LOW RECTAL CANCER
Aspects of surgical techniques and treatment results

Claes Anderin

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"Helheten är större än summan av delarna"
ABSTRACT

Rectal cancer is the 7th most common form of cancer in Sweden, both for men and women. About one third of all patients diagnosed with rectal cancer have a low tumour (i.e. 0-5 cm from the anal verge). Abdominoperineal excision (APE) is the most common surgical procedure in low rectal cancer, performed in approximately 80% of patients. While oncological outcomes in rectal cancer have improved in recent decades, the outcome after APE has remained poor and local recurrence rates have been reported in up to 23% of cases. This may be explained by technical difficulties encountered during APE, resulting in tumour perforations and positive circumferential resection margins. Moreover, many patients have a complicated postoperative recovery, marked by perineal wound complications. The APE technique has recently changed to a more radical procedure, entailing an extralevator approach (ELAPE), in an attempt to improve oncological outcomes. The aim of this thesis was to evaluate different surgical techniques in patients with low rectal cancer.

The objective of Paper I was to assess treatment and outcome in patients operated for low rectal cancer, focusing on differences related to the type of resection. All patients diagnosed with low rectal cancer from 1995 to 2003 in Stockholm were included in the study (n=613). The surgical procedures performed were APE, anterior resection (AR) and Hartmann’s procedure. Clinical data, including data on histopathology and outcome, were analysed in relation to the type of surgery performed. The study showed that intraoperative bowel perforation (IOP) was more common after APE (12%) than AR (4%) and Hartmann’s procedure (9%); p=0.03. Incomplete tumour clearance was also more common in the APE group (18%) than in the AR (5%) or Hartmann groups (14%); p<0.01. Although local control and survival were poorer after APE than after AR, the type of operation per se was not an independent prognostic factor.

In Paper II the objectives were to investigate if ELAPE improved oncological outcomes compared with standard APE (SAPE) and to analyse the morbidity associated with ELAPE. In this multicentre study, 176 ELAPE operations, performed by 11 European colorectal surgeons, were compared with 124 SAPE from one centre in the United Kingdom. Clinical and histopathological data were collected along with specimen photographs. Tissue morphometry was also performed on the distal ten slices of the specimen. The results showed that ELAPE removed more tissue from outside the smooth muscle layer per slice (median area 2120 versus 1259 mm²; p<0.001), leading to a reduction in the involved circumferential resection margin (CRM) (from 49.6 to 20.3%; p<0.001) and the intraoperative bowel perforation (IOP) (from 28.2 to 8.2%; p<0.001) compared with SAPE. However, ELAPE was also associated with an increased frequency of perineal wound complications (from 20 to 38%; p=0.019) compared with SAPE.

The objective of Paper III was to evaluate short-term outcomes with a gluteus maximus myocutaneous flap reconstruction (GMF) of the pelvic floor after ELAPE for low rectal cancer. The study included 65 consecutive patients operated with ELAPE and a one-sided GMF for low or locally recurrent rectal cancer at the Karolinska University Hospital between 2002 and 2008. Fifty-nine patients had received neoadjuvant RT or chemoradiotherapy. All perineal complications occurring within 30 days after surgery were registered. In addition, the status of the perineal reconstruction at 6 months and 1 year after surgery was assessed, based on medical records from outpatient visits. The result showed that 27 patients (41.5%) had one or more perineal wound complications. Most common was a minor wound infection, occurring in 15 patients, while 12 had either a more severe infection with dehiscence or a pelvic abscess. The reconstruction was completely healed in 91% of the patients at 1 year after surgery.

With SAPE the patient remains in the supine position during the perineal part of the procedure. However, turning the patient into the prone position may improve visualisation which could potentially reduce the risk of involved CRM and IOP and, thereby, improve local control. The objective of Paper IV was to evaluate local recurrence rates after APE in relation to the positioning of the patient during the perineal part of the procedure. This cohort study included 466 patients operated with APE for low rectal cancer in Stockholm from 2001 to 2010. Data were retrieved from the regional rectal cancer registry in Stockholm and from a retrospective review of medical notes. The study showed an incomplete resection in 12.4% of the patients after APE in the supine position and in 6.8% after APE in the prone position (p=0.038). Corresponding figures for IOP were 12.4% and 4.0% (p<0.001). Prone APE was associated with a 39% relative reduction rate in local recurrence events compared with APE in the supine position. However, this difference was not statistically significant, HR 0.61, (95% CI: 0.27-1.37).
# List of Publications

| I | C. Anderin, A. Martling, H. Hellborg, T. Holm  
A Population-based Study on Outcome in Relation to the Type of Resection in Low Rectal Cancer  
*(Diseases of the Colon & Rectum 2010; 53: 753–760)* |
|---|---|
| II | N. P. West, C. Anderin, K. J. E. Smith, T. Holm, P. Quirke  
Multicentre experience with extralevator abdomino-perineal excision for low rectal cancer  
| III | C. Anderin, A. Martling, J Lagergren, A. Ljung, T. Holm  
Short-term outcome after gluteus maximus myocutaneous flap reconstruction of the pelvic floor following extra-levator abdominoperineal excision of the rectum.  
*(Colorectal Disease, Accepted manuscript online: 8 Oct 2011)* |
| IV | C. Anderin, F. Granath, A. Martling, T. Holm  
Local recurrence after prone versus supine abdomino-perineal excision for low rectal cancer  
*(Manuscript)* |
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<td>Abdominoperineal excision</td>
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<tr>
<td>AR</td>
<td>Anterior resection</td>
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<td>ERUS</td>
<td>Endorectal ultrasound</td>
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<td>CT</td>
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<td>CRM</td>
<td>Circumferential resection margin</td>
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INTRODUCTION AND BACKGROUND

Definition and anatomy

Definition

The rectum is a continuation of the mobile sigmoid colon and is characterised by the absence of taeniae, epiploic appendices, haustra, or a well-defined mesentery. It begins at the level of the sacrum and coccyx and follows a curved course onto the pelvic floor where it is supported by the levator ani muscle. At the border of the levator ani/puborectalis muscle it penetrates the pelvic floor and becomes the anal canal.

When performing a rectoscopy the rectum starts at the anal verge (defined as the opening of the anus at the surface of the body) and extends approximately 15 cm. The upper third of the rectum (10-15 cm from the anal verge) is covered by the peritoneum, apart from a small segment posteriorly through which the mesorectum provides its blood supply from the superior rectal vessels. The middle third (5-10 cm from the anal verge) is only covered anteriorly. At this point the mesorectum becomes wider. The lower third (0-5 cm from the anal verge) has no peritoneal relationship.

Beneath the peritoneum the three taeniae coli fuse into a continuous longitudinal muscle coat surrounding the inner circular muscle of the rectum. This coat is fused with the puborectalis portion of the levator ani. Below the levator muscle, the mucous membrane of the anal canal is surrounded by the internal and external sphincter.

Mesorectum

The rectum, by definition, has no mesentery. The mesorectum is a distinct compartment enclosed by the mesorectal fascia (MRF). It contains fat through which vessels, lymphatic drainage and nerves run to supply the rectum. The mesorectum may be a metastatic site for rectal cancer and is removed during surgery for this cancer. Its removal is undertaken without clinical sequelae because no functionally significant nerves pass through it.
Arterial supply

The major blood supply to the anorectum is represented by the superior and inferior rectal arteries. The superior rectal artery is a branch from the superior rectal branch of the inferior mesenteric artery \(^1\). The contribution of the middle rectal artery varies with the size of the superior rectal artery; this may explain its controversial anatomy. Some authors report an absence of the middle haemorrhoidal artery in 40 to 88% of cases \(^2\). This vessel reaches the lower third of the rectum anterolaterally, close to the level of the pelvic floor and deep to the levator fascia. The middle rectal artery is more prone to be injured during low anterior resection. The paired inferior rectal arteries are branches of the internal pudendal artery which, in turn, is a branch of the internal iliac artery \(^1\). The inferior rectal artery needs to be ligated during the perineal stage of APE.

Lymphatic drainage

Lymph from the upper two thirds of the rectum drains exclusively upwards to the inferior mesenteric nodes and then to the para-aortic nodes. Lymphatic drainage from the lower third of the rectum follows not only the superior rectal and inferior mesentery arteries, but also laterally the middle rectal vessels to the internal iliac nodes \(^1,2\).

Innervation

The sympathetic supply arises from L-1, L-2, and L-3. These fibres synapse in the preaortic plexus and follow the branches of the inferior mesenteric artery and superior rectal artery to the left colon and upper rectum. The lower rectum is innervated by the presacral nerves, which are formed by a fusion of the aortic plexus and lumbar splanchnic nerves. Just below the sacral promontory, the presacral nerves form the hypogastric plexus. Two main hypogastric nerves, on either side of the rectum, carry sympathetic innervation from the hypogastric plexus to the pelvic plexus. The pelvic plexus lies on the lateral side of the pelvis at the level of the lower third of the rectum.

The parasympathetic supply derives from S-2, S-3, and S-4. These fibres emerge through the sacral foramen and are called the nervi erigentes. They pass laterally, forward, and upwards to join the sympathetic hypogastric nerves at the pelvic plexus. From the pelvic plexus, combined parasympathetic and sympathetic fibres are distributed to the left colon and upper rectum via the inferior mesenteric plexus and directly to the lower rectum and upper anal canal. The periprostatic plexus, a subdivision of the pelvic plexus situated on Denonvilliers' fascia,
supplies the prostate, seminal vesicles, corpora cavernosa, vas deferens, urethra, ejaculatory ducts and bulbourethral glands.

All pelvic nerves lie in the plane between the peritoneum and the endopelvic fascia and are in danger of injury during rectal dissection. Damage to the autonomic nerves may occur at several points. During high ligation of the inferior mesenteric artery, close to the aorta, the sympathetic preaortic nerves may be injured. Division of both superior hypogastric plexus and hypogastric nerves may also occur during dissection at the level of the sacral promontory or in the presacral region. In such circumstances, sympathetic denervation with intact nervi erigentes results in retrograde ejaculation and bladder dysfunction. An isolated injury to the nervi erigentes will completely abolish erectile function.

The dissection near the seminal vesicles and prostate may damage the periprostatic plexus, leading to a mixed parasympathetic and sympathetic injury. This can result in erectile impotence as well as bladder dysfunction. Sexual complications after rectal surgery are readily evident in men but are probably underdiagnosed in women ¹,².
The aetiology of rectal cancer

Risk factors

Adenoma is the precursor to rectal carcinoma. Approximately 10% of adenomas progress to invasive carcinomas through a well-defined sequence of genetic change called the adenoma-carcinoma sequence. This process may take 10 to 15 years \(^3\). Most cases of rectal cancer arise sporadically. The aetiology is multifactorial and includes risk factors such as: increasing age, male sex and previous colorectal cancer. Lifestyle factors may also contribute to a higher risk. Lack of physical activity, low fruit and vegetable intake, low fibre and a high fat diet, overweight and obesity, tobacco use and alcohol consumption have all been associated with a higher risk \(^4,5\).

Chronic colitis provides an up to 20% increased risk of rectal cancer, and in patients with ulcerative colitis lasting for more than 10 years the risk is increased by 5 to 6 times. An increased risk is also seen in patients with an onset of Crohn’s disease before the age of 30 years \(^6\).

Hereditary rectal cancer

About 20% of all rectal cancer cases might have a familial component. Most of the known familial syndromes are inherited in an autosomal-dominant pattern, resulting in a 50% risk for a child of an affected individual to bear the predisposition for the cancer form \(^7\).

FAP - Familial Adenomatous Polyposis

This syndrome is caused by a congenital alteration in the APC (Adenomatous polyposis coli) gene and is seen in approximately 250 known families in Sweden. The syndrome is characterised by hundreds to thousands of adenomatous polyps in the colon and rectum which usually appear during adolescence. All of these patients develop cancer, usually before the age of 40 \(^6\). In Sweden, a national registry including these families is administrated by the Karolinska University Hospital.
**HNPCC - Hereditary Nonpolyposis Colorectal Cancer**

This syndrome is about as frequent as FAP and is caused by three known gene mutations, which normally control mismatch repair. These patients have more polyps than the general population and a 70% increased lifetime risk of cancer development. They also have a higher risk for ovarian, stomach, small bowel, and urine bladder cancer. The average age of onset is at 40 years of age 6.

**HCRC - Hereditary Colorectal Cancer, non-FAP, non-HNPCC**

HCRC is also as frequent as FAP and HNPCC. This syndrome is characterised by a high lifetime risk of developing colorectal cancer, usually at an age of over 50 years. More adenomas and metaplastic polyps are seen in HCRC patients than in the general population. In some families, the tumours arise especially in the rectum, while in other families the tumour location is in the colon. The highest cancer risk is seen in the most distal adenomas 6.

Other familial hereditary syndromes with elusive aetiology (defined by two or more first-degree relatives) are seen in at least 20% of cases. These individuals have a 10-20% increased risk of colorectal cancer. Lifetime risk is estimated at approximately half compared with the syndromes mentioned above 7, 8.

**Epidemiology**

**Worldwide**

Rectal cancer is not uniformly distributed amongst all populations. Western Europe and North America have the highest incidence, whereas intermediate rates prevail in Eastern Europe. The lowest rates are seen in Asia, Africa and South America, excluding Argentina. However, there is some evidence that the incidence in Africa is increasing, probably as a result of a change in lifestyles 9.

Variations in incidence between countries are much larger than the variation within each country. This geographical difference may be due to a detection failure in areas of low incidence where techniques for diagnosis are perhaps less sophisticated and the patients’ tolerance of symptoms is higher 10. However, these differences account for only a small part of the variation, and do not explain, for example, the difference in rate between Denmark and Finland and the low rate in Japan. Lifestyle factors, mainly dietary habits, probably account for the major part of the incidence variations between different countries 10.
Sweden

Rectal cancer is the 7th most common form of cancer in Sweden, for both men and women. In 2009, 2121 patients were diagnosed (1233 men and 888 women). For unknown reasons, this type of cancer is more common in men than in women. Incidence rates have remained relatively stable over the past decade, with a slight tendency to increase (Figure 1).

Rectal cancer is rare before the age of 50 and 75% of those affected are over 65 years of age. The median age at diagnosis is 72 years. In 2009, the 5-year relative survival was 57.3% in men and 60.4% in women.\footnote{11}

\textbf{Figure 1a.} Age standardised incidence and mortality in rectal cancer per 100 000 male inhabitants in Sweden, 1970-2005.

\textbf{Figure 1b.} Age standardised incidence and mortality in rectal cancer per 100 000 female inhabitants in Sweden, 1970-2005.

Data: Swedish National Cancer Registry
Symptoms

Rectal cancer is often associated with a characteristic complex of symptoms. Bleeding is the most common, and frequently ignored by the patient. The blood is often red, but not bright red. It may be mixed in with the stool or passed separately and, although small amounts are usual, on occasions the volume may be alarming. Although bleeding may occur alone, bowel habits are often altered. The patient frequently has the urge to defecate but, on-going to the lavatory, passes only blood and mucus. This symptom is called “tenesmus” and is often most acute when the patient rises from bed.

If the growth of a tumour is constricting the rectum, abdominal colic may be the main complaint. Local anorectal pain is less common. This can occur if there has been a spread to local structures, particularly the sacral plexus or if the tumour invades downwards and encroaches on the anal canal or perineal skin. Invasion of the anal canal and anal sphincter may also lead to incontinence. Invasion of the perineal skin may result in fistulae.

Other structures in the pelvis may be invaded and give rise to specific symptoms. The bladder or urethra may be involved with the formation of rectourethral or rectovesical fistulae. The patient then often complains of recurrent dysuria and frequent micturition and sometimes pneumaturia. In females, tumour growth anteriorly may lead to a rectovaginal fistula. These fistulas will often result in the passage of blood, mucus and sometimes stool through the vagina.

Rarely, a rectal tumour may be so locally aggressive that it presents as a large pelvic mass. Invasion or compression of the pelvic blood vessels and lymphatics may produce unilateral or bilateral leg oedema.

Diagnosis and staging

Clinical examination

Due to the distal site, most of the low rectal cancers can be diagnosed by digital rectal examination. An assessment of size, level and mobility is mandatory. The level assessment is best measured from the anal verge with a rigid rectoscope. Mobility of the tumour determines, relatively crudely, if the tumour is fixed to adjacent tissues or not. A rigid rectoscopy, proctoscopy or flexible sigmoidoscopy with biopsies will establish the diagnosis. A colonoscopy should be performed after diagnosis to exclude synchronous tumours.
Imaging

*Magnetic Resonance Imaging (MRI)*

High-resolution MRI has been shown to be superior to clinical examination (digital rectal examination), CT, and endoluminal ultrasound (EUS) for the local staging of rectal tumours. Using high resolution MRI enables a detailed preoperative staging for the selection of patients that require preoperative therapy for tumour regression. This information can be used to initiate neoadjuvant therapy in those patients with poor prognostic factors.

MRI can give a preoperative staging according to the TNM classification. The major advantages of thin section MRI are the ability to differentiate malignant tissue from the muscularis propria and the clear delineation of the mesorectal fascia (MRF) (T), which forms the potential CRM. Absence or presence of regional lymph node metastasis (N) and extramural vascular invasion can also be assessed on MRI, although this is still a diagnostic challenge. Lymph node enlargement or heterogeneity can be seen as indirect signs of tumour involvement. MRI can also be valuable for undetermined lesions in the liver (M) seen on computed tomography. MRI is also used for early identification of a local recurrence.

*Figure 2. Tumour confined at the level of the puborectalis sling.*
**Computed Tomography (CT)**

A CT scan of the entire chest, abdomen and pelvis is used for the detection of metastatic disease. It is widely available and has faster acquisition times than MRI. However, it is not considered as the investigation of choice when it comes to assessing the layers of the rectal wall. Visualisation of pelvic structures using CT is limited by poor soft tissue contrast discrimination between the pelvic structures and image artefacts from the bony pelvis; hence it is not usually valuable for the local staging of rectal cancer and is certainly a poor choice for evaluating superficial rectal cancers 17.

The accuracy of CT to assess the tumour has been reported to be between 80-95% in patients with advanced local disease. The accuracy, however, decreased to approximately 63% when a broader spectrum of tumour sizes was analysed 18. Sensitivity to pick up nodal disease has been found to be between 55-70% 19. In a meta-analysis involving 5000 patients, CT showed accuracy for T staging of 73% and for nodal staging of 22-73% 20.

**Abdominal Ultrasound (US)**

Abdominal US is often used to evaluate the liver for metastases. A contrast-enhanced US can be valuable for the assessment of lesions in the liver detected by other modalities, e.g. CT. The false negative rate is reported to be around 8%. The technique, although inexpensive and widely available, is operator dependent. Intraoperative US is used when a synchronous rectal and liver resection is planned. Rapid advancement in other imaging modalities has made US a less favoured modality in rectal cancer staging 21.

**Endorectal Ultrasound (ERUS)**

ERUS is sensitive for early rectal cancers (T1-2 lesions) with an accuracy of 69-97% 22, 23. High resolution allows an assessment of the rectal wall but not of the mesorectal fascia or the lymph nodes. Due to this, over-staging has been a concern. Artefacts caused by faeces may lead to an ultrasound appearance that can be misinterpreted as a tumour. ERUS cannot reliably distinguish an irregular outer rectal wall due to peritumoural inflammation or transmural tumour extension. The accuracy of the T-stage evaluation varies from 62-92% 24. In a meta-analysis of 11 studies it has been shown that the sensitivity for superficial tumours is better than for more advanced lesions 25.
ERUS nodal staging accuracy is around 75% \(^{26}\). The results from a meta-analysis in 2005 suggest that ERUS cannot reliably detect metastatic nodal disease \(^{27}\). Obstructing lesions may be difficult to scan, especially with rigid probes, leading to suboptimal staging. Bulky, high, stenotic, advanced (T3-4) lesions or tumours downstaged after neoadjuvant therapy can be a challenge \(^{28}\). The scanning, although inexpensive and portable, is operator-dependent and has a steep learning curve.

**Positron Emission Tomography (PET)**

PET is based on the different metabolic profiles of tumours compared with normal tissue. Fluoro-deoxy-glucose (FDG) is the most commonly used PET tracer. Due to an increased metabolic activity from a change in the tumour biology, tumours usually show an increased uptake which results in what is called radiolabelling \(^{29}\). Although tumour selective, FDG also accumulates in areas of infection and inflammation and in organs with increased metabolic activity, such as the brain, myocardium, liver or kidneys, which may cause false positive results \(^{29}\). FDG uptake is also influenced by the presence of mucin. Therefore, PET is more useful in identifying non-mucinous than mucinous tumours.

Currently FDG/PET is not used as a primary staging modality in rectal cancer. It is mainly used in the assessment of local recurrences and in metastatic disease when conventional imaging is not sufficient. Interpretation of PET without anatomic correlation poses difficulties. PET-CT fusion scans, where the pictures of both investigations are fused using software are, therefore, an alternative and are sometimes used. This combination provides additional value in localising hot spots. There are, however, some technical limitations with this combination of imaging, with the false positive rates due to other disease and physiological processes.

The role of the PET-CT fusion scan has not changed compared with PET scans. However, a study from Heriot et al found that preoperative PET changed the management in 17% of patients, with improved staging accuracy in combination with CT \(^{30}\). Another study carried out by Gearhart, reported an altered management plan for 27% of patients using FDG-PET/CT imaging modality for low rectal cancer \(^{31}\).
Multidisciplinary Team Conference (MDT)

An MDT conference is a structured meeting with the participation of surgeons, pathologists, oncologists and radiologists. Each patient is discussed individually pre- and postoperatively. The aim of the conference is to decide the best individual treatment for each patient based on the available knowledge. Decisions on neoadjuvant RT/CRT, any inclusion in a study, and planning of the type of surgery required is made preoperatively. Postoperatively, the histopathology report should be discussed and each patient considered for adjuvant treatment.

The implementation of MDT conferences has been shown to improve survival and lower the rate of CRM involvement for patients with colorectal cancer.\textsuperscript{12,32}

Preoperative staging

An ideal preoperative staging system should provide reproducible objective images and accurately select patients for the optimal treatment; by surgery alone or in combination with neoadjuvant therapy. It should also monitor the effects of neoadjuvant therapy and guide surgical timing and strategy. Increasingly, MRI, CT and PET fulfil many of these aims. This has resulted in the adoption of sequential imaging as an accurate representation of the evidence of the presence or absence of metastatic disease.

Today, preoperative staging for rectal cancer is based on the clinical and radiological evaluation of the extent of spread, MRF/CRM involvement and TNM stage at presentation.

The availability of different neoadjuvant treatments has the need of an algorithm for classifying rectal cancer into three groups. This concept has been used in the Stockholm/Uppsala region and in the United Kingdom to recommend preoperative treatment. The rectal tumours are stratified into those having no negative prognostic factors on MRI, either for the risk of local or distant metastases (“good group”), those having features on MRI suggesting an increased risk of local recurrence and distant metastases (“bad”), or those with features suggesting high risks of local recurrence and distant metastases (“ugly”) (Figure 3)\textsuperscript{33}.

The MRI aspects in this stratification are the extramural extent of the tumour in millimetres, MRF/CRM involvement, presence of more than four lymph node metastases and extramural vascular invasion.
Figure 3. MRI-directed preoperative evaluation. Modified from Blomqvist/Glimelius.

<table>
<thead>
<tr>
<th>Favourable “good” group</th>
<th>Intermediate “bad” group</th>
<th>Advanced “ugly” group</th>
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<tbody>
<tr>
<td>Low rectum T1-2, T3a N0</td>
<td>Low rectum includes T3b-T4 with peritoneal or vaginal involvement only N1/N2</td>
<td>T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic side walls or floor, sacrum positive lateral lymph nodes</td>
</tr>
<tr>
<td>CRM clear</td>
<td>CRM clear</td>
<td>CRM positive</td>
</tr>
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</table>

Primary surgery  | Preop 5 x 5 Gy with immediate surgery  | Preop RCT or 5 x 5 Gy with delayed surgery

1 CRT signifies chemoradiotherapy to 50.4 Gy in 1.8 Gy fractions with 5-fluorouracil. 5 x 5 Gy with delayed surgery is used in patients not fit for RTCT. The relative antitumour efficacy of conventionally fractionated RT or the short-course schedule is not known with any greater certainty.  

34, 35
Preoperative treatment

In recent years, treatment protocols have redefined the management and outcome in rectal cancer. As mentioned before, modern imaging techniques allow physicians to more precisely determine tumour characteristics and prognostic factors in the preoperative setting. This knowledge has been used to improve cancer stage-specific treatments.

Simultaneously to the refinement of surgical techniques, especially TME, neoadjuvant therapy for rectal cancer has developed as a combination of chemotherapy and RT. Preoperative RT and chemotherapy are more effective in producing tumour necrosis both in the non-disturbed presurgical tumour bed and in the cancer cells of the tumour periphery compared to the hypoxic postsurgical bed. There are also several other advantages with preoperative therapy. Less radiation-induced small bowel injury in the pelvis and the ability to excise the affected rectal segment and to perform an anastomosis to a healthy, non-irradiated colon, results in an improved postoperative function. Furthermore, patient compliance to both radiotherapy and chemotherapy is decreased when they are given postoperatively compared with preoperatively. One advantage with postoperative RT is that only high-risk patients are selected after histopathological examination of the specimen, reducing the risk of overtreatment and potential side effects.

The improved preoperative imaging, better chemotherapy and more accurate and focused RT, have resulted in a higher probability of complete tumour responses, increased frequencies of tumour downstaging, and decreased local recurrence rates.

Radiotherapy (RT)

In the 1990s, several randomised studies compared preoperative RT therapy and surgery with surgical therapy alone to determine if there was a difference in outcome in rectal cancer. Two influential studies during this period included the Stockholm I Trial, the Swedish Rectal Cancer Trial (SRCT) and the Dutch Rectal Cancer Study Group Trial. All these trials showed a decrease in local recurrence rate of approximately 50-60% in the preoperative RT + surgery groups compared with the surgery alone groups. Unlike the SRCT, the two other studies did not find a difference in overall survival. The discrepancy in overall survival between the three studies may be due to the fact that TME surgery was not performed in the SRCT. In this study, the incidence of local recurrence was also higher.
In 2001, the Stockholm II Trial showed a reduction in the incidence of local recurrence from 25-12% after preoperative RT \cite{42}. The overall survival among all patients in the study showed no significant difference. Recently a Dutch trial investigated the value of preoperative RT in combination with TME \cite{43}. The primary endpoint in this study was local control with a median follow-up of 12 years. Secondary endpoints were distant recurrence, overall survival, and cancer-specific survival. In this study, preoperative short-term RT reduced 10-year local recurrence by more than 50% relative to surgery alone without an overall survival benefit. For patients with a negative resection margin, the effect of RT was irrespective of the distance from the anal verge and led to an improved cancer-specific survival. However, this improvement was nullified by an increase in other causes of death, resulting in an equal overall survival \cite{43}.

There are two conventions for the administration of neoadjuvant RT and the timing of surgery: the short-course and the long-course. The short-course RT protocol consists of a daily dose of 5 Gy delivered over 5 days (to a total of 25 Gy) with surgery carried out during the following 5-10 days. This schedule is commonly used in Northern Europe and is the most extensively studied of the two regimens. Short-course RT aims to improve local control by killing microscopic cancer cells in the surrounding tissue of the tumour.

Long-course RT, common in Southern Europe and the United States, uses conventional fractionated radiotherapy (45-50 Gy) divided into 1.8 or 2.0 Gy over 25-33 days simultaneously with chemotherapy. In this convention, surgery is typically carried out 4-8 weeks after CRT is given. The aim with long-course RT is downstaging of the tumour and thereby to facilitate a complete resection.

The Stockholm III Trial study is a randomised controlled trial comparing the different preoperative RT regimens and the timing of surgery. The patients are randomised to three different arms: 5x 5 Gy and immediate surgery vs. 5 x 5 Gy and delayed surgery vs. conventional fractionated 50 Gy and delayed surgery.

The aims are to address the questions of whether duration of radiation therapy and timing of surgery after radiation affect morbidity, mortality or downstaging/downsizing of the tumour. This is an on-going study and is currently recruiting participants. An interim analysis of this study has shown similarity between hypofractionated and conventionally fractionated RT regarding feasibility, compliance, severe early radiation toxicity and influence on the postoperative course. However, short-course RT and immediate surgery tended to be associated with more postoperative complications than the other schedules \cite{44}.

Today, RT is administered using a four-field technique. Organs at risk of radiation injury are the small bowel, anal sphincter, urinary bladder, ureters and nerves.
Acute complications related to RT are dermatitis, nausea, diarrhoea and enteritis. Chronic complications after RT are bowel obstruction, incontinence, diarrhoea, peripheral nerve injury, osteoradionecrosis, sexual and urinary dysfunction. Complications related to surgery are also seen after RT and CRT, such as anastomotic leakage and delayed perineal healing.

Overall, there is a clear association between pelvic RT and decreased local recurrence and a high, but somewhat less likelihood, of improved cancer-specific survival. There is still no evidence of improved overall survival after pelvic RT.

**Chemoradiotherapy (CRT)**

In 2004, the German Rectal Cancer Study Group evaluated RT combined with chemotherapy in stage II and III rectal cancer. In this study, a combination of preoperative CRT and TME vs. TME combined with postoperative CRT were evaluated. Preoperative CRT consisted of 50 Gy over 5 weeks with 5-fluorouracil (5-FU) during the first and fifth weeks of RT. TME was performed 6 weeks after treatment. The CRT was identical in the postoperative group, except for the delivery of a 540 cGy boost to the tumour bed. There was a significant decrease in local recurrence rate in the preoperative treatment arm compared with the arm receiving CRT in the postoperative treatment period (6% vs. 13%; p=0.006).

No difference in 5-year survival rates was found. Findings in the group receiving preoperative CRT also included evidence of tumour downstaging, assessed as earlier TNM stages and a more complete pathological response rate.

Moreover, improved treatment compliance and less acute grade 3 and 4 toxic side effects and long-term toxic effects were also seen in the preoperative treatment group. Although the primary outcome of overall survival did not differ between the groups, the study highlights some of the advantages of preoperative chemotherapy and RT in stage II and III rectal cancer.

In 2006, Gerard et al found similar results in their evaluation of preoperative RT and chemotherapy in patients with resectable T3 or T4, Nx, M0 rectal cancer. Patients were randomly assigned to preoperative RT alone, 45 Gy in 25 fractions over 5 weeks, or preoperative RT (same protocol) plus concomitant chemotherapy, consisting of 5-FU and leucovorin during the first and fifth weeks of treatment. Neoadjuvant chemotherapy plus radiation therapy resulted in increased complete pathological response rates and a decreased rate of local recurrence (8.1% vs. 16.5%; p<0.05).

Similar to the German Rectal Cancer Study Group, this trial did not find a difference in 5-year survival.

The European Organization for Research and Treatment of Cancer (EORTC)
22921 Trial 38 randomised 1011 patients with T3 or T4 resectable rectal cancer into four arms: preoperative RT, preoperative CRT, preoperative RT with postoperative chemotherapy, and preoperative CRT with postoperative chemotherapy. The preoperative RT consisted of 45 Gy delivered over a 5-week period. The chemotherapy course consisted of 5-FU and leucovorin, both given for a total of 5 days.

No difference in overall survival was found between the four groups. Patients who received preoperative chemotherapy, postoperative chemotherapy, or both were found to have significantly lower local recurrence rates compared with the group that received RT alone (8-10% vs. 17%) 38. Once again, adherence to the chemotherapy regimen was higher in the preoperative group compared with the postoperative chemotherapy groups (82% vs. 42.9%) 38. Additionally, preoperative chemotherapy resulted in significantly smaller tumours with less nodal involvement, less advanced pathological tumour stages, and less frequent lymphatic, venous and perineural invasion compared with preoperative RT alone 38.

A Nordic trial from 2008 on locally non-resectable T4 primary rectal cancer and local recurrence randomised 207 patients into two arms: preoperative CRT with additional postoperative chemotherapy 16 weeks after surgery and preoperative RT alone. In this study, preoperative RT consisted of 50 Gy delivered over a 5-week period. The preoperative chemotherapy course consisted of 5-FU and leucovorin, concomitant with RT on two consecutive days every two weeks. The postoperative chemotherapy was scheduled 4 to 6 weeks after surgery and continued for 8 cycles. Patients who received CRT were found to have improved control, time to treatment failure and cancer-specific survival compared with RT alone 50.

Multiple randomised trials have failed to show a survival benefit of CRT compared with RT alone in resectable rectal cancer. Despite this, there are consistently lower local recurrence rates with the addition of chemotherapy, whether it is given in the preoperative or postoperative setting. Furthermore, secondary outcomes in these trials have provided even more evidence of the advantages of using CRT in the preoperative setting as opposed to providing it postoperatively. The highlighted studies found increased rates of tumour downstaging, significantly higher complete pathological response rates, and improved treatment compliance in the groups who received CRT preoperatively 31, 37, 38. All of this together has led to the fact that CRT is now considered the standard of care in the treatment of locally advanced rectal cancer.
Surgery

Background

In 1826, Jacques Lisfanc was the first surgeon to report a successful excising of the rectum. He excised the anus and rectum via the perineum, resulting in the functional equivalent of a perineal colostomy. However, the perineal approach was limited to expose up to the upper rectum. In an attempt to improve access, Kraske introduced in 1885 the posterior approach of resecting the rectum through the sacrum, preserving the anus and sphincter muscles.

As surgical techniques and general anaesthesia developed, more extensive resections were undertaken. Several new approaches, such as transsphincteric and abdominosacral resections were introduced. Consequently, abdominoperineal resection, as introduced by Miles in 1908, became the standard treatment for rectal cancer until the 1940s. This was when Dixon described an abdominal approach with sphincter saving anterior resection (AR) with a colorectal anastomosis for proximal rectal cancer. With the introduction of stapling instruments in the 1970s, even low anastomoses were shown to be reliable.

The surgical techniques used in rectal cancer treatment have improved substantially over the past two decades. The most important advance has been the introduction of total mesorectal excision (TME), as proposed by Heald in 1982. He stressed the importance of recognising the “holy plane,” in which the surgeon’s dissection will include the malignancy and yet preserve autonomic neural function. The use of TME has greatly improved the treatment results in rectal cancer worldwide.

Surgical treatment of rectal cancer depends on a number of factors including disease stage, tumour location and the relationship of the tumour to the adjacent pelvic structures. In addition, patient characteristics including medical comorbidities and functional status, affect the choice of operation.
Figure 4. Original publication of W.E. Miles in the Lancet in 1908.

A METHOD OF PERFORMING ABDOMINO-PERINEAL EXCISION FOR CARCINOMA OF THE RECTUM AND OF THE TERMINAL PORTION OF THE PELVIC COLON.

BY W. ERNEST MILES, F.R.C.S. ENG., L.R.C.P. LOND.,
SURGEON TO THE CANCER HOSPITAL, BROMPTON, S.W., AND TO THE GORDON HOSPITAL FOR DISEASES OF THE RECTUM, VAUXHALL BRIDGE-ROAD, S.W.

Total Mesorectal Excision (TME)

TME was first introduced in 1982. Since that time, this technique has been adopted widely and is now considered the standard of care in rectal cancer surgery. TME relies on the sharp dissection of the avascular plane between the mesorectum and pelvic structures. In addition to being a relatively “bloodless” plane, dissection in this space ensures complete resection of the mesorectum associated with the tumour-bearing part of the rectum. TME improves the ability to achieve a complete tumour resection and enables the sparing of the pelvic autonomic nerves. The adoption of TME has dramatically improved local control. Reported local recurrence rates after this procedure are usually between 3 and 11%.

In low rectal cancer, the TME dissection is carried down to the levator ani muscles circumferentially, thus ensuring resection of the entire mesorectum. On the other hand, for mid- and upper rectal cancers, there is controversy over the need for resection of the entire mesorectum distal to the tumour. As lymph node metastases from upper rectal cancer are rarely found more than 5 cm distal from the primary tumour, advocates of a more limited resection believe that resection of
the mesorectum 5 cm below the tumour is adequate. Moreover, a more limited resection of the mesorectum allows an anastomosis to be placed higher in the rectum, decreasing the risk of anastomotic leakage and insufficient sphincter function.

In the mid-1990s, workshops in TME surgery were held at the Karolinska University Hospital in Stockholm, Sweden. These workshops consisted of video-based live surgery sessions and histopathology sessions with an emphasis placed upon the assessment of CRM involvement. The majority of the surgeons in Stockholm who treat colorectal cancer attended the symposia and assisted RJ. Heald and B. Moran in the operating room. The basis of the TME technique was taught, i.e. sharp dissection under direct vision. The main aim of both preparation and treatment was the surgeon’s removal of a perfect TME specimen with an intact mesorectal fascia and uninvolved CRM. In addition, local control and cancer specific survival was significantly improved.

Anterior Resection (AR)

Currently, AR is the most commonly used operative procedure for rectal cancer in Sweden and is performed in 50% of patients. Rectal tumours in the middle and upper rectum can be removed with this procedure. The rectosigmoid colon is mobilised, the pelvic peritoneum opened, and the inferior mesenteric artery ligated and divided. The rectum is then mobilised using the principles of TME, either to the pelvic floor or to a point 5 cm distal to the tumour. A mid to low rectal anastomosis is then created, either in a hand-sewn fashion or, more commonly, using a circular stapling device.

The invention of circular stapling devices has revolutionised rectal surgery and has greatly increased the number of sphincter-sparing operations that are technically feasible. Tumours located as low as 2 cm from the anal sphincter are often resectable with a low AR. This operation also uses the principles of TME, and the dissection is usually carried down to the level of the levator ani muscle circumferentially. An anastomosis is then created with a circular stapler. In some cases, a hand sewn colorectal anastomosis is created by suturing the proximal colon to the dentate line.

In Sweden, approximately 10% of patients experience clinical anastomotic leakage after AR. In those who have not received preoperative RT, or have other complicating factors, a primary anastomosis can usually be performed safely without the need of a diverting ileostomy. In patients with complicating factors predisposing for anastomotic leakage, i.e. low anastomosis, preoperative RT,
presence of intraoperative adverse events and male sex, a temporary ileostomy may be beneficial for preventing pelvic sepsis \(^4^6\).

Insufficient sphincter function, to various extents, has been reported in 50-70\% of patients operated on with AR \(^6^1\). Symptoms of insufficient sphincter function are referred to as “anterior resection syndrome”. This consists of fragmentation of faeces, increased frequency, urgency and incontinence. In patients with poor preoperative continence or who are wheelchair-bound, a permanent colostomy may be a better option than a low rectal anastomosis. In this setting, an intersphincteric APE or Hartmann’s procedure can be performed (see below). The colon or rectum is then resected without an anastomosis, a colostomy or ileostomy is created, and the distal rectum is excised or left as a blind pouch.

**Abdominoperineal Excision (APE)**

Approximately 80\% of all patients with low rectal cancer (i.e. 0-5 cm from the anal verge) have an APE to ensure an adequate distal margin. Also, patients with faecal incontinence may avoid poor functional outcome by an APE \(^6^2\).

While overall oncological outcomes in rectal cancer have improved over the last few years \(^4^1\), outcomes after APE have remained poor. The procedure has a high local recurrence rate of up to 23\% \(^6^3\). This may be explained by the technical difficulties encountered during an APE, resulting in tumour perforations and positive circumferential margins \(^6^3-6^5\). Moreover, in addition to the disability related to sphincter loss, patients often have a complicated postoperative recovery, marked mainly by perineal wound complications. This is particularly common after preoperative RT \(^6^6, 6^7\).

The technique for APE has recently changed to a more radical approach, with the aim of improving oncological outcomes (see below) \(^6^8\). In APE, the entire rectum, anal canal, and anus are removed. A permanent colostomy is created from the descending or sigmoid colon. Similar to the low anterior resection, the procedure follows the principles of TME in order to ensure an adequate radial margin to the tumour. The perineal dissection is designed to excise the anal canal (see below).

Ideally, the decision to perform this surgical procedure should be made preoperatively, based on objective clinical and/or radiological information. If the decision is made peroperatively, due to levator or external sphincter involvement, the dissection has most likely gone too far and the chances of achieving an R0 resection are decreased.
**Standard Abdominoperineal Excision (SAPE)**

In SAPE, the patient is placed in the supine position with the thighs flexed. This is practical as no major manipulations are required when the surgeon moves from the abdominal approach to the perineal field. The major disadvantage is that the position does not allow for a clear exposure of the operative area during the perineal part of the procedure.

After performing a TME all the way down to the pelvic floor, the anus is closed with a purse string suture. A circular incision is made 2 to 3cm around the anus and the rectum is dissected from posterior to anterior. The anococcygeal body is divided at the tip of the coccyx and the posterior abdominal plane of dissection is entered in front of the lower sacral vertebrae. The operator’s curved finger can then hook the levator muscles before dividing them. The anterior dissection is performed by incising the central perineal body. The dissection is pursued in contact with the bulb and posterior aspect of the prostate/vaginal wall until the plane of the anterior abdominal dissection is reached. Thereafter, the specimen can be delivered. The anterior dissection may be delicate in the male because of the risk of urethral injury at the level of the rectoanal junction.

The perineal dissection often runs too close to the levator plane and to the tumour. This leads to what is called “coning”. A “waist” of the specimen is therefore created at the sphincter level (Figure 5), which increases the risk of IOP or CRM involvement. An endcolostomy is thereafter constructed.

*Figure 5. Standard APE with classic surgical “waist” (Published with permission by John Wiley and Sons)*
**Extralevator Abdominoperineal Excision (ELAPE)**

In an ELAPE, the abdominal stage follows the general rules of a rectal resection. The main modification is to stop the abdominal dissection earlier, before entering the anatomic plane between the lower part of the mesorectum, near the tumour, and the levator floor. This is at the level of S2 posteriorly, the level of the pelvic plexus laterally and just below the vesicles in men, or just below the cervix uteri in women 68. In this manner, the abdominal dissection remains high, distant from the tumour, and the levators are not seen. The tumour-levator en bloc resection is performed during the perineal approach. The abdominal approach ends by performing a colostomy.

The patient is then rotated into the prone position. This position lifts the posterior perineum anteriorly and allows the surgeon to work under direct vision, facilitating dissection of the levators, the coccyx, and the presacral space without compromising the dissection of the anterior perineum. The goal is to achieve an en bloc excision of the portion of levator muscles and the specimen that were not removed through the abdominal part of the operation.

After anal closure, the perianal incision commences at the lower sacrum and includes the anus, then follows the outer surface of the external sphincter and along the inferior surface of the levator muscles up to a point laterally where these muscles originate from the pelvic sidewall. This point should be just inferior to the level where the abdominal procedure was terminated. The coccyx is often removed in continuity with the main specimen in order to improve direct visualisation of the dissection. If the resulting pelvic floor defect is too large for primary closure, a flap reconstruction or insertion of a prosthetic mesh may be performed.

Since the levator muscles are removed in continuity with the anal canal a more cylindrical specimen (Figure 6) is created with ELAPE. This increases the amount of tissue removed around the tumour and therefore reduces the risk of IOP or CRM involvement 69. The drawbacks created by this approach are the necessity of completing the abdominal stage before changing to the perineal approach, and the prolongation of operation time because of the changing of position.
**Figure 6. Extralevator APE with a cylindrical specimen**
*(Published with permission by John Wiley and Sons)*

**Perineal wound closure**

When APE was first described by Miles in 1908, the perineal wound was left open and allowed to heal by secondary intention. Although this method avoids some of the infectious complications associated with primary closure, the morbidity associated with a large, slowly healing wound is significant.

As mentioned before, one of the major problems associated with APE is complications due to the perineal wound, especially in patients who have received preoperative RT. Wound problems have been reported in up to 50% of patients receiving preoperative RT after APE with primary wound closure. Delayed healing and wound infection are the most common complications. For this reason, a number of surgical alternatives to primary closure have been proposed, including omental pedicle flaps (omentoplasty) and local rotational flaps (rectus abdominis, gluteus, and gracilis) (see below).

**Flap reconstruction of the pelvic floor**

Myocutaneous flaps have been used extensively for a variety of reconstructive procedures. The different techniques are well established and accepted. Data from controlled studies support the use of myocutaneous flaps for single-stage reconstruction after APE, especially after CRT. Several reports using the rectus abdominis, gluteus maximus and gracilis myocutaneous flaps have been published.
Rectus Abdominis Myocutaneous flap (RAM)
The RAM flap can be oriented horizontally (transverse RAM), obliquely (Taylor’s flap) or vertically along the muscle (vertical RAM). The RAM flap is the most commonly used myocutaneous flap and the overall complication rates vary from 10 to 50%. The healing rate ranges from 95 to 100%. Most studies, however, are small with less than fifty patients. This, combined with varying definitions of wound complication and follow-up periods, probably explains the reported differences in complication rate. The RAM flap offers adequate muscle bulk to satisfactorily fill the large pelvic space and provides a skin paddle for cutaneous healing. It is harvested without creating additional donor site wounds and has a wide arc of rotation.

Dissection, however, is technically demanding and circulation may be compromised, leading to flap necrosis. The RAM flap is denervated and is therefore prone to lose volume over time. Theoretically, it can lead to tension in the abdominal wound after closure. It may not therefore be suitable for reconstruction in patients with multiple stomas or after previous abdominal surgery. The main disadvantages of muscle and fascia harvesting are abdominal sequelae, particularly hernias, incisional hernias and parietal weakness.

Gluteus Maximus Myocutaneous Flap (GMF)
GMF is usually based on the inferior gluteal artery pedicle. This flap procedure is preferably carried out with the patient in the prone position. A split muscle technique, with the deep muscle left intact is used. For larger defects, a bilateral flap can be performed (Figures 7-8).

GMF does not cause any major donorsite morbidity and is not damaging to the abdominal wall. During its dissection, half to two-thirds of the muscle is spared at the lateral border so that most of its function can be maintained. However, so far only one study on physical performance after GMF has been made. In this study, Haapamäki et al showed impaired physical performance in many of the patients. This was measured with, for example, a “timed-stands test”; an integrated way to assess strength, balance, and absence of gluteal tenderness. Moreover, many of the patients also had an impaired ability to sit, mostly due to pain and discomfort. This technique also leaves scars more extensive than those resulting from primary closure.
**Figure 7.** Design of the gluteus maximus flap for reconstruction of the pelvic floor, unilateral (above) and bilateral (below) (Published with permission by John Wiley and Sons)

**Figure 8.** Unilateral gluteus maximus flap.
Gracilis flap

The gracilis flap originates from the pubic symphysis, the inferior pubic ramus and the ischium. It is then inserted distally into the medial condyle of the knee. The flap is vascularised by the medial femoral circumflex vessels. The flap is particularly useful in small defects that are relatively narrow and distal in the pelvis.

Although the gracilis flap is not a perforator flap per se, the remaining donor sequel is associated with minimal functional impairment. Other advantages with the gracilis flap in the setting of APE are primarily related to the avoidance of interfering with the colostomy site. Disadvantages include a high incidence of precarious vascularity, smaller muscle mass with decreased effectiveness in large perineal defects, and a high susceptibility to vascular spasm and cutaneous skin paddle ischaemia.

Biological mesh

The availability of biological mesh implants has led to an alternative method in pelvic floor reconstruction. Several advantages are observed with a biological mesh compared with larger plastic surgery techniques as mentioned above. The implantation of a mesh is easy to learn and can be performed without the assistance of plastic surgeons. Moreover, the operating time is reduced and the postoperative regimens are not as restrictive as for the myocutaneous flaps.

Recently, reconstruction using a biological mesh has gained popularity and studies have reported promising results. However, this technique must be regarded as experimental until more data become available.

In Sweden, a multicentre randomised controlled trial (Nordic Extralevator Abdominoperineal Excision Study) has just begun with the aim of comparing the gluteus maximus flap to Permacol® collagen mesh in respect of postoperative complications and functional outcome.

Hartmann’s Procedure (HP)

HP is performed in approximately 10% of patients treated by surgery for rectal cancer. This is a rectosigmoidal resection without restoration of bowel continuity. An endcolostomy is constructed and the rectal stump is left as a pouch. HP is often performed in a selected minority of patients, i.e. patients with incontinence or poor preoperative anal sphincter function.
**Local Excision (LE)**

LE procedures are part of routine treatment for early rectal cancers where the risk of nodal metastases is very low. Other indications for LE are when abdominal surgery constitutes a high risk of morbidity or mortality or in the palliative setting.

**Transanal Excision (TE)**

The distal 10 cm of the rectum is accessible transanally. Due to this, lesions in the mid and lower rectum are potentially resectable locally. Transanal excision involves either a submucosal or a full thickness excision of the lesion with a surrounding margin of normal rectal mucosa. Advantages of this approach include sphincter preservation in some cases and the avoidance of an abdominal procedure in patients who are medically compromised. Transanal excision is highly effective for treating benign lesions (adenomatous polyps) and is the procedure of choice in this setting. Local excision has also been used to treat small, early rectal cancers (T1-2). However, as experience has been gained with this technique, concerns have arisen regarding its oncologic efficacy. In addition, because a transanal excision does not resect the mesorectum, the pathologic examination of lymph nodes is not possible, so some patients may, thus, be understaged.

**Transanal Endoscopic Microsurgery (TEM)**

Transanal endoscopic microsurgery is an emerging technology. It is designed to allow local excision of lesions too high to be excised by traditional transanal techniques. The procedure uses a specially designed proctoscope, rectal insufflation, a stereoscopic telescope for magnification and specialised instruments to allow accurate, full-thickness excision of lesions as high up as the rectosigmoid junction.

Advocates have suggested that this approach allows the surgeon to obtain a better resection margin and may also potentially improve outcome for patients with early-stage cancer compared with TE. Long-term results, however, have yet to be determined, and the efficacy of this approach for rectal cancer requires prospective study.

**Minimally Invasive Surgery (MIS)**

Over the past two decades MIS has been adopted for the treatment of several different surgical diseases. Laparoscopy was first performed for gynaecological diseases and then for cholecystectomy, and is now offered for many diseases of both the colon and rectum. However, the utility of laparoscopy for the resection of colon or rectal cancer has been controversial. Early experiences suffered setbacks due to laparoscopic port-site recurrences and distant metastases. The main
question raised was whether a laparoscopic procedure achieved the same oncologic goals and outcomes as an open procedure.

Prospective randomised trials have now been completed to answer this question for colon cancer. In the hands of an experienced laparoscopic surgeon, results are equivalent for laparoscopy versus open resection regarding margin negative resection, lymph node clearance and survival 83-85. A number of centres have begun to report their experiences with laparoscopic resection for rectal cancer. Two meta-analyses have found that laparoscopic rectal cancer surgery results in decreased recovery time for the patient, and that the quality of the resected specimen is similar to that obtained in open surgery 86, 87.

Although these short-term outcomes are favourable, randomised controlled trials regarding local and distant recurrences, as well as 5-year survival, are not yet available. As technology continues to advance, robotic and teleroboticsurgery represent the next wave of minimally invasive surgery. This evolving technology offers the benefits of three-dimensional vision and improved instrumentation. Robotic colorectal surgery appears to be safe and feasible 88-90. However, with its costs and lack of significant outcome data, the role of robotic surgery in routine clinical practice remains to be determined.

Postoperative treatment

Adjuvant chemotherapy

In the late 1980s, studies investigated 5-FU-based chemotherapy and RT 91, or a combination given postoperatively. Overall, the results pointed to a significant benefit for the combination of CRT 92, 93. In these studies, however, only 5-FU-based chemotherapy was used.

Patients with rectal cancer have usually been excluded from eligibility in adjuvant trials with oxaliplatin 94 and irinotecan 95, drugs used for the treatment of colon cancer. Primary colonic and rectal tumours are anatomically closely linked. They appear similar both macroscopically and in terms of histology. It is therefore expected that the effectiveness of postoperative adjuvant chemotherapy in rectal cancer is similar to the results achieved in colon cancer 96, 97. As a result of this, adjuvant chemotherapy has been administered based on the results from colon cancer in many countries. This is despite the fact that there is no direct evidence to support this expectation, and particularly not in patients who have received preoperative RT or CRT.

Several studies have not shown a significant benefit for adjuvant chemotherapy in
terms of disease free survival or overall survival \(^{38, 98-100}\). In Sweden, adjuvant chemotherapy is not recommended outside clinical trials \(^{80}\).

**Palliative chemotherapy**

Chemotherapy has been shown to improve median survival from 6 months to 2 years in a palliative setting \(^{101}\). 5-FU/leucovorin is the most used first line therapy. However, combination therapies with other cytotoxic drugs, e.g. irinotecan and oxaliplatin, are becoming more common \(^{102}\).

In recent years, monoclonal antibodies such as bevacizumab, cetuximab and panitumumab have been developed in addition to cytotoxic drugs. Bevacizumab is a human monoclonal antibody with vascular endothelial growth factor as its target. For patients with refractory disease, the addition of bevacizumab in combination with 5-FU/leucovorin improves response rate, progression-free survival, and overall survival \(^{103}\). Cetuximab is a human-mouse monoclonal antibody against the epidermal growth factor receptor (EGFR). In the refractory setting, it has been shown to improve response rate and time to progression in combination with irinotecan \(^{104}\). Panitumumab is a fully human antibody that targets the extracellular domain of EGFR. Panitumumab in combination with the best supportive care improves progression-free survival, over the best supportive care alone, in patients previously treated with chemotherapy \(^{105}\).

Recent retrospective evidence from several randomised studies has established that advanced colorectal cancer patients with tumours harbouring a mutation in the KRAS gene do not derive benefit from the administration of epidermal growth factor receptor-directed monoclonal antibodies, such as cetuximab or panitumumab \(^{106}\).

**Pathology**

**Postoperative staging**

Histopathological staging of the specimen is important to select patients for adjuvant treatment and to predict prognosis. There are several different systems for the classification of rectal cancer. These are all based on tumour penetration into the rectal wall, involvement of lymph nodes, and the presence or absence of distant metastases. In the 1930s, Duke developed a classification system in three stages (A-C) which combined depth of tumour invasion and regional lymph node metastasis. Later, stage D was added, indicating concomitant distant metastasis.
In the 1950s the TNM system was developed (Table 1). There is a clinical as well as a pathological TNM classification. The clinical TNM assessment is predominately based upon preoperative radiological imaging and is indicated with the prefix “c”. Pathological assessment of the resected specimen is indicated with the prefix “p”. A third prefix, “y”, is also used when a tumour is staged after being given neoadjuvant treatment. This system is revised continuously.

**T-stage**

T-stage describes depth of invasion through the layers of the bowel wall of the primary tumour. T1, T3 and T4 stages are subdivided according to the extent of the invasion (Table 1). The risk of lymph node metastases increases with the increasing subclass 107. The T-stage is of prognostic value with worse prognosis by increasing depth of invasion 108.

**N-stage**

N-stage describes spread to regional and perirectal lymph nodes. It also describes the number of involved nodes. The N-stage is subdivided as shown in Table 1.

**M-stage**

M-stage describes the occurrence of distant metastases including metastases in non-regional lymph nodes. M1 disease is tumour growth in any distant organ, any non-regional lymph node, peritoneal carcinomatosis, and positive peritoneal fluid cytology (Table 1).

The American Joint Committee on Cancer (AJCC) developed a system based upon the TNM classification and Duke’s system indicating the prognostic value. (See Table 2 for a comparison of the different systems).
### Table 1. TNM classification

<table>
<thead>
<tr>
<th>TNM classification 7th edition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intraepithelial or invasion of lamina propria</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades submucosa</td>
</tr>
<tr>
<td>T1Sm 1</td>
<td>Invasion into the upper third of the submucosa</td>
</tr>
<tr>
<td>T1Sm 2</td>
<td>Invasion into the middle third of the submucosa</td>
</tr>
<tr>
<td>T1Sm 3</td>
<td>Invasion of the lower third of the submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Penetration through the muscularis propria into the serosa or perirectal fat</td>
</tr>
<tr>
<td>T3a</td>
<td>Minimal invasion: &lt;1 mm beyond the borders of the muscularis propria</td>
</tr>
<tr>
<td>T3b</td>
<td>Slight invasion: 1-5 mm beyond the borders of the muscularis propria</td>
</tr>
<tr>
<td>T3c</td>
<td>Moderate invasion: &gt;5-15 mm beyond the borders of the muscularis propria</td>
</tr>
<tr>
<td>T3d</td>
<td>Extensive invasion: &gt;15 mm beyond the borders of the muscularis propria</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour directly invades other organs or structures and/or perforates the visceral peritoneum</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour perforates the visceral peritoneum</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades other organs or structures</td>
</tr>
<tr>
<td>N0</td>
<td>No nodal involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases in 1-3 perirectal nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastases in 1 regional lymph</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastases in 2-3 regional lymph nodes</td>
</tr>
<tr>
<td>N1c</td>
<td>Tumour deposit (s), i.e. satellites, in subserosa, or in non peritonealised pericolic or perirectal soft tissue without regional lymph node metastases</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in 4 or more regional lymph nodes</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastases in ≥4-6 perirectal nodes</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastases in 7 or more regional lymph nodes</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastases confined to one organ</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastases in more than one organ or peritoneum</td>
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Table 2. Systems for the classification of rectal cancer.

<table>
<thead>
<tr>
<th>AJCC</th>
<th>TNM System 7th edition</th>
<th>Duke’s</th>
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</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis N0 M0</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>T1-2 N0 M0</td>
<td>A</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3 N0 M0</td>
<td>B</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T4a N0 M0</td>
<td></td>
</tr>
<tr>
<td>Stage IIC</td>
<td>T4b N0 M0</td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1-2 N1 M0 / T1 N2a M0</td>
<td>C</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3-4a N1 M0 / T2-3 N2a M0 / T1-2 N2b M0</td>
<td></td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T4a N2a M0 / T3-4a N2b M0 / T4b N1-2 M0</td>
<td></td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T1-4 N1-2 M1a</td>
<td>D</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T1-4 N1-2 M1b</td>
<td></td>
</tr>
</tbody>
</table>

Residual tumour classification

The residual tumour classification describes the tumour extent without considering treatment (Table 3). It is, therefore, a supplement to the postoperative staging classification. Hermanek et al have shown that the residual tumour classification is a strong predictor of local recurrence and survival \(^{110}\). A significant lower rate of local recurrence and increased survival were found after R0 resection compared with R1/R2 resection. A non-involved CRM (see below) cannot be equated with R0, although R also includes the other resection margins and the presence of distant metastases.

Table 3. Residual tumour classification.

<table>
<thead>
<tr>
<th>RX</th>
<th>Presence of residual tumour cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>No residual tumour</td>
</tr>
<tr>
<td>R1</td>
<td>Microscopic residual tumour</td>
</tr>
<tr>
<td>R2</td>
<td>Macroscopic residual tumour</td>
</tr>
</tbody>
</table>

Circumferential Resection Margin (CRM)

After evaluating the quality of the mesorectal excision, the pathologist opens the specimen, leaving 2 cm unopened above and below the tumour. The mesorectal tissue is then painted with black ink and the specimen is fixed in formalin for a minimum of 48 h. After fixation, sampling consists of transversal consecutive sections of 5 mm, which should include the tumour and the surrounding mesorectum. The whole-mount sections allow measurement of the distance
between the tumour and the CRM. This is confirmed by microscopic examination (Figure 9).

CRM is regarded as involved (CRM+) when the distance between the malignant cells and the margin is \( \leq 1 \) mm. Such involvement may be through direct continuity with the main tumour, tumour in veins, lymphatic or lymph nodes or tumour deposits discontinuous from the main growth. Some studies suggest that the distance between malignant cells and the CRM should be increased to 2 mm for rectal tumours \(^{111}\). In the lower rectum, the mesorectum reduces in size and disappears at the top of the sphincters. Below this level, the sphincter muscle forms the circumferential resection margin (CRM). Tumours of the distal rectum, therefore, will have less distance to traverse to reach the CRM than higher tumours, where the CRM is protected by a thicker mesorectum. Cross-sections are then placed on a smooth surface and digital photographs should be taken. The pathologist chooses the most representative section for microscopic analysis. In the report to clinicians, the pathologist should include the status of the CRM as well as the distance in millimetres from the tumour to the CRM, including whether it is a continuous tumoural front, a focal tumoural impact, or a lymph node with capsular breakdown \(^{112}\).

**Neoadjuvant therapy tumour analysis**

Neoadjuvant therapy has implications for the histopathological analysis. In specimens of patients treated with radiotherapy, tumour size, growing front of the tumour and peritumoural lymphoid inflammation can change. Due to this, the pathologist must sample from the fibrosis zone and carry out a careful study of the slices to identify residual malignant cells. It is also important to recognise histological changes in the tumour and the peritumour tissue as well as necrosis, fibrosis, decrease of tumour differentiation or mucinous differentiation \(^{112}\).

Dworak et al proposed a gradation system based upon desmoplastic reaction and the presence of malignant cell nests to evaluate the effectiveness of adjuvant treatment \(^{112,113}\) (Table 4).

**Table 4.** Dworak regression classification.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lack of regression</td>
</tr>
<tr>
<td>1</td>
<td>Minimal regression - tumour mass dominates fibrosis reaction</td>
</tr>
<tr>
<td>2</td>
<td>Moderate regression - fibrosis dominates tumour mass</td>
</tr>
<tr>
<td>3</td>
<td>Good regression - difficulty finding scantly tumour cells</td>
</tr>
<tr>
<td>4</td>
<td>Complete regression - lack of tumour cells</td>
</tr>
</tbody>
</table>
**Complete response**

The concepts of complete pathological response (pCR), complete clinical response (cCR) and tumour downstaging have developed from the clinical successes of providing preoperative RCT in the treatment of locally advanced rectal cancer. pCR refers to the absence of any residual tumour when performing histologic examination of a resected specimen. cCR is defined as the absence of a clinically detectable tumour following neoadjuvant therapy. Tumour downstaging refers to a change in tumour stage between pre-therapy clinical evaluation and post-therapy clinical or pathological evaluation.

These concepts have raised important issues in terms of designing the next step in treatment algorithms for patients with rectal cancer. Based on the experience of CRT for anal cancer, some advocate a “wait and see” approach for rectal cancers that appear to have a cCR following neoadjuvant therapy \(^{114}\). This tactic avoids immediate surgery in favour of careful observation of patients who appear to have a cCR. Others have suggested excising the bed where the primary tumour was located in the rectal wall followed by observation. This if the excised tissue is histologically negative \(^{115}\). However, tumour downstaging has been reported to occur in approximately 60% of patients who undergo preoperative CRT with 5-FU \(^{116}\). Unfortunately, cCR does not correlate with pCR in many studies \(^{117}\).

**Morphometry**

The tissue morphometry measurement technique is a method of calculating the area of tissue removed during surgery. The resected specimen is received fresh. It is then fixated in formalin and the resection margin is painted with ink. Serial slicing from the distal margin of the specimen, 3 to 5 mm intervals at the tumour level, are carried out. Digital photographic images of the whole specimen and of serial cross-sectional slices are taken alongside a metric scale.

The dimension and areas to be measured are then traced manually on the digital image of the transverse slice of the rectum. A precise measurement is obtained using a QWin image analyser (Leica Microsystems). Assessment of the tissue area is made by subtraction of the total area of tissue (lumen excluded) by the area of tissue outside the muscularis propria \(^{118,119}\) (Figure 9).
Figure 9. Digital image of a rectum slice showing the measurements made using morphometry. (Published with permission by Wolters Kluwer Health)

$\text{a = Anterior}$

$\text{CRM = white line}$

$i = \text{Invasion (dotted white line)}$

$p = \text{Posterior}$

$p = \text{Posterior}$

$l = \text{Lateral}$

$\text{cm}$
The Stockholm Colorectal Cancer Study Group

The Stockholm Colorectal Cancer Study Group (SCCSG) was established in 1980. The purpose was to improve outcome in patients with colorectal cancer. The group represents all seven hospitals in the Stockholm-Gotland region and consists of surgeons, oncologists, pathologists and radiologists. In 1980 the SCCSG established their first guidelines.

Since 1995, all patients in the Stockholm-Gotland region with rectal cancer have been prospectively registered. Variables such as demographic data, type of therapy, type of surgery performed, postoperative complications, pathological report and follow-up data such as local recurrence, distant metastasis and mortality are registered. These clinical data are reported to the Regional Oncological Centre, which creates a registry of its own. The register is regularly validated by crosschecking medical records and is frequently used in research projects.

In the present thesis, the clinical data were collected from the Regional Oncological Centre registry.
AIMS OF THE THESIS

The overall aim of this thesis was to improve treatment and outcome in patients with low rectal cancer.

The specific aims were:

**Paper I**

To analyse outcome in relation to type of surgical procedure performed in patients with low rectal cancer.

To assess if type of surgery was a prognostic factor.

**Paper II**

To assess if ELAPE can improve oncological outcome compared with SAPE.

To investigate morbidity associated with ELAPE.

**Paper III**

To assess short-term complications in relation to the gluteus maximus myocutaneous flap in patients operated with ELAPE for low rectal cancer.

**Paper IV**

To compare the frequency of local recurrence in supine vs. prone position, for the perineal dissection during APE for low rectal cancer.
PATIENTS AND METHODS

All patients in this thesis underwent operation for low rectal cancer and were consecutive included. The origin of the cohort and number of patients in each study are presented in Table 5.

Table 5. Patients with low rectal cancer included in the studies.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Cohort</th>
<th>Data collected</th>
<th>Numbers of patients</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>SAPE: Leeds General Infirmary</td>
<td>1997-2008</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ELAPE: The European ELAPE Study Group&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>176</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Karolinska University Hospital</td>
<td>2002-2008</td>
<td>65</td>
<td>2002-2009</td>
</tr>
<tr>
<td>IV</td>
<td>Stockholm-Gotland region</td>
<td>2001-2010</td>
<td>466: 249 prone; 217 supine</td>
<td>2001-2011</td>
</tr>
</tbody>
</table>

<sup>1</sup>The European Extralevator Abdominoperineal Excision Study Group is a multicentre European collaboration. Centres involved in this study were: University of Leeds, Leeds, UK; Karolinska University Hospital, Stockholm, Sweden; Leeds General Infirmary, Leeds, UK; Aarhus University Hospital, Aarhus, Denmark; University of Rochester Medical Centre, New York, USA; Castle Hill Hospital, Hull, UK; Hull Royal Infirmary, Hull, UK; Royal Devon and Exeter Foundation Trust, Exeter, UK; Pelican Cancer Foundation, Basingstoke, UK; University of Valencia, Valencia, Spain; Ninewells Hospital and Medical School, Dundee, UK.
Study I

The study was a prospective cohort study. It consisted of all patients operated on with an abdominal procedure for low rectal cancer < 6 cm from the anal verge in the Stockholm region from January 1995 to December 2003. Surgery was performed at eight different hospitals. Most of the data were retrieved from the register. Medical notes were scrutinised regarding preoperative treatment, type of surgery performed, pathological findings and tumour stage. The pathologists in Stockholm did not use assessment of tumour involvement within 1 mm of the CRM during the study period. Instead, the term “complete tumour clearance” was used if the proximal, distal, and circumferential resection margins were free from tumour. The term “incomplete tumour clearance” was used when tumour cells were found at the surface of any of the resection margins.

Surgeons reported a “complete tumour clearance” if they considered the primary tumour totally removed and an “incomplete tumour clearance” if any margin was macroscopically involved. They also reported if a bowel perforation occurred during surgery. The pathologists also reported if a perforation was found on the specimen. The follow-up period was until 31 December 2005, and included data on local recurrence, distant metastases, death and cause of death.

Statistical methods

The $\chi^2$ test or, when appropriate, the Fisher exact probability test, was used to determine the significance of differences in proportions. The Kruskal-Wallis test was used to assess differences in continuous variables. In the analysis of event-specific rates, patients were considered to be at risk of the studied event until the event occurred: death or the end of follow-up. Survival time was calculated from the date of surgery until the event occurred: either the time of death or the end of follow-up. All deaths among patients with tumour recurrences were defined as rectal cancer deaths, irrespective of the cause of death reported to the Cause of Death Registry. The Kaplan-Meier method was used to compare time to local recurrence and survival times between the groups, and the significance of differences was calculated by the log-rank test. A Cox proportional hazards regression model was used to estimate hazard ratio for time to local recurrence, time to metastasis, and overall mortality in relation to different potential prognostic factors. The date of surgery was the starting point for all three end points.

As the number of patients with a complete histopathological tumour response was low, they were included in the multivariate analyses together with patients with
stage I tumours and small tumours. In addition, four patients with missing data on
tumour stage or size were excluded from these analyses.

In the multivariate analyses, each prognostic factor was analysed with an
adjustment for all the other factors included in the model. Incidence proportions
(cumulative incidence) were estimated with R version 2.8.1 (R Foundation for
Statistical Computing, Vienna, Austria). All other analyses were conducted with
SPSS for Windows version 17.0.1 (SPSS Inc., Chicago, IL).

Study II

The study was an ambispective cohort study. Each centre participating in the
study collected clinical data. This was done by retrospective case note review and
included demographic, operative, pathological and short-term clinical outcome
data along with specimen photographs. Also, perineal, urinary or sexual
complications were determined from medical notes. A small number of
consecutive cases were collected prospectively.

In the ELAPE-group, 11 consultant colorectal surgeons based at nine European
institutions, all performing ELAPE surgery, were invited to submit a retrospective
series of patients. A small number of cases were also collected prospectively,
between 1 January 2008 and 30 November 2008. Extralevator surgery was
confirmed from specimen photographs and defined as the consistent presence of
an intact external sphincter, both front and back included. The minimum
contribution was two procedures per surgeon.

The SAPE group was a consecutive series of SAPE operations performed at Leeds
General Infirmary, UK, between 1 January 1997 and 30 November 2008. All
cases were identified retrospectively from the histopathological archives. All
cases of squamous cell carcinoma, any previous attempt of tumour removal,
recurrent rectal cancers, resections for benign disease and pelvic exenterations
were excluded. SAPE surgery was confirmed from the specimen photographs and
was defined as a consistent lack of additional levator ani muscle in the region of
the anal canal and lower rectum, resulting in an obvious “waist” on the specimen.

All specimens were dissected according to standard methods, including 48 h of
formalin fixation, painting the CRM and serial cross-sectional slicing through the
level of the tumour at 3-5-mm intervals. All pathological staging was performed
using the TNM system, 5th edition. CRM involvement was defined as the presence
of tumour cells located 1 mm or less from the painted resection margin,
determined microscopically. IOP was defined as any visible defect into the rectal
lumen, unless an adequate explanation was provided. This, in combination with
surgical notes, specimen photographs and pathology reports determined IOP. These also included specimens received in two pieces, which presumably represented conversions from failed anterior resections.

Statistical analysis

Statistical analyses were performed using Fisher’s exact test, the Mann-Whitney U test or the Kruskal-Wallis test as appropriate. A binary logistic regression model was used to determine the factors associated with CRM and IOP. The dependent variable, CRM or IOP status, was coded as a binary outcome, with patients with an involved CRM or IOP coded as 1 and those with a negative margin or no perforation as 0. Co-variables (explanatory variables) included age (per 10-year increase), sex, T category, N category, use of preoperative therapy, intent of operation and operation type. A p value <0.05 was considered statistically significant.

Study III

The study was a cohort of consecutive patients operated on for low rectal cancer with an ELAPE, using one-sided GMF for the pelvic floor reconstruction, at the Karolinska University Hospital in Solna, from January 2002 to December 2008. Four different plastic surgeons and one colorectal surgeon performed all the GMF operations. Patients operated on with this technique for other causes than rectal cancer were excluded.

Medical notes were scrutinised retrospectively for preoperative data such as demographic and postoperative short-term perineal complications associated with the GMF, within 30 days after surgery. The complications included minor perineal wound infections: defined as a tender swelling of the wound or surrounding tissue with purulent discharge. Breakdown of the perineal wound: defined as wound dehiscence, sinus or ulcer and abscess in the pelvis (verified by CT-scan). Patients who had any of these complications were followed for one year postoperatively for clinical outcome regarding long-term complications in relation to the myocutaneous flap. Records were eligible in all 65 patients and, thus, all cases were included for further analyses.
Study IV

A retrospective cohort study consisted of all patients operated on for low rectal cancer with APE in the Stockholm-Gotland region from January 2001 until December 2010. Patients with distant metastasis at the time of surgery were excluded. A total of 466 patients from nine different hospitals were included.

Medical notes were retrospectively scrutinised for data regarding patient characteristics, neoadjuvant treatment, surgical details, pathological tumour stage and surgical position. Clinical data on local recurrence were collected from the Regional Oncological Centre database. The surgical position was defined from medical notes.

Statistical analysis

The $\chi^2$ test was used to determine the significance of differences in proportions. A Cox proportional hazards regression model was used to estimate hazard ratio for time to local recurrence in relation to different prognostic factors. The estimated hazard ratios for local recurrence in relation to surgical position were adjusted for preoperative treatment, T-stage, sex and age. The data were modelled through logistic regression using the SAS statistical package. The parameters and standard errors in the models were converted to hazard ratios (HR) with 95% confidence intervals (CI).
RESULTS

Paper I

In the cohort, all patients were operated with an abdominal procedure due to low rectal cancer (n=616). AR was performed in 19%, APE in 72% and HP in 8% of the patients.

The proportion of men and women were similar in the three groups. Preoperative RT was given to a lesser extent than in the HP group compared with AR and APE (31% vs. 73%; 71%). There was no significant difference in distribution of tumour stage (stages I-VI) and T-stage (0-4) between the three groups. Tumour size was significantly larger in the APR and HP groups than in the AR group. In the HP group, there were significantly larger tumours compared with the other two groups (14 cm² and 21.4 cm² vs. 10.5 cm²).

In this study, it appeared that HP was performed in a highly selected minority of the patients. They were mainly older, had larger tumours, often with metastases, and only one-third received preoperative RT. The patients in the AR and APR groups were more comparable in terms of age, tumour stage and neoadjuvant treatment, although the tumours were lower and larger in the APR group, as mentioned above.

Incomplete resection margins were reported in similar proportions by both surgeons and pathologists. Both IOP and incomplete tumour clearance were significantly more common in the APE and HP groups compared with the AR group (IOP: 12% and 9% vs. 4%, incomplete tumour clearance: 18% and 14% vs. 4%).

After a follow-up period of 6.4 years (range: 2.0-10.9) the cumulative incidence of local recurrence rates at 5 years was 5.4% after AR (95% CI; 5.1-5.6%), 9.0% after APE (95% CI; 8.3-9.7%) and 9.8% after HP (95% CI; 9.5-10.0%), p=0.37 (Figure 10). In patients with local recurrence, regardless of surgery performed, 13% had an IOP and 26% had an incomplete resection margin.

The estimated overall survival in relation to the type of resection performed at 5 years was 62.9% in the AR group (95% CI; 53.4-72.4%), 49.3% in the APE group (95% CI; 44.2-54.4%) and 24.7% in the HP group (95% CI; 12.1-37.3%). These differences were significant (Figure 11).
The estimated hazard ratios for local recurrence in relation to different prognostic variables showed that preoperative RT and complete resection significantly reduced the risk of local recurrence. The hazard ratios were higher in the APE and HP groups, but not significantly higher than the AR group. Similarly, hazard ratios were increased for more advanced tumour stages and age above 72 years. Hence, these differences were not significantly related to these variables after adjustment for the other prognostic factors.

When the risk of distant metastases was analysed in a multivariate model, it was only increased in patients with T3 and T4 tumours and in patients with incomplete resection margins, but not significantly related to the other included variables.

In the univariate analysis, risk of death was increased after both APE and HP. After adjustment for other prognostic factors this difference was not statistically significant. When a mutual adjustment was carried out for the different variables in the multivariate analysis, overall mortality was significantly related to preoperative RT, depth of tumour invasion, distant metastases (stage IV), male sex, age and tumour-involved resection margin.

In conclusion, results from this population-based study suggested that there was an association between IOP and incomplete tumour clearance in relation to surgical procedure performed for low rectal cancer. The study could not confirm that local control and survival was related to surgical procedure per se.

Figure 10. Cumulative incidence of local recurrence in relation to type of surgical procedure (P=0.37).
Figure 11. Overall survival in relation to type of surgical procedure (p<0.01).

<table>
<thead>
<tr>
<th></th>
<th>Time (years)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>AR</td>
<td>114</td>
</tr>
<tr>
<td>APE</td>
<td>441</td>
</tr>
<tr>
<td>Hartmann</td>
<td>58</td>
</tr>
</tbody>
</table>

Individuals at risk

<table>
<thead>
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<th></th>
<th>AR</th>
<th>APE</th>
<th>Hartmann</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>114</td>
<td>441</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>99</td>
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<td>53</td>
<td>138</td>
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</tr>
<tr>
<td>12</td>
<td>53</td>
<td>110</td>
<td>14</td>
</tr>
</tbody>
</table>

Paper II

Of the 300 included patients, 176 were treated by ELAPE and 124 by SAPE. The median number of cases per surgeon was 11 (range 5-19) in the ELAPE group and 8 (range 2-35) in the SAPE group.

There were no significant differences between the groups according to sex, age at the time of surgery, tumour height from the dentate line and operative aim. However, patients who received curative APE were slightly older in the SAPE group than in the ELAPE. Although overall preoperative RT rates were similar in the two groups, more long-course RT was used in the ELAPE group along with more concomitant chemotherapy in those who had a potentially curative operation. Reasons for palliative procedures in the ELAPE group were: distant metastases (19 patients), local disease extent (2 patients) and not stated (1 patient). In the SAPE group, there were 9 patients with distant metastases and 6 with local disease extent. Distant metastases were recorded in the liver, lungs, peritoneum, iliac lymph nodes and para-aortic lymph nodes.

Operating time was longer in the ELAPE group compared with the SAPE group (300 min vs. 180 min; p<0.001). Several techniques were used for the perineal reconstruction in the ELAPE group: 60 gluteus maximus flaps, 12 rectus abdominis flaps, 1 latissimus dorsi flap and 11 Permacol™ collagen meshes.
Pathological staging showed a marked reduction in CRM involvement and IOP rate with ELAPE compared with SAPE surgery (Figure 12). The type of resection remained significantly associated with CRM (OR 0.23: 0.11-0.50) and IOP (OR 0.32: 0.13-0.79) status after adjusting for other factors such as age, sex, T+N-stage, preoperative treatment, aim of operation and IOP respectively CRM involvement.

Three surgeons switched from SAPE and ELAPE during the study period. In these cases, the CRM involvement rate decreased from 39 to 8% (p=0.048) and the IOP rate decreased from 19 to 0% (p=0.057).

The morphometric analysis from 97 ELAPE and 74 SAPE procedures showed significantly more tissue removed in the ELAPE group. This was from outside the internal sphincter/muscularis propria in the distal ten slices of excision (median area 2120 mm$^2$ vs. 1259 mm$^2$) (Figure 13), with an increased distance from the IS/MP to the anterior, posterior and lateral resection margins (Figure 14).

Short-term follow-up clinical data showed that time to discharge from hospital, and rates of sexual and urinary problems did not differ significantly between the groups. The incidence of wound complications was higher after ELAPE compared with SAPE (38% vs. 20%; p=0.019). There was a tendency towards a reduction in wound complications in the ELAPE group when a muscle flap was used, hence this was not statistically significant (33% vs. 43%; p=0.239).

In conclusion, this multicentre study showed that ELAPE surgery, with the perineal dissection in the prone position, can lead to substantial reductions in CRM involvement and IOP independent of other factors. However, it did appear to be an increase in perineal wound complications. This may be overcome partly by the use of myocutaneous flaps, rather than primary wound closure.
**Figure 12.** Rate of CRM involvement and IOP in patients with residual invasive tumour operated on with ELAPE and SAPE (p<0.001).

**Figure 13.** Tissue morphometric measurements for ELAPE and SAPE. A median area of tissue per slice outside of the internal sphincter/muscularis propria (p<0.001).

**Figure 14.** Median distance from sphincter/muscularis propria to the anterior, posterior and lateral CRM over the distal ten slices. ELAPE vs. SAPE. (Errorbars represent the interquartile range; p<0.001).
Paper III

The study included 65 patients operated on with ELAPE for low rectal cancer with a gluteus maximus myocutaneous flap (GMF) for the reconstruction of the pelvic floor. Ten of the patients had a local recurrence, 55 had primary rectal cancer. Of the primary cancers, 70.8% had locally advanced disease according to preoperative MRI staging. In the cohort, there were more men than women (61.5% vs. 38.5%). The median age did not differ significantly between the sexes. Preoperative treatment with RT and CRT was given in 91% of patients, with almost equal proportions. Due to previous radiation, 7.7% of patients did not receive preoperative RT. One patient did not receive neoadjuvant treatment due to old age and comorbidity.

The pathological staging showed a majority of T3 tumours (41.5%), followed by T4 (27.7%). T1 and T2 accounted for 18.4% of cases. 3.1% of the patients had a complete response after neoadjuvant radio-chemotherapy. Some of the patients with local recurrence (6 of 10) did not receive a T-stage at all after the pathologist’s assessment.

All of the patients were given a single dose antibiotic treatment before surgery. 35% of the patients had a prolonged antibiotic prophylaxis for a mean duration of 2.2 days after surgery. The median hospital stay after surgery was 17 days (range: 4-193 days).

In total, 41.5% of the patients had some complication in relation to the GMF within 30 days after surgery (Table 6). The most common complication was a minor perineal wound infection, defined as a swelling of the wound or surrounding tissue with purulent discharge, and was seen in 23.1% of the patients. These infections healed normally within a few weeks after discharge (range: 5-25 weeks). Breakdown of the perineal wound included any dehiscence, sinus or ulcer, and was seen in 15 (10.7%) of the cases. None of these patients had healed within 25 weeks after surgery. No partial or complete flap necrosis was seen. After 12 months, 7 (8.5%) of these patients were still not healed.

All 15 patients were given a regular wound dressing. Six of the 15 patients were also treated with negative pressure wound therapy. Only one of these patients healed within 12 months. An abscess in the pelvis was seen in 5 (7.7%) of the patients within 30 days after surgery. All of these 5 patients were successfully treated with antibiotics (2 patients) or ultrasonic-guided percutaneous abscess drainage (3 patients). Six (9.2%) of the patients died within 12 months after surgery. One of the patients died with a persistent defect 242 days after surgery. Of the remaining 61 patients, 91.5% were completely healed 1 year after surgery. None of the patients developed a perineal hernia during the follow-up period.
In conclusion, although the vast majority of the perineal reconstructions were healed at 1 year after surgery, the short-term perineal wound complication rate was high after gluteus maximus flap reconstruction of the pelvic floor.

**Table 6.** Complications related to the GMF within 30 days after surgery and time to healing.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complications (healed within 4 weeks)</td>
<td>38 (58.5)</td>
</tr>
<tr>
<td>Minor perineal wound infection (healed within 5-25 weeks)</td>
<td>15 (23.1)</td>
</tr>
<tr>
<td>Breakdown of the perineal wound (non-healed within 25 weeks)</td>
<td>7 (10.7)</td>
</tr>
<tr>
<td>Abscess in the pelvis</td>
<td>5 (7.7)</td>
</tr>
<tr>
<td>Perineal hernia</td>
<td>0 (-)</td>
</tr>
</tbody>
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**Paper IV**

Out of 466 patients in the cohort, 249 were operated in the prone position and 217 in the supine. There were slightly more men in the prone compared with the supine group (60.2% vs. 53.5%). Women had a higher median age in the supine group (72 vs. 66 years). In the prone group there were significantly more patients receiving neoadjuvant treatment. RT was given in approximately the same proportions to both groups. Only 2.3% of patients in the supine group received CRT compared with 17.7% in the prone group. In the supine group, 23.5% received no preoperative treatment compared with 11.5% in the prone group.

Histopathological depth of tumour invasion (T-stage) was similar between the two groups. There was a tendency of more T4 tumours in the prone group and less T3 tumours. Fifteen patients (6%) had complete response after neoadjuvant treatment in the prone group compared with 4 (1.8%) in the supine. More patients in the prone group had a concomitant resection of other organ (26.5% vs. 16.1%).

Between patients operated in the supine position there were significantly more cases of IOP and incomplete tumour clearance compared with the prone group (IOP: 12.4% vs. 4%) (incomplete tumour clearance: 12.4% vs. 6.8%).

The relative risk (HR) in the univariate analyses showed a 47% risk reduction for local recurrence in the prone group (HR 0.53: 0.24-1.18). The multivariate analyses showed a 39% risk reduction for local recurrence in the prone position compared with the supine group, however, this reduction was not significant (Table 7).
Table 7. Cox proportional hazards regression with 95% CI for local recurrence in relation to surgical position among patients operated for low rectal cancer.

<table>
<thead>
<tr>
<th>Surgical position</th>
<th>Person years</th>
<th>Number of events</th>
<th>HR(^1)</th>
<th>HR(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>979</td>
<td>18</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Prone</td>
<td>697</td>
<td>9</td>
<td>0.53 (0.24-1.18)</td>
<td>0.61 (0.27-1.37)</td>
</tr>
</tbody>
</table>

HR\(^1\) - hazard regression - crude.
HR\(^2\) - hazard regression - adjusted for T-stage, neoadjuvant treatment, sex, age.
We have shown that IOP and tumour involvement are more common after APE compared with AR in low rectal cancer. Moreover, performing an ELAPE procedure decreases the rate of IOP and CRM involvement significantly compared with SAPE. In addition, when rotating the patient from the supine to the prone position during the perineal part of the operation the frequency of IOP and incomplete tumour clearance further decreases. This rotation may also reduce the frequency of local recurrences of low rectal cancer. However, performing an ELAPE also creates a large pelvic cavity and the short-term complication rate, related to the pelvic floor reconstruction, is high. Although after one year the vast majority of patients are healed.

All studies in this thesis were observational cohort studies, and consisted of consecutive patients operated on for low rectal cancer. The advantage with a retrospective observational cohort study design is the ability to have a long follow-up period and to study various exposures and outcomes. As all of the material was prospectively collected, the risk of selection bias was diminished. Drawbacks are the risk of confounders and the fact of having to rely on existing data. This increases the risk of information bias such as missing information and misclassification. If the incidence is low, i.e. local recurrence after rectal cancer surgery, cohort studies require a large number of subjects over a long period to obtain a statistically significant result.

During the recent decade, refinement and enhancement of surgical treatment for rectal cancer has led to an improvement in patient outcome. Introduction of TME, preoperative RT and CRT have decreased the frequency of local recurrences after rectal cancer surgery \cite{40, 58, 60}. However, these improvements are seen mainly for tumours of the upper and middle part of the rectum.

Several studies have shown that IOP and CRM involvement increase the risk of local recurrence and death in low rectal cancer \cite{64, 120}. Eriksen et al showed a 5-year local recurrence rate of 28% in patients with IOP, compared with 9.9% in those without IOP \cite{120}. Another study from Norway described a reduction in 5-year survival with an adjusted HR of 1.5 (95% CI, 1.2-1.9) after IOP in low rectal cancer \cite{120}.

Quirke and colleagues observed that the amount of excised tissue varied from surgeon to surgeon. They also found that CRM involvement was an important
A local recurrence rate from 18 to 30.4% and a 5-year survival rate from 38 to 50% after APE with involved CRM have been described in patients with low rectal cancer 64, 111, 120. Even Nagtegaal et al described a significant decrease in 5-year survival from 72 to 38.5% in patients with CRM involvement after APE 64.

It has been shown that patients with a potential CRM involvement can be identified by preoperative MRI. This may be of prognostic value in rectal cancer and may be used to select patients for preoperative CRT and/or more radical surgery 122. Moreover, survival in rectal cancer has been shown not only to be dependent on resections with tumour free CRM and IOP, but also on R0 resection and nodal status 62, 64, 123. Altogether, several population-based studies from several different countries - Norway, Holland and Great Britain - show the same results. IOP and CRM involvement decrease survival and give a higher incidence of local recurrence 62-65, 111, 120, 121.

SAPE is the most common operation for low rectal cancer 120. Study I showed a significant increase in the rate of IOP and incomplete tumour clearance in SAPE compared with AR and Hartmann’s procedure. These disadvantages have been confirmed by several previous studies 63, 64, 68, 69, 124. Marr et al showed that patients treated by SAPE had a higher rate of CRM involvement (41% vs. 12%), a higher local recurrence rate (22.3% vs. 13.5%) and poorer 5-year survival (52.3% vs. 65.8%) compared with AR 63. Moreover, a Dutch study also showed a higher frequency of CRM involvement (26.5% vs. 12.6%), IOP (13.7% vs. 2.5%) and a poorer 5-year survival (38.5% vs. 57.6%) compared with AR 64. The greater risk of IOP and CRM involvement in SAPE surgery is partly due to an anatomical reduction in the natural mesorectal tissue volume in the distal rectum when following the mesorectal plane, resulting in less protective tissue around low-lying tumours 64, 69.

Together, all these factors have increased calls for a change in the approach of APE surgery 63, 64, 68, 69, 124. ELAPE has been introduced to improve specimen quality and oncological outcome in low rectal cancer. This surgical technique is more radical than SAPE. The ELAPE procedure removes levator muscles in continuity with the anal canal and mesorectum en bloc. The specimen becomes more cylindrical, more tissue around the tumour is removed, and therefore the risk of IOP and CRM involvement is reduced.

Study II compared ELAPE and SAPE in relation to IOP and CRM involvement. The results showed that ELAPE removed significantly more tissue from outside the smooth muscle layer per slice, leading to a significant reduction in CRM involvement and IOP compared with SAPE. One can criticise the fact that the comparison was between surgery of low quality and that of high quality from
specialised devoted centres in Europe. However, among the three surgeons who switched technique, from SAPE to ELAPE, during the study period, the rate of CRM involvement was 39% and IOP 19% out of a total of 58 SAPEs. These numbers decreased to 8% and 0%, respectively, in 18 ELAPE operations. This indicates that ELAPE as a surgical procedure, not the surgeon performing it, improves the specimen quality. Stelzer et al have recently described similar results, comparing ELAPE with retrospective data on SAPE. Their study showed a decrease in CRM involvement and IOP, from 4.9 to 0% and 15.2 to 0%, in SAPE compared with ELAPE.

In study II, the IOP rate in ELAPE was significantly lower when the perineal dissection was carried out in the prone rather than in the supine position (p=0.027). This was independent of other factors, OR 0.12 (95% CI; 0.02-0.67). A question that may arise is whether it is the ELAPE or the prone position per se that causes the decrease in IOP and CRM involvement.

Study IV compared patients operated on with APE in the prone position with patients operated on with APE in the supine position during the perineal part of the operation. Outcome in this study was local recurrence according to surgical procedure. A 39% risk reduction (not significant) for local recurrence was shown in patients operated in the prone position. An explanation for the lack of statistical significance could be that there were rather few events in both groups. The study may have had deficient power to detect a potentially true difference. Unfortunately, it could not control for the type of surgery performed in each group. The fact that some of the patients in the prone group had an ELAPE could lead to selection bias, creating a type I error. The risk reduction may be caused by the ELAPE procedure, not the surgical position.

Recently, de Campos-Lobato et al reported no difference in outcome related to the positioning of the patient. Moreover, a Dutch study has shown good oncological outcome in patients undergoing an ELAPE in the supine position during the perineal part of the surgery.

Altogether, it seems as if the ELAPE approach is the key factor for creating a high quality specimen, i.e. reducing the rate of IOP and CRM involvement, prior to the position of the patient. However, the perineal dissection is a challenge with several pitfalls. One should avoid CRM involvement, IOP and damage to the nerve plexus. For example, dissection near the prostate may damage the periprostatic plexus and result in erectile impotence as well as bladder dysfunction.

Taking this into account the need of good visualisation is, thus, of great value. The prone position allows a greater view of the structures, both for the surgeon
and the assistant compared with the supine position. It also has the advantage of revealing nerves and blood vessels. This may potentially reduce perioperative bleeding and postoperative sexual/urinary dysfunction. In addition, the greater visualisation can be of help when learning the procedure for both the surgeon and the assistant.

There seems to be a clear association between ELAPE and a reduction in IOP and CRM involvement. Even though we failed to show a significant result when rotating the patient into the prone position, it seems probable that the risk of local recurrence is reduced by this method when done in combination with extralevator surgery.

A disadvantage with ELAPE is that it often results in a large dead space in the pelvis, creating a major tissue defect. In study II, ELAPE was associated with an increased frequency of perineal wound complication (from 20 to 38%; p=0.019) compared with SAPE. The study also showed a tendency towards a reduction in wound complication in the extralevator group when a muscle flap was used, but this was not statistically significant, 33% vs. 43% (p=0.239). It has been reported that myocutaneous flaps of well-vascularised non-irradiated tissue to the post-irradiated pelvic defect results in improved perineal wound healing 127-130.

The most common myocutaneous flaps used after APE include the vertical RAM flap, gracilis flap and GMF. The RAM flap offers adequate muscle bulk to satisfactorily fill the large pelvic dead space. It provides a skin paddle for cutaneous healing and has a wide arc of rotation. However, dissection of such a flap is technically demanding and the circulation may be compromised, leading to partial flap necrosis. The flap is denervated, not contractile, and is prone to loss of volume over time 68, 72. Theoretically, RAM harvest can lead to areas of tension in the abdominal wound closure. It may therefore not be suitable for reconstruction in patients with multiple stomas or who have had previous abdominal surgery. Also, with a minimally invasive approach to the abdominal part of the procedure, a major trauma to the abdominal wall is not desirable. This flap is preferably done with the patient in the supine position.

In selected patients the gracilis flap may be a suitable alternative. However, its use for perineal reconstruction is limited due to a restricted arc of rotation. The bulk of the skin paddle is not as consistent as the RAM flap and, consequently, bilateral harvest is sometimes performed. The GMF, unlike the RAM flap, does not cause any major distant donorsite morbidity. The cosmetic outcome of the operation is important for some patients. This flap design leaves scars that are more extensive than those after primary closure but does not give any major alterations to the seat configuration, and is in most cases well accepted by the patients. More recently, reconstruction using a biological mesh has gained some popularity. However,
only a few studies have been done in the field, some reporting promising results \textsuperscript{78, 131}. The implantation of a mesh is easy to learn and can be performed without the assistance of plastic surgeons. Moreover, money can be saved using a biosynthetic mesh, mainly due to reduced length of hospital stay because the postoperative regimens are not as restrictive as for the myocutaneous flaps. However, there are situations were a biological mesh is not sufficient, e.g. large resections were the patient needs a bilateral flap reconstruction or large concomitant resection of the vaginal wall where total vaginal wound closure is not an option. There are some indications that short-term complications using a Permacol\textsuperscript{\textregistered} collagen mesh for reconstruction of the pelvic floor are approximately the same as for GMF. Recently, this question has been addressed in the running NEAPE study. The objectives in this study are to compare GMF to Permacol\textsuperscript{\textregistered} collagen mesh in different aspects of postoperative complications and functional outcome. Today, use of biological mesh for pelvic floor reconstruction must be regarded as experimental until more data become available.

Another factor increasing the risk of perineal wound complication after APE is preoperative RT. Although this treatment may offer benefits in terms of local recurrence and local control of the tumour, the rate of wound complication cannot be ignored. Bullard et al reported an overall perineal wound complication rate of 41\%, increasing from 23 to 47\% when using preoperative RT \textsuperscript{66}. This adverse effect of RT is directly related to a normal tissue injury through progressive vasculitis and fibrosis \textsuperscript{132}. In the pelvis, radiation-induced fibrosis, in addition to the major tissue defect after surgery, also limits the ability to close the perineum and the pelvic sidewall.

Study III showed a high wound complication rate (41.5\%) within 30 days in radiated patients after ELAPE with a GMF for the pelvic floor reconstruction. After 12 months, 91.5\% of the patients had a completely healed perineum. However, Haapamäki et al have shown drawbacks in physical performance and quality of life after GMF \textsuperscript{70}.

At present, there are no data from randomised studies available comparing different techniques for pelvic floor reconstruction, and knowledge concerning long-term outcome is insufficient. Despite the perineal complications it seems that, at present, oncological results justify ELAPE with a flap or biological mesh reconstruction of the pelvic floor. This is especially so when better alternatives are lacking. However, it is important to inform the patient preoperatively about the possibility of impaired physical function.

Overall, it seems that ELAPE may improve oncological outcome in low rectal cancer. However, regarding a future perspective, there are still many questions concerning this procedure. One of these questions is how the optimal pelvic floor
reconstruction should be performed. All myocutaneous flap procedures have drawbacks in both short- and long-term outcome. Early results from the use of biological mesh are promising but, as mentioned before, this method needs to be evaluated. There is also an on-going discussion regarding whether preoperative RT is needed for T2 and early T3 tumours when an ELAPE procedure is intended. This with the aim to decrease the number of long-term side effects related to RT (e.g. postoperative wound complications, sexual dysfunction, urinary dysfunction and osteoradionecrosis). On the other hand, some advocate preoperative CRT for these tumours with the objective of achieving a complete response, followed by a “wait and see” approach to avoid surgery in favour of careful observation.
CONCLUSION

Overall conclusion

Patients with low rectal cancer undergoing an APE procedure have worse oncologic outcome with a higher rate of both CRM involvement and IOP compared with AR. The oncologic outcome improves after ELAPE compared with SAPE.

After reconstruction of the pelvic floor with a gluteus maximus myocutaneous flap, the vast majority of the perineal reconstructions heal within one year. However, the short-term perineal wound complication rate is high.

Specific conclusions

SAPE, performed in low rectal cancer, is associated with an increased rate of IOP and incomplete tumour clearance compared with AR.

ELAPE surgery with the perineal dissection in the prone position can lead to substantial reductions in CRM involvement and IOP, independent of other factors.

Performing an ELAPE prolongs the operating time compared with SAPE. However, there is no evidence of increased blood loss, time to discharge from hospital, or sexual/urinary disturbance.

Early perineal wound complications are common with the gluteus maximus flap reconstruction of the pelvic floor after ELAPE. Despite this, the vast majority of patients heal within one year.

Performing APE in the prone position is associated with a reduction in local recurrence events compared with the supine position. However, this reduction is not statistically significant.
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