Implementation of Endoscopic Submucosal Dissection in a Western Institution

Rønnow, Carl-Fredrik

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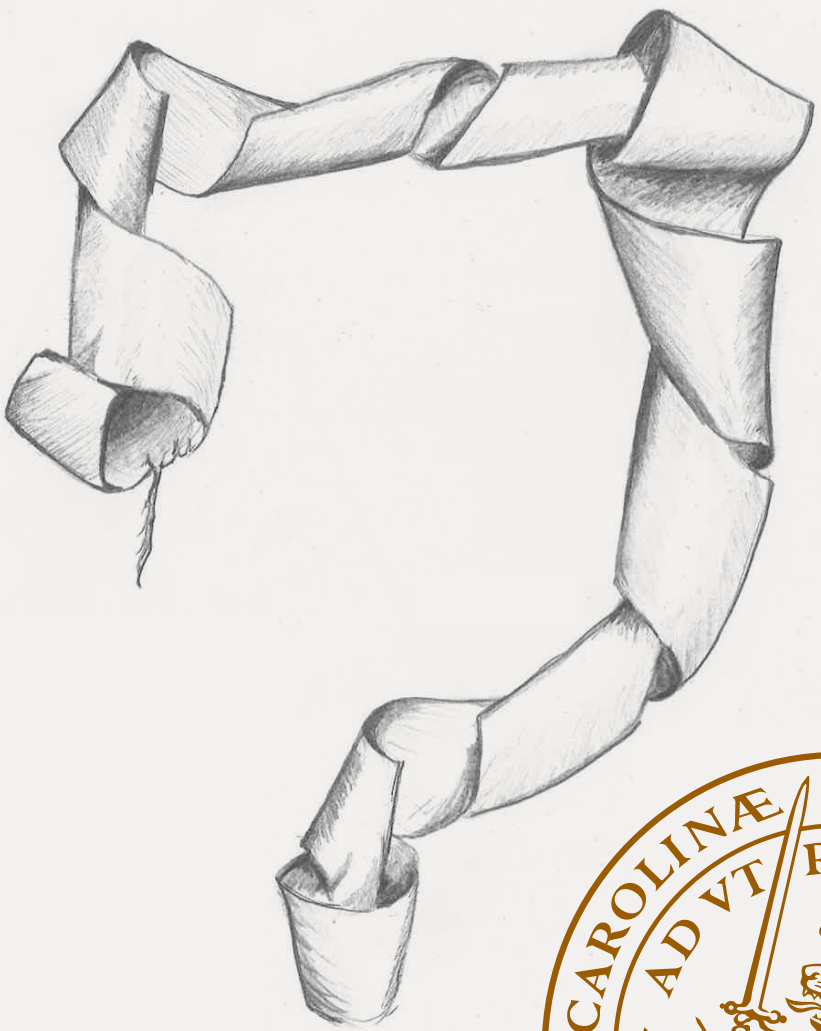
CARL-FREDRIK RÖNNOW
FACULTY OF MEDICINE | LUND UNIVERSITY



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LUND
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DOCTORAL DISSERTATION

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Faculty opponent
Naohisa Yahagi, M.D., Ph.D.

Professor of Medicine

Division of Research and Development for Minimally Invasive Treatment, Cancer Center, Keio University School of Medicine, Tokyo, Japan

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Title: Implementation of Endoscopic Submucosal dissection in a Western Institution
Subtitle: Work up, learning curve and management of advanced colorectal lesions

Abstract

Endoscopic resection of colorectal polyps reduce morbidity and mortality from colorectal cancer (CRC). Endoscopic submucosal dissection (ESD) is a highly efficient and established method for treating advanced colorectal lesions in Asia, but experience of ESD in Western countries is limited. Large non-pedunculated colorectal lesions are prone to malignant transformation and it is therefore important to resect these lesions in one piece (en bloc), which is obtainable with ESD but not with traditional endoscopic resection techniques.

This thesis focused on the implementation of ESD at the endoscopy center, Skåne University Hospital, Malmö. It was found that the learning curve of colorectal ESD is long and steep but excellent results in terms of efficacy and safety, can be reached. Thus, the en bloc rate increased from 60% to 98% during a five year long learning period comprising 301 lesions. However, lesions located in the proximal colon are challenging and all patients requiring emergency surgery (2%) had proximal colonic lesions. The role of ESD in resecting malignant colorectal lesions was also studied. Curative resection was obtained in 38% of malignant ESD resections according to current guidelines, but ESD served as final treatment in 76% of the patients. Thus this thesis provide evidence that colorectal ESD is highly feasible in the West and is an eligible method for advanced polyps and early CRC, limiting surgery to cases with a high risk of lymph node metastases (LNM).

Forceps biopsies are routinely obtained in the work up of colorectal lesions referred for endoscopic resection in the West. However, the reliability of biopsies in large colorectal lesions is unknown. In this thesis, we studied the accuracy of biopsies in reflecting the histology of large colorectal lesions and found biopsies to be concordant to resected specimen in 61%. Hence, biopsies underestimated and overestimated histologic grade of colorectal lesions in 29% and 9%, respectively. These findings question the role of forceps biopsies in the routine work up of lesions amenable to endoscopic resection.

Endoscopic resection of early CRC cancer is feasible, as shown in this thesis, although the risk of LNM and recurrence cannot be ignored. The risk of LNM, currently assessed mainly by depth of submucosal invasion, is decisive whether subsequent surgery or surveillance is recommended. In this thesis, we investigated risk factors of LNM in T1 CRC, and found that depth of submucosal invasion is not an independent risk factor of LNM. Lymphovascular invasion was the dominating risk factor with 40% risk of LNM when present. Mucinous subtype, perineural invasion and low age were also independent risk factors. Our findings are somewhat in contrast to current guidelines and provide new evidence for which risk factors to assess when managing locally resected T1 CRC.

Key words Colorectal polyps, Colorectal cancer, Polypectomy, Endoscopic submucosal dissection (ESD)

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Till Skatt och Alice

“If you understand everything, you must be misinformed”
Japanese proverb

Table of Contents

Original Papers

This thesis is based on the following original papers, referred to in the text by their Roman numerals:

I. Rönnow CF, Uedo N, Toth E, Thorlacius H. Endoscopic submucosal dissection of 301 large colorectal neoplasias: outcome and learning curve from a specialized center in Europe. Endoscopy International Open. 2018;6(11):E1340-E1348.

II. Rönnow CF, Elebro J, Toth E, Thorlacius H. Endoscopic submucosal dissection of malignant non-pedunculated colorectal lesions. Endoscopy International Open. 2018;6(8):E961-E968.

III. Rönnow CF, Uedo N, Stenfors I, Toth E, Thorlacius H. Forceps biopsies are not reliable in the work-up of large colorectal lesions referred for endoscopic resection: should they be abandoned? Biopsy reliability in colorectal polyps. Diseases of the Colon and Rectum. 2019;62(9):1063-1070.

IV. Rönnow CF, Arthursson V, Toth E, Krarup PM, Syk I, Thorlacius H. Lymphovascular infiltration, not depth of invasion, is the critical risk factor of metastases in early colorectal cancer. (Manuscript)

Abbreviations

CLE	Confocal laser endomicroscopy
CRC	Colorectal cancer
CT	Computer tomography
EFTR	Endoscopic full thickness resection
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
ESGE	European Society of Gastrointestinal Endoscopy
FAP	Familial adenomatous polyposis coli
HGD	High grade dysplasia
LGD	Low grade dysplasia
LNM	Lymph node metastases
LVI	Lymphovascular invasion
MRI	Magnetic resonance image
UEMR	Underwater endoscopic mucosal resection

Introduction

Colorectal cancer (CRC) represents a significant disease burden worldwide, being the third most common cancer diagnosed in Sweden and the second cause of cancer-related death worldwide[1, 2]. Encouragingly, CRC can be prevented by endoscopic removal of colorectal polyps, being known precursors[3, 4] . In fact, convincing data suggests that even selected cases of early cancer can be removed endoscopically which is eligible because of lower morbidity, mortality and better function in comparison to surgery[4-6]. However, large non-pedunculated colorectal lesions, prone to malignant transformation, are difficult to remove in one piece (en bloc) endoscopically. Traditional snare-based polypectomy techniques, such as endoscopic mucosal resection (EMR) often yield multiple tissue fragments, i.e. piece meal resection when lesion size exceeds 2cm, which is disadvantageous[7-9]. Piecemeal resection not only generate insecure pathology assessments but is also related to an increased rate of recurrence as compared to en bloc resection[7-9]. Hence, if a lesion harbouring cancer is resected piecemeal, the insecure radicality and risk of recurrence often result in subsequent surgery.

Endoscopic submucosal dissection (ESD) was developed as an alternative to surgery, allowing en bloc resection of non-pedunculated lesions in the gastrointestinal tract, in theory without any size-limitation. The technique was developed in Japan in the 1990s and ESD is now implemented as standard treatment at many expert centres in Asia[10-13]. The disadvantages of colorectal ESD lies in its high degree of technical difficulty and the risk of complications, such as perforation and bleeding. However, convincing evidence from large series, show that colorectal ESD can be performed with high en bloc and R0 resection rates, concomitantly with a low and acceptable risk of complications in Asia[10-13]. However, dissemination of ESD to the West has been slow and previously mentioned reports solely originate from Asian expert centres. Nevertheless, an increasing number of reports on colorectal ESD, originating from Western centres, have been published in recent years, indicating that the dissemination of ESD is ongoing, although currently restricted to a handful expert centres[14-18].

Moreover, it can be argued that en bloc resection is only a necessity when the lesion contains cancer and piecemeal-EMR, associated with less complications, is thus preferred for low risk lesions. The pre-resection diagnosis of large colorectal lesions is however known to be difficult in terms of accurately distinguishing lesions where

piecemeal resection is acceptable from lesions were en bloc is a necessity. Also, the role and reliability of forceps biopsies in the work up of advanced colorectal lesions, often obtained in the West, is elusive and poorly investigated.

Furthermore, the implementation of screening programs will increase the number of advanced colorectal lesions and CRCs detected at an early stage. The optimal treatment and management of patients with endoscopically resected T1 CRCs in regards of selecting the right patients for surgery secondary to a de facto risk of lymph node metastases (LNM) is crucial.

The aim of this thesis was to evaluate the implementation of colorectal ESD at a specialist centre in Sweden and investigate the role of biopsies in the work up of large colorectal lesions as well as the risk factors related to lymph node metastases in T1 CRC.

Background

Colorectal cancer

Incidence

Colorectal cancer stands for a significant morbidity and mortality worldwide with almost 2 million new cases diagnosed and over 800 000 cancer related deaths in 2018[1]. In Sweden, CRC is the third most frequent cancer and the fourth most common cancer related cause of death[2]. The median age at diagnosis in developed countries is approximately 70 years, and CRC is rare at ages lower than 50 years[1]. However, an alarming study from USA reported that the incidence of CRC is on the rise in adolescent and young adults, and that the aetiology causing this increase is unknown[19].

The highest incidence of CRC is found in countries in Europe, North America and Oceania, whereas the incidence is at its lowest in some countries in south and central Asia and Africa (Fig 1)[1].

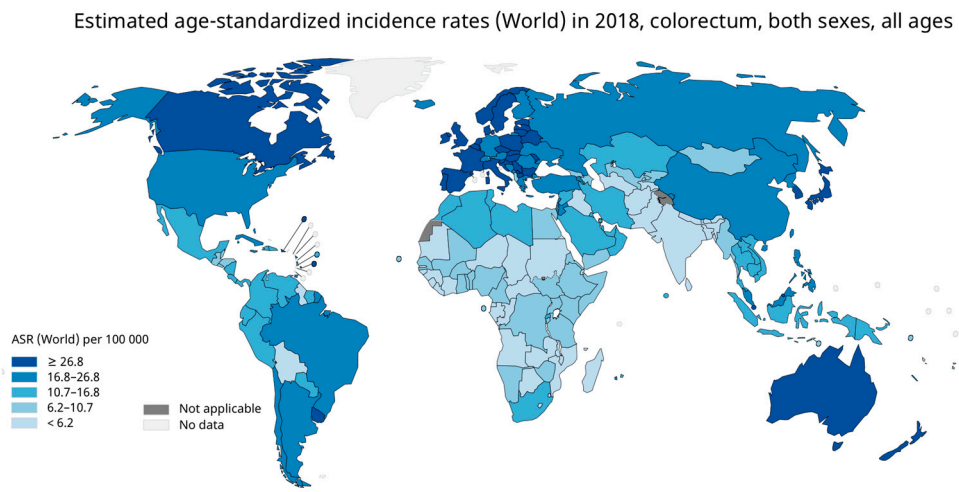


Figure 1. Incidence of CRC in the world 2018.

Aetiology

CRC develops from epithelial cells in the bowel mucosa, in general evolving from precursor lesions i.e. polyps. The most common precursor lesion in CRC is dysplastic adenoma, taking more than 10 years to develop into cancer[20-22]. The adenoma-carcinoma sequence, constituting a break-thorough in CRC research when presented by Vogelstein in 1988, provide an explanation to the genetic series of events culminating in the transformation from normal mucosa to carcinoma[23] (Fig 2). Mutation of the APC gene is the first step in the sequence, occurring in the majority of colorectal adenomas[24, 25]. The further progress to carcinoma is facilitated by activating mutations of the K-RAS oncogene and inactivation of the TP53 tumour suppressor gene, in general promoted by chromosomal instability[25, 26]. The adenoma-carcinoma sequence provides a base to investigate the genesis of cancer, as well as prerequisite for polypectomy, enabling prevention of CRC through endoscopic removal of precursor lesions[27]. However, the majority of adenomas do not progress into malignancy, given that approximately 40% of the Western population develop adenomas and only 3% will suffer from CRC[28-30].

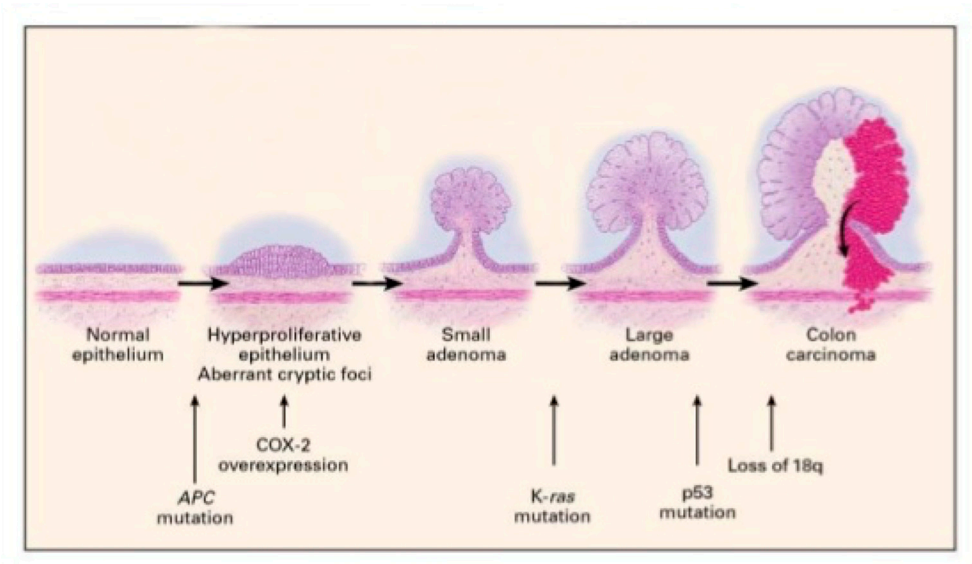


Figure 2. The adenoma-carcinoma sequence.

Notably, more than 20% of sporadic cancers do not develop through the adenoma-carcinoma sequence but rather through fundamentally different molecular pathways. The sessile serrated pathway is the most studied of these, originating from sessile serrated polyps, previously thought to have no malignant potential[31-33]. These lesions are often situated in the right colon and can easily be missed during

colonoscopy owing their flat and inconspicuous nature[34]. The sessile serrated pathway is characterised by the CpG island methylator phenotype and activated by mutations in the BRAF oncogene, often leading to a high-level of microsatellite instability phenotype (MSI-H)[35] (Fig. 3).

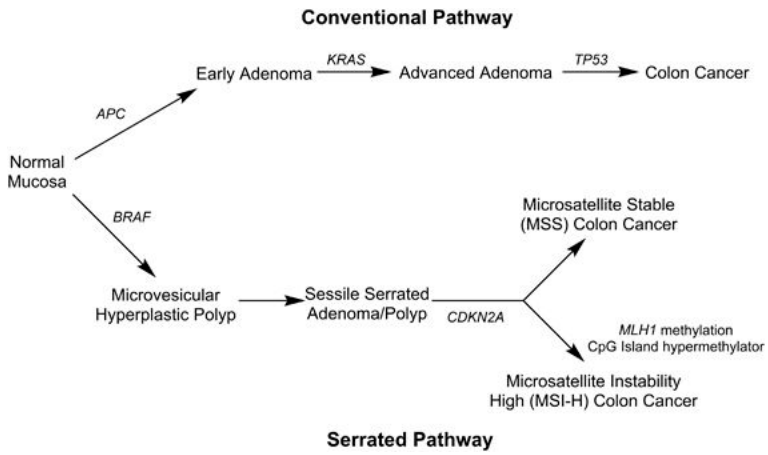


Figure 3. The serrated pathway to colon cancer.

Hereditary CRC stands for approximately 3-5% of all cases and the two most common forms are hereditary non-polyposis colon cancer (Lynch syndrome) and familial adenomatous polyposis coli (FAP)[36, 37]. In FAP, the APC-gene mutation is inherited and the cancers follow the classic adenoma-carcinoma sequence whereas in Lynch syndrome mutation and inactivation of DNA mismatch repair proteins follow the serrated pathway[36, 38, 39]. Both Lynch syndrome and FAP are autosomal dominant disorders and both are associated with a high risk of developing CRC. Notably, genetic factors determining the risk of CRC are not completely understood and a previous large study on twins has shown that 35% of CRC risk might be related to heritage[40].

Risk factors

Most of the risk factors of CRC are related to a so called Western lifestyle, including; smoking[41], high consumption of red and processed meat[42], excessive alcohol consumption[43], obesity[44] and diabetes[45]. Moreover, male gender and high age are risk factors as well as family history of CRC and inflammatory bowel disease [46, 47]. The modifiable risk factors have a lower relative risk but are more

common and hence account for a greater disease burden at a population level. However, the relative risk for CRC is highest (>2) for people with first degree relatives and IBD[46, 47]. The risk factors co-occur and interact and persons with a family history of CRC are at greater risk of CRC when subjected to the modifiable risk factors[48].

Finally, the role of various bacterial strains in the microbiota, such as Fusobacterium spp. and Helicobacter pylori are not entirely clear, but might also play a role in the pathogenesis of CRC[49-51].

Prognosis and staging

CRC is classified according to the TNM system, comprising the local tumour growth (T), lymph node involvement (N) and presence of distant metastases (M). The TNM system constitutes the basis of different staging manuals, the American joint committee on cancer (AJCC) staging manual, being the most commonly used, providing requisite for therapeutic decisions and prognosis[52].

Overall, the prognosis of patients suffering from CRC has improved over the past decades, owing better surgical techniques and improved neo-adjuvant and adjuvant treatment. In high income countries, such as USA, Canada, Australia and many European nations, the 5-year relative survival rate has reached almost 65%, whereas it has remained at just under 50% in low-income countries[53-55]. However, there are substantial differences in survival related to stage at diagnosis, constituting a key prognostic factor. Thus, the 5-year relative survival rate for patients in the USA was; 91% and 82% for Stage I and II (localised disease), respectively and decreased to 12% for Stage IV (distant metastases)[53].

Colorectal cancer treatment

Local excision

Early CRC (T1) can be treated with endoscopic resection or local excision in selected cases. Notably, the implementation of screening programs in combination with advances in minimal invasive techniques have increased the proportion of early CRCs amenable to local resection[56, 57]. However, it is vital to obtain R0 and en bloc resection of malignant lesions, to assure reliable histopathologic assessment and low risk of recurrence. ESD is therefore an eligible alternative and recommended in European guidelines for malignant non-pedunculated lesions, allowing en bloc resection without size limitation[58]. Furthermore, local excision of T1 rectal cancer by means of transanal endoscopic microsurgery (TEM) is another option and endoscopic full thickness resection (EFTR) has also been proposed as an alternative

for malignant colorectal lesions[59-61]. The different resection methods are discussed and compared in detail in the polypectomy section.

Regardless of resection method, flat and sessile lesions harbouring submucosal invasive cancer are reported to have a 6-17% risk of concomitant LNM[62-65]. Thus, patients with locally excised T1 CRC present a challenge in terms of settling with local/endoscopic treatment or recommending additional surgery. Numerous studies have investigated risk factors related to LNM in attempt to identify a low risk group where endoscopic resection can be regarded as final treatment. Early studies identified depth of submucosal invasion as a paramount risk factor, reporting risks of LNM to be 0-3% for Sm1, 8-10% for Sm2 and 10-25% for Sm3[64, 66, 67]. Subsequent studies have identified additional histopathological risk factors and current European guidelines recommend surgery if one or more of the following are present; deep submucosal invasion (>Sm1), lymphovascular invasion (LVI), tumour budding and poor differentiation (high grade cancer)[68]. However, these recommendations are based on a meta-analysis including mainly small retrospective cohort studies and the literature is highly inconsistent on virtually all potential risk factors for LNM, including depth of invasion[65, 69, 70]. It is crucial to accurately predict the risk of LNM in order to balance the benefits of local excision with the concomitant risk of LNM and reliable evidence is thus desirable.

Surgery

Surgery constitutes the base of treatment for CRC although the multidisciplinary approach has widened the therapeutic spectra to include radiation therapy and chemotherapy. Surgery aims at removing the bowel segment harboring the tumour and the corresponding mesentery, so called complete mesocolic excision[71, 72]. Thus, lymph nodes in the mesentery are analyzed in search for metastases, being an important prognostic factor and significant when considering adjuvant therapy[53, 54]. The blood supply and location of the tumour dictates the extent of resection, following the concept of central vascular ligation[71].

Anastomosis of the remaining bowel segments after colon cancer surgery is often attainable, although 8% of patients operated for colonic cancer in Sweden receive a permanent stoma[2]. However, rectal cancer surgery is more challenging, mainly due to the anatomic restrictions of the pelvis, and rectal anastomosis are associated with impaired function and more prone to complications, such as leakage [73-75]. Rectal cancer surgery therefore often results in a temporary or permanent stoma. In fact, 52% of patients operated for rectal cancer receive a permanent stoma and 43% receive a diverging temporary stoma, according to recent Swedish data[2]. Moreover, CRC surgery is associated mortality as well as morbidity, comprising incisional hernia, ileus, abscess formation, sexual dysfunction and faecal incontinence. Colon cancer surgery is associated with 23% morbidity and 2.4% mortality (90 days following surgery) whereas rectal cancer surgery is associated with 36% morbidity

and 1.2% mortality (90-days following surgery), in Sweden[2]. Approximately half of the complications are severe (Clavien-Dindo III-IV), leading to re-operations in 8% of the total number of CRC operations[2]. Notably, the data on CRC surgery in Sweden stated in this chapter, refers to elective surgery. The mortality, morbidity and risks of temporary or permanent stoma are higher when emergency surgery is performed, which is the case in 20% of all colon cancers[2]. Moreover, the evolvement of minimal invasive techniques during the past decades has widened the surgical arsenal to include laparoscopic and robotic assisted resection in addition to open surgery. The advantages of minimal invasive techniques comprise shorter hospital stay and earlier mobilization in comparison to open surgery, with equal morbidity, mortality and oncological outcomes[76, 77]. However, some previous studies have shown a decrease in the postoperative morbidity and mortality for laparoscopic colon cancer surgery in the elderly, in comparison to open surgery[78, 79].

Colorectal cancer screening

Given that most CRCs develop from adenomas over a relative long period of time (10-15 years) there is an interval were polypectomy can hinder the development to cancer[21, 22]. In addition, the prognosis is highly dependent on stage at diagnosis, making it of paramount importance to detect CRC in an early stage to minimize the morbidity and mortality[53]. However, adenomas and early CRCs rarely present any symptoms and screening is therefore highly desirable and recommended by international organizations and national authorities[80, 81]. It is well established from randomized controlled trials that screening programs reduce the mortality from CRC, there are however multiple screening options with individual advantages and disadvantages[82-90]. In general, screening can be divided in either stool-based test or imaging tests, the latter including endoscopy and computed tomography (CT). Non-endoscopic screening modalities are based on selecting cases with a high risk of CRC for colonoscopy, being the gold standard in diagnosing CRC. Furthermore, screening programs can either be organized, including a defined part of the population and controlled by an outside body or opportunistic, hence offered on request or initiated by a physician without any outside control. Screening is implemented in the majority of developed countries worldwide, but the means of screening differ. Countries with state financed health care systems tends to have organized screening programs whilst countries with private funded health care systems often have opportunistic screening. Notably, Sweden stands out as one of few countries in the European Union lacking a screening program. Implementation has been delayed due to a polarized debate on the topic and further challenges include insufficient access to colonoscopy resources and difficulties in reassuring quality control[91].

Stool based tests

The first screening method to be proven significant in reducing mortality from CRC is the Guaiac-based faecal occult blood test (gFOBT)[82, 84-87]. The test is based on peroxidase activity indicating the presence of haemoglobin in the stool. Furthermore, gFOBT is cheap, has a high specificity for detecting blood in the stool, but is not specific for human haemoglobin. There is thus a risk of false positivity after intake of red meat. Also, recommendations vary from testing with gFOBT once to twice a year, requiring three samples per test, possibly lowering the compliance[92]. Another frequently used and investigated screening method is the faecal immunochemical test (FIT), based on antibodies and hence specific for human haemoglobin. FIT has been shown to have a higher sensitivity (73-83%) and equal specificity (91-96%) for detection of CRC in comparison to gFOBT[28, 93-95]. Another advantage of FIT over gFOBT is its higher sensitivity in detecting advanced adenomas[96-99]. Furthermore, FIT is recommended as an annual test, resulting in a high compliance[100]. However, FIT is available as both a quantitative and a qualitative test and the challenge lies in setting the quantitative cut-off for a positive test at the right level, affecting the sensitivity. Furthermore, faecal DNA test has also been proposed as a stool-based screening modality. Currently there is only one test approved for use, which is Cologuard, combining DNA-markers such as KRAS-mutation with FIT. Cologuard was shown, in a large study investigating 9989 individuals, to have a higher sensitivity for CRC (92%) and advanced adenomas (42%) in comparison to FIT[93]. However, the specificity was lower for Cologuard (87-90%) in comparison to FIT (91-96%). Although Cologuard is recommended to be used every third year, it is still an expensive test in comparison to the other alternatives.

Imaged based screening

Computed tomographic (CT) colography is performed after bowel cleansing and utilizes contrast and air insufflation via a rectal catheter. The method has been proven equal to colonoscopy in detecting adenomas larger than 10 mm but has lower sensitivity (78-89%) and specificity (80-90%) for adenomas 6-10 mm[101, 102] (54,55). The advantage of CT colography in comparison to colonoscopy is primarily reduced patient discomfort. However, CT colography imply radiation, amounting to 5.2 mSv/investigation (2.6-14.7) and it is estimated that five out of 10 000 examinations cause radiation-induced cancers[103]. Another draw-back of CT colography as a screening modality, is incidental findings outside the colon, originating in 40-70% of the examinations, causing anxiety for the patient and the doctor and leading to additional investigations[94]. Finally, CT colography is, as of today, too expensive to merit as a screening modality and current indications comprise cases where complete colonoscopy is not possible.

Capsule colonoscopy is an intriguing technique, carried out by ingesting a camera capsule, able to visualize the mucosa of the gastrointestinal canal[104]. Capsule colonoscopy is eligible since it does not imply radiation or patient discomfort[105]. However, a complex laxative scheme must be followed and there is a risk, although minimal, of capsule retention[106]. Its potential role in screening is not yet clear although a recent study showed that capsule colonoscopy was superior to colonoscopy in detecting polyps >9 mm, in colorectal cancer screening individuals[107]. Currently, capsule colonoscopy is recommended for patients with incomplete colonoscopy and cases where colonoscopy is not possible[104].

Colonoscopy is the gold standard in investigating colon and rectum and has been shown to reduce CRC incidence by 50-77% and mortality by 31-90% when used as a screening modality[3, 108-111]. The advantages of screening colonoscopy are hence its superior sensitivity and specificity and the ability to remove precancerous lesions during the procedure. However, the compliance to colonoscopy in screening context is 10-27%, posing a major obstacle for implementation of colonoscopy as a primary screening method[112-115]. The low compliance is primarily related to patient discomfort and the extensive bowel preparations needed. Also, colonoscopy is related to complications and when used as a screening modality, perforations and major bleedings occur in four respectively eight cases per 10 000 procedures[94, 116]. Another drawback to screening colonoscopy is the high costs and lack of proficient colonoscopists. Also, the quality of colonoscopy is vital to maintain a high sensitivity and specificity, concomitantly minimizing the risk of complications. Regardless of whether colonoscopy is performed as primary screening or subsequent after a positive faecal blood test, it is crucial that implementation follows the quality assurance and guidelines set up by the council of the European Union[117].

Sigmoidoscopy has been proposed as a screening modality, given that two thirds of all CRCs can be reached during this procedure. Sigmoidoscopy is advantageous compared to colonoscopy since preparations are confined to clysma and full bowel preparation is thus not required. Furthermore, the procedure is more widely tolerated and associated with fewer complications as well as shorter procedural times, in comparison to colonoscopy. Previous studies have shown that screening sigmoidoscopy reduces CRC incidence by 18-23% and mortality by 26-31%[88-90, 118]. Hence, the reduction of CRC incidence and mortality is inferior to colonoscopy but sigmoidoscopy is advantageous because of lower costs and higher compliance. However, given that females more often have right sided colonic cancers, as compared to males, sigmoidoscopy is less effective in detecting cancers in the female population[119].

Endoscopy

Brief history

Endoscopy means to look inside, and its field of history starts in ancient Egypt and Greece where citations of procedures performed with speculums to inspect hollow organs of the body dates back to 2640 BC[120]. The evolvement of endoscopy was for centuries hindered by three major obstacles; creating or expanding entrances to the interior body, safely delivering enough light into the interior space and transmitting a clear and magnified image back to the eye. These obstacles were overcome by innovations and discoveries during the recent two centuries.

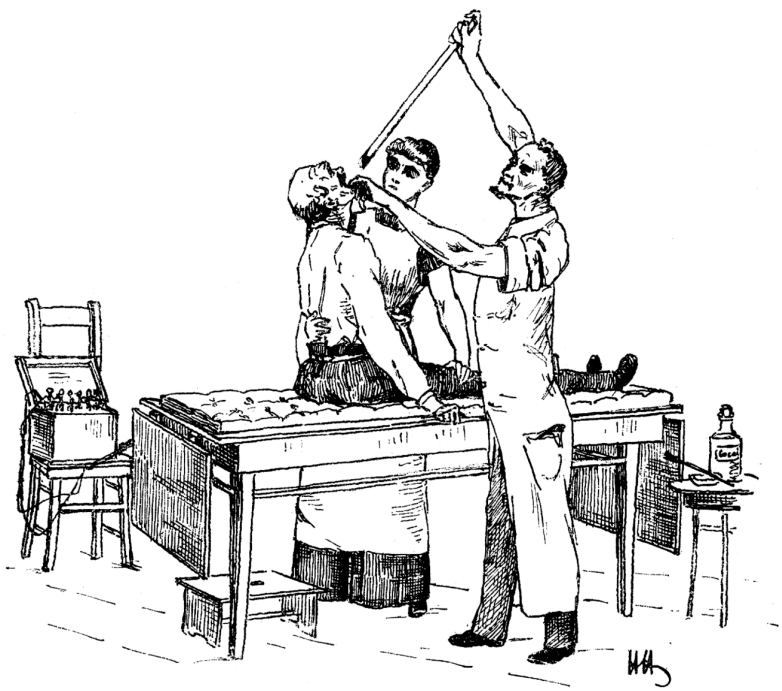


Figure 4. Illustration of a gastroscopy with the Kussmaul gastroscope, comprising a straight metal tube.

In the early 19th century, primitive metal tubes luminated with external light sources, such as wax candles, alcohol/turpentine candles were used. In 1806 Bozzini developed the ”lichtleiter” a device disapproved by the medical council of Vienna

and not used in patients until the French scientist Desormeaux redeveloped the device, naming it for the first time the "endoscope" in 1867[121, 122]. Further evolvement in the field of endoscopy comprise the first gastroscopy, performed by Kussmaul in 1868, intubating a sword-swallower with a 48cm long metallic tube (Fig4)[123]. However, the illumination was still a major obstacle for visualisation and was partly solved by Nitze, successfully attaching a miniaturized light bulb at the tip of an instrument in 1888[122].

The next major breakthrough in endoscopy was Hopkins invention in 1954 of glass fibre bundles transmitting high quality images even if bent, making the way for the flexible fiberscope developed by Hirschowitz in 1957[124]. The fiberscope revolutionised the field of endoscopy, since it was now possible to use external high intensity light sources "cold light", improving illumination substantially[120]. In parallel, Uri and Tasaka developed the "gastrocamera" allowing routine endoscopic examinations with photography[125]. The gastrocamera was used by two Japanese surgeons, Oshiba and Watanade to perform the first sigmoid intubation in 1965[126]. In an attempt to intubate the caecum, two Italian physicians, Provenzale and Reginas, described a method were the patient swallows a soft rubber hose, attached with a lead-weight making its way through the entire gastrointestinal tract during a period of 4-6 days and then used as a guidewire for retrograde intubation to the caecum[127]. This method luckily never reached clinical implementation. Instead, Hiromi Shinya, a Japanese resident in surgery and William Wolff, professor in surgery, at the Beth Israel Medical Center in New York, developed methods and devices culminating in the first modern colonoscopy in 1969[128]. Shinya discovered the manoeuvres necessary to intubate the colon, including in vivo observations of the "alpha loop" when performing colonoscopies on patients undergoing laparotomy. Shortly after performing the first complete colonoscopy with caecal intubation in 1969, Shinya developed the first polypectomy-snare, together with Olympus engineer Hiroshi Ichikawa[129]. Notably, colonoscopy was at the time controversial and found by many to be unnecessary and dangerous as compared to classical radiology[130]. This changed by the time of the first polypectomy in 1969, and the subsequent publication of 303 polypectomies performed and published by Shinya et al in New England Journal of Medicine in 1973[131]. The motivation to invent and perform endoscopic polypectomy can easily be understood given that colorectal polyps were either followed up with repeated radiology examinations if <1 cm or resected by open surgery if >1 cm.

The era of fiberscopes ended in the 1990s when the video-endoscope was introduced, derived from the TV-industry[122]. Now, the procedures were conducted by looking at a TV-screen also enabling picture enhancement and magnification. Numerous therapeutic techniques have been developed since, enabling diagnosis and treatment of multiple diseases throughout the gastrointestinal tract. The trend of innovation and creativity within the field of endoscopy is ongoing and capsule

endoscopy, allowing inspection of the entire gastrointestinal tract during one examination, with basically no patient discomfort, could be considered the latest breakthrough[104, 107, 132].

Colonoscopy

Colonoscopy is a frequently performed diagnostic and therapeutic procedure world-wide, in general performed to rule out or confirm cancer as well as to detect and remove colorectal lesions. Full bowel cleansing is required prior to the procedure by intake of laxatives, and the intubation to caecum and terminal ileum is made possible by insufflation of air, carbon dioxide or water. The tolerance to colonoscopy in terms of discomfort and pain is highly individual. Many patients can undergo the procedure without medication, whilst others require light sedation and a minority require anaesthesia.

Moreover, it is well proven that endoscopic removal of colorectal lesions reduces both the incidence and mortality of CRC, constituting the foundation for implementing CRC screening programs[3, 4]. However, failure to detect adenomas during colonoscopy decreases the diagnostic value of the procedure and increases the subsequent risk of cancer i.e. interval cancer. The adenoma detection rate (ADR) is a quality measure used to objectify the endoscopists individual performance, recommended to be used by specialist societies and health care bodies[133]. The proportion of screening colonoscopies yielding at least one histologically confirmed colorectal adenoma or adenocarcinoma constitute the endoscopists ADR. Current recommendations comprise ADRs of 20% or higher for female patients and 30% or higher for male patients[21, 134]. However, ADRs vary widely among endoscopists in both academic and community settings and a large study involving 136 gastroenterologists found ADRs in the range of 7-53%[135-139]. In fact, in the aforementioned study, ADR was inversely associated with the risks of interval cancer, including advanced-stage and fatal CRC[139]. It has been proven that meticulous inspection and longer withdrawal times are associated with a higher ADR, which is thus recommended[140-142]. Moreover, adequate bowel preparation is essential to ensure sufficient inspection of the colonic mucosa and to optimize the ADR[28, 143]. Previous studies report that every fourth colonoscopy is performed with inadequate bowel preparation, reducing detection of adenomas by 42-48%[144, 145].

Thus, colonoscopy is the gold standard in diagnosing and detecting adenomas as well as CRCs, but the quality and reliability of the examination is dependent on adequate bowel preparation and the endoscopists expertise.

Lesion assessment

In addition to optimizing the diagnostic quality of colonoscopy, adequate polypectomy, assuring radical removal of colorectal lesions and minimizing the risk of complications, is equally important. There are numerous polypectomy techniques and corresponding devices available. The choice of technique is based on local traditions and skills of the endoscopist, as well as polyp characteristics and lesion size. The assessment, including pre-workup of more advanced polyps is vital when deciding whether to resect, refer to a tertiary endoscopy centre or refer for surgery. The primary goal in the assessment of advanced polyps is to evaluate the risk of submucosal invasive cancer.

Macroscopic appearance

The Japanese endoscopic classification of superficial neoplastic lesions with numerous subgroups, were largely considered too complex for Western endoscopists and considered a "botanical hobby" by some[146]. This was the pre-requisite for the gathering of an international group of endoscopists, surgeons, and pathologists in Paris 2002, culminating in the Paris classification of superficial neoplasms[146].

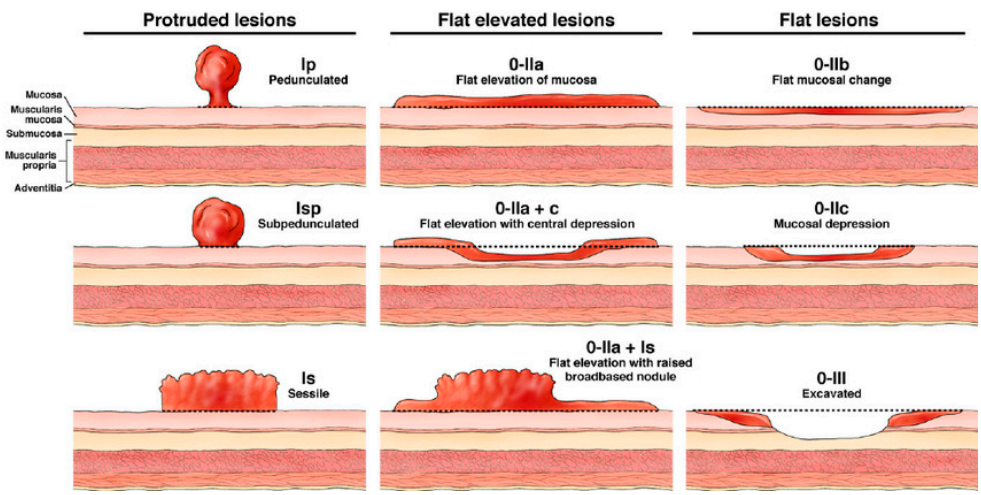


Figure 5. The Paris classification of superficial neoplasms.

The Paris classification provides a standardized means to describe colorectal lesions as well as allowing prediction of advanced histology[147-149] (Fig. 5). However, the interobserver agreement has been described as moderate with a pairwise agreement

of only 60% both before and after training[150]. Notably, the Paris classification was adapted from the Japanese Kudo classification of early colorectal cancers which also includes definition of laterally spreading tumours (LST), defined as flat lesions >1 cm. The LST classification differentiates lesions as either LST-granular (LST-G), subdivided as homogeneous or nodular-mixed type and LST-nongranular (LST-NG), subdivided as elevated or pseudo-depressed[151] (Fig. 6). Homogenous LST-G lesions have been proven to pose a minimal risk of harbouring submucosal invasive cancer whereas the other LST-types, especially pseudo-depressed LST-NG lesions and mixed type LST-G lesions, are more prone to harbour malignancy[149, 152-155]. Due to these substantial differences in risk of invasive cancer, European guidelines now include the LST classification in their recommendations[58, 156-158].

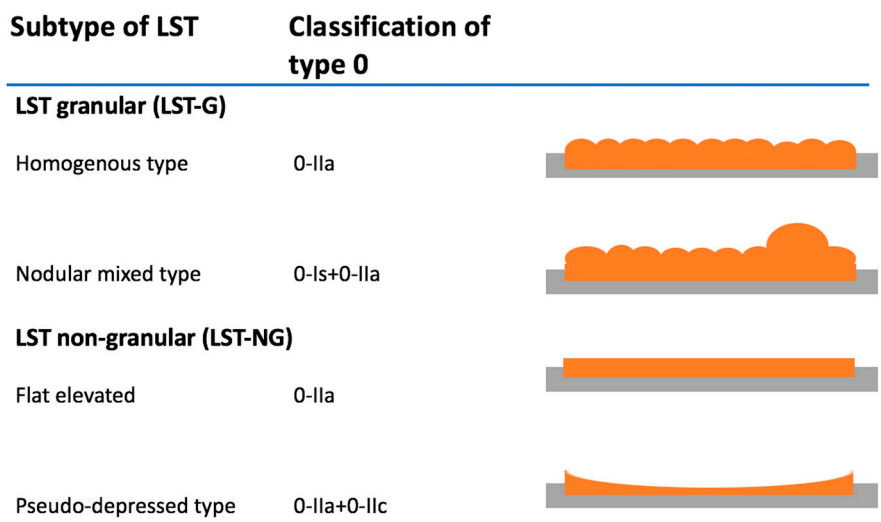
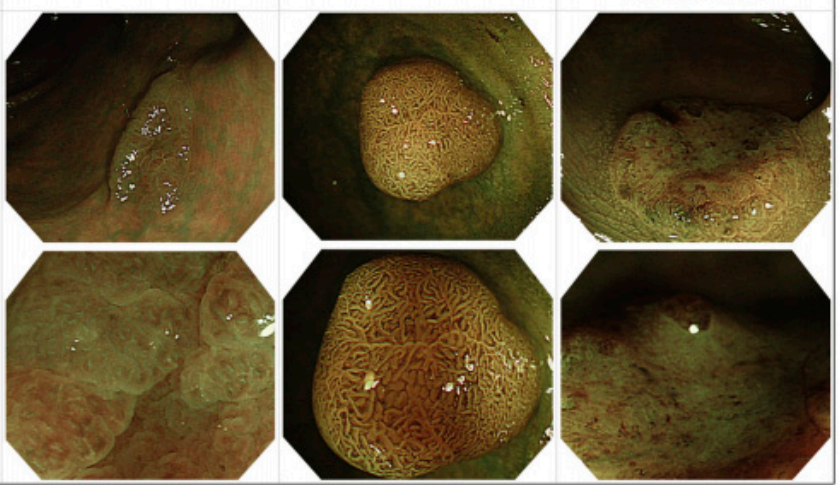


Figure 6. Laterally spreading tumours (LST) classification.

Apart from the macroscopic appearance, thorough inspection of the lesion surface can be used to predict the histology of colorectal lesions. When inspected with white light alone, the ability to give insight in the pathology is poor, but inspection with either dye, such as chromoendoscopy or advanced imaging techniques comprising narrow-band imaging (NBI), i-SCAN magnification endoscopy and Fuji intelligent colour enhancement, has been proven highly effective in predicting the histology[159-166]. NBI uses a narrowed wavelength light source to enhance haemoglobin light absorption allowing detection of altered micro vessels in the mucosa and submucosa, apparent in neoplastic tissue. Investigation of lesion surface includes evaluation of colour, pit pattern and vascular patterns. The NICE classification (NBI

international colorectal endoscopic) was developed as a practical, simple and internationally applicable classification for polyp histology using NBI, with or without optical magnification[167] (Fig. 7). Initially the NICE classification only included differentiation between hyperplastic polyps (Type 1) and adenomatous polyps (Type 2), but has thereafter been modified to include differentiation also to deep submucosal invasive cancer (Type 3)[167, 168].

NBI International Colorectal Endoscopic (NICE) Classification*

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structure surrounded by brown vessels**	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic**	**Adenoma*** **	**Deep submucosal invasive cancer**
Examples			

* Can be applied using colonoscopes with or without optical (zoom) magnification

** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.

*** Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Figure 7. The NBI international Colorectal Endoscopic (NICE) Classification.

Noteworthy, the size of colorectal lesions not only largely dictates the resection method, lesion size has also been proven repeatedly to be a predictive factor of

invasive cancer[10, 15, 16, 146-149, 169]. Hence, diminutive polyps <5mm, have basically no risk of harbouring malignancy (0-0.6%), whilst the incidence of invasive CRC is more than 10% in lesions >2cm[10, 16, 58, 169, 170].

MRI and endoscopic ultrasound

European guidelines recommend that either Endoscopic ultrasound (EUS) or MRI is used for staging of rectal cancers[68]. The literature on comparisons of EUS and MRI, and their ability to correctly stage rectal cancers, is inconsistent[171-173]. A prospective randomized study found no significant difference in accuracy of T and N stage comparing EUS and MRI for rectal cancer[174]. Another recent prospective study found that EUS was better at distinguishing between adenoma and early rectal cancer, accurate in 88% in comparison to 75% for MRI, but none of the two methods could distinguish T1 from T2. [175]. Moreover, a recent large meta-analysis found that EUS was superior to MRI in overall T and N staging but both EUS and MRI provided reasonable diagnostic accuracy in rectal cancer staging[176]. Notably, one advantage of MRI over EUS is its ability to provide information on distant metastases and the distance from the tumour to the mesorectal fascia, crucial in predicting the circumferential margin[177-179]. Notably, the introduction of high-frequency EUS and the miniprobe has allowed endoscopic ultrasound assessments to be applied also for colonic lesions[180]. Previous studies have shown high-frequency EUS to be accurate in staging colon cancer and superior to chromoendoscopy[180-182]. However, in terms of selecting cases with low risk of LNM, suitable for endoscopic resection, neither EUS nor MRI have been proven to reliably distinguish Sm1 from Sm2 and Sm3 tumours. Notably, reliable assessment of depth of submucosal invasion is only meaningful if there is a clear correlation between depth of invasion and the risk of LNM. The European Society of Gastrointestinal Endoscopy (ESGE) conclude that endoscopic resection is currently the best staging tool for early CRCs and advocate that lesions with suspected submucosal invasion, should be resected endoscopically en bloc[68].

Confocal laser endomicroscopy

During recent years, confocal laser endomicroscopy (CLE), was developed to obtain in vivo histological assessment of the gastrointestinal tract[183, 184]. The technique comprises iv. or topical administration of fluorescent agents and is based on tissue illumination by use of a low-power laser. Previous studies have shown promising results of CLE in the diagnostic accuracy of colorectal neoplasms[165, 185, 186]. A recent study also reported that CLE can be used to detect submucosal invasion and submucosal fibrosis[187]. However, the role of CLE is not yet fully investigated and the technique is currently limited by high costs. Notably, as with EUS and MRI, the value of differentiating depth of submucosal invasion is only useful if there is a clear correlation between deep submucosal invasion and LNM.

Forceps biopsies

Prior to referral of advanced colorectal lesions to tertiary expert centres, forceps biopsies are routinely obtained in the West. Indeed, ESGE recommend that complex colorectal lesions should be referred and handled at expert centres but do not include any policy on forceps biopsies[58]. Thus, the reliability of forceps biopsies in reflecting the true nature of large colorectal lesions is poorly investigated. Previous studies include three reports on forceps biopsies in small colorectal lesions, 6-20 mm in size, showing a 10-19% discrepancy in histology comparing forceps biopsies with resected specimens[188-190]. In contrast, the reliability of forceps biopsies in the work up of gastric lesions is more widely investigated, with numerous studies showing poor agreement in histology (56-76%) between biopsy captured fragments and resected specimens[191-194]. Noteworthy, biopsies in non-pedunculated lesions can cause submucosal fibrosis, aggravating future attempts of endoscopic resection[195-197]. Hence, submucosal fibrosis, can mimic invasive cancer, causing a false "non-lifting sign" otherwise apparent in deep submucosal invasive cancer but also after extensive manipulation with forceps biopsies[198, 199]. This constitutes one of the reasons why Japanese guidelines state that biopsies are not a necessity when deciding therapeutic strategies for colorectal lesions and dissuade from biopsies in lesions eligible for endoscopic resection[200]. Thus, the Japanese assessment of colorectal lesions and the risk of submucosal invasive CRC is largely based on the macroscopic appearance of the lesion, dictating treatment strategies such as endoscopic resection or surgery[200].

Polypectomy techniques

Colorectal polyps are heterogenous and the optimal polypectomy technique hence depend on polyp characteristics. Basic techniques vary from removing polypoid tissue with forceps biopsies to snaring techniques. More advanced polypectomy includes EMR where the lesion is lifted with submucosal fluid injections, creating a distance to the underlying muscle wall to ESD where the lesion is repeatedly lifted with fluid injections, dissecting the lesion with a cautery knife. The degree of difficulty a polyp presents in terms of resection is multifactorial. One way to objectify the difficulty of a polypectomy is the SMSA scoring system, grading the size, morphology, site and access of a polyp (Table 1)[201]. Based on the SMSA score, polyps can be divided in one of four levels with increasing difficulty, level 1 (4-5), level 2 (6-9), level 3 (10-12) and level 4 (>12).

Table 1. SMSA scoring system.

Factor	Benchmarks	Points
Size	<1cm	1
	1-1.9cm	3
	2-2.9cm	5
	3-3.9cm	7
	>4cm	9
Morphology	Pedunculated	1
	Sessile	2
	Flat	3
Site	Left	1
	Right	2
Access	Easy	1
	Difficult	3

Moreover, complications to polypectomy largely consists of bleeding and perforation, occurring at different rates dependant on lesion and technique. Complications occurring during the procedure can often be handled endoscopically. Haemorrhage can be stopped by means of haemostatic forceps, adrenalin injection or mechanical clips and perforations can be contained by means of clips[58].

Pedunculated lesions

The majority of pedunculated lesions can easily be removed completely by use of hot snare polypectomy (Fig. 8). However, the stalk of the polyp often contains a blood vessel, with increasing size in parallel to both polyp size and stalk diameter[202, 203]. Also, the risk of bleeding increases with proximal colonic location and when malignancy is present[204, 205]. Therefore, precautions can be taken to prevent bleedings, such as stalk infiltration with adrenaline, proven to significantly reduce the risk of bleeding[206, 207]. Pre-treatment of the stalk is recommended if the diameter exceeds 0.5 cm[58]. Interestingly, a randomised controlled trial showed that there was no significant difference in the risk of bleeding comparing stalk infiltration with saline and adrenaline[208]. Additionally, the stalk can be treated mechanically by means of a detachable snare or clip, also proven to reduce the risk of bleeding[209, 210].

Diminutive and small polyps (<9 mm)

Polyps <9 mm comprise 90% of lesions detected at colonoscopy and rarely harbour advanced histology or cancer[211]. Diminutive polyps, defined as lesions <5 mm, have an even lower and negligible risk of cancer, especially when hyperplastic and located in the rectosigmoid[170]. Therefore, two strategies have been proposed regarding resection; "diagnose and leave behind", applicable to hyperplastic diminutive lesions in the rectosigmoid and "resect and discard", applicable to diminutive adenomas[58, 212]. However, in order to follow these strategies, the endoscopic assessment of the histology needs to be highly accurate and is dependent on the expertise of the endoscopist. Furthermore, cold snare polypectomy is the preferred resection technique for small and diminutive polyps, due to high rates of complete resection, adequate tissue sampling for histology, and low complication rates[58, 213-215]. Notably, cold forceps biopsy resection has been proven inferior to cold snare resection in terms of complete polypectomy rates and time consumption[213, 214]. Hot forceps biopsy resection on the other hand is not recommended due to the risk of complications, secondary to thermal injury, and inadequate tissue yield[216-218]. Hence, ESGE recommend against forceps biopsy resections, both cold and hot, for small and diminutive polyps, recommending cold snare polypectomy[58].

Flat and Sessile polyps 10-20 mm

Hot snare polypectomy is the preferred resection method for flat and sessile lesions 1-2 cm in size, with higher likelihood of complete, en bloc resection and reduced risk of bleeding, in comparison to cold snare polypectomy[58]. However, hot snare polypectomy is associated with a risk of thermal injury to the underlying muscle wall. In addition, flat lesions can be difficult to capture with the snare. As a solution to these draw-backs, EMR was developed (Fig. 8). The technique involves submucosal fluid injections, creating a plane for the snare resection and hence decreasing the risk of thermal injury to the thin muscle wall. Simultaneously fluid injections protrude the lesion, making it easier to capture with the snare. The technique was described by Deyhle in 1973, but its popularity was first achieved after dissemination to Japan during the 1990´s[219]. Currently, EMR has become standard treatment for non-pedunculated colorectal lesions world-wide[220-222]. Numerous studies have shown excellent results of EMR, in regards of high en bloc and R0 resection rates and low risk of complications[58, 220, 221, 223, 224]. However, EMR often results in piece meal resection when the lesion dimension exceeds 2cm, resulting in insecure pathology and increased risk of recurrence[7-9]. In fact, the risk of recurrence after EMR has been shown in a previous study to be 3% after en bloc resection and 20% after piece meal resection[8]. Notably, underwater EMR (UEMR), was developed and described by Binmoeller in 2012 as an alternative to conventional EMR[225]. The method comprises full fluid immersion, eliminating the need for submucosal injections. When water is instilled, the submucosa and mucosa

including the lesion "floats", while the muscularis propria remains circular. A recent meta-analysis including seven prospective and three retrospective studies showed that UEMR is an efficient and safe technique for large and flat colorectal lesions with an en bloc rate of 57%[226]. Also, UEMR was proven superior to EMR in terms of higher en bloc and R0 resection rates for medium sized polyps (10-20 mm) in a multicentre randomized controlled trial[227].

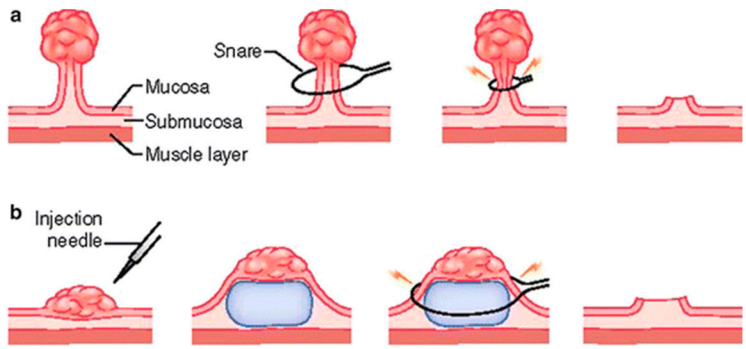


Figure 8. Illustration of snare-based polypectomy. a) hot snare polypectomy of pedunculated lesion, b) endoscopic mucosal resection of non-pedunculated lesion, including submucosal fluid injection creating a distance to the underlying muscle layer and subsequent electro snaring.

Large non-pedunculated lesions (>2 cm)

For many years treatment options for large non-pedunculated colorectal lesions were limited to either piecemeal-EMR or surgery. Piecemeal-EMR is, as previously mentioned, cumbered by the risk of recurrence and insecure pathology[7-9]. Surgery on the other hand, either as first line treatment or subsequent after piece-meal resection, is associated with higher morbidity, mortality and reduced quality of life in comparison to endoscopic resection[8, 68, 228]. Furthermore, in benign lesions and selected lesions with submucosal invasive cancer, surgery constitutes overtreatment because of the non-existent and low risk of LNM, respectively[229]. Notably, pre-resection diagnosis of submucosal invasion is notoriously difficult and it is well known that the risk of submucosal invasion, increase by incremental lesion size[10, 15, 16, 169, 189, 190]. Furthermore, the risk of LNM is presumably associated with several histopathological factors, attainable only by resection[229]. Hence, endoscopic en bloc resection is therefore recommended for large colorectal lesions with a risk of harbouring submucosal invasive cancer[68].

Endoscopic submucosal dissection

During the last decades, ESD has evolved as an alternative to surgery, allowing en bloc resection of non-pedunculated lesions throughout the gastrointestinal tract without any size limitation. The procedure comprises mucosal incision penetrating the muscularis mucosae, followed by submucosal dissection, facilitated by repeated fluid injections to maintain a submucosal tension (Fig. 9).

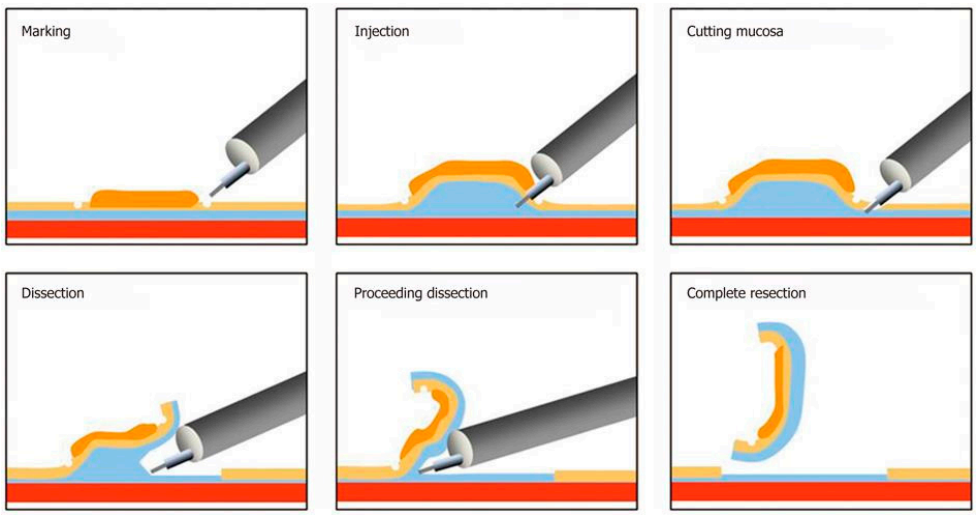


Figure 9. Illustration of endoscopic submucosal dissection.

The dissection is ideally performed beneath the horizontal ramified vascular network of the submucosa, dissecting at an avascular plane just above the muscularis propria[230]. After obtaining the appropriate depth of submucosal dissection, the next important step is to get the transparent hood into and under the submucosal layer, creating a mucosal flap. The dissection can then continue in the same avascular plane, whilst extending the mucosal incision in a stepwise manner (Fig. 10). During the dissection, vertical blood vessels in the submucosa, going from the horizontal vascular network into the muscle layer, can be identified and pre-coagulated with haemostatic-forceps. Notably, once the blood vessels are damaged by mistake, the subsequent haemorrhage radically impairs the field of vision and the tissue is furthermore toughened by uncontrolled coagulation, making dissection both strenuous and increasing the risk of subsequent perforation[230]. Thus, the difficulty of ESD is considered to arise from ignorance of the vascular structure and failure to follow the appropriate dissection plane in the gastrointestinal wall[230]. Also,

traction and counter traction is a basic principle of surgery, and is equally important when performing ESD. In conventional ESD, the traction is gained by submucosal fluid injections as well as using gravity by means of patient positioning. Numerous methods aiming at enhancing the traction in ESD has been proposed such as, clip and thread, sinker-assisted method, anchor-method as well as more advanced techniques such as, robot-assisted ESD[231]. Some of these methods show promising results and it is highly possible that traction assisted ESD will find its place in the routine practice in the near future[231, 232].

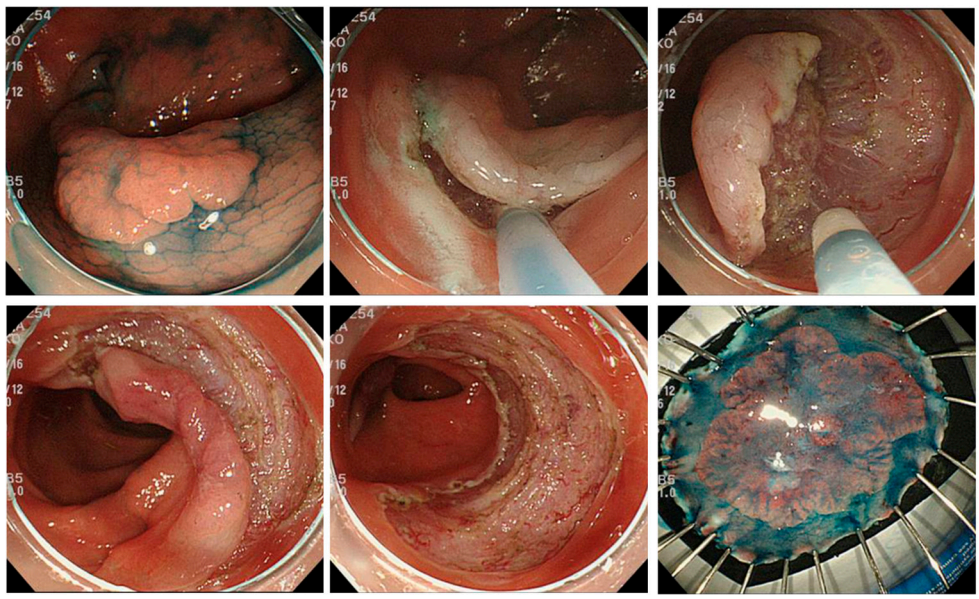


Figure 10. Example of ESD procedure.

Moreover, ESD was initially developed in Japan during the 1990s for superficial gastric tumours but has thereafter been introduced for colorectal lesions[10-12, 233]. However, colorectal ESD is technically more challenging than gastric ESD due to the thin colonic wall and difficult manoeuvrability and the technique was initially burdened by long procedural times and the risk of complications[152, 234-237]. However, since its introduction, numerous reports have shown that colorectal ESD is a safe and highly efficient method for large non-pedunculated colorectal lesions[10-13]. Notably, a recent meta-analysis on colorectal ESD, found that en bloc and R0 resection rates were 93% and 86% respectively in Asia[238]. Furthermore, complication rates in Asian studies amount to 5% perforations and 2.4% bleedings

and emergency surgery is required in 1% of patients undergoing colorectal ESD[238, 239]. As of today, ESD is implemented in the standard treatment of large and challenging lesions throughout the gastrointestinal canal in Japan and many other Asian countries, with well documented efficacy[10-13, 240]. However, implementation of colorectal ESD in the West has been slow and hampered by the long learning curve, risk of severe complications, few starting cases in the stomach, lack of structured training programs and lack of experts to learn from[238, 241, 242]. Nevertheless, an increasing number of colorectal ESD reports from Western centres have been published during the last years, and centres with comprehensive and proficient ESD programs have begun to form[14-18]. In addition, ESGE have recently published a core curriculum for ESD practice and training, further facilitating ESD dissemination in the West[243]. Notably, in a recent review on Western experience of colorectal ESD, the overall en bloc and R0 rates were found to be 70% and 83% respectively and complications required emergency surgery in 2% of the patients[244]. Hence, the implementation of ESD in the West is ongoing, and although recent reports show far better results in comparison to early discouraging studies, there is still room for improvement to reach equivalence to Asian centres[245].

Alternatives to ESD

TEM was described already in 1983 by Professor Buess[246]. The method comprise inserting a 40mm diameter proctoscope, covered by a sealing faceplate containing ports for the angled stereoscopic optic system and instruments[59]. The TEM device is a closed proctoscopic system with constant CO^2 insufflation. TEM is performed by dissecting around the lesion and down in the mesorectal fat, completing a full thickness resection. There is thus a risk for intrusion of the peritoneum, which if not repaired promptly requires emergency surgery[247]. Closure of the defect after TEM when the peritoneum is left intact, is frequently debated. Notably, a randomised trial found no significant differences in terms of complications comparing closure with non-closure[248]. When compared, TEM and ESD show equal results in regards of en bloc and R0 resection rates[249-251]. However, ESD is advantageous because of its minimal invasiveness, avoidance of anaesthesia, shorter hospital stays and lower health care costs[250, 252, 253]. Notably, since TEM involves full wall resection and dilatation of the anal canal, the scope of adverse events is extended in comparison to ESD, including temporary functional impairments, such as faecal incontinence, pneumoretroperitoneum and more advanced bleedings[254]. Importantly, there are no oncological advantages in resecting the entire wall of T1 CRCs, since local resection is limited by the risk of LNM. Furthermore, it is well known that salvage surgery after TEM, results in higher morbidity and higher rates of abdominoperineal resections and permanent stomas as compared to surgery as first line treatment[255-259]. Hence, given that unfavourable histopathologic factors justifying surgery are only attainable after resection, ESD is preferable since it does not imply poorer outcomes of subsequent surgery as compared to surgery as first line treatment.

Moreover, endoscopic full thickness resection (EFTR) has evolved during recent years, in part by means of the full thickness resection device[260, 261]. The lesion is pulled into a transparent cap, followed by closure of an over the scope clip including all layers of the bowel wall, and subsequently resected. EFTR has shown promising results for subepithelial lesions such as gastrointestinal stromal tumours and neuroendocrine tumours otherwise referred for surgery[60]. Furthermore, EFTR can be used to resect colorectal adenomas and presumably early CRCs in selected cases where ESD is not feasible. For instances, lesions inside or in close proximity to diverticulas are challenging with ESD, as well as lesions with extensive submucosal fibrosis causing a non-lifting sign. However, to be able to resect a colorectal lesion by means of EFTR it has to fit within the cap, currently limiting resection to lesions <2cm in diameter[60]. Currently, EFTR constitutes a compliment to ESD and further studies on its implementation in the management of advanced colorectal adenomas and early CRC are warranted.

Aims

The general aim of this thesis was to investigate the feasibility of implementing colorectal ESD in a Western institution and overall management of advanced colorectal lesions and early CRC.

Specific aims

Paper I

To evaluate the implementation of colorectal ESD in the treatment of large non-pedunculated neoplasias in a Western institution, including learning curve and analysis of variables effecting outcome.

Paper II

To evaluate the potential role of ESD in the management of non-pedunculated malignant colorectal lesions in a Western institution.

Paper III

To investigate the reliability of forceps biopsies in the routine work up of large colorectal lesions referred for endoscopic resection.

Paper IV

To identify clinical as well as histopathological risk factors of lymph node metastases in T1 colorectal cancer, including the distinction of independent and dependent risk factors.

Material and Methods

Patients and tumours

Paper I-III

Paper I, II and III are retrospective cohort studies, including patients undergoing endoscopic resection of advanced colorectal lesions at the endoscopy unit, Skåne University Hospital in Malmö, Sweden. All patients with large (>2cm) or recurrent non-pedunculated lesions undergoing ESD were included in Paper I and II. All benign lesions (including HGD) resected between January 2013 and November 2017, were included in Paper I and all malignant ESD lesions (i.e. submucosal invasive cancer) resected between Jan 2014 and Dec 2016 were included in Paper II. The cohort of Paper III comprise all patients undergoing endoscopic resection of advanced colorectal lesions between Jan 2014 and Dec 2016 where biopsies had been obtained prior to resection. Cases with biopsy confirmed cancers were in general referred directly for surgery and not included in Paper III, with the exception of four cases, referred for endoscopic resection despite cancer positive biopsies.

Paper IV

Paper IV is based on prospectively collected data from the Swedish Colorectal Cancer Registry (SCRCR), analysed retrospectively. We identified and included all patients undergoing surgical resection for T1 CRC between Jan 2009 and Dec 2017 in the SCRCR. Patients receiving neoadjuvant treatment and patients with synchronous CRCs were excluded as were cases with missing data on analysed lymph nodes and/or depth of submucosal invasion.

We validated the results in Paper IV by analysing a cohort consisting of equivalent patients in the Danish colorectal cancer group database (DCCG). Patients undergoing surgical resection of T1 CRC between 2016 and 2018, were identified and included. Equivalent exclusion criteria used on the Swedish cohort were applied to the Danish cohort.

Table 2. Overview of patients and tumours Paper I-IV.

Paper	Aims	Time period	Procedure	Inclusion	Exclusion
I	Evaluate the implementation of ESD in sweden, incl. learning curve	2013-2017	ESD	Colorectal ESD resections	Cases with malignant PAD (adenocarcinoma and carcinoid tumours)
II	Evaluate ESD in the management of T1 CRC	2014-2016	ESD	All malignant ESD resections	Carcinoid tumours
III	Examine biopsy reliability in large colorectal lesions	2014-2016	ESD EMR UEMR	Colorectal lesions biopsied 1 year prior to resection	Resected specimen lost. Multiple lesions with insequre biopsy-lesion relationship
IV	Identify clinical and histological risk factors of LNM in T1 CRC	2009-2017	Surgical resection	All surgically resected T1 CRCs in Sweden (SCRCR)	Neoadjuvant treatment. Synchronus cancers. Missing data (lymph node status, SM-class,)
IV	Identify clinical and histological risk factors of LNM in T1 CRC in a validation cohort	2016-2018	Surgical resection	All surgically resected T1 CRCs in Denmark (DCCG)	Neoadjuvant treatment. Synchronus cancers. Missing data (lymph node status, SM-class,)

Methods

Lesion assessment, choice of resection method

In total, 872 large (>2cm), non-pedunculated or recurrent colorectal lesions, referred for ESD, underwent endoscopic resections (ESD, EMR, U-EMR) between 2013 and 2017, at the endoscopy unit at Skåne University Hospital in Malmö, Sweden. Prior to choosing resection method, lesions were thoroughly investigated to assess the most optimal endoscopic resection technique, taking patient age, comorbidity, lesion size and location into consideration. Macroscopic appearance was defined according to the Paris classification and the NICE classification was adopted to evaluate the risk of invasive cancer. Lesions were inspected after topical administration of 0.4% indigo carmine and/or narrowband imaging (NBI) in addition to inspection with white light. EMR and U-EMR were in general chosen for lesions smaller than 3cm with low suspicion of submucosal invasive cancer (NICE class 1-2). ESD was in general chosen for lesions larger than 3cm, lesions with suspicion of submucosal invasive cancer as well as recurrences non-suitable for EMR (Nice 1-3). During the study period, 535 lesions were resected with either EMR or underwater EMR and 337 lesions were resected with ESD. Only lesions resected with ESD were included in Paper I-II, since comparison of EMR vs. ESD was not in the scope of this thesis. In total, 36 malignant lesions were resected with ESD, 29 of these were included in Paper II, and the remaining seven where not

included since; three were carcinoids and four were resected after Paper II was finalized.

Work up

Cases were in general assessed by the referring endoscopist and subsequently referred directly for ESD. Cases with macroscopically suspected submucosal invasion as well as cases with cancer positive biopsies underwent MDT review prior to resection. All patients discussed at MDT conference underwent Computed tomography (CT) of thorax and abdomen to investigate potential metastases and rectal lesions were investigated and staged with magnetic resonance imaging (MRI).

Biopsies

The choice to obtain biopsies, number of biopsies and type of biopsy forceps used, was decided by the referring endoscopist. 502 out of 607 lesions undergoing resection of advanced colorectal lesions were biopsied within one year prior to endoscopic resection during the period Jan 2014 to Dec 2016, investigated in Paper III. Cases with cancer positive biopsies were in general referred for surgery, exceptions were made in four cases with cancer positive biopsies referred for endoscopic resection due to comorbidities and/or high age. After excluding cases were the specimen was lost or partly lost as well as cases with multiple lesions making lesion-biopsy relationship uncertain, a total of 485 cases were included in paper III.

Endoscopic submucosal dissection

All ESD procedures were performed by one experienced endoscopist (HT) who started with ESD after attending ESD tutorial courses and animal ex vivo training in Europe and Japan followed by performing ESD under supervision of Japanese experts.

A conventional gastroscope was used for lesions located in the left colon and rectum and a conventional colonoscope was used in the right and transverse colon (GIF-H180J and CF-H180AI, Olympus, Hamburg, Germany). A disposable hood was attached on the tip of the endoscope (D-201-11804 or D-201-15004, Olympus, Hamburg, Germany). ESD was carried out in a standardized manner, lifting the lesion with hyaluronate sodium solution and dissecting with the flush knife (Fujifilm Europe GmbH, Düsseldorf, Germany) connected to a water jet pump. Bleedings were prevented and treated with haemostatic forceps (Coagrasper, FD-411UR, Olympus).

Learning curve

In order to study the learning curve of ESD, we divided the 301 ESD cases included in Paper I in five chronological time periods, comprising 60 to 61 lesions in each period. This division was decided prior to data analysis to minimize bias. The different periods were compared in regards of lesion size, location, en bloc, R0 and proficiency i.e. resection speed (cm^2/h).

Specimen and Histology

Resected specimens were pinned onto a hard plate and subsequently measured and submerged in 10% formalin. Lesion area was calculated by using the formula for ellipse shaped objects (A=abπ), hence multiplying the minor radius with the greater radius, multiplied with π (Fig. 11). This formula is applicable also for circular lesions.

$$A = ab\pi$$

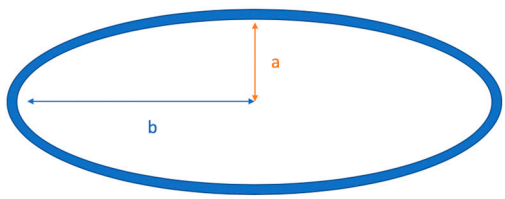


Figure 11. Formula for calculating the area of an ellipse.

All tissue was embedded for histologic analysis after being sectioned serially at 3mm intervals. Neoplasms were classified according to the Vienna classification of gastrointestinal neoplasia and malignant specimen were further sub-classified based on depth of invasion (Sm1; <1000µm, Sm2; >1000µm, <2000µm and Sm3; >2000µm).

Resection margins were assessed as; R0 when tumour free, R1 when tumour cells were present and RX when margins couldn't be reliably assessed.

The term "Curative resection" was adopted from the ESGE guidelines applicable for malignant lesions, defined as RO resection of low risk lesions (limited submucosal invasion (Sm1), no lymphovascular invasion, moderate to well differentiation and no tumour budding)[68].

In cases where the pathology report was unclear on depth of invasion, lymphovascular invasion or degree of differentiation, specimens were re-evaluated by a senior gastrointestinal pathologist (JE). All pathology reports stating "Sm1/2" were re-evaluated to Sm2.

Hospitalization, complications and further management

Prior to ESD, the patients´ need for hospitalization were assessed based on lesion location, size and the general state of the patient (age and comorbidities). As the number of completed ESD procedures increased the need for hospitalization of patients with distal colonic and rectal lesions were evaluated solely by patient related factors and not size. Hence, even very large rectal and distal colonic lesions were managed as outpatients in absence of other factors favouring hospitalization. Scheduled outpatients were admitted to the hospital after the procedure if complications occurred or if there was an increased risk of delayed complications.

Complications were defined as haemorrhage or perforation occurring within 30 days from the procedure. The medical records of all patients undergoing ESD were carefully reviewed to detect complications. Immediate perforation was defined as defects of the muscle layer with visible omentum or other tissue detected during the procedure. Immediate bleeding was defined as haemorrhage leading to abortion of the procedure or leading to blood transfusion, whilst smaller bleedings, frequently occurring during ESD, were not classified as complications. Delayed perforation was defined as either being detected on X-Ray/CT as free air or apparent at emergency surgery. Delayed bleeding was defined as evidence of haematochezia after the procedure, either leading to prolonged stay at the hospital or readmission to the hospital.

In general follow-up was scheduled according to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines[58]. Patients wish, age and comorbidities were however considered, explaining why some patients were not followed up according to guidelines.

The Swedish Colorectal Cancer Registry

The Swedish national quality registry for colorectal cancer (SCRCR) was founded in 1995, initially including only rectal cancers and extended to include also colonic cancers in 2007. SCRCR contains prospectively collected data including; preoperative staging, perioperative surgical details, postoperative histopathology, oncologic treatments and complications during the 5-year follow up. We included patients operated for T1 CRC in Paper IV from 2009, marking the year when depth of submucosal invasion was introduced in the SCRCR. During the study period

(2009-2017) the coverage of the SCRCR compared to the compulsory Swedish Cancer Registry was 99.0% for colon cancer and 98.9% for rectal cancer.

The Danish Colorectal Cancer Group database

The Danish colorectal cancer group database (DCCG) was started in 2001 and include prospectively collected data on colorectal cancers in Denmark. The DCCG has >95% completeness in included data and comprise equivalent variables as the SCRCR making it highly eligible for validation. The cohort used for validation in Paper IV consisted of all patients undergoing surgical resection for T1 CRC during the period 2016-2018. The pathology section of the DCCG was fully digitalised in 2016, and earlier cases have a high rate of incomplete data on LVI and perineural invasion, why 2016 was chosen as inclusion start.

Statistics

Data are given as median and range in all four papers. Computations and analysis were conducted with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) in Paper I and III and with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) in Paper IV. P values < 0.05 were considered significant.

Paper I

To investigate potential impact on the main outcomes (en bloc, R0, proficiency and recurrence) the following variables were tested with univariate and multivariate regression analysis; lesion localisation, area, Paris type and histologic grade. Furthermore, to investigate differences during the five time periods, the main outcomes were compared with the Chi-squared test (categorical variables) or the one-way Annova test with the Bonferroni-Holm correction (continues variables). Linear by linear association was used to evaluate trends in categorical parameters over time.

Paper III

To investigate possible differences in histologic grade and type between biopsies and completely resected specimen (paired), the Sign test was used. To determine potential impact on whether biopsies had underestimated (upgrade) or overestimated (downgrade) the histology, the Chi squared test was used on the following variables; lesion size, duration from biopsy to resection, number of biopsies and macroscopic lesion type. Furthermore, the same variables were investigated with the Spearman correlation test to investigate potential correlation to concordance, upgrade and downgrade.

Paper IV

To investigate a possible relationship between potential risk factors (age, gender, tumour location, depth of submucosal invasion, histologic grade, LVI, perineural invasion and mucinous subtype) and LNM, univariate and multivariate logistic regression analysis were used. To test for goodness of fit, the Hosmer-Lemeshow test was calculated. To adjust for missing data, values were imputed with multiple imputation, using 100 burn-in iterations and 10 imputations. We compared analysis with imputed values and analysis with complete data (non-imputed) as a sensitivity test. Identical statistical analysis and computations were performed on the validation cohort.

Ethics

All studies in this thesis were carried out in accordance with the ethical principles of the Declaration of Helsinki. Furthermore, ethical approval was granted prior to each study by the Regional Ethical Review Board, Lund University and by the Danish national committee on health research ethics (Paper IV). Informed consent was obtained from all patients undergoing ESD after being thoroughly informed of the procedure (risks of complications and the possibility of additional surgery due to complications or histological diagnosis of resected specimens). All data was coded and anonymity was guaranteed.

Results

Paper I

The study cohort of Paper I consisted of 301 cases of large or recurrent colorectal lesions undergoing ESD with benign histology, during the period January 2013 to November 2017 (Fig 12).

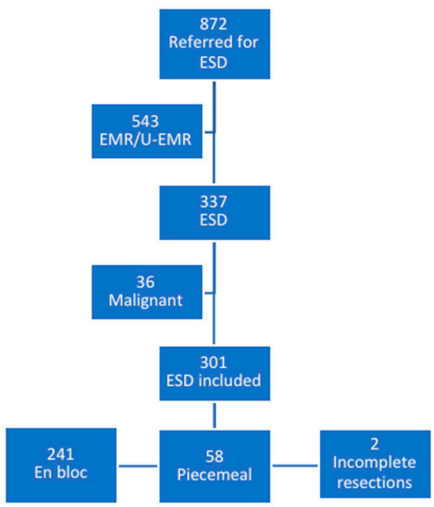


Figure 12. Flowchart of Paper I

Patient and tumour characteristics can be seen in Table 3. En bloc resection rate was 241/301 (80%), R0 resection rate was 207/301 (69%) and median lesion size was 4cm for the entire study period.

Table 3. Patient and lesion characteristics.

	P1	P2	P3	P4	P5	Total
Number of cases	60	60	60	60	61	301
Residual lesions	8	4	1	1	3	17
Age	73 (46-96)	77 (40-89)	72 (40-90)	69 (35-90)	68 (37-89)	72 (35-96)
Gender						
Female	25	27	34	25	31	142
Male	35	33	26	35	30	159
Localisation						
Rectum	30	32	33	39	39	173 (57%)
Distal colon	14	16	14	12	16	72 (24%)
Proximal colon	16	12	13	9	6	56 (19%)
Paris type						
Is	27	22	35	31	33	148
IIa	30	36	23	24	24	137
IIa/Is	3	2	2	5	4	16
Histology						
Serrated	1	1	-	1	2	5
Adenoma LGD*	40	38	43	43	38	202
Adenoma HGD**	19	21	17	16	21	94
Lesion size						
Diameter (cm)	3 (1.5-8)	4 (1-8)	4 (1.5-10)	5 (2-11)	5 (2-12.5)	4 (1-12.5)
Area (cm^2)	6.3 (1.1-44)	9.4 (0.8-38)	10.6 (1.1-56)	13.9 (2.5-69)	14.1 (3.1-78)	11 (0.8-78)

* LGD, low-grade dysplasia. **HGD, high-grade dysplasia.

Learning curve

The five different time periods were investigated for differences in lesion location, lesion size (area), macroscopic type and histopathology. Lesion size was the only parameter with significant differences, with larger lesions in the fifth period (14.1cm2) compared to the first period (6.3cm2) (P<0.001). ESD performance improved significantly over the time periods in regards of proficiency, en bloc resection and R0 resection. Proficiency improved from P1 to P3-5 (P<0.001), en bloc resection improved throughout the five periods (P<0.001) and R0 resection rate tested significant over time with linear by linear association (P=0.017) (Table 4).

Table 4. ESD outcome according to the five time periods (P1-5)

	P1	P2	P3	P4	P5	Total
Number of cases	60	60	60	60	61	301
Resection						
En bloc	36 (60%)	45 (75%)	49 (82%)	51 (85%)	60 (98%)	241 (80%)
Piecemeal	22 (37%)	15 (25%)	11 (18%)	9 (15%)	1 (3%)	58 (19%)
Incomplete	2 (3%)	-	-	-	-	2 (1%)
R0	36 (60%)	37 (62%)	46 (76%)	39 (65%)	49 (80%)	207 (69%)
R1	3 (5%)	-	1 (2%)	4 (7%)	3 (5%)	11 (4%)
RX	21 (35%)	23 (38%)	13 (22%)	17 (28%)	9 (15%)	83 (27%)
Procedural time (min)	133 (19-588)	122 (28-260)	75 (10-300)	78 (16-362)	91 (32-312)	98 (10-588)
Proficiency (cm^2/h)	3.6 (2.4-10)	5.4 (0.6-26)	9.6 (0.6-31)	10.2 (2.4-35)	10.8 (2.4-56)	7.2 (0.6-56)
Hospitalised	39 (66%)	26 (43%)	20 (33%)	14 (23%)	14 (23%)	113 (38%)
Median stay	1 (1-18)	1 (1-5)	1 (1-4)	1 (1-103)	1 (1-6)	1 (1-103)

Factors influencing outcome

Uni- and multivariate analysis of variables affecting main outcomes (en bloc, Ro, proficiency and complications) are shown in Table 5. Lesion location was the only variable significantly affecting all four outcomes in both uni- and multi-variate analysis (Table 5). Lesion area had significant impact on both R0 resection rate (multivariate) and proficiency (uni- and multi-variate). Proficiency was also significantly affected by Paris type (Table 5).

Table 5. Factors influencing outcome.

Variable	Univariate		Multivariate	
	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Impact on en bloc resection				
Localisation				
Rectum	2.70 (1.50-4.84)	0.001	2.64 (1.45-4.80)	0.001
Distal colon	1.48 (0.72-3.03)	0.286	1.55 (0.75-3.24)	0.24
Proximal colon	0.19 (0.10-0.35)	<0.001	0.17 (0.01-0.34)	0.001
Impact on R0 resection				
Localisation				
Rectum	1.91 (1.16-3.16)	0.010	2.14 (1.27-3.62)	0.004
Distal colon	0.82 (0.46-1.45)	0.489	0.75 (0.41-1.35)	0.332
Proximal colon	0.47 (0.26-0.86)	0.013	0.44 (0.23-0.82)	0.011
Size (Area)	0.98 (0.97-1.00)	0.066	0.98 (0.96-1.00)	0.04
Impact on complications				
Localisation				
Rectum	0.21 (0.06-0.77)	0.010	0.20 (0.05-0.78)	0.020
Distal colon	2.11 (0.67-6.67)	0.195	2.30 (0.69-7.67)	0.175
Proximal colon	2.88 (0.90-9.16)	0.063	3.18 (0.86-11.78)	0.083
Impact on proficiency				
	BETA*	*P*-value	BETA*	*P*-value
Localisation				
Rectum	0.223	<0.001	0.113	0.025
Distal colon	-0.053	0.364	-0.020	0.695
Proximal colon	-0.224	<0.001	-0.124	0.015
Macroscopic type				
Is	0.060	0.302	0.145	0.004
IIa	-0.078	0.183	-0.121	0.017
IIa/Is	0.038	0.516	-0.046	0.368
Size (Area)	0.526	<0.001	0.532	<0.001

*Beta; stsndardized regression coefficient, applied for continues variables.

Outcome according to lesion location can be seen in Table 6. The significant differences in R0 and en bloc rates according to lesion location were not significant in P5 (rectum; en bloc 39/39 (100%), R0 32/39 (82%), distal colon; en bloc 15/16 (94%), R0 12/16 (75%), proximal colon; en bloc 5/6 (83%), R0 5/6 (83%).

Table 6. ESD outcome according to lesion location

	En bloc	**R0**	**Proficiency** (cm^2/h)		**Complication**		**Recurrence**
				Perforation	Bleeding	Total	
Rectum N=173	150 (87%)	128 (74%)	9 0.6-56	3 (2%)	3 (2%)	6 (4%)	4 (2%)
Distal Colon N=72	61 (83%)	46 (64%)	7.2 0.6-30	4 (6%)	1 (1%)	5 (7%)	2 (3%)
Proximal Colon N=56	29 (54%)	33 (59%)	4.8 1.2-20	10 (18%)	3 (5%)	13 (23%)	1 (2%)

Complications and follow-up

In total, we experienced 24 complications (8%), whereof 13 were immediate (12 perforations, one bleeding) and 11 delayed (five perforations, six bleedings). A conservative approach, including observation, fasting, antibiotics and blood transfusions in selected cases, could be applied in 18 (Clavien-Dindo II) of the 24 complications (75%). All of the six patients requiring emergency surgery (6/301, 2%), had lesions located in proximal colon. One patient with a delayed caecal perforation needed intensive care post-surgery (Clavien-Dindo IV), the other five patients undergoing emergency surgery had no postoperative events (Clavien-Dindo IIIb).

Follow-up was completed in 204 patients (68%), with a median follow up time of 13 months (range 3-53). In total, seven recurrences (3%) were detected of which four were resected piecemeal (2 RX and 2 R1) and three were resected en bloc (2R0 and 1 incomplete resection).

In total, 188 patients (62%) were outpatients and 113 patients (38%) were hospitalized, whereof four patients were unscheduled and admitted after ESD for observation. The hospitalization rate was significantly higher during the first period (39/60, 66%) as compared to the fifth period (14/61, 23%) ($P<0.001$).

Paper II

The study cohort of Paper II comprised 29 patients with T1 CRC undergoing ESD between January 2014 and December 2016 (Fig. 13).

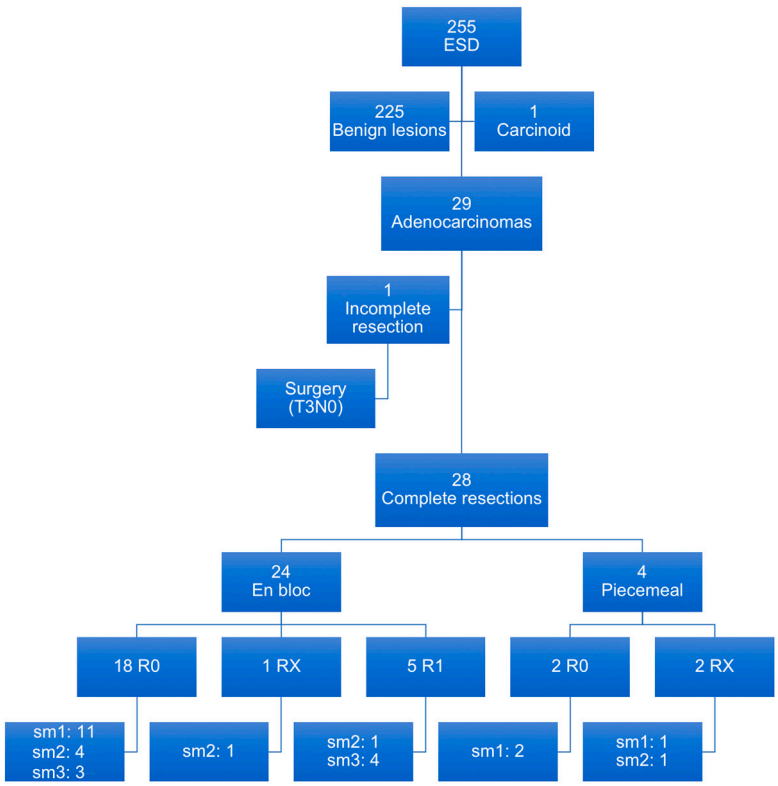


Figure 13. Flowchart of Paper II.

Work up

In total, 13 patients underwent MDT review prior to resection. Three of these where biopsy confirmed cancers and ten cases were submitted to MDT review due to malignant macroscopic appearance. All 13 patients reviewed at the MDT conference underwent CT of thorax and abdomen, whereof none revealed any malignant processes. Ten cases were rectal lesions and were staged by MRI as T0 in five cases, T1 in one case and T2 in four cases.

ESD outcome

Patient and tumour characteristics can be seen in Table 7. Complete resection was attained in 28 of 29 cases (97%), the en bloc rate was 24/29 (83%) and the R0 rate was 20/29 (69%) (Fig. 13). The incomplete resection was due to a perforation in the sigmoid colon requiring emergency surgery, pathology assessment revealed a T3N0 tumour. The remaining four complications, three immediate perforations and one delayed bleeding, could be manged conservatively.

Table 7. Patient and tumour characteristics

Age (years)	69 (range 44-89)
Gender, male : female	16 : 13
ASA score I : II : III : IV	10 : 12 : 6 : 1
Tumour size (mm)	40 (range 20-70)
Localization	
Rectum	16 (55%)
Sigmoid colon	10 (35%)
Transverse colon	2 (7%)
Caecum	1 (3%)
Type (Paris classification)	
IIa	10 (35%)
Is	14 (48%)
IIa+Is	5 (17%)
LST type (Paris type IIa)	
Granular	10
Nongranular	5
Risk of cancer *	
IIa	9%
Is	11%
IIa+Is	31%

Further management and follow-up

All patients underwent post-ESD MDT conference and investigation was completed with CT of thorax and abdomen for the 14 patients not undergoing pre-ESD MDT review. The basis for MDT decision including pre-ESD work up and histology is depicted in Table 8. Eight patients were recommended surgery, all of whom had deep submucosal invasion (≥sm2). Two patients refused surgery and one of the six patients undergoing surgery had residual tumour. Additionally, 9 cases were non-curative resections according to the ESGE guidelines, a conservative approach was

however chosen in these patients due to high age, comorbidity and patient reluctance to surgery. One recurrence (3%) was detected in the 20 patients undergoing follow up with a median follow up time of 13 months.

Table 8. ESD performance, histopathology and management

Biopsy	Pre-ESD Diagnosis	Resection	Lateral margin	Deep Margin	Invasion depth	Lympho-vascular invasion	Further management (months)	Result
LGD	Adenoma	En-bloc	R0	R1	SM3	Yes	Surgery	No residual cancer in resected specimen
LGD	Adenoma	Aborted*	-	-	-	No	Emergency resection	T3N0 tumour in resected specimen
HGD	Adenoma	En-bloc*	R0	R0	Sm1	Yes	Endoscopy (18)	No recurrence or residue
LGD	Adenoma	En-bloc	R0	R0	Sm1	No	Endoscopy (28)	No recurrence or residue
LGD	Adenoma	En-bloc	R0	R0	Sm1	No	Endoscopy (6)	No recurrence or residue
HGD	Adenoma	En-bloc	R0	R0	Sm2	Yes	Endoscopy (19)	No recurrence or residue
LGD	Adenoma	En-bloc	R0	R0	Sm1	No	No follow-up**	-
LGD	Adenoma	Piecemeal*	R0	R0	Sm1	No	Endoscopy (10)	No recurrence or residue
LGD	Adenoma	En-bloc	R0	R0	Sm1	Yes	Endoscopy (12)	No recurrence or residue
LGD	Adenoma	En-bloc	R0	R1	Sm3	No	Surgery	No residual cancer in resected specimen
LGD	Adenoma	En-bloc	R0	R0	Sm3	No	Surgery	No residual cancer in resected specimen
LGD	Adenoma	En-bloc	R0	R0	Sm3	No	Endoscopy (6)***	No recurrence or residue
HGD	Adenoma	En-bloc	R0	R0	Sm3	No	Surgery	No recurrence or residue
-	Adenoma	En-bloc	R0	R0	Sm1	No	Awaits endoscopy	No recurrence or residue
-	Adenoma	En-bloc	R0	R0	Sm1	No	Endoscopy (4)	No recurrence or residue
LGD	Adenoma	En-bloc	R0	R0	sm2	No	MRI + endoscopy (3)	No recurrence or residue
LGD	Suspected Ca	Piecemeal	R0	R0	Sm1	No	No follow-up**	-
LGD	Suspected Ca	Piecemeal	RX	R0	SM1	No	Endoscopy (20)	No recurrence or residue
LGD	Suspected Ca	Piecemeal	RX	RX	Sm2	Yes	MRI + Endoscopy (24)	No recurrence or residue
HGD	Suspected Ca	En-bloc	R0	R0	Sm1	No	Endoscopy (21)	No recurrence or residue
LGD	Suspected Ca	En-bloc	R0	R0	Sm2	No	Surgery	No residual cancer in resected specimen
Ca	Confirmed Ca	En-bloc*	R0	RX	Sm2	No	Surgery	Residual cancer in resected specimen
HGD	Suspected Ca	En-bloc	R0	R0	Sm1	No	Endoscopy (15)	Recurrence, Radiation therapy or surgery
Ca	Confirmed Ca	En-bloc	R0	R1	Sm3	No	Endoscopy (2)	No recurrence or residue
HGD	Suspected Ca	En-bloc	R0	R0	Sm2	Yes	MRI + Endoscopy (7)***	No recurrence or residue
HGD	Suspected Ca	En-bloc	R0	R0	Sm1	No	Endoscopy (8)	No recurrence or residue
HGD	Suspected Ca	En-bloc	R0	R0	Sm1	No	Endoscopy (6)	No recurrence or residue
Ca	Confirmed Ca	En-bloc	R0	R1	Sm3	No	Endoscopy (3)	No recurrence or residue
LGD	Suspected Ca	En-bloc	R0	R1	Sm2	No	Endoscopy (14)	No recurrence or residue

LGD; low-grade dysplasia. HGD; high-grade dysplasia. Ca; cancer. MRI; magnetic resionance imaging. MDT; multidisciplinary-team.
*Perforation during ESD. **Due to metastasized non-colorectal cancer. ***Patient refused surgery despite MDT recommendation

Paper III

The study cohort of Paper III consisted of 485 endoscopically resected large or recurrent colorectal lesions where biopsies had been obtained prior to resection (Fig. 14).

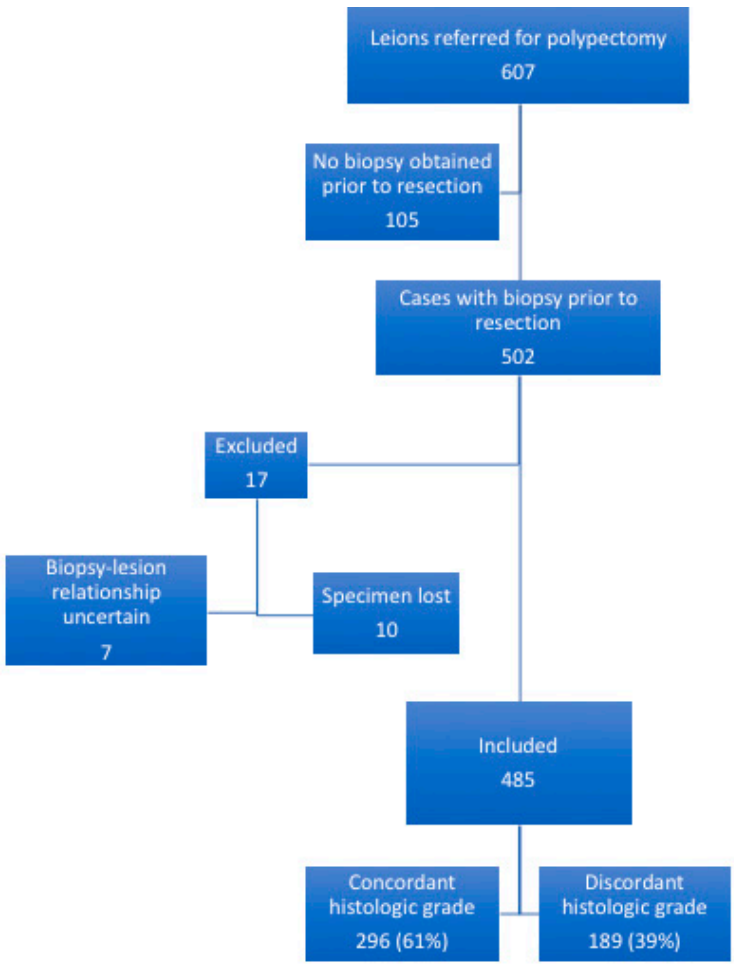


Figure 14. Flowchart of Paper III.

Median lesion size was 3cm and median duration from biopsy to resection was 111 days (range 14-338). Lesions were resected with EMR in 101 cases, UEMR in 154 cases and ESD in 230 cases.

Forceps biopsies were correct in regards of the histologic grade i.e. concordant, in 296 of 485 cases (61%) and hence discordant in 189 instances (39%) (Sign test, P<0.001) (Table 9).

Table 9. Concordance of dysplasia between forceps biopsy and resected specimen

	Resected specimen				Biopsy concordance
Biopsy	No dysplasia	LGD	HGD	Carcinoma	
No dysplasia	14	20	2		14/36 (39%)
LGD	23	256	78	30	256/387 (66%)
HGD	1	21	23	13	23/58 (40%)
Carcinoma			1	3	3/4 (75%)
Total	38	296	105	46	296/485 (61%)

LGD; Low grade dysplasia, HGD; High grade dysplasia

Forceps biopsies underestimated the histologic grade (upgraded), in 143 cases (29%) and overestimated the histologic grade (downgraded), in 46 cases (9%) (Table 10). Noteworthy, 33 of the 143 cases of upgrades (23%) were "double-upgraded", hence upgraded from no dysplasia to HGD or from LGD to cancer. Moreover, 80 of the 105 resected lesions (74%) with HGD were underestimated by biopsies and hence upgraded after resection.

Table 10. Discordance in grade of dysplasia

Upgrade		
Biopsy	Resected specimen	
No dysplasia	LGD	20
No dysplasia	HGD	2*
LGD	HGD	78
LGD	Cancer	30*
HGD	Cancer	13
Total upgrade		143 (29%)
Downgrade		
Biopsy	Resected specimen	
Cancer	HGD	1
HGD	LGD	21
HGD	No dysplasia	1
LGD	No dysplasia	23
Total downgrade		46 (9%)

LGD; Low grade dysplasia, HGD High grade dysplasia. * Double upgrade

The proportion of invasive cancer in our cohort was 46/486 (9%), whereof three were confirmed by biopsies prior to resection. The remaining 40 cases of cancer were classified by biopsies as LGD in 30 instances and HGD in 13 instances. Hence, 8% (30/387) of the lesions classified by biopsies as LGD and 22% (13/58) of the lesions classified as HGD, were in fact invasive cancer (Table 11)

Table 11. Overview of carcinoma

Number of cases	46
Time from biopsy to resection	
Median (months)	95 (26-228)
Biopsy <3 months	19
Biopsy 3-6 months	21
Biopsy 6-12 months	6
Size	
Median (cm)	4 (1.5-7)
SG1 (1-2cm)	9
SG2 (2-4cm)	20
SG3 (M 4-11cm)	17
Number of biopsies obtained	
Median	3 (1-18)
Single biopsy	15
2-3 biopsies	10
>3 biopsies	21
Paris type	
Ip	3 (6%)
Is	27 (59%)
IIa	12 26%)
IIa+Is	4 (9%)
Biopsy	
LGD	30 (65%)
HGD	13 (28%)
Carcinoma	3 (7%)

SG; Size group, LGD; Low grade dysplasia, HGD; High grade dysplasia

Variables affecting biopsy reliability

Extent of concordance/discordance as well as upgrade and downgrade according to investigated variables can be seen in Table 12. Lesion size was the sole variable significantly affecting the extent of upgrade (P=0.014) and downgrade (P=0.028). Lesion size also correlated to concordance, upgrade and downgrade when tested with the Spearman correlation test, (P<0.001). Hence, Larger lesions were upgraded to a greater extent (P<0.001), and smaller lesions were downgraded to a greater extent (P<0.001). None of the other variables; time from biopsy to resection, number of biopsies or lesion type, significantly affected concordance/discordance or upgrade/downgrade.

Table 12. Concordance/Discordance and Upgrade/downgrade according to variables.

Variables	N	Concordant	Discordant	Upgrade	Downgrade
Total	485	296 (61%)	189 (39%)	143 (29%)	46 (9%)
Time from biopsy to resection					
Biopsy <3 months	189	126 (67%)	63 (33%)	48 (25%)	15 (8%)
Biopsy 3-6 months	221	123 (56%)	98 (44%)	75 (34%)	23 (10%)
Biopsy 6-12 months	75	47 (63%)	28 (37%))	20 (27%)	8 (11%)
Divided according to size					
SG1 (1-2cm)	156	98 (63%)	58 (37%)	34 (22%)	24 (15%)
SG2 (2-4cm)	201	131 (65%)	71 (35%)	56 (28%)	14 (7%)
SG3 (4-11cm)	128	67 (52%)	61 (48%)	53 (41%)	8 (6%)
Divided according to number of biopsies					
Single biopsy (size: M 3cm, range 1-10)	162	97 (60%)	65 (40%)	49 (30%)	16 (10%)
2-3 biopsies (size M: 3cm, range 1-10)	169	100 (59%)	69 (41%)	51(30%)	18 (11%)
>3 biopsies (size M: 4cm, range 1-11)	154	100 (65%)	54 (35%)	43 (28%)	11 (7%)
Divided according to lesion type					
Ip	25	10 (40%)	15 (60%)	12 (48%)	3 (12%)
Is	245	151 (62%)	94 (38%)	75 (31%)	19 (8%)
IIa	195	125 (64%)	70 (36%)	49 (25%)	21 (11%)
IIa+Is	20	10 (50%)	10 (50%)	7 (35%)	3 (15%)

SG; Size group

Paper IV

The study cohort of Paper IV consisted of 1439 patients with T1 CRC undergoing surgical resection between 2009 and 2017 (Fig 15).

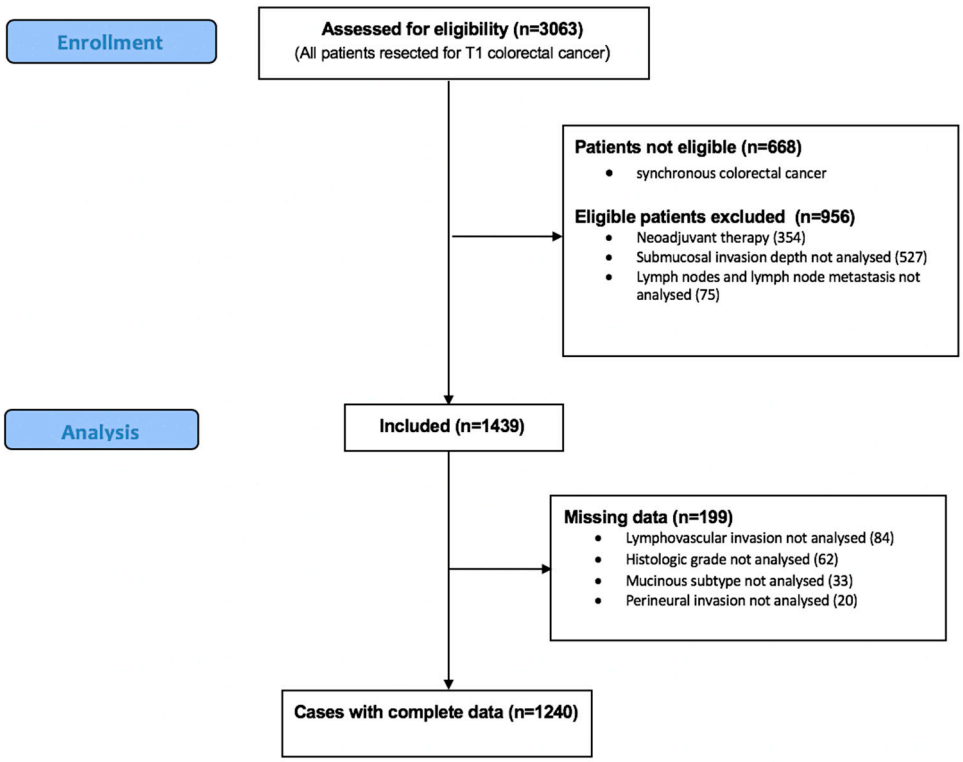


Figure 15. Flowchart of Paper IV.

In total, 150 of the 1439 included patients (10%) had LNM and the median number of analysed lymph nodes was 15 (range 1-99). Background characteristics and LNM according to clinical and histological variables can be seen in Table 13.

Table 13. Lymph node metastases according to histopathological characteristics and location

	Available for analysis	Total	Lymph node metastases
Gender	1439		
Male		752 (52.3%)	80 (10.6%)
Female		687 (47.7%)	70 (10.2%)
Location	1439		
Colon		1054 (73.2%)	105 (10.0%)
Rectum		385 (26.8%)	45 (11.7%)
Submucosal invasion	1439		
Sm1		490 (34.1%)	40 (8.2%)
Sm2		334 (23.2%)	34 (10.2%)
Sm3		615 (42.7%)	76 (12.4%)
Histologic grade	1348		
Low grade		1243 (92.2%)	126 (10.1%)
High grade		105 (7.8%)	19 (18.1%)
Missing		91 (6.3%)	5 (5.5%)
Lymphovascular invasion	1355		
Absent		1240 (91.5%)	100 (8.1%)
Present		115 (8.5%)	45 (39.1%)
Missing		84 (5.8%)	5 (6.0%)
Perineural invasion	1327		
Absent		1311 (98.8%)	131 (10.0%)
Present		16 (1.2%)	10 (62.5%)
Missing		112 (7.8%)	9 (8.0%)
Mucinous subtype	1369		
Absent		1276 (93.2%)	127 (10.0%)
Present		93 (6.8%)	18 (19.4%)
Missing		70 (4.9%)	5 (7.1%)

The incidence of LNM according to depth of submucosal invasion was; Sm1 40/490 (8%), Sm2 34/334 (10%) and Sm3 76/615 (12%). The incidence of LNM was 45/115 (39%) when LVI was present and 10/16 (63%) when perineural invasion was present. The risk of LNM when only one risk factor was present is shown in Table (14).

Table 14. Risk pf lymph node metastases with one risk factor only.

	Sm1	Sm2	Sm3	Total
Submucosal invasion, only	17/336 (5.1%)	21/240 (8.8%)	36/424 (8.5%)	74/1000 (7.4%)
LVI, only	7/21 (33.3%)	5/11 (45.5%)	16/40 (40%)	28/72 (38.9%)
Perineural invasion, only	1/1 (100%)	1/2 (50%)	2/4 (50%)	4/7 (57.1%)
Mucinous subtype, only	1/16 (6.3%)	2/10 (20%)	5/30 (16.7%)	8/56 (14.3%)
High grade, only	1/17 (5.9%)	0/11 (0%)	2/25 (8%)	3/53 (5.7%)

LVI; Lymphovascular invasion

All potential risk factors were investigated with uni- and multivariate analysis. Depth of submucosal invasion (Sm1 vs Sm3), high-grade cancer, LVI, perineural invasion, mucinous subtype and young age were statistically significant when tested with univariate analysis. Depth of submucosal invasion and high-grade cancer were however not significant when tested with multivariate analysis, and hence only dependent risk factors. Thus, LVI, perineural invasion, mucinous subtype and age <60 years were the risk factors identified as statistically significant and independent (Table 15).

Table 15. Uni- and multivariate analysis of risk factors for lymph node metastases

		Univariate analysis			Multivariate analysis		
	Number	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Submucosal invasion							
Sm1	490	1	Ref		1	Ref	
Sm2	334	1.275	(0.789-2.060)	0.322	1.274	(0.763-2.128)	0.355
Sm3	615	1.586	(1.060-2.372)	0.025	1.479	(0.961-2.278)	0.075
Histologic grade							
Low grade	1243	1	Ref		1	Ref	
High grade	105	1.950	(1.151-3.305)	0.013	0.942	(0.502-1.766)	0.851
Lymphovascular invasion							
Absent	1240	1	Ref		1	Ref	
Present	115	7.445	(4.837-11.459)	<0.001	7.311	(4.582-11.665)	<0.001
Perineural invasion							
Absent	1311	1	Ref		1	Ref	
Present	16	14.592	(5.005-42.549)	<0.001	9.717	(2.856-33.064)	<0.001
Mucinous subtype							
Absent	1276	1	Ref		1	Ref	
Present	93	2.277	(1.321-3.926)	0.003	2.451	(1.302-4.613)	0.006
Location							
Colon	1054	1	Ref		1	Ref	
Rectum	385	1.196	(0.826-1.733)	0.343	0.934	(0.620-1.408)	0.745
Gender							
Male	752	1	Ref		1	Ref	
Female	687	0.953	(0.679-1.337)	0.781	1.147	(0.794-1.657)	0.464
Age*	1439	0.980	(0.966-0.994)	0.005	0.975	(0.960-0.990)	0.001
Age <60 years	1439	2.103	(1.419-3.117)	<0.001	2.654	(1.670-3.935)	<0.001

OR; Odds ratio, CI; Confidence interval. * Age is increasing by one year.

The risk of LNM in absence of the statistically significant risk factors (LVI, perineural invasion mucinous subtype and age <60 years) was 51/882 (6%). The Risk of LNM according to age is shown in Table 16.

Table 16. Risk of Lymph node metastases in the absence of the independent risk factors.

	Lymph node metastases
No significant risk factors[a]	77/1053 (7.3%)
Adjusted for age	
<50 years	8/48 (16.7%)
50-59 years	18/123 (14.6%)
60-69 years	15/264 (5.7%)
70-79 years	22/391 (5.6%)
≥80 years	14/227 (6.2%)

*Lymphovascular invasion, perineural invasion, mucinous subtype

Validation

The validation cohort obtained from the DCCG, consisted of 578 patients undergoing surgical resection of T1 CRC between 2016 and 2018 in Denmark (Fig. 16).

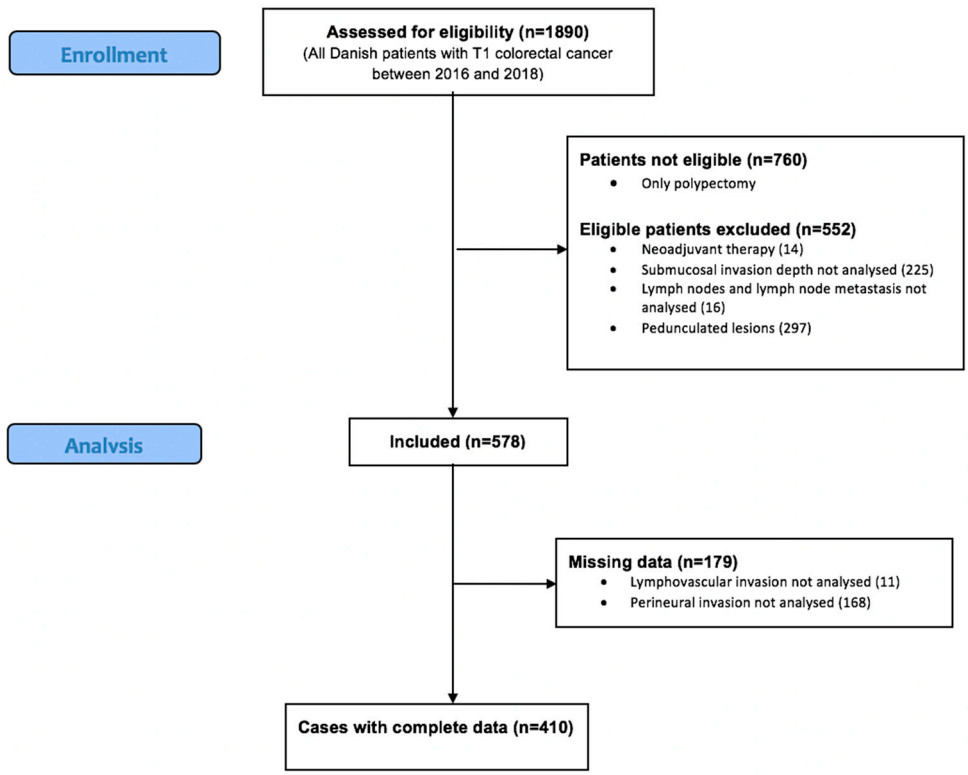


Figure 16. Flowchart of the validation cohort in Paper IV.

In total, 81 of the 578 included patients (14%) had LNM. Background data and incidence of LNM according to investigated variables can be seen in Table 16. The incidence of LNM according to depth of submucosal invasion was; Sm1 4/74 (5%), Sm2 19/165 (12%) and Sm3 58/339 (17%).

Table 17. Lymph node metastases according to histopathological characteristics and location in the validation cohort

	Available for analysis	Total	Lymph node metastases
Gender	578		
Male		312 (54.0%)	48 (15.4%)
Female		266 (46.0%)	33 (12.4%)
Location	578		
Colon		375 (64.9%)	49 (13.1%)
Rectum		203 (35.1%)	32 (15.8%)
Submucosal invasion	578		
Sm1		74 (12.8%)	4 (5.4%)
Sm2		165 (28.5%)	19 (11.5%)
Sm3		339 (58.7%)	58 (17.1%)
Histologic grade	578		
Low grade		548 (94.8%)	71 (13.0%)
High grade		30 (5.2%)	10 (33.3%)
Lymphovascular invasion	567		
Absent		447 (77.3%)	35 (7.8%)
Present		120 (20.8%)	43 (35.8%)
Missing		11 (1.9%)	3 (3.7%)
Perineural invasion	410		
Absent		405 (70.1%)	58 (14.3%)
Present		5 (0.9%)	2 (40.0%)
Missing		168 (29.1%)	21 (12.5%)
Mucinous subtype	578		
Absent		559 (96.7%)	79 (14.1%)
Present		19 (3.3%)	2 (10.5%)

Identical statistical analysis used on the primary Swedish cohort were performed on the validation cohort. The following variables were significant in both uni- and multi-variate analysis; LVI, high-grade cancer and young age (Table 17). Depth of submucosal invasion was significant only in univariate analysis (Table17).

Table 18. Uni- and multivariate analysis of risk factors for lymph node metastases in the validation cohort.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Submucosal invasion						
Sm1	1	Ref		1	Ref	
Sm2	2.28	(0.75-6.95)	0.148	1.84	(0.56-6.08)	0.316
Sm3	3.61	(1.27-10.29)	0.016	2.48	(0.80-7.71)	0.115
Histologic grade						
Low grade	1	Ref		1	Ref	
High grade	3.36	(1.51-7.47)	0.003	2.77	(1.09-7.04)	0.032
Lymphovascular invasion						
Absent	1	Ref		1	Ref	
Present	6.47	(3.89-10.76)	<0.001	5.24	(3.08-8.91)	<0.001
Perineural invasion						
Absent	1	Ref		1	Ref	
Present	2.04	(0.28-14.67)	0.448	1.25	(0.12-13.02)	0.841
Mucinous subtype						
Absent	1	Ref		1	Ref	
Present	0.72	(0.16-3.15)	0.658	0.92	(0.18-4.59)	0.916
Location						
Colon	1	Ref		1	Ref	
Rectum	1.25	(0.77-2.02)	0.373	0.92	(0.54-1.59)	0.769
Gender						
Male	1	Ref		1	Ref	
Female	0.78	(0.48-1.26)	0.305	0.87	(0.51-1.46)	0.588
Age[a]	0.95	(0.93-0.98)	<0.001	0.96	(0.93-0.99)	0.004
Age<60 years	2.20	(1.28-3.77)	0.004	2.02	(1.11-3.67)	0.022

Discussion

CRC is one of the most frequent malignancies world-wide and convincing data show that polypectomy is meaningful in reducing morbidity and mortality. The incidence of advanced colorectal lesions and early CRCs will most likely increase as a result of screening programs, implicating a shift in T-stage at diagnosis. The role of colorectal ESD in the West is unclear as is the overall management of this group of patients, comprising the scope of this thesis.

Herein we have shown that colorectal ESD can be implemented at a tertiary expert center in the West, reaching equivalent results as Japanese expert centers after a long and steep learning curve. Also, ESD seems to be a safe and effective treatment of patients with T1 CRC, circumventing unnecessary surgery. Furthermore, we have shown that forceps biopsies are unreliable in the work up of colorectal lesions amenable to endoscopic resection. Surprisingly, we found that depth of submucosal invasion is not an independent risk factor for LNM in T1 CRC whereas LVI is the predominate risk factor to carefully consider when selecting patients for subsequent surgery.

Implementation and learning curve of colorectal ESD in the West

Although colorectal ESD has been proven superior to other endoscopic techniques for selected colorectal lesions, dissemination to the West has been tedious[10, 238, 241, 242, 262]. One frequently used argument to this hesitance is the lack of gastric lesions suitable for ESD in the West. Thus, colorectal ESD is traditionally learnt in Japan after acquiring proficiency in gastric ESD where the maneuverability is better and the thicker muscular wall of the stomach impedes the risk of perforation. In fact, it is recommended that colorectal ESD is first attempted after 20-50 gastric ESD cases, which almost seems impossible to achieve during a reasonable time period in Western conditions[13, 263-265]. However, a growing number of reports suggests that colorectal ESD can be learnt without prior experience in gastric ESD and it is suggested that 40 supervised procedures are sufficient to attain competence level[263, 264, 266]. This claim is supported by our results in Paper I and II, given that all ESD procedures were performed by a colorectal surgeon without prior experience in gastric ESD. Hence, the lack of gastric lesions suitable for ESD is not an unsurpassable obstacle. However, the lack of Western experts supervising ESD procedures during the learning phase constitute a more manifest obstacle. Thus,

ESD enthusiasts have been required to obtain experience and tutoring form Japanese experts, which is not conceivable for the majority of Western endoscopists. Nevertheless, ESD proficient centers in Europe have begun to form, as have pioneering experts from the West, constituting the key factor on further implementation[14-18].

Moreover, the long learning curve comprise another obstruction to the dissemination of ESD to Western countries. Hence, we found that the en bloc and R0 rates significantly increased gradually during the five consecutive time periods in Paper I, stretching over a 5-year long time period, comprising 301 colorectal ESD procedures. During the last period, en bloc and R0 rates surged to 98% and 80% respectively, reaching levels in parity to leading expert centers in Japan[10, 11, 267]. However, a commonly used definition of competence level in colorectal ESD is to attain en bloc resection rate of >80% concomitantly with <10% complications[268]. The complication rate was <10% already during the first period (60 ESD cases) and en bloc resection rate reached 75% after 60 procedures and 82% after 120 procedures. However, rates of en bloc and complications as quality measures are subject to bias, since they are strongly influenced by location and lesion size, as shown in Paper I. Proficiency, defined as dissection speed, is therefore possibly a more just way of objectifying ESD efficacy since the size-factor is eliminated. A dissection speed of 9 cm/h has been suggested by Oyama et al as marking adequate proficiency, reached after 120 ESD procedures in our material[269]. Hence, the learning curve is long, and we found proximal colonic lesions to be indicative of piecemeal resection, RX resection and complications. However, the impact of lesion location was diminished and non-significant after 240 ESD procedures. Therefore, it is suggested that proximal lesions should first be attempted when sufficient experience with rectal and then distal colonic lesions have been gained. Also, it should be noted that size had a significant impact on en bloc resection and proficiency, which should be taken into account during the learning phase.

Furthermore, complications are feared in ESD and constitutes another profound obstacle in the implementation to Western centers. The overall complication rate in paper I was 8% (24/301) which is within the range of previous publications from Japan[10, 263, 270]. However, the complication rate was higher for the malignant lesions, 17% (5/29), in Paper II. Thus, submucosal invasion seemingly increases the difficulty of ESD, although the relatively small number of cases in Paper II limits this conclusion. All the same, from the patient's perspective, one has to look at the alternatives to ESD which in many cases would have been surgery. Colonic cancer surgery is associated with 23% morbidity and 2.4% mortality and rectal cancer surgery with 36% morbidity and 1.2% mortality, in Sweden[2]. Although direct comparisons of the aforementioned patients cannot be made, given that they comprise CRC stage I-IV, it is notable that there was no mortality related to the ESD resections and the overall morbidity was 9% (29/330) in Paper I and II combined.

Also, the vast majority of the ESD complications (22/29, 76%) were Clavien-Dindo 2 and handled conservatively, and 2% (7/330) of the patients undergoing colorectal ESD, required emergency surgery. Notably, all cases necessitating acute surgery in Paper I were located in the proximal colon, again stressing the higher degree of difficulty and increased risk of complications these lesions present.

Moreover, one could argue that piecemeal EMR would have been a preferred alternative for the benign lesions presented in Paper I. However, many of the lesions resected with ESD, including those with benign histology would have been very hard, if not impossible to resect with piecemeal-EMR. Thus, lesion size and proximal location are indicators for complications and failed endoscopic therapy when performing EMR[58, 220-222, 271-273]. Also, it has been reported that postprocedural bleedings occur in 5-7%, perforations in 3% and intraprocedural bleedings in 11% when performing piecemeal EMR for lesions >2cm[274-276]. Hence, piecemeal EMR for advanced and large non-pedunculated lesions is also associated with a risk of complications, in addition to the increased risk of recurrence and insecure pathology assessment related to fragmentation of the lesion. Additionally, the pre-resection diagnosis is known to be insecure, and not even the recent Japanese classification system has been shown to accurately distinguish lesions that can be resected piecemeal from lesions that necessitates en bloc resection[277].

The potential role of ESD in early colorectal cancer

Endoscopic resection of early CRC is associated with lower morbidity, mortality, health care costs and better function compared to surgical resection[4-6]. However, the risk of recurrence and LNM associated with local excision of T1 CRC cannot be ignored. To reliably assess the risk of LNM and reduce the risk of recurrence, en bloc resection is essential[278-280]. Therefore, ESD is a highly eligible alternative, providing en bloc resection regardless of lesion size and limiting surgery to cases with a high risk of LNM.

As described previously, the experience of colorectal ESD in the West is restricted and experience in resecting early CRC by means of ESD in Western countries is even more limited. We found a cancer incidence of 12% in the cohort of Paper II, comprising 255 non-pedunculated lesions >2cm. This is in line with comparable studies reporting cancer rates of 13% to 23%[10, 15, 169]. Moreover, the en bloc and R0 resection rates of the malignant ESD cases were 83% and 69%, respectively. These results are also aligned with previous studies investigating ESD of malignant non-pedunculated polyps[15, 169]. However, curative resection is defined in European guidelines as R0 resection of T1 CRC with limited submucosal invasion (Sm1) in the absence of LVI, tumour budding and low differentiation[58]. Thus, ESD was deemed curative according to these criteria in 38% (11/29) of the malignant ESD cases in Paper II[68]. This is within the range of studies from Japanese centers

reporting curative resection rates of 16% to 50%[10, 169, 281, 282]. All the same, ESD was non-curative in 18 cases, due to deep submucosal invasion in 15 cases, LVI in 2 cases and RX in 1 case. Hence, ESD was curative in 11 of the 12 potentially curable malignant lesions, illustrating that ESD is an eligible method for early CRC.

Notably, the complication rate was 17% (5/29) in Paper II, comprising four immediate perforations and one delayed bleeding. All but one of the complications could be managed conservatively. Hence, one perforation in the sigmoid colon led to abortion of the procedure and required emergency surgery. Pathologic assessment of the resected bowel segment surprisingly revealed a T3N0 tumour. This case illustrates that pre-therapeutic evaluation is difficult, given that the macroscopic appearance was deemed non-consistent of deep submucosal invasion and biopsies had shown LGD.

Moreover, post-ESD management was highly individual and partially non-coherent to guidelines in terms of recommending surgery for non-curative resections[58]. Hence, surgery was not strongly recommended in 9 non-curative cases owing that the risk related to surgical resection overweighed the risk of LNM, taking patients age, comorbidities and whishes into account. However, surgery was recommended in eight patients, and 6 patients underwent surgical resection whereof 1 residual cancer was detected but no positive lymph nodes were found in any of these patients. Two patients refused surgery and were put in intense surveillance. In total, ESD served as final treatment in 76% (22/29) of the patients with submucosal invasive cancer presented in Paper II.

The limited follow up time of 13 months hampers conclusions on long-term outcomes in paper II. Nonetheless, in the 20 patients followed up, one recurrence was detected, 15 months after a curative ESD resection. This is surprising, given that 10 out of the 20 patients in surveillance were non-curative resections and the only recurrence detected was hence in a patient with an en bloc, R0 resected lesion with the mildest pathology. One possible explanation to this recurrence could be free floating cells adhering to the ESD wound, raising the question whether it could be beneficial to wash the ESD wound after malignant resections in analogy to rectal washouts in anterior resections of rectal cancers[283].

Lesion assessment and the role of forceps biopsies

Optimal management of patients with colorectal lesions depend on correct diagnosis and staging prior to resection. In Japan, this assessment is performed with endoscopic staging, using image-enhanced endoscopy. In the West, endoscopic staging is less well-developed, instead biopsies are often obtained in the work up of advanced colorectal lesions. In paper III we investigated the reliability of such biopsies and found that the discordance between biopsies and resected specimen was 39%. The literature is scarce on comparable studies, however three reports

investigating small colorectal polyps found a 10-19% discrepancy between forceps captured fragments and resected lesions, supporting our findings[188-190].

Moreover, we found that lesion size significantly correlated with discordance, and large lesions were upgraded in histologic grade more frequently than smaller lesions. Presumably, this is related to the morphological heterogeneity in polyps, which increases with incremental size[284-287]. Also, biopsies are less representative in sheer tissue volume when lesions are larger. Even more, the intra and interobserver agreement among pathologists in terms of grading dysplasia is known to be poor to moderate[288-290].

Furthermore, the reliability of biopsies was neither influenced by time from biopsy to resection nor by number of obtained biopsies in Paper III. However, we were unable to conduct any analysis on the impact of the endoscopists obtaining the biopsies. Thus, it is highly plausible that biopsies obtained by endoscopists experienced in image enhanced endoscopy would be more accurate, targeting the biopsies to areas with a more sinister appearance. Nevertheless, it is well established that biopsies in non-pedunculated lesions can cause submucosal fibrosis apparent as a "non-lifting sign", also typical for deep invasive cancer[195-197]. Hence, submucosal fibrosis can make future attempts of endoscopic resection more strenuous and it can be difficult to distinguish from invasive cancer, further aggravating endoscopic resection.

Moreover, the pre-resection work up of polyps often aims at confirming or excluding adenocarcinoma. However, according to our findings, there is a 22% risk that a lesion diagnosed as HGD by biopsies in fact harbors submucosal invasive cancer and if biopsies show LGD the risk of cancer is 8%. Noteworthy, the scope of paper III was to assess the reliability of biopsies in large colorectal lesions referred for endoscopic resection. Hence, biopsies confirming cancer, in general referred directly for surgery, were therefore not included in this study and conclusions on the cancer mis-rate of biopsies cannot be drawn. Nevertheless, given that submucosal invasive CRC with low risk of LNM can be resected endoscopically, the need to rule out cancer in lesions amenable to endoscopic resection is redundant. Thus, even if biopsies were more correct in reflecting the histologic grade of colorectal lesions, they cannot bring insight in the key elements predicting curative resection.

Risk factors of lymph node metastases in T1 colorectal cancer

The advantages of endoscopic resection in comparison to surgery must carefully be balanced with the risk of concomitant LNM. The incentive to investigate risk factors related to LNM is thus to identify a low risk group where endoscopic resection can be regarded as final treatment. In paper IV we found that the overall incidence of LNM in T1 CRC was 10% which is within the range of previous publications, reporting 6-17%[62-65]. However, the risk factors identified as independent and significant in paper IV were; LVI, mucinous subtype, perineural invasion and low age. These findings are in conflict with current European guidelines stating that deep submucosal invasion, LVI, low differentiation and tumour budding are independent risk predictors of LNM[58].

Notably, depth of submucosal invasion has for decades been pivotal in the assessment of LNM. Thus, early studies reported LNM risks of 0-3% in Sm1, 8-10% in Sm2 and 10-25% in Sm3[64, 66, 67]. In contrast, depth of submucosal invasion was only a significant risk factor when comparing Sm1 to Sm3 in univariate analysis, and hence not an independent risk factor in our study. Notably, a growing number of more recent publications support our claim that depth of invasion is only a dependent risk factor[65, 69, 70]. In pursuit of an explanation, we found a previous study showing that lymphatic vessels have a significantly higher density in the superficial third of the submucosa (Sm1) compared to deeper layers (Sm2-3)[291]. This observation supports our findings since there is no incentive in the vascular anatomy that increasing submucosal depth would generate a higher risk of LNM. Also, the significant relationship between depth of invasion and LNM found in previous studies might be explained by the fact that Sm3 lesions potentially have a wider and larger surface area in contact with lymphatic vessels in the superficial layers of the submucosa[292]. This theory would also serve as an explanation to Sm3 being a significant dependent risk factor in our study. Hence, the relationship between deep invasion and LNM disappears when taking confounders into account.

In Paper IV, we found LVI to be the critical risk factor of LNM in T1 CRC. In fact, the risk of LNM increased from 8% when LVI was absent to 39% when present and LVI was significant in both uni- and multi-variate analysis. Also, the risk of LNM related to LVI was persistent, and did not change significantly in absence or presence of other risk factors. Indeed, most comparable studies have also identified LVI as a significant risk factor for LNM, although reporting slightly lower risks of LNM in the range of 19-32% when LVI is present (19-32%)[64-66, 293-295].

Furthermore, perineural invasion has been reported to be a poor prognostic factor in all stages of CRC but is seldom included in studies investigating risk factors for LNM in T1 CRC[296-298]. We found perineural invasion to be an independent risk factor, increasing the risk of LNM from 10% when absent to 63% when present.

However, perineural invasion as a risk indicator in clinical practice is hampered by its low incidence, only present in 1.2% of the cases reported in Paper IV.

Moreover, high grade cancer i.e. low differentiation has previously been shown to be an independent risk factor for LNM and is included in European guidelines as a factor prompting surgical resection[65, 69, 294, 295]. In contrast, we only found high grade cancer to be a dependent risk factor and hence not significant in multivariate analysis. Two previous studies lend some support to this notion, reporting that high grade cancer is not a risk factor for recurrence after local excision of T1 CRC[299, 300].

Another interesting finding in paper IV is that low age was a significant and independent risk factor. Hence, in absence of other risk factors, the risk of LNM was more than two-folded if the patient was younger than 60 years (15% risk of LNM) compared to if the patient was older than 60 years (6% risk of LNM). In alignment, two previous studies have reported higher incidences of LNM in young vs old patients with rectal cancer[301, 302]. Moreover, there is an increasing body of evidence that CRC presented at a lower age is of a more aggressive nature and more prone to metastasize. Thus, it has been reported that younger patients with CRC have an increased mortality, increased risk of local recurrence and a higher presentation of metastatic disease as compared to older patients[301-304]. Regardless of underlying factors behind the differences in CRC presented at young versus old age, it seems reasonable to take age into sincere consideration when deciding therapeutic strategies.

According to our results, the low-risk group is defined as absence of LVI, mucinous subtype and perineural invasion, in patients older than 60 years, with a 6% risk of LNM. This is contradictory to previous studies defining the low risk group as superficial submucosal invasion alone or in combination with absence of other risk factors with as little as 0-4% risk of LNM[64-67, 294, 295]. Hence, one is easily baffled by the conflicting results found on basically all potential risk factors for LNM in the literature. A possible explanation to these inconsistencies is the heterogeneity of previous studies in terms of inclusion, analysis and outcome. Thus, some studies include both T1 and T2 CRC[67, 69, 293], some include both surgically and endoscopically resected patients[65, 67, 294, 295], one study investigated the risk for LNM and recurrence[67], one study differentiated between micro and macro metastasis[295] and some studies do not include multivariate analysis[67, 70]. Also, even in the studies including multivariate analysis, the factors investigated differ, which also possibly contribute to the variating results found in the literature.

Moreover, when considering our findings, in light of the management of the patients in Paper II one is easily despaired. Age was not taken into consideration in Paper II and patients under the age of 60 years have a minimum of 15% risk of LNM, which was not known at the time. Furthermore, in Paper II, four patients were recommended surgery solely on the presence of deep submucosal invasion, and would have been in the low-risk group according to our results. In fact, three of

these patients underwent surgery, whereof none had residual cancer or LNM. Also, it is possible that surgery would have been more strongly recommended in non-curative cases where LVI was present, given that these patients have a 40% risk of LNM according to our data.

Noteworthy, Paper IV comprise a validation cohort obtained from the Danish colorectal cancer database. Indeed, the Danish data confirmed the major findings from the Swedish cohort. Hence, depth of submucosal invasion was only a dependent risk factor, LVI was the strongest risk factor and age was identified as an independent risk factor, in the Danish cohort. There were however some differences when comparing the two cohorts. The Danish material had a higher overall incidence of LNM (14% vs 10%) and a higher incidence of both LVI (21% vs 8.1%) and deep submucosal invasion (Sm2-3, 87 % vs 66%) as compared to the Swedish cohort. Thus, the Danish group, seemed more sinister overall, possibly explained by national differences in selecting cases for surgery as opposed to local excision. Also, the differences between incidence of LNM related to depth of submucosal invasion were more profound in the Danish cohort (Sm1 5%, Sm2 12%, Sm3 17%). However, these differences were not significant in multivariate analysis, consistent to the Swedish data. Furthermore, in contrast to the Swedish results, perineural invasion and mucinous subtype were not significant risk factors in the Danish cohort. This could potentially be explained by the inferior sample size and few cases where perineural invasion and mucinous subtype were present in the Danish material. Finally, high grade cancer was a significant, independent risk factor for LNM in the Danish cohort but not in the Swedish. Although this could be an effect of smaller sample size in the Danish material, it raises caution regarding neglecting high grade cancer as a predictor of LNM in T1 CRC, especially considering that the Danish findings are supported by the overall literature[65, 69, 294, 295].

Limitations

The studies included in this thesis have certain limitations. Paper I-III are retrospective cohort studies constituting a limitation, although we have taken precautions to minimize the risk of bias and included analysis of confounders when applicable. Furthermore, all ESD procedures analyzed in paper I-II were performed by one endoscopist at a single expert center and it is therefore unclear if our results can be generalized to other institutions. Another limitation is the restricted follow up time in paper I and II hampering conclusions on long term results after ESD resection. Moreover, Paper III is limited by not including cases with biopsy confirmed cancers referred for surgery, limiting conclusions on the cancer mis-rate of biopsies, falling outside the scope of this investigation. Paper IV is mainly limited by not including analysis of tumour budding and lesion size, which have shown to be independent risk factors in previous studies.

Conclusions

The overall conclusions based on the studies comprising this thesis are:

- ◊ ESD can be implemented in a Western center, achieving equivalent results as Japanese expert centers after a long and steep learning curve. Patient and lesion selection is vital during the learning period of ESD and it is recommended that large and proximal lesions, associated with an increased risk of complications, should first be attempted after mastering rectal and distal colonic lesions of incremental size. Furthermore, ESD seems to be a safe and eligible alternative for patients with suspected or known early CRC, limiting surgery to cases with a high risk of LNM.
- ◊ Forceps biopsies are not reliable in the work up of large and advanced colorectal lesions referred for endoscopic resection. Our results question the role of biopsies in the routine praxis of lesions amenable to endoscopic resection and it is suggested that forceps biopsies should be limited to cases requiring surgical resection.
- ◊ Depth of submucosal invasion is only a dependent risk factor for LNM whereas LVI, perineural invasion, mucinous subtype and low age are independent risk factors. Thus, deep submucosal invasion should not be used as a single factor prompting surgery after locally resected T1 CRC. The role of high-grade cancer as an independent risk factor of LNM is somewhat unclear and should be treated with caution.

Svensk sammanfattning

Kolorektalcancer är den tredje vanligaste maligna sjukdomen i Sverige och den andra vanligaste cancerrelaterade dödsorsaken i världen. Det är välkänt att polyper i tjock och ändtarm är förstadium till cancer, och endoskopisk polypektomi har därför visats reducera både cancer-relaterad sjuklighet och dödlighet. Risken för att en polyp skall innehålla cancer ökar med ökande polypstorlek. Även polypens växtsätt har visats spela in på cancerrisken och platta polyper har högre risk för cancer än stjälkade polyper. Behandling av kolorektalcancer är i första hand kirurgi men vid tidig cancer kan endoskopisk resektion vara tillräcklig, förutsatt att polypen är borttagen i en bit och inte fragmenterad. Vinsterna med endoskopisk behandling jämfört med kirurgi är stora för patienten och innefattar minskad sjuklighet och dödlighet samt bevarad tarm-kontinuitet. Stora och platta polyper är dock svåra att ta bort i en bit med konventionell polypektomiteknik och kirurgisk resektion har länge varit det enda alternativet för dessa polyper. Detta ändrades på 1990-talet när man i Japan utvecklade endoskopisk submukosadissektion (ESD), initialt framtagen för polyper i matstrupe och magsäck. Tekniken innebär att hela polypen, oavsett storlek, skärs bort i en bit från underliggande tunna muskellager, med en elektrisk nål-kniv. ESD fick snabbt spridning i Japan och andra asiatiska länder och på 2000-talet började man även använda ESD som behandling av kolorektala polyper. Spridningen av ESD till västvärlden har dock varit begränsad. ESD är nämligen tekniskt utmanande och innebär risk för tarmperforation vilket är en allvarlig komplikation som kan kräva akutkirurgi. I tillägg har ESD en lång inlärningskurva och avsaknaden av västerländska ESD-experter som kan lära ut tekniken, har ytterligare bromsat införandet av ESD i västvärlden.

Vårt mål med denna avhandling var att studera implementeringen av kolorektal ESD på endoskopienheten, Skånes Universitetssjukhus Malmö. Sekundära mål var att undersöka om biopsier är lämpliga i utredningen av polyper som remitteras för endoskopi samt utreda vilka faktorer som påverkar risken för lymfkörtelmetastasering vid tidig kolorektalcancer.

Delarbete I-III är retrospektiva registerstudier där vi granskat alla patienter som genomgått ESD för benigna (n=301) och maligna polyper (n=29) samt alla endoskopiska resektioner där man tagit biopsier som led i utredning innan polypektomi (n=485). Delarbete IV är en retrospektiv studie utförd på prospektivt

insamlad data från det svenska kolorektalcancer registret, innefattande patienter som opererats för tidig kolorektalcancer (T1) i Sverige (n=1439).

I denna avhandling har vi visat att kolorektal ESD kan implementeras i västvärlden, med resultat i paritet med japanska expert centra. ESD har en lång inlärningskurva och polyper i höger kolon är tekniskt utmanade och innebär större risk för komplikationer. Samtliga sex patienter i delarbete I (2%) som krävde akutkirurgi hade polyper i höger kolon. Vi fann även att ESD är en lämplig endoskopisk behandling av tidig kolorektalcancer. ESD var slutgiltig behandling i 76% av fallen med maligna polyper och kirurgi kunde således undvikas för dessa patienter.

Biopsier används ofta för att diagnostisera kolorektala polyper, men deras tillförlitlighet är dåligt studerad. I denna avhandling fann vi att biopsier gav fel histologisk diagnos i 39% av de undersökta fallen. Polypstorlek hade signifikant påverkan på biopsiernas tillförlitlighet och stora polypers maligna potential undervärderades i större utsträckning jämfört med små. Våra fynd ifrågasätter biopsiers roll i rutinutredning av kolorektala polyper där endoskopisk behandling är möjlig.

Risken för lymfkörtelmetastasering vid tidig kolorektalcancer är avgörande för om endoskopisk behandling är tillräcklig eller om kompletterande kirurgi skall rekommenderas. För närvarande bedöms denna risk framförallt genom att bedöma hur djupt cancern växer i det submukosala skiktet. I delarbete IV fann vi att djupet av cancerinväxt endast är en beroende riskfaktor och borde således inte ensamt vara utslagsgivande för ev. kompletterande kirurgi. Den dominerande riskfaktorn i vårt material var lymfovaskulär invasion som medförde 40% risk för lymfkörtelmetastasering. Vi fann även att risken för lymfkörtelmetastaser var dubbelt så stor för patienten yngre än 60 år, jämfört med patienter äldre än 60 år.

Sammantaget ger denna avhandling värdefull information om utredning, behandling och hantering av avancerade kolorektala polyper och tidig kolorektalcancer. Det är värt att nämna att denna patientgrupp med största sannolikhet kommer att öka i takt med att nationell kolorektalcancer screening införs i Sverige.

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