Abdominoperineal excision for distal rectal carcinoma

Oncological outcome and aspects of self-assessed quality of life

Mattias Prytz

Department of Surgery
Institute of Clinical Sciences
Sahlgrenska Academy at University of Gothenburg

UNIVERSITY OF GOTHENBURG

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Cover illustration: Schematic picture of ELAPE by Hanna Bringman

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mattias.prytz@vgregion.se

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To my beloved children

Ludwig, Theodor and Wilmer

Great minds discuss ideas; average minds discuss events;

small minds discuss people.

Eleanor Roosevelt

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Göteborg, Sweden

ABSTRACT

In recent years an adjusted method of performing an abdominoperineal excision (APE) - so called extralevator APE - has been developed and internationally spread. It has been proposed to decrease intraoperative perforations and non-radical surgery and therefor improve local cancer control and decrease rates of local recurrences as compared to standard APE. This thesis aims to investigate if the oncological outcome of ELAPE is superior to standard APE and to explore the association between patient reported intrusive thoughts and QoL as well as to type of surgery performed three years after surgery and to compare outcome to that found in a normative Swedish cohort.

Data on all Swedish patients operated with any kind of APE in the years 2007-2009 were collected from the Swedish ColoRectal Cancer Registry and short-term oncological outcome was measured (i.e. perforations and non-radical surgery) as well as short-term complications and mortality. In order to be able to differ between APE and ELAPE, all patients' operation notes were collected from the hospital charts where they had been operated, and analysed with regard to which operating technique had been used. When 3-years local recurrence data were available in the registry these data were also collected from the registry and analysed with regard to what operation had been performed. Furthermore, a special questionnaire was developed in order to be able to measure a number of health-related QoL parameters specific for this group of patients. The questionnaire was sent to all patients alive 3 years following surgery and data on QoL was compared to data from a Swedish normative population.

Short-term oncological results were the same for both groups with regard to perforation and non-radical surgery. There were fewer intraoperative perforations for a subgroup of the most distal tumours in the ELAPE group but not for the entire group. There were more wound infections for the ELAPE-group.

Local recurrences after 3 years were significantly more common in the ELAPE group as compared to standard APE but there was no difference between groups in overall survival. Intraoperative perforation was significantly associated with higher risk of local recurrence.

A large proportion of survivors after abdominoperineal excision for rectal cancer have a quality of life comparable to a normative population, however many suffer from a symptom of stress, negative intrusive thoughts, which significantly decrease overall quality of life.

Oncological outcome following ELAPE is not superior to standard APE. ELAPE is associated with more perineal wound complications. This method should be used in selected patients with high risk of intraoperative perforation.

Keywords: Rectal cancer, Abdominoperineal excision, Extralevator Abdominoperineal excision, ELAPE

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SAMMANFATTNING PÅ SVENSKA

Ändtarmscancer är den 9:e vanligaste cancersjukdomen i Sverige och drabbar årligen ca 2000 svenskar. Den orsakar ungefär 800 dödsfall årligen i Sverige och är inte sällan förenad med mycket lidande för de drabbade patienterna.

För att kunna uppnå bot vid ändtarmscancer krävs oftast en operation där man opererar bort hela cancer-tumören och en del av- eller hela ändtarmen. Om tumören sitter väldigt långt nere i ändtarmen, nära ändtarmsöppningen, blir det ofta aktuellt med en operation där hela ändtarmen (inklusive analkanalen och ändtarmsöppningen) opereras bort, s.k. ändtarmsamputation (engelsk förkortning: APE). Det innebär att patienten i samtliga fall får en stomi (”påse på magen”). Trots att man gör en så omfattande operation så uppnår man inte alltid bot, och jämfört med operation där det är möjligt att ta bort tumören och ändå koppla ihop tarmen igen, så är resultaten efter APE sämre. Det är vanligare med lokalt återfall i tumörsjukdomen (s.k. lokalrecidiv) efter APE än efter andra ändtarmsoperationer för cancer.

Med syfte att förbättra resultaten efter APE lanserades under början av 2000-talet en variant av APE där man gör en utvidgad operation som innebär att man tar med hela bäckenbotten-muskulaturen vid operationen (kallas då ELAPE). Avsikten var att minska risken att tumören spricker (intra-operativ perforation) i samband med operationen, och öka chansen att få bort hela tumören (radikal kirurgi) och på så sätt minska risken för lokalrecidiv. Det finns indikationer från tidigare studier att det kan stämma men det finns inga säkra data som visar att återfallen verkligen minskar efter ELAPE.

Vi genomförde därför en studie för att undersöka om ELAPE kan minska risken för lokalrecidiv och också vilka konsekvenser operationen har för patienternas livskvalitet.

I princip alla svenska patienter som behandlas för ändtarmscancer registreras i det svenska tjocktarms- och ändtarmscancer-registret. Vi utgick därför från alla patienter som hade opererats med ändtarmsamputation mellan 2007-2009, och registrerats i det svenska registret, ca 1300 patienter. Vi samlade in alla data som finns i registret avseende, komplikationer, vårdtider, re-operationer m.m. samt lokalrecidiv-resultat 3 år efter operationen.

Hur operationen utförts (APE eller ELAPE) registrerades dock inte. För att kunna avgöra om patienterna opererats med traditionell APE eller med den nya metoden (ELAPE) samlades alla patienters operationsberättelser in (från

de sjukhus där de blivit opererade), lästes och analyserades. I enbart 55 % av fallen kunde man definiera att en traditionell APE eller ELAPE hade utförts. I 45 % av fallen gick det inte att utifrån operationsberättelserna avgöra vilken sorts operation som hade gjorts avseende bäckenbotten.

För att få information specifikt om patienternas allmänna livskvalitet och förekomst av så kallade negativa påträngande tankar om operationen och cancer-diagnosen samt andra aspekter av operationen så sammanställdes ett studiespecifikt frågeformulär. Frågeformuläret skickades till alla de patienter som efter tre år fortfarande var i livet och som – efter en telefonkontakt – bedömdes kunna, och sade sig vilja svara på det. Utöver patientgruppen tillfrågades 3000 slumpmässigt utvalda individer om de kunde tänka sig att besvara likartade livskvalitets-relaterade frågor. Efter en första kontakt skickades 2094 frågeformulär ut och 1078 svarade. Dessa kom att utgöra en normativ svensk jämförelsegrupp med avseende på livskvalitet.

Resultat: Grupperna var inte helt och hållet jämförbara. ELAPE-gruppens tumörer var belägna mer anus-nära än i APE-gruppen och ELAPE-gruppens patienter var också något yngre och hade fått strålbehandling och cellgifter innan operation i något större utsträckning än APE-gruppens patienter. Det var ingen skillnad mellan grupperna i korttids-resultat gällande totala mängden komplikationer, reoperationer eller dödsfall efter operation. Det var dock fler sårinfektioner efter ELAPE. Det var ingen skillnad mellan APE och ELAPE vad gäller intra-operativa perforationer eller icke-radikal kirurgi men för en subgrupp med tumören mindre än 5 cm från anus så var det färre perforationer med ELAPE-teknik.

Risken för lokalrecidiv visade sig inte vara lägre efter ELAPE, snarare tvärtom, trots att de i större utsträckning hade fått strålbehandling och cellgifter före operation. I sub-gruppen med tumören mindre än 5 cm från anus var det inga skillnader i risken för lokalrecidiv. Det var inga skillnader i total överlevnad mellan grupperna.

Negativa påträngande tankar var vanligt förekommande i patientgruppen och var associerat med försämrad livskvalitet 3 år efter operationen. Det var ingen skillnad i förekomst av sådana tankar beroende på vilken operationsteknik som hade använts. Den allmänna livskvaliteten i patientgruppen i sin helhet var jämförbar med den i referensgruppen men hos männen i patientgruppen var livskvaliteten signifikant lägre än i jämförelsegruppen. Orsaken till det är inte fullt känd.

De cancermässiga resultaten efter ELAPE är inte bättre än efter APE. ELAPE är förenat med ökad risk för sårinfektioner och bör därför inte rekommenderas som standard-operation för ändtarmscancer som kräver ändtarmsamputation utan reserveras för utvalda fall.

Negativa påträngande tankar är vanligt tre år efter ändtarmsamputation och är associerat med försämrad livskvalitet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Prytz M, Angenete E, Haglind E.

"Abdominoperineal extralevator resection."

Dan Med J (2012) 59(9): A4366.

II. Prytz M, Angenete E, Ekelund J, Haglind E.

"Extralevator abdominoperineal excision (ELAPE) for rectal cancer - short-term results from the Swedish Colorectal Cancer Registry. Selective use of ELAPE warranted."

Int J Colorectal Dis. (2014), 29(8): 981-987.

III. Prytz M, Angenete E, Bock D, Haglind E.

"Extralevator Abdominoperineal Excision for Low Rectal Cancer - Extensive Surgery to be Used With Discretion Based on 3-Year Local Recurrence Results: A Registry-based, Observational National Cohort Study."

Ann Surg. 2016 Mar; 263(3): 516-21

IV. Prytz M, Ledebo A, Bock D, Angenete E, Haglind E.

"Association between operative technique and intrusive thoughts on health related quality-of-life three years after APE/ELAPE for rectal cancer

Manuscript

CONTENT

ABBREVIATIONS

APE	Abdominoperineal Excision
AR	Anterior Resection
CRF	Clinical Record Form
CRM	Circumferential Resection Margin
CRT	Chemoradiotherapy
CT	Computer Tomography
ELAPE	Extralevator Abdominoperineal Excision
FCR	Fear of cancer recurrence
GMF	Gluteus Maximus myocutaneous Flap
HRQL	Health Related Quality of Life
LARS	Low Anterior Resection Syndrome
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
NIT	Negative Intrusive Thoughts
OR	Odds Ratio
PME	Partial Mesorectal Excision
RR	Relative Risk
RT	Radiotherapy
SCRCR	Swedish Colorectal Cancer Registry

TAMIS	Trans Anal Minimally Invasive Surgery
TEM	Trans anal Endoscopic Microsurgery
TME	Total Mesorectal Excision
TNM	Tumour- Nodes- Metastasis-classification
VRAM	Vertical Rectus Abdominus Myocutaneous flap
QoL	Quality of Life

1 INTRODUCTION

1.1 The rectum

The rectum is defined as the most distal part of the large intestine, with its proximal border approximately at the sacral promontory and distal border at the pelvic floor where it passes through the levator ani/puborectalis muscle and becomes the anal canal. The rectum differs from the sigmoid colon in the absence of appendices epiploicae, haustrae, muscular taeniae and a well-defined mesentery. The taeniae are joined about 5 cm above the recto-sigmoid junction to form two wide muscular bands which descends anteriorly and posteriorly in the rectal wall[1]. The length of the rectum is generally considered approximately 15 cm measured with a rigid rectoscope starting from the anal verge (the anal verge defined as the opening of the anus at the outer surface of the body). The rectum is generally divided into three parts based on the presence or absence of peritoneum; the upper rectum (approx. 10-15 cm from anal verge) is covered by peritoneum on its anterior and lateral aspects, the middle rectum (approx. 5-10 cm from anal verge) only on its anterior aspect and the lower/distal rectum (0-5 cm from anal verge) is completely situated infra-peritoneally.

1.1.1 The mesorectum

In books on anatomy the mesentery to the rectum is not considered to be a distinct and true mesentery. In rectal cancer surgery there is however a well-defined and in-depth studied anatomical entity generally named the mesorectum. It is defined posteriorly by a visceral fascia enclosing the fat, vessels, lymph nodes and nerves surrounding and supplying the rectum and separated from the parietal sacral- and coccygeal- fascia by a loose areolar, spiderweb-like avascular tissue. This visceral fascia is sometimes less evident on the lateral aspects of the rectum but nonetheless it´s there. On the anterior aspect of the rectum the mesorectum is condensed into a thicker and dense fascia called the Denonvillier´s fascia. In males it separates the mesorectum from the seminal vesicles and the upper border of the prostate. In females it is often not as evident but forms the fascial border to the posterior aspect of the vagina.

1.1.2 Arterial vascular supply of the rectum

The rectum receives its vascular supply from two different routes. The superior rectal artery originates from the inferior mesenteric artery and is located in the mesorectum where it divides into two separate branches near the level of the third sacral vertebrae and further into smaller branches inside the mesorectum. The middle and inferior rectal arteries have their origin in the internal iliac artery. The middle rectal arteries usually arises together with the inferior vesical arteries, reach the mesorectum in the lower part of the rectum and anastomose with branches from the superior and inferior rectal arteries and supply the mid and lower part of the rectum[1]. The presence of the middle rectal arteries is varying and it is said to be absent in up to about 80% of the cases. The inferior rectal arteries arise from the pudendal arteries and supply mainly the anal canal and skin. They anastomose with branches of the superior and middle rectal arteries.

1.1.3 Nervous supply

The sympathetic nerve supply to the rectum derives from the L1-L3 roots and the parasympathetic supply from the S2-S4[1, 2]. The fibres form a complex network of descending sympathetic nerves via the superior hypogastric plexus dividing into hypogastric nerve-bundles on each side of the pelvic sidewall to the left and right inferior hypogastric (pelvic) plexuses. The parasympathetic nerves on each side pass through the sacral foramina and fuse to form the erigent nerves, which together with the sympathetic fibres from the hypogastric nerves form the inferior hypogastric plexuses[2, 3]. These are situated on the lateral pelvic sidewall, lateral and dorsal to the seminal vesicles in man. The parasympathetic nerve fibres also ascend via the hypogastric nerves to the sigmoid and descending colon.

1.2 Rectal cancer

The aetiology of rectal cancer is like for most cancer forms not fully known. There is evidence for the adenoma-carcinoma sequence; i.e. the development of carcinoma from benign adenoma of the rectum (and colon) in a series of mutational steps[4, 5]. This is a development that takes between 10-15 years and in the end can result in the forming of an invasive carcinoma. Several risk factors for the development of rectal cancer are known among which the most important are hereditary factors, smoking, dietary factors (high intake of red meat and low intake of dietary fibres), obesity and the presence of colitis due to inflammatory bowel disease[6, 7].

1.2.1 Incidence

Rectal cancer is the 9th most common cancer form in Sweden[8], stands for 3.4% of all new cancer diagnoses and together with colon cancer the third most common cancer form, exceeded only by breast- and prostate cancer. Rectal cancer is the cause of about 800 deaths annually (469 male, 336 women 2011) in Sweden. The incidence is around 2000 new cases annually (1979 new cases diagnosed 2011). Rectal cancer is more common in men with approximately 60% male cases. The median age of diagnosis is 72 years and the relative 5-year survival is 62.9% for men and 64.2% for women in Sweden (2011).

1.2.2 Diagnosis and assessment

The suspicion of a rectal tumour if often based on the presence of blood in the stools and/or symptoms of altered defecation commonly in the form of so-called tenesmus. Tenesmus is characterized by the frequent urge to defecate, but with only small amounts of faeces and – in the case of a rectal neoplasia - often with the presence of blood and mucus in the stool. These symptoms demand for a rectal examination with digital palpation and a rectoscopy where - in most cases - the tumour is diagnosed macroscopically. The definitive cancer diagnosis is then based on the histopathological assessment of biopsies from the primary on further examination with rigid rectoscopy or flexible colonoscopy by a colorectal surgeon or medical gastroenterologist. Often the tumour is palpable and can be evaluated on digital rectal examination. Assessment of the level of the tumour, the location within the rectum (anterior/posterior/circumferential etc.) and the extent of constriction of the rectal lumen can be done with these simple means. Gross assessment of the size of the tumour and signs of advanced tumour growth can and should also be performed during this examination.

Further examination of the patient serves to assess the local tumour spread and any signs of metastatic disease. In most cases a full CT scan of the thorax and abdomen are performed to evaluate metastatic disease, sometimes complemented with intravenous contrast enhanced ultrasound or MRI of the liver. A high resolution MRI of the pelvis and rectum is performed to in detail assess the local growth of the tumour[9] and of the local lymph nodes. Together with the metastasis evaluation of the CT scan this forms the final clinical TNM-classification (cTNM) upon which treatment recommendations are based[10, 11].

The TNM-classification

The TNM-classification was developed in the 1950´s and has over the years undergone revisions. The version now in use in Sweden is the 7th version (Table 1). It aims to classify tumour stage in three different levels: tumour level i.e. depth of tumour invasion in the rectal wall and/or on to adjoining organs, degree of lymph node engagement, and the presence or absence of distant metastases.

Table 1: TNM-classification (version 7)

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour invades submucosa
T1sm1	Invasion into the upper third of the mucosa
T1sm2	Invasion into the middle third of the mucosa
T1sm3	Invasion of the lower third of the mucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria and into subserosa or perirectal fat
T3a	Minimal invasion: <1 mm beyond the borders of the muscularis propria
T3b	Slight invasion: 1-5 mm beyond the borders of the muscularis propria
T3c	Moderate invasion: 5-15 mm beyond the borders of the muscularis propria
T3d	Extensive invasion: >15mm beyond the borders of the muscularis propria
T4	Tumour directly invades other organs or structures and/or perforates the visceral peritoneum
T4a	Tumour perforates the visceral peritoneum
T4b	Tumour invades other organs or structures
NX	Regional lymph nodes cannot be assessed
N0	No nodal involvement
N1	Metastases in 1-3 perirectal lymph nodes
N2	Metastases in 4 or more regional lymph nodes
M0	No distant metastases
M1	Distant metastases
M1a	Metastases confined to one organ
M1b	Metastases in more than one organ or peritoneum

A pre-treatment – clinical – TNM-evaluation (cTNM) is performed based on the preoperative radiological and clinical findings.

1.3 Multidisciplinary Treatment of rectal cancer

In a multidisciplinary team (MDT) conference - with surgeons, radiologists, medical and radiological oncologists, pathologists and (in the Swedish setting) an oncological team nurse present – the optimal treatment for each individual patient is decided based on the pre-treatment assessment/cTNM-classification and the patients medical history and comorbidity[12-14].

1.3.1 Radiotherapy

There is strong evidence that external radiotherapy (RT) administered to the tumour site/rectum leads to decreased risk of local recurrence[15-17]. Several large studies performed in 1990s showed increased local control following preoperative external RT in comparison to postoperative or no irradiation[18-21]. There is also a positive effect on disease-free survival[22] but still no significant effect has been shown on overall survival after preoperative external RT. There are two main fractioning standards of the radiotherapy: short course therapy with 5 doses of 5 Gy each, administered over the course of a week, and generally followed by surgery within 5-10 days after completion of the radiation. There is also the conventional or long-course radiotherapy with 1.8 or 2 Gy fractions up to a total dose of 45-50 Gy administered over 25 to 33 days. The aim of the short course RT is to kill microscopic tumour deposits outside - what will become - the surgical specimen and in this way increase local tumour control. The aim of the long course RT is to achieve tumour regression i.e. to shrink/downstage an advanced tumour in order to make it possible to perform a radical resection with tumour-free margins. Long course radiotherapy is often combined with neoadjuvant chemotherapy.

1.3.2 Chemoradiotherapy and chemotherapy

Studies have shown that the addition of chemotherapy concomitant with preoperative RT (chemoradiotherapy CRT) or as postoperative adjuvant treatment decreases local recurrence rates as compared to RT alone but has no effect on overall survival[19, 23, 24]. The studies have also shown that preoperative CRT has higher treatment compliance than postoperative CRT[19]. Furthermore a Cochrane review from 2012[25] support the use of postoperative adjuvant 5-FU-based chemotherapy in patients who has undergone radical surgery for rectal cancer.

1.3.3 Surgery

Surgical treatment of rectal cancer includes both local excisions and radical bowel resections. Local excision can be performed in several different ways and techniques: traditional trans anal excision, Trans anal Endoscopic Microsurgery (TEM), Trans Anal Minimal Invasive Surgery (TAMIS) and several other flexible endoscopic techniques[26, 27]. A common trait for these techniques is that they only allow for local excision of the tumour within the lumen of the bowel and not for the entire section of the bowel with adjoining vessels, lymph nodes and fat tissue. The indication for these surgical techniques and their combination with radio- and chemotherapy are under investigation but it is up until now regarded to be early stage cancer (or precancerous lesions) without lymph node engagement and preferably in elderly patients who cannot tolerate more invasive procedures[28-31]. The following section will focus on rectal cancer surgery with different types of bowel resections and not on local excisions.

"The Miles procedure"

Resection of the rectum via a combined abdominal and perineal procedure was first performed by Czerny in 1884 but it was the British surgeon W Ernest Miles who first described and published a series of combined abdominoperineal resections for rectal cancer in 1908[32]. Before Miles' publication most attempts to resect rectal cancer was through a perineal approach and resulted - in nearly all cases - in early local recurrences. Miles described a procedure where he – if there were signs of obstruction - two weeks prior to resection performed a left sided loop colostomy. He then performed the resection through a combined abdominal- and perineal approach where he after entering the abdominal cavity divided the colon just distal to the colostomy, dissected the distal colon and rectum as far as he could down to the pelvic floor through sharp dissection of the peritoneum and the "lateral ligaments" and blunt dissection posteriorly to the sacral fascia and anteriorly to the back of the bladder and in males the upper border of the prostate. He emphasized the importance of removing the cellular tissue of the pelvic mesocolon by staying close to the "anterior sacral ligaments" to completely rid the pelvis of the lymph nodes of the pelvic mesocolon and to do this in one piece. The peritoneum of the pelvis was then sutured in order to re-establish the pelvic floor and the abdominal wound closed. Patients were turned in a lateral, semi-prone position and the anus was closed with a purse string suture. An incision was done from the sacro-coccygeal joint towards an inch from the anus and a wide semi-circular incision around the anus was done with the anterior end in the centre of the perineum. The coccyx was removed and the dissection was done up to the levator muscle.

The levator was divided as laterally as possible and the last part of the dissection from the sacrum was performed. The rectum was then pulled out of the wound and the dissection anteriorly towards the posterior and caudal aspects of the prostate or vagina was performed. Care should again be taken to include all cellular tissue on the anterior aspect of the rectum. The wound was irrigated with saline and the skin margins brought together with sutures. Drains were placed in the perineal wound. The operation should – in Miles opinion – take only an hour and a quarter to an hour and a half and in that way the patients "suffers from no more shock than after an ordinary perineal excision". In his first series of 12 patients (9 males, 3 females) the mortality was 41.6% but Miles reasoned that the majority of the deaths were preventable and that he could decrease mortality by improving the technique.

Miles' procedure was subsequently considered gold standard for surgery for rectal cancer for several years until the development and spread of the Anterior Resection of the rectum[33] with formation of a colo-rectal anastomosis and preservation of intestinal continuity, thus avoiding the need for a permanent colostomy.

Total Mesorectal Excision – The TME-concept

Rectal cancer surgery has improved in the last 30 years probably mainly through the introduction of Total Mesorectal Excision (TME) by Heald in the 1980s[34, 35]. The concept of TME-surgery is that you under direct vision dissect the fascial layer covering the mesorectum sharply from the surrounding tissue, thus keeping it intact during surgery. In this manner you will be able to produce a surgical specimen with an intact mesorectal fascia and perform a complete resection of the rectum with its mesentery and within that mesorectum all the lymph nodes and vessels belonging to the rectum. The spread of the TME-surgery is considered to be responsible for much of the improvement in local recurrence rates following rectal cancer surgery. TME-surgery has in several studies been reported to decrease local recurrence rates from previously 15-25% to 5-10%[35-37 38].

Anterior Resection

Since Dixons publication of the results of anterior resections for rectal cancer[33] and later on the development of the technique with the TME-concept, the introduction and improvement of stapling devices, this procedure has become the operation of choice in the majority of cases when the level of the tumour allows bowel-division distal to the tumour and yet with the possibility to perform an anastomosis. In Sweden approximately 40% of all patients with rectal cancer undergo operation with an anterior resection (AR)[39] and of all operations for rectal cancer, AR stands for about 50% of

procedures. To perform a low colo-rectal or colo-anal anastomosis is not without difficulties despite modern techniques. In Sweden the incidence of clinical anastomotic leakage is around 10% according to the Swedish ColoRectal Cancer Registry[39, 40] and in studies up to 20%[41]. The reoperation rate is also around 10% with anastomotic leakage being the most common cause together with deep fascial rupture and bleeding[40]. Since the 2000s the use of a diverting loop-ileostomy has increased steadily in Sweden to about 80% of patients operated with an AR[39]. The objective with the ileostomy is to reduce the consequences of a leakage[41] but there has not yet been a corresponding decrease in clinically significant leak-rates as one might have expected[39]. Another concern has been functional outcome after an AR with a low anastomosis. Symptoms of poor function of the neo-rectum are commonly referred to as Low Anterior Resection Syndrome (LARS), and include frequent bowel movements, incontinence of flatus and stools, stool fragmentation and clustering and urgency[42-44]. The frequency of poor function - as defined by a high LARS-score – has been reported as high as 40-50% of patients with neoadjuvant treatment and low anastomosis (i.e. a complete TME as compared to Partial Mesorectal Excision - PME) as independent risk-factors[42, 43].

Hartmann´s procedure

In selected patients when an anastomosis is possible to perform but for other reasons not suitable a Hartmann´s procedure is performed. It is a recto-sigmoid resection according to the TME-principles but with a closure of the distal part of the rectum and a formation of an end-colostomy. In Sweden it is performed in around 10% of patients with rectal cancer[39, 40] and mainly in patients with comorbidity where a reoperation due to anastomotic leakage is important to avoid and in patients with a poor anal sphincter function preoperatively.

Abdominoperineal Excision – APE

In those patients where the tumour is located too distally or where the growth of the tumour is such that you cannot perform safe distal bowel division and radical surgery with an AR an abdominoperineal excision (APE) is performed. The standard APE (figure 1) is in most cases a procedure where the abdominal part is performed with traditional open technique – or more recently increasingly often with laparoscopic technique – according to the principles of TME surgery. The abdominal dissection is performed all the way down to the pelvic floor and the levator ani muscle. The mesorectum is posteriorly and laterally dissected free from the levator ani muscle and anteriorly the dissection is performed past the seminal vesicles to the base of the prostate (in men) and to the vaginal top (in women). Often a surgical

swab is placed posteriorly as deep as possible in order to easier find the dissection plane from the perineal route. A colostomy is formed and the perineal part of the procedure is then generally performed with the patient in a lithotomy-position with the legs spread. An oval incision is done from the apex of the coccyx to the centre of the perineum around the anus and dissection is performed through the subcutaneous and ischiorectal fatty tissue up to the levator ani. The posterior perineal body is incised at the coccyx and the formerly dissected pre-sacral space is entered. The levator muscles are divided on both sides of the distal rectum close to the bowel. The dissection is performed anteriorly to the apex of the prostate or the posterior aspect of the vaginal wall and the anterior abdominal space is entered and the specimen is free and delivered through the perineal opening. The produced surgical specimen should typically have a shiny intact fascia covering the mesorectum and a waist in the plane where the mesorectum ends and the levator muscle is divided. Finally the perineal wound is closed with sutures in several layers. The oncological results following APE has in several studies been shown to be inferior to those of AR, with 5 year overall survival rates of around 60% for APE and 70% for AR[45-49]. The improvement in local recurrence rates for patients operated with anterior resection according to TME-principles and receiving neoadjuvant RT has not been at all as evident for patients operated with APE for rectal cancer. The true reasons for this is not fully known but much of the proposed explanations have been attributed to the surgical procedure itself[49] and to the higher rates of intraoperative perforations and engaged circumferential margin (i.e. non-radical surgery) following APE[48] as compared to AR.

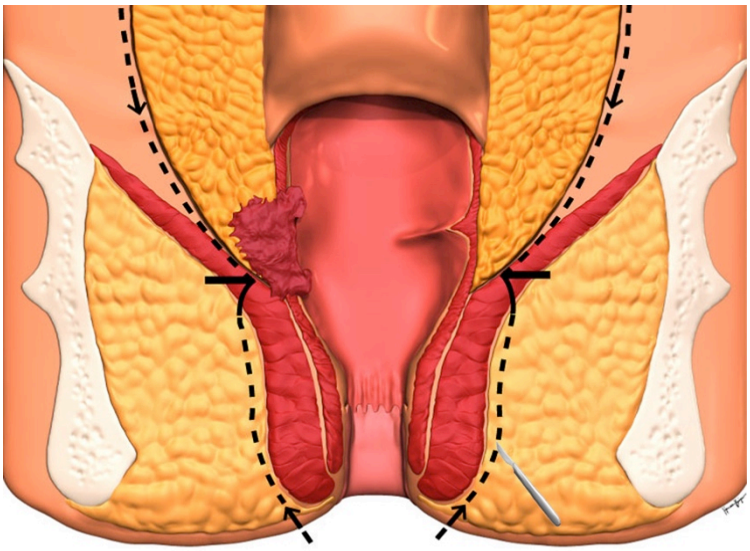


Figure 1. Standard APE

Extralevator Abdominoperineal Excision – ELAPE

In later years the APE procedure has been in the focus of change[50] and a more radical method has been proposed in order to meet the problems of intraoperative perforations and engaged CRM[51]. The alternate procedure, often referred to as Extralevator APE (ELAPE) was described by Holm and colleagues in 2007[50]. It is actually more like the original description of the APE by Miles in the aspect of levator dissection and division. ELAPE is performed in the same two-way-approach as standard APE with the abdominal part performed according to TME-principles either with open surgical technique (as described by Holm) or laparoscopically[52]. However the pelvic dissection stops posteriorly before reaching the pelvic floor at the level of the upper border of the coccyx - so as to not detach the mesorectum off the levator muscle[53, 54]. Anteriorly the dissection should stop just below the

seminal vesicles or cervix uteri. Antero-laterally the dissection is stopped just below the inferior hypogastric plexus. This is essential to do in order not to get a coning of the specimen at the level of the levator, as you would otherwise get.

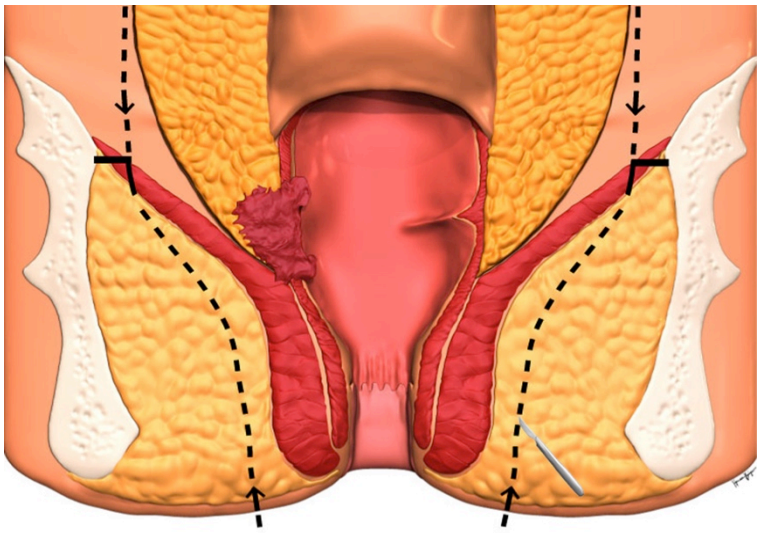


Figure 2: Extralevator APE

As in standard APE a swab is left deep in the pelvic cavity to act as a guide for the perineal part of the dissection. A terminal colostomy is then performed and the abdomen closed. The patient is then turned in a prone Jack-Knife position with the legs apart. The anus is closed with a purse string suture and a tear-drop-shaped incision is performed from the apex of the coccyx and around the anus. The dissection is then performed up through the subcutaneous and ischiorectal fat just outside the border of the subcutaneous part of the external sphincter. The inferior aspect of the pelvic floor is then dissected free round its entire lateral and posterior circumference. The coccyx is disarticulated, the pre-sacral fascia divided and the pelvic cavity - with the guiding swab - is entered. Disarticulation of the coccyx is not mandatory but often helps delivering the specimen through the wound. The levator muscle is divided at its origin at the pelvic sidewall around the circumference. The

specimen is delivered out through the perineal wound and in that way the final part of the dissection can be performed using lateral and inferior traction and counter-traction. The specimen is carefully dissected off the posterior aspect of the prostate or vaginal wall and finally the last part of the anterior levator muscle is divided and the specimen can be completely delivered and inspected. The specimen now typically has a cylindrical shape without the waist or coning at the level of the levator plane, as is common following the standard APE procedure. The last part of the operation is now to close the perineal wound. This can be done in several different ways and there is no solid evidence what is the best method[55-61].

Perineal wound closure

The traditional way of closing the perineal wound is by suturing of the remnant part of the pelvic floor. Following an ELAPE there is no or nearly no levator muscle left for suturing and therefore the closure of the wound by suturing will be by suturing the ischiorectal- and subcutaneous fat in layers as well as the skin[62]. An alternative way of closing the pelvic defect after an ELAPE is by using some kind of mesh to replace the excised levator muscle. Often in studies - and clinical practice - a biological/collagen mesh[60 63] (permacol©, surgisis©, strattice©) has been used. The mesh is sutured with interrupted sutures to the remnant of the levator muscle and the subcutaneous tissue and skin are then sutured in layers. There is at least one on-going study[64] comparing the outcome of perineal wound closure with a biological mesh as compared to primary suturing. A third often used method of performing a closure of the pelvic defect and perineal wound is by use of a myocutaneous flap. There are several different flap-techniques described and in use. The uni- or bilateral gluteus maximus myocutaneous flap (GMF) was the method first described by Holm[50] and used in the first series of patients described. The technique uses a part of the gluteus maximus muscle with adjoining subcutaneous fat and skin as a rotational flap with intact vascular supply (from the superior gluteal artery) and innervation (from the inferior gluteal nerve). If the defect in not too large a unilateral flap will be enough to cover the defect but in case of larger defects a bilateral flap can be used[50, 65]. It has the advantage of not adding any other donor-site complications but the disadvantage of using tissue that has been - at least partially – in the field of the external radiotherapy and therefor the inherent risk of impaired healing. Another possible disadvantage is the adding of further local functional loss in the perineal area since the use of a large portion of the gluteal muscle can affect both sitting and rising up to standing[66]. It is preferably performed by a plastic surgeon but can also be done by the colorectal surgeon[50, 65]. Another –

technically more demanding – flap reconstruction is the Vertical Rectus Abdominus Myocutaneous (VRAM) flap. This flap is constructed by part of the rectus abdominis muscle with preserved circulation from the inferior epigastric artery but without preserved innervation. It is more complicated to perform than the GMF and generally requires specialised plastic surgical skills. It has the advantage of using non-irradiated tissue for the repair but is more complex and has the inherent problem of atrophying over time since the muscle is denervated. There are several published series of both techniques[66-68] but no randomised controlled study comparing the techniques against each other[69].

Outcome of ELAPE

Initial studies on the efficacy of the ELAPE-technique to improve the oncological outcome – as compared to standard APE – concentrated on pathology-related short-term outcome measures[51, 70]. In the initial study by West and colleagues, morphometry, CRM involvement and intraoperative perforations of 27 ELAPE specimen (10 operated in the UK - Leeds - and 17 in Stockholm) were compared to 101 standard APE operated in Leeds between 1997-2007 (n=99) and Stockholm between 2001-2006 (n=2). The amount of tissue removed with ELAPE was significantly higher and there were significantly lower rates of perforations and involved CRM with ELAPE. The oncological result of the standard APE control-group was however not impressive with a perforation-rate 22.8% and an involved CRM in 40.6% of cases. There were no data on local recurrence rates[51]. In another study by the same author 176 ELAPE-procedures performed by 11 different European Colorectal Surgeons were compared to 124 standard APE-procedures operated in a single UK centre in Leeds by 8 different surgeons. ELAPE resulted in a significant reduction in CRM involvement (from 49.6 to 20.3 %) and intraoperative perforations (from 28.2 to 8.2 %) compared with standard APE surgery. However, ELAPE was associated with an increase in perineal wound complications (from 20 to 38 %). Again the perforation rate and CRM-positivity rate of the control group was high (28.2% and 49.6% respectively). There were no local recurrence data[70].

Other studies have reported conflicting results[52, 71]. In the study by Welsch and colleagues the oncological results of 30 patients operated with open or laparoscopic ELAPE seemed promising with only 7% involved CRM and no local recurrences within a median follow up of 28.3 months. However 46.6% of patients had a perineal wound complication and 50% reported persistent perineal pain at follow-up. The perineal wound closure was performed with different flap-techniques, suturing, mesh or (most commonly) an omentoplasty. There was no control group[52]. Asplund and colleagues[71]

presented retrospective data from a Swedish single-centre study of 158 (79 ELAPE, 79 standard APE) patients with curative resections for rectal cancer. CRM positivity did not differ significantly between groups (ELAPE: 17%; standard APE: 20%). Intraoperative perforation (13% vs. 10%) or local recurrence (seven in each group) was no different. Perineal wound infection was significantly more common after extralevator APE (46% vs. 28%). The patients were operated on in different time-spans so there were differences between groups regarding time for follow-up: median 45 months for standard APE and median 26 months for ELAPE. The perineal wound closure was in all patients performed with plain suturing in layers.

Three review articles[72-74] came to different conclusions as to what extent ELAPE was oncologically superior compared to standard APE. Stelzner and colleagues concluded from their systematic review of 14 non-randomized studies from 1997 to 2011 on 'extended APE' and 50 studies on traditional APE from 1991 to 2011 that 'extended APE' had a reduced risk of intraoperative perforation. The effects on local recurrence and survival rates were not possible to analyse. The review was mainly based on observational studies and case series, or on prospective randomized studies in which the results of APE in relation to surgical technique was not an end point. A series of factors may confound their pooled adjusted analysis especially of local recurrence rates, but also of CRM status. Such factors discussed by the authors being: preoperative imaging, selection of the study population in respect to treatment intent, case mix and tumour stage, use of neoadjuvant therapy, lengths and schedule of follow-up, mode of data collection, statistical tests used, and not least the definition of what constitutes a local recurrence. The data in their systematic review regarding local recurrence rates and CRM status have therefore to be interpreted with caution and the authors concluded with a suggestion to use registry data - such as the Swedish Cancer Registry – to study whether extended APE (such as extralevator APE) provides superior results compared to standard APE[72]. Krishna and colleagues concluded in their comparison of published rates of CRM involvement and intraoperative bowel perforations from 8 studies between 1993-2008 and registry-data from the Australian Concord Hospital registry of resected colorectal cancers for the period 1995–2010 that there was no convincing evidence that ELAPE results were better than those for standard APE[73]. In a review and meta-analysis of 8 studies (one of which is included in the review by Krishna) on a total of 949 patients (ELAPE 496, APE 453) published between 2008-2012 Yu and colleagues suggested that ELAPE had a lower intraoperative bowel perforation rate, positive CRM rate, and local recurrence rate than standard APE[74]. Based on the data in these

studies they suggested that in selected low rectal cancer patients, ELAPE is a more efficient and equally safe option to replace standard APE.

There is only one randomized, controlled trial comparing ELAPE and standard APE regarding oncological outcome with local recurrence rate as one of the end points. The study by Han et al. reported a reduced recurrence rate following 'cylindrical APE' after median follow-up of 29 months, suggesting that there was an oncological advantage with 'cylindrical APE' as compared to standard APE in patients with T3 and T4 tumours[75]. However, the study was small (n = 67, 35 ELAPE, 32 standard APE), it is unclear what the primary endpoint was and no power calculation was presented. No details of external or internal validity were reported, and less than 30 % of the patients received neoadjuvant treatment.

The Swedish National Board of Health and Welfare (Socialstyrelsen) stated 2014 in their "National Guidelines for colon and rectal cancer – scientific basis" (Nationella riktlinjer för tjock- och ändtarmscancer - Vetenskapligt underlag, page 116)[14] that ELAPE for distal rectal cancer without evidence of tumour engagement of the levator muscle should only be performed within clinical trials (FoU).

1.4 Health related Quality of Life

The concept of Quality of Life (QoL) is a broad concept without one single clear definition. There is however considerable agreement that quality of life is a multidimensional concept. A way of addressing this concept is by categorising QoL in five dimensions: physical wellbeing, material wellbeing, social wellbeing, emotional wellbeing, and development and activity[76].

The interest for QoL-related outcome in relation to health-related research has increased in the last four decades and the term Health Related Quality of Life (HRQL) has been used. A prominent trait of HRQL-data is that it is based directly on patients' subjective reports of symptoms and functional outcome, and not on "objective" measurements as is standard in other parts of health-research. The data collection is primarily done by the use of different kinds of questionnaires[77] and there is an abundance of validated questionnaires for different medical conditions and treatments[78].

There has been much HRQL-research in relation to rectal cancer treatment[52, 79-95]. The knowledge with regard to long-lasting symptoms from the perineal wound following APE is however not extensive and even less so when it comes to ELAPE. A problem in this regard is probably the lack of validated

specific questionnaires with this focus. There is a need for further studies within this field of rectal cancer research[96].

1.5 Negative Intrusive Thoughts

Negative intrusive thoughts (NIT) are involuntary and unwelcome thoughts that appear suddenly and repeatedly. Negative intrusive thoughts are part of post-traumatic stress disorder and have been regarded as a marker of incomplete cognitive processing of the psychological trauma caused by for example a cancer diagnosis. It is related to and part of the concept of "fear of cancer recurrence" (FCR)[97, 98]. Intrusive thoughts and FCR have been recognised as important factors associated with poor quality-of-life outcome following surgery for other malignancies; i.e. prostate and breast cancer as well as functional impairment and the presence of psychological symptoms[99, 100, 101].

2 AIM

The overall aim of this thesis was to explore the oncological and functional outcome of ELAPE as compared to standard APE in a Swedish national cohort of patients operated with any kind of APE between 2007-2009.

The specific aims were:

To investigate short term oncological outcome of standard APE and ELAPE with regard to intraoperative perforations and involved CRM in this population.

To investigate the three-years local recurrence rates following standard APE and ELAPE in the same population.

To explore associations between patient reported intrusive thoughts and QoL as well as to type of surgery performed three years after surgery and to compare outcome to that found in a normative Swedish cohort.

3 PATIENTS AND METHODS

The results of the papers in this thesis are based on the APER-study with the primary endpoint 3-years local recurrence rates following abdominoperineal excision for rectal carcinoma.

Secondary endpoints were to study postoperative morbidity, late morbidity, overall mortality, functional results and quality of life following abdominoperineal excision.

The hypotheses of the study were that ELAPE reduced local recurrence at three years, increased postoperative morbidity, decreased late morbidity and improved quality of life at 36-48 months postoperatively.

The study is registered in the National Institute of Health´s (NIH) governed Clinical Trials-database under the acronym APER, with the ClinicalTrials.gov identifier: NCT01296984.

3.1 Data from the Swedish Colorectal Cancer Registry

The patients were collected from the national database formed by the Swedish Colorectal Cancer Registry (SCRCR). The registry collects data on all Swedish patients diagnosed with colorectal cancer independent of residential geography, treatment modality, curative or palliative intention etc. The registry covers nearly 100%[40 102] and virtually no patient undergoes surgery for rectal cancer in Sweden without being included in the registry[39].

The study was approved by the local ethical committee (the Ethical Committee in Gothenburg, no. 406-2010).

All patients operated with an abdominoperineal excision in Sweden in the years 2007-2009 and present in the registry were collected. Data on cTNM-classification, tumour height from anal verge (as determined with a rigid rectoscopy), patient demographics (weight, length and American Society of Anaesthesiologists' (ASA)-classification), pre- and post-operative non-surgical treatment, certain aspects of the operative technique (open or laparoscopic operation, level of vascular division), perioperative complications (including perioperative bleeding, perforation of the specimen), operating time, pathology report (including pTNM-classification,

CRM, distal margin, lymph node harvest), postoperative complications (including infections, wound complications, cardiovascular complications, etc.), reoperations, postoperative intensive care treatment, re-admittance within 30 days and death within 30 days were all collected from the registry. When the data on three years local recurrence rates were available, this data was also collected from the registry.

3.2 Data from operative notes

Information on the type of APE performed is not registered in SCRCR. Operative notes for each patient were retrieved from the hospital where the operation was performed. A Clinical Record Form (CRF) was used to collect data from the operative notes including points such as division of the levator muscle, removal of the coccyx – i.e. how the perineal part of the procedure was performed – to determine if a standard APE or an extralevator APE had been performed. Technique for the perineal repair was collected, if present. All retrieved operative notes were read and analysed using the CRF. The operating notes were reviewed by one of the colorectal surgeons in the study group – i.e. myself. The operation was considered an ELAPE if the operation was described in the operating chart as a "Holm procedure", if it was described as a cylindrical specimen or if it was stated that the levator muscle was dissected laterally or at a distance from the rectum. In cases where there was uncertainty as to how the dissection was performed, the two other colorectal surgeons in the research group also reviewed the operative notes. The operation type was classified as "not stated" if no consensus was reached or if all three agreed that the perineal part was not possible to classify. I also registered in the CRF at what level the vascular division was made, if there was any damage to the specimen during the operation, if the perineal part was performed in lithotomy, prone Jack-Knife or any other position.

3.3 Data from questionnaire

Information regarding the presence of negative intrusive thoughts after surgery was obtained through a study-specific questionnaire. The questions on intrusive thoughts were part of an extensive questionnaire that also covered many other aspects of functional outcome after abdominoperineal excision. The development and validation of this questionnaire is illustrated in figure 3 and has been described in detail in other publications[96, 103]. The process involved interviews with patients with rectal cancer and subsequent analysis with qualitative methods, content validation in a multidisciplinary group of experts with extensive clinical experience in the field, and face-to-

face validation, where patients were asked to complete the questionnaire in the presence of a specialist nurse to detect any problems, misinterpretations, or concerns. Questions were revised accordingly, and the process continued until no uncertainties remained. Also included in the questionnaire were questions on post-operative perineal wound healing and the EQ-5D visual analogue scale (VAS) question on global health-related quality of life.

The questionnaires were sent out according to a well-established routine in our research group: Each patient alive three years after the operation received a letter with information about the study informing the patient that a member of the study staff would contact the patient by telephone shortly. During the telephone conversation, the study staff ascertained that the patient had understood the written information in the letter. Next, the patient was asked if he/she consented and if the answer was yes, the patient was further asked if we could send the questionnaire. If the answer was yes, the questionnaire was sent. The questionnaire included contact information to be able to contact the study-office and patients were invited to call if she/he needed further information or if any questions arose. Two weeks after send-out, a thank you/reminder letter was sent, and after this there were no further active contacts with the patient. With this routine 85% of eligible patients agreed to receive the questionnaire and 77.5% of eligible patients answered and returned the questionnaire.

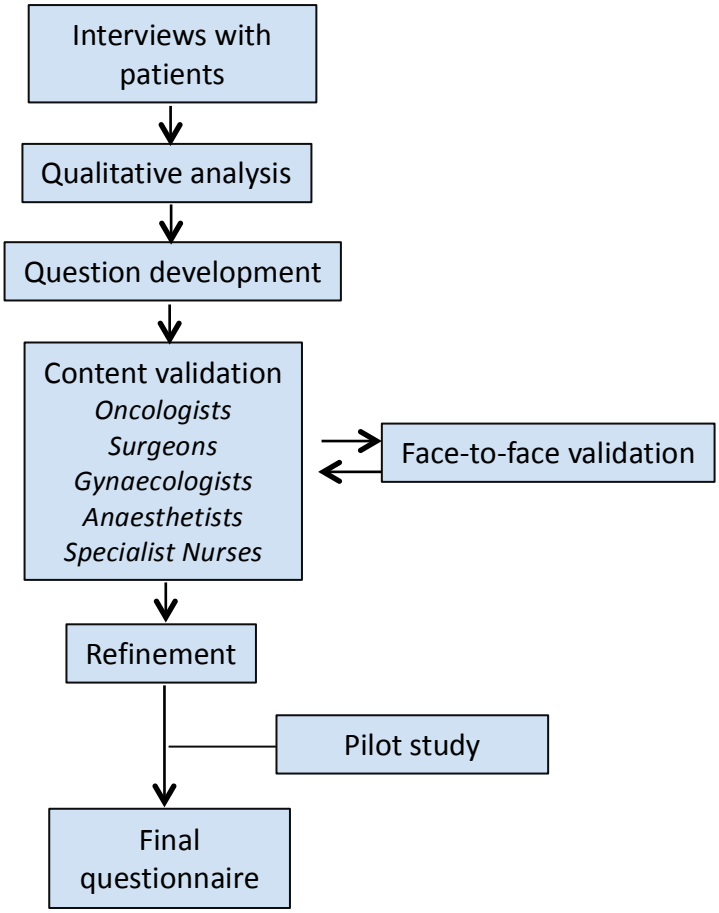


Figure 3: Development of a study-specific questionnaire

3.4 Patient populations

All three studies were performed on the same population (or part of the same population – Paper IV) derived from the SCRCR. The population was defined as all patients in the registry having undergone any kind of APE in Sweden in the years 2007-2009.

In paper IV a normative reference population was used as comparison. The population was randomly collected with help of the Swedish Tax Agency;

3000 persons were identified through the Swedish Tax Agency. An introductory letter was sent to 2955 persons, 1636 of whom we were subsequently able to contact by telephone. 2094 questionnaires were sent out to persons who gave oral consent by telephone (n=775) or were unreachable by telephone (n=1319). 1078 questionnaires were returned and formed the reference population (figure 4).

3.4.1 Papers II and III

1397 patients were identified in the registry´s database. Following the analysis of the operative notes 24 patients were found to be incorrectly registered, as having undergone an APE, when in fact they had not. 54 patients' operative notes were not possible to obtain despite our best efforts thus resulting in 1319 patients available for analysis in papers II and III. For the 54 patients excluded because of the lack of surgical notes (4%), clinical and demographic data from the registry did not differ compared with the patients included in the study.

3.4.2 Paper IV

The patients in this study were derived from the same population as in the previous studies. Of the 1319 patients 853 patients were alive three years after the surgery and eligible for inclusion in the questionnaire part of the study. A total of 596 patients agreed to receive the questionnaire by mail and 545 returned the questionnaire and were included in the analysis. See figure 5 for details. In addition to this study-population a randomly selected normative Swedish population consisting of 1078 individuals was collected and used as a reference population as described above (figure 4).

Figure 4: Flow-chart of normative population in Paper IV

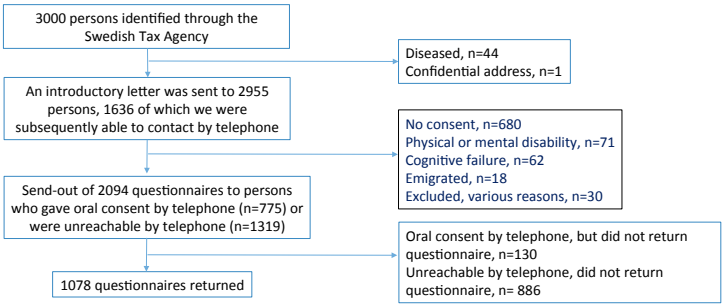
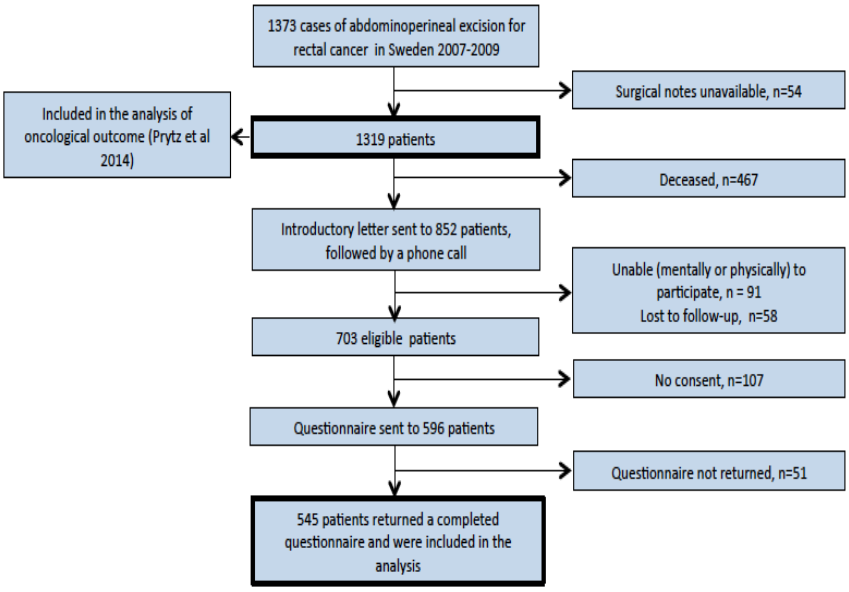


Figure 5: Flow-chart of patients in Paper IV



3.5 Statistical methods

All data were collected in a database, and statistical analyses were performed using SPSS 21.0 (IBM SPSS Inc. Armonk, NY, USA) and SAS v. 9 (SAS institute).

In paper II continuous outcome variables were compared between the two groups (APE and ELAPE) using Wilcoxon's rank-sum test; categorical data were compared between the two groups using Fisher's exact test or the chi-square test, as deemed appropriate.

In paper III patient characteristics were summarized descriptively. Continuous outcome variables were compared between the three groups (APE, ELAPE and "not stated") using analysis of variance, and categorical data were compared between the three groups using the Kruskal-Wallis test. To assess the primary objective of comparing APE and ELAPE with regard to local recurrence within three years, odds ratios were estimated by logistic regression. Relative risk was estimated by Poisson regression with robust error variances[104] because of failure of convergence of the log-binomial model. The results are presented with corresponding 95% confidence intervals.

There were a number of variables regarded as potential confounders, i.e. co-varying with and influencing local recurrence and groups. When quantifying the group-specific risk of local recurrence, identifying and adjusting for these variables was needed. The pool of variables was clinical and pathology T- and N-stage, CRM, sex, ASA, bleeding (mean centred), operating time (mean centred), perioperative perforation, and preoperative radiotherapy. Variables not included were "*presented in preoperative multidisciplinary therapy conference*", as this was at such high levels in all three groups that further distinction of the influence of this variable was impossible, and tumour level from the anal verge. Tumour level was not included as data suggested that this factor was part of the rationale for choice of ELAPE versus APE. For each variable considered potentially clinically relevant and represented in both surgical techniques, a regression model including operative technique was fit. A bivariate logistic regression was performed and possible confounding variables with a p-value > 0.20 were removed and all other variables were incorporated into a multivariate logistic regression model. For calculation of the Relative Risk (RR) a Poisson regression model was used. Odds Ratios (OR) and RR with confidence intervals were calculated for the included covariates (table 2). Included covariates were: cT-stage, pN-stage, bleeding (≥500 ml) and intraoperative perforation - as well as operating

technique. The same multivariate logistic regression was performed for the subgroup of patients with tumour level ≤4 cm from anal verge. A Kaplan-Meier plot on overall survival for the three groups was computed.

In paper IV the association between QoL, negative intrusive thoughts and type of surgery was analysed with a proportional odds model[105]. The proportional odds assumption was evaluated and results were presented as odds ratios with 95% confidence intervals. To account for potentially influential variables, these were adjusted for by including them as covariates in the model. The variables were: sex, age, ASA-classification (I-IV), tumour stage (T0-T4), comorbidity (characterized as "Yes" if a patient reported at least one of cardiovascular disease, diabetes or chronic obstructive pulmonary disease), marital status (partner, no partner) and educational status (university education, no university education). For sensitivity assessment, results for unadjusted analyses are presented as well.

The comparison with the normative data was made using a Cochran-Mantel-Haenszel test of general association[105], stratified by age group (0-49, 50-59, 60-69, 70-79, 80- years). The analyses were made for each sex separately.

4 RESULTS

4.1 Paper I

The first paper of the thesis is the methodological description of the APER-study. The APER-study is the basis of the studies in the following three papers as well as in further studies by our research group. The methods are described in detail as well as the statistical power calculation performed prior to initiating the study. There are no clinical results presented in the paper.

4.2 Paper II

The short-term results – i.e. results based on the pathology report, perioperative data and data on complications from the registry – are presented in this paper.

The initial analysis of the operative notes revealed that 55% of the patients in the cohort from the registry (n=1319) could be classified as having been operated with either standard APE (n=209) or ELAPE (n=518). In the remaining 45% (n=592) of the patients in the cohort, the operative notes did not allow for a definitive classification to either of those groups and they were classified as "not stated". The epidemiological data on all three groups were presented and the further analysis and presentation of results were focused on the two surgically/anatomically-defined groups (i.e. standard APE and ELAPE).

The epidemiological data showed that the three groups significantly differed with regard to mean tumour height (as measured with rigid rectoscopy at the distal border of the tumour). The ELAPE-group had a mean tumour height of 3.4 cm from anal verge whereas the APE-group had a mean height of 6.6 cm and the "not stated"-group was in between with 4.1 cm. The mean height for the entire cohort (n=1319) was 4.2 cm. The patients in the ELAPE-group were significantly younger (median age 68 years) than the APE-patients (median 71 years). There were also a significantly higher proportion of patients who had received preoperative RT and CRT in the ELAPE-group as compared to the APE-group. There were no differences in pT- or pN-stage between groups.

The short-term oncological outcome of ELAPE did not result in fewer intraoperative perforations or involved circumferential resection margins as

compared with standard APE. There was no difference between groups in short-term (30 days) mortality (APE: 2.4%, ELAPE: 2.1%) or overall complication rate (APE: 41.6%, ELAPE: 45.9%).

When a subgroup-analysis for the group of patients with the most distal tumours (≤4 cm) was performed, the intraoperative perforations were found to be significantly fewer for patients operated with ELAPE (n=28/386) compared with standard APE (n=9/58) (p=0.043) and for early (pT0–T2) T-stages (ELAPE: n=3/172 versus APE: n=6/75; p=0.025).

There were significantly more post-operative wound infections after ELAPE (n=106, 20.4 %) than after APE (n=25, 12.0 %; p=0.011). The wound infections relate to all wound locations, not only the perineal wound, since the distinction between the two was not made in the registry.

4.3 Paper III

The primary end-point of the APER-study is presented in this paper. The cohort of patients is the same as in paper II. The results were completed with the 3years local recurrence data from the registry. Analysis of overall survival was also performed.

Results regarding local recurrence were calculated for all three groups (ELAPE, standard APE and "not stated"). The median follow-up was for all patients 3.4 years and for separate groups: APE: 3.4 years; ELAPE: 3.4 years; not stated: 3.4 years.

The local recurrence rate was significantly higher for ELAPE compared with APE (OR: 4.10, 95% CI: 1.19-14.08) (table 2). Perioperative perforation was also associated with an increased risk of local recurrence (RR: 3.62, 95% CI: 2.13-6.13) (table 3). There was no difference in 3-year overall survival between APE and ELAPE (figure 4). In the subgroup of patients with very low tumours (≤4 cm from the anal verge), no significant difference in the local recurrence rate could be observed.

Table 2. Multivariate Logistic Regression Analyses with Odds Ratios indicating the Risk of Local Recurrence. All patients, n=1319

Variable	*P*	Odds ratio (95% CI)
Group	0.076	-
APE	-	Reference
ELAPE	0.025	4.10 (1.19 - 14.08)
Not Stated	0.082	3.06 (0.87- 10.78)
Pathology N-stage	0.011	-
0	-	Reference
1	0.206	1.63 (0.76 - 3.48)
2	0.003	2.98 (1.47 - 6.04)
Clinical T-stage	0.091	-
1-2		Reference
0		N/A[1]
3	0.244	1.83 (0.66 - 5.09)
4	0.022	3.33 (1.19 - 9.29)
Bleeding (500 mL)	0.043	1.09 (1.00 - 1.19)
Perioperative perforation	<0.001	-
No	-	Reference
Yes	<0.001	5.30 (2.64 - 10.66)

[1] No recurrence in Clinical T-stage 0, therefore not possible to calculate

Table 3. Multivariate[1] Poisson Regression Analyses with Relative Risk of local recurrence. All patients, n= 1319

Variable	*P*	Relative Risk (95% CI)
Group	0.006	-
APE	-	Reference
ELAPE	0.007	4.91 (1.53 - 15.74)
Not Stated	0.087	2.82 (0.86 - 9.26)
Perioperative perforation	<0.001	-
No	-	Reference
Yes	<0.001	3.62 (2.13 - 6.13)

[1] Additional covariates are Pathology N - stage, Clinical T-stage, Nodes and Bleeding

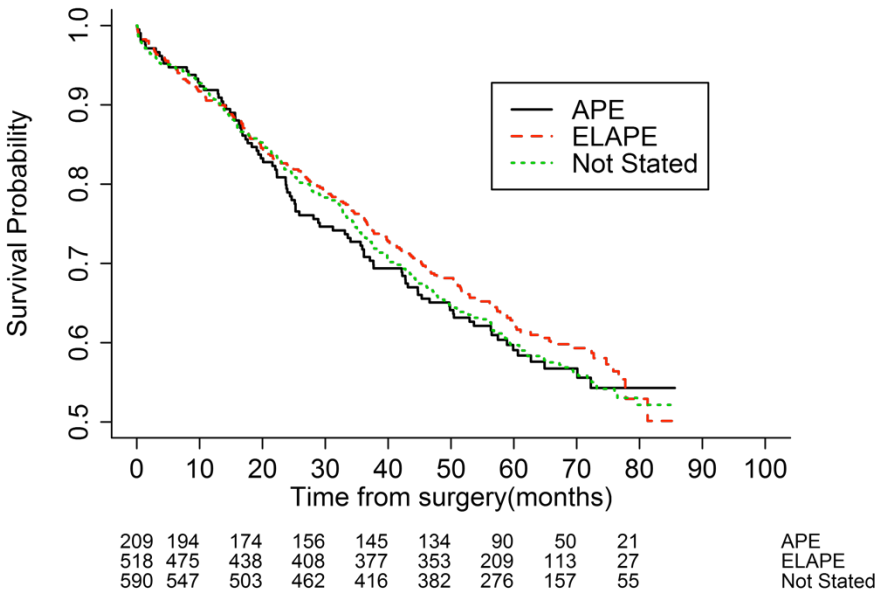


Figure 4: Kaplan-Meier plots of overall survival for the three groups

4.4 Paper IV

In this paper we investigated the association between negative intrusive thoughts and quality of life three years after surgery for rectal cancer. Quality of life was also assessed in relation to type of surgery performed - i.e. APE or ELAPE. Overall quality of life in this cohort of patients was furthermore compared to that of a normative Swedish population.

The results are based on data from firstly the self-reported symptoms from the 596 patients alive and willing to answer the study-specific questionnaire three years after the operation and the data are from the 545 patients that returned the questionnaire (the APER-population) and secondly the randomly selected normative Swedish population consisting of 1078 persons collected and used as a reference population.

In the APER population 60 % were male. The median age was 69 years at the time of filling out the questionnaire and did not differ between men and women. More men lived in a relationship (83% vs. 59% p=0,04). There were no differences regarding level of education or retirement. There were no differences between the sexes regarding self-reported comorbidity or depression.

Quality of life was assessed using two different measurements: Overall QoL was assessed by a 7-point Likert scale anchored by 0 (no QoL) and 6 (best possible QoL). High and low QoL was dichotomized with a cut off between 4 and 5 in the Lickert scale. Global health-related QoL was assessed by using the EQ5D visual analogue scale (VAS). Both these instruments were part of the questionnaire and reported by the patients in the APER study and the persons in the normative population.

56% of the APER population reported a low overall quality of life with no significant difference between the sexes. In men there was a difference in overall QoL, with a larger degree of high QoL in the normative population (48%) compared with the male APER population (39%). The median score for global health-related QoL (EQ5D VAS) was 80 for both sexes and in both cohorts.

Negative intrusive thoughts were reported by 52% of women and by 44% of men (p = 0,04). 19% of the females and 15 % of the males respectively, reported such thoughts at least once weekly three years after their surgery for rectal cancer. 9% regarded the severity of the intrusive thoughts as

"Moderately intrusive" or "Very intrusive" with no difference between the sexes.

After three years there was no difference in overall QoL after standard APE compared with extralevator APE. Negative intrusive thoughts, as such, as well as their frequency and severity was significantly associated with a low overall QoL.

Self-reported depression was associated with negative intrusive thoughts, OR (95% CI): 3.61(1.99; 6.56).

5 DISCUSSION

To study the outcome – both short- and long-term – of a new operative technique like ELAPE in comparison to a gold standard like APE a prospective, randomised, controlled study would be the preferred method - as has been done for example for laparoscopic colon- and rectal- cancer surgery[106-109]. A multicentre study would have been needed to achieve a rapid, and - based on a calculation of sample size needed in relation to the chosen primary outcome measure for the comparison – adequate inclusion of patients. In doing so one would be able to minimize selection bias, control for confounding factors and have a good possibility to have control of the surgery performed. The inherent problems of such a study with regard to risk of prolonged inclusion time and poor external validity would have been addressed and as far as possible met.

When the early reports on ELAPE were published and discussed in the Swedish colorectal society, such a study was proposed by a member of our research group (SSORG), but it was at that time considered unnecessary and perhaps even unethical since the data in the published case series – despite the fact that the endpoints in the studies were only surrogate markers/risk factors for a bad oncological outcome, not local recurrence - indicated superior results for ELAPE. The discussion was instead focused on another important topic related to ELAPE, i.e. the best way of closing the perineal defect. A randomised multicentre study – the NEAPE-study – was subsequently initiated by Haapamäki and colleagues at the Umeå University[110]. The study is still recruiting patients.

Since a randomised, controlled, national Swedish study therefore would be nearly impossible to conduct, other study-designs had to be considered. The aim was to test and find support for the proposed superior oncological outcome of ELAPE in comparison to standard APE with regard to hard-end oncological outcome, i.e. local recurrence-rates. The Swedish Colorectal Cancer registry with data on virtually all Swedish patients operated for colo-rectal cancer was considered a good basis for this study.

Data on patients is reported to the registry from all Swedish hospitals performing colo-rectal cancer surgery. The regional cancer centres (RCC´s) meticulously monitor the registration and contact hospitals in the region when the reports are lacking. The data on operated patients are prospectively registered so even if such a study had to be a retrospective study – by definition – the data were collected prospectively. The cohort collected from

the registry is thus a national cohort and the problem of selection of patients from different centres – with- or without special expertise – is avoided. A national cohort reflects the practice at the time, without selection bias. This is true for the performed surgery but also for the pathology report. The pathological analysis was performed by different pathologists from different centres all over Sweden and not only by colorectal pathological subspecialists as in other studies[48]. To what degree this will have an effect on the pathology report standard is not clear, but from a methodological point of view it contributes to the external validity of the results.

However a selection bias may still be present, if surgeons and centres select patients for one or the other method for one or more reasons. In a registry such as SCRCR a large number of clinical details are reported, and to some extent it is possible to adjust for selection, when analysing the data.

A possible issue with retrospective studies is missing data. Standardisation of the data collected may differ between centres and physicians. The data in SCRCR is however standardised as to what data is registered and also how it is reported to the registry. The SCRCR is well established, has a stable and high coverage and is validated and updated[40, 102, 111]. In the registry, registration of complications, including reoperations, are standardised, but in the timeframe of our study, complications were not graded according to the Clavien-Dindo classification[112, 113] – as they are today. Since the Clavien-Dindo classification system now is the standard in most surgical studies the lack of it in this study is a weakness. The complication rates may also be underreported[111] and this must be taken into account when interpreting results on complications but the total incidence of complications is similar to other prospective studies of rectal cancer surgery[106] and there is no reason to believe that there is a reporting bias to the registry due to operating technique.

There are other weaknesses with a retrospective study-design. Although the coverage in SCRCR is high, there will always be missing data in a registry. For most variables reported, the rate of missing data is small and ranges from 0 to 3 % for the variables used in our study, with the exception of the numerical value (in mm) for the CRM. For this variable there was missing data in 20 % of cases, whereas the data on involvement of the CRM and intraoperative perforation were missing in less than 1 %. Our results regarding the absolute value of the CRM must therefore be interpreted with caution. The finding of a tendency towards a wider CRM in millimetres for the traditional APE-group may also be due to a larger number of tumours situated higher in the rectum in the traditional APE group that consequently

have a wider distance to the CRM - since some would be covered by the mesorectum.

A major strength of our study is the cohort size and the fact that the patients included comprises 94 % of all Swedish patients operated with any kind of APE in the years 2007–2009. Thus, the results are population-based. Selection bias is not a problem in this aspect. This is a strength compared with other reports comprising selected case series and historical controls with oncological results that differs significantly when compared to more recent oncological outcome. Another advantage with a registry-based study is that it gives the opportunity to have a large cohort of patients collected in a time frame that is both short and recent avoiding comparisons with historical data as in previous studies[51, 70, 96].

The 3-year follow-up time has the advantage of a more rapid presentation of results, but the limitation of a relatively low event rate and a lack of long-term outcome (5-10 years) with a risk of missing differences between groups in the long-term. According to recent reports a 3-year follow-up should be sufficient to identify the majority of local recurrences and a clinically relevant follow-up time[114-116]. The overall survival data presented in our study (paper III) is also longer than three years since all-cause mortality data could be collected at a later time-point than 3-year local recurrence.

A major concern with the study design is of course that the registry does not include details of the perineal part of the operation, and therefore, details of this had to be collected separately. Our preferred method to obtain this information was by collection of the primary data from the operative notes from the respective hospitals, on each and every one of the included patients. This – besides the drawback of being a time- and effort-consuming method – gave first hand data on the operations performed and was done in order to fill this vital lack of data from the registry. The analysis of all charts was performed by individuals with expert knowledge about the surgery performed – i.e. colorectal surgeons. The extraction of data from the operative notes had to be standardised and based on surgical/anatomical descriptions rather than (well-formed) interpretations of the notes. A CRF was constructed and the interpretation of the notes was performed (as described earlier, see “patients and methods”) forming a conclusion of whether a standard APE or an ELAPE had been performed. Unfortunately, it became evident that Swedish surgeons often did not include anatomical details of the perineal dissection in their operative notes, and in a large portion of patients it could not be decided as to which procedure had been performed. It is worth mentioning that at this stage nothing was known of the short- or long-term outcome for the patients.

However despite the large portion of patients in the "not stated"-group the remaining sample is still large and by setting such "hard" criteria for definition the patients of the ELAPE- and standard APE-groups can be regarded as well defined. Also the "not stated"-group can be analysed as a separate group (as was done in paper III) to see if there are major differences in demographics or in oncological outcome. There is – based on the oncological results for the "not stated"-group - no indication that the lack of detail regarding the description of the perineal dissection performed is an indication of poor surgery.

Another kind of outcome data that we were interested in and which the registry – thus far – did not have, was patient-reported health related QoL-data. To obtain valid knowledge on patients' experience and how the surgery had impacted on their daily lives, a study-specific questionnaire was developed within our research group. The aim with the questionnaire was to be able to gain knowledge of how the patients themselves reported their loss of function and effects on QoL, not only a few months, but rather three years after the surgery. The questionnaire was developed according to known standards and based on the development and knowledge of similar questionnaires[103, 117] for other malignant tumours in the pelvis. The questionnaire covers several aspects of the health related QoL following the treatment for rectal cancer[96] and the parts of the questionnaire used in this thesis are those concerning overall quality of life and the presence or absence of negative intrusive thoughts. Other aspects were also covered in the questionnaire and are the focus of previous[118] and coming analyses. The data obtained from the patients alive three years after the surgery is a major strength in this study since it adds knowledge that has not previously been available. As the data represents a national cohort of patients it is valid not exclusively for a small group of patients in highly specialised surgical centres. The generalizability of this data should therefor also be considered high.

The study was not a randomised study in design, but based on a national cohort of patients prospectively registered but retrospectively analysed. There are consequently differences between the groups. We found that ELAPE was already widely spread among Swedish surgeons in 2007–2009, and it was used with some discrimination mostly for rectal cancers situated low to very low in the rectum. This was evident in the demographic data, where the mean tumour height for ELAPE was 3.4 cm from the anal verge as compared to the 6.6 cm for the standard APE group. The mean height in the "not stated"-group was between the two, thus indicating that it probably was a mix of both APE and ELAPE-operated patients. There were also differences between the

two groups with regard to preoperative adjuvant radio- and chemoradiotherapy more commonly administrated to ELAPE-patients. This selective use made the comparison of outcomes between the ELAPE- and the standard APE-group more demanding.

To address the problem of differences between groups we performed a subgroup-analysis of the cohort of patients with the most distal tumours (≤4 cm from anal verge, n= 444). In the study of oncological and clinical short-term endpoints (paper II) there was a significantly lower rate of intraoperative perforations for the ELAPE group as compared to standard APE. This could represent an indication that ELAPE is really superior to APE in this regard – as proposed in previous studies. It should be kept in mind that subgroup-analyses have the inherent disadvantages of smaller sample size with the risk of making both type I (false positive) and type II (false negative) statistical errors when interpreting the results.

In the further analyses of local recurrence rates and the relationship between negative intrusive thoughts and overall quality of life the statistical analyses was strengthened and complemented with multivariate regression models in order to compensate for differences between groups regarding confounding factors. The multivariate adjustments for possible confounders was as is standard in epidemiological research done with the purpose of adjusting for differences between the groups thus making outcome differences between groups more likely to be true. Odds ratios and relative risks of local recurrence (both for the entire cohort and the subgroup of distal tumours) were calculated. In these analyses, previously known risk factors for local recurrence i.e. intraoperative perforations, more advanced T-stage and lymph-node-stage was found to be associated with increased risk of local recurrence, but also ELAPE itself when compared to standard APE. For the subgroup of the more distal tumours ELAPE was not associated with higher risk for local recurrence but no advantage could be shown with ELAPE compared to standard APE as was the primary hypothesis of the study, this despite the fact that the ELAPE-group had received significantly more neoadjuvant treatment.

Due to the exploratory and hypothesis generating nature of the objectives, no correction for multiple hypothesis testing were made. Hence, the familywise error rate, i.e. the probability of making at least one type I error, were inflated. Consequently, statistical results should be interpreted cautiously with this in mind and not be considered as conclusive evidence.

In this study of a large national three years cohort of patients operated with APE, we found no reduction in 3-year local recurrence for ELAPE compared with standard APE in a multivariate analysis. There was no difference in 3-year overall survival between the groups. However, risk factors for local recurrence were more advanced tumours (T4- and N2-stages) and intraoperative perforation.

The results confirmed previous findings of a higher rate of post-operative infectious complications in the ELAPE group as compared to standard APE[52, 70, 71], but we found no differences between the groups regarding reoperation rate, overall complication rate or short-term mortality. Data on wound-related infections were retrieved from the national registry, and the rates that we found were not in the higher ranges among the reported. We have however no reason to suspect that there was any bias in reporting complications to the Swedish Colorectal Cancer Registry between the two types of procedures. In future studies based on data from the SCRCR complementary data from the Swedish National Patient Registry could be collected to further validate the data on reoperations from the SCRCR.

A majority of the patients received neoadjuvant treatment, and this was more common among the patients in the ELAPE group, which could have influenced long-term results. Whether this, to some extent, can explain the increased wound infection rate is not possible to elucidate in this study.

The finding of fewer intraoperative perforations for the early tumours (pT0–pT2) with ELAPE is perhaps somewhat unexpected and should be mentioned. A plausible hypothesis is that such perforations to some extent is due to down-staging of tumours from neoadjuvant radiotherapy which renders the tumours more fragile and susceptible to perforations when the dissection is performed in closer vicinity to the tumour as in traditional APE.

Other variables that can be attributed to the results of both standard APE and ELAPE are surgeon-related variables such as level of training, past experience and annual numbers of operations performed. Swedish colorectal surgeons at the time (2007-2009) could be considered well trained due to well-attended workshops in TME surgery. However, in the study, there were both high caseload centres and centres that performed less than 10 procedures annually, so there was definitely a variation in surgeon-related competence. Since the study included all Swedish patients and centres during these years, the results are valid on a national basis. Whether a large proportion of the patients operated with ELAPE was operated in high caseload centres or not,

has not been the focus of our studies so far. This is however a valid question and caseload is the focus of research both nationally and internationally[119-121].

Another factor that might influence results is patient positioning during the perineal part of the operation; however, since the prone jack-knife position was used in the majority of the ELAPE procedures and the lithotomy position in the majority of the traditional APE procedures, the influence of this factor was not possible to analyse.

Since the start of our study in February 2011 further studies has been performed internationally. Two large - nationally based - studies from Spain and Denmark have been completed and published: Ortiz and colleagues presented propensity score-matched data on 914 patients from 2008-2013 with no advantage for ELAPE on intraoperative perforations, involved CRM, local recurrence or mortality[122]. Their study was a prospective, large, multicentre study. Not all Spanish centres took part and this may represent a possible selection bias. In the nationwide database-study by Klein and colleagues from Denmark on all Danish patients (all patients from the Danish Colorectal Cancer Group's prospective database) operated with standard APE or ELAPE (n=554) from 2009 to August 2012 there was no benefit for ELAPE regarding short-term oncological outcome i.e. involved CRM in multivariate analysis compared with standard APE. Intraoperative perforations or local recurrence rates were not reported in that study[123].

In 2015 a systematic review and meta-analysis by Zhou and colleagues was published. The study included the two studies[122, 123] and also the study in paper II of this thesis as well as other studies. This meta-analysis did not find a statistically significant advantage of ELAPE over conventional APE in terms of CRM positivity. There was a borderline risk reduction for ELAPE regarding intra-operative bowel perforation with a RR of 0.61 (95% CI: 0.37–1.00).

The cumulative results on the different outcome variables of the ELAPE-technique are still not overwhelming within the literature. There is a clear indication in several studies that ELAPE was associated with increased morbidity in relation to the perineal surgical wound, and since this is well in line with what could be expected this is likely to be a true disadvantage of this technique[71, 118]. The principle hypothesis that ELAPE by decreasing intraoperative perforations and involved CRM can decrease the rates of local recurrence has however not been shown with clarity. In our study of Swedish patients operated with standard APE and ELAPE, ELAPE did not single out as a factor associated with a decreased risk for 3years local recurrence, rather

the opposite. There was of course the problem with differences between groups with regard to tumour height and the large group of "not stated". But the subgroup as well as the multivariate regression-analyses did not indicate superior outcome for the ELAPE-group as was hypothesised, rather that ELAPE itself was a risk factor for local recurrence. The finding of decreased rate of intraoperative perforations for the distal tumours with ELAPE is interesting but since it is a subgroup-analysis this finding should be interpreted with caution. The multivariate analysis of local recurrence in this subgroup did not reveal decreased local recurrence rates after ELAPE and again interpreting the results with caution is advisable. It should be kept in mind that our study lacked the statistical power in this regard. . The other two large nationally based studies by Ortiz[122] and Klein[123] do not support the superiority of ELAPE for the most distal tumours (≤4 cm from anal verge) but we still lack a randomised study of sufficient sample size to give further information. Our results do not support the use of ELAPE as standard surgery for all distal rectal cancer.

As was previously known, intraoperative perforation of the specimen is an independent and important risk factor for local recurrence. In our study this was again evident, and a plausible suggestion is that the ELAPE-concept has a place in the surgery of distal rectal tumours where the preoperative MRI reveals tumour growth on the levator muscle and when there is high risk of intraoperative perforation due to local tumour growth at what will otherwise (i.e. with standard APE) become the resection margin.

6 CONCLUSION

Summary of results

ELAPE was used in a large proportion of patients operated for distal rectal cancer in Sweden 2007-2009.

Patients operated with ELAPE had significantly more distal tumours than patients operated with standard APE.

There was no difference between standard APE and ELAPE with regard to mortality, overall complications or reoperations within 30 days after surgery.

There were significantly more postoperative wound infections following ELAPE than standard APE.

There were no differences between standard APE and ELAPE with regard to intraoperative perforations or involved CRM for the entire groups.

For the subgroup of the most distal tumours (≤4 cm from anal verge) there were fewer intraoperative perforations with ELAPE.

The relative risk for local recurrence in a multivariate analysis was significantly higher for patients operated with ELAPE than standard APE.

The relative risk for local recurrence in a multivariate analysis for the subgroup of the most distal tumours (≤4 cm from anal verge) was not significantly different between patients operated with ELAPE and standard APE.

A large proportion of survivors after abdominoperineal excision for rectal cancer have a quality of life comparable to a normative population, however many suffer from a symptom of stress, negative intrusive thoughts, which significantly decrease overall quality of life.

General conclusion

ELAPE should not be suggested as a standard operative technique for all low rectal cancers.

ELAPE should be used with discretion, primarily for cases with high risk of intra operative perforation - which is a major risk factor for local recurrence.

7 FUTURE PERSPECTIVES

Clearly there is still need for improvement of the treatment of rectal cancer in general, and distal rectal cancer in particular.

In order to improve results, understanding the underlying pathophysiological and biological properties of the disease, is crucial. Hopefully further studies on the genetic and biological mechanisms of the disease itself and the pathways of local recurrence will help improve the treatment. This is of course within a somewhat different field of research than the focus of this thesis but there will always be the need of cooperation between the clinical (macro) and the more basal/cellular (micro) research fields.

When it comes to the surgical aspects of the treatment of distal rectal cancer there is still much more to do. Large-scale, high-quality, registry-based studies or even better randomised controlled trials of new treatment modalities will always be needed. Studies on radical chemoradiotherapy to achieve complete tumour response are on-going and knowledge of both oncological results and patient reported HRQL are important to evaluate the place of this nonsurgical modality in the treatment of rectal cancer. When it comes to ELAPE, the results on local recurrence rates from the Danish registry will be of great interest, and it would be valuable to also have firm results on the most distal tumours with and without tumour engagement of the levator muscle to conclude whether these patients gain from ELAPE or if ELAPE mainly contributes with morbidity.

To understand the functional and HRQL aspects of rectal cancer treatment, much more knowledge is needed. It is clear that all treatments affect patients´ quality of life. This outcome must be further studied in order to better understand the mechanisms and minimize the negative impact of the treatment. This is even more important in an era of better oncological results and improved disease-free long-term survival.

An aspect of the functional outcome not much studied so far are the functional losses following surgery. Studies on how to address and treat functional deficiencies following surgery are much needed in order to improve the HRQL. Improved treatment of for example sexual- and urinary morbidity are perhaps the first to be addressed since these are common and are known to have great impact on patients QoL.

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