6.2). Variation in the size of

the excised specimen was also observed with a mean or median diameter between 1.7cm and 3.6cm in diameter[173, 237-242].

Six studies[173, 237, 239-242] reported placing mucosal markings (diathermy or India ink) to serve as a simulated lesion and the quality of the excised specimen was assessed in five studies[173, 237, 239, 241, 242]. Only two research groups[173, 241] reported a well-defined clearance margin. Rieder et al.[241] placed T-tags in each quadrant surrounding the lesion in order to draw the delineated area into the OTSC cap and four sutures were present in all resected specimens. During the FLEX procedure[173] circumferential APC marks were placed 1cm away from the edge of the lesion with the excision line being between the APC marks and BBs visible endoluminally. Adequate clearance margin was achieved in all cases. Unfortunately, the authors were unable to maintain adequate endoscopic traction during resection. Consequently, the excision was tangential to the inverted bowel with the diameter of the excised mucosa being larger than that of the serosa. Similar findings were reported by Rajan et al.[239] who used tissue manipulators to pull the delineated area of the colon into the head of the FTRD. Although diathermy markings representing a simulated lesions were evident in all specimens, the mucosal surface was wider [mean 3.8 (SD 0.9) cm] than the serosal surface [mean 2.41 (SD 0.6) cm]. Rajan et al.[239] did not comment on adequacy of the lateral clearance margin. Schurr et al.[237] and Von Renteln et al.[242] reported that the diathermy markings used to simulate the lesion were visible in all resection specimens but again did not comment on the lateral clearance margin.

#### *6.3.4.4 Post-operative complications and post-mortem examination*

Post-operative complications were observed in 4/48 (8%) of the survival cases[173, 239, 240] (Table 6.4). Rajan et al.[239] described two complications occurring in two animals (transient hind leg weakness post-procedure and an oedematous anal skin tag), both of which resolved spontaneously. Failure to thrive was observed by Raju et al.[240] in 1/19 cases. Following the FLEX procedure[173] re-suturing of a laparoscopic port site was required in one animal.

Post-mortem examination was performed by all research groups but abnormal findings were only observed by two[239, 240]. Rajan et al.[239] reported ulceration at the stapled resection line in three out of four animals terminated at 14 days, but normal anastomoses in animals terminated at 28 days. They also noted adhesions between the resection margin and adjacent small bowel in one animal. Raju et al.[240] were the only research group to describe post-resection closure method in survival experiments, reporting a high incidence of abnormal findings on post-mortem (84%).

***Table 6.4 Post-operative complications and post-mortem examination findings***

| Study authors | Survival | Post-operative complications | Abnormal findings on post-mortem examination |
|---|---|---|---|
| **Schurr et al., 2001[237]** | 5/5 (100%)<br>5/5 (100%) | 0/5 (0%)<br>0/5 (0%) | 0/5 (0%)<br>0/5 (0%) |
| **Rajan et al., 2009[239]** | 8/8 (100%) | 2/8 (25%) | 4/8 (50%) |
| **Raju et al., 2009[240]** | 19/20 (95%) | 1/19 (5%) | 16/19 (84%) |
| **Von Renteln et al., 2011[242]** | 7/8 (88%) | 0/7 (0%) | 0/7 (0%) |
| **Kennedy et al., 2011[173]** | 4/4 (100%) | 1/4 (25%) | 0/4 (0%) |
| **Total** | **48/50 (96%)** | **4/48 (8%)** | **20/48 (42%)** |

These included mild fibrinous peritoneal deposits (n = 1), local (n = 6) adhesions, small abscesses (<5mm) at the closure site (n = 2), away from the closure site (n = 3) as well as distant abscess (n = 1). A small anastomotic leak was demonstrated using methylene blue in one animal which failed to thrive during the recovery period. The authors also reported that two of the total 132 TAS used, were inserted into the adjacent viscera.

## 6.4 Discussion

This is the first systematic review that summarizes clinical outcomes following colonic EFTR as well as description of complete procedures published to date. Current experience is limited to pre-clinical studies only and although the concept appears to be feasible, further

advances in technology are necessary before this research can be translated into clinical practice. To date, EFTR has only been successfully performed in 89% of animal experiments presented in this review, with an overall survival rate of 96%.

Although several EFTR procedures have been described, problems exist with every approach. Full thickness resection of the colonic wall was successfully performed using all techniques but secure closure appears to be a major obstacle. Post-resection closure with systematic application of TAS was reported to be effective in 95% of cases[240]. The post-mortem findings in this study however suggest that the risk of peritoneal contamination with this method of colotomy closure is high. Many colonic polyps managed surgically carry a risk of containing a focus of malignancy[183] and therefore during this procedure potentially malignant cells could seed into the peritoneal cavity. Pre-resection closure methods such as those described by Von Renteln et al.[238, 242], Rider et al.[241] and Kennedy et al.[173] are clearly preferable as they minimise the risk of peritoneal contamination. Although several pre-clinical and clinical studies evaluating effectiveness of Natural Orifice Transluminal Endoscopic Surgery have suggested that the risk of intra-abdominal sepsis following trans-gastric or trans-vaginal approach is low[244-247], in the context of EFTR for complex colonic polyps this should be avoided in the view of their malignant potential.

It is difficult to consistently provide large colonic specimens with adequate lateral clearance margins using the grasp-and-snare techniques described to date. Additional risks with this approach include damage to the specimen with malignant potential and bowel perforation. The authors of the FLEX technique[173] successfully addressed these issues by defining the resection line to be between the APC marks and BBs and performing the procedure with laparoscopic assistance. The resulting specimens had adequate mucosal clearance but due to tangential resection, a significantly smaller serosal surface area was observed. Similar findings were reported by Rieder et al.[241] using the grasp-and-snare pre-resection closure method. This limitation may only be rectified by development of an endoscope with

additional, independent retracting arms and better endoluminal or extraluminal retraction as demonstrated by Kennedy at al[173].

The method of closure needs to be carefully considered. Anastomotic leakage is a major problem following colorectal surgery, increasing morbidity and occasionally resulting in death. Automatic stapling devices are the most frequently utilised technique of colorectal anastomosis and for this reason, the cutting and stapling device (FTRD) described by Schurr et al.[237] and Rajan et al.[239] was initially met with enthusiasm. The lack of further development of this device presumably reflects dissatisfaction with its performance. Two research groups[238, 241, 242] have demonstrated that pre-resection compression closure with OTSCs although feasible, can lead to luminal obstruction and/or damage of surrounding structures[237, 238, 240] following application of one or more clips. It is possible that the risk of luminal obstruction secondary to OTSC application would be lower when applied in human colon as the pigs used in these studies were relatively small (range 20 – 58kg). In addition, traction of the polyp rather than suction resulted in less collateral damage, although safety during closure could potentially be further enhanced with laparoscopic overview or assistance[173, 241]. More importantly however, the risk of anastomotic dehiscence following a partial circumferential anastomosis remains. Prior to translating this research into clinical studies, the safety of the chosen anastomotic closure technique should be formally tested using anastomotic bursting pressure analysis. At present, it is difficult to formulate a conclusion on anastomotic quality following OTSC compression closure based on the bursting pressures reported in a single acute study[238]. If compression closure devices are to be considered as an alternative to other closure methods, further survival studies are necessary to demonstrate their safety.

## 6.5 Conclusion

Current experience with colonic EFTR is limited to porcine models only. Findings presented in this review suggest that the concept is feasible however none of the techniques described to date are suitable for translational studies. The review however does highlight several challenges that need to be addressed in future studies. Oncological principles must be followed and therefore minimal handling of the lesion and precision during resection are required in order to provide a full thickness specimen with adequate clearance margin. Luminal obstruction and peritoneal contamination with endoluminal content must also be avoided. A purely endoscopic full thickness resection technique is unlikely to be successful with the currently available technology, and development of a hybrid procedure with laparoscopic overview or assistance may minimise the risk of collateral damage.

# Chapter 7 *Ex vivo* evaluation of the FLEX technique

## 7.1 Introduction

The original FLEX technique was successfully performed in three acute and four survival animals. Following interrogation of the literature published to date, it is evident that very few documented EFTR techniques follow oncological principles. Only the authors of the FLEX technique[173] and Rieder et al.[241] clearly defined a clearance margin before applying a pre-resection closure method with laparoscopic overview. Although no major intra- or post-operative complications were encountered, four main issues precluded its application in a clinical setting: 1) maintenance of the airtight seal was difficult despite using a prototype anal sealing device to maintain pneumocolon following insertion of two separate endoscopes; 2) the inability to maintain adequate traction by the retracting endoscope led to tangential excision of the specimen with the diameter of the excised mucosa being larger than that of the serosa; 3) the median size of the excised specimen was 2.5cm (range 2 to 3cm) and if the technique is to be applied in patients with large, complex colonic polyps, the ability to reliably deliver specimens exceeding 3cm in diameter is necessary; 4) lastly, the procedure itself was lengthy with a median duration of 233 minutes (range 201 to 245 minutes).

In this chapter, experiments to address the aforementioned limitations of the FLEX technique are described. These aimed to increase the size of the excised specimen whilst avoiding tangential excision and reducing procedure time in an *ex vivo* setting.

## 7.2 Detailed evaluation of the FLEX technique

### 7.2.1 Introduction

*In vivo* modifications of the originally described FLEX technique could not be justified. In order to avoid unnecessary sacrifice of animals, a major component of the experiments

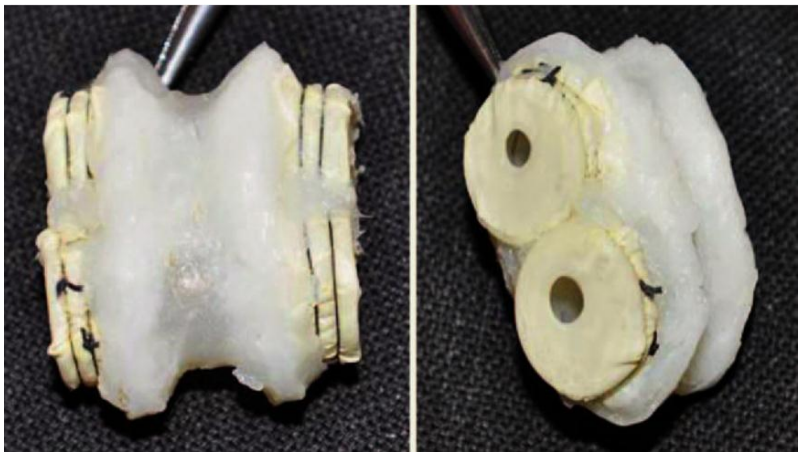
presented in this chapter was development of an appropriate *ex vivo* model in which step-wise improvements to the FLEX technique could be assessed.

### 7.2.2 Materials and methods

#### *7.2.2.1 Modification of the anal sealing device*

The original anal sealing device was made using two pieces of corrugated anaesthetic tubing (length 60mm, internal diameter 20mm). The fingers of a surgical glove (size 8) were cut off and a 6mm skin biopsy cutter was used to make a hole at the fingertip. A glove finger was placed tightly over each end of the tube, stretching the hole to accommodate endoscopes exceeding 9.8mm in diameter. The tubes were joined using thread and secured with silicone (standard bathroom sealant) (Figure 7.1). Silicone ridges were created at each end so once inserted into the anus, the sphincters lay between the two ridges to increase the quality of the seal and to assist in retaining the position of the device.

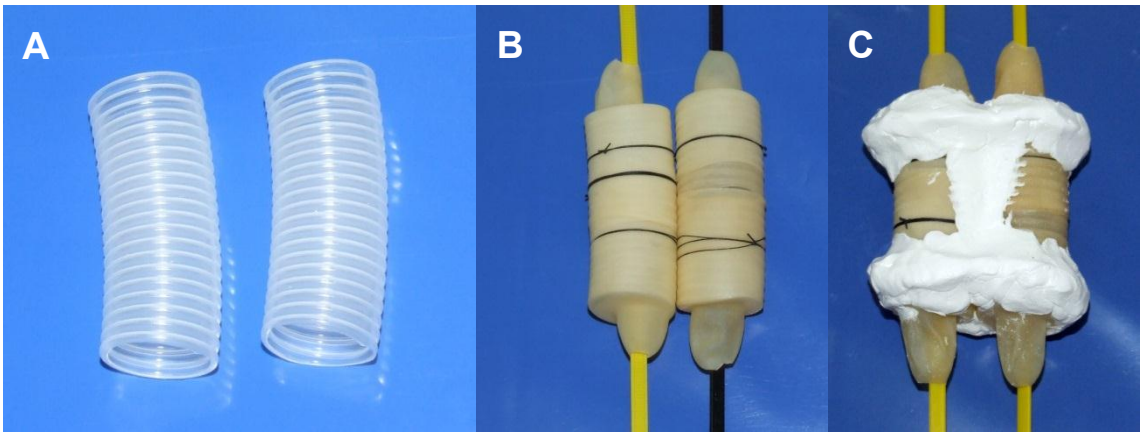
***Figure 7.1 The original anal sealing device***



Although the endoscopes were easily inserted into the colon, movement in any direction other than back and forth led to air leakage through the glove finger holes, compromising insufflation.

To improve the seal and enable the use of endoscopes of different external diameters, two separate glove fingers (one inside the other) were loosely placed on the end of each tube to avoid stretching of holes, allowing gripping of the endoscopes at two different points at each end of the anal sealing device. In addition, different diameter holes (range 3 to 8mm) were made depending on the combination of endoscopes planned for experimental work. The device was assembled as described previously (Figure 7.2).

***Figure 7.2 Assembly of a modified double lumen anal sealing device***



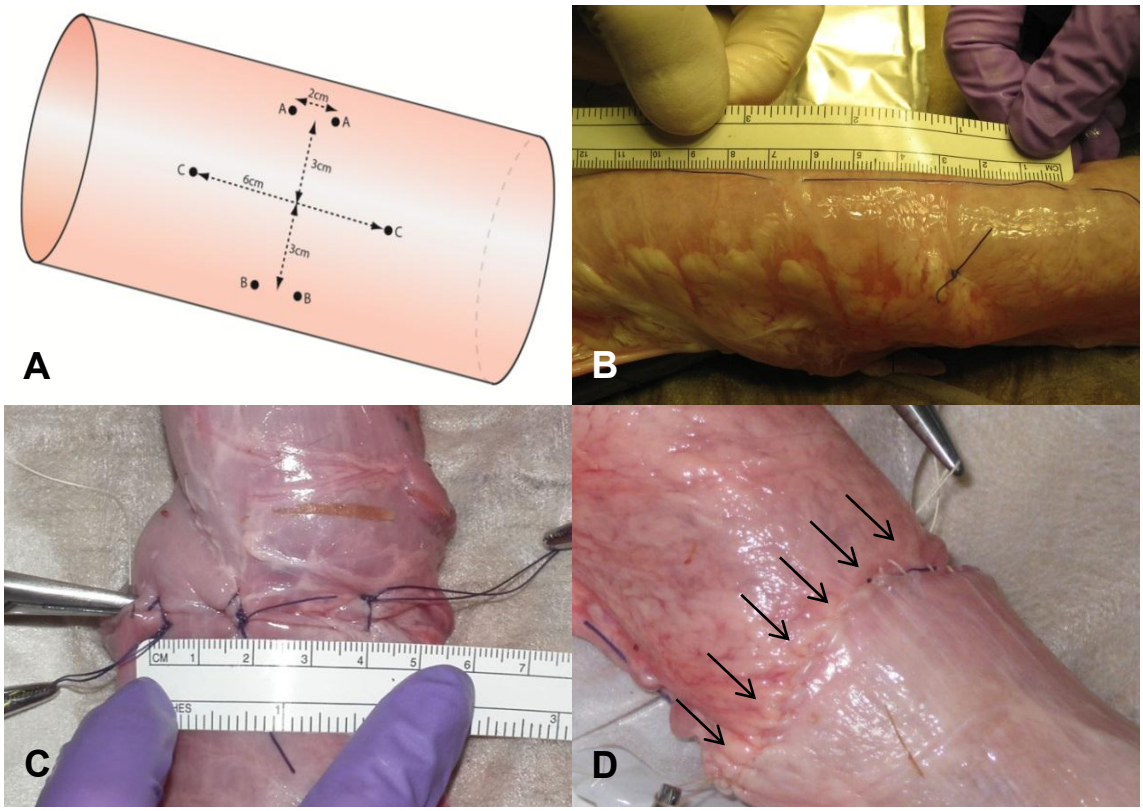

***A.*** *Anaesthetic corrugated tubing;* ***B.*** *Two layers of pierced glove fingers placed over each end of the tube. The tubes are stabilised by thread;* ***C.*** *Configuration is further reinforced using silicone sealant used to make ridges at each end*

### *7.2.2.2 Specimen preparation*

Cadaver bowel specimens were collected from pigs euthanized during unrelated experiments. The distal colon up to the spiral segment (approximate length 50cm), anus, bladder and an area of perianal skin were excised *en bloc.* All specimens were washed and stored at -20ºC. Short segments of sheep bowel were harvested and stored in the same way, in case no porcine terminations were scheduled. Specimens were defrosted 12 hours prior to each experiment. The anal sealing device was inserted with a colonoscope *in situ* and a crushing bowel clamp was placed at the proximal end of the colon to allow colonic insufflation. Due to the shortage of the prototype BraceBar$^{TM}$ system, dyed 3.0 Vicryl suture (Ethicon, Endo-Surgery) was used instead, so that stitches could be identified endoluminally.

A 6cm segment of the colon was measured longitudinally and transversely on the anti-mesenteric border (Figure 7.3, A & B) and three pairs of stitches were placed (positions A, B and C as described in Chapter 6) to invert the segment (Figure 7.3, C). The inversion area on the serosal surface was over-sewn using undyed 3.0 Vicryl suture (Ethicon, Endo-Surgery) as described previously (Figure 7.3, D).

***Figure 7.3 Inversion of the pseudopolyp in a cadaver bowel specimen***




***A & B.*** *Serosal diathermy marks (A, B and C) are used to guide placement of sutures;* ***C.*** *Inverting sutures visible on the serosal surface;* ***D.*** *Inversion area is over-sewn (arrows)*

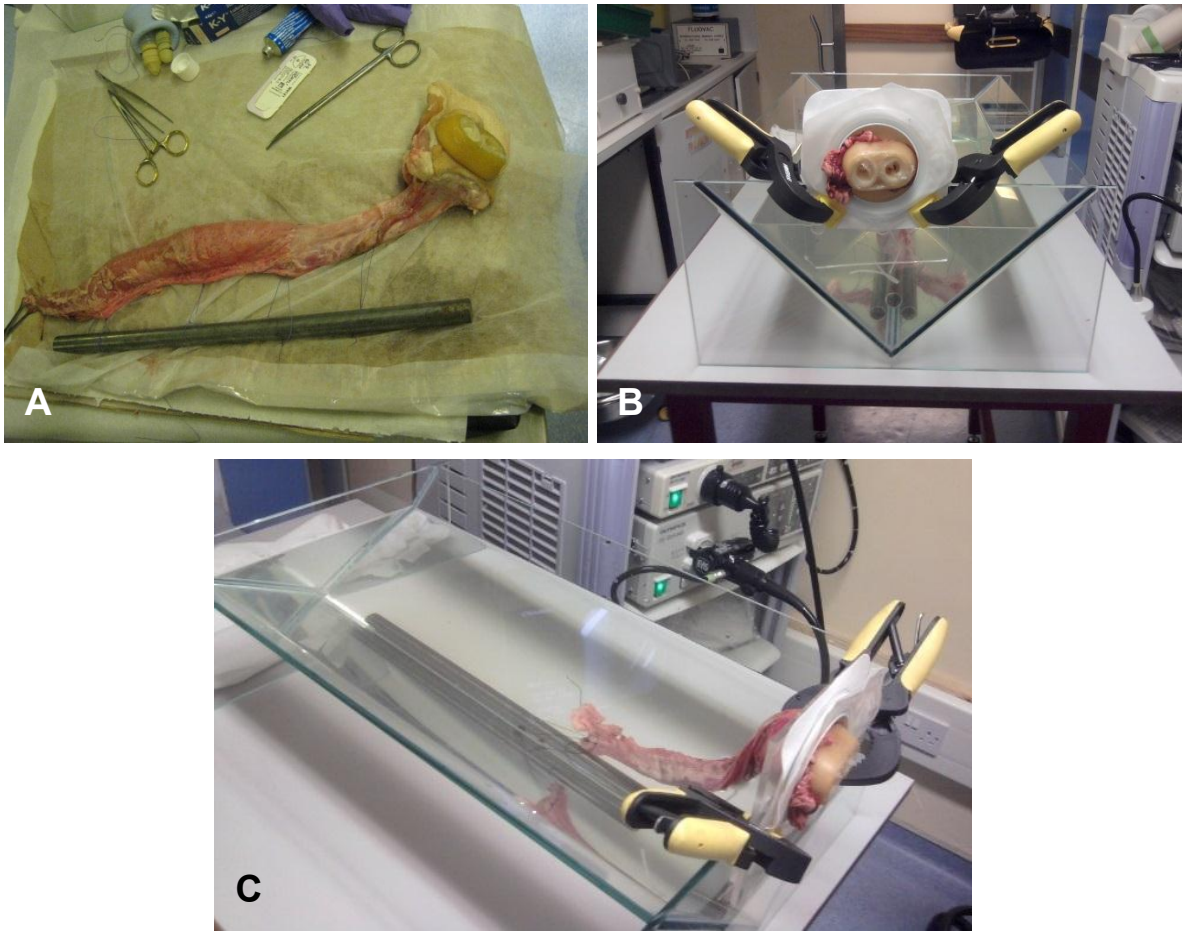
### *7.2.2.3 Development of a purpose built jig*

The *ex vivo* set up evolved over several experiments. The jig designed for the first experiment was a two-part structure including a V-shaped glass gutter filled with water and a separate perspex plate (Figure 7.4). A hole, 7cm in diameter, was created in the perspex plate and a colostomy bag baseplate was placed over it. The hole in the silicone baseplate

was expanded sufficiently to allow passage of the bowel into the jig and stabilise the anus with the anal sealing device *in situ*. The perspex plate was then secured to the jig using clamps and the colon was suspended in the water (Figure 7.4, C).To prevent the specimen from floating to the surface when insufflated, several interrupted loose stitches were placed on the mesentery starting 10cm away from the anal verge (Figure 7.4, A). A metal rod was inserted through the loops and placed at the bottom of the jig, suspending the bowel. A diathermy plate was placed over the perianal skin covered with gauze soaked with 0.9% sodium chloride (NaCl) to improve conduction.

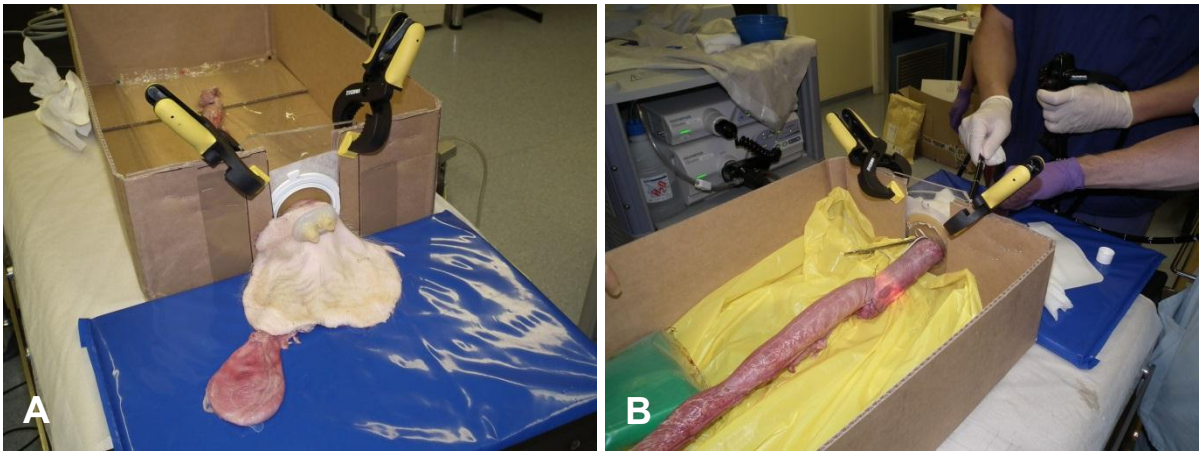
Although this jig was successfully used, the arrangement was simplified in following experiments. A shallow cardboard box lined with a plastic bag was used instead as it allowed horizontal placement of the colon (Figure 7.5). A window was cut in the anterior wall to allow placement of the perspex segment as described above. The floor and the anterior wall of the jig were reinforced using wide strips of cardboard and the perspex segment stabilised using clamps (Figure 7.5). Excess perianal skin and/or bladder (required for current conduction) were secured to a corkboard with pins and a diathermy plate applied over it as before. The bowel was sprayed with water or 0.9% NaCl throughout the experiment to prevent drying.

***Figure 7.4 Specimen with anal sealing device in situ suspended in the water jig***




***A.*** *Bowel specimen with a metal rod passed through a series loose mesenteric stitches;* ***B.*** *The perspex plate secured to the anterior wall of the glass gutter with clamps. The anus is stabilised with application of a stoma silicone baseplate onto the perspex plate.* ***C.*** *Side view of the specimen sumberged under the water and held down with a metal rod*

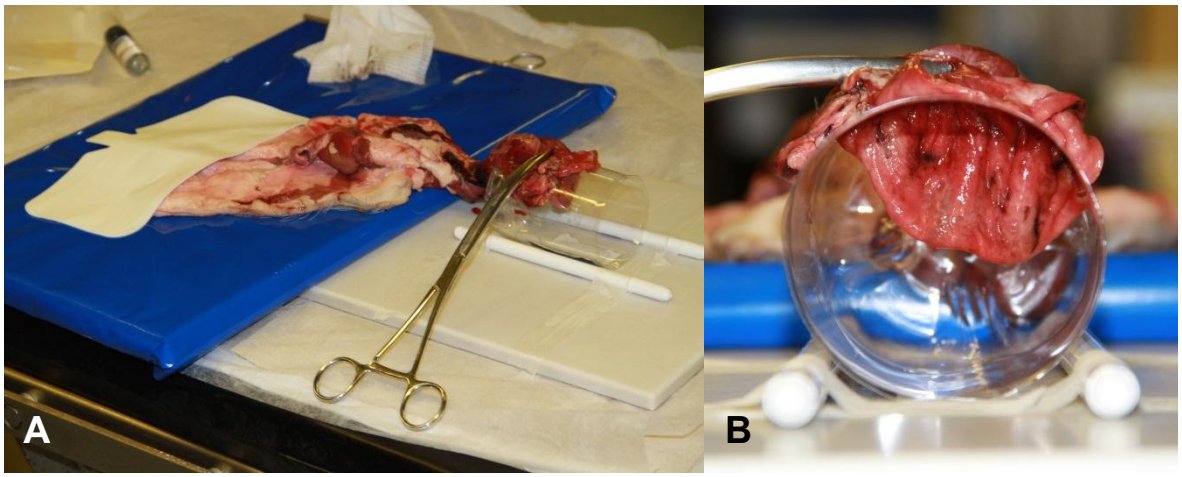
***Figure 7.5 Horizontal placement of the porcine colon in a cardboard jig***




***A & B.*** *Horizontal placement of the colon enables more than one procedure to be performed on the same specimen*

An additional jig was developed to establish the relationship of endoscopes during retraction and examine the efficacy of a single working endoscope with a fixed retracting endoscope (Section 7.2.2.4). The body of a plastic bottle (with the bottleneck cut off) was secured on a cutting board using tape with a pen placed on either side to stabilise it. A 1 to 4cm incision was made circumferentially in the bottle wall between the 10 and 2 o'clock positions to allow insertion of an artificial colonic fold created after transverse closure (using sutures) of a 6cm longitudinal segment of the bowel (Figure 7.6). Diathermy or a permanent marker pen was used to delineate mucosal markings simulating the APC marks described in the original paper. The diathermy pad was applied to the excess perianal skin as described above.

***Figure 7.6 Plastic jig developed to assess the working relationship between the cutting and retracting endoscope***




***A & B.*** *Colonic fold inserted into a transparent plastic bottle enabling visualisation of both endoscopes during resection*

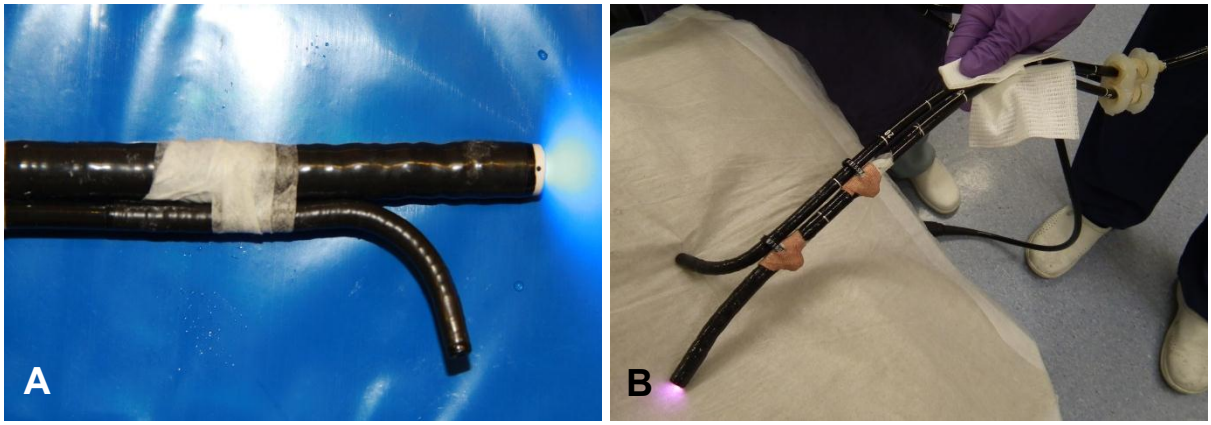
### *7.2.2.4 Development of a single working endoscope with an fixed retracting arm*

The original set of experiments was performed using two independently operated endoscopes. We decided to compare the efficacy of this 2-scope approach with the concept of a single working endoscope incorporating a retracting endoscope. In order to achieve this several combinations of different endoscopes were evaluated. The GIF-Q20 (Olympus, Keymed) gastroscope that was used in our original study was damaged and therefore

unavailable. Instead, a single channel prototype GIF-2TQ-260M (working length 1030mm, channel size 3.2mm) (Olympus Keymed) and a PCF-240S (working length 950mm, channel size 3.2mm) (Olympus Keymed) were used as two choices of working endoscope.

The XST-28CH-M (Olympus Keymed) is a prototype blind probe similar to an endoscope but devoid of endoscopic functions such as optics, insufflation, suction and light source[248]. It is a 1000mm long flexible tube, with an external diameter of 6mm and a working channel of 2.8mm. Its multi-bending tip is the main feature of this scope, allowing retroflexion of up to 250º which may be useful in areas difficult to access. The tip has two bending sections, which are both steerable in up/down direction only. Left/right movement is obtained by applying rotational torque to the shaft of the scope. This scope was utilised as the retracting arm either attached to one of our chosen working endoscopes ('single working endoscopic configuration with a retracting arm') or separate to it, as described in the original study. Positioning of the retracting endoscope had to be performed under direct vision of the working endoscope.

***Figure 7.7 Single working endoscope configuration***




***A.*** *GIF-2TQ-260M & XST-28CH-M arrangement allowing movement of the XST-28CH-M in one direction only;* ***B.*** *PCF-240S & XST-28CH-M arrangement stabilised with plastic fasteners to allow independent (back and forth) movement of the XST-28CH-M but fixing it in relationship to the working endoscope*

For experiments aiming to assess the efficacy of a single working endoscope with a retracting endoscope configuration, the XST-28CH-M was aligned with the working

endoscope (PCF-240S or GIF-2TQ-260M) and secured with tape proximal to the first articulating joint of the XST-28CH-M. This was repeated at regular intervals for approximately 20cm to further stabilise the arrangement. This set up allowed movement of the tip of the retracting endoscope in one direction only (90º tip down), perpendicular to the cutting endoscope. This single working endoscope configuration was introduced into the bowel through a single channel anal sealing device. The combination and relationship of endoscopes utilised in these experiments is presented in Table 7.1.

***Table 7.1 Combination of endoscopes utilised in experimental work***

| PCF-240S | GIF-2TQ-260M | XST-28CH-M | Arrangement |
|---|---|---|---|
| | **W** | **R** | Independent |
| **W** | **R** | | Independent |
| **W** | | **R** | Independent |
| | **W** | **R** | Single endoscope |
| **W** | | **R** | Single endoscope |

### 7.2.3 Results

#### *7.2.3.1 Optimisation of the ex vivo set up*

Although the glass jig was found to be 'fit for purpose', the cardboard jig was preferred as inadvertent bowel perforation during resection would cause water leakage into the colon. It also enabled us to perform more than one resection on the same specimen. In addition when suspended in the glass jig, due to the distance from the perspex plate, a 15 to 20cm segment of the bowel was left above the water and could not be utilised (Figure 18C). Since the length and diameter of the bowel harvested varied significantly with the weight of animals at termination, with the shortest segments being approximately 40cm long, this also became a limiting factor.

Pneumocolon was easily maintained in all experiments using the modified anal sealing device which permitted movement of endoscopes in all planes without air leakage. At times

however, insertion of the device into the anus was difficult due to the diameter created by silicone ridges (>6cm). Freezing of the specimens adversely affected the quality of defrosted tissue and it was difficult to create a simulated lesion with submucosal injection of ink as described in the original study. On all occasions, a 4 to 6cm segment of the bowel was successfully inverted by placement of dyed sutures at positions A, B and C. Although the midline stitch (position C) was easily identified, endoluminal visualisation of the stitches placed at position A and/or B was more challenging. In addition, the absence of a simulated lesion made it difficult to maintain an accurate transverse resection line due to the lack of reference points. We attempted to address this in the bottle jig but preliminary testing showed that mucosal diathermy markings placed on a segment of sheep bowel quickly disappeared and marker pen used on mucosa of porcine bowel was wiped off during frequent repositioning of grasping forceps. Preliminary tests also showed that sheep bowel was too thin and friable to withstand traction during the resection process and therefore was not used in formal experiments.

#### *7.2.3.2 Ideal endoscopic combination*

The results of five different combinations of endoscopes are presented in Table 7.2. The most effective combination of 2 endoscopes used independently was the GIF-2TQ-260M for grasping and retraction and the PCF-240S as a working endoscope. Time taken to excise the specimen from first incision was 45min. Although GIF-2TQ-260M was rigid enough to apply good traction to the colonic fold, tangential excision could not be avoided. When traction was applied by the assisting endoscope, as well as being pulled perpendicular to the bowel wall, the fold was simultaneously pulled distally (towards the anus), away from the midline and forming an arc. This was easily visible on the screen and in an attempt to correct for the inadvertent traction towards the anus the retracting endoscope was pushed forward (away from the anus). It was extremely difficult to maintain adequate traction perpendicular to the bowel wall in isolation and during the excision both endoscopes and the colonic fold were pushed forward (away from the anus). This resulted in tangential excision with the

***Table 7.2 Results***

| PCF-240S | GIF-2TQ-260M | XST-28CH-M | Arrangement | Procedures performed | Jig | Inversion area, cm | Procedure time, min | Size of the excised specimen, cm |
|---|---|---|---|---|---|---|---|---|
| | **W** | **R** | Independent | 1 | Glass | 6 | 82 | 5.1 |
| **W** | **R** | | Independent | 2 | Cardboard | 4 | 45<br>- | 4.0<br>procedure abandoned |
| **W** | | **R** | Independent | 1 | Cardboard | 4 | - | procedure abandoned |
| | **W** | **R** | Single endoscope | 2 | Cardboard<br>Bottle | 6<br>6 | 72<br>57 | 2.8<br>5.6 |
| **W** | | **R** | Single endoscope | 1 | Bottle | 4 | 63 | 3.8 |

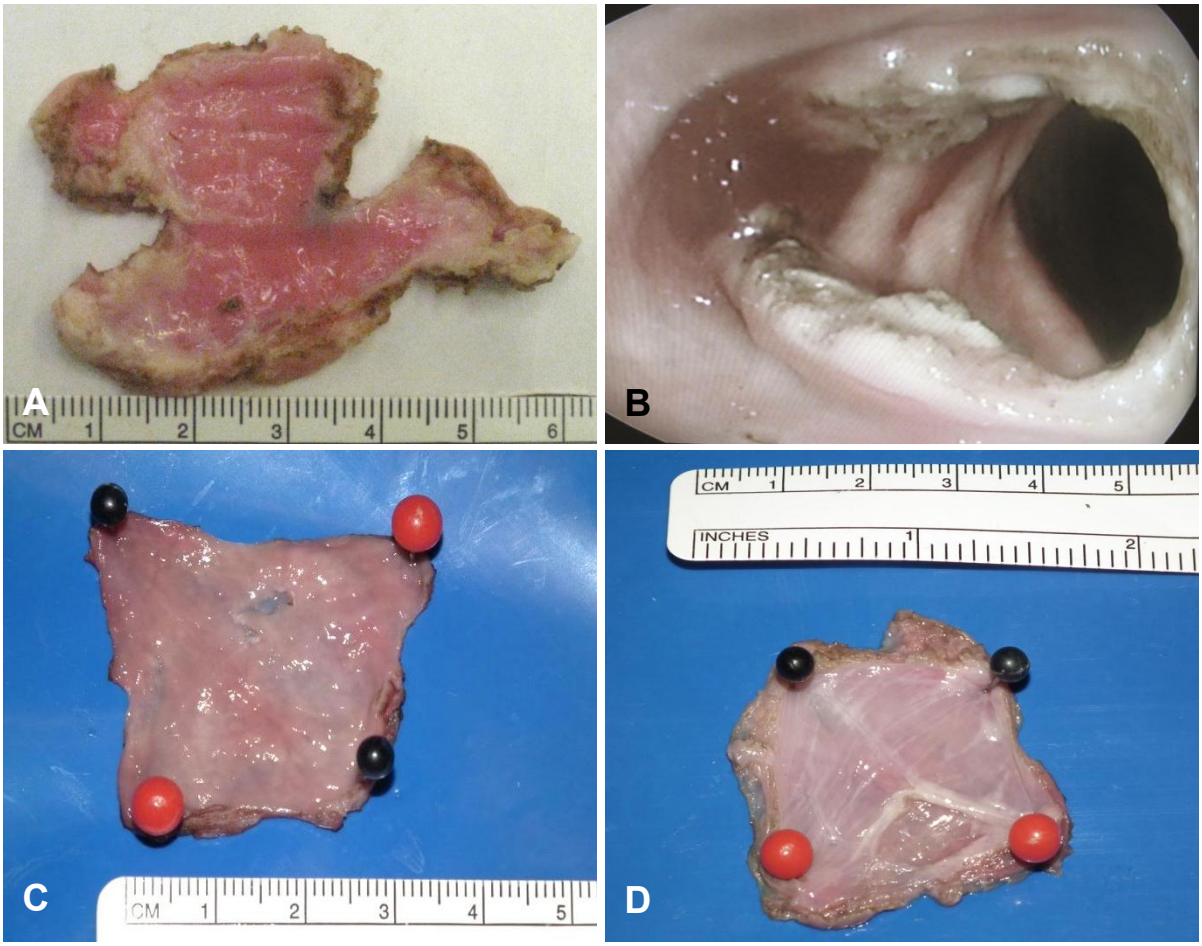
*W-working endoscope, R-retracting endoscope*

serosal surface of the excised specimen being slightly smaller than that of the mucosa (3.8cm *vs.* 4.0cm) (Figure 7.8, C & D). We were unable to reproduce these results as the colonic lumen used in the subsequent experiment was too narrow to accommodate two endoscopes with an external diameter exceeding 9.8mm.

When the XST-28CH-M was used for retraction alongside the GIF-2TQ-260M as the working endoscope, it was found to lack the rigidity necessary to apply effective traction to an inverted area of area 6cm. During this experiment, the inversion stitches placed at positions A and B were not visible endoluminally and contact between the diathermy plate and perianal skin was lost intermittently. When contact between the plate and the tissue was established, only the coagulation setting was found to be working, creating a lot of smoke during the excision and obscuring the view. As the XST-28CH-M allows movement in one direction only, combined with a lack of imaging capability and a tip position located distal to the tip of the working endoscope, controlling the direction of tip flexion and therefore retraction of the inverted bowel proved too difficult. This resulted in a poor quality specimen (Figure 7.8, A) and due to technical difficulties with orientation and retraction the subsequent experiment with the PCF-240S as a working endoscope was abandoned altogether.

The internal diameter of the corrugated tubing used to make the anal sealing device did not permit evaluation of the GIF-2TQ-260M and PCF-240S as a single endoscopic configuration. Instead, both endoscopes were assessed as working endoscopes using XST-28CH-M as a fixed retracting endoscope. This arrangement was first assessed in the cardboard jig resulting in a 2.8cm specimen despite inverting a colonic fold of 6cm in diameter (Table 7.2). In this experiment the endoscopes were secured with tape placed at 2cm intervals. Although we hoped that fixation of the retracting endoscope would improve retraction of the inverted bowel perpendicular to the long axis of the bowel, the arrangement was very unstable with the tip of the retracting endoscope slipping around the working endoscope as the strips of the tape became wet.

***Figure 7.8 Specimens achieved with independent combination of endoscopes***

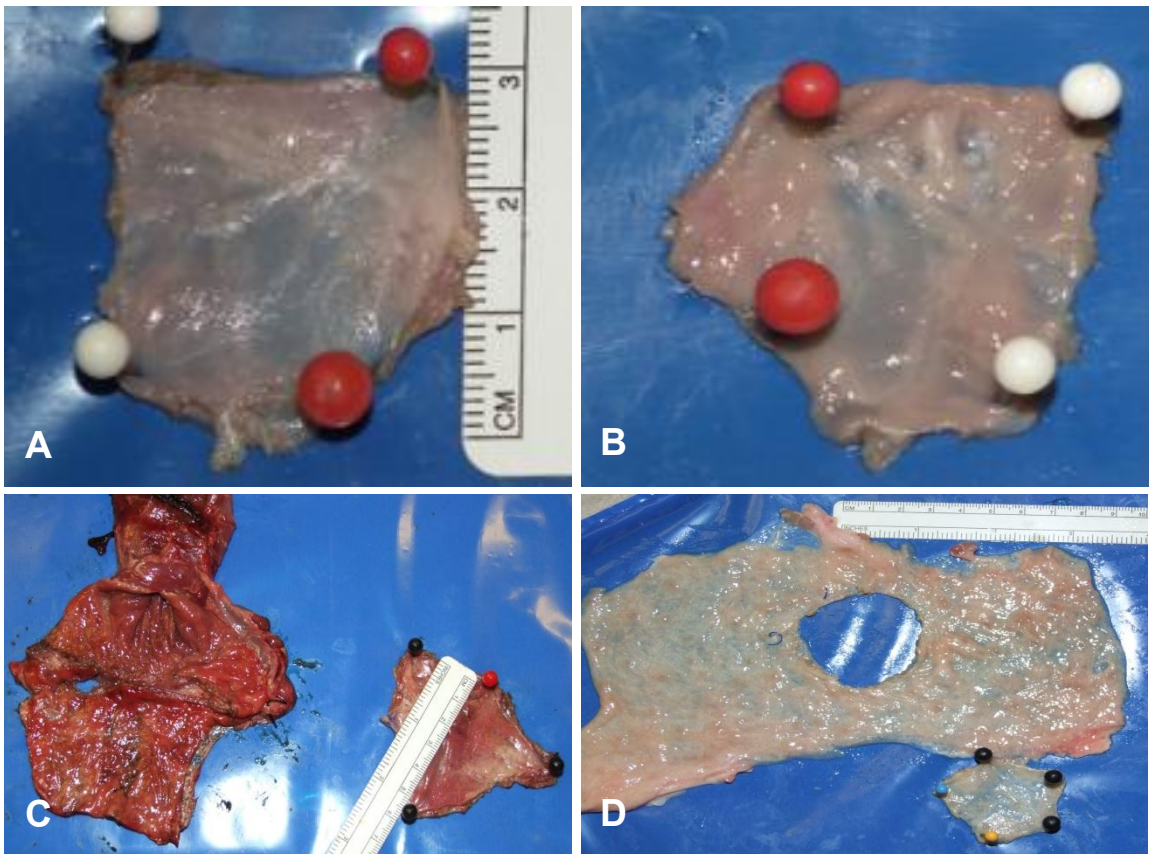



***A & B.*** *Poor orientation and retraction in the experiment assessing the efficacy of the XST-28CH-M and GIF-2TQ-260M as two independent endoscopes resulted in an irregular specimen with the edges burnt with the coagulation diathermy. Colonic lumen post resection was patent;* ***C & D.*** *Although the quality of the specimen is far superior with the GIF-2TQ-260M utilized as the independent retracting endoscope and the PCF-240S as a working endoscope, a 2mm discrepancy in the diameter of the mucosa and serosa is visible. In addition, mucosal surface is damaged by grasping forceps*

In order to examine the relationship between two endoscopes in a greater detail, the arrangement was assessed in the bottle jig. In subsequent experiments the tape was applied continuously along both endoscopes for approximately 40cm to further stabilise the arrangement. Although this made the handling of the two endoscopes somewhat easier, it became apparent that when traction was applied by the retracting endoscope, the movement still occurred in both vertical and horizontal planes (away from the midline), but to a lesser degree. As both endoscopes were fixed, we were unable to correct the horizontal movement of the colonic fold by forward movement of the retracting endoscope and a discrepancy

between the serosal and mucosal diameter was observed again. In addition, due to resistance encountered during tissue retraction, the retracting endoscope would push the working endoscope upwards, against the roof of the jig. This made it difficult to perform an accurate resection, resulting in an irregular specimen and on one occasion, perforation of the colonic segment (Figure 7.9, C).

***Figure 7.9 Excised specimens following utilisation of a single endoscope configuration***




***A & B.*** *Combination of GIF-2TQ-260M and XST-28CH-M as a single working endoscope configuration in a paper and a bottle jig respectively;* ***C.*** *Single working endoscopic configuration PCF-240S (working) and the XST-28CH-M (retracting) in a bottle resulted in colonic perforation;* ***D.*** *Specimen and colonic defect following assessment of the PCF-240S and XST-28CH-M as two independent endoscopes*

In order to allow independent back and forth movement of the retracting endoscope and the ability to adjust for horizontal movement during retraction, the endoscopic arrangement was further modified. In the last experiment, loops made out of plastic fasteners were created and secured at 2cm intervals along the shaft of the PCF-240S (Figure 7.7). This stabilised the XST-28CH-M alongside the working endoscope while independent forward and

backward movement as well as torque were retained. This arrangement was more stable when compared to the same combination of endoscopes when not attached to each other. Upward movement of the working endoscope when retraction was applied however could not be avoided, resulting in a disruptive effect on the resection process. In addition, frequent repositioning of the grasping forceps caused mucosal injury.

## 7.3 Discussion

The experimental work presented in this chapter ultimately led to the development of an optimal *ex vivo* arrangement for the evaluation of colonic EFTR. Full thickness excision was successfully performed in all jigs presented in this chapter, with the cardboard jig being the most practical. Pneumocolon was successfully maintained with the modified anal sealing device that could be used for a single or double endoscope procedure. This set-up is cheap, easily reproducible and suitable for *ex-vivo* assessment and development of EFTR techniques for colon and potentially stomach. In addition, it could also be used as a training tool for advanced endoscopic techniques provided that freshly harvested specimens are available.

The FLEX technique described in the original paper allowed inversion of a colonic fold with formation of a simulated lesion (polyp) with margins delineated by BBs and mucosal APC markings. For the procedure to be applicable in a clinical setting, the ability to consistently provide a high quality specimen is paramount. One of the key lessons in training for laparoscopic surgery is that counter-traction applied to the target tissue is a fundamental principle for accurate resection[248]. Several authors have described techniques to help lift the lesion away from the submucosa during the gastrointestinal ESD procedure utilizing clips[249], magnetic anchor system[250], O-rings[251], spring devices[252] or even using double-endoscope approach[253], however many of them are time consuming with limited effectiveness and mostly applied for gastric lesions. Effective traction using a double endoscope approach was

difficult to achieve in the original study[173] and discrepancy in the serosal and mucosal diameter was observed in the excised specimens.

We attempted to improve retraction during resection using either an independent (as part of a two endoscope procedure) or a fixed retraction endoscope (attached in some form to a working endoscope) but with no success. The best quality specimen achieved in this series of experiments was excised using an independent combination of the GIF-2TQ-260M (retracting) and PCF-240S (working) endoscopes, similar to that described in the original paper. The prototype XST-28CH-M utilised either independently or as part of a single endoscopic configuration lacked the rigidity to apply effective traction, with disruptive effects on the working endoscope during cutting. Although attaching the XST-28CH-M to the working endoscope did enable more controlled traction, it was evident that independent movement of the retracting endoscope (forward and back) as part of a single endoscopic configuration is necessary to allow correction for traction in the horizontal plane. This was only feasible when we combined the PCF-240S and XST-28CH-M together using plastic fasteners however it was not possible to evaluate this set-up *in vivo*. The inability to correct the issues with retraction resulted in small, poor quality specimens. In addition, the time taken to excise the specimens was in excess of 60 minutes meaning that it was unlikely that the overall procedure time could be reduced significantly.

## 7.4 Conclusion

Combined experience from the original study and findings of experimental work presented in this chapter indicated that the inversion, two-endoscope technique was unlikely to progress to a clinical study/ Major technical developments in both the endoscopes and other equipment used is likely to be required. The technique could also be further developed if a stable endoscopic working platform was available in order to avoid tangential specimen excision.

# Chapter 8 Eversion FLEX technique: proof of principle *ex vivo* experimental work

## 8.1 Introduction

The results of the experimental work outlined in Chapter 7 demonstrated that further development of the originally described *inversion* FLEX technique is limited by the equipment currently available. In this chapter, four sets of experiments are presented describing development of the *eversion* FLEX (eFLEX) technique in an *ex vivo* setting. The aim was to assess the feasibility of everting a fold of colonic segment into the peritoneal cavity using BBs, followed by laparoscopic excision of the specimen. In the original technique, mucosal APC markings and BBs clearly delineated the resection margin and therefore, for the eversion method to be effective, the surgeon must have the equivalent landmarks on the serosal surface. In addition, the resulting specimen and the excision site on the colon should be closed, at least temporarily, to avoid peritoneal contamination. This would allow a controlled extraction of the specimen and perhaps laparoscopic over-sewing of the temporary partial circumferential anastomosis.

These experiments aimed to define procedural steps of the eFLEX technique whilst examining whether the quality of the excised specimen could be improved and procedure time reduced.

## 8.2 Proof of principle experiment: eversion of the colonic fold

### 8.2.1 Introduction

The aim of this experiment was to create a simulated mucosal lesion with well-defined clearance margins on the serosal surface of the bowel, evert a colonic fold containing the simulated polyp and excise the specimen using bipolar diathermy.

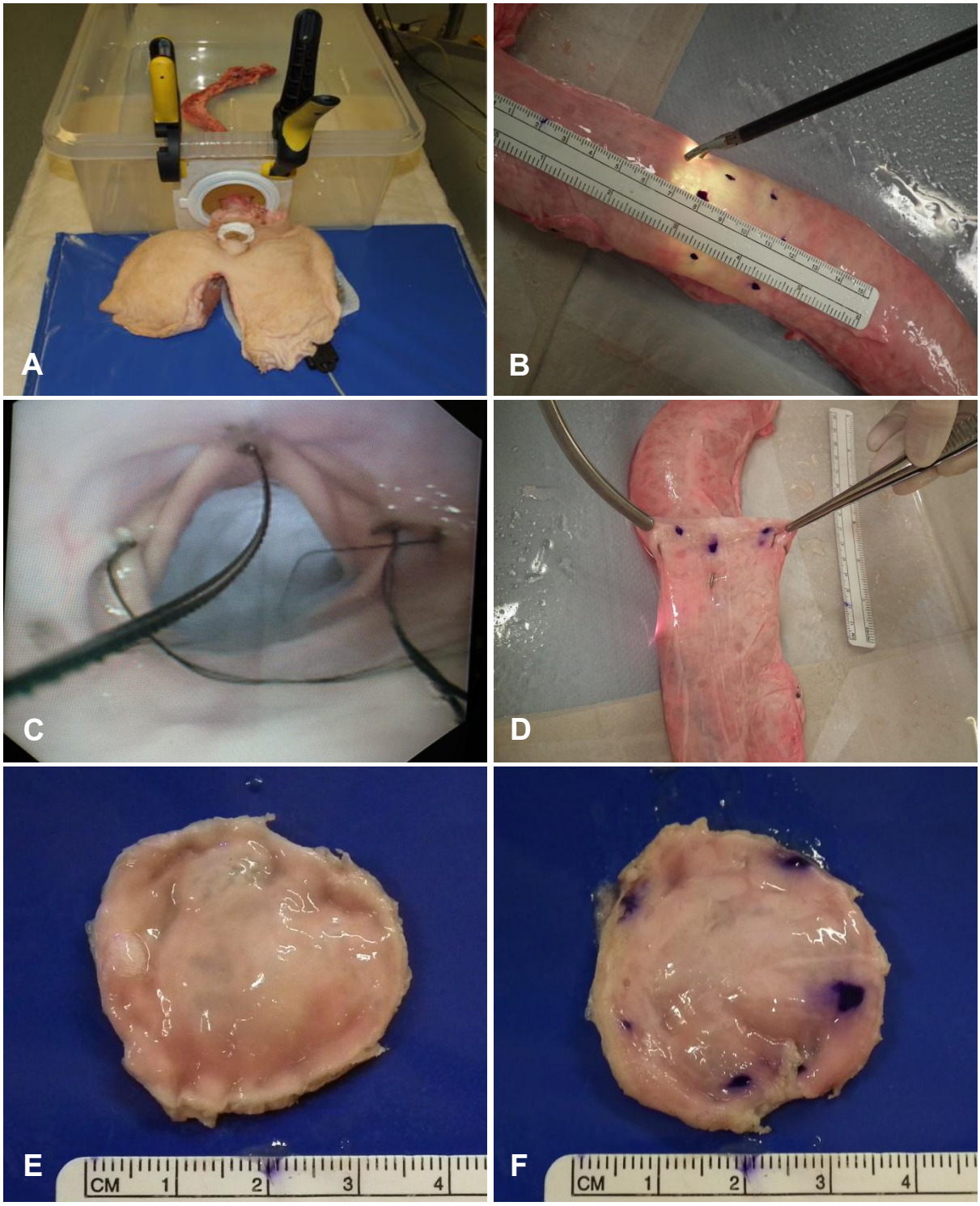
### 8.2.2 Materials and methods

The cardboard jig described in section 7.2.2.3 (Page 120) was replaced with a plastic box with a circular defect created in the anterior wall to accommodate the perspex piece with the specimen *in situ*. Defrosted porcine colon was placed in the jig as described before. A single lumen anal sealing device was inserted into the anus to maintain pneumocolon. The PCF-240S was used as a working endoscope and a simulated 2cm polyp was created on the anti-mesenteric side by submucosal injection of water. Although we initially planned to place diathermy marks on the serosa 1cm away from the edge of the lesion guided by the endoscopist, the diathermy machine was not available for this experiment. Instead, serosal circumferential marks (equivalent to the endoluminal APC marks described in the original technique)[173] were placed on the serosal surface using a permanent marker pen (Figure 8.1, B). To ensure accurate placement, the endoscopist used biopsy forceps to apply pressure on the bowel wall indicating a 1cm margin around the simulated polyp. Three pairs of BBs were placed endoluminally and laparoscopic graspers were used to apply pressure over the distended colon, approximately 1cm away from the serosal marks, indicating A, B and C position for BBs (Figure 8.1, B). Once all three pairs of BBs were tightened (Figure 8.1, C), the everted colonic fold was retracted using laparoscopic graspers and the specimen excised with bipolar diathermy and cut using serosal markings and BBs for guidance.

### 8.2.3 Results

The colonic fold was successfully everted by endoscopic placement of BBs. Blue serosal markings and BBs were clearly visible on the serosa, demarcating the resection line (Figure 8.1, C). Following excision, all three pairs of BBs remained within the resection line in the colon, as described in the original procedure, but neither the specimen nor the colotomy site were sealed temporarily. Mucosal and serosal diameter of the excised specimen was 3.5cm (Figure 8.1, E & F).

***Figure 8.1 Procedural steps for proof of principle eversion experiment***




***A.*** *Colonic segment placed into a re-usable plastic jig equivalent to the cardboard jig;* ***B.*** *Serosal markings demarcating circumferential margin (marker pen marks) and laparoscopic grasper indicating position of BB;* ***C & D.*** *Endoluminal and serosal view following endoscopic deployment of BBs;* ***E & F.*** *Mucosal and serosal surface of the specimen, with serosal permanent pen markings delineating the clearance margin*

### 8.2.4 Discussion

This proof-of concept experiment demonstrated the feasibility of everting a colonic segment containing a simulated lesion by endoscopic placement of BBs. The serosal circumferential marks and BBs clearly defined the resection margin (Figure 8.1, D). Using laparoscopic graspers to apply adequate traction perpendicular to the bowel wall prevents tangential excision, improving the quality of the excised specimen as demonstrated by equal diameters of the mucosa and serosa. As expected however, standard bipolar diathermy did not provide even a temporary seal of the excised specimen or the excision site, an issue that needed to be addressed in further experiments. In addition, excess thread from BBs present endoluminally (Figure 8.1, C) interfered with placement of the subsequent BBs and therefore needed to be removed in the next experiment.

## 8.3 Proof of principle experiment: stapled *vs.* Enseal® excision

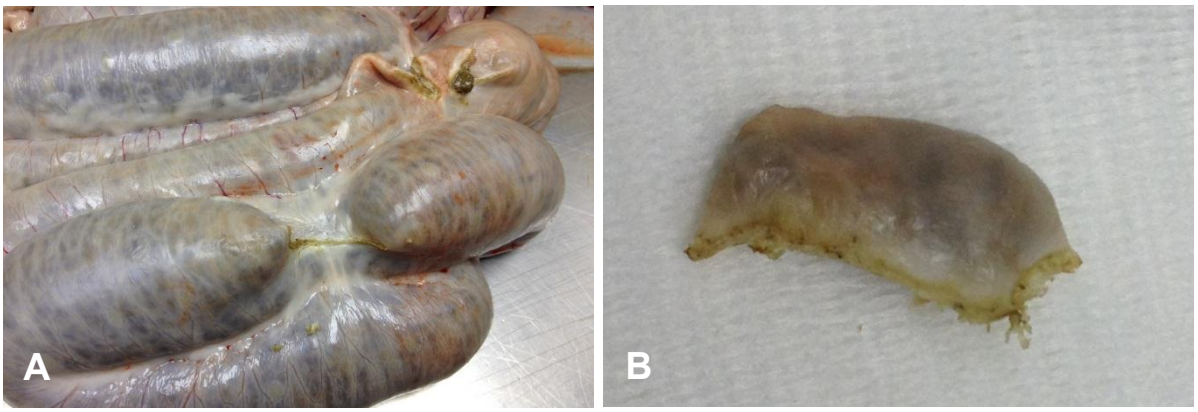
### 8.3.1 Introduction

Anastomotic leakage is a major cause of morbidity and mortality following colorectal surgery. Stapling devices have been refined over the years and reproducibility of the results have made them most frequently utilised technique of colorectal anastomosis. The standard width of the currently available laparoscopic stapling devices however is 1cm and if applied in the eFLEX procedure, the distance between the serosal circumferential markings and BBs needed to be increased in order to avoid misfiring of the staples if BBs were accidentally included in the staple line.

The ENSEAL® (Ethicon, Endo-Surgery) is a device designed for bipolar coagulation and transection of tissue during laparoscopic and open surgery[254]. It uses a patented temperature-controlled bipolar energy delivery system with a unique cutting mechanism known as the I-BLADE™ that delivers high compression uniformly across the sealing area whilst minimising thermal spread to the surrounding tissues[255]. The device can be used to

cut and seal vessels up to 7mm diameter. Having tested the device on a freshly harvested segment of the bowel (Figure 8.2), we formed a hypothesis that this energy device could be used to provide a closed excision specimen and a temporary colonic anastomosis that could be subsequently over-sewn laparoscopically.

***Figure 8.2 Wedge excision using the ENSEAL® device***




***A.** Sealed colotomy site following wedge excision in a freshly harvested porcine cadaver bowel; **B.** Closed wedge excision specimen*

The aim of this experiment was to assess the effectiveness of two excision methods, stapled *vs.* ENSEAL® during the eFLEX procedure.

### 8.3.2 Methods

The experiment was performed on an animal (approximate weight 55kg) terminated following an unrelated experiment. Three hours after termination, the animal was placed in a supine position and three laparoscopic ports were inserted into the abdomen. Colonic lavage was performed using the CF-Q240ZL (Olympus, Keymed). After detailed planning, the procedure involved the following steps:

1. Creation of two simulated 2cm sigmoid polyps at 30cm and 45cm from the anal verge, by submucosal injection of Spot® (GI Supply)

2. Laparoscopic placement of circumferential diathermy marks on the serosal surface 1cm away from the edge of the polyp guided by the endoscopist by application of pressure at predetermined site endoluminally using biopsy forceps

3. Placement of additional serosal diathermy marks 1cm away from circumferential markings to demarcate positions for BBs

4. Endoscopic placement of BBs (A, B and C positions) with laparoscopic guidance and overview to ensure correct deployment

5. Tightening of the BBs to evert the colonic segment into the abdominal cavity and cutting off the excess nylon thread using endoscopic scissors (Prototype Endoscopic Scissors, Ethicon Endosurgery) and removing it through the endoscopic channel using grasping forceps (Boston Scientific)

6. Laparoscopic excision of the specimen with either laparoscopic stapler (ETS-45, Ethicon Endo-Surgery) or the Enseal® bipolar diathermy device (Ethicon, Endo-Surgery), using BBs and serosal diathermy marks for guidance

Following completion of both procedures, the abdominal cavity was filled with water and colon insufflated whilst observing resection sites for air bubbles. Duration of the procedure was defined from the placement of initial diathermy marks to specimen excision.

### 8.3.3 Results

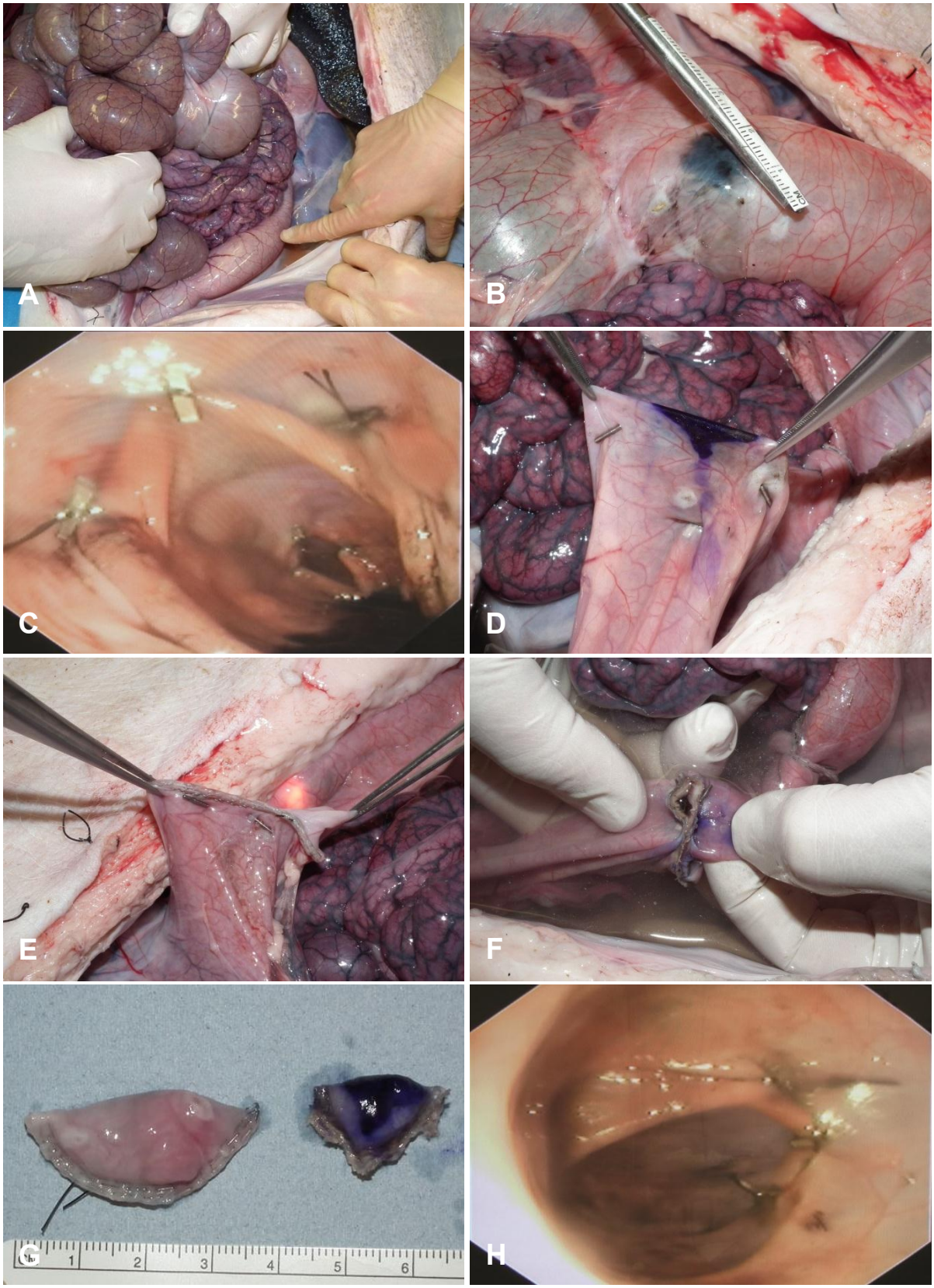
Initial laparoscopic examination of the abdomen revealed distended loops of colon and despite increasing the intra-abdominal pressure, the laparoscopic view was limited. Animals undergoing terminal anaesthesia are not starved prior to the procedure and therefore the gastrointestinal tract contained large amounts of semi-solid fermenting material. In addition, the procedure was commenced three hours after termination. Midline laparotomy was performed in order to mobilise the distended loops of spiral colon and procedural steps described above were performed on the exposed sigmoid colon (Figure 8.3). Due to

progressive distension and thinning of the colonic wall, only one simulated polyp was created by submucosal injection of Spot®. Instead, a permanent pen was used to simulate the second polyp.

A satisfactory eversion fold (4cm maximum diameter) along with a full thickness local excision of the simulated polyp was achieved during both procedures. Some difficulties were encountered during application of BBs in both experiments, including failure to deploy requiring withdrawal of the endoscope from the colon, and partial deployment. With partial deployment the plunger that forces the BB out of the needle slid past it, releasing only one of the two metal BBs. The BB was released with extraluminal assistance by using forceps to pull the nylon thread. Although the resection line between serosal diathermy marks and BBs was visible, the distance of >1cm was not uniform throughout, therefore, some of the diathermy marks were included in the staple line potentially compromising the predetermined clearance margin.

Stapling excision required three reloads with the overall procedure time of 42 minutes. Procedure duration with the Enseal® device was slightly shorter at 37 minutes and the resulting specimens had maximum diameters of 3.7cm and 1.8cm respectively (Figure 8.3, G). Macroscopic examination of sigmoid colon revealed closure of both anastomoses with BBs *in situ* and colonoscopy revealed patent colonic lumen. Following immersion of the bowel and colonic insufflation, the Enseal® resection line failed almost immediately whereas the staple line held as expected (Figure 8.3, E & F).

***Figure 8.3 Procedural steps Enseal® vs. stapled excision***




***A & B.*** *Sigmoid colon with a simulated lesion exposed;* ***C & D.*** *Endoluminal and serosal view following eversion of the colonic fold;* ***E & F.*** *Stapled and Enseal® excision sites with BBs in situ (respectively);* ***G & H.*** *Excised specimens stapled vs. Enseal® excision and endoluminal view of the stapled anastomosis*

### 8.3.4 Discussion

Although conversion to open procedure occurred during the early stages of the experiment due to poor visualisation secondary to bowel distension, it was possible to draw several conclusions. Our hypothesis that the Enseal® device would create a temporary partial circumferential anastomosis and allow laparoscopic over-sewing was rejected, as the resulting anastomosis was too weak to withstand even minimal manipulation of the colon, thereby exposing the abdominal cavity to colonic content. In addition, the thermal nature of the device caused contraction of the specimen, which was significantly smaller than that produced by stapling resection (1.8cm *vs.* 3.7cm). This would have an adverse effect on the quality of the excised specimen and the subsequent histological assessment. The quality of the specimen following stapling excision was far superior although some of the circumferential marks were included in the staple line indicating that if the same procedural steps were to be followed, the distance between BBs and circumferential marks needs to be increased further to ensure adequate clearance margins. Although we anticipated that the linear nature of a laparoscopic stapling device was likely to cause extensive narrowing of the colonic lumen; endoscopic findings suggested otherwise (Figure 8.3, H). All BB systems utilised in this experiment were pre-loaded a week prior to the procedure. Nylon thread has a great deal of memory when deformed for a prolonged period of time and this is likely to have contributed to the problems during BB deployment. The results of this experiment however suggested that this modified single endoscope eFLEX procedure utilising laparoscopic stapling excision of the specimen is a feasible and quicker alternative to the original inversion technique.

## 8.4 Modification of the stapled eFLEX technique

### 8.4.1 Introduction

Our previous *in vivo* experiment performed on a terminated animal demonstrated the feasibility of linear stapling for excision of the everted bowel segment in a timely manner. To simplify the steps of the procedure and possibly reduce the inflammatory reaction by decreasing the amount of the foreign material remaining at the anastomotic site, two separate *ex-vivo* experiments were performed in which the BBs were removed with the excised specimens. The aim of these experiments was to simplify and standardise operative steps of the eFLEX procedure and establish the feasibility of using BBs to delineate polyp clearance margins.

### 8.4.2 Methods

The previously described experimental jig containing a defrosted specimen was placed into a neoprene cylinder to simulate a laparoscopic training box (Figure 8.4, A). Three laparoscopic ports were inserted into the simulated abdominal wall and the insufflated colon was visualised inside the box. Two simulated polyps, approximately 2cm in diameter, were created as described previously and the operative steps included the following:

1. Placement of endoluminal circumferential diathermy marks 1cm away from the edge of the simulated polyp

2. Endoscopic placement of BBs at A, B and C positions just lateral to circumferential markings with laparoscopic overview

3. Tightening of the BBs everting the colonic segment into the laparoscopic box and cutting off the excess nylon thread

4. Laparoscopic excision of the specimen using a linear laparoscopic stapler below BBs visible on the serosal surface so that they are included in the excised specimen

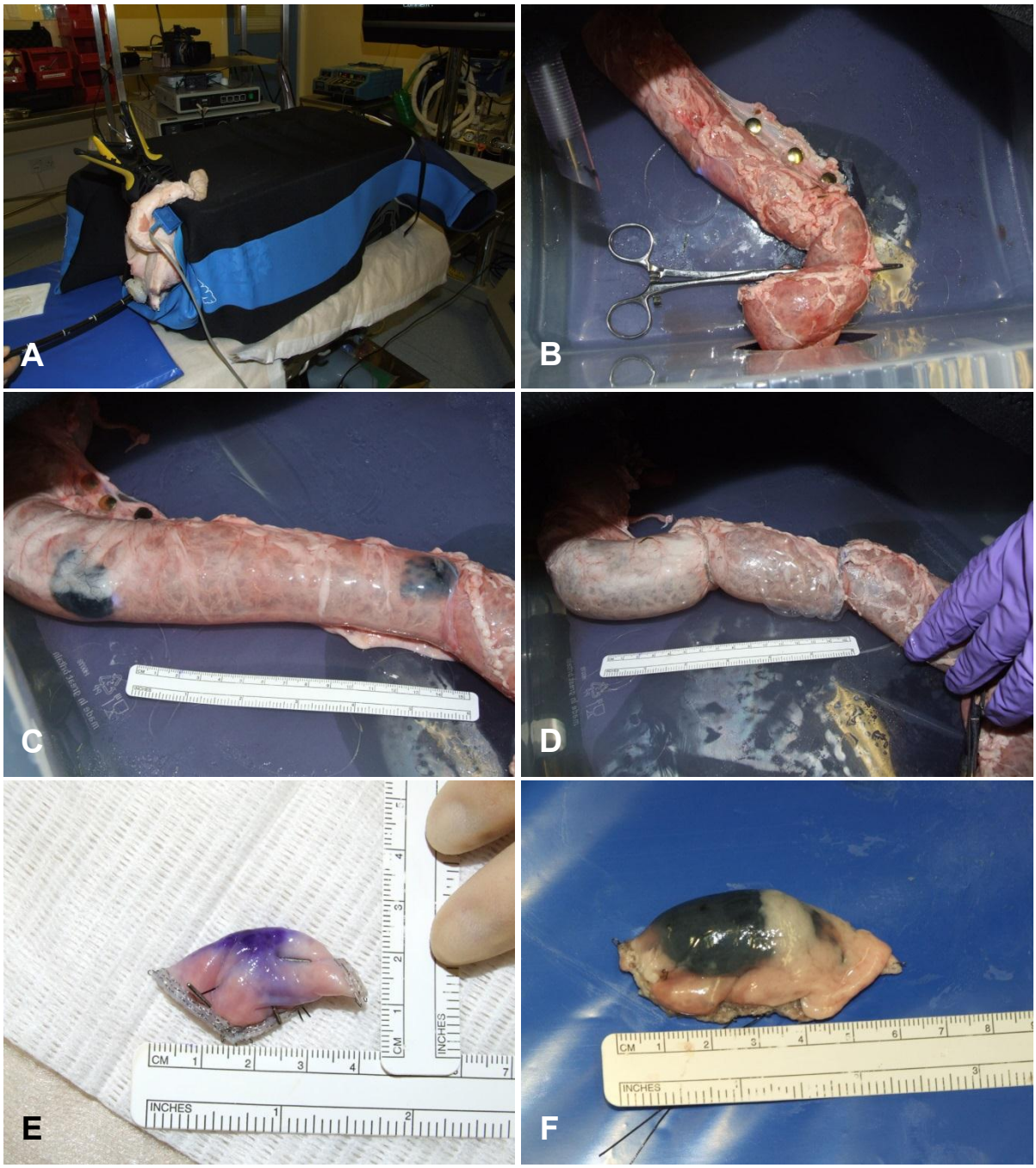
The duration of the procedure was defined from placement of initial diathermy marks to complete excision of the specimen. The resulting anastomoses were assessed at the end of each experiment by colonic insufflation under water.

### 8.4.3 Results

The first two procedures were performed with only three members of the team. Despite a seemingly good contact between the diathermy plate and perianal skin, diathermy was not effective. This is likely to be due to the defrosted nature of the specimen. We were therefore unable to place circumferential endoluminal marks (Step 1). Instead, a permanent pen was used to place serosal circumferential clearance marks with endoscopic assistance. The colon was very mobile in the laparoscopic box and due to the lack of manpower to provide the necessary counter traction on either side of the specimen BB placement was inaccurate. As a result, the everted colonic fold was tangential to the bowel axis. Only four stapling reloads were available for this experiment, and therefore due to limited resources, the decision was made to abandon the procedure for the first polyp.

Prior to creating the second polyp, several drawing board pins were used to stabilise the specimen by placing them through the remnants of the colonic mesentery and fixing it to the floor of the box. The second polyp was created on the anti-mesenteric border 30cm from the anal verge, with permanent marker pen markings delineating the serosal clearance margin. The same procedural steps were followed as described above. On this occasion, handling of the bowel was more controlled due to the anchor point and therefore placement of the BBs was more accurate. Although the resection line was still to some extent tangential, a 4cm specimen containing three pairs of BBs was successfully excised with three stapler firings (Figure 8.4, E).

***Figure 8.4 Modification of the stapled eFLEX procedure***




***A, B & C.*** *Colonic segment with simulated lesions placed in a hand-made laparoscopic training box;* ***D.*** *Stapled anastomoses;* ***E & F.*** *Closed excised specimens*

A week later, two additional procedures were performed with five members of the team ensuring that both the surgeon and the endoscopist had an assistant. The specimen was stabilised again by placement of drawing pins through the remaining mesentery. The same

issue with the diathermy was encountered and serosal circumferential clearance markings were placed with a permanent pen. Thereafter, both procedures were performed satisfactorily without further deviation from the protocol. A full thickness local excision of the colonic wall was performed with each specimen containing three pairs of BBs. Procedure duration and size of the excised specimens are presented in Table 8.1.

***Table 8.1 Procedural details***

| | Procedure duration, min (range) | Size of the excised specimen, cm |
|---|---|---|
| **Procedure 1** | abandoned* | - |
| **Procedure 2** | 62 | 4 |
| **Procedure 3** | 49 | 5 |
| **Procedure 4** | 34 | 6 |
| **Median (range)** | **48.3 (34 – 62)** | **5 (4 – 6)** |

*(*) Eversion occurred tangential to the colonic wall axis and due to limited availability of staple reloads, the procedure was abandoned*

### 8.4.4 Discussion

This simplified protocol provided an effective way for excising full thickness colonic specimens with a median diameter of 5cm (range 4cm - 6cm) using a single endoscope. Procedure duration decreased significantly with each successive experiment with the median procedure time of 48.3 minutes (range 34 – 64 minutes). The efficacy and safety of the stapling devices are well documented and this pre-resection closure method would minimise the risk of peritoneal contamination. BBs defining the lateral clearance margins were easily visible on the serosa during laparoscopic retraction of the colonic fold and their inclusion in the excision specimen is likely to reduce the risk of micro-abscess formation at the anastomotic site. In addition, the resulting specimen was sealed, further minimising the risk of peritoneal contamination.

## 8.5 Conclusion

This simplified, single endoscope *eversion* FLEX procedure can be performed in a timely manner. The procedure in the jig described required a team of at least five members but the results of these experiments suggest that this modified technique could be tested *in vivo*.

# Chapter 9 eFLEX technique: a survival porcine study

## 9.1 Introduction

The results of experiments presented in the previous chapter summarise the development of a single-endoscope eFLEX technique. In this chapter, we describe a survival porcine study designed to assess safety and efficacy of the eFLEX procedure in a pre-clinical setting.

The aim of this set of *in vivo* experiments was to perform a full thickness, R0 resection of colon defined as a specimen that contained three pairs of BBs delineating the clearance margin with a secure, partial circumferential colonic anastomosis. Secondary outcomes were duration of the procedure, related intra- and post-operative complications and histological assessment of the anastomotic line.

## 9.2 Methods

### 9.2.1 Animals and pre-operative preparation

Procedural steps were standardised in a series of experiments described in Chapter 8. The study was approved by the Northwick Park Institute for Medical Research ethics review process. All procedures were performed on Large White Landrace-Crossbreed pigs in compliance with the UK Home Office regulations (license number PPL 80/2297) and in line with the ARRIVE guidelines[256]. The median weight of animals included in this study was 70kg with the aim to simulate the dimensions of human colon. In order to demonstrate the safety of the procedure, an acute study involving one animal was performed first. Following this, further four pigs underwent surgery and were terminated eight days later.

All animals were habituated for a week prior to the procedure as per departmental policy. Four days prior to the procedure oral intake of grower nuts was reduced to half and two days prior to surgery, standard feed was replaced with liquid diet (Complan®). Pens were lined

with rubber mats instead of straw during this period. Animals were fasted overnight before surgery but water was allowed *ad libitum* throughout. Pre-anaesthesia was administered using ketamine and xylazine. General anaesthesia was induced and maintained using isoflurane with oxygen and nitrous oxide delivered via endotracheal tube. A saline drip was established via an ear vein and skin preparation was performed using alcoholic chlorhexidine.

### 9.2.2 Equipment

Standard laparoscopic instruments were used including atraumatic laparoscopic graspers, conventional suture holders and camera (Olympus Keymed). Colonic lavage was performed using a CF-Q240ZL colonoscope whereas PCF-240S was used as a working endoscope. The prototype endoscopic BraceBar™ system was used for endoscopic eversion of the colonic fold containing a simulated mucosal lesion as described previously. The colonic fold was excised using a laparoscopic linear stapler. Additional accessories included injection needle, Gelofusine® solution (B. Braun Medical, Ltd.), Spot®, APC, prototype endoscopic scissors and endoscopic biopsy forceps. The equipment used in this study was kindly provided by Olympus Keymed and Ethicon Endo-Surgery.

### 9.2.3 Operative technique

The anaesthetised animal was placed in the supine position and four laparoscopic ports were inserted into the abdomen. A soft bowel clamp was placed laparoscopically at approximately 45cm from the anal verge to prevent proximal inflation. Distal colon was inspected and colonic lavage using warm water performed when necessary. A simulated sigmoid polyp of approximately 3cm diameter was created endoscopically by submucosal injection of a mixture of Spot® and Gelofusine®. All polyps were created on the anti-mesenteric border at between 25cm and 35cm from the anal verge. Procedural steps are illustrated and presented in Figure 9.1 and Figure 9.2. As described previously, circumferential APC marks were placed endoscopically 1cm away from the edge of the lesion. In order to maintain orientation of the endoscopic view, additional mucosal marks

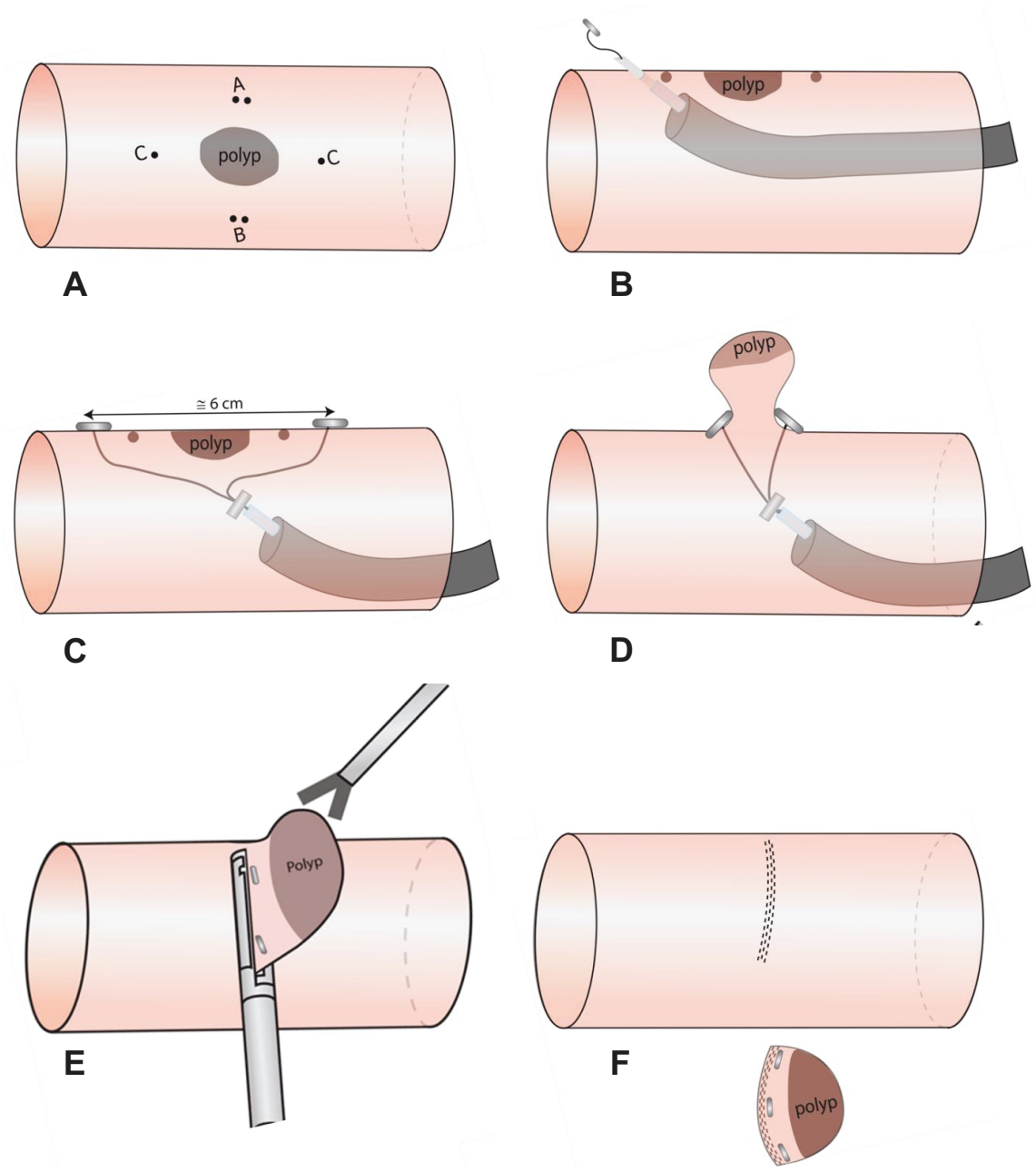
were placed as the experiments progressed. Three and two APC marks were placed outside the existing circumferential to define the proximal and distal edge of the polyp respectively (position C), and single marks were also placed at positions A and B (Figure 9.1). Using the APC marks for orientation, three pairs of BBs were placed endoscopically at positions A, B and C, at predetermined sites. All BBs were deployed under direct laparoscopic vision to prevent damage to the surrounding structures. After tightening the thread and approximating the BBs, excess monofilament thread was cut and removed using biopsy forceps. An atraumatic laparoscopic grasper was used to retract the everted colonic fold and manipulate it into the laparoscopic stapler ensuring that the stapler was placed below the three pairs of BBs visible on the serosal surface. The excised specimen was removed through a laparoscopic port incision with the BBs *in situ*. The abdominal cavity was inspected to ensure haemostasis prior to closure of laparoscopic port sites using 2.0 Vicryl suture (Ethicon, Endo-Surgery).

### 9.2.4 Post-operative care and assessment

The animal used in the acute study was euthanised under general anaesthesia immediately after the procedure. The subsequent four animals were recovered successfully following administration of appropriate analgesia and a single dose of Cefuroxime. Regular feeding was recommenced immediately after the procedure and animals were euthanised after eight days.

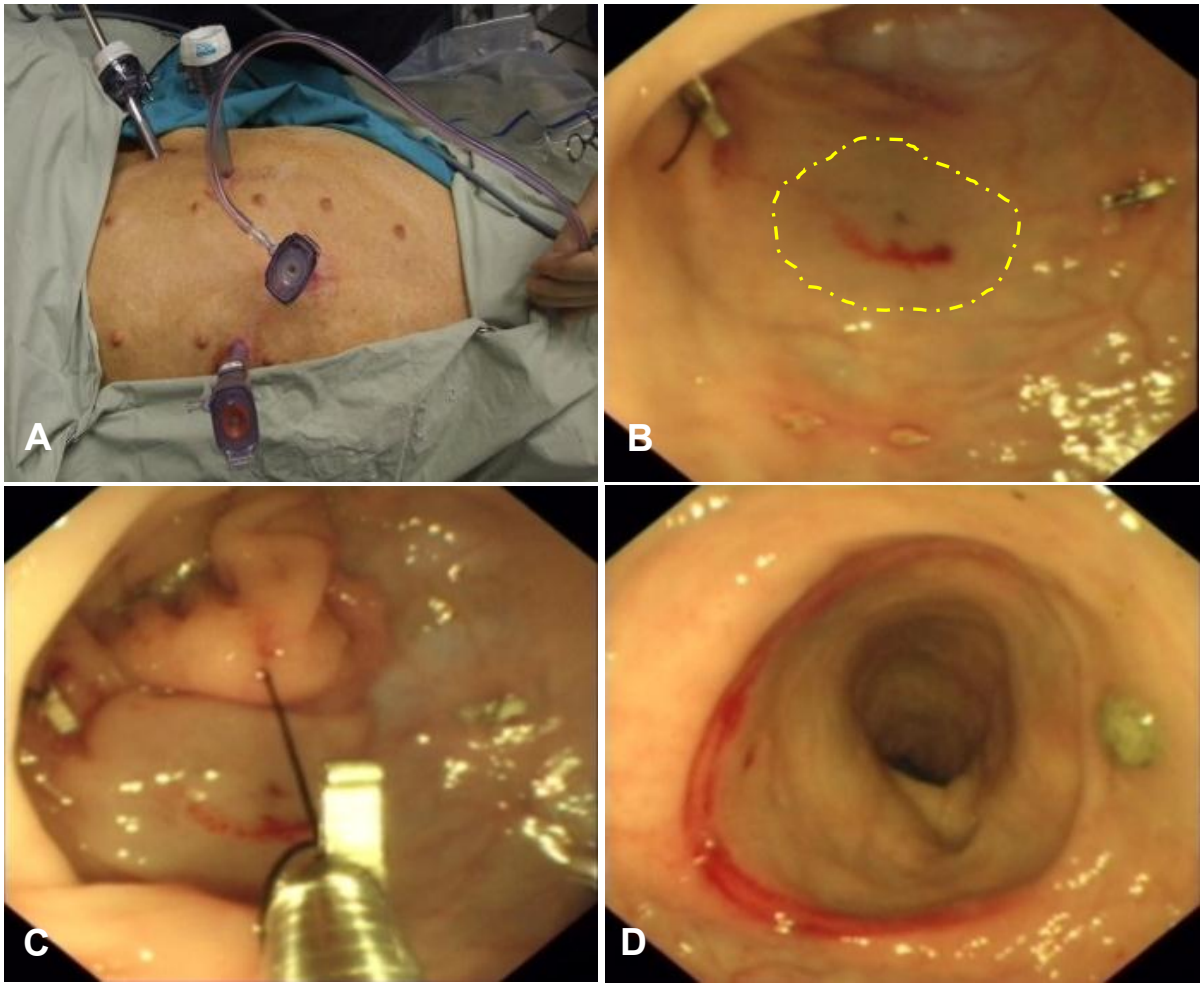
All animals were terminated under general anaesthesia and a post-mortem examination was performed in every case. Midline laparotomy allowed full inspection of the peritoneal cavity for procedure related complications and close examination of the sigmoid colon. Endoscopic examination was performed in two animals under terminal anaesthesia in order to assess the colonic lumen. Bursting pressures of stapled anastomoses are well documented in the literature and although the eFLEX technique results in partial circumferential anastomosis, additional bursting pressure analysis was deemed unnecessary[257, 258].

***Figure 9.1 Schematic illustration of the technical steps of the eFLEX technique***




***A.*** *Endoluminal positions of BBs as guided by the mucosal APC markings;* ***B.*** *Endoscopic placement of BBs at predetermined sites;* ***C.*** *Maximum spacing of the BBs at position C;* ***D.*** *Approximation of BBs results in eversion of the colonic fold;* ***E.*** *The fold is retracted using laparoscopic graspers and linear stapler placed below BBs visible on the serosal surface;* ***F.*** *The excision results in a simultaneous colonic closure producing a sealed full thickness specimen*

***Figure 9.2 In-vivo eFLEX procedure***




***A.*** *Position of laparoscopic ports;* ***B.*** *Endoluminal view of the simulated polyp (yellow line) with BB tighteners visible in A and B positions (3 and 9 o'clock);* ***C.*** *Approximation of BBs placed in position C;* ***D.*** *Endoluminal view post-resection*

### *9.2.4.1 Tissue preparation*

A 10cm segment of the sigmoid colon including the anastomotic line was excised from the four surviving animals and macroscopic examination of the serosal and mucosal surfaces performed. To prevent tissue drying and desiccation, all specimens was rinsed, placed on a corkboard and immersed in 10% neutral buffered formal saline (10% NBF) (Genta Medical) for a minimum of 48 hours for fixation. Following fixation, sections of the bowel approximately 1cm wide were taken perpendicular to the anastomotic line (one in the midline, and one or two on either side of the midline). Staples were carefully removed and tissue samples were placed into labelled processing cassettes. These were processed in the

Tissue Tek-VIP processor to allow dehydration and clearing of tissue samples, which were then embedded in paraffin using the Tissue-Tek III embedding centre.

#### *9.2.4.2 Slide preparation and staining*

Sectioning of the blocks was performed using a Shandon microtome producing sections of 5μmthickness. Sections were mounted onto labelled slides which were then placed on a hotplate at 60ºC overnight. The sections were immersed in two consecutive xylene baths for 5min to remove the wax. For haematoxylin and eosin (H&E) staining all slides were de-waxed in xylene (Genta Medical), rehydrated in descending grades (100%, 95% and 70%) of Industrial Methylated Spirit (IMS) (Genta Medical) and washed in tap water. Slides were then placed in Gill's III Haematoxylin (Leica Microsystems, UK Ltd.) for 90 seconds, washed in tap water, differentiated in acid alcohol (1% hydrochloric acid in 70% IMS) and washed again in tap water before being placed in 0.5% aqueous eosin (Pioneer Research Chemicals) for 5 minutes. After staining was complete, the sections were again washed in tap water and dehydrated in ascending grades of industrial methylated spirits (IMS) (70%, 95%, and 100%) and finally cleared by treating with xylene before being cover-slipped. Cells were differentially stained; nuclei appearing a dark purple/blue, the cytoplasm-stained pink, muscle fibres and elastic fibres stained deep pink and collagen stained light pink.

For staining with the Picro Sirius Red (BDH) in combination with the Miller's elastic stain (Leica Microsystems, UK Ltd.), de-waxed and rehydrated slides were placed in 0.5% acid potassium permanganate (Sigma). After rinsing in de-ionised water, the slides were placed in 1% oxalic acid (Sigma). They were rinsed again in de-ionised water followed by 95% IMS before being placed in Miller's stain for 1 hour. After this, the slides were rinsed in 95% IMS followed by tap water and placed in Weigert's haematoxylin (Pioneer Research Chemicals) for 10 minutes. After this, the slides were rinsed in tap water, differentiated in acid alcohol and rinsed again before being placed in Picro Sirius Red solution 45min. Once the staining process was complete, the sections were again washed in de-ionised water and dehydrated by treating with serial alcohol washes (ascending grades) and finally cleared in xylene before

application of a cover slip. When assessed in the white light microscopy the collagen is red on a pale yellow background with black/brown nuclei. When examined in polarised light however, the large, mature collagen fibres are bright yellow/orange with thin, new collagen fibres being green.

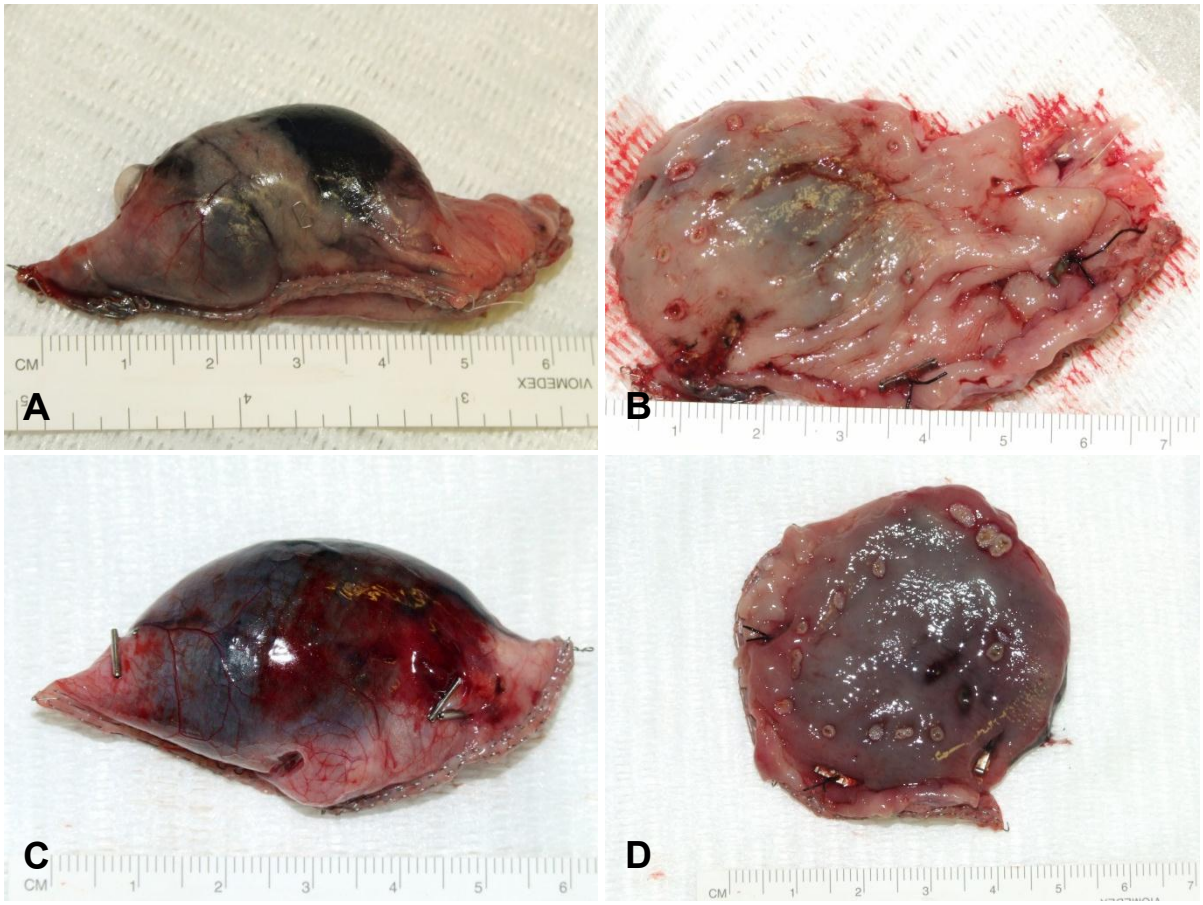
## 9.3 Results

### 9.3.1 eFLEX procedures and survival

Full thickness resection of colonic lesions was successfully performed in all cases. The median time taken to perform the eFLEX elements of the procedure, defined from placement of mucosal APC marks to excision of the specimen was only 26 minutes (range 20 - 31 minutes) (Table 9.1). All five specimens included APC markings and BBs, which was considered the equivalent of full thickness R0 resection. The median diameter of the specimen was 5.1cm (range 4.5 - 6.3cm) (Figure 9.3).

Technical difficulties encountered during the procedure were mostly related to the equipment. On four occasions the second metal tag of the BB pair was jammed in the needle and failed to deploy. This was rectified with laparoscopic assistance and BBs were successfully released. In one case, the deployed BB remained in a vertical position in line with the needle and was pulled back into the colon through the puncture site. Unfortunately, the BBs are too wide to be withdrawn through the endoscopic channel and the pair was released from the needle into the colonic lumen. New BraceBar$^{TM}$ system was used and original BBs withdrawn with the endoscope at the end of the procedure.

***Figure 9.3 eFLEX specimens***




***A & B.*** *Tangential excision of the specimen in Animal 3 resulting in additional 2cm of tissue excised;* ***C & D.*** *Open and closed specimen Animal 4*

Mucosal APC marks placed at position B were not clearly visible in one animal and the BBs were deployed at approximately the 7 o'clock position instead of 9 o'clock, further away from the edge of the polyp than anticipated. The everted fold was rotated anti-clockwise resulting in tangential excision of the specimen. An additional 2cm of healthy tissue was included in the specimen (Figure 9.3, A & B) and the resection line extended to the mesentery where it bled. The bleeding point was easily controlled by placement of laparoscopic sutures. Minimal bleeding at the staple line was also observed in one additional animal, requiring laparoscopic over-sewing. Anastomotic line was inspected endoscopically following resection and patent lumen was visualised in all animals (Figure 9.4).

The survival period was uneventful. All animals tolerated normal diet immediately after the procedure and thrived during the post-operative period. Median time to first bowel movement was 3 days (range 2 – 4 days) with the median weight of animals at termination of 66kg.

***Table 9.1 Procedural duration***

| *Table 1* | Animal 1, (min) | Animal 2, (min) | Animal 3, (min) | Animal 4, (min) | Animal 5, (min) | Median, (min) |
|---|---|---|---|---|---|---|
| **Laparoscopy and bowel lavage** | 41 | 29 | 27 | 30 | 26 | **29** |
| **Polyp creation** | 8 | 6 | 7 | 4 | 2 | **6** |
| **APC marking** | 3 | 4 | 3 | 6 | 3 | **3** |
| **BB pair 1** | 7* | 6 | 5 | 4 | 4 | **5** |
| **BB pair 2** | 6 | 8* | 5* | 3 | 5 | **5** |
| **BB pair 3** | 7*¥ | 4 | 5 | 3 | 3 | **4** |
| **Polyp excision** | 8 | 9 | 6 | 10 | 5 | **8** |
| **Skin closure** | N/A | 15 | 17 | 30≠ | 14≠ | **16** |
| **Total procedural steps time** | **80** | **81** | **75** | **90** | **62** | **80** |
| **eFLEX time** | **31** | **31** | **24** | **26** | **20** | **26** |

*(*) Second BB jammed in the needle*

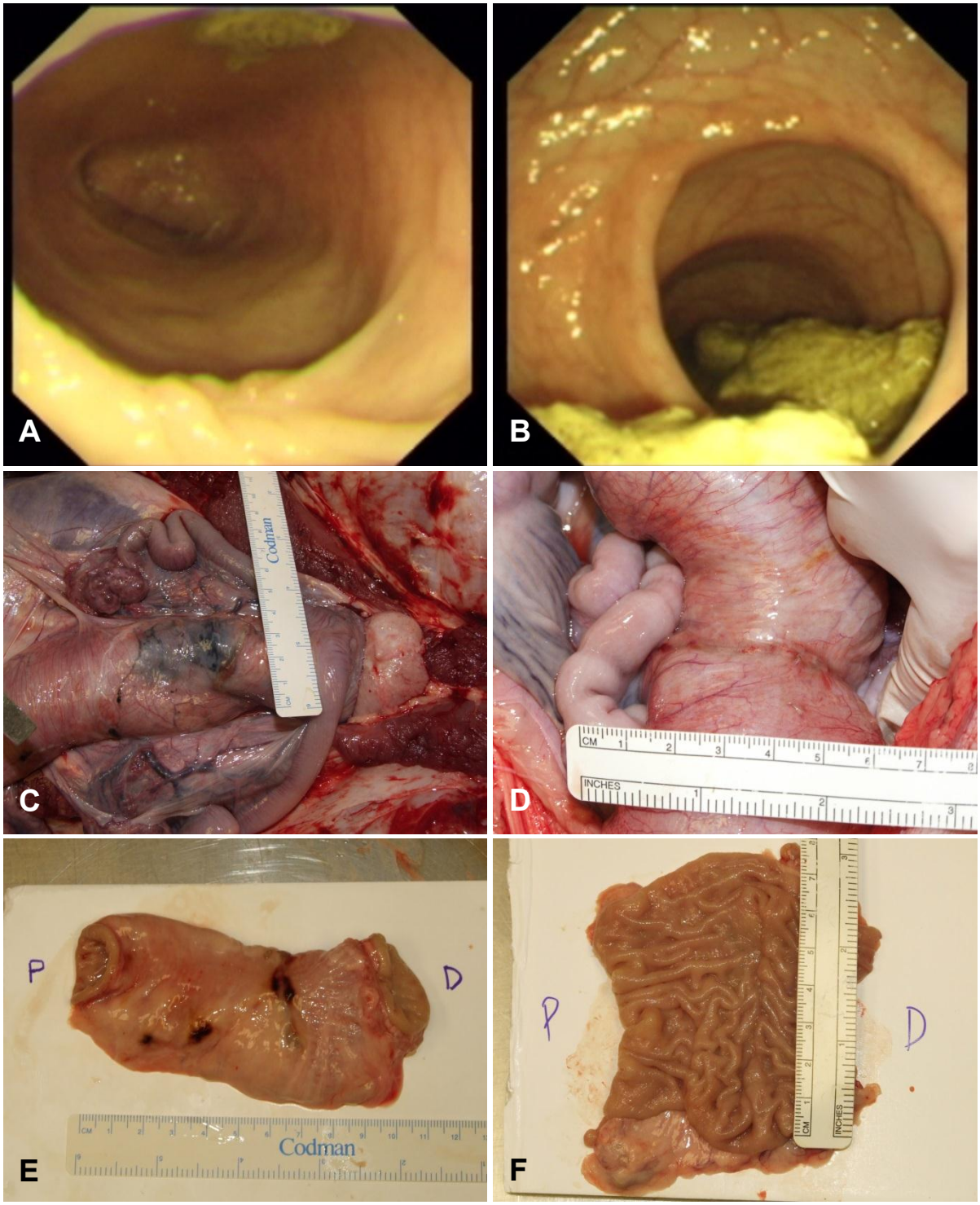
*(¥) BB retracted into the colon through the puncture site*

*(≠) Resection line extended to the mesentery resulting in mesenteric bleeding*

### 9.3.2 Post-mortem examination and histological examination

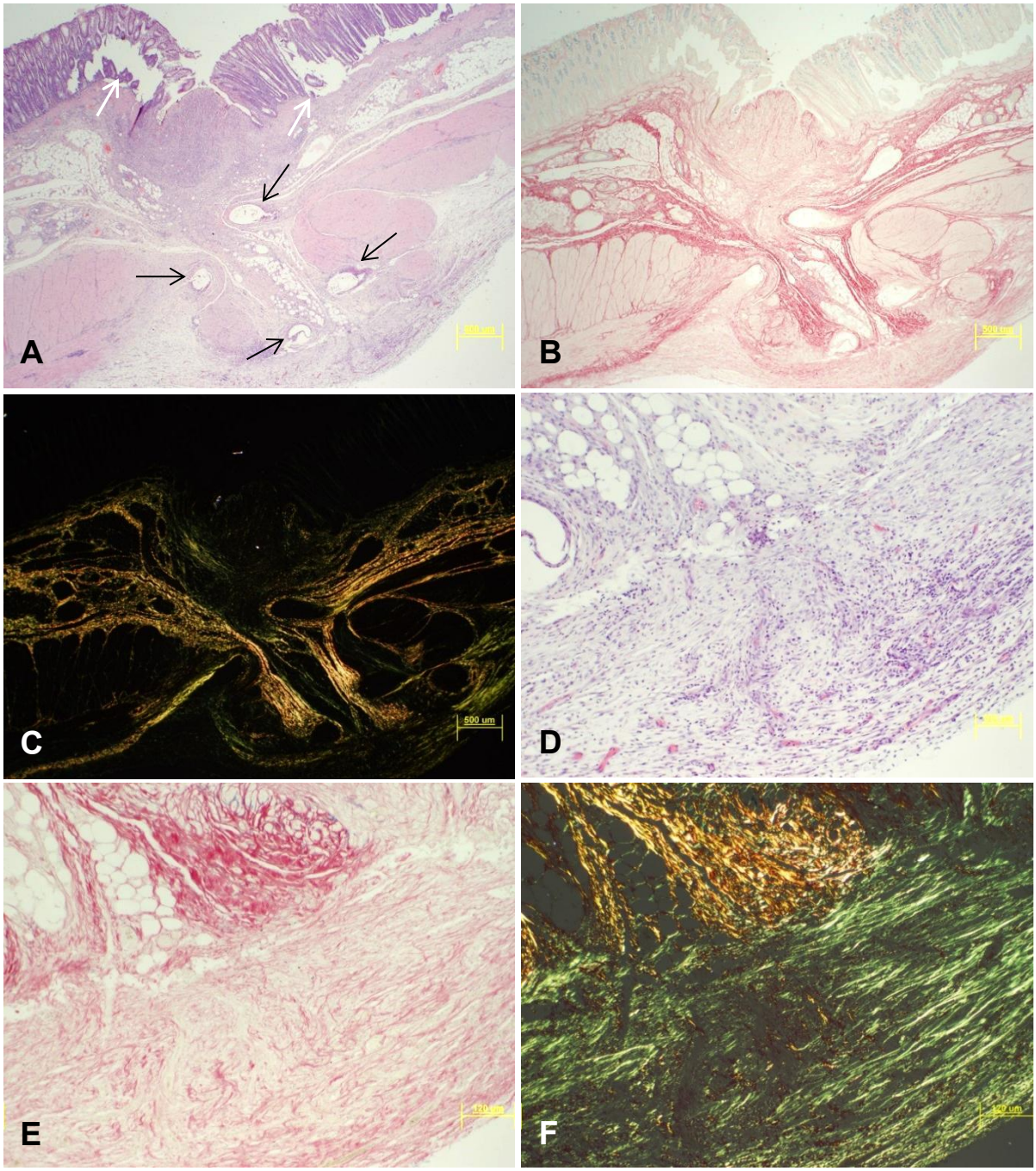
Endoscopic examination of the resection site at 8 days revealed no evidence of luminal obstruction with fully healed mucosa (Figure 9.4). In one animal, the anastomosis was only identified endoscopically following laparotomy and placing pressure on distended colon from the outside. Examination of peritoneal cavity at laparotomy was normal in all animals with no evidence of local or distant abscesses. Small serosal haematomas were observed in two animals proximal to the anastomosis at the position of the bowel clamp (Figure 9.4, E). Macroscopic examination revealed healed anastomotic line on both serosal and mucosal surface (Figure 9.4, E & F).

***Figure 9.4 Post-mortem examination***



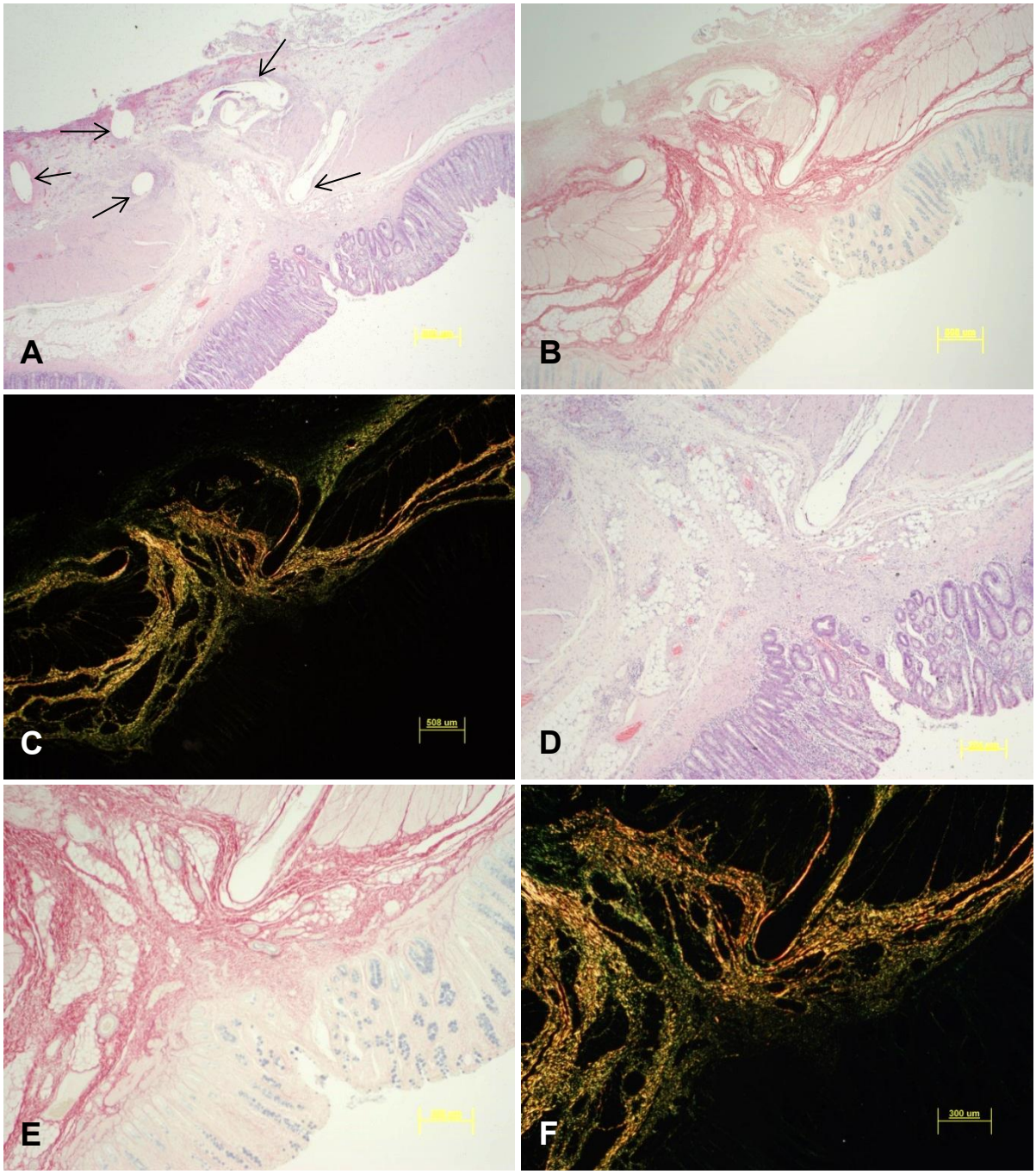

***A & B.*** *Endoscopic evaluation of the anastomoses in Animals 4 and 5;* ***C & D.*** *Serosal examination of anastomoses Animal 2 (tangential excision) and Animal 4;* ***E & F.*** *Serosal and mucosal view of the anastomosis Animal 4*

***Figure 9.5 Histological examination of anastomosis, Animal 2***




***A.*** *H&E stain of representative strip taken perpendicularly across the anastomosis demonstrating regeneration and continuity of both subumosa and serosa. White arrows indicate tissue loss during specimen preparation and black arrows indicate tissue defects created by staples;* ***B & C.*** *Non-polarized and polarized view following Picro-Sirius red staining demonstrate maturing and new collagen formation across the anastomosis;* ***D & E.*** *H&E and Picro-Sirius staining of the serosa demonstrate normal inflammatory cells and collagen;* ***F.*** *New collagen formation at the subserosa and serosa*

***Figure 9.6 Histological examination of anastomosis, Animal 4***




***A.*** *H&E stain of the healed anastomotic site. Black arrows indicate tissue loss following removal of staples. Good repair and continuation of the mucosa (with formation of neomucosa)a and submucosa as well as serosa is evident;* ***B & C.*** *Non-polarized and polarized view following Picro-Sirius red staining demonstrate maturing and new collagen formation across the anastomosis;* ***D & E.*** *H&E and Picro-Sirius staining of the mucosal surface and submucosa demonstrate normal inflammatory cells and collagen;* ***F.*** *New collagen formation in the submucosal layer*

Histological assessment showed good abuttal of neomucosa and serosa. Regeneration and restoration of continuity of the submucosal layer was clearly visible with good apposition of muscularis mucosae containing inflammatory cells as expected (Figure 9.5 and Figure 9.6).

Picro-sirius red staining showed that collagen was continuous beneath the neomucosa, with neo-collagen formation at the junction of submucosa and muscularis mucosae. This confirms complete and maturing closure at the full thickness resection site without micro-abscess formation.

## 9.4 Discussion

The results of this survival porcine study demonstrate the feasibility and safety of localised full thickness resection of colonic lesions in adherence with the established oncological principles. With application of a modified, single-endoscope eFLEX technique, we successfully achieved R0 excision of colonic specimens with the largest median diameter reported to date in a pre-clinical study. The overall duration of the procedure was significantly reduced when compared to the original technique (median 80 *vs.* 233 minutes respectively), with the duration of the procedure performed later in the series being reduced with experience. More importantly, the median time taken to delineate circumferential margins of the lesion, evert the colonic fold and excise the specimen resulting in a stapled, partial circumferential anastomosis was 26 minutes (range 20 – 31 minutes).

At a median diameter of 5.1cm, the size of the specimen resected is larger than previously achieved by hybrid or EFTR techniques. In addition, all specimens contained three pairs of BBs defining the circumferential margin. The literature suggests that an inadequate resection margin (<2 mm) is a poor prognostic factor and an indicator of increased risk of local recurrence and/or nodal disease[26] and therefore to ensure completeness of resection, all BBs were placed 1cm away from the edge of the polyp (in excess of the required 2mm reported in the literature). This approach allows the excision to be sufficiently accurate to ensure the precise removal of target lesions.

This modified, single endoscope eFLEX technique is likely to overcome the issues reported in the literature describing ‘rendezvous’ laparo-endoscopic techniques in human as well as

those encountered in preclinical studies evaluating effectiveness of colonic EFTR. As discussed previously, clinical application of the laparo-endoscopic procedures is limited with experience restricted to few centres. All endoscopically or laparoscopically assisted full thickness resection techniques evaluated in pre-clinical model for colonic lesions presented in Chapter 6 have limitations regarding safety, reproducibility and secure wall closure. The eFLEX procedure is an accurate excisional technique that removes only a portion of circumference of the bowel and should impair blood supply less than conventional colectomy, potentially reducing the risk of anastomotic leakage and ileus leading to a faster recovery. Pre-resection closure of the colonic wall results in a stapled anastomosis, with a well-documented safety profile and a closed specimen which prevents spillage of endoluminal contents or potentially malignant cells into peritoneal cavity. Laparoscopic overview and assistance minimises the risk of inadvertent damage of the surrounding organs during application of BBs.

This proof-of-concept survival study has several limitations. Further animal work is unlikely to progress the technique as porcine models are limited by their differences from human anatomy, particularly with regard to the vasculature and retroperitoneal portions of human colon. Presence of spiral colon limits the evaluation of the technique in this pre-clinical model to the long sigmoid colon only, although we anticipate that application of this single-endoscope technique for right sided colonic lesions should not be technically challenging. Colonic mobilisation would be required for lesions located at flexures or retroperitoneum in order to optimise endoluminal exposure of the lesion as described by Franklin et al.[143] and Wilhelm et al.[144]. This, however, is difficult to assess in a straight segment of the porcine sigmoid colon. In addition, the porcine mesentery is very short and all procedures presented in this chapter were performed for lesions located on the anti-mesenteric side. Therefore there will be issues to overcome regarding the mesentery and marginal vessels potentially impeding the procedure in humans and eFLEX procedure may not be appropriate for such lesions. Utilisation of pre-operative imaging such as CT colonography to ascertain location of

the lesion in relation to the mesentery and retroperitoneum would facilitate pre-operative planning and avoid unnecessary conversion to laparoscopic hemicolectomy.

# Chapter 10 Conclusion

## 10.1 Summary

Over thousand patients undergo hemicolectomy with *en bloc* mesenteric excision for the treatment of complex benign colonic polyps in England each year. Such patients are at risk of major morbidity, mortality and long-term functional problems associated with this procedure. This thesis presents evidence regarding short-term morbidity and long-term functional problems after colectomy for benign polyps. It also details the development of a precisely targeted full thickness excision technique suitable for translational work in the human.

## 10.2 Short-term outcomes following hemicolectomy for treatment of benign colonic polyps: local and national data

The study presented in Chapter 3 describes outcome data following surgery for benign colonic polyps, comparing results to those after equivalent resection for colonic cancer. Both hospitals included in this study were tertiary referral centres for endoscopy with expertise available in complex EMR and ESD procedures. Data from this study suggest that the size of the lesion is the commonest indication for surgery in this patient cohort, followed by difficult endoscopic access and suspicious morphological/histological features. Over 60% of patients underwent right hemicolectomy, confirming that right sided lesions represent a challenge even for experienced endoscopists. Although the majority of the patients underwent laparoscopic surgery within an enhanced recovery programme, post-operative complications, re-operation and re-admission rates were similar to the cancer group. The results of this study suggest that benign diagnosis does not reduce the risk of post-operative morbidity.

The sample size in this study, however, was small and it may affect the generalizability of our conclusions. In order to find more meaningful differences between the two cohorts and establish the true risk of morbidity, we conducted a second study analyzing national data from the HES database. Data for all elective colorectal resections performed between 2000 and 2007 were available, enabling us to evaluate post-operative outcomes of 8 659 patients who underwent colorectal resection for the treatment of benign colorectal polyps and 111 047 for CRC. The results of this study confirmed that over 60% of colonic resections were performed for right sided polyps and no difference in re-admission rates was observed between benign and malignant groups. Post-operative morbidity was lower in the benign cohort, most probably because patients undergoing surgery for colonic polyps are younger, with less co-morbidity, when compared to the cancer cohort. Multiple regression analysis demonstrated that male sex, advanced age, high comorbidity and social deprivation were all independently associated with an increase in 30-day mortality. The histological diagnosis of the lesion had no effect on mortality.

In conclusion, both studies analysing outcomes after colectomy for benign colonic polyps show that the morbidity is similar to that following resection for colonic cancer. This provides impetus to development of new treatments that will improve outcomes by reducing post-operative morbidity.

## 10.3 Functional outcomes and QOL following hemicolectomy

The results of the study presented in Chapter 5 suggest that although patients seem to have a total MSKCC score that is comparable to healthy controls as early as six months after surgery, certain elements of bowel function remain altered several years after hemicolectomy. At 12 months follow-up patients reported having difficulty with gas-stool discrimination and at two to four years, difficulty controlling the passage of wind. In addition, patients reported a significantly higher number of bowel movements when compared to

healthy controls, but with no adverse effect on their QOL. At six and 12 month follow-up however, patients with low total MSKCC score, symptoms of urgency and those reporting incomplete bowel emptying had worse QOL. Similarly, those recruited for assessment of the 'intermediate' bowel function reported worse QOL if they were unable to differentiate between wind and solid stool or completely empty their bowels.

Although the MSKCC questionnaire has only been validated in patients undergoing rectal surgery, the results of this study suggest that hemicolectomy for the treatment of invasive or non-invasive neoplasia may have an adverse effect on patients' bowel function even few years after surgery. Although these findings are yet to be confirmed in a larger, prospective study, bowel dysfunction following hemicolectomy could potentially be avoided if targeted, localised excision could be offered as an alternative definitive treatment.

## 10.4 Development of a localised full thickness colonic excision technique

Chapter 6 is the first systematic review published to date that summarises the outcomes following colonic EFTR techniques, with the current experience being limited to pre-clinical models only. The results suggest that pre-resection closure is preferable as it is associated with fewer intra- and post-operative complications. It minimises the risk of peritoneal contamination with endoluminal content and potentially malignant cells. In addition, traction of the colonic wall rather than suction seems likely to result in less collateral damage and laparoscopic overview or assistance improves the safety of the procedure.

The review also highlights the importance of safety and reliability of the anastomotic closure method. Colotomy closure using endoscopically placed Tissue Apposition System was time consuming and post-mortem findings from the survival study suggested that the risk of peritoneal contamination was high. It is difficult to formulate any conclusions regarding anastomotic quality following pre-resection Over-The-(endo)Scope-Clip (OTSC)

compression closure. In fact, bursting pressures analysis following a survival study has only been reported by one research group and further studies are necessary to demonstrate their safety.

*Ex vivo* experimental work designed to assess limitations of the originally described FLEX technique resulted in the development of a cheap, practical jig and a modified anal sealing device that maintained a pneumocolon for all procedures. Despite utilising several endoscopic combinations, we were unable to maintain effective traction on the inverted colonic fold during resection. As a result, the quality and diameter of the excised specimens were inconsistent. Although the inversion FLEX procedure could potentially be applied for lesions located in any part of the colonic circumference, further advances in technology such as the development of a stable endoscopic platform during retraction, and an endoscopic cutting and sealing device to shorten the procedure time, are necessary.

Anastomotic leakage following colorectal surgery is a major cause of morbidity and, at times, mortality. Stapling devices have been refined over the years and the speed of application and reproducibility of the results has made them the most frequently utilised technique for colorectal anastomosis[259]. The results of the systematic review presented in Chapter 6 and experimental work in Chapter 7 have led to the development of the single-endoscope *eversion* FLEX (eFLEX) technique. This simplified procedural protocol provided an effective way of excising a full thickness colonic specimens in excess of 5cm in diameter in an *ex vivo* model. We were able to perform the procedure in less than 30 minutes resulting in a stapled, partial circumferential anastomosis, and a closed specimen. Safety and efficacy of the eFLEX procedure was subsequently demonstrated in a survival animal model with no intra- or post-operative complications. The study suggested that colonic eFLEX can be performed in such way that oncological principles are respected for lesions located on the anti-mesenteric side throughout the colon.

# Chapter 11 Future work

## 11.1 Full-thickness laparo-endoscopic excision for benign colonic polyps in human

Pre-clinical bench and survival animal studies presented in this thesis have demonstrated the likely feasibility and safety of the eFLEX procedure for colonic lesions located on the anti-mesenteric border. Data analysis from two teaching hospitals presented in Chapter 3 suggests that approximately 50% of patients referred for hemicolectomy have polyps <5cm in diameter and as such are potentially suitable for the eFLEX procedure. A study protocol is currently in development to translate the eFLEX technique into clinical practice in a representative sample of patients with complex benign colonic polyps. A protocol for a descriptive cohort study is currently under development in line with the IDEAL (Idea, Development, Exploration, Assessment, Long-term follow-up) guidelines[260]. Specific objectives of the study are likely to include the completion of the eFLEX procedure (completeness of excision and the proportion in whom it is suitable), conversion rates to hemicolectomy with lymphadenectomy, and details of post-operative morbidity and mortality. The study will also enable standardization of the technique, as due to the differences between porcine and human anatomy certain elements of the procedure could not be assessed in a pre-clinical study. There will be issues to overcome regarding the mesentery and marginal vessels potentially impeding the procedure in a proportion of these patients when lesions lie on the mesenteric border. Retroperitoneal location of the lesion is likely to require colonic mobilization to allow access and pre-operative utilisation of computed tomography may clarify polyp location in relation to the mesentery and retroperitoneum, facilitating surgical planning.

## 11.2 Feasibility and diagnostic yield of EUS as an assessment tool of early colonic neoplasia

Studies reporting outcomes of surgically treated colonic polyps thought to be benign pre-operatively show that the incidence of unexpected invasive malignancy can be as high as 20%[183, 261], suggesting that such lesions should be treated with caution. Provided that the safety and efficacy of the eFLEX procedure is demonstrated in the aforementioned clinical study, this novel technique could potentially be offered as a definitive treatment for a proportion of this patient cohort. Careful preoperative selection of patients least likely to have a malignant polyp may be appropriate.

EUS is used routinely in the preoperative staging of neoplasms of upper gastrointestinal and rectal neoplasms. In contrast, it has not gained widespread use for the staging of colonic lesions because, until recently, such accurate preoperative local staging information had no relevant therapeutic consequences. However, with advances in endoscopic techniques, growing interest in minimally invasive surgery and the success of screening programmes, accurate staging of colonic lesions has become more relevant. Several authors have reported some experience with endoscopic radial scanning probes of differing frequencies in early stage colonic tumours[54, 262]. Technical difficulties encountered include limited depth of tissue penetration, unsatisfactory water immersion coupling for lesions located at flexures and, more importantly, operator experience. Application of a curved linear array endoscope for assessment of the right sided lesions has been recently reported as safe and feasible[263]. This novel front-view 14.2 mm endoscope (125-cm insertion length) with a 3.7-mm working channel provides a forward-arrayed EUS images which may overcome some of the issues encountered using mini-probes and thus improve the pre-operative selection process of patients potentially suitable for eFLEX procedure.

## 11.3 A study to assess NIR laparoscopy with ICG for intra-operative SLN mapping in early colon cancer

Application of the eFLEX procedure for the treatment of localised colonic carcinoma is an attractive clinical possibility. T1 malignant lesions that are less than 3.5cm in diameter have been shown by Cahill and colleagues [150] to be associated with positive lymph nodes in only 5% of cases. In patients confirmed to have a T1 tumour on colonic EUS, those at high risk of postoperative morbidity, or those who elect to pursue a potentially safer postoperative course, eFLEX may be a preferable treatment option, even if oncological clearance equivalent to conventional resection cannot be guaranteed. Alternatively, the combination of eFLEX with laparoscopic SLN biopsy using NIR immunofluorescence identification is a possible solution for determining which patients require hemicolectomy to clear the nodal basin. A *post hoc* analysis of the two largest SLN biopsy databases[150] reported a sensitivity of 89% and a negative predictive value of 97% when SLN mapping was performed by experienced surgeons patients with selected T1 and T2 lesions. In the cohort of 186 patients, the authors reported a false positive rate in 7.5% (12) of patients whereas under-staging would have occurred in only three patients (false negative rate 1.6%).

The ability to identify accurately the exact lymphatic drainage pattern of the primary tumor in real time and to ascertain lymph node involvement before definitive resection could allow decisions regarding a tailored operative approach to be made intra-operatively. While previous attempts have been made to use SLN mapping in colon cancer, these studies and their accuracy have often been compromised by the inclusion of advanced stage cancers[155]. The appropriate Medicines Health Regulatory Agency and National Research Ethics Service (12/LO/1406) approvals are currently in place to conduct a pilot trial of NIR ICG laparoscopy for SLN mapping in patients with colonic cancer at St. Mark's Hospital. The primary objective of the trial is to establish whether it is possible to identify the first order draining mesocolic lymph nodes (SLNs) in patients with suspected T1 and T2 colonic cancer, using ICG and a laparoscopic NIR system. In addition, the extent to which the tumour-bearing status of

SLN(s) corresponds with lymph node status of the entire basin will be assessed using standard pathological examination (H&E) of excised nodes with additional immunohistochemistry of negative SLN(s).

## 11.4 Conclusion

Much remains to be done before a full thickness, localised excision technique can be offered as an alternative to hemicolectomy to patients with complex, benign colonic polyps. Studies presented in this thesis demonstrate high post-operative morbidity, mortality and prolonged in-hospital stay associated with the current treatment and emphasise the need to improve the way that these patients are managed. In the meantime, these patients might benefit from a referral to tertiary centres offering advanced endoluminal therapies in order to minimise the risk of complications.

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