Detection And Removal Of Sub-Centimetre Polyps

(Thesis for degree of MD)

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Abbreviations

ADR	Adenoma Detection Rate
AFI	Autofluorescence Imaging
APC	Argon Plasma Coagulation
BCSP	Bowel Cancer Screening Programme
BCSS	Bowel Cancer Screening System
BSG	British Society of Gastroenterology
CBF	Cold Biopsy Forceps
CS	Cold Snare
CCCG	Cochrane Colorectal Cancer Group
CRC	Colorectal Cancer
CWT	Colonoscopy Withdrawal Time
EMR	Endoscopic Mucosal Resection
FAP	Familial Adenomatous Polyposis
FICE	Fuji Intelligent Color Enhancement
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
HD	High Definition
HBF	Hot Biopsy Forceps
HS	Hot Snare
NBI	Narrow Band Imaging
RCT	Randomised Controlled Trial
SPT	Suction Pseudopolyp Technique
SSP	Specialist Screening Practitioner
WLE	White Light Endoscopy
WMD	Weighted Mean Differences

Abstract

Introduction

Colonoscopic polypectomy has been shown to reduce the incidence and mortality of colorectal cancer. Most polyps encountered during colonoscopy are small and approximately 10% will have advanced pathology. Therefore, it is important that colonoscopy and polypectomy is performed to a high standard.

Aim

To determine if simple interventions can be used to improve the detection and removal of sub-centimetre polyps.

Methods

1. A systematic review of 7 randomised controlled trials was performed to determine if chromoendoscopy increased the polyp detection rate compared with conventional white light endoscopy.
2. Data from the English BCSP was analysed to describe the variation in polypectomy techniques employed for the removal of sub-centimetre polyps in relation to polyp characteristics, completeness of histological excision and safety.
3. An observational prospective study was undertaken to determine the efficacy of cold snare polypectomy with a thin wire mini-snare (0.30mm) versus a thick wire mini-snare (0.47mm).
4. A single centre, randomised controlled trial was performed to compare the efficacy of standard cold snare polypectomy versus a novel suction pseudopolyp technique

Results

In the systematic review, chromoendoscopy showed a significant increase in the detection of neoplastic and non-neoplastic polyps, but there was no increase in the detection of larger or advanced polyps compared with conventional white light endoscopy.

Analysis of the BCSP database showed that removal of sub-centimetre polyps is safe despite wide variations in practice. The use of cold resection techniques and EMR has increased over time ($p<0.001$). However, assessment for the completeness of histological resection is limited with almost two thirds of cases reported as not assessable.

In the observational prospective study, completeness of endoscopic excision was significantly better with the thin wire snare compared with the thick wire snare (90.2% vs. 73.3%, $p<0.05$). In the RCT comparing standard cold snare polypectomy with the suction pseudopolyp technique, no clinically significant difference was observed between the two techniques (92.6% vs 98.6%, $p=0.08$). No perforation or bleeding requiring hemostasis occurred in either of these two studies.

Discussion

From this body of work it is apparent that chromoendoscopy, cold snare polypectomy with a thin wire snare and the suction pseudopolyp technique are safe, quick and effective. These simple interventions are easy to learn and can be performed by all colonoscopists to improve the detection and removal of polyps.

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Introduction

The detection and removal of polyps have been shown to prevent colorectal cancer and death (1, 2). Endoscopists will use a variety of proven, simple and effective methods to optimise the adenoma detection rate (ADR), which is regarded as a key indicator of high quality colonoscopy (3). These include excellent bowel preparation (4), dynamic position change (5), cap assisted endoscopy (6) and adequate withdrawal times (7). Image enhancement with dye-based chromoendoscopy is relatively under utilised and upon adenoma detection, a range of polypectomy techniques and devices can be used with considerable variation in practice.

This thesis will therefore try to understand the reasons for the wide variation in polypectomy practice. It will test the hypothesis that simple methods such as chromoendoscopy, snare type or polypectomy technique improves the detection and removal of sub-centimetre polyps.

Aims

1. To determine if pan colonic dye spraying with indigo carmine increases the detection of polyps during colonoscopy
2. To describe the variation in polypectomy practice in the National Bowel Cancer Screening program and the factors that influence this.
3. To determine if the completeness of polyp resection is influenced by the device and technique used.

Objectives

1. This thesis will examine the factors that influence the adenoma detection rate, in particular if chromoendoscopy enhances the detection of polyps and neoplasia during endoscopic examination of the colon and rectum.

2. This thesis will describe the techniques employed for the removal of sub-cenitmetre polyps in the English Bowel Cancer Screening Programme (BCSP) according to polyp size, site and morphology and how it relates to the completeness of histological resection and occurrence of major complications.

3. Different devices and techniques are used to remove polyps with the primary intention of achieving complete and safe polypectomy. This thesis will examine the effectiveness of two different cold snare devices and techniques on the quality of polyp resection and complications.

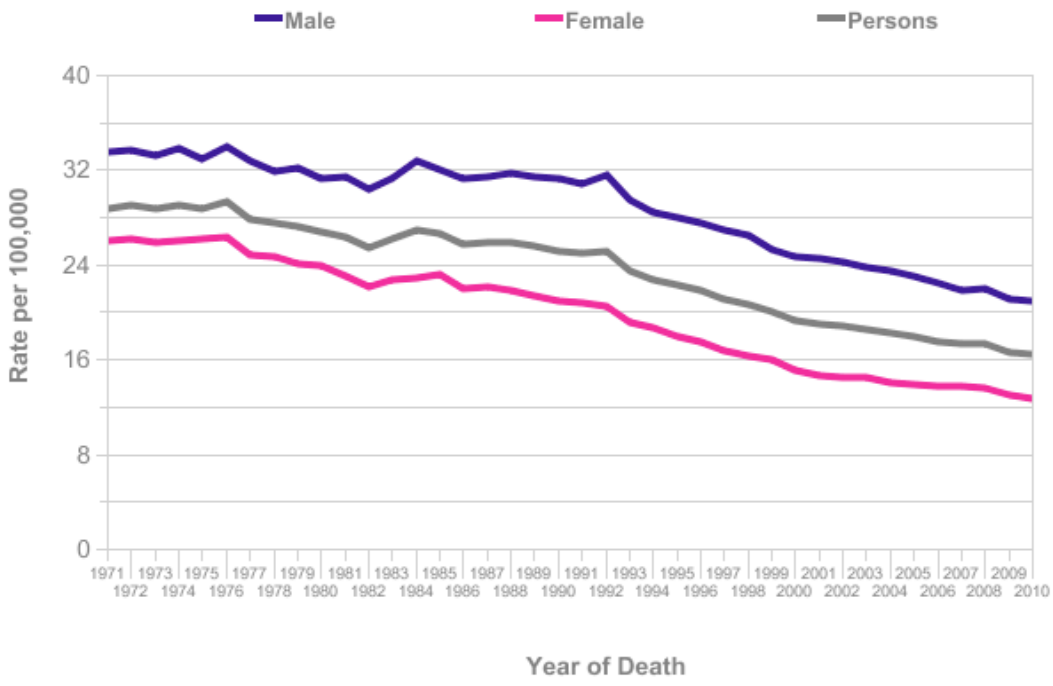
The thesis is presented with a review of the literature and a series of papers each with a brief introduction and detailed discussion addressing the aims and objectives outlined above. It will also attempt explore other questions raised by this work.

Chapter 1: Literature review

1.1.0 Incidence and Mortality of Colorectal Cancer

Colorectal cancer (CRC) has a high morbidity and mortality rate and represents 9% of all cancer incidences worldwide (8-10). In 2012 it was ranked the 4th most common cause of cancer death worldwide and the 2nd most common in the UK accounting for 8-10% of all cancer deaths (10, 11). Countries with the highest incidence rates include Australia, New Zealand, United States and parts of Europe (9). Risk factors associated with CRC include low dietary fibre intake, high consumption of processed red meats, smoking, lack of exercise and obesity (12-16). A shift towards this type of lifestyle led to a rapid increase in CRC incidence in Japan between 1983 and 2002, whereas Middle Africa and Central Asia have the lowest incidence due to the absence of this type of lifestyle (10). More than 90% of colorectal cancer occurs in people over the age of 50 (16, 17) with a high male to female preponderance (11). Since the early 1970's the UK mortality rate has halved (Figure 1) with the biggest decline over the latter part of the last decade primarily due to widespread uptake of colonoscopy and significant improvements in surgical and medical treatments.

Figure 1 Bowel Cancer (C18-C20), European Age-Standardised Mortality Rates, UK, 1971-2010 (11)



1.1.1 Polyps

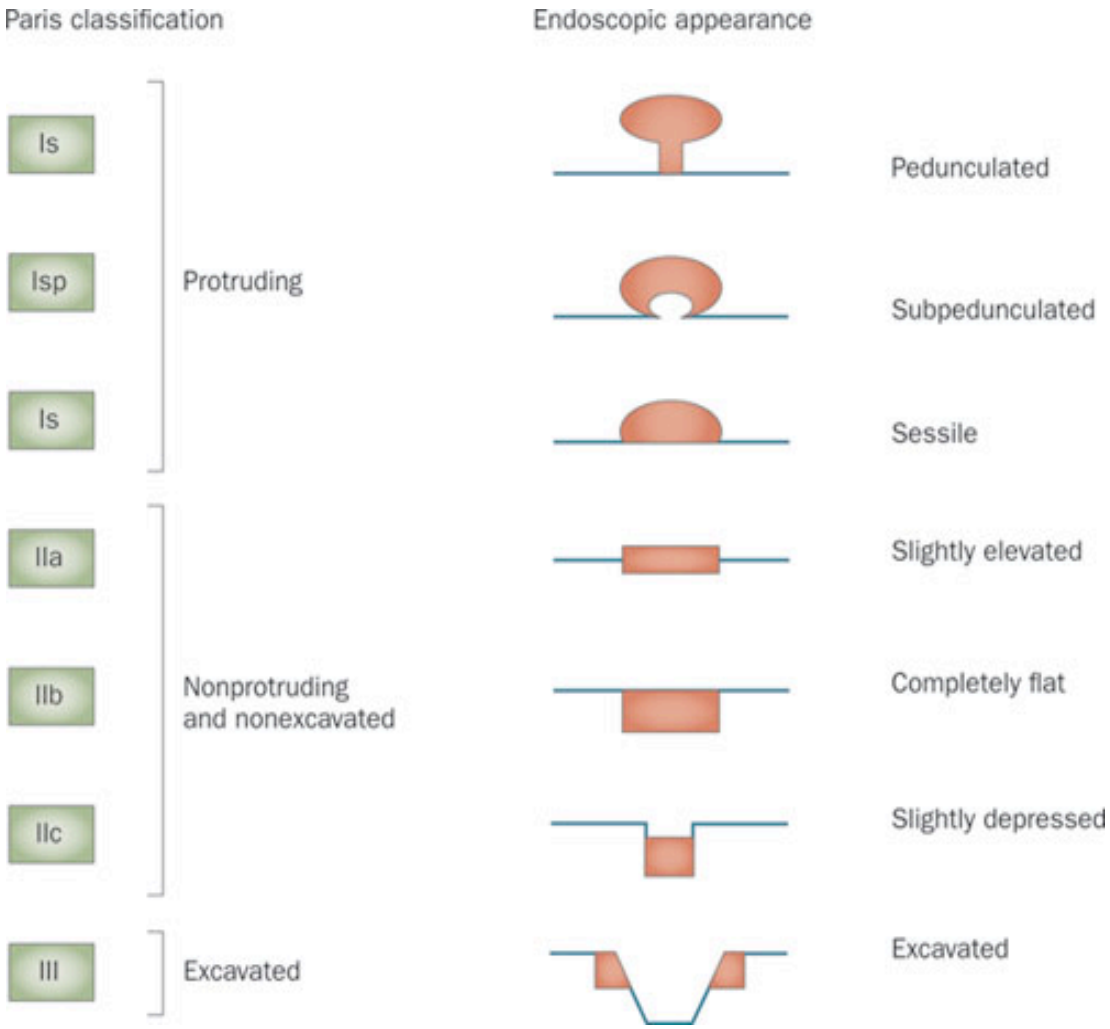
Colonic polyps are abnormal tissue growths in the lining of the colon and rectum. Histologically, they are classified as neoplastic or non-neoplastic (Table 1). All adenomas are neoplastic and show low or high grade dysplasia responsible for most colorectal cancers, which subsequently develop from mutations in epithelial stem cells via the adenoma-carcinoma pathway (18). According to the World Health Organisation adenomas are architecturally classified as tubular, tubulovillous or villous types (19). Hyperplastic polyps are non-neoplastic and histologically characterised by the presence of straight crypts extending from the mucosal surface down to the muscularis mucosa (20). Sub-types of hyperplastic polyps can give rise to serrated lesions that exhibit hypermethylation and develop into cancer via alternative serrated pathways (*KRAS-mut* and *BRAF-mut)* (21). In contrast to hyperplastic polyps, 'boot', 'L' or 'anchored' shaped crypts are seen at the base of the polyp (22, 23).

Table 1: The histological classification of polyps

Histology	Polyp type	Malignant potential
Neoplastic	Tubular adenomas (<25% villous)	Yes
	Tubulovillous adenomas (25-75% villous)	
	Villous Adenoma (75-100% villous)	
	Sessile/Traditional serrated adenoma	
Non-neoplastic	Hyperplastic	No
	Inflammatory	
	Hamartomas	
	Lymphoid	

In terms of their structure, polyps are described as stalked, sessile, flat or depressed with the Paris-Japanese classification used to give an exact description (24). Figure 2

Figure 2: The Paris endoscopic classification of polyps



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1.1.2 The Field Effect Theory

The adenoma carcinoma sequence, described by Fearon and Vogelstein (25), is widely accepted as the proposed mechanism for colorectal tumor genesis, which involves transformation of normal epithelium to carcinoma via various aberrant genetic mutations. Therefore, interrupting this pathway by detection and removal of polyps would be an effective method to prevent colorectal cancer.

Two competing pathways have been advocated to explain adenoma morphogenesis. The "top down theory" suggests that dysplastic cells in the lining of the colon spread both laterally and downwards forming new crypts by connecting to pre-existing crypts before replacing them (26). The "bottom up theory" suggests that the transformation of stem cells to monocryptal adenoma takes place at the crypt base, which can then spread to adjacent crypts by fission (27). This can cause areas of aberrant mucosa anywhere in the colon described as 'field defects'. These defects look macroscopically normal and occur in the presence of cancer or adenomatous polyps. It has been suggested that the presence of adenomatous polyps can cause field changes in the lining of the bowel by exerting their effects on crypt cell proliferation, maturation and differentiation, which may predispose it to the development of other polyps even after complete polypectomy (28, 29). There is little evidence to support this notion, but a small study by Nava *et al.* showed that 59% of patients developed new adenomas after polypectomy (30). 81% of these recurred in the same polypectomy segment and it is possible that these polyps were incompletely resected. This is particularly important considering that numerous studies have portrayed the relationship between polyp frequency and size with increased risk of recurrence and malignancy (1, 31-34). Consequently, this forms the basis of the British Society of Gastroenterology (BSG) surveillance guidelines after index colonoscopy.

1.1.3 Evidence that polypectomy prevents colorectal cancer

Multiple studies have shown that polypectomy prevents CRC (35-37). The National Polyp Study (1) was the first to provide the strongest evidence of a marked reduction in the incidence of CRC compared to three reference populations, but similar studies have not been able to reproduce these findings (31, 38, 39). Furthermore, five patients developed CRC between the initial and follow up colonoscopy. Although cancer may have developed during this short period, missed lesions were more likely. In 2012, the authors of the National Polyp Study examined 2602 patients who had a polypectomy with a median follow up time of 16 years. The mortality due to CRC in the adenoma polypectomy group was compared with the expected mortality from CRC in the general population, estimated from the Surveillance Epidemiology and End Results database and observed mortality from CRC patients with non-adenomatous polyps. This showed an impressive reduction in CRC mortality by 53% after adenomatous polypectomy compared with historical controls (1, 2). The main limitation of this study was that endoscopists were all from expert centres. However, similar reductions have also been reported in two Canadian studies, particularly when colonoscopy was complete and performed by a gastroenterologist (35, 40). It is important to note that these studies lacked the strength of a randomised controlled trial (RCT) with mortality as the endpoint. Such a study would provide the best definitive evidence of benefit, but it will be difficult to justify ethically or clinically because of the known potential for adenomas to progress to carcinoma.

1.1.4 Adenoma prevalence

There is wide variation in the reported prevalence rates of adenomas in autopsy and endoscopy studies. In autopsy studies, stretching the bowel, opening folds and crevices and using a magnifying glass to examine the dissected specimen increases the ADR of small and proximal adenomas. Conversely, colonoscopy studies are prone to selection bias as patients are usually symptomatic and prevalence of adenomas increases with age for both men and women.

Sigmoidoscopy and colonoscopy studies have estimated prevalence rates of 10% and 25% respectively with a less than 1% risk of CRC in asymptomatic, average-risk patients (41). A prevalence of 30-40% has been reported in screening colonoscopy and post mortem studies at 60 years of age with a lifetime cumulative incidence of 5.5% for developing CRC (42-44). These studies are old and the prevalence is likely to be underreported as the cancer risk is increasing in some of these countries.

1.1.5 Importance of sub-centimetre polyps

Over 90% of polyps encountered during colonoscopy are diminutive (1-5mm) or small (6-9mm) (45, 46). They are detected in more than half of the patients undergoing screening colonoscopies where 50% are diagnosed as adenomas (47, 48). Adenomas that contain a substantial villous component (>25%), exhibit high grade dysplasia or larger than 1cm are defined as 'advanced adenomas' and are clinically relevant precursors of CRC (49). Table 2

Table 2: Advanced adenoma and cancer prevalence by polyp size

Author	Country	≤5mm		6-9mm		≥10mm	
		Advanced	Cancer	Advanced	Cancer	Advanced	Cancer
Lieberman 2008 (46)	USA	1.7% 62/3744	0% 1/3744	6.4% 77/1198	0.17% 2/1198	27.9% 265/949	2.6% 25/949
Yoo 2007 (50)	Korea	0.15% 3/3303	0% 1/3303	2.2% 31/1432	0.49% 7/1432	15.2% 192/1261	1.6% 20/1261
Graser 2009 (51)	Germany	1.7% 7/418	0% 0/418	10.7% 6/56	0% 0/56	51.4% 19/37	2.7% 1/37
Rex 2009 (52)	USA	0.9% 79/8798	0.05% 4/8798	5.3% 68/1282	0% 0/1282		

The wide variations in these studies are likely to reflect differences in the patient population characteristics and polyp categories.

Although sub-centimetre adenomas are less likely to be become malignant, it is highly recommended they be removed. This can be justified by the following arguments.

1. Non-polypoid adenomas (depressed or flat) may progress more quickly than the polypoid variants and in Japan 10-30% of CRC have been attributed to these flat adenomas (53, 54).

2. Small adenomas have the potential to undergo transformation into advanced adenomas and cancer in the colon and this increases with polyp size, number, villous component and age. For instance an individuals future risk of advanced neoplasia is increased two and half fold if three or more small adenomas are detected (55).

3. In the studies that have shown a reduction in the CRC incidence (1) and mortality (56-58), all detected adenomas were removed. Therefore, for this reason all detected adenomas should be removed in the BCSP.

4. The detection and removal of small adenomas is a good indicator of the quality of colonoscopy. In the study by Kaminski et al (3), colonoscopists who had a low adenoma detection rate (ADR) were more likely to have missed a cancer (interval cancer) compared to those who had a higher ADR.

1.1.6 Interval Cancers

Interval (post colonoscopy) cancers are defined as cancers that are diagnosed between screening or surveillance episodes and are associated with the quality of colonoscopy. Multiple studies have reported incidence rates of 1.7-2.4/1000 person years of observation (38, 59-61). This has raised concerns about the effectiveness of colonoscopy and polypectomy with studies reporting that colonoscopy does not offer complete protection against CRC, especially in the right colon (35, 62). Three possible reasons have been suggested for the development of interval CRC; missed adenomas that progress to cancer during follow up, incompletely resected lesions (either a cancer or adenoma that progressed to cancer) and the development of new fast growing cancers.

Missed lesions

According to the English BCSP, ADR is defined as 'the number of colonoscopies at which one or more histologically confirmed adenomas is found divided by the total number of colonoscopies performed. The incidence increases linearly with age (63, 64) and is higher in men (65). The ADR is a key performance quality indicator and high rates have been shown to correlate with a lower incidence interval cancer (3). Earlier studies of close CRC surveillance demonstrated that colonoscopy and polypectomy prevented 76-90% of interval cancers (1, 66, 67). More recent studies have reported a much higher incidence of interval cancers (38, 68, 69), with one study reporting that over half of the interval cancers were either missed or occurred at the previous polypectomy site (60). A retrospective study of the American screening programme found that 27% of interval cancers (defined as colorectal cancers that

developed within 5 years of a complete colonoscopy) developed at the previous polypectomy site, suggesting that the remaining lesions could have been missed (61). Back-to-back colonoscopy studies have shown miss rates of 13-26% for small polyps <10 mm and 0-6% for polyps >10 mm (25, 70, 71). Screening studies examining the importance of interval cancers found that endoscopists who had an Adenoma Detection Rate (ADR) of less than 20% had a significantly higher risk of interval CRC; 10 times higher if the ADR dropped below 11% (3). In this study by Kaminski *et al,* the caecal intubation rate did not affect the ADR as the patient cohort was younger (40-66 years of age) and thus less likely to have proximal colon cancers compared to older patients (40). The caecal intubation rate is a key quality measure in bowel cancer screening. This is because a significant proportion of CRC are located in the proximal colon and caecum, with interval cancers three times more likely than sporadic cancers (61, 72).

According to the English BCSP, an ADR of >35% (compared with 25% in men and 15% in women in the American Screening program) is one of the measures of high quality colonoscopy (72, 73). However, it is not known how much further protection is derived from CRC if the ADR continues to increase above 50%, but trying to achieve this standard depends on multiple factors, including time, endoscopy technique and technological factors.

1.1.7 Factors that influence the ADR

The effects of time and technique on the ADR

It has been shown that endoscopists who spend more than 8 minutes examining the bowel during colonoscopy withdrawal had a higher ADR compared to those who spent less than 8 minutes (37.8% vs 23.3% P<0.001) (74). Further increases have been reported by dynamic position change, when the right colon was examined with the patient lying in the left lateral position, the transverse colon in the supine position and the left colon in the right lateral position as a result of improved bowel distension (5).

The effects of bowel preparation and procedure time on the ADR

In a retrospective study by Harewood *et al.*, good quality bowel preparation produced only a 2.8% increase in polyps detected less than 9mm in size compared to poor quality preparation, with no real difference being observed for larger polyps (4). The main disadvantages of poor bowel preparation quality are associated with a prolonged procedure time, increased difficulty and reduced caecal completion rates. All of these factors contribute to missing polyps, as the endoscopists' concentration is directed towards suctioning and washing areas of the bowel to prevent big lesions from being overlooked and completing the procedure in a reasonable time. This is particularly important for colonoscopies carried out in the afternoon. Recent work has shown that fewer polyps are detected in afternoon colonoscopies compared to those performed in the morning (75). Operator fatigue and reduced concentration as the day progressed have been implicated as the possible causes (76). It is also likely that the timing of the bowel preparation is a confounding factor, but was not assessed in either study.

The effects of cap assisted colonoscopy on the ADR

This technique uses a transparent plastic cap attached to the tip of the colonoscope to help flatten folds and improve mucosal visualisation. A meta-analysis of 6 RCTs showed no significant increase in the ADR compared with regular colonoscopy (77).

The simple strategies described above should be standard practice in all routine colonoscopies for improving the detection of small polyps. The effect on the timing of colonoscopy is difficult to measure unless endoscopic and patient related factors could be standardised with little evidence for the use of cap assisted colonoscopy.

Finally, the morphological appearances of the polyp may influence the miss rate. Polyps that are flat, slightly elevated or depressed are often difficult to see using standard white light endoscopy (WLE) and may just appear as distortions in the bowel mucosa (78, 79).

1.1.8 Image enhanced techniques to increase the ADR

Chromoendoscopy involves spraying the lining of the colon with contrast enhancing dyes. It is very effective for lesion detection, characterisation and highlighting subtle mucosal irregularities. Indigo carmine is most commonly used, as it is neither absorbed nor reacts with the mucosal surface. It is used in varying concentrations of 0.2-1.0% and can applied in a targeted fashion to highlight areas of irregular mucosa detected or applied to the whole colon (pan-colonic) as part of a surveillance test. For target lesions, indigo carmine is delivered via a syringe that is flushed through the working channel of the colonoscope followed by air and for pan-colonic surveillance a spray catheter is used. Chromoendoscopy has been recommended by the American Society of Gastroenterology as a method to increase the polyp detection rate, particularly flat lesions (80). A Cochrane review of 5 RCT's analysed 1059 patients outside the setting of polyposis syndromes or colitis and showed a significant increase in the ADR of three or more adenomas when compared to WLE (81). A potential limitation of this review was the significant heterogeneity between the studies. Three other RCT's have shown a significant increase in the ADR when comparing chromeoendoscopy with high definition WLE, including flat and small adenomas (48, 82, 83). Although, chromoendoscopy with indigo carmine is simple and cheap, it is labour intensive, time consuming, increases the colonoscopy withdrawal time (CWT) and results in pools of dye and can be messy. It is impractical for general colorectal cancer screening, but is helpful to define flat lesions and has an important role in inflammatory bowel disease (IBD) surveillance and surveillance of patients with polyposis syndromes.

Virtual Chromoendoscopy

Involves using image enhancement technology that is built into the endoscope to alter wavelengths of white light to enhance mucosal topography without using dyes. Multiple image-enhanced technologies are available and a brief introduction is given of the most common ones below.

Narrow Band Imaging (NBI)

NBI is most widely used and extensively studied. It uses spectral narrow band filters (red, blue and green bands), which all have different wavelengths of light. Blue light penetrates superficially as it has a shorter wavelength whereas red light penetrates more deeply as it has a longer wavelength. It is already incorporated as part of most standard colonoscopy equipment and can be operated by simply pressing a button. Several systematic reviews have revealed no significant difference when compared with standard white light colonoscopy (84-86).

High Definition Colonoscopy

High definition colonoscopy leads to high quality images and a marginal increase in ADR compared to standard definition colonoscopy. The increase in ADR is however small and is estimated to be approximately 3.5% according to a meta-analysis with pooled data of five studies in 4422 patients (87).

Fuji Intelligent Colour Enhancement (FICE)

FICE is a computed spectral estimation technology and enables the endoscopist to choose between different wavelengths of light for optimal examination of the colon. Only a few studies have evaluated this technology and no significant benefit was demonstrated in randomised back to back studies that compared FICE with WLE (88, 89) or NBI (90)

Auto fluorescence Imaging (AFI)

AFI uses blue light to excite tissue fluorescence that can be detected and displayed as different colours during colonoscopy. Normal mucosa is coloured green and neoplastic mucosa varying tones of red or purple. Three back to back studies showed improvements in the ADR when compared to WLE (91-93).

Third-eye Retroscope

This is a new device that provides additional retrograde views behind proximal folds (blind spots). In one randomised back-to-back multicentre study, an improvement in the adenoma detection rate was observed (94). A potential disadvantage with this device is that the procedural time may be prolonged if the third eye needs to be removed from the working channel to allow access of the biopsy forceps or snare.

Full spectrum endoscopy (FUSE)

FUSE is a new colonoscope that provides high-resolution, 330-degree views of the lumen without compromising on the features of a traditional forward viewing colonoscope. Preliminary results indicate an increased ADR with FUSE (95).

In summary, a combination of excellent bowel preparation, dynamic position change and meticulous visual inspection with or without chromoendoscopy are simple interventions that may be used to increase the diagnostic yield of colonoscopy.

1.1.9 Incomplete polypectomy

Recurrence is defined as the presence of adenomatous or carcinomatous tissue on follow up examination at the previous polypectomy site (96). Thus, complete polypectomy is critical to reducing recurrence as residual adenomatous tissue may grow and develop into colorectal cancer (97). Studies have shown that 10-27% (61, 98, 99) of interval cancers occur due to ineffective polypectomy (Table 3) and has mainly been associated with the size and histology of the polyp (100). These studies are limited as calculations are based on the assumption that no polyps were missed in that segment of bowel and quality of the baseline colonoscopy was not assessed.

In the Complete Adenoma Resection (CARE) study, Pohl and colleagues (100) looked at flat and sessile polyps measuring 5–20 mm. Biopsies were taken from the resection margins of 346 polypectomy sites after endoscopists were completely confident that resection was complete. Physicians had the option of confirming this with NBI or chromoendoscopy and treating any residual tissue with argon plasma coagulation (APC). Despite their efforts, 10.1% were incompletely resected. This occurred more frequently for polyps >10mm in size and almost half of all the large sessile serrated adenomas. The completeness of resection varied widely between endoscopists, which are likely to be explained by differences in the polypectomy technique, endoscopic assessment and sampling errors used to obtain residual tissue.

Table 3 Incidence of incomplete polypectomy rates

Author	Year	Polyps	Polyp Size (mm)	Polypectomy Method	Incomplete Resection Rate (Histological)
Liu (101)	2012	65	≤5mm	22 Standard Biopsy 18 Jumbo forceps 18 Hot snare 7 Cold snare	60% 20% 10% 10%
Pohl (100)	2013	346 neoplastic	5-7mm 8-9mm 10-14mm 15-20mm	All methods to ensure completeness of resection	5.8 9.4 33.4 23.3
Peluso (102)	1991	62	<6mm	Hot biopsy	17%
Efthymiou (103)	2011	54	≤5mm	Cold Biopsy forceps	38%
Urquhart (104)	2012	57	3-10mm	Cold snare	0%
Lee (105)	2013	117	≤5mm	Cold snare Cold biopsy forceps (double biopsy)	6.8% 24.1%
Draganov (106)	2012	305	≤6mm	Standard forceps Jumbo forceps	22.6% 17.6%

1.2.0 Polypectomy Methods

There is a wide variation in polypectomy practice and outcomes, particularly for the removal of small sessile or flat polyps measuring less than 10 mm. A 2004 survey of American gastroenterologists found significant variations in the use of polypectomy techniques for the removal of sub-centimetre polyps. In this study hot and cold biopsy forceps dominated for the removal of 1-3mm polyps and hot snare dominated for 7-9mm polyps. However, for polyps 4-6mm in size, a range of techniques were used, hot snare was used by 59%, cold snare by 15%, cold biopsy forceps by 19% and hot biopsy forceps by 21% (107). This study however, did not examine polyp characteristics or anatomical location.

The polypectomy technique employed is often influenced by several factors i.e. the size, site and morphology of the polyp (Paris criteria), endoscopist experience and equipment available. The main modalities currently employed are hot biopsy forceps, cold biopsy forceps, hot snare, cold snare and endoscopic mucosal resection, which all vary in completeness of removal, safety and histological quality. There is still considerable uncertainty regarding the optimal polypectomy technique due to a lack of RCT's. Evidence and recommendations are frequently based on expert opinion and uncontrolled observational studies (108-112).

Cold Biopsy Forceps

Cold biopsy forceps (CBF) is often used to remove diminutive polyps. It is a very safe and simple technique with tissue retrieved almost 100% of the time. However, it is associated with high incomplete resection rates (29-61%) (101, 103, 113-115) and not recommended for polyps >3mm as multiple bites are needed. The use of large capacity forceps may mitigate this risk as the polyp may be completely engulfed by the forceps cups. However, a recent RCT demonstrated that even jumbo forceps left residual tissue behind in 18% of polypectomies (106).

Hot Biopsy Forceps

Hot biopsy forceps (HBF) is similar to cold biopsy, but applies electrocautery to destroy any residual tissue. This technique has fallen out of favour, as it is associated with a risk of perforation and delayed bleeding (102, 116) and incomplete resection rates of 16% to 28% have been reported (102, 115). The American Society for Gastrointestinal Endoscopy recommends avoiding this technique for polyps greater than 5 mm (117) and the BSG advises against using this technique in the right side of the colon (118).

Hot snare

Hot snare (HS) also applies electrocautery to remove polyps that may be difficult to guillotine with cold snare or to reduce the risk of immediate bleeding. Incomplete resection rates have been reported to be significantly lower than cold snare polypectomy (115, 119). In the most recent RCT, 92% of small polyps were completely resected with HS compared to 79% with cold snare, without additional complications (119). Although this is reassuring, a larger comparative study is needed before HS is recommended as first line therapy due to the risk of delayed bleeding

and perforation (120, 121).

Cold Snare

The cold snare (CS) technique is effective for removing polyps 3-7mm in size, as it is more likely to capture a rim of normal tissue ensuring comprehensive resection. It is recommended that 1-3 mm rim of normal tissue should be resected with the polyp to ensure complete polypectomy (122-124). Lipper states that this is the only reliable way to predict poor outcomes if malignant cells are present at the resection margin (125). However, only a few studies have looked at the effectiveness of small polyps utilising the cold snare technique and incomplete resection rates of 7%-14% have been reported (105, 115, 126). Polypectomy with cold snare is extremely safe as reported in several studies and (111, 127). Therefore, for selected small and diminutive polyps CS has been recommended as first line therapy due to its safety profile, speed of resection and effectiveness compared to other techniques (110).

Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) is used for the removal of small flat polyps that are difficult to capture with a snare, large polyps and pedunculated polyps with a thick stalk. EMR involves submucosal injection between the submucosa and muscle layer to create a cushion, followed by hot snaring the polyp. The cushion effect reduces the risk of transmural injury when diathermy is applied and allows easier ensnaring of the polyp. The injection solution usually contains a mix of gelofusin to maintain the cushion, dilute adrenaline to reduce the risk of immediate bleeding and indigo carmine to assist in the identification of the deep and lateral margins. Normal saline is also commonly used but is rapidly absorbed necessitating multiple injections. Resection of polyps can be performed *en bloc* or piecemeal according to the size and

location of the lesion. EMR is associated with a low risk of complications, but recurrence rates of 0-46% have been reported after colorectal polyp EMR (128-132).

After large piecemeal EMR, APC has been used to destroy any remaining residual tissue and eradication rates of >90% have been achieved (133). Despite this reduction in recurrence, APC can still leave residual tissue behind 50% of the time and repeat surveillance colonoscopy is needed every 3 months until completeness of resection has been achieved (134, 135).

Endoscopic Submucosal Dissection (ESD)

This technique is similar to EMR, but instead of using a snare the submucosal plane is dissected with an electrosurgical knife. This enables en-bloc resection of larger and deeper lesions. It achieves higher rates of complete resection, but at the expense of a longer procedure time and high perforation rates (136, 137).

1.2.1 The Polypectomy Snare Device

Choosing the right snare to some extent is an individual choice or dictated by the device available in the department. The snare is a self-contained metal wire ring, deployed from a plastic sheath, used to trap and remove polyp tissue. There is a wide selection of snares that differ in size, shape, thickness and wire quality, but there have been very few comparative studies to assess which is superior. A recent study by Galloro *et al.* found that polypectomy in pig models with a steel snare wire produced deeper tissue injury compared to tungsten in pure cut mode (138).

Snare wires are usually made from stainless steel due to its mechanical properties combining strength, conductivity and flexibility. The wire is usually 0.30–0.47 mm in diameter and enclosed within a flexible synthetic polymer sheath that is typically 7.0F in diameter, for a minimal channel size of 2.8mm, and 230cm. The catheter material must have adequate strain relief or axial stiffness to withstand changes in length when under tension or compression. This is known as Young's modulus (E) defined as the ratio of stress to strain along an axis (Nm2). According to Hooke's law, $F=KX$ where F is the force applied, K is a constant for a particular spring or its stiffness and X is the deformation (139)**.**

Mini snares have loop diameters of 1.0–1.5 cm and lengths of 2–3 cm and are effective for removing small polyps (140) as they are easier to manipulate and an oval shape is particularly advantageous for polyps in the appendix or diverticulum. Stiffer snares facilitate tissue capture and serrated snares enable entrapment of normal tissue at the lesion margin. Thin or monofilament snares are useful for cold resection of small polyps as they achieve a cleaner cut compared to thick or braided snares, which provide effective coagulation during diathermy for larger polyps.

As for the ideal polypectomy method, the ideal snare device has also yet to be defined. Currently, only a compromise is available to achieve the desired effect of safety, completeness of resection and specimen retrieval. Due to the paucity of data further studies are needed in these areas.

1.2.2 The Suction Pseudopolyp Technique

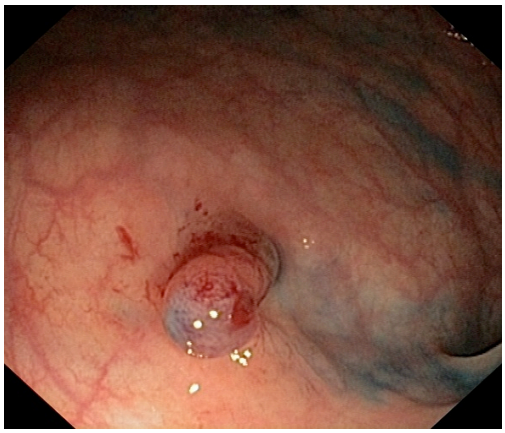
The suction pseudopolyp technique (SPT) is a novel technique and was first described by Pattullo *et al,* (figure 3) (112). This involves aspirating small polyps, flat or sessile into the suction channel of the colonoscope and maintaining suction for several seconds before the colonoscope is gently withdrawn. This stretching of the polyp from the mucosa transforms it momentarily into a broad based pedunculated polyp, thus entrapping a bigger rim of normal tissue with it. This can then be easily snared and resected. In their prospective study, 126 flat polyps measuring less than 10 mm in size (Paris-Japanese classification 0-11a & 0-11b) were removed by this method with 100% complete endoscopic resection without any immediate or delayed complications. Due to the small size of the lesions and diathermy artefact the completeness of histological excision could not be reliably assessed. This technique has also been simulated to create artificial diminutive polyps in a porcine colon model to compare the safety and efficacy of hot biopsy versus hot snare (141). Cap endoscopy employs a similar strategy for larger polyps, but is not widely used.

Figure 3 Identification of flat polyp and the creation of pseudopolyp (111)

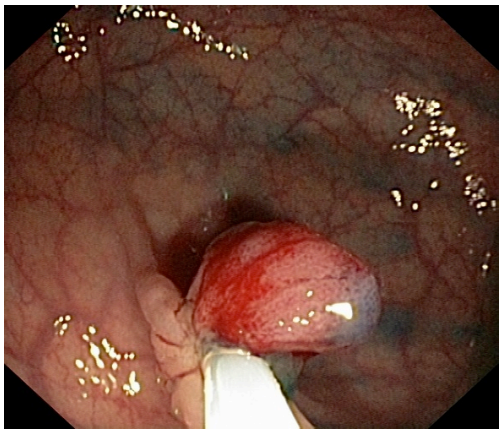
Small flat colorectal lesion

Dilute IC applied to delineate margins

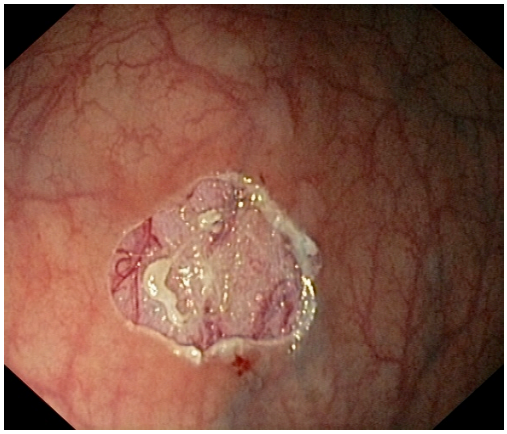
Pseudopolyp after release of suction



Ensnared Pseudopolyp



Post resection margins after diathermy



1.2.3 Image Enhance Technology to assess completeness of polypectomy

The optimal method for assessing completeness of resection at the time of polypectomy has yet to be defined. Image enhanced technology has been used to improve the ADR and to classify polyps, but data to support the role for confirming completeness of resection is limited and is an area that requires further evaluation. A study by Hurlstone *et al.* (79) in 2004 found that high magnification chromoscopic endoscopy (HMCC) had a high sensitivity (80%) and specificity (97%) for predicting residual tissue after saline EMR polypectomy. This method allows enhanced characterisation and delineation of the polypectomy site using a high magnification colonoscope after spraying with 0.5% indigo carmine dye spray. Using this method, Tanaka and colleagues reported a 17-fold reduction in cancer recurrence of flat EMR lesions >2 cm (142). However, Konishi et al demonstrated that high resolution chromoendoscopy is just as effective and can be used to identify normal Kudo type I pit patterns, which may also be adequate for assessing residual tissue after polypectomy (143). It can be inferred that high definition and high resolution chromoendoscopy is probably just as effective as HMCC with the additional advantage of a shorter learning curve and ease of use. The identification of an accurate modality to predict completeness of resection is needed.

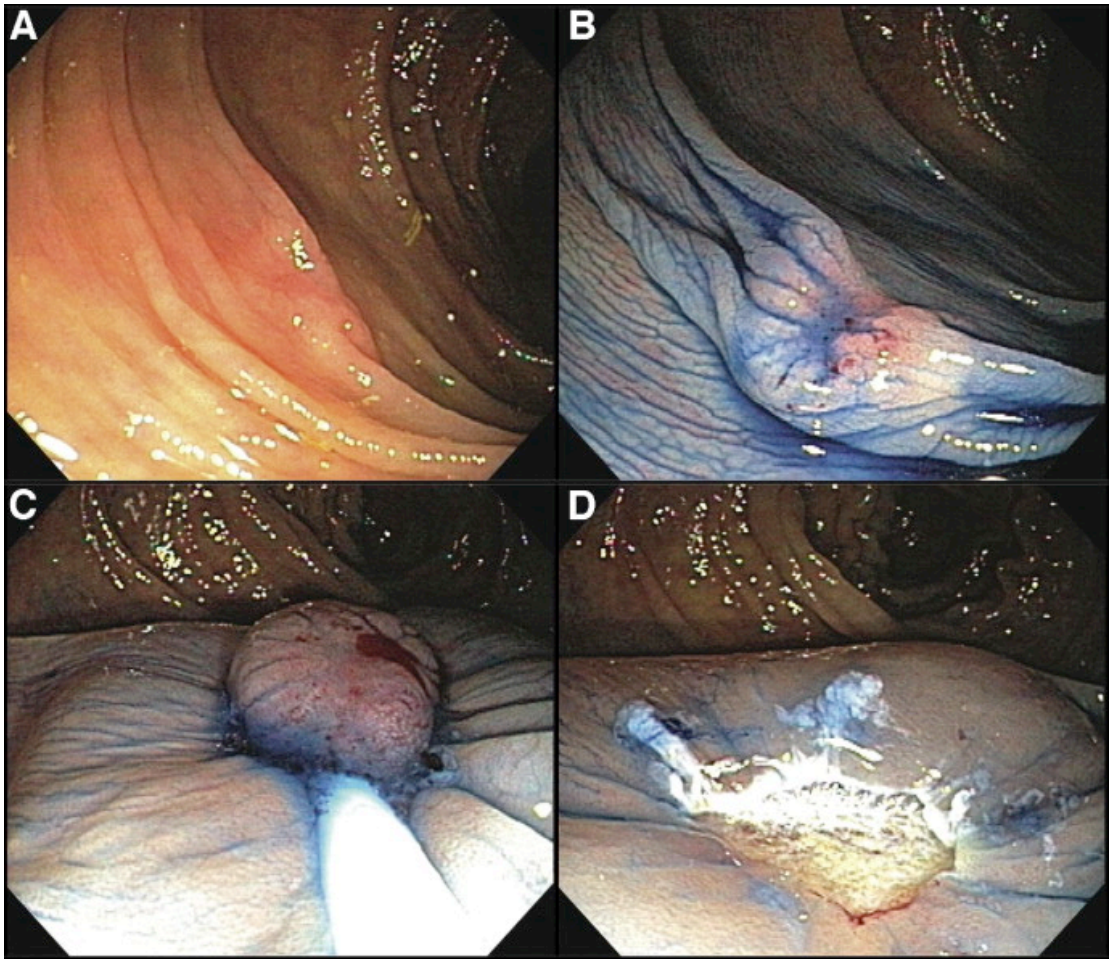


Figure 4 Image Enhanced Endoscopy of a depressed colorectal neoplasm.

"(A) Slightly reddish mucosal area was visualized during standard colonoscopy. (B) Diluted indigo carmine (0.2%) was used to further characterise the lesion and delineate its borders. (C) EMR inject-and-cut technique was used. (D) Following EMR, no residual tissue was identified. Images from VA Palo Alto, California" (144)

1.2.4 Histology to assess completeness of polypectomy

The histological assessment of polyps to identify clear resection margins is currently the gold standard. However, this method is unreliable for small sessile polyps and has been poorly studied. Due to wide variations in the polypectomy technique and removal methods, assessing the status of the polyp margin can be difficult. A recent study by Turner et al of 28 bowel cancer screening pathologists demonstrated a low level of agreement for assessment of complete excision (*kappa* = 0.24) (145), with frequent use of the uncertain category for cases clearly classified as completely or incompletely excised. This leaves diagnostic uncertainty and can have a potential impact upon patient management in the form of further resection and surveillance.

The reasons for the wide variation in assessing completeness of resection are multiple. These include the presence of diathermy artifact when electrocautery is applied or tissue injury that can occur with other techniques even without electrocautery (146, 147). The piecemeal resection of polyps or fragmentation by suction forces during the retrieval process makes assessment virtually impossible. Other difficulties pathologists encounter include variations in the mounting process and examination of a 3D specimen using a 2D microscope, so that the entire polyp margin is not seen and thus reported as 'not assessable'. Furthermore, some pathologists may not be as thorough in their assessment of the resection margin, as they are only required to verify the completeness of excision for all malignant polyps and those with high grade dysplasia according to the NHS BCSP and European recommendations (73, 114).

Studies have mainly relied upon the biopsy of the base and margin of the polypectomy site to confirm completeness of excision. However, this is prone to sampling errors as marginal biopsies are only likely to represent part of the margin. EMR of the polypectomy site has been used as a method of assessing completeness of resection in only one recent study. Efthymiou et al found that overall completeness of resection was much lower with CBF (39%) (103) compared with another study where biopsies were taken from the polypectomy site (71%) 3 weeks after resection (113).

Bowel cancer screening histopathologists undergo no formal accreditation process and quality assurance is achieved via external quality assessment schemes and annual training sessions (148). Implementation of a formal accreditation processes is clearly warranted. Additionally, establishing reliable endoscopic methods to assess the polypectomy site for completeness of excision requires further analysis. The optimal method may be to combine image enhanced technology and real time histological at the time of polypectomy to confirm completeness of resection. This would allow polypectomy to be repeated if required, as trying to identify the resection site later in the absence of a tattoo is virtually impossible. If by chance this has been identified then the patient is exposed to the additional risk of trying to resect fibrosed residual tissue.

1.2.5 Fast growing Adenomas

It has been suggested that some of these interval cancers are due to fast growing *de novo* adenomas that are four times more likely to exhibit microsatellite instability (MSI) and 'mismatch repair' gene pathways compared to non-interval (sporadic) cancers. They are smaller in size and three times more likely to occur in the right colon with no real difference in tumour characteristics or the 5-year survival (Figure 5). No association between bowel preparation quality and endoscopy experience was found (61, 149). These Interval cancers cannot be prevented unless screening intervals are decreased, but this would be extremely costly. Patients who have a high risk of developing CRC, as a result of familial polyposis syndromes or a strong family history, will need to be identified early by genetic counselling and gene mutational analysis so patient specific surveillance intervals can be determined.

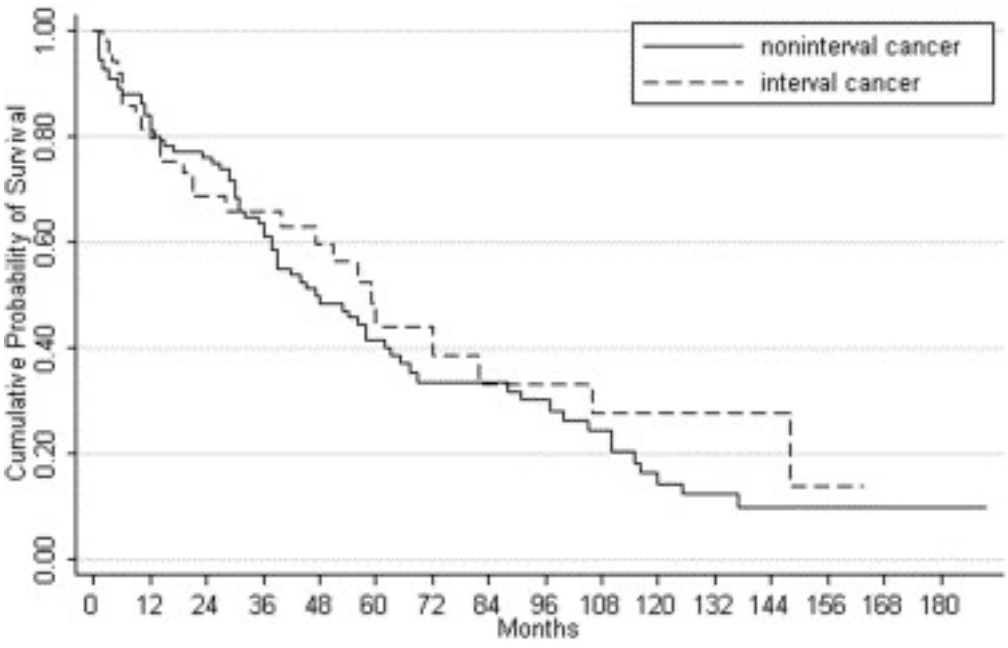


Figure 5 "Kaplan–Meier survival estimates for subjects with interval cancer compared with subjects with non-interval cancer. Analysis time represents months since cancer diagnosis" (149)

1.2.6 Summary

There is a large body of evidence to suggest that colonoscopy and polypectomy reduce mortality from CRC. However, the rates of interval cancer remain a concern. The three most important contributing factors are missed polyps, incomplete polypectomy and fast growing *de novo* adenomas. There are several colonoscopy and technological-related factors that will increase the ADR, but the findings are mixed and further integration is needed between the two to improve the quality of colonoscopy even further.

Polypectomy has evolved considerably in recent years and, despite different techniques and a wide range of equipment, there is still considerable variation in polypectomy practice, particularly for the removal of sessile or flat polyps <1 cm. The reasons for this are unclear and this may reflect the paucity of RCT's that have looked at the association between polypectomy technique, completeness of resection and complications. The other effects of field changes on metachronous adenomas and MSI on aggressive tumour growth is not completely understood and this is likely to play an important role in future surveillance strategies. A multipronged approach is needed, which is directed at improving the quality of colonoscopy, the effectiveness of polypectomy and its safety.

Chapter 2: Chromoendoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum

This is a draft and pre-peer review version of a Cochrane Review. Upon completion and approval, the final version is expected to be published in the Cochrane Database of Systematic Reviews *(www.thecochranelibrary.com).*

2.1.0 Abstract

Background Colonoscopy is the gold standard test for the detection of polyps, but sensitivity for diminutive and flat polyps is low. A systematic Cochrane review of RCT's in 2007 reported that chromoendoscopy increased the detection of these polyps (150). Since then several other studies have been performed (48, 82, 151).

Aim The aim of this study was to update the findings of the systematic review and determine if chromoendoscopy still enhances the detection of polyps.

Methods All abstracts from electronic databases, relevant meetings and citations between 1980-2014 were identified. Prospective randomised controlled trials comparing chromoendoscopy with conventional white light endoscopy of the whole colon were included. Exclusion criteria included, inflammatory bowel disease, polyposis syndromes and any studies that combined chromoendoscopy with additional interventions. The detection of polyps (neoplastic and non-neoplastic), diminutive lesions, number of patients with multiple neoplastic lesions and the extubation time were the outcomes measured.

Results Seven trials met the inclusion criteria. Chromoendoscopy significantly increased the polyp detection rate for all detection outcomes, despite differences in the study design. Chromoendoscopy is likely to yield significantly more patients with

at least one neoplastic lesion (OR [fixed] 1.53, CI 1.31-1.79) and significantly more patients with three or more neoplastic lesions (OR [fixed] 3.16, CI 1.7-5.9). Chromoendoscopy extubation times were slower.

Conclusions Chromoendoscopy enhances the detection of neoplasia in the colon compared to conventional white light endoscopy. This is likely to reduce the interval cancer rates in any surveillance programme due to missed lesions.

2.1.1 Background

As described in the first chapter, the detection and removal of adenomatous polyps reduces the risk of colorectal cancer and death (1, 2). The gold standard test commonly used to achieve this is standard white light colonoscopy (WLC). But with reported miss rates of 15-27% for sub-centimetre adenomas (70, 152, 153), a significant risk of interval CRC exists (154). Potential causes include inadequate withdrawal times, poor bowel prep and not being able to see flat or depressed polyps (7, 155). Strategies to enhance the mucosal topography with a contrast enhancing dye might therefore improve the ADR and reduce the risk of interval CRC. A Cochrane review performed 7 years ago established that indigo carmine (chromoendoscopy) increased the ADR (150).

Since then more data has emerged and we aimed to retest the hypothesis that chromoendoscopy enhances polyp detection compared with standard WLC.

2.1.2 Methods

The interventions and outcomes measured are based on the 2007 Cochrane protocol (150).

Polyps were defined as neoplastic (adenoma or carcinoma) or non-neoplastic (hyperplastic or inflammatory) lesions. Diminutive polyps were defined as ≤5mm in size.

Inclusion Criteria

1. Prospective randomised controlled trials comparing chromoendoscopy with standard WLC for the detection of polyps.

Exclusion Criteria

1. Inflammatory bowel disease
2. Polyposis syndromes; familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC)
3. Studies where the whole colon was not examined
4. Studies that combined chromoendoscopy with other methods i.e. Cap assistance or water perfusion

Patients

Trials in which patients underwent standard WLC or chromoendoscopy to investigate their symptoms and screening or surveillance of polyps, colorectal cancer or family history of colorectal cancer.

Interventions

RCT's that compared chromoendoscopy +/_high resolution versus standard WLC.

Outcome measures

1. Total number of neoplastic and non-neoplastic polyps detected
2. Total number of neoplastic polyps detected
3. Total number of patients with at least 1 neoplastic polyp detected
4. Total number of diminutive neoplastic polyps detected
5. Total number of patients with >3 neoplastic polyps detected
6. Colonoscopy withdrawal time

Table 4 Selection and Searches to identify studies

Abstracts, Citations (1980-2014) and relevant meetings searched	**Search terms**
Cochrane Register of Controlled Trials (May 2014)	Randomised controlled trials
MEDLINE Ovid (January 1966 to May 2014)	Chromoendoscopy
EMBASE Ovid (January 1980 to may 2014)	Colonoscopy
European Association of Coloproctology	Dye spray
American Society of Colon & Rectal Surgeons	Chromo-endoscopy
Royal Society of Medicine coloproctology section	Indigo-carmine
Association of Coloproctology of Great Britain and Ireland,	Magnifying endoscopy
BSG	
American Gastroenterology Association	

Each reviewer independently assessed all relevant trials by applying the selection criteria and was not blinded to the authors, institutions or journals of the studies.

Data collection and analysis

This was performed in compliance with the recommendations of the Cochrane Collaboration (156), Cochrane colorectal cancer group (CCCG) and Review Manager 5.2 software (157).

Risk of bias assessment

Methodologies for the RCT's were assessed for:

- Randomisation and concealment,
- Blinding of patients to the intervention,
- Details of incomplete outcome data
- Selective reporting
- Other bias

These parameters were described as yes, no or unclear, figures 6 and 7. This was performed using the Cochrane handbook for systematic reviews of interventions in chapter 8.5 "The Cochrane Collaboration's tool for assessing risk of bias" (156).

Statistical analysis

Data analysis was performed according to the method described in the 2007 Cochrane review (150) using the RevMan Analyses statistical programme in the software review manager (version 5.0.2.):

"Mantel-Haenszel method and a fixed model effect were used to calculate odds ratios and 95% confidence intervals for dichotomous outcomes. Fixed effect meta-analyses of (weighted) mean differences (WMD) were used to analyse continuous variables using mean and standard deviation values. The results for each of the outcomes of the meta-analysis were presented as Forest plots. The Chi^2 test and I^2 statistic was used to examine statistical heterogeneity. P value of <0.10 for Chi^2 was used to indicate statistically significant heterogeneity. The I^2 statistic describes the percentage of variance across studies due to heterogeneity rather than random chance. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity; Values >50% indicate substantial heterogeneity."

2.1.3 Results

The search identified 444 hits of which 7 trials (2727 patients) met the inclusion criteria. These trials were published in peer reviewed journals and the details of each are summarised in table 5.

Table 5 Description of included studies

Study	Methods	Patients	Interventions	Outcomes
Brooker 2002 (158)	Concealed allocation Randomised at caecum Single centre 4 experienced endoscopists	Average and high risk patients with symptoms, polyps or history of CRC	Standard WLC Chromoendoscopy	No of polyps (neoplastic and non-neoplastic) per patient No of neoplastic lesions /patient No of neoplastic lesions <5mm /patient Extubation time
Hurlstone 2004 (79)	Allocation: Randomised at caecum when sealed envelopes opened Single centre 2 experienced endoscopists	Average and high risk patients	Standard WLC with saline spray Chromoendoscopy	No of polyps (neoplastic and non-neoplastic) per patient No of neoplastic lesions /patient Withdrawal time (minimum of 8 mins)
Kahi 2010 (48)	Allocation: Randomisation via computer generated sequence. Sealed envelopes opened when caecum reached. 4 hospitals in the USA	Average risk >50 years old undergoing first time screening	High definition WLC Chromoendoscopy	No of polyps (neoplastic and non-neoplastic) per patient No of neoplastic lesions /patient Withdrawal time (examination time standardized to 6 mins)

Lapalus 2006 (159)	Allocation: Randomisation process unclear Multicentre in France	High risk patients symptoms, high risk of CRC (previous polyps +/- first degree family history)	Standard WLC first pass + randomisation to chromoendoscopy second pass versus tandem standard WLC (Double Intubation)	No of polyps (neoplastic and non-neoplastic) per patient No of neoplastic lesions /patient No of neoplastic lesions <5mm /patient Withdrawal time
Le Rhun 2006 (160)	Central computer generated random allocation sequence Randomised before intubation Multicentre, France	High risk patients Polyp surveillance, Family history Screening in first degree relative >60 years old with symptoms	Standard WLC High resolution chromoendoscopy (segmental examination before and after chromoendoscopy)	No of polyps (neoplastic and non-neoplastic) per patient No of neoplastic lesions /patient No of neoplastic lesions <5mm /patient Withdrawal time
Stoffel 2008 (151)	Allocation: Block randomisation stratified by study site. Sealed envelopes opened when caecum reached. Multicentre USA, Canada, Lebanon and Israel	High risk patients Polyp surveillance (previous history of 3 or more polyps or colorectal cancer)	First exam standard WLE plus second with chromoendoscopy versus a second intensive colonoscopy (lasting more than 20 minutes). (Double intubation)	No of polyps (neoplastic and non-neoplastic) per patient No of neoplastic lesions /patient Withdrawal time
Pohl 2011 (82)	Allocation: Randomised lists with consecutive patient numbers linked to one of the two study arms carried out by nurses. Randomised on caecal intubation 2 German centres 5 experienced colonoscopists	Average and high risk patients, >45 years attending primary screening or surveillance, alarm symptoms	Standard WLC Withdrawal using indigo-carmine with a low-volume spraying technique	No of polyps (neoplastic and non-neoplastic) per patient No of neoplastic lesions /patient Withdrawal time (minimum of 8 mins)

All 7 studies examined the effects of chromoendoscopy versus WLC for polyp detection. The indications for colonoscopy varied and standard WLC was used in all studies except by Lapalus (159), Kahi (48), and Le Rhun (160) where high resolution colonoscopy was combined with chromoendoscopy.

In the studies by Lapalus (159) and Stoffel, (151) standard WLC was performed first in both study groups followed by chromoendoscopy or repeat standard WLC. In the study by Le Rhun (160), high resolution chromoendoscopy of each colon segment was performed in the intervention group, whereas in the control group each colonic segment was first examined with maximal air insufflation and then with minimal air insufflation.

The dye spraying technique was not described in detail by Lapalus (159) and Le Rhun (160) and in the studies by Hurlstone (79), Pohl (82) and Kahi (48), a minimum withdrwal time was set to ensure adequate mucosal visualisation to control for the effect of dye spraying.

Risk of bias in included studies

Reporting of the trials suggest fair methodological quality and the results of the validity assessment are presented in figure 6 and 7.

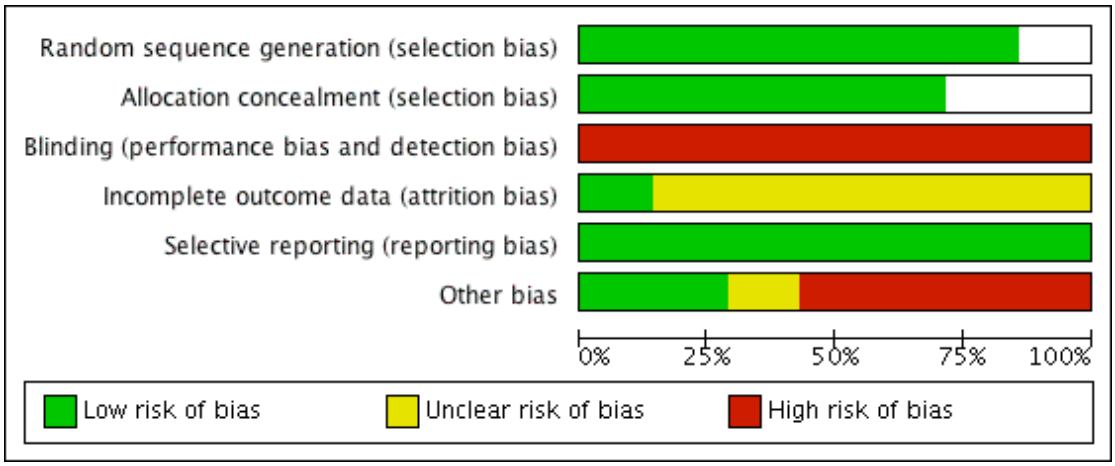


Figure 6 Methodological quality graph: Judgments about each methodological quality item presented as percentages across all included studies

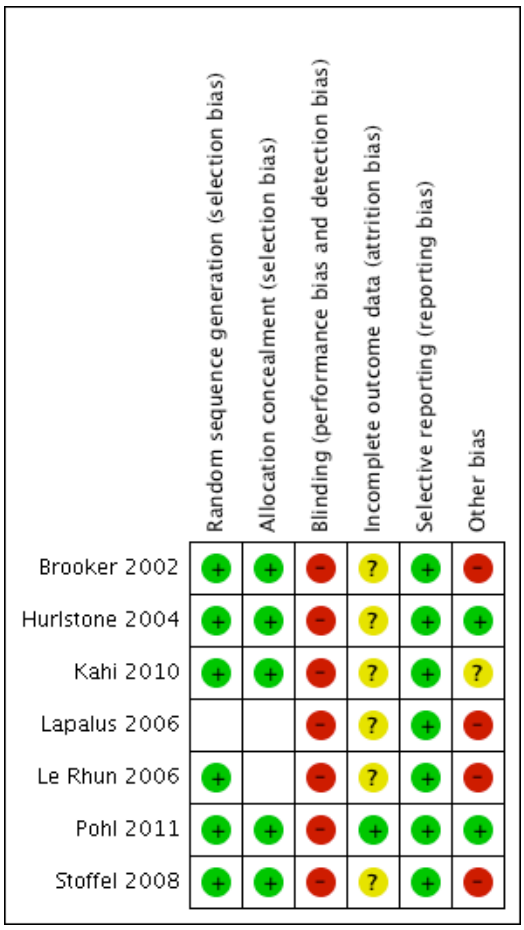


Figure 7 Methodological quality summary: review authors' judgements about each methodological quality item for each included study

Blinding (performance bias and detection bias)

It was not possible to blind endoscopists to the technique used. To control for the effect of the dye spray, Hurlstone et al applied normal saline to the entire colon to ensure a detailed and comprehensive examination (79), whereas minimum withdrawal times were set to ensure a slower and more thorough examination of the mucosa by Kahi (48) and Pohl (82).

Patient populations differed between the studies and did not influence the number of polyps detected. For example, Kahi (48) detected the highest number of polyps per patient in their cohort of average risk patients compared to studies with high risk patient populations. The reasons for this include, experienced endoscopists, use of high definition colonoscopes and a greater proportion of diminutive polyps.

Incomplete outcome data (attrition bias)

The details of drop outs was provided by Lapalus (159) and Pohl (82), whereas details of withdrawals was only provided by Stoffel et al (151). Except for the study by Lapalus et al (159), the potential drop out rate was low as patients were randomised after ceacal intubation.

Other potential sources of bias

The power calculation in three studies was based on historical estimates of the expected neoplastic polyp detection rate obtained by Brooker et al (158). Pohl (82) and Kahi (48) did their own power calculation based on assumptions of historical data and Le Rhun (160) based it on a preliminary analysis. No power calculation was performed in the study by Stoffel et al (151). Between 117-396 patients were required in each group to be adequately powered, however Kahi et al (48) failed to meet their recruitment target.

Effects of interventions

A significant difference was observed in support of chromoendoscopy for all detected outcomes. The mean number of polyps detected was higher in all studies and the effect was even greater after combining the studies, weighted mean difference (WMD) (fixed) 0.89 (CI 0.74-1.04). Figure 8

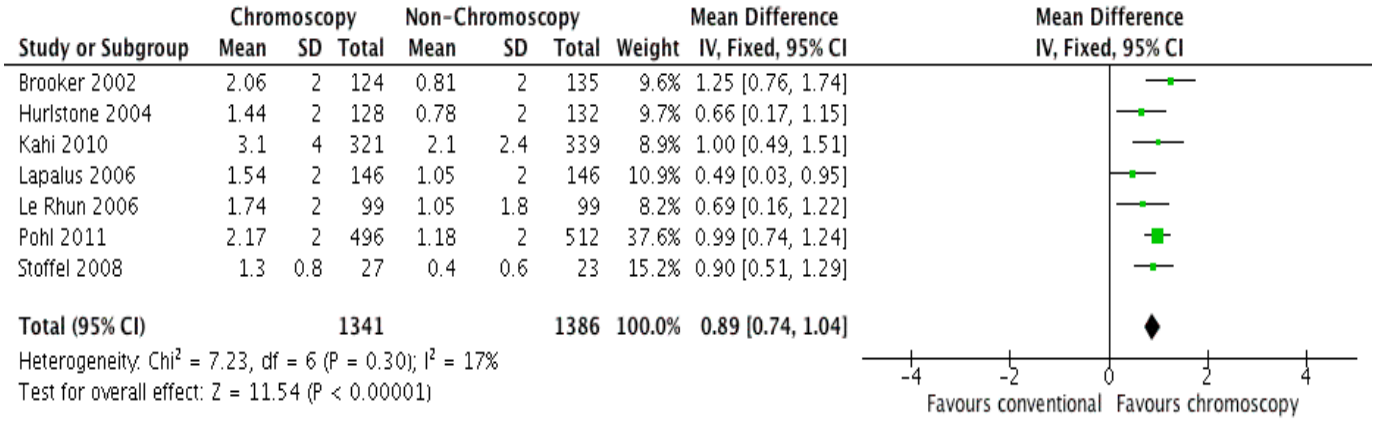


Figure 8 Forest plot of comparison: Total number of polyps (neoplastic and non-neoplastic) detected

The enhanced yield was maintained if only neoplastic polyps were assessed, WMD (fixed) 0.33 (CI 0.22-0.41). Figure 9

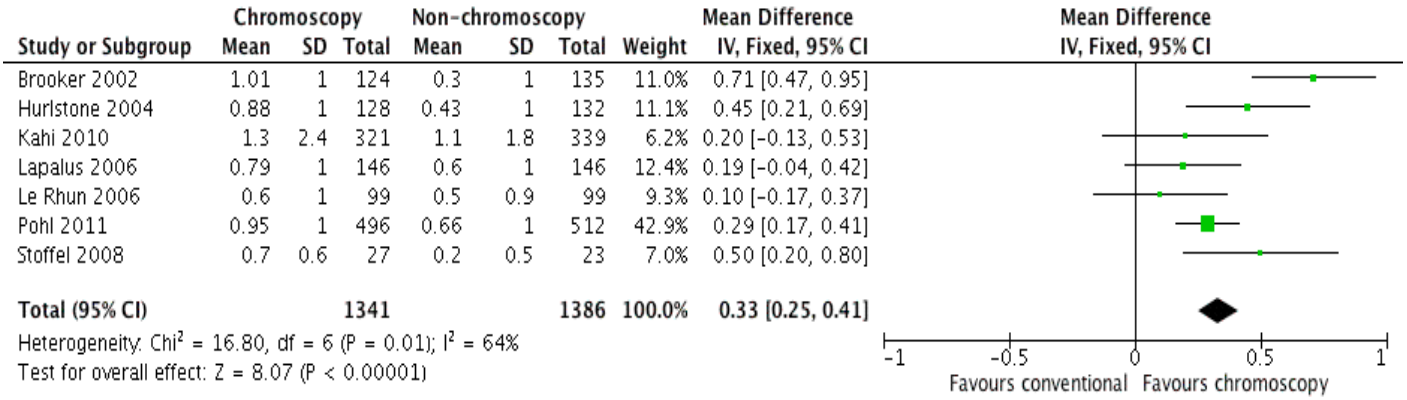


Figure 9 Forest plot of comparison: Total number of neoplastic lesions detected

There was significant heterogeneity in this group. Firstly the studies by Lapalus (159), and Stoffel (151) involved a form of back to back design (double intubation), which has been known to increase the polyp yield (70, 152). Secondly, in the study by Le Rhun (160) fewer polyps were found in the chromoendoscopy group than other studies, suggesting endoscopists had limited experience. Thirdly, high definition imaging has been shown to increase the ADR (47) and was found to be higher in the control group by Kahi et al (48), than chromoendoscopy in all the studies.

A significant difference in favour of chromoendoscopy was found in the total number of patients with at least one neoplastic polyp only (OR (fixed) 1.53 (CI 1.31-1.79) (Figure 10).

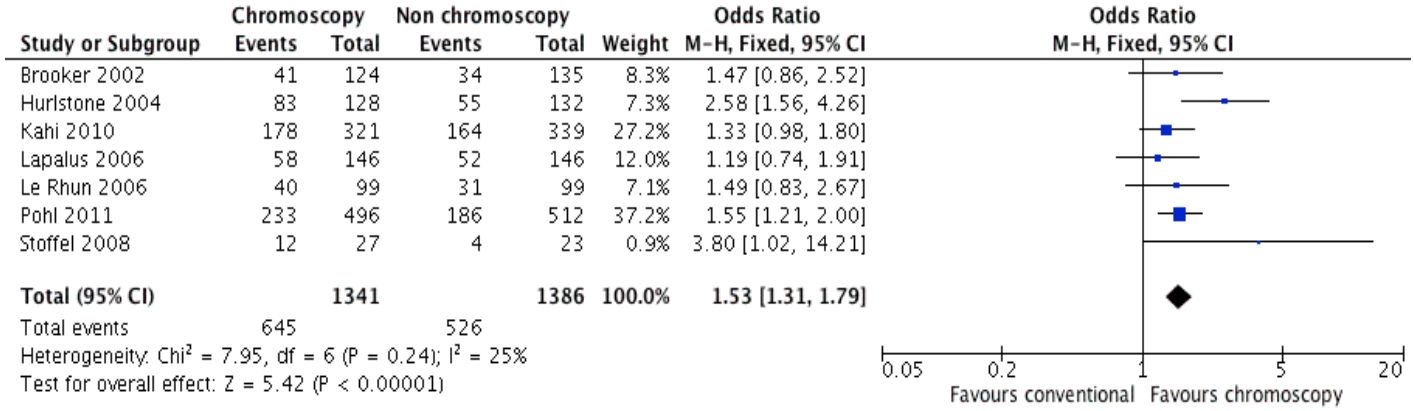


Figure 10 Forest plot of comparison: Total number of patients with at least one neoplastic lesion detected

The total number of diminutive neoplastic polyps was increased in favour of chromoendoscopy, WMD (fixed) 0.21 (CI 0.10-0.32) in the four studies (1409 patients) where this outcome was measured (Figure 11)

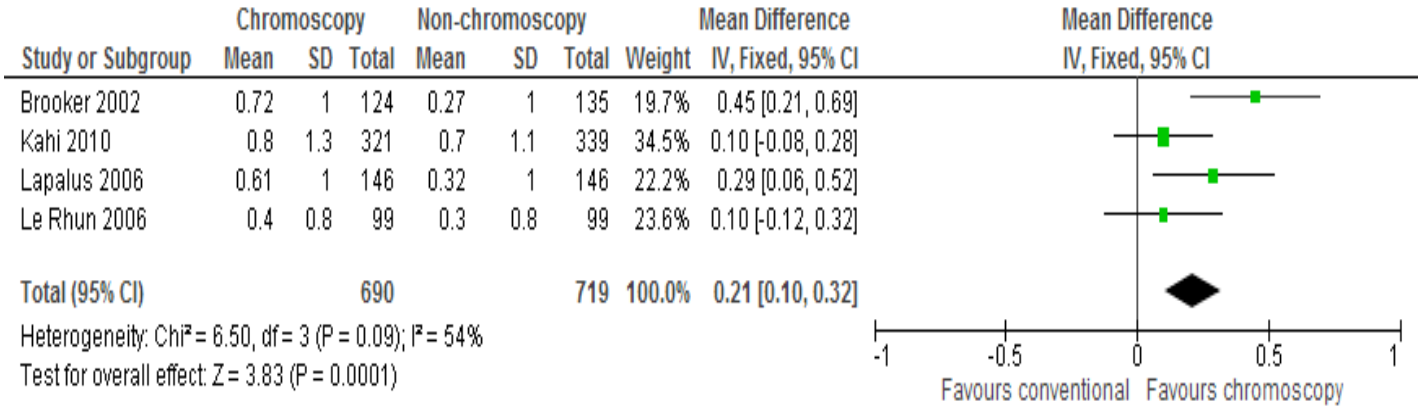


Figure 11 Total number of diminutive neoplastic polyps

There was no significant difference between chromoendoscopy and standard WLC for the number of patients with 3 or more neoplastic polyps (OR (fixed) 1.34 (0.96-1.87) assessed in 5 studies (1669 patients). Figure 12

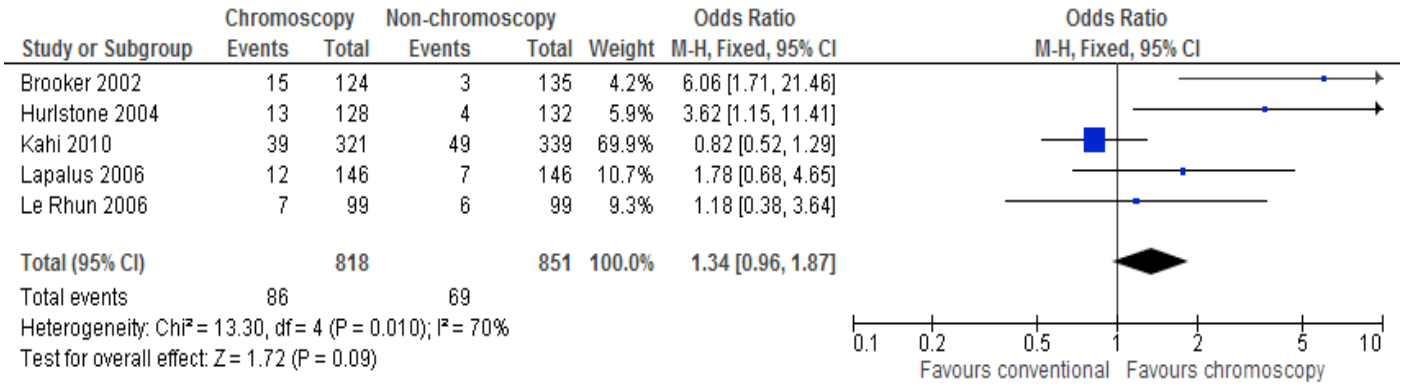


Figure 12 Total number of patients with 3 or more adenomas

The significant heterogeneity observed is most likely due to the use of high definition colonoscopes by Kahi (48) and Le Rhun (160).

The analysis of withdrawal time was always going to be difficult due to the marked heterogeneity between the studies. For example, withdrawal time was recorded in all studies except by Lapalus (159) where the whole procedure time was recorded. Le Rhun et al (160) examined each colonic segment with maximal and minimal insufflation, whereas Hurlstone (79) standardised the withdrawal time in the control arm by using saline spray. Minimum withdrawal times of 6 and 8 minutes were set by Kahi (48) and Pohl (82) respectively with 20 minutes for inspection of the colonic mucosa set by Stoffel (151). The comparison of withdrawal times in all studies demonstrated that chromoendoscopy took longer (3-86 minutes) than the control group (2-60 minutes).

2.1.4 Discussion

The findings of this meta-analysis demonstrate that chromoendoscopy increases the polyp detection rate despite significant heterogeneity between the studies. Chromoendoscopy appears to have a high sensitivity for detecting all neoplastic and non-neoplastic polyps, but lacks specificity as the detection of non-neoplastic (hyperplastic) polyps was also increased. A possible explanation for the increased sensitivity is that chromoendoscopy takes longer and allows more time to visualise and appreciate the subtle mucosal abnormalities in the colon, particularly flat and depressed polyps. There is good evidence to suggest that a minimum withdrawal time of 6 minutes to inspect the colonic mucosa increased the polyp detection rate (7). Hurlstone et al controlled for this effect by using saline spray in the control group and other studies (48, 82, 151) set minimum withdrawal times. More patients with >3 polyps were seen in the control group by Kahi et al (48), implying that high definition colonoscopes may be as good as chromoendoscopy.

Other simple strategies that may increase the polyp detection rate include dynamic position change on withdrawal (161), bowel preparation given on the day of colonoscopy (162) and afternoon procedures (163). These are all less time consuming and require little effort and should be used in conjunction with chromoendoscopy.

Despite significant advances in image-enhanced technology as described in the first chapter, they have all proved to be less convincing than chromoendoscopy. The results of our detailed review indicate that chromoendoscopy is simple and effective, but can be time consuming and messy. As no increase in the detection of larger or advanced lesions was seen with chromoendoscopy, feasibility for routine practice is questionable. National guidelines recommend pan-chromoendoscopy surveillance for

patients with IBD and polyposis syndromes as improvements in the detection of dysplasia and cancer have been shown (164-167).

Although the caecal intubation rate is a good indicator of colonoscopy quality, perhaps just as important is a thorough and careful inspection of the colonic mucosa during withdrawal with or without chromoendoscopy. Therefore endoscopy training should focus on simple interventions to optimise this with adequate time to perform a thorough examination. Due to advancements in image-enhanced technology, further research is required in this area in the form of well designed studies.

Chapter 3: Removal of sub-centimetre polyps; variation in a national colorectal cancer screening programme

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SD, AB, SR conceived and designed the study. SD acquired, analysed and interpreted the data and drafted the original manuscript. All authors contributed to critical revisions and approved the final manuscript.

3.1.0 Abstract

Introduction Most colonic polyps are small and several polypectomy techniques are available with wide variations in practice.

Methods Data relating to the removal of sub-centimetre polyps between Jan 2010 and Dec 2012 were retrieved from the English Bowel Cancer Screening Programme database. We compared variation in polypectomy practice between colonoscopists and completeness of histological excision between different centres.

Results 147, 174 sub-centimetre polyps were removed during 62, 679 procedures. For pedunculated polyps, hot snare was most common in the left (median 92%, IQR 83.3-97.0%) and right colon (median 75%, IQR 3-92%). For non-pedunculated polyps, cold snare was most common in the right colon (median 24%, IQR 9-47%); whereas hot snare remained most common in the left colon (median 32%, IQR 19-49%). Twelve (0.03%) bleeding episodes required transfusion with no polypectomy technique dominating and 16 (0.04%) perforations with 81% of polypectomies performed using diathermy-assisted techniques. There was substantial variation between screening centres for the completeness of histological excision. The use of cold techniques and EMR has increased over time, whereas hot biopsy forceps and hot snare has decreased ($p < 0.0001$).

Conclusions The removal of sub-centimetre polyps within the BCSP is safe despite wide variations in practice. The use of cold resection techniques and EMR has increased over time. The histological assessment for completeness of excision is limited. Endoscopic completeness of excision should be confirmed at the time of polypectomy

3.1.1 Introduction

It is widely accepted that adenomas have a pre-malignant potential and several studies have shown that polypectomy prevents colorectal cancer (35, 36). However, over 90% of polyps are less than 10mm in size (168, 169) and although the vast majority will never progress to cancer, prevalence rates of advanced histology have been reported in 0.9%-2.8% of polyps ≤5mm and 5.3%-15.5% of polyps between 6 and 9mm (46, 170, 171).

Several techniques are available for the removal of such polyps, but the optimal technique for a given polyp remains somewhat unclear and recommendations are frequently based on expert opinion and observational studies (107, 109, 110, 118, 168, 172). Size, site and morphology are factors that influence the choice of polypectomy technique. For some polyps e.g. pedunculated lesions in the left colon, the choice of standard snare polypectomy is clear, but for diminutive (≤ 5mm) and small (6-9mm) polyps different techniques have been used. In 2004, a survey of American gastroenterologists found significant variation in the techniques used for the removal of sub-centimetre polyps. Hot and cold biopsy forceps dominated for the removal of 1-3mm polyps, with wide variation in techniques used for 4-6mm polyps and hot snare dominating for 7-9mm polyps (107).

In recent years a number of recommendations have been published regarding safe and effective polypectomy techniques (118, 168, 172), but there are few reports of current polypectomy practice. This is important for improving the safety and quality of polypectomy and may encourage endoscopists to reflect on their own clinical practice as a motivator for change or reassurance.

Using data from the English National Health Service Bowel Cancer Screening Programme (NHSBCSP), we describe the current polypectomy practices used for the removal of sub-centimetre polyps and relate this to polyp characteristics, completeness of excision and safety.

3.1.2 Methods

Data Source

The English NHSBCSP began in 2006. Men and women between the ages of 60-74 (including some younger and older patients who may opt in) are invited for biennial faecal occult blood testing, and patients with a positive result are offered a colonoscopy. Patient demographics, colonoscopy and polypectomy details are prospectively recorded by a specialist screening practitioner (SSP) and entered into a national database, the Bowel Cancer Screening System (BCSS). In addition, patients are formally followed up by the SSP the day after the procedure and receive a 30-day questionnaire asking about adverse events and any medical advice they have sought. This system has been established as a reliable method of capturing colonoscopy-related adverse events (173).

Study procedures

Data relating to the removal of polyps less than 10 mm over a 3-year period (January 2010 to December 2012) were retrieved from the BCSS and retrospectively examined. Polypectomy practices were analysed according to polyp size, site, and morphology and related to completeness of histological excision and occurrence of major complications. The variation between individual colonoscopists and between screening centres were noted. In addition, polypectomy practices of physicians and surgeons were compared and time trends over the 3-year study period were analysed.

For the purpose of analysis, polyps were grouped according to endoscopic size; ranging between 1-3mm, 4-6mm and 7-9mm. Singh et al has reported significant variations in the technique between these groups (107). The wall of the right colon is anatomically much thinner than the left colon and more susceptible to polypectomy injury. The right side of the colon was categorised as proximal to the splenic flexure and left side of the colon distal to and including the splenic flexure. The ceacum was analysed independently due to the increased risk of complications (174, 175). Morphology was classified as pedunculated or non-pedunculated. Completeness of histological excision was classified as: completely excised, incompletely excised or not assessable, based on the pathologist's assessment of the resected specimen. Major post-polypectomy adverse events were defined as: bleeding episodes requiring transfusion or colonic perforation within 30 days of the procedure. Polyps ≥10mm were excluded from the analysis, as were those that had multiple excisions performed with 2 different devices.

The study was approved by the BCSP Research Committee.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics (v21). Categorical variables are presented as a proportion (%). Mean (range) was presented for the continuous variables with normal distribution or as median, interquartile range (IQR) and range for the continuous variables with non-normal distribution. Categorical data was compared using Pearson's chi-squared test with p values <0.001 being reported as significant.

3.1.3 Results

During the study period, 62, 679 therapeutic procedures were performed on 55, 419 patients. The mean age was 66 years (range 59-93 years with 98.9% 60-74) and 68.7% were men. A total of 147, 174 sub-centimetre polyps were removed by 290 endoscopists at 59 screening centres. Figure 13

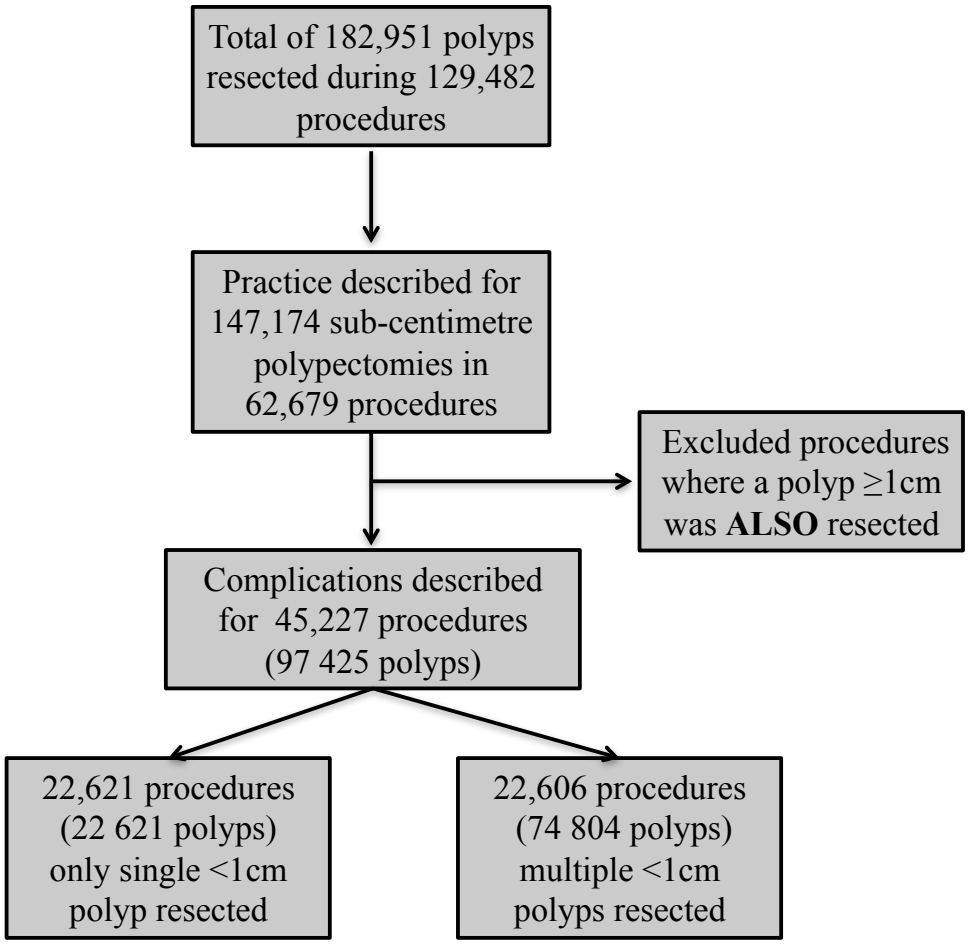


Figure 13 Study flowchart

Physicians performed 73% of the polypectomies, surgeons 19.3%, nurse endoscopists 6.2% and general practitioners 1.4%.

Overall, 57.2% of polyps were 1-3mm in size, 31.5% were 4-6mm and 11.3% were 7-9mm. More polyps were located in the left side of the colon (57.2%) and most were non-pedunculated (89.4%).

All polypectomy techniques were used (cold biopsy forceps [CBF] 19.7%, cold snare [CS] 22.1%, hot biopsy forceps [HBF] 12.2%, hot snare [HS] 35.1% and EMR 10.9%), but with considerable variation depending on the polyp size, site and morphology (Table 6).

		Right Colon (%)					**Left Colon (%)**				
Size	**Morphology** (N)	**CBF**	**HBF**	**CS**	**HS**	**EMR**	**CBF**	**HBF**	**CS**	**HS**	**EMR**
1-3mm	**P** (1811)	10.0	10.5	30.1	45.6	3.9	5.5	13.5	14.4	64.7	1.9
	NP (82, 429)	36.1	10.1	31.8	14.9	7.2	27.8	24.5	20.7	22.8	4.1
4-6mm	**P** (6810)	2.9	1.7	17.7	71.1	6.6	0.7	1.5	6.4	87.6	3.9
	NP (39, 492)	7.9	4.3	30.3	34.4	23.2	5.7	9.4	19.0	51.9	14.1
7-9mm	**P** (6931)	0.1	0	4.9	84.3	10.7	0.1	0.4	1.2	93.6	4.7
	NP (9701)	1.0	0.7	10.1	42.1	46.1	1.0	0.7	4.9	64.1	29.4
Overall <1cm	**P** (15, 552)	3.6	3.0	16.7	69.6	7.2	0.9	2.1	4.6	88.3	4.1
	NP (131, 622)	25.4	7.7	29.8	22.5	14.7	19.0	18.1	19.0	34.8	9.1

CBF (cold biopsy forceps), HBF (hot biopsy forceps), CS (cold snare), HS (hot snare), EMR (endoscopic mucosal resection), P (pedunculated polyps), NP (non-pedunculated polyps)

Table 6 Polypectomy technique by size, site and morphology

Pedunculated polyps

Overall, pedunculated polyps were most commonly removed using HS (84.7%), although this technique was used somewhat less frequently in the right side of the colon than in the left side for all polyp sizes (69.6% vs. 88.3%, $p < 0.001$). Utilisation of HS for pedunculated polyps varied between colonoscopists and was affected by site with a median (IQR) of 92% (83-97%) in the left side of the colon and 75% (53-92%) in the right side.

Non-Pedunculated polyps

For non-pedunculated polyps, a broader range of techniques were employed, although HS was still the most commonly used technique overall (29.2%). CS was more commonly used in the right side of the colon (median 24%, IQR 9-47%) than the left side (median 11%, IQR 3-32%), $p <0.001$. Hot snare was the most common technique in the left side of the colon (median 32%, IQR 19-49%) compared with the right side (median 17%, IQR 9-30%), $p <0.001$. EMR was also used more often in the right side of the colon (median 9%, IQR 2-20%) than the left side (median 3%, IQR 1-10%), $p < 0.001$.

There was wide variation (median, interquartile range and range) in the polypectomy techniques used by individual colonoscopists (Table 7). This occurred to a greater degree for 1-3mm and 4-6mm non-pedunculated polyps.

Size	Technique	Right Colon (%)			Left Colon (%)		
		Median	IQR	Range	Median	IQR	Range
1-3mm	CBF	29	10-58	0-98	16.0	3-45	0-94
	HBF	2	0-12	0-84	7.0	1-36	0-99
	CS	26	10-50	0-96	12.0	3-35	0-96
	HS	9	3-19	0-80	17	8-35	0-90
	EMR	2.0	0-7	0-79	1.0	0-4	0-58
4-6mm	CBF	2.0	0-9	0-68	2	0-5	0-66
	HBF	0	0-4	0-75	1	0-12	0-86
	CS	23	7-48	0-87	8	2-27	0-84
	HS	30	16-52	0-100	55	32-75	1-100
	EMR	14	3-39	0-96	5	0-21	0-97
7-9mm	CBF	0	0	0-40	0	0	0-67
	HBF	0	0	0-33	0	0	0-33
	CS	4	0-17	0-100	0	0-5	0-61
	HS	40	12-66	0-100	75	49-89	0-100
	EMR	40	17-67	0-100	17	0-46	0-100
Overall <1cm	CBF	20	7-41	0-81	11	2-30	0-80
	HBF	1	0-10	0-83	4	1-27	0-94
	CS	24	9-47	0-85	11	3-32	0-85
	HS	17	9-30	0-84	32	19-49	1-93
	EMR	9	2-20	0-83	3	1-10	0-76

CBF (cold biopsy forceps), HBF (hot biopsy forceps), CS (cold snare), HS (hot snare), EMR (endoscopic mucosal resection), IQR (interquartile range)

Table 7 Individual colonoscopist variation in the polypectomy techniques used for the removal of non-pedunculated polyps

Caecum

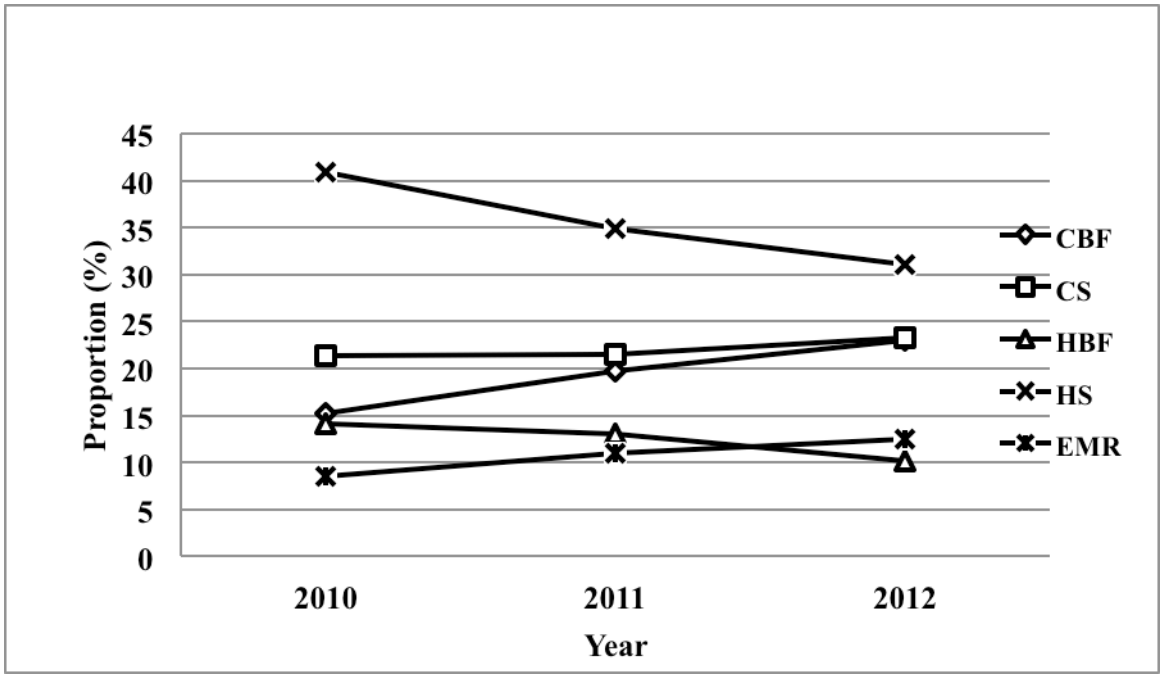
The majority of polyps removed from the cecum were non-pedunculated (97.4%), which were most commonly removed with cold techniques and EMR. Practices again varied widely between colonoscopists with a median (IQR) use of CBF of 29% (12-49%), CS of 28% (11-50%) and EMR of 11% (3-23%).

Surgeons versus Physicians

Surgeons were more likely than physicians to use diathermy-assisted techniques (HS, HBF & EMR) irrespective of size, site or morphology (65.6 vs 56.5%, $p < 0.001$).

Trends over time

Between January 2010 and December 2012, there was a significant increase in the use of CBF, CS and EMR techniques, whereas the use of HBF and HS decreased, $p < 0.001$ (Figure 14). In the right side of the colon, for 1-3 mm polyps, CBF use increased from 28.9% in 2010 to 40.0% in 2012, ($p < 0.001$), whereas HBF decreased from 12.1% to 8.1% ($p < 0.001$). For 7-9 mm polyps in the right side of the colon, the use of EMR increased from 32.7% to 44.1% ($p < 0.001$), whereas hot snare decreased from 54.6% to 46.0% ($p < 0.001$). In the left side of the colon, for 1-3mm polyps, CBF use increased from 20.1% to 32.7% ($p < 0.001$), whereas HBF use decreased from 28.3% to 20.1% ($p < 0.001$). For 7-9 mm polyps, EMR increased from 10.7% to 20.9% ($p < 0.001$) and HS decreased from 85.2% to 75.1% ($p < 0.001$).



CBF (cold biopsy forceps), HBF (hot biopsy forceps), CS (cold snare), HS (hot snare), EMR

Figure 14 Changes in polypectomy techniques over time

The histological assessment for completeness of excision

In 60% of polypectomies, the pathologist reported that the completeness of excision was not assessable. 21.2% were reported as completely excised, 5.8% incompletely excised and the completeness of excision was not stated in 13% of cases. There was marked variation between screening centres with respect to those polyps judged as not assessable (median 64%, IQR 55-69%, range 11-84%). Variation between centres was also most marked for non-pedunculated polyps judged as completely excised, whereas for pedunculated polyps removed by HS substantial agreement was observed. Table 8. For pedunculated polyps, EMR and HS techniques achieved complete histological excision in similar proportions, 42.3% and 42.0% respectively. For non-pedunculated polyps, complete excision was more common after EMR (23.4%) compared to other techniques (CBF 17.7%, CS 15.1%, HBF 19.1%, HS 21.5%).

Size	Techniqe	Pedunculated (%)			Non-pedunculated (%)		
		Median	IQR	Range	Median	IQR	Range
1-3mm	CBF	0	0	0-74	30	10-52	0-87
	HBF	0	0-3	0-100	10	2-23	0-84
	CS	0	0-24	0-98	17	8-35	0-74
	HS	74	40-100	0-100	18	8-27	0-84
	EMR	0	0	0-65	3	0-11	0-52
4-6mm	CBF	0	0	0-12	1	0-7	0-47
	HBF	0	0	0-16	1	0-6	0-92
	CS	2	0-7	0-18	11	5-26	0-62
	HS	90	85-97	41-100	51	38-69	5-98
	EMR	1	0-7	0-49	16	3-30	0-91
7-9mm	CBF	0	0	0	0	0	0-8
	HBF	0	0	0-6	0	0	0-4
	CS	0	0-1	0-13	1	0-6	0-18
	HS	97	87-99	53-100	65	43-84	0-100
	EMR	2	0-9	0-47	34	5-55	0-100
Overall <1cm	CBF	0	0	0-5	17	5-29	0-67
	HBF	0	0-1	0-7	6	1-13	0-84
	CS	1	0-4	0-13	14	6-25	0-56
	HS	93	87-96	49-100	38	25-48	3-85
	EMR	2	0-9	0-48	13	3-21	0-75

CBF (cold biopsy forceps), HBF (hot biopsy forceps), CS (cold snare), HS (hot snare), EMR (endoscopic mucosal resection. IQR (interquartile range)

Table 8 The histological variation between centres for polyps classified as completely excised

Adverse Events

Of the 45, 227 procedures where only sub-centimetre polyps were removed, a single polyp was removed in 22, 621 patients and more than one polyp removed in 22, 606 patients. Overall, there were 12 (0.03%) cases of bleeding that required transfusion and 16 (0.04%) perforations. The rate of bleeding requiring transfusion was 0.01% (1 in 11, 310) for single polypectomy and 0.04% (1 in 2260) for multiple polypectomy. The perforation rate was higher for procedures associated with multiple rather than for single polypectomy (1 in 2055 (0.05%) vs. 1 in 4524 (0.02%), $p = 0.53$.

The number of adverse events was too small to allow meaningful interpretation with respect to age, sex, endoscopist and the technique used. However, in patients who had bleeding requiring transfusion, 71% of polyps were located in the right side of the colon and 56% of polypectomies were performed using cold techniques (CBF or CS). In patients who had a perforation, 67% of polyps were located in the left side of the colon and 81% were removed using diathermy-assisted techniques. Ceacal location did not increase the risk of bleeding (12.5%) or perforation (15.4%).

3.1.4 Discussion

Polypectomy is the most commonly performed endoscopic therapy and safe and effective practice is an essential skill for colonoscopists. A range of techniques is available and experts recommend tailoring the choice of technique to the size, site and morphology of the polyp. For many polyps, experts agree on the appropriate technique e.g. large left sided pedunculated lesions removed by hot snare techniques and flat right sided lesions by EMR. For small and diminutive polyps, however, opinion is divided and practice varies. Surprisingly few randomised controlled trials are available to guide practice. Two recent studies reported that jumbo forceps (106) and cold snare (105) were more effective than standard CBF, which was often associated with incomplete resection (103, 113). HBF, once thought to be an acceptable alternative, is falling out of favor due to the risk of delayed bleeding, perforation and recurrence (115, 116). National societies now recommend avoiding HBF for polyps >5mm (117) and those in the right colon (118). Such studies have prompted guidance on the use of alternative techniques, such as cold snare for sessile polyps up to 7mm (110, 172) and hot snare and EMR for polyps >7mm (118). The implementation of such guidance however is not clear and there have been few recent studies of polypectomy practice. We therefore aimed to study polypectomy practice in the English NHSBCSP.

In the present study we have demonstrated wide variation between colonoscopists in the polypectomy techniques used for the removal of sub-centimetre polyps, particularly non-pedunculated polyps. A more uniform approach was seen for the removal of larger (7-9mm) non-pedunculated polyps, where HS predominated in the left side of the colon and EMR in the right side of the colon, whereas for

pedunculated polyps the HS technique appear to predominate overall. These findings are similar to those previously reported by groups in America a decade ago and in Israel more recently (107, 176). Interestingly, over the 3-year study period endoscopists appear to be changing practice, choosing cold techniques and EMR in the right side of the colon and avoiding HBF. The reasons for variability in practice are not well understood, but may reflect the lack of standardised polypectomy protocols, differences in training and experience, mis-sizing of polyps, awareness of and adherence to professional guidance, concern regarding adverse events and time constraints.

Despite considerable variation in the polypectomy techniques used, major adverse events were rare. Bleeding requiring transfusion occurring with a frequency of 3 in 10, 000 and perforation of 4 in 10, 000. This is particularly reassuring, as the vast majority of sub-centimetre polyps will never become clinically significant. Although the results of different studies are not directly comparable, two previous studies report similar rates of bleeding requiring transfusion (8 in 10, 000) and perforation (6 in 10, 000) following endoscopic resection of similar sized polyps (177, 178). In the present study, it is unclear which particular technique led to the adverse event, however perforations primarily occurred in patients using diathermy assisted techniques, whereas bleeding requiring transfusion appeared to occur with both hot and cold techniques. This is in contrast to previous studies where a nine-fold increase in the risk of perforation and bleeding has been associated with diathermy assisted techniques (101, 107, 179). Ceacal location was not associated with more adverse events. A recent study reported an association between Ceacal location and increased

risk of adverse events, but unlike the present study this included polyps of all sizes (175).

Recognising incomplete resection is important to prevent polyp recurrence and reduce the risk of interval cancer. It is clear that pathologists are unable to assess completeness of excision in the majority of cases, hence it falls on the endoscopist to be thorough and inspect the site carefully. Recent evidence from the complete adenoma resection (CARE) study suggests that endoscopists do not do this well (100). In the present study, it was surprising that pathologists found it easier to assess completeness of excision following hot snare rather than cold snare and to a lesser extent EMR. However, there was a surprisingly large range between centres in the reporting of completeness of resection even following hot snare polypectomy. Studies examining agreement regarding pathologists assessment for completeness of excision are conflicting (145, 180). Variations in the polypectomy technique used (hot versus cold), method of removal (en-bloc versus piecemeal), and mounting process may lead to difficulties with confirming the absence or presence adenomatous tissue at the resection margin. Furthermore, some pathologists may undertake a less detailed assessment of the resection margin, as they are only required to verify the completeness of excision for malignant polyps and those with high grade dysplasia (73, 114). Variation could also be due to endoscopists technique, as some will remove a rim of normal tissue with cold snare, whereas other do not.

The present study has a number of strengths. It is the largest study to date to describe polypectomy practice within a national screening programme. Data is collected prospectively and independently of the endoscopist. Case ascertainment is high with

comprehensive inclusion of data from all centres and all endoscopists. Data was available over a 3-year period allowing time trends to be observed. Patients are formally followed up at 24 hours and 30 days post colonoscopy to capture any adverse events. The current study has a number of limitations. The study design is retrospective and observational in nature and lacks the strength of a randomised controlled trial. This is inherently at risk of bias due to confounding factors not included in the analysis. Detailed information on patient data (co-morbidities and anti-thrombotic medication), potential determinants of completeness of excision such as Paris classification, diathermy settings and snare choice are not routinely recorded.

In conclusion, removal of sub-centimetre polyps is safe despite wide variation in polypectomy practice within the English NHSBCSP. The use of cold resection techniques and EMR has increased over time and use of HBF has decreased. Histological assessment of completeness of resection is limited with considerable variation between screening centres. Further research focusing on the optimal polypectomy technique and endoscopic methods to assess completeness of excision is needed.

Chapter 4: Cold Snare Polypectomy: Does Snare Type Influence Outcomes?

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SD and SAR conceived and designed the study. SD analysed and interpreted the data and drafted the original manuscript. All authors (SD, SAR, AJB, SSJ, PK) contributed to critical revisions and approved the final manuscript.

Null hypothesis

There is no difference in the completeness of resection between the two snare devices

Alternative hypothesis

We hypothesise that cold snare of polyps 3-7mm in size with the Exacto snare achieves higher complete resection rates compared to the Olympus snare device.

4.1.0 Abstract

Background Cold snare techniques are widely used for the removal of small and diminutive polyps. The influence of snare type on the effectiveness of cold snare polypectomy is unknown.

Method Cold snare polypectomy of 3-7mm polyps was undertaken using either a thin wire mini-snare (0.30mm) or thick wire mini-snare (0.47mm). The primary outcome was endoscopic completeness of excision. Consensus regarding the endoscopic assessment of completeness of excision was standardised and aided by chromoendoscopy. Secondary outcomes included: completeness of histological excision, polyp 'fly away', polyp retrieval rate, early or delayed bleeding and perforation.

Results 157 polyps were removed ranging from 3 to 7mm, 62% were situated in the left side of the colon and 89.4% were sessile. Endoscopic completeness of excision was significantly higher with the thin wire snare compared to the thick wire snare (90.2% vs. 73.3%, $p < 0.05$). There was a numerical trend towards a higher complete histological excision rate with the thin wire snare, but this did not reach statistical significance (73.3% vs. 65.2%, $p = 0.4$). There was a fair level of agreement (kappa = 0.36) between endoscopic and histological completeness of excision. Polyp 'fly away' occurred less often with the thin wire snare (14.6% vs. 35.3%, $p = 0.002$), but there was no significant difference in the polyp retrieval rate (84.3% vs. 83.8%, $p = 0.94$). There were no complications with either snare.

Conclusion Snare type appears to be an important determinant of completeness of excision when removing small polyps by the cold snare technique.

4.1.1 Background

Over 90% of polyps removed during colonoscopy are small (<10mm) (45, 168) and have a low risk of containing advanced pathology or developing into cancer (33, 181). Resection techniques should therefore be both safe and effective. Whilst many studies have shown that the removal of small polyps is safe, residual or recurrent tissue may be found in 29-61% following removal with biopsy forceps (101, 103, 113-115) and 3-14% following snare polypectomy (115, 126, 182). This is of importance as interval cancer rates of 10-27% have been associated with incomplete polyp resection (61, 98, 99). Furthermore, incomplete or uncertain histological excision can lead to diagnostic uncertainty and impacts on surveillance intervals.

The cold snare technique has been recommended for the removal of small polyps due to its safety profile, speed of resection and effectiveness (110, 172). However, a large selection of snares is available which differ in size, shape and wire thickness, but the comparative effectiveness of snare type is not known.

The Exacto mini snare was specifically designed for cold snare polypectomy. Anecdotal reports suggest the Exacto snare is more effective for cold snare polypectomy. Therefore we performed a service evaluation, which compared the efficacy of the Exacto snare with the Olympus snare during a switch over of the snare used within our endoscopy department. The purpose of this study was to establish the feasibility of conducting a larger RCT comparing these 2 snares.

4.1.2 Methods

Study Approval

The study and associated documents were registered and approved as a service evaluation by the Sheffield Teaching Hospitals Clinical Effectiveness Unit (project number 5927). All patients signed a written informed consent form so that they could be contacted following their colonoscopy.

Patients

This was a prospective single centre study, conducted at Northern General Hospital, Sheffield, UK, between July 2013 and January 2014. Consecutive adult patients attending for diagnostic colonoscopy, who were found to have one or more, sessile or flat polyps measuring 3-7mm were considered eligible for the study. Patients taking anticoagulants or Clopidogrel were excluded from the study, as were those where polyps were identified behind folds making assessment of completeness of excision difficult.

Process to standardise completeness of endoscopic excision

Prior to the study, 5 participating endoscopists viewed 20 video clips of cold snare polypectomy and the mucosal defect, before and after spraying with indigo carmine dye. This process was completed over two rounds in order to establish the criteria for the assessment of completeness of endoscopic resection. Completeness of excision was classified as 'complete' (no evidence of residual tissue at the excision margin or polyp base), 'incomplete' (any evidence of residual tissue at the excision margin or polyp base) or 'uncertain'.

Through two rounds of the consensus process (Tables 9 and 10), the multi-rater kappa agreement was 0.49, (95% CI 0.27-0.70) and 0.51 (95% CI 0.32-0.71) respectively, suggesting a moderate level of agreement in the endoscopic assessment of completeness of excision**.**

	SAR Expert	SSJ Expert	SD Fellow	JC SPR	AJB Fellow	Histology
Video 1	2	1	1	2	3	1
Video 2	1	1	1	1	1	1
Video 3	1	1	1	2	1	1
Video 4	3	2	2	3	3	NA
Video 5	1	1	1	1	1	1
Video 6	2	2	2	3	2	NA
Video 7	2	2	2	2	2	2

(1 complete excision, 2 incomplete excision, 3 uncertain, NA not assessable)

Table 9 Round 1 of the consensus process for the assessment of completeness of excision

	SAR Expert	SSJ Expert	SD Fellow	JC SPR	AJB Fellow	Histology
Video 1	2	2	2	2	3	2
Video 2	1	2	1	1	2	1
Video 3	2	1	2	2	2	1
Video 4	1	1	1	1	1	1
Video 5	2	2	2	2	2	2
Video 6	3	2	2	3	3	2
Video 7	1	2	1	2	2	1
Video 8	1	1	1	1	1	1
Video 9	2	1	1	2	2	1
Video 10	1	1	1	1	1	1
Video 11	1	1	1	1	1	1
Video 12	1	1	1	1	1	1

(1 complete excision, 2 incomplete excision, 3 uncertain)

Table 10 Round 2 of the consensus process for the assessment of completeness of excision

Differences between the snares (Table 11, Figure 15)

The Exacto snare has been exclusively developed for cold polypectomy. It is made from 3 stainless steel wires braided together and is 33% thinner than traditional mini snares. This allows for a more precise clean cut and helps to reduce polyp fly away. The wire loop itself is designed in the form of a 'shield' and this feature appears to help with snare placement. In contrast, the Olympus snare is made from 9 strands of wire braided together and is oval in shape. It can be used to remove polyps with or without diathermy, hence making it more cost effective as a different snare does not need to be used for other polyps requiring diathermy. The increased surface area of the Olympus snare helps to prevent deep transmural injury when diathermy is applied as the effect of the current is more localised. Cold snaring is known to exert a greater mechanical force than hot snaring, therefore the catheter of the Exacto snare is designed to have increased axial stiffness to prevent the wire from buckling under pressure.

Snare	Loop design	Sheath diameter (mm)	Length (cm)	Loop diameter (mm)	Loop wire diameter (mm)
Exacto ™	Shield	2.4	230	9	0.30
Olympus SD-210-10	Oval	2.6	230	10	0.47

Table 11 Summary of snare characteristics

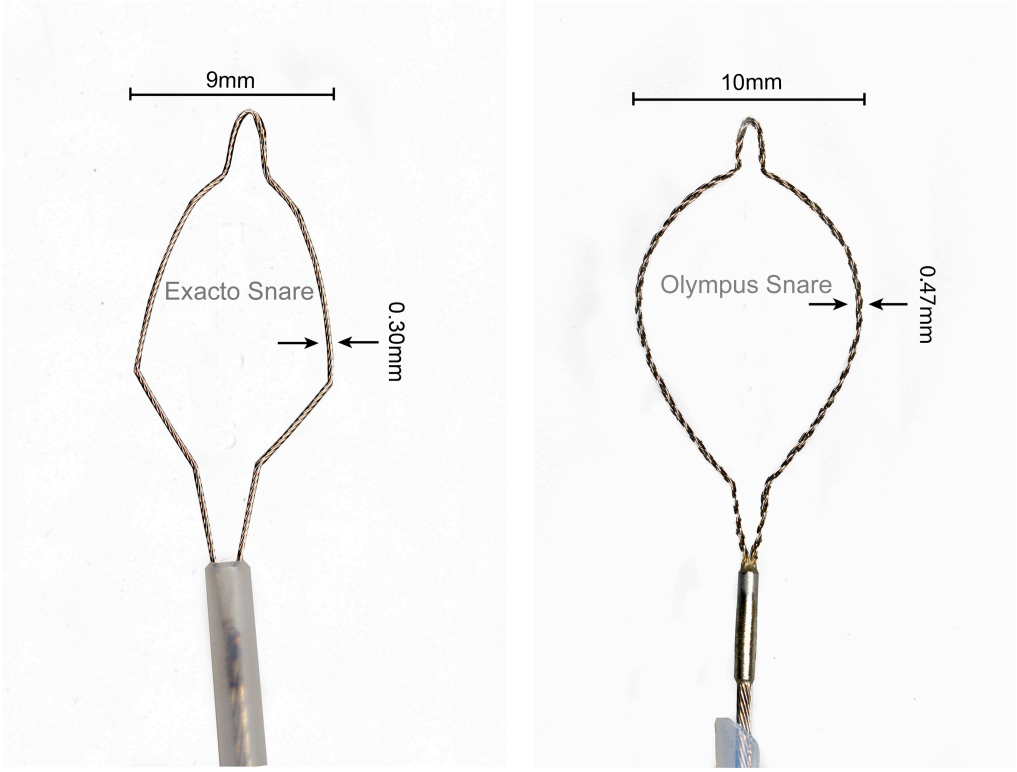

Figure 15 Fully opened mini-snares

Polypectomy protocol

Four experienced endoscopists performed all procedures using conventional colonoscopes (CF-Q260 AI, CF-H260AI; Olympus Medical Systems, Tokyo, Japan). Prior to the study, endoscopists familiarised themselves with the Exacto snare for a trial period to avoid bias due to the learning curve effect.

Prior to polypectomy, polyp size, site and morphology were noted. Polyps were sized using large capacity biopsy forceps (Boston Scientific 1332-40) as a guide (closed diameter 2.4mm, fully open jaw tips 8mm). When the polyp margin was not clearly apparent, the site was sprayed with dilute indigo carmine (0.1%) prior to polypectomy. Polyps were excised without tenting in the 5-8 o' clock position with the aim of capturing a rim of normal mucosa. When more than one polyp was encountered during the procedure the same snare was used. Polyps were retrieved by suctioning through the biopsy channel of the colonoscope into a polyp trap. The polypectomy site was then visually assessed for any evidence of residual tissue by washing the site with water, ensuring good luminal distension and applying 0.1% indigo carmine. When excision was judged incomplete or uncertain, targeted biopsies were taken from areas of residual tissue, margin and base using large capacity biopsy forceps. The polypectomy site was reassessed to ensure resection was complete and dye applied to confirm. All samples were sent in separate pots to an expert pathologist who was blinded to the endoscopic findings. The criteria for confirming completeness of histological excision were based on the NHS bowel cancer screening pathology guidelines (73) and defined by the absence of residual tissue at the resection margin in any dimension.

All patients were followed up by a phone call 48 hours and 2 weeks after the procedure to assess for any complications.

Study outcomes

Primary outcome measure

1. Endoscopic completeness of excision.

Secondary outcome measures

1. Completeness of histologic excision
2. Polyp ‘fly away’ (polyp remains within or adjacent to the polypectomy site)
3. Retrieval rate
4. Early bleeding (48 hours)
5. Delayed bleeding (2 weeks)
6. Perforation.

Statistical analysis

Kappa statistics (k) and 95% confidence intervals were calculated to assess interobserver agreement between the multiple raters using the formula by Fleiss (183). Kappa values were classified as: poor, 0.00 to 0.20; fair, 0.21 to 0.40; moderate, 0.41 to 0.60; good, 0.61 to 0.80; and excellent, 0.81 to 1.00 (184).

Cold snare technique has a reported complete excision rate of 86%-89% (115, 126, 182). We determined that at least 56 patients per group would be required comparing the two snares with an α -value of 0.05 and a power of 80%. In the first half of the study, polypectomy was performed with the Exacto snare before switching to the Olympus snare.

Categorical variables were compared using the $\chi 2$ test or Fisher's exact test, where appropriate. Student's t-test was used for continuous variables. The *p*-values of < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 21.

4.1.3 Results

112 patients were included in the study (mean age 63.5 years, range 29-85 years, 65.2% male). There were slightly more males and older patients in the Exacto polypectomy group, but no significant differences in the polyp characteristics between the two groups. Table 12

	Exacto snare (n=56)	**Olympus snare (n=56)**	***P*- value**
Male/Female	42/14 75%	32/24 57.1%	0.05
Age (years)*	66 ± 10.9	61 ± 10.3	0.015
Number of eligible polyps detected (161)	89	72	
Median polyp size (range)	4.0mm (3-7mm)	4.0mm (3-7mm)	0.16
Location Right colon (proximal to splenic flexure) Left Colon	 38 51	 23 49	
Paris 1s 2a	 78 (87.6%) 11 (12.4%)	 66 (91.7%) 6 (8.3)	 0.4
Histology Adenoma Serrated Hyperplastic Others †	 57 (61.8%) 2 (2.2%) 19 (21.3%) 13 (14.6%)	 39 (54.2%) 0 22 (30.6%) 11 (15.3%)	

Table 12 Patient details and polyp characteristics

* Results are expressed as mean ± standard deviation.

† Not assessable or Not retrieved

161 eligible polyps were detected and cold snare resection was technically feasible in 157 polyps. Median polyp size was 4.0mm (3-7mm), 62% were located in the left colon, 89.4% were sessile (Paris 1s) and most were tubular adenomas (60%). There was a failure to resect 4 polyps with the Olympus snare and polypectomy was performed using diathermy.

For the accurate attribution of completeness of excision, we restricted the analysis to those polyps where excision was judged as complete or incomplete. Endoscopic completeness of excision was significantly better with the Exacto snare compared to the Olympus snare (90.2% [95%CI, 81.7-95.7%]) vs. (73.3%, [95%CI, 60.3-83.9%]), $p = 0.008$. There was also a numerical trend towards a higher complete histological excision rate with the Exacto snare, but this did not reach statistical significance (73.3% [95%CI, 60.3-83.9%]) vs. 65.2% [95%CI, 49.8-78.7%]), $p = 0.4$. There was no statistically significant difference between the Exacto and Olympus snares when we combined the polyps classified as uncertain, with those that were incompletely excised for the completeness of endoscopic (83.1% vs. 68.8%, $p = 0.008$) and histological excision (49.4% vs. 44.1%, $p = 0.5$). Where the completeness of excision was assessable, there was a fair level of agreement (kappa = 0.36) between endoscopic and histological assessment.

Polyp 'fly away' occurred less often with the Exacto snare (14.6% vs. 35.3%, $p = 0.002$), but there was no significant difference in the polyp retrieval rate between the two groups (84.3% vs. 83.8%, $p = 0.9$). There were no complications with either snare. The overall effectiveness of the two snare types is described in table 13.

	Exacto snare N=89	95%CI	Olympus snare N=72	95%CI	*P*- value
Endoscopic excision					
Complete	74 (83.1%)	73.7-93.7	44 (61.1%)	48.9-72.4	0.008*
Incomplete	8 (9.0%)	4.0-17.0	16 (22.2%)	13.3-33.6	
Uncertain	7 (7.9%)	3.2-15.5	8 (11.1%)	4.9-20.7	
Failed to resect	0		4 (5.5%)		
Complete omitting 'Uncertain'findings	82 (90.2%)	81.7-95.7	60 (73.3%)	60.3-83.9	0.008
Histological excision					
Complete	44 (49.4%)	38.7-68.3	30 (44.1%)	30.2-53.9	0.5*
Incomplete	16 (18.0%)	10.6-27.6	16 (23.5%)	13.3-33.6	
Uncertain	29 (32.6%)	23.0-43.3	22 (32.4%)	20.2-42.5	
Complete omitting 'Uncertain' findings	60 (73.3%)	60.3-83.9	46 (65.2%)	49.8-78.7	0.4
Polyp fly away	13 (14.6%)	8.0-23.7	24 (35.3%)	22.7-45.4	0.002
Retrieval rate	75 (84.3%)	75.0-91.1	57 (83.8%)	68.0-87.8	0.94
Complications					
Early bleeding	0		0		
Late bleeding	0		0		
Perforation	0		0		

Table 13 Overall summary of the effectiveness and safety of the snares

* Comparison between completion rates for the two techniques with the "Uncertain" results included in the total polypectomies.

4.1.4 Discussion

Some endoscopists may assume that leaving a small amount of residual adenoma may be safe because of the low risk of malignant transformation. However, incomplete resection has been implicated in 10-27% of interval colorectal cancers (61, 98, 99, 154). Although, this is more likely to occur for larger polyps (100, 135), most polyps encountered during colonoscopy are small (<10mm) (45, 168). Studies have reported incomplete resection rates of up to 61% with standard cold biopsy forceps (103, 110), 18% with jumbo forceps (185) and 17% with hot biopsy forceps (186) . Snaring with or without diathermy is a better alternative with incomplete resection rates of 5% and 11% respectively (115, 126), but risk of delayed bleeding and perforation is increased with hot snare (120, 121). Cold snare polypectomy may therefore offer a good compromise.

The present study suggests that cold polypectomy with a thin wire snare (Exacto) is more effective than a thick wired snare (Olympus). However, completeness of histological excision was not statistically significant, despite a numerical trend in favour of the Exacto snare. We have calculated that it would require 266 patients per group to determine if there was a 10% difference in histological completeness of resection between the snares with an α -value of 0.05 and 80% power.

Despite fair agreement between the endoscopic and histological findings, the discrepancy between the histological and endoscopic completeness of resection with both the Exacto (73.3% vs. 90.2%) and Olympus snares (65.2% vs. 73.3%) is likely to be due to a lack of biopsies from all the polypectomy sites and differences in the mounting process, crush artefacts or fragmentation of small polyps. Previous studies

have consistently shown lower histological than endoscopic complete resection rates (105, 187).

As no published studies have assessed the efficacy of the Exacto snare, comparisons could not be made. However, higher rates of complete endoscopic and histological excision have been reported with the Olympus snare comparing cold snare with double biopsy forceps technique (105). Unlike the present study, most polyps were 5mm and removed by a single operator. Criteria for confirming completeness of excision was not stated nor examined by a single expert histopathologist. In the present study, assessment of the polypectomy site was standardised and enhanced by using indigo carmine. Targeted biopsies were only taken when excision was judged to be uncertain or incomplete, as we felt this was more likley to reduce sampling errors and increase the detection of residual tissue.

Polyp 'fly away' occurred significantly less with the Exacto snare, but surprisingly this did not translate into an improved retrieval rate. The reason for this difference is not clear, but it may relate to the thinner snare wire diameter requiring less squeeze pressure to achieve a clean cut compared to the thicker snare wire diameter of the Olympus snare. Polyp retrieval rates in our study are comparable to other series of similar sized polyps (81%-96%) (120, 127, 188). Reduced polyp 'fly away' is of benefit as more time can be spent examining the polypectomy site and ensuring excision is complete.

Although our study was not powered to detect the difference in complications, none occurred with either snare. This is in keeping with the findings of several studies where cold snare polypectomy has been reported to be extremely safe (111, 127).

Variations in the polypectomy technique, endoscopists attitudes about how aggressive their removal strategy will be and difficulties of assessing the post-polypectomy site are all important factors that may influence the quality of polypectomy. Therefore, rates of complete polypectomy may actually be lower in practice. The only reliable way to ensure residual tissue is not left behind is to resect a 1-3mm rim of normal tissue during cold snare polypectomy (122-124). This may be influenced by the choice of snare and technique used. For instance, stiff or barbed snares facilitate tissue capture and entrapment of normal tissue at the lesion margin, whereas thin or monofilament snares enable a more precise and cleaner cut compared to thick or braided snares. Despite choosing the correct snare, failure to assess the extent of the lesion may result in inaccurate snare placement, potentially leaving residual tissue behind.

Although, endoscopists are in a good position to assess completeness of excision, findings of the complete adenoma resection (CARE) study suggests that some endoscopists do this poorly with over a three fold variation between them (100). Chromoendoscopy has been shown to enhance the characterisation and delineation of the polypectomy site and may assist the endoscopist (79, 143), but the role of other image-enhanced technologies is uncertain. It is therefore reassuring to have histological confirmation of complete excision despite its limitations.

Our study has several important strengths. Endoscopic assessment for completeness of excision was standardised with a low threshold for excluding cases considered uncertain. We believe our strategy to assess evidence of residual tissue was particularly robust due to the time spent washing the post polypectomy site and applying indigo carmine. This was also a multi-operator study and the results are

generalizable to a typical endoscopy unit. The present study has a number of limitations. The endoscopists could not be blinded to the snare type and the study design was open such that the results are susceptible to investigator bias. Biopsies were not taken from the margin and base of all polypectomy sites as this is prone to sampling errors and completeness of excision was not verified in follow up examinations.

Our findings suggest that snare type may be an important factor determining polypectomy outcomes. A larger randomised controlled trial powered according to the findings of the present study would be useful to confirm which snare type is best.

Chapter 5: A Randomised Comparison Of Standard Snare Polypectomy versus a Suction Pseudopolyp Technique

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SD and SAR conceived and designed the study. SD analysed and interpreted the data and drafted the original manuscript. All authors (SD, SAR, AJB, SSJ, PK) contributed to critical revisions and approved the final manuscript.

Null hypothesis

There is no difference in the completeness of resection between the two techniques.

Alternative hypothesis

We hypothesise that the suction pseudopolyp technique achieves higher complete resection rates compared to standard snare polypectomy.

5.1.0 Abstract

Background

Cold snare techniques are widely used for the removal of diminutive and small colorectal polyps. The influence of resection technique on the effectiveness of polypectomy is unknown. We have therefore compared completeness of excision and complications following standard cold snare polypectomy (CSP) with a newly described suction pseudopolyp technique (SPT).

Method

In this single centre study, 112 patients were randomised to either CSP or the SPT. The primary outcome was endoscopic completeness of excision. Consensus regarding the endoscopic assessment of completeness of excision was standardised and aided by chromoendoscopy. Secondary outcomes included: completeness of histological excision, polyp 'fly away', polyp retrieval rate, early bleeding (48 hours), delayed bleeding (2 weeks) and perforation.

Results

148 polyps were removed. Polyps ranged in size from 3 to 7mm, 60% were situated in the left colon and 90% were sessile. Endoscopic completeness of excision was higher with SPT compared with CSP, but this was not statistically significance (98.6% vs. 92.6%, p=0.08). There was also a numerical trend towards a higher complete histological excision rate with SPT, but again the difference did not reach statistical significance (76.3% vs. 63.8% p = 0.14). There was no significant difference in the polyp retrieval rate between the SPT and CSP (89.5% vs. 88.9%, p = 0.91). No perforation or bleeding requiring hemostasis occurred in either group.

Conclusion

In the present study both the suction pseudopolyp and standard cold snare polypectomy techniques appeared safe and highly effective for the removal of 3-7mm flat and sessile colorectal polyps.

5.1.1 Background

It is widely accepted that colonoscopic polypectomy reduces the incidence and mortality of colorectal cancer by disrupting the polyp-cancer sequence. However, the vast majority of polyps encountered during routine colonoscopy are diminutive (1-5mm) or small (6-9mm] and 9%-10% will have advanced histology (168, 189). It is not known which of these polyps will progress to cancer so all are removed.

Several polypectomy techniques are available for the removal of small polyps, with the choice of technique influenced by the size, site and morphology of the polyp and the practice of the colonoscopist. Many advocate the use of cold snare for the removal of diminutive and small polyps since it avoids diathermy-associated complications. However, incomplete resection rates of 7%-21% have been reported with cold snare techniques (105, 115, 119, 126).

In an attempt to improve completeness of resection, Patullo et al described a novel method (the pseudopolyp technique) for the removal of small polyps and achieved complete endoscopic resection rates of 100% without any immediate or delayed complications (112). These impressive results, however, were non-comparative and no assessment was made of the histological completeness of excision.

We have therefore undertaken a randomised comparison of the suction pseudopolyp technique and standard cold snare polypectomy and incorporated an assessment of the histological completeness of excision.

5.1.2 Method

Study population and design

The study was a single centre, prospective randomised controlled trial of outpatients undergoing routine diagnostic colonoscopy between January 2014 and August 2014. The study protocol was approved by the local research ethics committee and was performed in compliance with the Helsinki declaration. The trial was reported according to the CONSORT guidelines and was registered at www.clinicaltrials.gov (NCT02208401). Written informed consent was obtained from all patients including recording the procedure and telephone follow up. Patients over the age of 18 years who were found to have one or more sessile or flat polyps measuring 3-7mm were considered eligible. Those taking antiplatelet agents (except Aspirin) or anticoagulant therapy and those with polyps identified behind folds making endoscopic assessment of completeness difficult were excluded.

Randomization and concealment

Patients were randomly assigned with a 1:1 ratio to SPT or CSP. The website www.random.org was used to generate a randomisation sequence and was concealed by placing the assignments in fully opaque, sequentially numbered envelopes. When an eligible polyp was identified during the procedure, a nurse opened the envelope to reveal the polypectomy technique. If more than one eligible polyp was encountered in the same patient, polypectomies were carried out using the same technique.

Process to standardise completeness of endoscopic excision

The process to standardise completeness of endoscopic excision was performed previously (Chapter 3); 5 participating endoscopists viewed 20 video clips of cold snare polypectomy and the mucosal defect, before and after the defect was sprayed with indigo carmine dye. This process was completed over two rounds in order to establish the criteria for the assessment of completeness of endoscopic resection. Completeness of excision was classified as 'complete' (no evidence of residual tissue at the excision margin or polyp base), 'incomplete' (any evidence of residual tissue at the excision margin or polyp base) or 'uncertain'.

Through two rounds of the consensus process, the multi-rater kappa agreement was 0.49, (95% CI 0.27-0.70) and 0.51 (95% CI 0.32-0.71) respectively, suggesting a moderate level of agreement in the endoscopic assessment of completeness of excision**.**

Polypectomy protocol

Patients were prescribed standard bowel preparation with either Picolax (Ferring) or Kleanprep (Norgine). Three experienced endoscopists, from among the five who had established the kappa values, performed the procedures using Olympus CF 260 colonoscopes (Olympus Medical Systems, Tokyo, Japan). Prior to the study, each endoscopist practiced the suction pseudopolyp technique as described by Pattullo et al (112) for a trial period to avoid bias due to the learning curve effect.

All polyps were removed with the Exacto mini snare without diathermy. Prior to polypectomy, polyp size, site and morphology were noted. Polyps were sized using the Boston Scientific biopsy forceps (1332-40) as a guide (closed diameter 2.4mm,

fully open jaw tips 8mm). When the polyp margin was not clearly apparent, the site was sprayed with dilute indigo carmine (0.1%) prior to polypectomy.

Conventional cold snare polypectomy was performed as follows:

1. Slight deflation of luminal air
2. Excision of polyp without tenting in the 5-8 o' clock position with the aim of capturing a rim of normal mucosa.

The suction pseudopolyp technique was performed according to the method described by Pattullo et al (112):

1. Slight deflation of luminal air
2. Passage of the snare down the working channel of the colonoscope until it is 15-20cm from the end of the colonoscope
3. Centre of polyp aligned with the suction channel
4. Polyp aspirated into the suction channel and continuous suction applied whilst gently pulling the colonoscope backwards for a distance of 2-5cm
5. Suction released and colonic wall springs back with the formation of a pseudopolyp
6. Rapid cold snare excision of the pseudopolyp to prevent the polyp from going back into its original shape.

Polyps were retrieved by suctioning through the biopsy channel of the colonoscope into a polyp trap. The polypectomy site was then visually assessed in real time for any evidence of residual tissue by washing the site with water, ensuring good luminal distension and applying 0.1% indigo carmine (Figures 16 and 17).

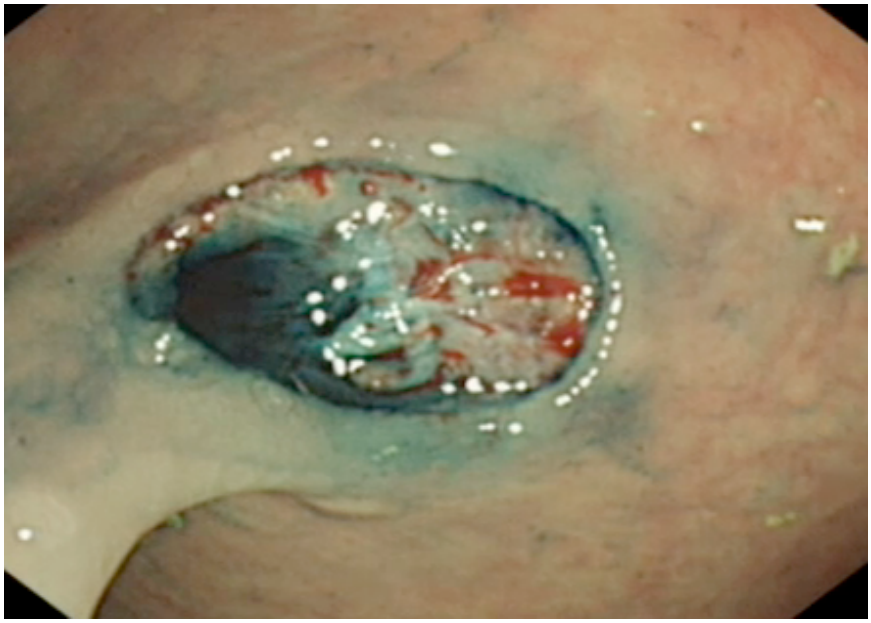


Figure 16 Endoscopic appearance of a completely excised sessile polyp with SPT after application of indigo carmine

Figure 17 Endoscopic appearance of an incompletely excised sessile polyp with CSP after application of indigo carmine

When excision was judged incomplete or uncertain, targeted biopsies were taken from areas of residual tissue, margin & base using large capacity biopsy forceps. All samples were sent in separate pots to an expert pathologist who was blinded to the endoscopic findings and technique used. The criteria for confirming completeness of histological excision were based on the NHS bowel cancer screening pathology guidelines (73) and defined by the absence of residual tissue at the resection margin in any dimension (Figures 18 and 19). All patients were followed up by a phone call 48 hours and 2 weeks after the procedure to assess for any complications.

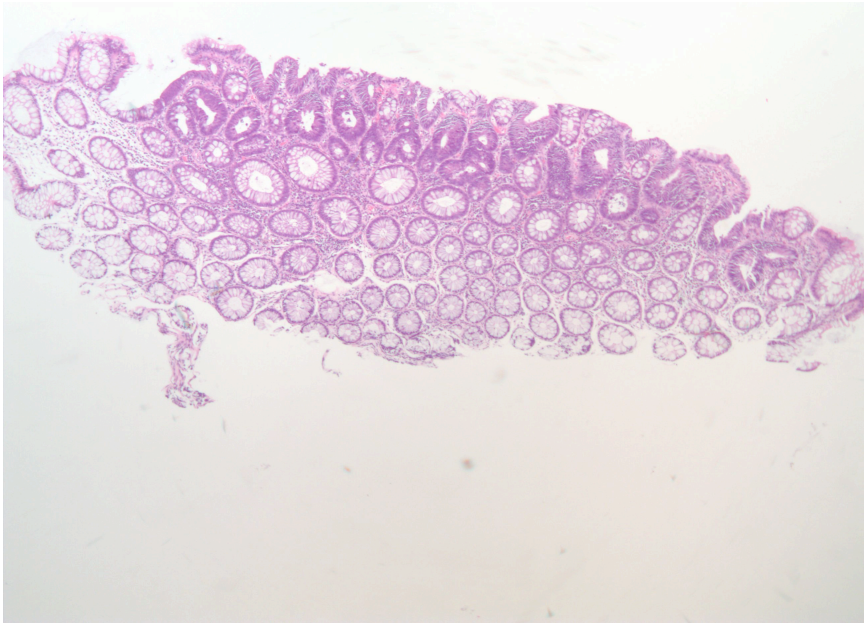


Figure 18 Histology of a completely excised sessile tubular adenoma as indicated by the presence of normal mucosa at the lesion margin

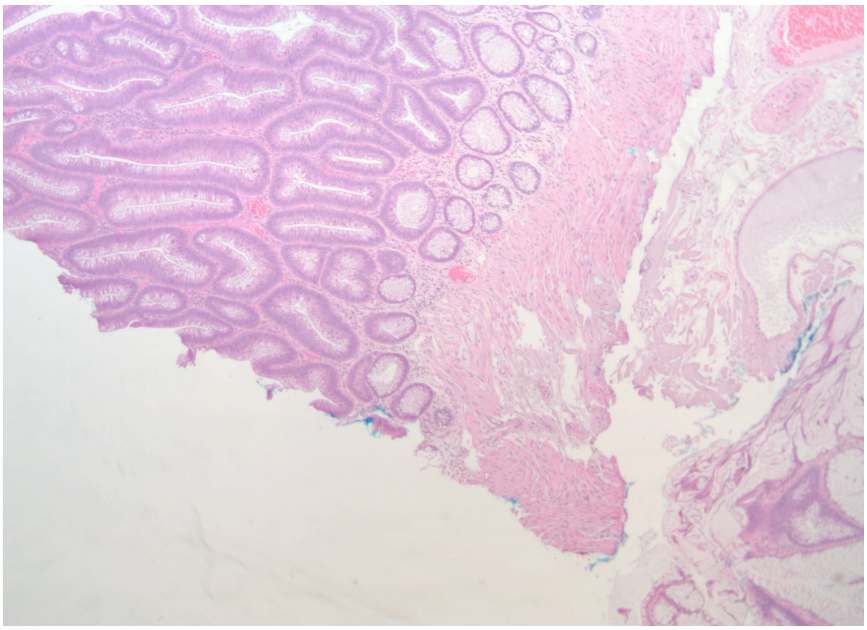


Figure 19 Histology of an incompletely excised tubular adenoma as indicated by the presence of dysplastic tissue at the inked blue lesion margin

Study outcomes

The primary outcome was endoscopic completeness of excision. Secondary outcome measures were: completeness of histologic excision; rate of polyp "fly away" (when the polyp does not remain within or adjacent to the polypectomy site); polyp retrieval rate; early bleeding (48 hours); delayed bleeding (2 weeks); and perforation.

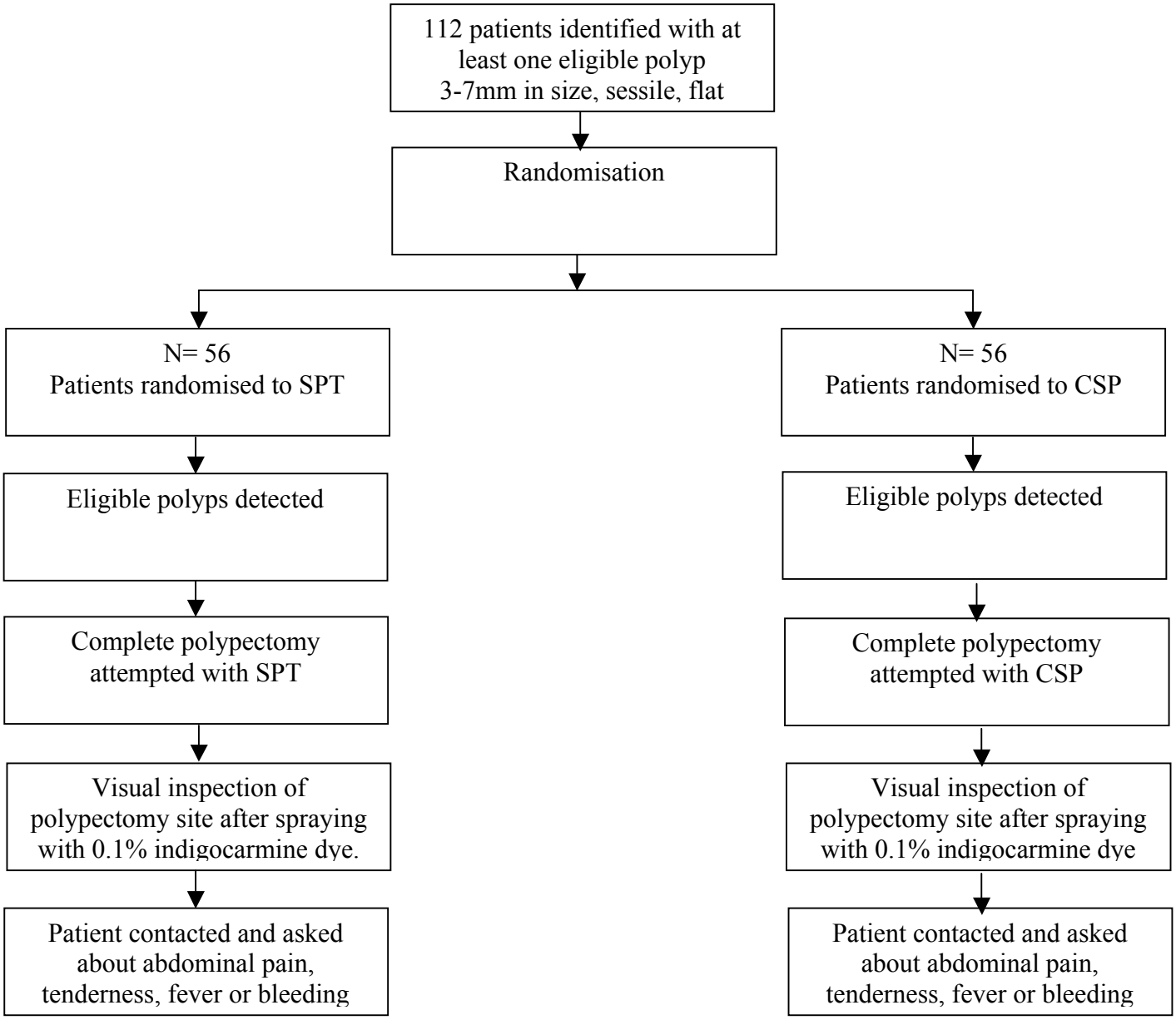
Statistical analysis

The sample size calculation was based on the results of a previous study that reported 86% of polyps were completely resected using the cold snare technique (115). We determined that at least 56 patients per group would be required to compare the two techniques with a significance level alpha 0.05 and statistical power of 0.80 in order to detect a clinically relevant increase in the completeness of resection of at least 14%. Categorical variables were compared using the χ^2 test or Fisher's exact test, where appropriate. Student's *t* test or the Mann–Whitney Wilcoxon test were used for continuous variables. Statistical analysis was performed using SPSS version 20.

Kappa statistics (k) and 95% confidence intervals were calculated to assess inter-observer agreement between the multiple raters (183) . The strength of agreement for a kappa value was classified as: poor, 0.00 to 0.20; fair, 0.21 to 0.40; moderate, 0.41 to 0.60; good, 0.61 to 0.80; and excellent, 0.81 to 1.00 (184).

5.1.3 Results

Figure 20 Patient flow through the study



112 patients (67.9% men, mean age 63.7 years; range 31-86) were found to have at least one sessile or flat polyp measuring 3-7mm and were randomised to undergo polypectomy with SPT (n = 56) or CSP (n =56). Patient demographics, indications for colonoscopy and polyp characteristics were similar between the two groups (Table 14). A total of 148 eligible polyps were detected and 76 were removed using SPT and 72 with CSP. The median polyp size was 4.0mm, 89 (60%) were located in the left colon and 125 (84.5%) were sessile. 132 polyps (89.1%) were retrieved for histology and 13 (10%) had features consistent with advanced pathology, of which 12 (92%) were tubulovillous and one (8%) was a sessile serrated lesion. No lesion harbored high grade dysplasia or invasive carcinoma.

Table 14 Patient details and polyp characteristics

	SPT (n=56)	CSP (n=56)	p- value
Male	38 67.9%	38 67.9%	0.78
Age (years)*	63.5 ± 12.5	64 ± 10.4	0.83
Indication			
Surveillance	27	22	
Change in bowel pattern	13	11	
Rectal bleeding	6	12	
Other	10	11	
Number of small polyps	76/51.4%	72/48.6%	
Median polyp size (range)	4.0mm (3-7mm)	4.0mm (3-7mm)	0.94
Location			
Right colon (proximal to splenic flexure)	28	31	
Left Colon	48	41	
Paris			
1s	66 (86.8%)	67 (93.1%)	0.21
2a/2b	10 (13.2%)	5 (6.9%)	
Histology	68/76	64/72	
Tubular Adenoma	42 (61.8%)	46 (71.9%)	
Tubulovillous Adenoma	8 (11.8%)	4 (6.3%)	
Hyperplastic	17 (25%)	14 (21.9%)	
Serrated	1(1.5%)	0	

***** Results are expressed as mean ± standard deviation.

For the accurate attribution of completeness of excision, polyps judged as uncertain were excluded from the analysis. Endoscopic completeness of excision was higher with SPT (98.6% [95%CI, 92.7-100%]) compared with CSP (92.6% [95%CI, 83.7-97.6%]), but this was not statistically significant (p = 0.08). There was also a numerical trend towards a higher complete histological excision rate with SPT, but again this difference did not reach statistical significance (76.3% [95%CI, 63.4-86.3%]) vs. (63.8% [95%CI, 50.1-76.0%]), p = 0.14). There was no significant difference in the polyp fly away (11.8% vs. 11.1%, p = 0.89) or retrieval rates (89.5% vs. 88.9%, p = 0.91) between the SPT and CSP. No immediate or delayed postpolypectomy bleeding requiring endoscopic hemostasis or other significant complications associated with the techniques occurred in either group. The overall effectiveness of the both polypectomy techniques is shown in Table 15.

Table 15 The overall efficacy and safety of the two techniques for all polypectomies

	SPT	95%CI	CSP	95%CI	*P*- value
Endoscopic excision	n=76		n=72		
Complete	73 (96.1%)	88.9-99.2	63 (87.5%)	77.6-94.1	0.06*
Incomplete	1 (1.3%)	0.03-7.2	5 (6.9%)	2.3-15.5	
Uncertain	2 (2.6%)	0.3-9.2	4 (5.6%)	1.5-13.6	
Complete omitting 'Uncertain' findings	73 (98.6%)	92.7-100	63 (92.6%)	83.7-97.6	0.08
Histological excision					
Complete	45 (59.2%)	47.3-70.4	37 (51.4%)	39.3-63.4	0.34*
Incomplete	14 (18.4%)	10.5-29.0	21 (29.2%)	19.1-41.1	
Uncertain	17 (22.4%)	13.6-33.3	14 (19.4%)	11.1-30.5	
Complete omitting "Uncertain" findings	45 (76.3%)	63.4-86.3	37 (63.8%)	50.1-76.0	0.14
Polyp fly away	9 (11.8%)	5.6-21.3	8 (11.1%)	4.9-20.7	0.89
Retrieval rate	68 (89.5%)	80.3-95.3	64 (88.9%)	79.3-95.1	0.91
Excluded polyps (behind folds)	0		0		
Methods used to prevent bleeding	None		None		
Complications					
Early bleeding	0		0		
Late bleeding	0		0		
Perforation	0		0		

* Comparison between completion rates for the two techniques with the "Uncertain" results included in the total polypectomies

5.1.4 Discussion

It has been suggested that the incomplete resection of colorectal polyps may be responsible for up to one third of all interval colorectal cancers (60, 61, 98). Although this probably relates to larger advanced neoplastic polyps, advanced neoplasia is found in 9-10% of sub-centimetre polyps (168, 189). It is therefore important that such polyps are removed safely and completely.

Several techniques are available for the removal of diminutive and small colorectal polyps. The cold biopsy technique is often used for the removal of diminutive polyps, but incomplete resection rates of up to 61% have been reported with standard biopsy forceps (103) and 18% with jumbo forceps (106). The hot biopsy technique is sometimes used in the hope of ablating residual tissue, but incomplete removal has been reported in 17% (186) and the technique is not widely recommended due to the risk of complications and poor quality of tissue obtained (117, 190).

Alternatively, many endoscopists employ snare techniques with or without diathermy. Hot snare technique achieves higher rates (92%) of completeness of resection (119), but is associated with a small risk of delayed bleeding and perforation (120, 121).

Cold snare polypectomy is increasingly recommended for the removal of 3-7mm flat and non-bulky sessile polyps (110, 118, 172) and avoids the risk of diathermy-associated complications. Several cohort studies have shown no excess of post procedural bleeding (120, 121, 127, 168). The technique aims to remove 1-3mm rim of normal tissue around the polyp to reduce the risk of recurrence, but incomplete resection rates of up to 21% have been reported (105, 115, 119, 126). Since this may relate to inaccurate identification of the polyp margin or imprecise placement of the snare, Pattullo et al (112) describe a suction pseudopolyp technique, which more

readily enables the endoscopist to resect the lesion and a rim of surrounding normal tissue. The technique is simple, quick and easy to learn and less costly than saline injection techniques.

The present study supports the safety of SPT, but was not powered to detect differences in complications. The retrieval rates in our study are similar to other series of cold snare polypectomy (127, 188), but are never likely to be 100% since small polyps may be lost.

Completeness of histological excision with SPT was much higher in the present study than in that reported by Patullo (59.2% vs 30%) (112), but is likely to reflect differences in the study design. Confirming completeness of histological excision can be challenging, as small polyps are more likely to be damaged and fragment as they pass through the suction channel. Furthermore, the pseudosuction technique may deform the polyp making analysis more difficult. Variations in the mounting process may also make it difficult for the pathologist to assess the polyp margins with certainty. It has therefore been suggested completeness of resection is best assessed endoscopically at the time of polypectomy (60, 191), but this too can be unreliable (100).

The present study has several strengths. It utilised a randomised controlled design with standardised chromoendoscopy technique. Konishi et al report that high resolution chromoendoscopy is just as effective as magnification chromoendoscopy for assessing residual tissue after polypectomy (143). We also assessed multiple operators to account for the possible variation of technical skills in performing polypectomy.

The study has a number of limitations. Firstly, we did not routinely biopsy the base and margin of all the polypectomy sites, which has been advocated by some (100, 101). EMR of the polypectomy site has also been employed as a means of assessing completeness of excision and would be considered gold standard, but may lead to an increased risk of complications. Secondly, we based our power calculation on the published difference in completeness of resection between the two techniques (100 % versus 86%) (112, 115). Based on these figures a rate for endoscopic completeness of resection that is 14% higher than that of cold snare polypectomy is possible and this is clearly clinically relevant. In the present study we fell just short of a 100% complete endoscopic resection with SPT (95%CI, 92.7-100%), and were unable to demonstrate a significant benefit over standard CSP (95%CI, 83.7-97.6%) because of our much better than expected performance. To power a study for a 6% difference in efficacy (the difference in the present study) would require 200 patients per group. A study of this size will take a prolonged period to complete and we believe the present study demonstrates the superiority of SPT over the historically established efficacy of cold snare. Thirdly, several polyps were sometimes detected in the same patient introducing a lack of statistical independence. Finally, since this was an open study, unintended researcher bias may have influenced the results.

In conclusion, both techniques are safe and highly effective for the removal of 3-7mm polyps. This is important, especially as more and more, healthy, asymptomatic individuals are undergoing endoscopy for colorectal cancer screening.

Chapter 6: Conclusions and Future work

The vast majority of polyps encountered during routine colonoscopy are diminutive or small (45, 168), and removal of these has been shown to reduce the incidence and mortality of CRC (35, 36). The aim of thesis was to look at simple interventions that could improve the detection and removal of sub-centimetre polyps.

The Cochrane update presented in chapter 2, reconfirmed that chromoendoscopy significantly improved the detection of neoplastic and non-neoplastic polyps. However, this improvement was limited to small polyps, the significance of which is debated as few as 1% will progress to cancer (192). There was no apparent increase in the detection of larger or advanced adenomas, which would have been a significant finding considering these lesions represent a greater risk of malignancy (50, 171, 193). Another Cochrane review comparing NBI with conventional colonoscopy showed no improvement in the ADR (194). Randomised studies comparing other newer techniques are needed to investigate if they are any better than chromo-endoscopy. The evidence for other image-enhanced technologies is lacking. Further research looking at the detection of advanced adenomas, interval cancer rates and the threshold at which the magnitude of protection begins to plateau is needed. This may also identify colonoscopists who are regarded as 'super detectors' and other elements of best practice that could be adopted i.e. dynamic position change, CWT, bowel preparation quality and timing of colonoscopy.

In chapter 3, the multi-centre observational study assessed the effectiveness of polypectomy according to the technique used, polyp characteristics and complication rates of sub-centimetre polyps. Although, the results support the findings from the

existing literature that polypectomy practice is highly variable (107, 176), the reasons for this is not entirely clear. Polypectomy practice may be influenced by several factors, some of which may include insufficient time on the list to perform polypectomy, errors in judgment in choosing the appropriate technique due to operator fatigue, lack of experience and adherence to and awareness of professional guidelines. Whilst there is some guidance informing polypectomy practice, further research is needed in this area to improve polypectomy outcomes and standardise practice across the UK. A study to look at the variation between non-screening endoscopists would allow useful comparisons to be made with this study. In addition a survey to look at training opportunities, courses attended and average number of procedures performed may give an indication why such variation in practice exists.

It was reassuring to see that complications were rare despite endoscopists' preference for the HS technique. Nevertheless, bleeding requiring transfusion and perforation should never really occur when removing such small polyps. This is especially important in a screening programme that consists of healthy, asymptomatic patients where the procedure is performed by colonoscopists who have undergone a rigorous assessment and accreditation process. There is some evidence to suggest that colonoscopy performance by endoscopists who have a low procedure volume is associated with increased risk of perforation and bleeding (195) and would be an area worthy of study.

Another important finding from this study was that histological assessment for completeness of excision was limited with wide centre variation. Bowel cancer screening histopathologists undergo no formal accreditation process and quality

assurance is achieved via external quality assessment schemes and annual training sessions (148). Given the limitations of histological assessment, the implementation of a formal accreditation process for screening pathologists, double reporting and development of minimum diagnostic standards may improve the quality of pathological evaluation.

This study also highlighted that cold snare polypectomy is being performed sub-optimally despite increasing data supporting the use of this technique (21-23). Improving education and training in the technical skills needed to perform cold snare polypectomy is clearly required. A recent study suggested that hot snare polypectomy achieved higher rates of complete polypectomy without additional risk (119). This is in contrast to other studies which report an increased risk of complications (121) with little difference between polyp removal and retrieval rates (120, 121, 127). Therefore, at present HS cannot be recommended as first-line therapy. Alternatively, EMR is safe, effective and a viable option, but can be time consuming and costly.

The effectiveness of interval CRC prevention relies on the completeness of polypectomy and appropriate surveillance thereafter. Therefore, the correct polypectomy technique and device is essential to reduce this risk, but has been poorly researched. The cold snare technique has been advocated for the removal of diminutive and small polyps (105, 115) and the study in chapter 4 directly compared two different snares. It showed that snare type does influence polypectomy outcomes, but the study lacked the strength of a RCT. In chapter 5, two different techniques were compared using the superior snare. Although, the safety and utility of both CSP

and SPT were confirmed, there was no significant difference between the resection techniques.

In both of these studies routine biopsies were not taken from the margin and base of the polypectomy defect. Although, this would have been a much better gold standard, it is prone to sampling errors and may over estimate completeness of resection. Instead, a study where EMR of the polypectomy site after endoscopic assessment would provide the histological proof needed to confirm completeness of resection. This may increase the risk of complications but could be mitigated by applying clips prophylactically to close the mucosal defect. Both studies include small cohorts and only represent a tiny fraction of the total number polypectomies performed in the UK. Given the findings, there is a need to replicate these studies addressing the limitations.

Visual inspection was the primary endpoint in these studies, but despite a robust assessment process it was not as reliable as we thought. If a sufficiently accurate real time optical method of assessment can be achieved, this may result in a paradigm shift in assessing completeness of resection. Furthermore, it would allow real time histological assessment of diminutive polyps and a strong case for the 'resect and discard' strategy, which is based on the assumption that polyps are completely resected. This would significantly reduce costs without compromising efficacy.

Future challenges therefore remain for establishing the ideal polypectomy technique, device, and imaging technologies. From this body of work, it is apparent that the simple interventions investigated are safe, quick and easy to learn and can be performed by all colonoscopists to improve the detection and removal of polyps.

6.0 Summary

1. Pan-chromoendoscopy increases the detection of all polyps (neoplastic & non-neoplastic), but the detection of non-neoplastic (hyperplastic) polyps was also increased. There was no apparent increase in the detection of larger lesions or advanced pathology.

2. There is a lack of standardised polypectomy protocols guiding practice for sub-centimetre polyps.

3. The removal of sub-centimetre polyps within the BCSP is safe, despite wide variations in practice.

4. The use of cold resection techniques and EMR has increased over time and use of HBF has decreased.

5. Histological assessment of completeness of resection is limited with considerable variation between screening centres.

6. Histologically confirmed complete excision was more common after EMR (23.4%) for flat and sessile polyps compared to other techniques in the BCSP.

7. An improvement in training and attention to the technical aspects of cold snare polypectomy is required to ensure completeness of resection.

8. Cold polypectomy with a thin-wired Exacto snare is more effective than a thick-wired Olympus snare.

9. Both the suction pseudopolyp and standard cold snare polypectomy techniques appeared safe and highly effective for the removal of 3-7mm flat and sessile colorectal polyps.

6.1 Publications arising from this thesis

Din S, Ball AJ, Taylor E, Rutter M, Riley SA, Johal S. Polypectomy practices of sub-centimeter polyps in the English Bowel Cancer Screening Programme. Surg Endosc. 2015 Nov; 29(11) 3224-30

Din S, Ball AJ, Riley SA, Kitsanta P, Johal S. Cold snare polypectomy: Does snare type influence outcomes? Dig Endosc. 2015; Jul 27(5) 603-608

Din S, Ball AJ, Riley SA, Kitsanta P, Johal S. A Randomised comparison of cold snare polypectomy versus a suction pseudopolyp technique. Endoscopy 2015; Nov 47 (11) 1005-1010

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