Aspects on colostomy construction, complications and stoma function

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Dedicated to

***Danaela, Sofia and Luis Fernando**, my beloved children!*

Work hard and give your best every day!

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ABSTRACT

Aim The aim of this thesis was to evaluate the importance of surgical technique for stoma complications as well as stoma function in patients operated with colostomy.

Methods Five papers are included: Three observational studies (three papers), one randomized control trial (two papers). Clinical data has been collected from medical records, operative notes, the Swedish Colorectal Cancer Registry, prospectively registered clinical records forms and patient reported data through questionnaires.

Results: The incidence of stoma related complications is high and may be affected by surgical technique but not stoma function (paper I). Most patients seem to live a full life with their stoma (paper II). A loop colostomy does not seem to reduce the risk for postoperative complications after surgery for obstructing colorectal cancer but it does affect the stoma related complications (paper III). The incidence of parastomal hernia was not affected by the surgical technique used under colostomy construction (paper IV-V).

Conclusion Surgical technique when colostomies are performed influences the occurrence of short-term complications in patients operated with abdominoperineal excision. Parastomal hernia incidence is not affected by the surgical technique used for colostomy construction. Stoma type does not affect the risk for postoperative complications.

Keywords: colostomy, surgical technique, stoma related complications.

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SAMMANFATTNING PÅ SVENSKA

En stomi är en avledning av tarmen igenom bukväggen där avföringen samlas in i en påse. Den kan vara permanent eller temporär. En stomi får sitt namn beroende på vilken del av tarmen som tas ut igenom bukväggen (tjocktarmsstomi – kolostomi eller tunntarmsstomi – ileostomi) och hur den konstrueras (änd, loop, eller split). Indikationen för att anlägga en kolostomi varierar från godartade till elakartade tillstånd och kan anläggas antingen som en avlastning av tarmen eller där man tar bort en bit tarm och där det inte går att göra en ihopkoppling av tarmen. Komplikationsfrekvensen är hög med en frekvens mellan 21-70% enligt rapporter från olika studier. Det är angeläget att försöka minska komplikationsfrekvensen så mycket som möjligt för att uppnå god stomifunktion och för att minska påverkan på patientens livskvalitetet.

Riskfaktorer relaterade till stomikomplikationer har identifierats. Patient-relaterade faktorer såsom hög ålder, högt BMI, akut kirurgi och diabetes, är de vanligaste riskfaktorerna men det finns också kirurgiska faktorer. Tekniken för att konstruera en stomi är sparsamt evidensbaserad och det finns fortfarande många frågeställningar om hur man på bästa sätt konstruerar en stomi för att förbättra funktion och minska risken för komplikationer. Några viktiga aspekter av den kirurgiska tekniken under stomikonstruktion är: vilken sorts stomi, placeringen av stomin i bukväggen, hur tarmen dras igenom bukväggen, hur snittet i muskelskidan i bukväggen utförs, vilken storlek öppningen i bukväggen har, samt om det är nödvändigt att förstärka bukväggen runt stomin med ett nät.

Detta doktorandprojekt är uppbyggt av delar som syftar till att identifiera riskfaktorer for stomikomplikationer, kolostomier, identifiera och försöka standardisera tekniken vid kolostomikonstruktion samt studera komplikationer och stomifunktion.

Delarbete 1: En retrospektiv studie om stomirelaterade komplikationer hos patienter som opererats med abdominoperineal resektion för rektalcancer (2004-2009) på SU/Östra samt skillnader i stomirelaterade komplikationer om patienterna delvis opererades i ryggläge (Standard Abdominoperineal excision S-APE) eller bukläge (Extended abdominoperineal excision ELAPE). Fler postoperativa stominekroser identifierades i ELAPE gruppen jämfört med S-APE gruppen, men det var ingen skillnad i antalet reoperationer. Det fanns inte heller några skillnader i stomifunktion ett år postoperativt.

Delarbete 2: Här studerades frekvens, allvarlighetsgrad och besvär av stomirelaterade symtom, stomifunktion och patientens acceptans av sin stomi hos patienter som opererats med abdominoperineal resektion för ändtarmscancer i Sverige 2007-2009. Vi studerade också potentiella riskfaktorer för utveckling av symptomatisk parastomal bråck. Data hämtades från det nationella kvalitetsregistret för kolorektal cancer (n=1397). Patienter som var i livet 3 år postoperativt i hela Sverige kontaktades per brev och därefter per telefon och tillfrågades om deltagande i en livskvalitetstudie. Total 495 patienter inkluderades och analyserades i studien. Av dessa patienter, utvecklade 56 (11%) symtomatiskt stomibråck. Den enda riskfaktorn som kunde identifieras som associerad med symtomatiskt parastomalt bråck var högt BMI. Ca 90% av patienterna hade inga begränsningar i sitt liv trots sin stomi.

Delarbete 3: Retrospektiv kohortstudie där skillnader i postoperativ komplikationsfrekvens studerades och relaterades till vilken stomityp (loop eller änd kolostomi) som använts vid avlastning av obstruerande kolorektalcancer. Kohorten inkluderade patienter i Västra Götalands Regionen mellan 2011- 2015 som identifierades via operations- och diagnoskoder. Total 289 patienter inkluderades i studien: 147 patienter fick änd kolostomi, 140 patienter fick loop kolostomi och för två patienter var det inte möjligt att identifiera vilken typ av stomi som var upplagd. Antal postoperativa komplikationer eller reoperationer skilde sig inte signifikant mellan grupperna. Tiden mellan indexkirurgi (när avlastande kolostomi konstruerades) till start av onkologisk behandling eller resektionskirurgi studerades och den var liknande i båda grupper. Patienterna med loop kolostomier drabbades av mer stomirelaterade komplikationer jämfört med patienter med änd kolostomier där retraktion och prolaps var de vanligaste.

Delarbete 4: Metodartikel där studieprotokollet för Stoma-Const presenteras. En randomiserad, kontrollerad studie med syftet att skapa kunskap om kolostomikonstruktion genom att jämföra tre typer av kirurgiska tekniker under kolostomiformation (Kryssincision i fascian, cirkelincision i fascian och nätförstärkning i bukväggen) avseende utveckling av parastomalt bråck ett år postoperativt.

Delarbete 5: Här presenteras resultaten från Stoma-Const studien. Totalt 209 patienter randomiserades i de tre armarna av studien: n=74 kryssincision, n=72 cirkelincision, och n=63 i profylaktiskt nät. Parastomalt bråck bedömdes med CT buk ett år postoperativt men också genom klinisk bedömning av kirurg samt stomisjuksköterska. Vi fann inga signifikanta skillnader i förekomsten av parastomalt bråck ett år postoperativt inom de tre olika kirurgiska tekniker som användes för stomikonstruktion.

Konklusion: Stomival och medvetenhet om kirurgisk teknik under konstruktion av en kolostomi kan minska frekvensen av stomikomplikationer och förbättra stomifunktionen samt patienternas livskvalitet.
Resultaten i avhandlingen visar att kirurgisk teknik under kolostomikonstruktion inte påverkade förekomsten av parastomalt bråck. För att förebygga stomirelaterade komplikationer måste vi identifiera möjliga riskfaktorer preoperativt. Majoriteten av de patienter som har en kolostomi har ändå ett fullvärdigt liv med sin kolostomi.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals (I-V).

I. Angenete E, **Correa-Marinez A**, Heath J, Gonzalez E, Wedin A, Prytz M, Asplund D, Haglind E.
Ostomy function after abdominoperineal resection- a clinical and patient evaluation
Int J Colorectal Dis. 2012; 27(10): 1267-1274.

II. **Marinez AC**, Gonzalez E, Holm K, Bock D, Prytz M, Haglind E, Angenete E.
Stoma-related symptoms in patients operated for rectal cancer with abdominoperineal excision.
Int J Colorectal Dis. 2016; 31(3): 635-641.

III. **Correa-Marinez A**, Grenabo J, Bock D, Wedin A, Angenete E.
The type of stoma matters-morbidity in patients with obstructing colorectal cancer.
Int J Colorectal Dis. 2018; 33(12): 1773-1780

IV. **Correa-Marinez A**, Erestam S, Haglind E, Ekelund J, Angerås U, Rosenberg J, Helgstrand F, Angenete E.
Stoma-Const- the technical aspects of stoma construction: study protocol for a randomized controlled trial.
Trials 2014; 15(1): 254.

V. **Correa-Marinez A**, Bock D, Erestam S, Engstrom A, Kälebo P, Rosenberg J, Haglind E, Angenete E.
Colostomy construction did not affect parastomal hernia rate: results from Stoma-Const a randomized controlled trial.
Manuscript

CONTENT

ABBREVIATIONS

APE	Abdominoperineal Excision
ASA	American Society of Anesthesiologists physical classification system
BMI	Body mass index
CRF	Clinical record form
CT	Computed tomography
ELAPE	Extralevator Abdominoperineal Excision
EORTC	European Organization for Research and Treatment of Cancer
HRQoL	Health-related Quality of Life
ICD-10	International Classification of Diagnosis codes
Mm	Millimeter
NOMESCO	The Nordic-Medico Statistical Committee
OR	Odds Ratio
QoL	Quality of Life
RCT	Randomized Control Study
RR	Relative Risk
SCRCR	Swedish Colorectal Cancer Registry
SSORG	Scandinavian Surgical Outcomes Research Group

1 INTRODUCTION

A stoma is defined as an exteriorization of the intestine trough the abdominal wall. The word "stoma" comes from the Greek "stomat" that means mouth [1]. The first stomas were intestinal fistulas due to trauma or incarcerated hernias [2]. Morbidity and mortality were very high and the only chance of survival was when a spontaneous entero-cutaneous fistula was formed [3]. It was not until 1710 that Littre, French physician and anatomist, suggested the concept of colostomy for bowel decompression in case of obstruction. In 1793, Duret performed a colostomy in an infant with congenital anorectal malformation. After that, some attempts were made during the 19th and beginning of the 20th century to relieve intestinal obstruction with a stoma.

There were advances in anesthesia at this time, and during the beginning of the 20th century resection of colorectal cancer became possible. Since then there have been attempts to improve the surgical technique of stomas and it continues today [1].

1.1 COLOSTOMIES IN COLORECTAL SURGERY

Colostomy formation has become a common procedure in colorectal surgery. What type of stoma and where on the abdominal wall this is placed, depends on the indication of the surgery and also on patient-related factors. The stoma can be temporary or permanent and is named according to which part of the bowel is externalized (jejunostomy, ileostomy or colostomy) and how this is performed (end, loop or split) [4].

An end colostomy means that the proximal part of the bowel is exteriorized and the distal part, if there is one, remains closed in the abdomen. In a loop or split stoma both ends of the bowel are exteriorized [4]. However, in the case of a loop stoma a part of the bowel is preserved as a bridge between the ends, while in a split stoma the bowel is completely divided in two ends. What type of colostomy is chosen in each case depends of the indication of the surgery, patients' habitus, bowel's conditions and sometimes surgeon's preferences.

The indications for a colostomy vary from congenital to acquired, benign or malignant gastrointestinal conditions [4]. It may be performed in both acute and elective surgery [5-8].

Most common indications for a colostomy are:

- Colorectal Cancer
- Complications of inflammatory bowel disease (Ulcerative Colitis, Crohn disease)
- Complications of diverticular disease (abscess, fistula, obstruction, fecal peritonitis)
- Perineal infections.
- Congenital malformation
- Incontinence
- Trauma

1.2 SURGICAL TECHNIQUE OF STOMA CONSTRUCTION

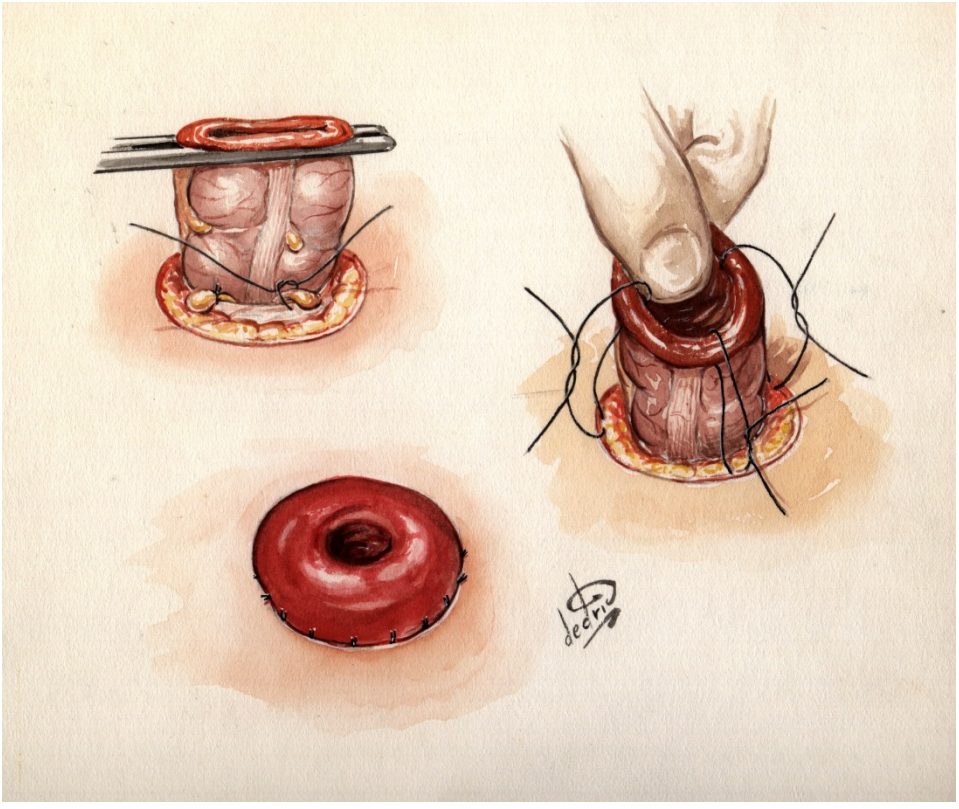


Figure 1. By permission of Leif Hultén

The evidence behind different surgical techniques for the construction of a stoma is still quite limited and the complication rate after stoma formation is still high. There are some studies that have investigated technical details, but unanswered questions remain about how to improve the technique to enhance function and reduce complications [9,10].

Since patient life expectancy has increased in the last decades, reduction of complications and improved function for better quality of life is important. It is possible that improved surgical techniques may be a key factor.

Which size and height the stoma should have, what form, and how to perform the opening in the abdominal wall, and whether there is a need to reinforce the abdominal wall with a mesh are examples of questions regarding the construction of a stoma.

1.2.1 HOW TO PERFORM A STOMA?

Incision in the abdominal wall

According to the literature, the most common description of the surgical technique for the construction of a stoma, is to perform a cruciate incision in the fascia and extract the bowel through the resulting hole, sufficient in size, out of the abdominal cavity [11]. A circular incision in the fascia instead for a cruciate has been another suggestion but this concept has only been tested in few studies [12,13].

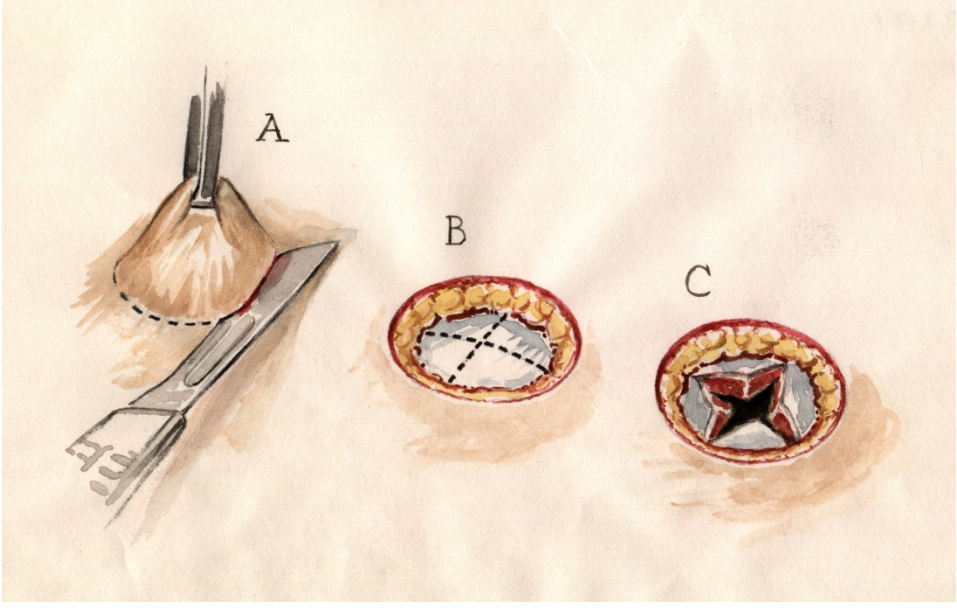


Figure 2. By permission of Leif Hultén.

The size of the trephine opening

According to most textbooks and also in accordance with our own clinical experience, the standard measure used is “two fingers width” or “just enough for passage of the bowel”. Both definitions are very unprecise; too large trephine opening increases the risk of parastomal hernia and too small trephine can cause ischemia or obstruction of the bowel. One study found that each extra millimeter was relevant and increased risk of parastomal hernia [14].

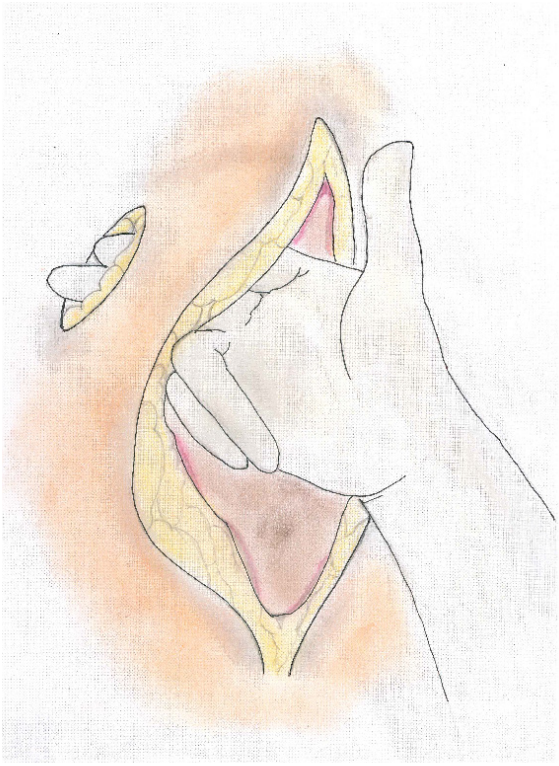


Figure 3. Size of opening in abdominal wall

Nguyen [15] attempted to standardize the skin incision to two-thirds of the width of the bowel although the impact of this on the functional outcome of the stoma was not presented. The width (W) of the flattened end of the bowel was measured and it was equal to half of the bowel's circumference. Bearing in mind that the diameter of a circumference is calculated from perimeter of the circumference (2W) divided with π (~ 3.1416), he concluded that this measure would be the optimal measure to the skin diameter was equal to 2/3 of the diameter of the bowel.

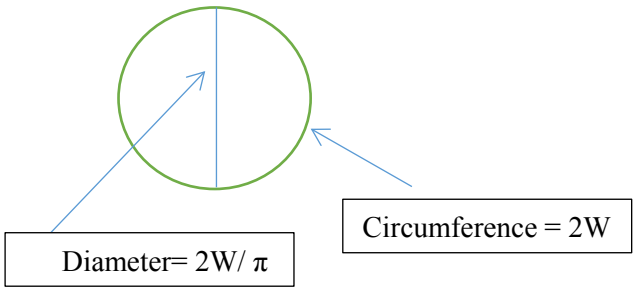


Figure 4. Diameter of the trephine opening was similar to 2/3 of the flattened bowel.

Other authors tried to explain the size of the aperture by tangential forces working according to the law of Laplace and concluded that the opening should be small enough to safely allow the passage of the intestine through the abdominal wall which would be a diameter of 25-30 mm for an end colostomy [16]. Others have designed a mechanical cutting device that cuts through all layers of the abdominal wall and the size for the trephine opening could be changed to 17, 25 and 32 mm of diameter [13]. An observational pilot study was performed at Sahlgrenska University Hospital, Östra Campus, in Gothenburg, Sweden in 2012 with the aim to standardize the surgical technique of colostomy construction. The information about the construction of the stoma and different measures of the bowel and abdominal wall was registered in 26 consecutive patients who received an end colostomy at the department.

Diameter, length of the bowel, size of the opening in the abdominal fascia, subcutaneous depth as well as the width of the "two fingers" of each surgeon,

(digit 2 and 3, the traditional measure for the size of the opening) were some examples of measurements we registered during the surgery.

We found that the measure of "two fingers width" varied in the team of surgeons between 32 and 43 mm, which represents a significant difference in the size of the opening of a colostomy. We could also see that there was a possible relationship between the width of the bowel at the level of anterior rectal abdominal sheath and the diameter of the trephine opening that could probably be approximated to 50%. This measure was then used in the randomized controlled trial in this thesis.

Extraction of the bowel through the abdominal wall

Whether the stoma should be taken through or lateral to the rectus abdominis muscle [10,17-19] has been debated. There are not randomized studies, only retrospective studies in this topic. Two retrospective studies found lower frequency of parastomal hernia, if the bowel was taken through the rectus muscle [10,20], but other authors did not find this difference[17,21]. The argument behind going through the rectus muscle is that it may work as support around the bowel, minimizing the risk of parastomal hernia. This way is the most common used. However, taking the bowel lateral to the muscles may reduce denervation of the abdominal wall, and a lower frequency of parastomal hernia by using this technique has been reported in a recent study [19]

Extraperitoneal vs intraperitoneal route for the extraction of the bowel has also been a topic of discussion [9,22-24]. The difference is that in the extraperitoneal route a tunnel is created to allow an oblique passage of the bowel, through the abdominal wall to the skin, closing the lateral space near to the bowel while in the intraperitoneal route the bowel is taken out directly through the peritoneum and the abdominal wall. In a meta-analysis of seven retrospective studies the results were in favour of extraperitoneal route regarding risks of parastomal hernia formation [25], but this technique is not yet widely used.

The height of the stoma

The height of a colostomy is recommended to be at least 1-2 cm above the skin in order to reduce skin problems and retraction of the stoma [26,27]. That means that the length of the exteriorized colon should 3-4 cm in order to create an eversion [28]. This requires good mobilization of the bowel to reduce tension in the

stoma [28]. However, there are some cases where fatty and shortened mesentery or bowel conditions make this step somehow difficult [29].

Reinforcement of the abdominal wall

The placement of a mesh around the stoma at the time of stoma construction, in order to reinforce the abdominal wall and prevent the formation of the parastomal hernia, has lately become a controversial issue in colostomy construction.

Different types of mesh have been tested [30]. The material, pore size, capacity of absorption and weight of the mesh varies and includes different types of synthetic and biological variations. Polypropylene, Expanded-polytetrafluoroethylene (e-PTFE), Polyglactin and Composite meshes are examples of synthetic meshes. The degree of ingrowth into the tissues and the tensile strength of them also vary, causing different inflammatory responses in the tissues with a risk for adhesions and possible erosion to the bowel [30].

Biological meshes have emerged as another option [31] with the aim to minimize the risks of synthetic meshes (erosion to the bowel, adhesion and stricture) [32,33], but there is currently low evidence to recommend this use.

The mesh can be placed in an onlay position above the anterior sheath of the fascia, sublay or retromuscular position, above the posterior sheath of the fascia/ peritoneum [34-40] or intraperitoneal onlay position (IPOM), that is posterior to the posterior fascia and peritoneum [41-43].

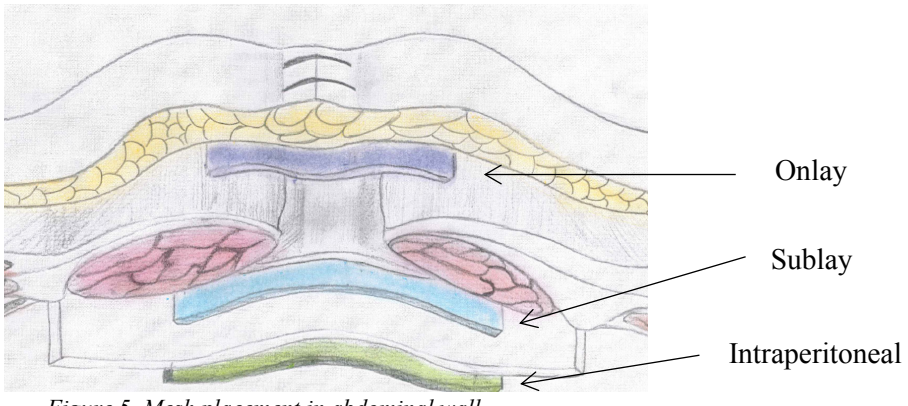


Figure 5. Mesh placement in abdominal wall

Open [35-39,44,45] as well as laparoscopic [40-43] approach has been used in different studies with diverse results in different series. However, open surgery seems to have a lower incidence of parastomal hernia with better evidence support than laparoscopic [46]. The use of a large mesh in the sublay position may reduce the chance of mesh migration [47].

Despite that a large number of prospective studies [35-45,47-53] have concluded that the use of the prophylactic mesh at the time of the construction of a colostomy significantly reduces the risk of parastomal hernia, this technique has not yet been accepted worldwide [54], even though the use of the mesh is strongly recommended nowadays [33,46]. This topic will be discussed in more detail later (page 16- 21).

1.3 COMPLICATIONS OF THE STOMAS

The main purpose of improving the surgical technique of stoma construction is to reduce the frequency of stoma complications and improve stoma function and hopefully the patients' quality of life.

Complication rates after stoma formation are still high and varies depending on the type of stoma (ileostomy or colostomy) and the type of stoma (end, loop or split). In different studies the complication rate varies from 20 to 70 % [26,55-61]. The incidence is highest in the first five years after stoma formation, but the risk for complications is lifelong [21]. Complications are usually classified as early if they appear within the first 4-6 weeks after operation and late, after 6 weeks postoperatively.

BMI, age, acute surgery, diabetes, gender, type of the stoma and surgical technique are some risk factors that have been associated with higher incidence of stoma complications [21,57-62].

Preoperative marking of the position of the stoma in the abdomen has been shown to be an important measure to minimize stoma complications [63]. An inappropriate placement of the stoma can lead to bandaging problems, leakage and skin problems. In elective situations it is recommended that a stoma care nurse meets the patients preoperatively for marking and to give instructions regarding stoma care [64].

Stoma complications can represent suffering for the patient [57]. Colostomies have lower complication rates compared to ileostomies [26,57]. Nevertheless, complications such as parastomal hernia are more common in patients with colostomies [58,65]. Stoma-related complications are more common in loop colostomies than end colostomies, probably due to their bulk, and they are associated with a high incidence of retraction, prolapse and hernia [29,59,60]. Bandaging and leakage problems are also associated with this type of stoma.

The most common complications of colostomies are:

1.3.1 ISCHEMIA AND NECROSIS

Ischemia may be associated with impaired blood perfusion of the colon, either because of tension or damage of its vascular arcades [4]. Often, in the immediate postoperative period, stomas become edematous followed by venous congestion and may look dusky [29]. This will usually disappear after a few days and is not the same thing as a necrosis. Lasting ischemia and subsequent necrosis varies in incidence between 1-13 % [26,66].

Necrosis can be partial, where only a part of the mucosa is affected. “Wait and see” management is usually effective. However, necrosis may also affect all layers of the bowel and reach deep below the fascia plane. In those cases a re-operation with a reconstruction of the stoma is often required [26,29,57,58,60].

1.3.2 RETRACTION

Retraction is defined as a stoma below the skin level and is probably caused by a tension of the bowel [61]. This complication is more common in colostomies than ileostomies with a reported incidence between 5-15 % in different studies [21,26,57,62]. Good mobilization of the bowel, including taking down the splenic flexure and/or central division of the inferior mesenteric vessels, are measures to reduce the tension, and is recommended to minimize this complication [59]**.** Convex bandaging can help to prevent secondary leakage but repair surgery may be necessary. An "end loop" can be a helpful surgical solution, leaving the end of the bowel stapled and constructing the stoma a few cm proximally of this by opening the anti-mesenteric side of the intestine. [67].

1.3.3 PROLAPSE

Prolapse is defined as a protrusion of the bowel through the stoma. If this occurs intermittently it is considered as a sliding, (for example when there is an increase of the intra-abdominal pressure), but a prolapse can also be constant or fixed [29,59]. This type of complication is more common in loop transverse colostomies with a frequency of up to 25 % in some series and an important reason why this type of stomas have been abandoned and seldom used [56,68-70]. It has been suggested that mesentery fixation could prevent its occurrence [29] but not all authors agree on this [21]. Prolapses often cause difficulties with bandaging and clothes but can also lead to incarceration and strangulation of the bowel [57].

Osmotic therapy with sugar has been suggested as initial treatment but surgery may be needed [68,71,72] with resection of the redundant bowel, relocation, and refashioning or closure of the stoma (when this is feasible).

1.3.4 STENOSIS

Ischemia, or retraction of the stoma, is usually a long-term consequence after early postoperative muco-cutaneous separation, with an incidence between 2 to 10%, mainly seen in end ileostomies but also in end colostomies [21,62,69,73]. The stricture may cause noise with the passage of flatus and can also cause emptying difficulties and even obstruction in some cases [57]. If the stenosis is only at the level of the skin or subcutis, it may be possible to treat by a local revision of the stoma, but if the stoma is low and there is a traction in the bowel, a laparotomy with mobilization of the bowel may be necessary [57].

1.3.5 PARASTOMAL HERNIA

Definition and incidence

Parastomal hernia is considered as an incisional hernia related to the trephine opening of a stoma [74]. It has been defined as a protrusion in the vicinity of a stoma [35]. This wide definition makes uniform reporting of parastomal hernia difficult and makes the differentiation between bulge and a real hernia a challenge [75].

The etiology of a parastomal hernia is not well understood. One theory is that herniation is a result of a pathological disorder in collagen metabolism, resulting in loss of tensile strength in the abdominal wall [76]. Another theory suggests it is caused by denervation of parts of the abdominal wall when constructing the stoma.

The incidence varies in different reports and depends on the type of stoma, the time for follow-up and how the assessment of the hernia was done. It is considered the most common long-term complication of colostomies [10,17,21,47,49,50,59-61,65,77-79] and has been reported in up to 81 % within 5 years postoperative [80]. The prevalence of parastomal herniation is expected to rise due to the increasing rate of colorectal cancer survivors and also due to the increasing obesity in the population [81].

Diagnosis and Clinical Manifestations

Most patients with a parastomal hernia are asymptomatic [74]. However, some patients have manifestations such as pain or discomfort, emptying difficulties, leakage, bandaging and skin problems, cosmetic complaints and difficulties to find properly fitting clothes [82,83].

The diagnosis of a parastomal hernia is challenging with low inter-observer reliability [84]. Traditionally, clinical assessment has been the diagnostic method used. The patient is assessed in supine and erect position and with the addition of Valsalva maneuver to increase intra-abdominal pressure [35]. However, it can be difficult to differentiate between a hernia and a bulge with this approach. Digital examination of the stoma to try to assess the opening in the fascia may be helpful, although this is not easy and demands experience.

Radiological evaluation with CT scan of the abdomen has also been used [36,85,86]. CT scan in supine position has low sensitivity to detect small hernias [87,88]. Addition of Valsalva maneuver could help to improve diagnosis but this is difficult to perform with patients in supine position. With patients in prone position intra-abdominal pressure can be directed towards the stoma, improving diagnostic sensitivity [89]. Endoscopic ultrasound with three dimensional reconstructions is another diagnostic tool to detect parastomal hernia with good reliability and lower cost. Ultrasound is operator-dependent and requires special training to assess parastomal hernia [87,90-92].

Clinical and radiological approach has been proposed for better diagnostic accuracy, but a standard clinical or radiological classification is still not validated [33,75,88,93,94]. Nevertheless, it is suggested to use the European Hernia Society classification for uniform research reporting [33]. This classification considers the size of the hernia defect with a cutoff of 5 cm for differentiation between small and large parastomal hernia and also the presence or not of incisional hernia in the middle line. See Table 1.

Table 1.

European Hernia Society of parastomal hernia classification			
		Parastomal hernia size	
		Small < 5 cm	Large >5cm
Concomitant Incisional Hernia?	No	Grade I	Grade III
	Yes	Grade II	Grade IV

*Classification European Hernia Society [75]

Risk Factors

Several risk factors for the development of parastomal hernia have been identified related both to patient factors and surgical technique. Among the patient related are older age [21,95-97], BMI>25 kg/m^2 [21,55], cancer [21,55], comorbidity such as diabetes [21,55], and waist circumference more than 100 cm [81]. Other variables that have been suggested as risk factors are malnutrition, smoking, use of corticosteroids and chronic coughing [82,98].

Factors related to surgical technique can be the size, form and placement of the trephine opening of the stoma, the route that the stoma is taken trough the abdominal wall [9,10,18,25] as well as the type of the surgical approach. Laparoscopic surgery has been suggested by some as a risk factor for development of parastomal hernia [99,100], but others do not agree with this [101]. A careful and improved surgical technique may be one of the most important steps in the prevention of stoma related complications. As minimally invasive surgery is steadily increasing it is very important to resolve this issue and work with prevention of parastomal hernia in this patient group as well [98].

Treatment

Conservative treatment of parastomal hernia without surgery is the most common. A change of the type of bandage, and in some cases a corset, could be useful [102-104]. However, if symptoms increase, a surgical intervention will be required [65,78,79,105].

The recurrence rate after repair of a parastomal hernia varies depending of the surgical technique used: local repair, relocation of the stoma, mesh repair with stoma in the same place or relocation of the stoma with a prophylactic mesh at the new stoma site. Suturing repair of the trephine opening has the highest recurrence rate up to 70-80%, which explains why this technique has been more or less abandoned. This recurrence rate has been reduced with the use of the mesh during the repair of the hernia but still remains around 20% [106]. In the case of acute obstruction, that leads to strangulation, ischemia and/or perforation of the bowel involved in the hernia, acute surgery can be needed [82].

Due to high recurrence rates after parastomal hernia repair, prevention of parastomal hernia at the time of construction has been suggested [98,106-109]. Attempts to reduce the rates of parastomal hernia have been made in the last few years with a placement of a mesh around the stoma at the time of stoma construction. Fears of infections or stoma complications, related to the presence of foreign material near or in contact with the bowel, have resulted in skepticism and a reluctance to implement the technique. However, these risks seem to be low [34,35,39,52]. A large number of prospective studies, [35-38,41,47-52] have reported reduced rates of parastomal hernias with the use of a prophylactic mesh, but the same results have not been possible to obtain in other studies [39,110]. See Table 1 and Table 2 [33,46].

Recommendations

The European Hernia Society Guidelines of 2018 [33] recommend the use of prophylactic mesh at the primary colostomy construction to reduce the incidence of parastomal hernia. After these guidelines were published, the results of a Swedish randomized study with large sample size, "STOMAMESH", has shown no reduction of the incidence of parastomal hernia by the use of prophylactic mesh [39]. A Cochrane review was published thereafter (July 2018) and the STOMAMESH trial was included in the analysis. The review concluded that there is still a considerable reduction of the rate of parastomal hernia with the use of prophylactic mesh but the evidence grade is considered low due to the heterogeneity in the studies[35-37,39,41,42,47-52,110-112] .

Table 2. *RCT studies evaluating parastomal hernia rate using prophylactic mesh at the time of stoma creation in open surgery.*

RCT studies Open Surgery	Stoma type	Mesh location and type of mesh	Sample size	Follow up	Rate of PH n(%) mesh vs no mesh	Hernia Assessment
Jänes et al [35]	End Colostomy	Retromuscular Vypro lightweight	54	1 Year 5 Years	0/16 (0) vs 8/18 (44,4) 2/15 (13,3) vs 17/21 (80)	Clinical
Serra-Aracil [36]	End Colostomy	Retromuscular Ultrapro lightweight	54	1 Year	4/27 (14,8) vs 11/27 (40,7) 6/27 (22,2) vs 12/27 (44,4)	Clinical CT
Hammond et al [37]	Loop stoma	Preperitoneal Permacol	20	1 Year	0/10 (0) vs 3/10 (30)	Clinical or present at reversal
Lambretch et al[38] 2 center	End Colostomy	Retromuscular/ polypropylene, ProlLite Ultra or Parietene	58	2 Years	2/32 (6) vs 12/26 (46) 8/32 (25) vs 11/26 (42)	Clinical CT
Odensten et al [39] Multicenter	End Colostomy	Retromuscular lightweight polypropylene	232	1 Year	30/104 (29) vs 32/107 (30) 33/104 (32) vs 36/107 (34)	Clinical CT
Brandsma et al[44] Multicenter	End Colostomy	Retromuscular lightweight polypropylene	150	1 Year	3/67 (4,5) vs 16/66 (24,2)	Clinical CT
Tarcoveanu et al[45]	Loop and End colostomies	Retromuscular Polypropylene	42	20 Months	0/20 (0) vs 6/22 (27)	Clinical and Ultrasound
Fleshman et al [40] Multicenter	Ileostomies colostomies	Retromuscular PADM(Porcine-derived acellular dermal matrix)	113	2 Years	5/49 (10,2) vs 7/53 (13,2)	CT and operative find

Table 3. *RCT studies evaluating parastomal hernia rate using prophylactic mesh at the time of stoma creation in laparoscopic surgery*

RCT Studies Laparoscopic Surgery	Stoma type	Mesh location and type of mesh	Sample size	Follow up	Rate of PH n(%) mesh vs no mesh	Hernia Assessment
Lopez-Cano et al[41]	**End Colostomy**	**Intraperitoneal/Onlay PROCEED (large pore lightweight)**	**36**	**1 year**	**9/18 (50) vs 15/16 (93,8)**	**CT**
Lopez-Cano et al[43]	**End Colostomy**	**Intraperitoneal Polypropylene Physiomesh**	**52**	**1 Year**	**6/24(25) vs 18/28(64)**	**CT**
Vierimaa et al[42] Multicenter	**End Colostomy**	**Intraperitoneal Onlay, dual component**	**70**	**1 Year**	**5/35 (14,3) vs 12/35 (32,3)** **18/35 (51,4) vs 17/35 (53,1)**	**Clinical** **CT**

1.4 QUALITY OF LIFE AND STOMA FUNCTION

The World Health Organization (WHO) defined health as "a state of complete physical, mental and social well-being, and not merely the absence of disease" [113]. This is a broad concept that is difficult to apply in clinical medicine. Health-related Quality of Life (HRQoL) has become a more common expression in an effort to define the quality of life in relationship to diseases and their treatments from patients' points of view in many relevant aspects such as: general health, physical functioning, cognitive functioning and social well-being [113].

Within colorectal surgery the construction of a colostomy is a common procedure and may be considered relatively easy. However, a colostomy implies a change in the patient's lifestyle (psychological, social and sexual) that may influence their quality of life (QoL) in one or more ways.

Quality of life instruments

To assess HRQoL in patients with stomas there are generic instruments as well as condition-specific. *Generic instruments* are designed to give a wide assessment of the quality of life of the patients (EQ-5D, SF36), while condition specific instruments are more disease oriented. The European Organization for Research and Treatment of Cancer (EORTC) has developed different questionnaires such as QLQ-C30 (generic for patients with any cancer) and QLQ-C29 (previously QLQ-C38) for patients with colorectal cancer [114].

There are also instruments to assess psychological, physical and social adjustment in patients with stomas where the most used one is "Ostomy adjustment scale" (OAS). This scale consists of 36 items with possible total scores ranging from 36 to 216, where lowest is worst [115,116]. Other questionnaires have been developed by different groups of researchers, some with good reliability and validity [84].

How is quality of life affected by a colostomy?

Some studies have reported inferior HRQoL in patients with a stoma compared to patients without stoma after rectal cancer resection with an additional negative impact in those with a bulge or a hernia [117-120] while others have reported little or no impact on quality of life resulting from the stoma [121-123]. Nevertheless, since

most patients with parastomal hernia are asymptomatic, it has been difficult to address how much their Quality of Life (QoL) is influenced by the hernia in reality [124].

A well-functioning colostomy increases the chance of patient acceptance and may not in itself negatively affect the patient's QoL. A study from our own group, Scandinavian Surgical Outcomes Research Group "SSORG", explored well-being and body image 3 years after APE in a population-based cohort. Three topics of importance were highlighted: bodily limitations (where stoma related problems are included), mental suffering and acceptance. Eighty percent of the patients expressed acceptance of their stoma regardless of body limitations or mental suffering, however almost 20% expressed the opposite [125]. Another prospective Swedish study explored adjustment to live with an ostomy one year after surgery using the Ostomy Adjustment Scale and found better adjustment in patients with a colostomy operated due to cancer than in patients who had an ileostomy. The lowest adjustment scores were in areas of sexual activities, attractiveness, and physical activities [126]. How the patients' quality of life is influenced after a stoma is still debated and a Cochrane review has indicated that there is a lack of high-level evidence [127].

Symptoms associated with stoma complications

Constipation, diarrhea, flatulence, loud flatulence, smelling flatulence, leakage and problems of stoma care are some of the most common symptoms reported by patients with stomas [83]. Frequency and severity of these symptoms are also important factors that influence in patients' daily life. Patients with parastomal bulging may also express a feeling of heaviness, cosmetic problems and difficulties with bandaging that leads to leakage and skin problems [128].

2 AIM

The overall purpose of this thesis was to evaluate the importance of surgical technique for stoma complications and stoma function in patients operated with colostomy.

The specific aims were:

- Evaluate the effect on colostomies of a new surgical technique for abdominoperineal excision in patients with rectal cancer regarding stoma complications and stoma function.

- To identify different risk factors and stoma related symptoms in patients with symptomatic parastomal hernia.

- Evaluate if the stoma type influenced postoperative and stoma related complications in patients operated due to obstructing colorectal cancer.

- To compare three different surgical techniques for construction of a colostomy regarding the development of parastomal hernia.

3 PATIENTS AND METHODOLOGY

3.1 STUDIES AND STUDY DESIGNS

This thesis is based on three methodologically different studies in patients who have received a colostomy after resection surgery for cancer or benign causes or only as decompression of the bowel. Patients' data has been collected in special clinical record forms (CRFs). Questionnaires regarding stoma function and quality of life have been developed by our research group and given to the patients at different time points in each study for follow-up and analysis. Hospital records and the Swedish Colorectal cancer Registry (SCRCR) have been other sources of data.

Table 4. *Overview of Studies and Methods used*

	Study Design and Methodology	Total patients	Groups
I	Retrospective Cohort study	69 pat	S-APE* n= 31 ELAPE** n= 38
II	Cross sectional	495 pat	Symptomatic PH¥ n= 56 Asymptomatic PH n= 439
III	Retrospective Cohort study	289 pat	End Colostomy n= 147 Loop Colostomy n= 140 Indeterminate n= 2
IV- V	Randomized RCT	209 pat	Cruciate incision n = 72 Circular incision n = 74 Prophylactic mesh n = 63

**Standard Abdominoperineal excision,*
***Extralevator Abdominoperineal excision,*
¥: Parastomal Hernia

3.2 PATIENTS AND BACKGROUND OF STUDIES

PAPER I

This paper reports the results of a retrospective study that aimed to evaluate the impact of a new technique for abdominoperineal excision including a colostomy construction. Patients operated with an abdominoperineal excision (APE) due to rectal cancer at Sahlgrenska University Hospital in Sweden between 2004 and 2009 where included for analysis.

With the aim of improving the oncological results of abdominoperineal excision due to rectal cancer, the surgical technique for the perineal part of the dissection was modified in 2006 [129]. This change included modifications in the patient's position during the perineal part of the dissection from lithotomy (patient lying on back) in S-APE to prone position (patients lying on the abdomen) in ELAPE. Timing of the stoma construction varied from being constructed at the end of the operation in S-APE (after perineal dissection was performed) to before the patient was turned into prone position in ELAPE. The impact of this change on the newly constructed colostomy was unknown. Clinical observation and concerns of stoma complications secondary to this change were the reasons behind the decision to perform this study.

The patient cohort was divided in two periods (2004-2006) and (2007-2009) in which patients were operated with abdominoperineal excision in lithotomy and prone position respectively. Medical records, surgical charts and notes form stoma care nurses were analyzed for data regarding operative technique, stoma related data and stoma related complications. Quality of life questionnaires were sent to all patients alive 3 years after the operation, to get information about stoma function and quality of life. A total of 69 patients were possible to assess with answers from both sources.

PAPER II

This paper reports the results of a cross-sectional study that aimed to evaluate stoma related symptoms; symptomatic parastomal hernia, distresses associated with the colostomy, colostomy acceptance as well as to identify potential risk

factors for development of symptomatic parastomal hernia after abdominoperineal excision in Sweden.

All patients operated due rectal cancer between 2007 and 2009 were identified from the Swedish Colorectal Cancer Registry. Living patients were contacted 3 years after the study inclusion time (2012). Those who agreed to participate in the study and returned the questionnaire and who had received a newly constructed colostomy at the index operation were included in this study. Symptoms such as constipation, diarrhea, flatulence, leakage and skin irritation where assessed. Frequency, intensity and distress associated with the symptoms were evaluated.

Operative notes were analyzed retrospectively with focus on the abdominal part of the surgery when the stoma was constructed. The surgical technique of stoma construction was analyzed and possible risk factors for development of symptomatic parastomal hernia and stoma related complications were explored as well as patients' reported symptoms and quality of life.

PAPER III

This paper reports the results of a retrospective study that aimed to evaluate if the stoma type (loop colostomy or end colostomy), used for deviation of the bowel in the case of a obstructing left side colorectal cancer without resection of the tumor, influenced the rate of postoperative complications (primary endpoint) as well as the time until starting neoadjuvant or palliative oncological treatment or definitive surgery. Patients were identified using NOMESCO-codes and ICD-codes (JFF23, JFF24, JFF26, JFF27, JFF30, JFF31). Patients operated in five hospitals in Region Västra Götaland, Sweden who fulfilled the inclusion criteria between January 2011 and December 2015, where included in this study.

End colostomy as well as loop colostomy may be used for deviation of fecal stream in the case of distal obstruction and there is little known about which type of stoma should be preferred to minimize the risk for postoperative complications and stoma related complications. When an end colostomy is performed, the distal part of the bowel above the tumor is stapled/sewn and there is a risk for dehiscence of this suture (blow-out), causing leakage of bowel content and septic complications in the abdomen and/or the pelvis. It is thought that this type of complication does not to occur in patients with a loop colostomy

because the bowel is exteriorized providing colonic decompression in both directions. However, the risk of infection in the pelvis around the tumor remains.

There was no consensus among the colorectal surgeons in Region Västra Götaland and both types of colostomies were used. This made it possible to gather a representative study population that included patients with both loop colostomy and end colostomy.

No previous studies on this topic were found in the literature and that was the basis for this retrospective study.

Data was retrospectively collected. Medical records, operative notes and notes from stoma care nurses were analyzed to address the differences between the two groups as well as stoma function, and patients' quality of life were also explored.

PAPER IV –V

Paper IV describes the background and the design of the Stoma-Const trial; a multicenter, randomized trial with the aim to compare three different surgical techniques used during the colostomy construction and the impact this has on the rate of parastomal hernia: cruciate incision (control group), circular incision in the fascia or reinforcement of abdominal wall with a mesh around the stoma.

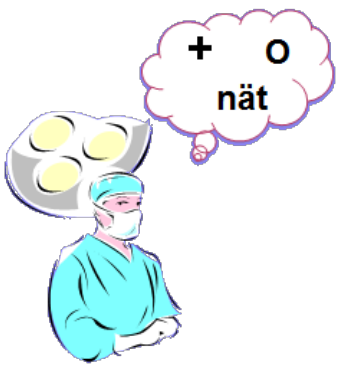


Figure 6.

The study was initially planned as a two arms study that would compare cruciate incision with circular incision. However, at this time results from studies that compared prophylactic mesh (intervention) with no mesh (control) at the time of stoma construction proclaimed many beneficial results using prophylactic mesh. Such studies were from single centers with small sample size and they did not describe in detail the surgical technique used in the control arm. Besides, there were still fears about the use of mesh around the bowel, the risk of long-term complications, reoperations, stoma function and quality of life; factors that were not assessed in any of the studies.

We decided to include a third arm in design of Stoma-Const trial before it started, to also evaluate prophylactic mesh compared with circular incision and cruciate incision (control arm). Inclusion and exclusion criteria were defined and we decided to include only permanent colostomies to enable a 1 year follow-up. Surgical techniques for each arm of the study were described with the aim to standardize them, thus minimizing risk of bias.

Some questions were still undefined i.e. the size of the incision in the fascia. This had traditionally been determined by the operating surgeon's two fingers width that varies depending on the surgeon. Bearing this in mind, we used data from our pilot study performed in 2012 (described in the introduction of this thesis) and we concluded that the best measure for the trephine opening would not depend on the width of the surgeon's fingers but on patient factors. In this pilot study we found that the diameter of the fascia incision was close to 50% of the width of the patient's left colon including the mesocolon, and this measure could be applicable to all three arms of the study to achieve a more standardized technique.

3.3 METHODS AND METHODOLOGICAL CONSIDERATIONS

The research questions behind this doctoral thesis are:

1- Does the position of the patient during the perineal dissection of an abdominoperineal excision affect the colostomy?
2- Which are the symptoms associated with symptomatic parastomal hernia?
3- Are postoperative complications influenced by which type of stoma is used in the case of obstruction of the bowel due to colorectal cancer?
4- Does the incidence of parastomal hernia within 1 year depend on surgical technique during stoma construction?

THE OBSERVATIONAL STUDIES

Paper I and Paper III are both *retrospective studies* where medical charts review was performed. In retrospective studies the quality of the results depends of the quality of registered data and this varies significantly. Clinical measures refer to variables that are assessable by health care professionals, who sometimes interpret and document it in different ways. With the aim to obtain the most complete possible data, all medical notes, operative notes and nurse's notes were reviewed in both studies.

Paper II is a cross sectional and register based study. Part of the data was collected from The Swedish Colorectal Cancer Registry (SCRCR) and from a quality of life questionnaire which was send to all living patients 3 years postoperatively. Operative notes were also analyzed retrospectively with the focus on the abdominal part of the surgery, especially the stoma construction.

How a condition is defined affects the measured incidence, which is another problem to consider. An example is parastomal hernia that has been defined as "a protrusion in the vicinity of the stoma" [35]. This wide definition allows for great variations of the reported incidence of parastomal hernia in different trials. There is also a difference between the doctors' assessment and the patients'

perception. In paper II the purpose was to explore parastomal hernia incidence from the patients' perspective and identify symptomatic parastomal hernia. In that study symptomatic parastomal hernia was considered if patients reported symptoms from the stoma or problems due to stoma herniation or reoperation of the colostomy. Contrary to this, in paper V an effort was made to reach an objective number of parastomal hernia with radiological and clinical assessment.

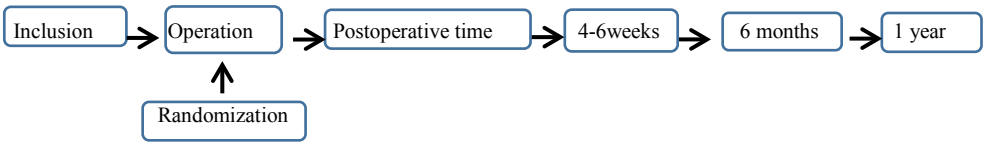
THE RANDOMIZED CONTROLLED TRIAL

A study protocol was written and ethic permission obtained before the inclusion started. Specific clinical record forms as well as patient questionnaires were used.

The target group was all patients who were scheduled to receive an end colostomy, regardless of the underlying indication for surgery.

Patients were randomized to one of the three arms of the study, cruciate incision (control group), circular incision and prophylactic mesh. Patients were followed up by surgeons and stoma nurses during the postoperative time until 1 year postoperative as shown in Figure 7.

Figure 7. F. Follow up Stoma-Const



Surgical complications, stoma-related complications and re-admissions, among other variables, were registered in specials CRF (clinical record form) at different times. Patient symptoms and experiences were also registered. At one year postoperatively, all patients were assessed clinically and radiologically with the aim of evaluating the rate of parastomal hernia in the study population.

Randomization

In the Stoma-Const trial participating centers were allowed to randomize between the control group and one or both experimental arms. Two of three centers randomized in all three arms of the study, but the third center only randomized patients between cruciate incision (control group) and circular incision.

Randomization was stratified by hospital with a block of six in closed envelop systems in each participating hospital. Block randomization is used to ensure a balance in sample size across groups over time and stratification is achieved by generating a separate block for each combination in the different centers to avoid imbalance in the sample size [130]. Randomization was performed during the operation just before the colostomy was constructed to avoid any alteration of surgical technique depending on which group the patient was allocated to.

Sample size

To calculate sample size in the Stoma-Const study we considered a difference in parastomal hernia rate of 20% from 30% for control group to 10% in the interventions' groups, to be clinically relevant between control and intervention's arms. With a power of 80% and 5% level of significance we would require 62 patients per group. We planned to include 80 patients per group to cover possible drop outs.

The study duration and inclusion time were longer than expected, which is a common problem in clinical trials. The study was stopped after we reached the sample size we had calculated as necessary.

Surgical technique

With the aim to standardize the surgical techniques, step by step specifications were agreed on for each arm of the study. Different measures were taken and registered in perioperative CRF during stoma construction, for example subcutaneous depth, diameter of the bowel, diameter of the fascia incision, length of the bowel above the skin before it was everted, as well as diameter and height of the finished stoma.

We standardized the size of the opening depending of the patient's bowel as follows: The width of the left colon and its mesocolon was measured at the point where it passed through the fascia and this size was used to calculate the diameter of the fascia incision. It was expected to be equivalent to 50% of the bowel diameter and this measure was used in all three arms of the study. If surgeons found that this size did not work in a particular patient, he/she could adjust it (smaller or bigger) and register the resulting size.

VALIDITY OF THE DATA

In observational studies, particularly in retrospective studies, data is collected from medical records and the results depend on the quality of the registered original data, in contrast to prospective studies where more control of how data are registered is possible. For instance, in paper II we aimed to find possible associations between the surgical technique during stoma construction and symptomatic parastomal hernia, with information from operative notes. Details of the construction of the stomas were scarcely documented and not available for all patients, in contrast to Stoma-Const where data was prospectively collected in clinical records during the operation, thus reducing possible missing values.

External validity refers to how well the results of a study may be generalizable to other patients outside of the study with same condition. Inclusion and exclusion criteria of the study may affect this. In paper II the accessibility of information about symptomatic parastomal hernia in patients with end colostomy was facilitated as the national cohort includes all patients operated by abdominoperineal excision in Sweden. Data from The Swedish Colorectal Cancer Registry has been studied and reported to be of high validity [131]. Very close to 100% of Swedish patients with colorectal cancer are registered in SCRCR. This precludes selection bias, which might occur when patients from only one center are included, and also when only some patients from several centers are included.

In paper V we assessed all patients planned to receive an end colostomy, regardless of underlying disease, in both open and laparoscopic surgery, which reflects the clinical reality and increases the generalization of the results.

3.4 OUTCOME MEASURES

3.4.1 POSTOPERATIVE COMPLICATIONS

Postoperative complications were part of the main endpoints in papers III and V. For this evaluation we used the Clavien-Dindo classification [132], which consists of a five grade scale depending on the required treatment of the postoperative complication.

Table 5. Clavien-Dindo classification*

Grade I	Any deviation from normal postoperative course. - No pharmacological treatment (antiemetics, analgetics, diuretics, electrolytes are allowed) - No endoscopic or surgical or radiological treatment. - Superficial wound infection
Grade II	Requiring pharmacological treatment other than in Grade I. Blood transfusion and parenteral nutrition.
Grade III	Requiring surgical, endoscopic or radiologic intervention IIIa: Intervention not under general anaesthesia IIIb: Intervention under general anaesthesia
Grade IV	Life-threatening complication requiring Intensive Care IVa: Single organ dysfunction (including dialysis) IVb: Multiorgan dysfunction
Grade V	Death

**Clavien Dindo classification of surgical complications* [132,133]

Postoperative complications may be under-graded or over-graded depending on how they are interpreted and who does the documentation in the medical charts (doctors or nurses) [133]. The Clavien-Dindo classification reveals the magnitude of each complication, but not the complete burden of postoperative morbidity. Moreover, often only the most serious complication is reported thus underestimating the effect on the patient of more than one complication.

The comprehensive complication index (CCI) is an added tool in the evaluation of postoperative complications that integrates all complications in a patient to

one value [134]. It is based on the Clavien-Dindo classification, giving a value to each Clavien-Dindo grade and summarizing the postoperative morbidity on a scale from 0 (no complication) to 100 (death), making the comparisons of the postoperative burdens more uniform. CCI may better reflect the real difference between the treatments [134].

The Clavien-Dindo classification has been used in the retrospective study in paper III for evaluation of postoperative complications between the two types of colostomies in obstructing colorectal cancer. We decided to only consider the highest grade of complication for each patient; this limited the ability to calculate CCI but otherwise reflected the clinical question we assessed in this paper.

Stoma related complications

Data related to the stoma was documented in the medical charts by specialist stoma care nurses. Stoma related complications were recorded retrospectively from medical charts in paper I and III and prospectively in paper V, where stoma nurses registered information about stoma and stoma complication in conjunction with patients' assessment.

A clinical record form (CRF) for the randomized study was developed in collaboration with the stoma care nurses to document the height and diameter of the stoma, color, skin irritation, stoma related complication (if relevant) and bandaging problems.

3.4.2 THE QUESTIONNAIRE

The questions about stoma symptoms, which were used in all studies in this thesis, were part of an extensive questionnaire developed by Scandinavian Surgical Outcomes Research Group.

This questionnaire covers many aspects of functional outcome after abdominoperineal excision that has been analyzed and published by others [135,136]. The questionnaire was developed after in-depth interviews with patients operated by abdominoperineal excision. The interviews then underwent content analysis, and based on this questions/answers were formulated, followed by an expert validation, where surgeons, stoma nurses and research nurses took part.

Finally the resulting questionnaire was face validated and revised before being used in the study. This method for development and validation has been described in detail by other authors [136-138].

Questions about the stoma included not only the type of complication but also the quality, frequency and intensity of the complications, and the associated level of distress. The symptoms explored included constipation, diarrhea, flatulence, loud flatulence, smelly flatulence, leakage, skin irritation and stoma care related problems.

Some of the questions were dichotomized when analyzed to distinguish the presence of symptoms from no symptoms and then related to the surgical technique, but also related to stoma acceptance.

3.5 STATISTICAL CONSIDERATIONS

In clinical research the results of studies contain some uncertainty due to chance. P-value (probability value) expresses the chance of showing a difference between two treatments. In clinical research numerous statistical tests are used to analyze the data, and the selection of the correct tool is important. Choosing the wrong test makes the p-value inaccurate, and this can result in wrong conclusions.

Some variables may affect the association between other variables, which can interfere with the consistency of the results and demonstrate false associations; they are confounding factors and affect the validity of the results. A confounding factor is a variable that may affect both the exposure and the outcome. Known confounding factors must be taken in account before the exposure and the results must be adjusted. Stratification of the data, subgroups analysis and multivariate analysis are examples of methods to manage confounding factors.

In this thesis the Chi-square test and Fisher's exact test were used for categorical variables and the Mann–Whitney U analysis was used for continuous variables. Statistical significance was defined as a two-sided p-value <0.05 in most of the studies in this thesis and a multiple hypothesis test was performed in Stoma-Const. Relative risk (RR) or Odds ratio (OR) were used to analyze risk factors and 95% confidence intervals were reported.

Multiple hypothesis testing

Two types of errors may be made in the process of testing of the study hypothesis: Type I error means rejecting a null hypothesis when it is true, and Type II error means failing to reject a null hypothesis when the alternative hypothesis is true. However, when several hypothesis tests are performed it increases the risk type I error or familywise error [139]. Familywise error means that the risk of drawing at least one erroneous conclusion will be larger than 5% (pre-specified p-value) and this risk increases as more test are performed. There are various strategies available to reduce the risk of error and to prevent inflation of the familywise error rate caused by using several hypothesis tests. One of these strategies is the Bonferroni correction, where the p-value is multiplied by the number of planned tests; this achieves a higher p-value and makes it harder to mistakenly reject the null hypothesis. Another way is a fixed sequence

procedure where the primary hypothesis is tested and only if this null hypothesis is rejected will a second hypothesis be tested. In Stoma-Const we used the Parallel Bonferroni gatekeeping which is a combination of the two methods already described.

Missing values

One of the biggest challenges of clinical studies is missing data. In regard to quality of life missing data is a recurring problem. There are three types of missing data. The first is 'missing completely at random' (MCAR), when missing data is completely independent of other observable or unobservable factors/variables and the probability of missing is the same for the whole study population. The second is 'missing at random' (MAR), when missing data may have a possible dependence with already observed data but not additional dependence with the unobserved data and the third is 'missing not at random' (MNAR), where the probability of missing is explained by or depends on other unobservable data. Trying to characterize the pattern of the missing data is important for the validity of the results as it may lead to biased results and wrong conclusions. Sometimes imputation methods are needed to handle missing data. Imputation means that missing values are replaced by estimated values from observed data. Multiples values are imputed for each missing observation to generate a complete database.

3.6 ETHICAL APPROVALS

Paper I:

The local ethics committee approved the study (#407-10), and the study was registered at ClinicalTrials.gov, NCT01323166.

Paper II:

The Regional Ethical Review Board in Gothenburg approved the study (Dnr 406–10, 407–10).

Paper III:

This study has been approved by the ethical committee of Gothenburg EPN 412-15.

Paper IV and V:

The trial has been approved by the Swedish Ethical Committee (EPN/Göteborg Dnr 547-12) and the Swedish radiotherapy protection committee (Dnr 12-38). It has been approved by the Danish ethics committee (Protocol H-4-2013-061), and by the Danish Data Protection Agency (no. HEH-2013-049, I-Suite no:02418).

The study was registered at www.clinicaltrials.gov (NCT NCT01694238)

4 RESULTS

4.1 PAPER I

There were 96 patients that could be assessed and 77 agreed to participate. Exclusion reasons from this point are shown in Figure 8

.

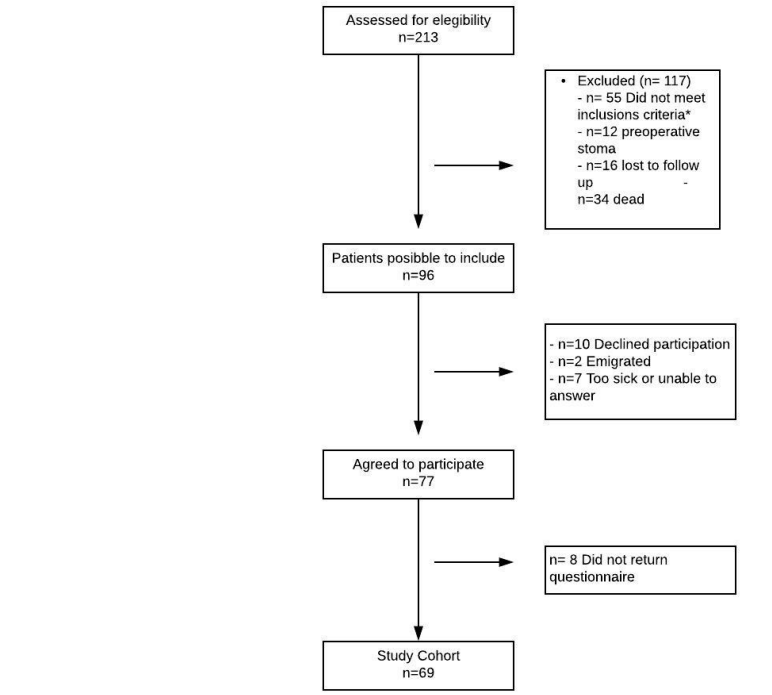


Figure 8. Flow Chart of included patients

In a total of 69 patients could be analyzed regarding stoma function and stoma related' data. Almost 90% of the participating patients answered the questionnaire. Stoma height was significantly lower in S-APE in the early postoperatively time and at 6 months.

There was a significant increase of necrosis or partial necrosis, in the ELAPE group, but this did not correspond to an increased number of reoperations.

In 146 patients early post-operative complications were analyzed albeit not published. In the early postoperative phase there was trend towards more necrosis, dehiscence and infection around the stomas in the ELAPE group as shown in Table 6, but stoma function could not be evaluated in all those patients, as not all answered the questionnaire.

Table 6.

	Standard APE (n=71)	Extralevator APE (n=75)	p-value
Stoma complications			
Necrosis	11 (15.5%)	20 (26.7%)	0.073
Bleeding	7 (9.9%)	1 (1.3%)	0.026
Dehiscence	2 (2.8%)	6 (8%)	0.156
Infection	0 (0%)	6 (8%)	0.017

The frequency of symptoms did not differ between the groups, and patient reported distress was associated to the presence of symptoms. Close to 90% did not feel that their stoma limited their life.

4.2 PAPER II

Out of 495 patients eligible to assess, 56 (11%) developed symptomatic parastomal hernia. A high body mass index (BMI) was significantly associated with symptomatic parastomal hernia (p-value 0.03).

Flatulence increased the risk for symptomatic parastomal hernia by 53%.

Almost 90% of all patients felt unlimited by their stoma in their daily life. Surgical details regarding colostomy construction were also analyzed. No relation between any of the registered details and the development of parastomal hernia was observed.

4.3 PAPER III

A total of 289 patients were eligible to be included in this study (see the flow chart in the article). The study cohort was divided in two groups for analysis: end colostomy (n=147) and loop colostomy (n=140). Two patients were excluded from the analysis as it was impossible to determine the type of stoma.

The characteristics of the groups were similar, except that patients in the loop colostomy group were more often operated in an emergency setting than those in the end colostomy group (48% and 28% respectively). Postoperative complications were assessed according to the Clavien-Dindo classification and the most severe complication per patient was reported. About 56% of patients in the end colostomy and 47% in the loop colostomy groups had no postoperative complication.

Complications were dichotomized as mild (CD I-II) and severe (CD => III). No significant differences between the groups (end colostomy/loop colostomy) were found regarding postoperative complications OR 0.99 (95% CI: 0,60; 1,63) nor in reoperations 2.01 (0,82; 4,93).

The time from the index surgery (when the diverting colostomy was performed) to the start of oncological treatment was also evaluated (37 and 40 days respectively), as well as the time from the index surgery to resection surgery (139 and 115 respectively). No significant differences were found between the groups (n.s). Analysis of the data was adjusted by age, gender, ASA, BMI and elective/acute surgery, which are recognized risk factors for postoperative complications as well as stoma related complications, with the aim to reduce confounding factors to influence the results. No differences in postoperative complications were demonstrated, neither in unadjusted nor in adjusted analysis of the data.

The diameter of the stoma was larger and the stomas were lower in the loop colostomy group compared to the end colostomy group. Patients with a loop colostomy had more problems with leakage, bandaging and prolapse, and retraction was also more common in patients with a loop colostomy compared to an end colostomy See Table 7.

Table 7. Stoma Related Data

	Postoperatively		4-6 weeks postoperatively		4-6 months	
	End Colostomy n=141	Loop colostomy n=135	End Colostomy n=115	Loop colostomy n=74	End Colostomy n=69	Loop Colostomy n=29
Stoma height (median, mm)	20(0-50)	15(0-100)	15*(0-40)	10(0-55)	10(0-30)	10(0-130)
Stoma diameter (median, mm)	38(25-60)	45*(25-70)	30(20-45)	35*(20-95)	28(20-40)	35*(25-90)
Stoma complications	N=141	N=135	N=118	N=92	N=76	N=36
Necrosis	24(17%)	17(12%)	8(6.7%)	4(4.3%)	0(0%)	0(0%)
Dehiscence	3(2.1%)	2(1.5%)	8(6.8%)	3(3.3%)	0(0%)	0(0%)
Prolapse	0(0%)	2(1.5%)	1(0.8%)	6(6.5%)*	1(1.3%)	4(11.1%)*
Hernia	0	0	1(0.8%)	1(1.1%)	5(6.6%)	6(15.8%)
Skin irritation	23(16.3%)	16(12.1%)	32(27.1%)	28(31.5%)	14(19.4%)	9(26.5%)
Retraction	2(1.4%)	10(7.4%) *	4(3.4%)	13(14.1%)*	3(3.9%)	4(11.1%)
Stenosis	0	0	1(0.8%)	0(0%)	0(0%)	0(0%)
Granuloma	0	0	2(1.7%)	3(3.3%)	2(2.6%)	1(2.8%)
Total stoma complications	52(37%)	47(35%)	57(48%)	58(63%)	25(32%)	24(67%)
Leakage	18(12.7%)	12(8.9%)	12(10%)	23(24.7%)*	5(6.6%)	7(19.4%)
Bandaging problem	11(7.8%)	14(10.4%)	15(12.3%)	27(28.1%)*	10(12%)	7(17.5%)

4.4 PAPER IV-V

Paper IV describes the design of the trial and the colostomy construction technique in detail. Paper V shows the results at the primary endpoint of the study, ie parastomal hernia rate within one year postoperatively

Five hundred and sixty-three patients were assessed for inclusion. Out of those 354 (62%) were not possible to include, 104 did not meet inclusions criteria and 204 did not want to participate. Some of the reasons for not meeting inclusion criteria were: anastomosis of the bowel was performed during the operation instead of colostomy, a loop colostomy was performed instead for end colostomy, patients who were planned to have an elective operation were acute operated etc.

Reasons for non-inclusion due to concomitant disease were that the patients had already had an abdominal hernia, the surgeon assessed that mesh could not be inserted, long operation time, etc. 20 patients were missed for inclusion and 26 were not included for reasons that were unclear.

A total of 209 patients were randomized to one of the three arms of the study: cruciate incision n=74, circular incision n=72 and prophylactic mesh n=63. The evaluation at the primary endpoint of the rate of parastomal hernia within 12 months of colostomy construction was made with CT, abdomen in prone position or supine position in absence of the first, as well as clinical assessment by surgeon or stoma nurse in cases where CT was not available.

A total of 185 patients were available for assessment within one year. Thirty-two (50.8%) in the cruciate group, twenty-four (37.5%) in the circular group and twenty-three (39.7%) in the mesh group developed parastomal hernia within 12 months. No significant differences were observed in unadjusted or adjusted analyses regarding the development of parastomal hernia, complications, readmissions or reoperations.

Age was the only risk factor found to be significantly associated with development of parastomal hernia in the bivariate and multivariate analysis. High BMI, subcutaneous depth, diameter of the fascia and CCI were significant in the bivariate analysis but not in the multivariate analysis.

The size of the trephine opening in the fascia, which was tested in this thesis, was performed according to the recommended measure i.e. 50% of the width of the patient's left colon with mesocolon measured at the point where it passed through the fascia without any adjustment, in only 60% of the cases. In 40% of cases this measurement was adjusted by the surgeon during operation.

5 DISCUSSION AND FUTURE PERSPECTIVES

This thesis evaluated the importance of the surgical technique of colostomy construction, and whether the surgical technique affected colostomy function, using data from different sources including one randomized and three non-randomized trials that allow us to analyze this topic from different points of view.

Surgical Technique and Stoma related complications

The overall purpose of the collection of initial patient data in paper I was to compare the oncological outcome of new surgical techniques in rectal cancer surgery: "ELAPE" compared with the traditional "APE" [140]. In paper I the clinical observations confirmed more necrosis in the stomas in patients operated in prone position (ELAPE). However, whether the difference of when the stoma was constructed, or if there were other factors during the construction of the stoma, that could lead to more necrosis, could not be addressed in this study. Besides, the low number of reoperations due to stoma complication and no differences in the bowel function between the groups after surgery did not confirm necrosis as an important long-term clinical problem.

Body weight pressure on the newly constructed stoma during the prone jackknife position could be an explanation for the higher number of necrosis in this group; more care of the stoma when patient is in the prone position has since been taken. The lack of mobilization of splenic flexure resulting in high tension and perfusion problems could be another explanation for necrosis, but it could not be addressed in our study due to the low number of patients in each group who had their flexure mobilized. The correlation between stoma height and bandaging problem puts emphasis on the importance of adequate height of the stoma, which is in accordance with other reports [26,141]. The results of this study led to a change in the care taken of the newly constructed stoma, when the patient was turned into prone position during the operation, using padding to form a supporting circle around the stoma for protection.

In the Swedish national cohort included in paper II, most of the important technical details for stoma construction were analyzed, i.e preoperative meeting

with a stoma nurse, how the incision of the fascia was performed, the use of mesh, anchoring sutures and three-point sutures. Unfortunately, almost 40% of the data could not be assessed due to lack of information in operative notes. This fact may in some way reflect that colostomy construction might be considered a trivial part in an otherwise extensive surgical procedure, possibly giving room to carelessness during the construction of the stoma that may generate problems for the patient, who will live with the stoma the rest of their life.

Assessing the total incidence of parastomal hernia at the time of a 3-year follow-up in this national populate based study would have been interesting but almost impossible; the information was gathered from a patient reported questionnaire and we know that it is very difficult to distinguish between a hernia and what is only a bulge. For this reason we decided that it would be more reliable to ask about symptomatic parastomal hernia. A precise definition of symptomatic parastomal hernia was formed to minimize the risk of faulty interpretation, i.e. including only clinically relevant details such as reoperation due to hernia, readmission to the hospital due to problems associated with parastomal hernia or patient-reported symptoms considered as symptomatic of a parastomal hernia.

Using this definition it was possible to address symptomatic parastomal hernia in 56 patients (11%) of the study population. This number may be considered too low, compared with the reported incidence in other trials [21,65,82], but this is the number of patients, who actually required surgery due to parastomal hernia [105]. That almost 90% of the patients with a colostomy felt unhindered in their daily life is valuable information to give to patients about to receive an stoma and gives them hope for the quality of their future life.

Many efforts to improve surgical technique with the aim to reduce the incidence of parastomal hernia have been made before the prophylactic mesh started to be used [9,10,25], and after it many trials have compared surgical techniques with and without prophylactic mesh at the time of colostomy construction (Table 2 and Table 3). A multicenter, randomized study is the best way to achieve more trustworthy results. The Stoma-Const trial was designed to compare three different surgical techniques of colostomy construction and the impact that they have on the rate of parastomal hernia and the impact on patient-reported stoma related symptoms.

Diverting stoma in obstructive colorectal cancer

In some cases colorectal cancer requires extensive radiologic and endoscopic assessment preoperatively and neoadjuvant treatment for down-staging the tumor to make it operable. In case of obstruction, the bowel must be decompressed before the oncological treatment is started; a procedure that in some situation has to be done in acute conditions where a diverting colostomy is necessary. Acute surgery is associated with poor short- and long-term outcomes [142,143]. There is still a lack of evidence to support the clinical decision of what type of colostomy is better in those situations to reduce the risk for postoperative complications. Theoretically, a loop colostomy that decompresses both the upper and the lower part of the bowel could be advantageous to reduce the risk of blow-out. However, the evidence to support this clinical decision is weak.

Postoperative complications can lead to a delay in starting oncological/surgical treatment. We did not find any significant differences in postoperative complications within 90 days regarding the time oncological/ surgical treatment was started (paper III). We observed that even in the group that received a loop colostomy, deep infections around the tumor were possible. More loop colostomies were performed in emergency settings, which could in part explain the high rates of postoperative complications in this group. However, the multivariate analysis, where timing of surgery was included as an adjusting variable, did not reveal any difference from the unadjusted results. The high incidence of stoma related complications in the loop colostomy group, followed by more bandaging problems with a stoma larger in diameter and lower in height, may present an argument for considering an end colostomy as the first alternative in order to reduce stoma-related complications, mainly in patients who will keep the colostomy for the rest of their lives. A loop colostomy as a temporary stoma is not a good option; it does not seem advantageous from our study of stoma related complications and it did not reduce the number of postoperative complications. In addition, it may cause technical problems during the upcoming resection surgery unless it is planned well. It may also increase the risk for parastomal hernia development due to the large trephine opening in abdominal wall made during the loop colostomy construction.

No randomized control trials are published on this topic. After the results of this retrospective study it would not be ethical to perform one, but further follow-up and continuous evaluation of our results is of value.

Parastomal hernia

With the improvement of long-term survival after colorectal cancer surgery, it is evident that some complications, that were not a problem previously, will become one, for example parastomal hernia.

The identification of risk factors associated with parastomal hernia may be key to prevent the development of parastomal hernia. High age was the only significant risk factor in the multivariate analysis of Stoma-Const and this is in agreement with other studies [21,61,62]. High BMI, subcutaneous depth, fascia diameter and CCI were significant in the bivariate analysis but not in the multivariate. An interaction effect between subcutaneous depth and fascia diameter was observed, as well as with body mass index. Subcutaneous fat thickness >23mm as well as high BMI > 25kg/m^2 and diameter of the fascia incision >25mm have been reported by other authors as significant predictors of parastomal hernia [21,41,55,144]. Eleven randomized control trials have now been published on this topic. The trials compare prophylactic mesh with no mesh during the stoma construction in open and laparoscopic surgery. Many meta-analysis and systematic reviews have been performed and all of them conclude that mesh insertion at the time of colostomy construction reduce the incidence of parastomal hernia [65,79,98,105,123,145,146]However, this conclusion must be interpreted with caution due to differences between the trials and risk for bias. The methodological approaches of the trials, the use of different meshes, different place for insertion in the abdominal wall, variety of postoperative assessment and follow-up are some examples of those differences.

There seems to be no increase in short-term complications due to meshes, but long-term complications are not well studied. Reoperation due to parastomal hernia appears to be lower with prophylactic mesh, but more long-term data is needed [46]. All these reasons could explain why this technique has not been universally accepted, even though that it was recommended in the last European hernia society guidelines published in 2018.

The primary outcome – parastomal hernia is difficult to assess. Both radiological approaches and clinical assessment was performed in our study. CT abdomen in prone position was performed for more accurate results as shown in other studies [89] and radiologist was blinded to improve the quality of the results. No radiology classification was used, and the existing classifications have not been validated

[33]. In the Stoma-Const study we did not find any significant differences between the surgical techniques compared. However, what constitutes a clinically relevant difference can be debatable. The observed difference of around 10% between the control group and the intervention group requires further study to confirm if it is a true difference.

Our results are in accordance with the results of a recently published randomized[39], multicenter control Swedish trial "STOMAMESH" which also had a large sample size and compared mesh with no mesh under the construction of the stomas. Even with the same surgical approach with placement of mesh in sublay position as in Stoma-Const the trial did not find any benefit with the use of the mesh compared with no mesh.

General discussion

It is mandatory to evaluate the effects of new surgical techniques on complications and function. This thesis was designed with the aim to explore the impact that the surgical technique has on colostomy construction and other surgical techniques that affect the colostomy, such as postoperative complications, stoma related complications and stoma function.

Identifying possible risk factors for the development of complications may lead to changes preoperative that could improve the outcome after surgery.

The learning curve and uptake of a new a surgical technique could impact on results and complications. We could, however, observe no differences in our data relating to the surgeon's experience. We included both open as well as laparoscopic surgery to reflect the clinical reality. The outcome with the use of prophylactic mesh laparoscopic in sublay position has been considered as similar with open surgery by other authors[53]

One of the strengths with this thesis is the inclusion of both observational and experimental studies. Most of the included studies also have a large sample size. Although colostomy construction technique has evolved during the last two centuries, scientific knowledge is still low and improving the technique with a more standardized approach is essential.

Another strength of this thesis is the inclusion of data from different sources, for instance clinical data from medical charts and operative notes, from SCRCR and

patient-reported outcomes questionnaires to enable a wide assessment of stoma complications from a clinical as well as a patient perspective.

6 CONCLUSIONS

The choice of the stoma and awareness of surgical technique during the construction of a colostomy may reduce the rate of stoma complications and improve stoma function and thus also improve quality of life.

The main conclusions of the papers of this thesis are

1- Surgical technique may affect stoma related short-term complications in patients operated with abdominoperineal excision but not long-terms complications or stoma function.

2- Most patients feel unhindered by their colostomy in their daily life.

3- The type of colostomy does not affect the incidence of postoperative complications after surgery for obstructing colorectal cancer, but a loop colostomy has more stoma related complications. End colostomy should thus be considered as the first alternative for these patients.

4- Surgical technique during the construction of a colostomy does not significantly affect the incidence of parastomal hernia within 1 year postoperative. Further evidence is needed before prophylactic mesh is adopted as a routine.

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