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Functional and oncological outcomes in advanced colorectal cancer

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Functional and oncological outcomes in advanced colorectal cancer

Functional and oncological outcomes in advanced colorectal cancer

Hanin Assi



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DOCTORAL DISSERTATION

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Abstract

Advanced colorectal cancer (CRC) often requires extensive surgery to achieve tumour-free resection margins, the most important predictive factor for long-term survival. The performed surgery may result in substantial tissue loss and the need for perineal, vaginal and urological reconstructions. This thesis evaluates quality of life (QoL), functional, oncological and survival outcomes in patients with advanced pelvic malignancy using local and national cohorts.

Paper I evaluated aspects of QoL in patients with advanced pelvic malignancy requiring perineal flap reconstruction. High general health scores were recorded despite difficulties in mobility, anxiety/depression, pain/discomfort and fatigue. Sexual dysfunction was common, affecting both sexes. Physical tests showed adequate functionality in everyday life.

Paper II studied short-term postoperative outcomes in patients with pelvic malignancy requiring perineal flap reconstruction. Approximately one-fourth of the patients experienced surgical complications classified as Clavien-Dindo $\geq$ III. Flap-related complications were common but were usually treated conservatively. Patients undergoing reconstruction with a vertical rectus abdominis myocutaneous flap had higher complication rates compared with patients who received a gluteal flap.

Paper III provided a step-by-step description of the gluteus maximus special flap used to reconstruct the posterior vaginal wall.

Paper IV examined survival as well as local and distant recurrence in patients with CRC undergoing urinary tract resections. Patients who underwent total cystectomy were compared with those who underwent partial cystectomy and ureter resection. There was no difference in 5-year overall survival or distant recurrence between the groups. Ureter resection was associated with significantly higher rates of local recurrence.

Paper V evaluated short- and long-term complications after CRC surgery including urinary tract resections, focusing on urological complications. Urological complications were common. Ureteral stricture was the most common indication for long-term intervention. Patients undergoing total cystectomy had higher complication rates compared with other resections. One-third of patients experienced a decline in kidney function.

Key words: Colorectal cancer (CRC), Perineal reconstruction, Quality of life (QoL), Urological resections, Survival, Oncological outcome, Complications

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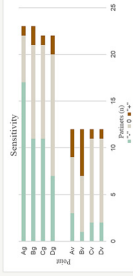
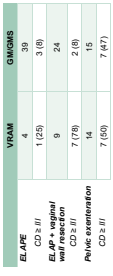
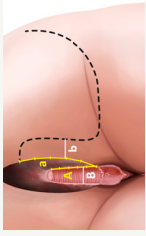
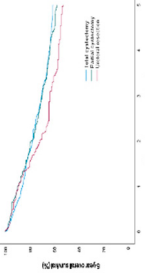
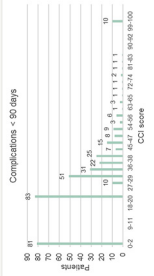
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List of papers

This thesis is based on the following original papers, referred to by the Roman numeral.

- I. Sexual and functional long-term outcomes following advanced pelvic cancer and reconstruction using vertical rectus abdominis myocutaneous and gluteal myocutaneous flap.
Assi H, Persson A, Palmquist I, Öberg M, Buchwald P, Lydrup ML.
Eur J Surg Oncol. 2021 Apr;47(4):858-865.
- II. Short-term outcomes following beyond total mesorectal excision and reconstruction using myocutaneous flaps: A retrospective cohort study.
Assi H, Persson A, Palmquist I, Öberg M, Buchwald P, Lydrup ML.
Eur J Surg Oncol. 2022 May;48(5):1161-1166.
- III. New technique for pelvic and vaginal reconstruction in abdominoperineal rectal excision: combination of gluteus maximus flap and fasciocutaneous flap
Assi H, Guné H, Buchwald P, Lagergren J, Lydrup ML, Öberg M.
Plast Reconstr Surg Glob Open. 2023 Oct 9;11(10):e5317.
- IV. Survival after urological resections in colorectal cancer – a Swedish nationwide study
Assi H, Valdimarsson V, Angenete E, Buchwald P, Lydrup ML.
Eur J Surg Oncol. 2025 Aug;51(8):110078.
- V. Urological complications in advanced colorectal cancer patients with concomitant urological resections
Assi H, Afshari K, Valdimarsson V, Kollberg P, Angenete E, Buchwald P, Lydrup ML.
Unpublished manuscript.

Thesis at glance

Paper	Aim	Study design	Key figure	Main findings
I	Evaluate QoL and functional outcomes after perineal flap reconstruction treating advanced pelvic cancer	Retrospective cohort study including 36 patients assessed at outpatient visits		Preserved QoL and functional abilities. Adequate neovaginal measurements. Impaired sexual function and sensitivity in the surgical area
II	Assess short-term (90-day) postoperative outcomes after perineal flap reconstruction for advanced pelvic cancer treatment	Retrospective cohort study with medical record reviews of 105 patients		One quarter of patients experienced surgical complications classified as Clavien-Dindo $\geq$ III. Low mortality rates
III	Describe the construction of a gluteus maximus special flap	Step-by-step description of a surgical technique		Gluteus maximus special flap surgical description
IV	Evaluate volume, oncological outcome and survival of urinary tract resections in CRC patients in Sweden	National registry-based study that included 1 093 patients		Similar survival and distant recurrence rates between the different urinary tract resections. Ureter resections had higher rates of local recurrence
V	Assess short and long-term complications in CRC patients undergoing urinary tract resections	Retrospective cohort study with review of medical and registry records of 373 patients		Total cystectomy was associated with higher rates of short- and long-term complications, including reoperations and a decline in kidney function

Abbreviations

APE	Abdominoperineal excision
ASA	American Society of Anesthesiologists
CAPOX	Capacitabin and oxaliplatin
CCI	Comprehensive Complication Index
CEA	Carcinoembryonic antigen
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COS	Core outcome set
CRC	Colorectal cancer
CRT	Chemoradiotherapy
CT	Computer topography
eGFR	Estimated glomerular filtration rate
ELAPE	Extended abdominoperineal resection
EOCRC	Early onset colorectal cancer
FIT	Faecal immunochemical test
FOLFOX	Folinic acid and oxaliplatin
FSFI	Female Sexual Function Index
GM	Gluteus maximus
GMS	Gluteus maximus special
HDI	Human Development Index
HR	Hazard ratio
ICD	International Classification of Diseases
IIEF	International Index of Erectile Function
LARC	Locally advanced rectal cancer
LRRC	Locally recurrent rectal cancer
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high

PAP	Profunda artery perforator
PE	Pelvic exenteration
PME	Partial mesorectal excision
QoL	Quality of life
RCT	Randomised controlled trial
SCRCR	Swedish Colorectal Cancer Registry
SUS	Skåne University Hospital
TME	Total mesorectal excision
TNM	Tumour-Node-Metastasis
TNT	Total neoadjuvant treatment
TST	Timed Stands Test
VRAM	Vertical rectus abdominis myocutaneous

Introduction

The earliest descriptions of tumorous diseases appear in ancient Egyptian medical papyri dating to c. 1600 BCE, describing the fatal nature of bulging tumours that had spread throughout the body. Around c. 400 BCE, Hippocrates introduces the term *karkinos* (Greek for “crab”), visualising the infiltrative growth pattern of tumours (1).

Surgical treatment for tumoral mass was limited before the 19th century, prior to advances in anatomical pathology, ether anaesthesia and antiseptic methods. The father of modern surgery, William S. Halsted, provided one of the earliest descriptions of wide removal of tumours and surrounding tissue, a procedure known as *en bloc* resection (2).

In 1908, abdominoperineal excision (APE) for rectal cancer was described introducing *en bloc* resection of the rectum, anus and surrounding mesorectal tissue (3). Another landmark was Bill Heald’s introduction of total mesorectal excision (TME) in the 1980s, showing that precise dissection along embryological planes reduced local recurrence and improved survival (4). These principles were subsequently extended to colon cancer surgical treatment through complete mesocolic excision and central vascular ligation (5).

Pelvic exenteration (PE) represents an important milestone in the treatment of advanced colorectal cancer (CRC). The procedure was first described in 1948 by Alexander Brunschwig as a palliative treatment for cervical cancer (6). Initially, PE was performed in a few centres due to its radical nature and high mortality (7). Today, PE is an established treatment for advanced pelvic malignancies, with survival outcomes comparable to conventional CRC surgery (8).

Colorectal cancer

Epidemiology

CRC is the third most common cancer type and the second leading cause of cancer-related death globally, after lung cancer (9). In 2022 there were over 1.9 million new CRC cases worldwide, with the highest rates in countries with a high Human Development Index (HDI), such as those in Europe, North America, Australia and

Eastern Asia (9). The incidence of CRC is lower in low-HDI countries (6.4 vs 28.6 per 100 000 people), while an increasing incidence is seen in developing economies, likely reflecting lifestyle changes (9).

CRC is more common in men than in women, with the most pronounced difference in rectal cancer (10). These disparities are attributed to differences in risk factor exposure and hormonal influences (11). The median age of diagnosis in Sweden is 72 years for colon cancer and 70 years for rectal cancer (12).

In recent years there has been a notable shift in CRC epidemiology. In some high-HDI countries, CRC incidence and mortality are declining among older adults, likely due to screening, improved treatment and healthier lifestyles (13). In contrast, the incidence of early-onset colorectal cancer (EOCRC), affecting adults aged 50 years or younger, is rising (13). The rise in EOCRC is not fully understood and could be explained by a combination of genetic, environmental and lifestyle factors (14). With the rise of EOCRC, the median age of diagnosis is expected to decrease.

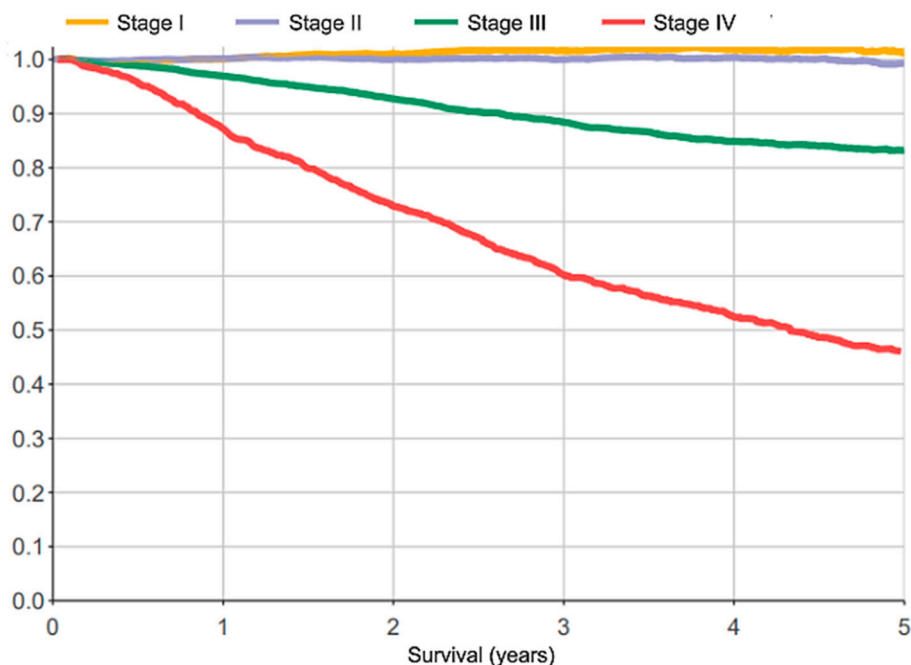


Figure 1: Survival in patients with colon cancer

Relative survival in patients undergoing elective surgery for colon cancer diagnosed between 2018 and 2024. Similar patterns are seen for patients with rectal cancer. Source: The Swedish Colorectal Cancer Registry via Cancercentrum (15).

In Sweden, approximately 8 000 CRC cases are diagnosed annually, of which two-thirds are colon cancer and one-third is rectal cancer (16). Over time, the incidence of colon cancer has increased, while the incidence of rectal cancer has remained stable (17). Mortality from CRC has declined over recent decades, with nationwide 3-year adjusted survival rates reaching 94% for colon cancer and 96% for rectal cancer (stage II-III) (15, 18). Long-term survival is strongly associated with tumour stage (Figure 1) (15, 18).

Since 2022, Sweden has had a nationwide faecal immunochemical test (FIT)-based CRC screening programme targeting individuals aged 60-74 years. During the first 5 years of screening, participation was 64.3%, colonoscopy adherence was 82% and the CRC detection rate in FIT-positive patients was 6.6%, demonstrating high diagnostic performance (19). Screening has been shown to reduce CRC mortality, with further improvements expected with FIT-based testing (20).

Risk factors

Risk factors associated with CRC include both genetic and environmental contributors. The genetic factor has been well described, with a family history of CRC being a strong risk factor, particularly in first-grade relatives with diagnoses before 50 years of age (21, 22). Other well-known hereditary syndromes are familial adenomatous polyposis and Lynch syndrome, accounting for 20% of all EOCRC (23). Non-modifiable risk factors for CRC are higher age and male sex (10, 24).

Chronic inflammatory bowel disease is another well-known risk factor through genetic instability, epigenetic changes and dysregulation of immune signalling (25). The risk increases with the extent, duration and severity of the inflammation (26). Medical therapy with regular coloscopy controls are essential to reduce the risk in this patient group (26).

Most CRC cases are, however, driven by environmental and lifestyle factors such as obesity, smoking, alcohol, physical inactivity, low-fibre diets, high intake of processed meat, metabolic syndrome and diabetes. It is suggested that these risk factors promote chronic inflammation, metabolic dysfunction and gut microbiome dysbiosis (27). High intake of dietary fibre, vitamin D, folate, calcium and regular physical activity lowers the risk for CRC, likely through anti-inflammatory and metabolic mechanisms and modulation of the gut microbiome (28).

Diagnostics and classification

Classical symptoms of CRC are rectal bleeding, altered bowel habits, anaemia, abdominal pain and/or unexplained weight loss. When a patient presents with these symptoms, a standardised care pathway is started, according to the Swedish national CRC programme. Diagnostics include colonoscopy, carcinoembryonic antigen

(CEA), computed topography (CT) of the abdomen and thorax, and pelvic magnetic resonance imaging (MRI) and rectal ultrasound in suspected rectal cancer (22).

Accurate diagnosis and staging of the rectal cancer location is crucial for deciding on oncological and surgical treatment (29, 30). Tumours are categorised as low (0-5 cm), middle (6-10 cm) or high (11-15 cm), measured from the anal verge using rigid proctoscopy (29). MRI is used to describe the location, potential involvement of lymph nodes, sphincter, mesorectal fascia and surrounding organs (29, 30).

Diagnostic findings can determine clinical cancer stage according to the Tumour-Node-Metastasis (TNM) classification (Table 1), originally developed by Pierre Denoix and currently in its 8th edition (31, 32). The combined assessment defines the stage and predicts the prognosis (Table 2) (32, 33).

Table 1: The TNM classification system

T-	Primary tumour
T1	Tumour invades the submucosa
T2	Tumour invades the muscularis propria
T3	Tumour invades through the muscularis propria into the peri-colorectal tissues
T4a	Tumour penetrates to the surface of the visceral peritoneum
T4b	Tumour directly invades or is adherent to other organs or structures
N-	Regional lymph nodes
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
M	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis to other organ/organs or peritoneum

Table 2: Staging system based on pathological TNM classification

Stage	T	N	M
I	T1-T2	N0	M0
II	T3-T4	N0	M0
III	Any T	N1-N2	M0
IV	Any T	Any N	M1

Multidisciplinary team

A multidisciplinary team (MDT) has been established as a standard of care due to the complexity of cancer diagnosis, treatment and follow-up (34). The team usually consists of experienced surgeons, pathologists, radiologists, oncologists and nurses.

The need for an MDT has been presented as the significant change in the assessment and treatment of CRC, resulting in higher rates of neoadjuvant treatment, resection-free margins and long-term survival (35-37). Other advantages of MDT meetings include providing a platform for study inclusion, fostering a learning environment

and facilitating knowledge exchange between different professions. However, an MDT does not involve direct patient participation, is resource intensive, may delay treatment and is unlikely to alter management in early-stage tumours (38).

For advanced and recurrent CRC, associated with a high risk of relapse and poor survival, specialised MDT meetings are crucial (39). Tumour staging after neoadjuvant treatment is challenging due to fibrosis and inflammation, leading to discrepancies between clinical staging and final pathological reports (40, 41). This highlights the importance of centralised radiological expertise within an MDT, as well as senior expertise in oncology, pathology and surgery.

The Swedish Colorectal Cancer Registry

The Swedish Colorectal Cancer Registry (SCRCR) is a nationwide quality registry established in 1995 for rectal cancer and for colon cancer in 2007. The goal of the SCRCR is to improve treatment and subsequent patient survival, reduce any regional and hospital-level differences achieving equitable care. The secondary aims include enabling follow-up of national health programmes, such as recommended diagnostics and treatment, and to serve as a database for research projects and clinical studies (16).

The registry is prospective and comprehensive in its design and includes patient demographics, tumour characteristics, surgical and oncological treatments, pathology reports, complications, oncological outcomes, patient-reported outcomes and survival (16).

The registry has near-complete coverage, with completeness rates of 98.5% for colon cancer and 98.8% for rectal cancer, supported by several validation studies (42-44). A recent comprehensive national validation showed a 93% agreement for categorical variables, particularly high in the registration and surgical report (42, 43). There was lower concordance for Clavien-Dindo $\leq$ IIIa complications (60%) and local recurrence (86%) (42). A separate validation revealed underreporting of local recurrences, with 43% missing registrations among patients with rectal cancer diagnosed in 2016-2017 and treated with surgery (45). Other limitations of the registry include a lack of consensus regarding certain definitions, missing values and registration errors (42, 46).

Treatment

Treatment of CRC often involves a combination of oncological and surgical therapy. Oncological treatment has a well-established neoadjuvant role in rectal cancer. In colon cancer, neoadjuvant treatment is reserved for selected locally advanced and recurrent cases (47, 48). The aim of neoadjuvant treatment is to reduce the tumour burden, shrink the tumour, increase the likelihood of organ preservation and reduce the risk of recurrence (49, 50).

For most patients, definitive treatment of CRC remains surgical resection using different approaches depending on the location and classification of the tumour. The surgical principles include assessment of the primary tumour and potential intra-abdominal metastases, as well as *en bloc* resection with respect to the anatomical planes (2, 5). In locally advanced CRC (T3-4, N+, MRF+), extended surgery beyond the regular mesocolic/mesorectal planes is needed to achieve clear margins, a key predictor of long-term survival (39, 51, 52).

Adjuvant treatment aims to reduce the risk of both local and distant recurrence by targeting micrometastatic disease. It is primarily used in patients who have undergone radical colon cancer surgery without evidence of metastatic disease (22).

Surgical treatment

Local resection has emerged as a safe and feasible treatment for patients with early-stage CRC (T1N0M0, without risk factors) (53). For colon tumours requiring surgery, the affected bowel segment is excised with longitudinal margins of approximately 10 cm (54). Whenever feasible, minimally invasive approaches are preferred, and bowel continuity is restored (55). Surgical procedures include right hemicolectomy, left hemicolectomy, sigmoid resection and Hartmann's procedure. The latter includes resection of the sigmoid/upper rectum with closure of the rectal remnant and construction of a colonic stoma.

For tumours in the upper rectum, high anterior resection with anastomosis and partial mesorectal excision (PME) is the treatment of choice (56). Hartmann's procedure is a reliable alternative in frail patients, patients with poor sphincter function, patients with a high risk of anastomotic leakage or by patient preference (57).

A low anterior resection with anastomosis is the treatment of choice for middle or low rectal cancer (22, 58). A temporary loop ileostomy is sometimes used to mitigate the clinical consequences of anastomotic leakage (59). A low Hartmann procedure can be performed in patients who are not suitable for low anastomosis.

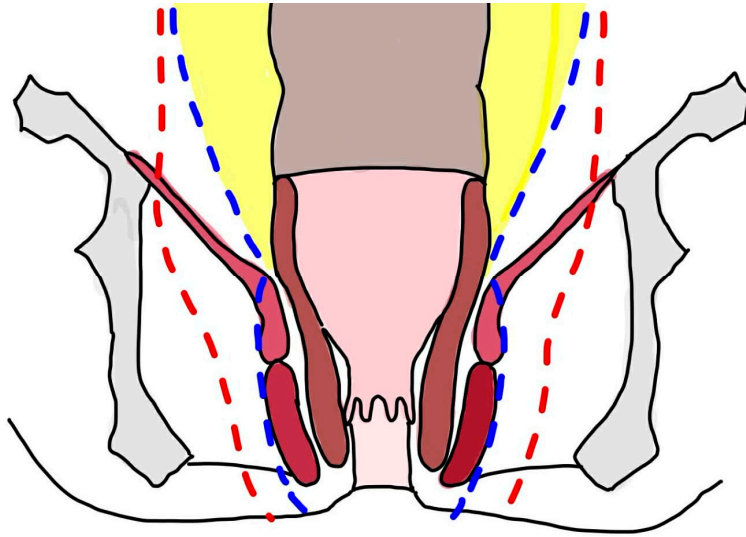


Figure 2: Abdominoperineal excision versus extended abdominoperineal excision

Abdominoperineal excision is marked in blue lines. If the tumour involves the levator muscles, then an extended abdominoperineal excision is performed, marked in red lines.

APE is performed for low rectal tumours, where both the anus and rectum are excised according to the principles of TME (60). If tumour growth is locally advanced and involves the levator muscles, then an extra levator abdominoperineal excision (ELAPE) should be considered (Figure 2) (61). These surgeries are also applicable in anal malignancy.

In low rectal tumours, the distal rectum lies in direct contact with surrounding tissues, including the levator muscles, vaginal wall and prostate, increasing the risk of locally advanced disease. With locally advanced rectal cancer (LARC) or locally recurrent rectal cancer (LRRC), resection beyond TME plane resections is needed to achieve clear margins (39).

Neoadjuvant treatment

Colon cancer

Patients with colon cancer are usually treated with direct surgery without any prior oncological therapy, although recent publications on advanced colon cancer (T3-4, N0-2) have challenged this approach. The FOxTROT study demonstrated significant tumour downstaging and reduced recurrence in patients receiving neoadjuvant fluorouracil, folinic acid and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) compared with upfront surgery (48). These findings have

been both supported and questioned by subsequent studies (62, 63). A recent randomised control trial (RCT) reported no difference in 3-year disease-free survival between patients receiving neoadjuvant therapy (CAPOX or capecitabine monotherapy) compared to upfront surgery. However, neoadjuvant treatment was associated with greater tumour downstaging and reduced need for adjuvant therapy (63). Radiotherapy has been sparsely studied in colon cancer, with no RCTs to date.

Immunotherapy

In recent decades, immunotherapy has emerged as a major advance in the treatment for selected CRC cases, most evidently in patients with microsatellite instability-high (MSI-H) tumours, occurring in 10%-15% of all colon cancers and 3%-5% of rectal cancers (22, 64). For patients with MSI-H tumours, checkpoint inhibitor immunotherapy targeting PD-1 (pembrolizumab) has shown benefit in objective response rate and progression-free survival (64, 65). Dual checkpoint blockade, targeting PD-1 (nivolumab) and CTLA-4 (ipilimumab), has shown improved clinical benefit (66). The Swedish national guidelines for CRC currently recommend direct surgery for respectable MSI-H tumours, with an exception for conversion therapy (22). Based on emerging evidence from ongoing studies, current recommendations might change (22).

Rectal cancer

In Sweden, different neoadjuvant strategies are applied depending on tumour stage in rectal cancer, presented in Table 3 (22). In early-stage rectal cancer with a low risk for local recurrence ($< 5\%$ - 6%), direct surgery is recommended (67). In patients with intermediate risks ($\geq 6\%$ - 8%), short-course radiotherapy (SCRT, 5×5 Gy) is recommended, followed by either immediate (2-4 days) or delayed (4-8 weeks) surgery (49, 50). Delayed surgery offers several potential advantages, including the possibility of complete tumour regression, organ preservation and preoperative optimisation (22). This treatment might also be better suited for elderly patients or those who are too frail for long-course radiotherapy or chemotherapy.

In LARC and LRRC, studies have shown improved oncological outcomes in patients obtaining neoadjuvant treatment (47, 68, 69). Neoadjuvant chemoradiotherapy (CRT), administered in doses of 1.8-2 Gy with a total dose of 45-50.4 Gy is the standard of care in many parts of the world prior to surgery for patients with advanced rectal tumours (58, 68).

Table 3: Indications for neoadjuvant radiotherapy in rectal cancer

Indications for neoadjuvant radiotherapy in rectal cancer are based on cTNM staging using magnetic resonance imaging.

Source: The Swedish national guidelines for CRC (22)

	T1-T3ab	T3cd	T4a*	T4b easy to resect	T4b hard to resect	N0-N1	N2	EMVI	MRF+ primary	MRF+, TD or lgh+ extranodal	Lateral lgh+
High > 10-15 cm (above PR ¹)	0	0	TNT ³	0**	TNT	0	0**	0**	-	-	-
High > 10-15 cm (not above PR ¹)	0	0	TNT	0**	TNT	0	0**	TNT	TNT	5 × 5	TNT
Middle > 5-10 cm	0	5 × 5	TNT	TNT	TNT	0	TNT	TNT	TNT	5 × 5	TNT
Low 0-5 cm (above ISP ²)	0	5 × 5	-	TNT	TNT	0	TNT	TNT	TNT	5 × 5	TNT
Low 0-5 cm	5 × 5	5 × 5	-	TNT	TNT	0	TNT	TNT	TNT	5 × 5	TNT

*In T4a tumours with a limited extent, primary surgery may be considered.

**Included in the RAPIDO trial; short-course radiotherapy followed by chemotherapy may be an option. Chemotherapy alone may also be considered.

¹Peritoneal reflection

²Intersphincter plane

³Total neoadjuvant therapy

In recent years, total neoadjuvant therapy (TNT) has been proposed as an alternative treatment for advanced rectal cancer. In this approach, all oncological treatment, including chemotherapy traditionally given in the adjuvant setting, is administered before surgery (70). The potential advantages of TNT compared to CRT include an improved oncological outcome, complete remission and organ preservation (70-72). The disadvantages include delayed surgery and treatment-related toxicity that may negatively affect the patient's performance status (73).

In the RAPIDO trial, Bahadoer et al. (47) demonstrated a decrease in distant metastases and an increase in pathological complete response for patients receiving SCRT followed by preoperative CAPOX compared to standard CRT and selective adjuvant chemotherapy. However, the authors did not observe a difference in disease-free survival (47).

Organ-preserving therapy

Organ-preserving strategies, primarily in rectal cancer, are a safe option for patients with an excellent response to neoadjuvant therapy (74). The aim is to avoid TME and associated postsurgical morbidity. In the OPRA trial, patients achieving a complete or near complete clinical response after TNT for stage II/III rectal cancer

were offered a watch-and-wait strategy (74). Approximately one-third of patients within the watch-and-wait group developed local regrowth. In 94% of these patients, the regrowth occurred within the first 2 years. Disease-free survival was similar between patients who underwent TME after restaging and patients in the watch-and-wait group who underwent TME after regrowth (74). Contact brachytherapy, delivering high radiation doses, in combination with CRT has also shown promising results for organ preservation (75).

A complete clinical response is defined by the absence of a palpable tumour, no endoscopic signs of residual disease and no evidence of residual tumour or lymph node metastases on MRI (22). In Sweden, *opportunistic* watch-and-wait is offered to patients who achieve a complete clinical response after standard neoadjuvant treatment. Another approach is *intentional* watch-and-wait, where neoadjuvant therapy is offered to patients with early-stage tumours to induce a complete clinical response (22). Follow-up in watch-and-wait programmes includes digital rectal examination, MRI and endoscopy every 3 months for 3 years (22).

Targeted therapy

In patients with metastatic CRC, the addition of targeted therapy is considered based on tumour-related biomarkers and tumour location (22). In Sweden, the arsenal includes a variety of monoclonal antibodies – anti-epidermal growth factor receptor (cetuximab) and anti-vascular endothelial growth factor (bevacizumab) – as well as a BRAF-targeted tyrosine kinase inhibitor and HER2 inhibitors (22).

Adjuvant treatment

Adjuvant therapy has an established role in colon cancer treatment and is offered based on the pathological stage and risk of relapse. Its benefit in rectal cancer remains debated, with studies reporting divergent results (22, 76).

For patients with colon cancer and an estimated relapse risk of $\geq 15\%$ -20%, adjuvant chemotherapy should be offered (22). A single treatment with fluoropyrimidine for 6 months reported a 20% lower risk of recurrence in stage II disease. The addition of oxaliplatin provides a further risk reduction (77). Some studies suggest non-inferiority of a 3-month treatment duration compared with 6 months (78).

In CRC stage I-III with a PIK3 mutation, 3 years of adjuvant acetylsalicylic acid reduced the risk of recurrence by half in a Swedish RCT (79). That study may influence molecular testing practices for CRC in Sweden, highlighting the need for risk-benefit evaluation and national guidelines (22).

Outcome measurements

To facilitate systematic reporting of outcome measures and improve data interpretation, core outcome sets (COS) have been developed. A COS is a set of agreed, standardised outcomes that should be measured and reported in trials for a specific condition, as defined by the Core Outcome Measures in Effectiveness Trials (80). For rectal cancer, COS include variables such as overall survival, locoregional recurrence, distant recurrence, margin status (R0 resection) and organ preservation (81).

Pelvic exenteration

PE is defined as an *en bloc* resection of multiple pelvic organs, typically including the colorectum, urinary bladder and internal reproductive organs, illustrated in Figures 3 and 4. There are several pelvic tumour classification systems that aid surgeons in planning resection, such as the Royal Marsden Hospital, Mayo Clinic and Memorial Sloan Kettering classifications. Tumours are commonly categorised into pelvic compartments, in some considering symptoms, fixation points and bone involvement, each with various prognostic significance (82-84). The plan is ultimately tailored to the patient's tumour anatomy, while balancing comorbidity and the need to preserve organs, function and expected quality of life (QoL) (8, 85).

Advancements in surgical techniques have challenged previous contraindications such as bone, nerve, vessel or sidewall involvement and metastatic disease (86, 87). Resection for tumours infiltrating the pubic bone have been described with an R0 rate – microscopically negative margins – of 76% (88). The current absolute contraindications are primarily related to the patient's performance status and expected morbidity rather than technical or anatomical limitations.

International collaborations have played a pivotal role in the development of PE. PelvEx, an international PE collaborative established in 2015, has expanded to include more than 100 institutions globally. Its mission is to offer a platform for clinical studies with the aim of defining guidelines and improving treatment strategies (89). This collaborative has resulted in several publications, including clinical guidelines, consensus statements and large-scale multicentre publications (8, 51, 90-92).

Types of pelvic exenterations

Total pelvic exenteration

Total pelvic exenteration involves *en bloc* resection of all pelvic organs, including the rectum, anus and urinary bladder. In men, the resection includes the prostate and seminal vesicles, while in women it includes the uterus, cervix, ovaries and part or all of the vagina (Figures 3 and 4). Depending on tumour infiltration, this treatment might be combined with resection of lateral compartments, which may include the ureter, external/internal iliac vessels, lateral pelvic nodes, sciatic nerve and S1-2 nerve roots. Lateral lymph node involvement should be suspected if the nodal size is ≥ 7 mm before neoadjuvant treatment. Resection is indicated if the nodal size is > 4 mm after neoadjuvant treatment (93).

While LARC and LRRC are the most common indications, total PE can be performed in a variety of pelvic malignancies such as gynaecological and anal cancers (39, 92). It can also be performed in palliative settings with a heavy tumour burden, for malignant wounds or in selected non-malignant cases such as severe fistula formations (94).

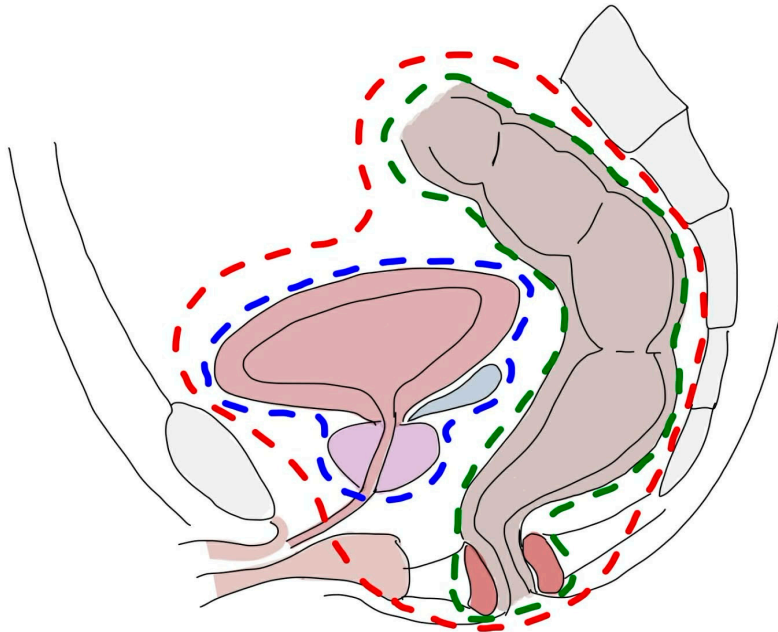


Figure 3: Pelvic exenteration in men

The red lines indicate the organs resected in total pelvic exenteration. The blue lines indicate anterior pelvic exenteration, commonly referred to as cystovesiculoprostatectomy. The green lines indicate posterior pelvic exenteration, which in males corresponds to an abdominoperineal excision.

Anterior pelvic exenteration

Anterior PE implies different procedures for men and women (Figures 3 and 4). In men, the resection includes the urinary bladder, seminal vesicles and prostate, commonly referred to as a cystovesiculoprostatectomy. In women the resection includes the urinary bladder, uterus, cervix, part or all of the vagina and the ovaries, if necessary. Anterior PE is commonly performed in extensive urological and gynaecological malignancies.

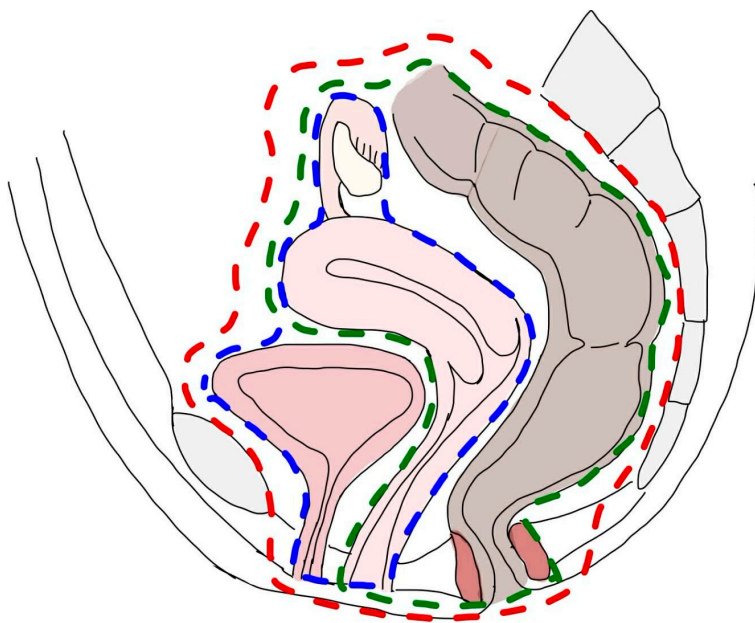


Figure 4: Pelvic exenteration in women

The red lines indicate organs resected in total pelvic exenteration, while the blue lines indicate anterior pelvic exenteration and the green lines indicate posterior pelvic exenteration. Resections may include part or all of the vagina and ovaries, if necessary.

Posterior pelvic exenteration

Posterior PE in women includes the rectum, anus, uterus, cervix, part or all of the vagina and ovaries, if necessary (Figure 4). As men have only two anatomical compartments, APE including ELAPE or sacrectomy may be sufficient for posterior tumours extending beyond the mesorectal fascia (Figure 3). Posterior PE is usually performed in women with advanced CRC invading the internal reproductive organs.

Rectal cancers in women with anterior invasion often involve the vaginal canal, requiring resection of the posterior vaginal wall. A thorough assessment of vaginal involvement both through imaging and gynaecological examination is crucial prior to surgery. Suspected overgrowth should always be included as an *en bloc* resection, increasing the chances of cancer-free margins.

Preoperative assessment

Surgery for advanced CRC often involves extensive multivisceral resection, which is associated with high morbidity (95). Careful patient selection is essential and requires consideration of the patient's general health, comorbidities and preferences. In our setting, preoperative evaluation often begins at the outpatient visit after an MDT discussion. Patients meet a team consisting of a colorectal surgeon experienced in procedures beyond TME, a urologist, a plastic surgeon, a specialist nurse and a stoma therapist. Orthopaedic and vascular surgeons are consulted when needed.

Preoperative optimisation is crucial to reduce perioperative risk and improve surgical outcomes (96). According to Swedish CRC guidelines, modifiable risk factors such as anaemia, diabetes, hypertension, malnutrition and low physical activity should be optimised before surgery (16). Correction of anaemia may reduce the need for allogeneic blood transfusion, which is linked to poorer outcomes (97). Exercise and physical conditioning are increasingly recognised as beneficial preoperative interventions, delivered through home-based programmes or supervised by physiotherapists (98).

Effective preoperative planning relies on high-volume, specialised MDT conferences that integrate clinical, imaging, pathology and oncological data (22). This ensures that all relevant perspectives are considered before the operation. Clinical scoring systems are widely used to predict postoperative outcomes. The American Society of Anesthesiologists (ASA) physical status classification is the most employed tool in both clinical practice and research. Other instruments include the Eastern Cooperative Oncology Group performance status (99).

Given the high likelihood of stoma formation, preoperative stoma education is essential, aiming to improve body image and self-care, reduce stoma-related complications and maintain QoL (100). In Swedish cohorts, stoma formation has not adversely affected overall QoL (101).

National highly specialised care

Recognising the complexity of advanced pelvic surgery, the Swedish National Board of Health and Welfare designated advanced pelvic surgery as national highly specialised care in 2022. Three centres provide this expertise in Sweden: Karolinska University Hospital, Sahlgrenska University Hospital and Skåne University Hospital (SUS), with annual evaluations of provided care (102, 103). This centralisation aims to improve outcomes by concentrating expertise for low-volume procedures and standardise care pathways.

Reconstructive techniques

Pursuit of R0 resection often requires extensive surgery with complex reconstruction involving colorectal, urological, plastic and occasionally orthopaedic expertise. The objectives of reconstructions extend beyond restoration of anatomical continuity and function, as they play a critical role in recovery (104).

Reconstruction of the urinary tract

Following total cystectomy

Several techniques for urinary tract reconstruction following total cystectomy have been described, utilising either the ileum or colon, including non-continent and continent options.

Currently, the most used urinary diversion is the uretero-ileal non-continent conduit, first described by Bricker in 1950. A 10-15 cm segment of ileum is isolated approximately 20 cm proximal of the ileocecal valve. The ureters are anastomosed with the ileal conduit over stents. The distal end of the conduit is diverted as an ileostomy usually placed in the right lower abdominal quadrant (Figure 5) (105, 106).

Both the transverse and sigmoid colons have been described for urinary diversion. This approach has been used numerous times in patients with a heavily radiated ileum. A 10-20 cm segment of colon is isolated with an intact mesentery supply. When the colon is used for reconstruction, there is a risk of malignancy in the conduit, necessitating surveillance (107).

Continent urinary diversions can be constructed using several methods, such as the appendix, the nipple valve mechanisms and the ileocecal valve in right colon reservoirs. Orthotopic neobladder is another option, created using segments of intestine connected to the urethra (108). These reconstructive techniques are seldomly used in PE due to the risk of complications.

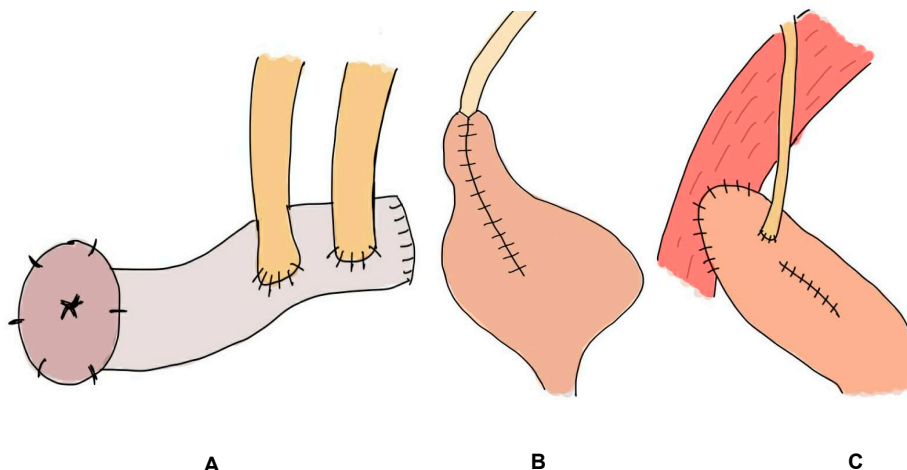


Figure 5: Reconstruction of the urinary tract

A. A Bricker conduit created using the ileum. B. A Boari flap. C. A psoas hitch.

In early descriptions of PE, urinary reconstruction was performed as a wet colostomy, diverting urine and faecal content through a single stoma (109). This led to faecal exposure of the upper urinary tract, causing recurrent pyelonephritis, kidney failure, malodour and electrolyte imbalances (109).

The double-barrelled wet colostomy is an emerging alternative. It is associated with less morbidity compared with double stomas, leading to increased popularity in recent years (110, 111). With this technique, faeces and urine are kept separate by implanting the ureters on the antimesenteric side of the sigmoid colon (112).

Following partial resections of the urinary bladder

Partial cystectomy may be an option in cases of limited malignant overgrowth. In such cases, the urinary bladder is typically closed in two layers to ensure a watertight closure using resorbable sutures. A urinary catheter is placed for approximately 2 weeks, to prevent tension on the suture line, allow healing and reducing the risk of urine leak.

Following ureter resections

In patients undergoing ureter resection, the reconstructive approach is determined by the level of resection. Following distal ureter resections, the ureter is usually reimplanted into the urinary bladder. If the remaining ureter is too short to allow direct reimplantation, techniques to mobilise the bladder and reduce tension may be employed, such as a Boari flap or a psoas hitch (Figure 5) (113, 114).

In cases of more proximal ureter resection, ureteroureterostomy may be performed, either to the ipsilateral ureter if sufficient length remains or to the contralateral ureter. In selected cases, the ureter may be ligated without reconstruction, with drainage via nephrostomy. Another option is ureteroureterostomy with a nephrostomy.

Perineal reconstruction

The perineal defect following surgery for advanced CRC can be substantial, and healing is often challenging, particularly in patients who have undergone radiation and with fibrotic, avascular tissue and fluid accumulation (115).

Flap reconstruction provides healthy, non-irradiated tissue with improved healing potential into the surgical wound. It facilitates obliteration of dead space, enables reconstruction of the perineum and reduces the risk of perineal herniation and sinus formation (116). The literature provides descriptions of several reconstructive options, including biological mesh as well as myocutaneous and fasciocutaneous flaps. There are currently no RCTs or large cohort studies comparing different reconstructive techniques for perineal reconstruction.

Omental flaps can be used to fill pelvic dead space, although this approach is often inadequate as a sole reconstructive solution (116). For small perineal defects, biological mesh can be a suitable option, as it provides structural support (117). Myocutaneous and fasciocutaneous flaps are frequently used for reconstruction of larger perineal defects, with the added possibility of vaginal reconstruction. Flap options include a vertical rectus abdominis myocutaneous (VRAM) flap, a gluteus maximus (GM) flap, a gracilis flap, a profunda artery perforator (PAP) flap and local V-Y flaps.

Internationally, VRAM is the most used flap. It provides non-irradiated, substantial soft tissue bulk, with a wide arc of rotation (115). Harvesting a VRAM flap is technically demanding and results in significant abdominal wall weakness, often necessitating mesh reconstruction. This is particularly challenging in patients requiring both a colostomy and a urostomy, as one stoma must traverse the reconstructed abdominal wall, increasing hernia risk (118). In a systematic review including 1 827 patients who received a VRAM flap, the mean perineal flap morbidity was 27% and complete flap loss occurred in 1.8% of patients (119).

In the Swedish setting, a GM flap is commonly used. This flap is relatively easy to harvest, follows natural skin creases and has a reliable vascular supply (120). For larger defects, bilateral GM flaps provide sufficient tissue bulk. The disadvantage of this option is the restricted arc of rotation to anterior defects, insufficient bulk when used unilaterally and radiated fasciocutaneous tissue.

A gracilis flap is transposed through the inner groin to fill the pelvic defect and may be used to create a neovagina (121). When raised bilaterally, a gracilis flap can reconstruct defects following total vaginectomy. A PAP flap offers soft tissue bulk for perineal coverage, reliable vascularisation and can be performed without repositioning the patient from the lithotomy position. A possible drawback is the technically demanding perforator dissection.

Local fasciocutaneous flaps raised in a V-Y fashion have been described in several publications, offering a flexible reconstructive option (122). These flaps can be tailored to the existing perineal defect, ranging from a small unilateral to larger bilateral flaps. The advantages of a shorter operative time, low donor-site morbidity and preserved muscle must be weighed against the increased risk of perineal hernia formation (122).

Vaginal reconstruction

Vaginal resection requires reconstruction to restore pelvic anatomy, reduce morbidity and potentially preserve sexual function (123, 124). In limited resections, a primary suture is an option while in larger resections, including the posterior vaginal wall or following total colpectomy, different flaps can be used.

Internationally, VRAM is the most used flap for neovaginal reconstruction. An altered GM flap are frequently used in the Swedish setting, referred to in this thesis as gluteus maximus special (GMS) (123). Other options include a gracilis flap. Vaginoplasty, using segments of sigmoid colon or ileum has also been described, offering the advantage of a self-lubricating neovagina with good long-term patency (125). However, this approach involves bowel resection and anastomosis, with the associated risk of anastomotic leakage and possible long-term bowel-related complications.

Complications

Complications following advanced CRC surgery are common and may be severe. A standardised classification system facilitates assessment of the postoperative course and comparisons across studies. Several attempts have been made to accurately describe the postoperative course. However, the lack of clear definitions and universally accepted classification systems has resulted in substantial variation in the used descriptions, such as *minor/major* or *moderate/severe*.

Clavien-Dindo Classification system

The Clavien-Dindo classification is perhaps the most widely used system for grading postoperative complications, designed to be simple, reliable and reproducible (Table 4). The classification has been validated across multiple patient populations and surgical procedures, demonstrating high consistency (126).

Table 4: Clavien-Dindo Classification System

Grade	Definition
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
III	Requiring surgical, endoscopic or radiological intervention - not under general anaesthesia - under general anaesthesia
IV	Life-threatening complication [‡] requiring IC/ICU management - single organ dysfunction - multiorgan dysfunction
V	Death of the patient

[‡] Brain haemorrhage, ischaemic stroke and subarachnoid bleeding, but excluding transient ischemic attacks (TIA); IC: intermediate care; ICU: intensive care unit

Comprehensive Complication Index

In 2013, Slankamenac et al. (127) introduced the Comprehensive Complication Index (CCI) to capture the overall morbidity burden by accounting for all postoperative complications (127). Unlike traditional complication grading systems that record a dichotomous outcome (complication vs no complication) or only the most severe event, the CCI integrates all postoperative complications. Complications are graded according to the Clavien-Dindo classification and assigned predefined severity weights. These are summarised into a single continuous numerical score ranging from 0 (no complication) to 100 (death).

As a result, multiple minor complications can cumulatively result in a higher CCI score than a single moderate complication, reflecting the patient's true postoperative course. This is particularly valuable in complex surgical settings. The CCI has shown greater sensitivity in detecting differences in postoperative outcomes compared to traditional endpoints and is increasingly used in surgical research (128, 129).

Complications after surgery

The surgical management of advanced CRC is often associated with prolonged recovery, longer hospital stays and high complication rates. These include haemorrhage, cardiovascular events, infections, delayed healing, anastomotic and urinary leakage, pelvic abscesses and fistula formation (130). The short-term mortality rate remains low, reportedly 1%-2% (131, 132).

A systematic review evaluating morbidity following PE for rectal cancer demonstrated substantial variability in complication rates. Severe complications, defined as Clavien-Dindo grade $\geq$ III, ranged widely from 5% to 65%, with a reported mean incidence of 33%. Factors influencing morbidity include the extent of the resection, the need for perineal reconstruction and neoadjuvant therapy (132). This heterogeneity underscores the significant procedural and patient-related variability inherent to advanced pelvic oncological surgery.

Data from the PelvEx Collaborative illustrate evolving surgical practice and its impact on postoperative outcomes by comparing outcomes for 2004-2014 to 2017-2021. Improved oncological outcomes were suggested, with higher R0 resection rates achieved despite increasingly advanced cancers (51). Notably, these improvements were achieved alongside a reduction in major complications from 38% to 23%. This suggests that centralisation of care and increasing surgical expertise may lower postoperative risk, despite greater surgical complexity (51).

Empty pelvis syndrome describes a spectrum of complications arising from the dead space created after multiorgan resection in the pelvis (133). The syndrome includes infected pelvic collection, small bowel obstruction, enteroperineal fistulas and chronic perineal sinuses (133). It occurs in approximately one-third of patients undergoing PE, with varying rates depending on the performed procedure (134). Preventative strategies focus on filling the pelvic cavity using, for example, omentoplasty, biological mesh or flaps (133, 134).

Urological complications are common following urinary tract resection in advanced CRC, with rates varying from 23% to 59% (135-138). Long-term complications include ureteral stones, ureteral strictures and renal insufficiency. The increased risk of ureteral stones is thought to be related to the presence of foreign material, such as surgical staples or intermittent self-catheterisation (139). Ureteral strictures may develop at the uretero-ileal anastomosis, for which surgical revision is superior to endourological procedures (140). Renal function decline may result from metabolic acidosis caused by electrolyte absorption and secretion in intestinal urinary diversions (141).

Perineal complications represent a major contributor to postoperative morbidity, with suggested reduced rates in patients with flap reconstructions (104). A systematic review of four perineal flap reconstructions (abdominal, gluteal, upper thigh and gluteal fold/perineal) following PE found flap dehiscence (15%-32%) and infection (8%-16%) to be the most common complications. Flap necrosis (2%-4%) and complete flap loss (0%-2%) were uncommon (142).

Quality of life

For many years, long-term survival was considered the primary endpoint of pelvic oncological surgery. Advances in oncological and surgical treatments has shifted attention towards clinical and patient-centred outcomes (8, 51, 131). Health-related QoL, sexual function and physical functioning have emerged as essential outcome measures (143).

Health-related quality of life

Health-related QoL is a subjective, multidimensional concept reflecting how the health status, disease, symptoms and treatment affect physical, psychological and social functioning as well as overall well-being (144).

PE is associated with a marked short-term deterioration in health-related QoL, followed by gradual recovery over time. Prospective and retrospective studies demonstrate significant reductions across physical, emotional, social and role-functioning domains in the early postoperative period (145-147). Physical functioning typically recovers more rapidly than the emotional and social domains. Nevertheless, most QoL measures show a return to, or approximate, preoperative baseline levels by 12 months (145, 146, 148, 149). This pattern of longitudinal recovery is also seen in patients requiring perineal flap reconstruction, even when experiencing flap-related complications (150).

Baseline QoL emerges as a predictor of postoperative outcomes (149). Patients with high preoperative QoL scores maintain higher QoL throughout follow-up (151). Patients requiring flap reconstruction report lower baseline QoL scores, indicating advanced disease (150). Predictors of worse QoL scores largely reflect the surgical extent: nerve resection, increased blood loss, operative time, length of stay, positive margins and bone resection (152). Older patients (≥ 65 years) reported preserved or even better QoL, despite lower overall survival, likely due to non-oncological comorbidity (153).

Importantly, QoL outcomes must be interpreted in the context of the alternative non-surgical approach (154). Pellino et al. (154) demonstrated that patients with LRRC

achieving R0 resections reported QoL scores comparable to non-recurrent control subjects (154). Patients who do not undergo surgery experience a progressive decline in QoL, driven by worsening local tumour-related symptoms (148).

Sexual function

Sexual dysfunction is a common and often profound consequence of oncological and surgical CRC treatment. It affects both men and women and contributes to long-term impairment in QoL (155). Despite its clinical importance, sexual function remains underreported in the literature.

Sexual dysfunction reflects both anatomical and psychological consequences, with reported impaired body image and decreased sexual interest. In men, erectile problems may result from prostate/seminal vesicle resection, nerve injury and/or oncological therapy (156). Impaired sexual desire, lubrication, dyspareunia and neovaginal strictures have been described in women (123, 124). In women with vaginal resection, reconstruction with a flap may improve body image and emotional wellbeing. However, functional outcomes remain limited, with a minority of patients returning to sexual activity (157). This highlights the multifactorial nature of postoperative sexual function.

Physical abilities

Pelvic surgery with subsequent perineal flap reconstruction imposes limitations on physical function, which can last months to years after surgery (158). Published evaluations have revealed that functional impairments are present even before surgery (159). Physical activity levels after PE are suggested to decrease in the early postoperative period but typically return to preoperative levels within 6 months (160). Higher preoperative activity appears to correlate with better postoperative outcomes, suggesting a potential role for prehabilitation (160). Persistent impairments in physical function often co-exist with limitations in sexual health and emotional well-being, emphasising the multifactorial nature of survivorship challenges after exenteration (161).

*The injury does not end in the operating room; it
continues in the life the patient must rebuild*

-Ghassan Abu Sittah



Aims

This thesis investigates functional and oncological outcomes in patients treated for advanced CRC requiring extensive resections with subsequent reconstructions.

Paper I

To evaluate long-term QoL, sexual function, physical ability, sensitivity and neovaginal measurements in patients treated for advanced pelvic cancer undergoing flap reconstruction using a VRAM or gluteal flap.

Paper II

To assess short-term (90 days) medical and surgical complications after advanced pelvic cancer surgery with perineal flap reconstruction using the Clavien-Dindo classification system.

Paper III

To describe the surgical technique and anatomical principles of the GMS flap used to reconstruct the posterior vaginal wall.

Paper IV

To describe, in a national Swedish cohort, the case volume, oncological outcomes and long-term survival in patients with primary CRC undergoing surgery with concomitant urinary tract resection.

Paper V

To assess short- and long-term outcomes in patients undergoing primary and recurrent CRC surgery with urinary tract resections, focusing on urological complications.

Methods

Papers I and II

Study cohort

Patients undergoing surgery treating advanced pelvic cancer requiring perineal flap reconstruction between 1 January 2010 and 1 August 2016 at SUS were included in *Papers I* and *II*. Eligible patients were identified using the operating surgery program “Orbit” with the aid of operation and diagnostic codes based on the International Classification of Diseases, 10th revision (ICD-10).

Medical chart review

In *Paper II*, a review of medical charts was performed. Data on patient characteristics, oncological treatment, surgical details, pathological assessment and complications during the first 90 postoperative days were analysed.

Postoperative complications were assessed using the Clavien-Dindo classification system, including medical complications defined as grade $\geq$ II and surgical complications as grade $\geq$ III. Flap-specific complications were recorded independently of the Clavien-Dindo grading. Flap dehiscence or necrosis was defined as partial when less than half of the flap was affected and total when more than half was involved. Perineal wound healing was evaluated at hospital discharge and at routine outpatient follow-up, usually 5-6 weeks after surgery.

Patients were stratified by the type of resection and reconstruction: ELAPE, ELAPE with posterior vaginal wall resection, and PE with VRAM or gluteal flap reconstructions.

Outpatient ward visit

Patients that were alive in August 2016 were invited to a follow-up visit at the outpatient ward for participation in *Paper I*. During the visit, patients met the research team, consisting of a colorectal surgeon, a plastic surgeon, a research nurse

and a physiotherapist. Participating patients filled in validated self-report questionnaires assessing QoL and sexual function. They also performed two physical tests and a sensitivity test. For women with vaginal reconstructions, the neovagina was measured using silicon gauges.

Self-report questionnaires

The EQ-5D assesses five health-related dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It also includes a visual analogue scale assessing overall health ranging from 0 (worst imaginable health) to 100 (best imaginable health) (162). The Quality of Life Questionnaire-Core 30 (QLQ-C30) is a 30-item cancer-specific questionnaire assessing functional domains (e.g. physical, emotional and social functioning), symptom scales (e.g. fatigue, nausea/vomiting, pain and constipation) and the global health status during the past week (163).

The Female Sexual Function Index (FSFI) is a 19-item questionnaire assessing female sexual function during the past 4 weeks across six domains: desire, arousal, lubrication, orgasm, satisfaction and pain. Domain scores were calculated by summing item responses and applying domain-specific weighting factors. The total score, obtained by summing the six domain scores, ranges from 2 to 36, with higher scores indicating better sexual function. A score of ≤ 26.55 indicates sexual dysfunction (164).

The International Index of Erectile Function (IIEF) was used to assess male sexual function. This 15-item questionnaire covers five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Each domain score is calculated by summing item responses, with higher scores indicating better sexual function. The maximum erectile function domain score is 25, with a cut-off of ≤ 7 indicating severe erectile dysfunction (165).

Sensitivity

Sensitivity in the surgical area of the buttocks and posterior thigh was assessed using four standardised points, comparing the operated and non-operated sides in patients with gluteal reconstruction. Point A was placed closest to the surgical scar of the donor site. Points B-D were placed on a straight line under point A along the back of the thigh (see Figure 6). The points were placed symmetrically on the non-operated side for comparison. Each point was tested using five different sizes of monofilaments, and each filament was tested three times. The sensitivity of the operated side was either worse (-), equal (0) or better (+), compared with the non-operated side. Patients who received a VRAM flap were included as a reference group to evaluate the method, with the left side of the buttocks as the reference.

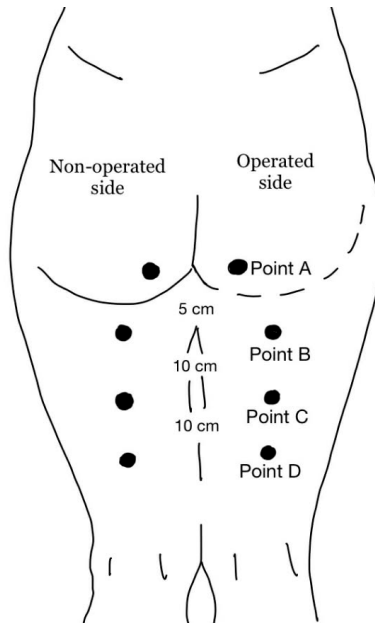


Figure 6: Sensitivity test

Patients who underwent gluteal flap reconstruction were assessed for sensory function of the buttocks and posterior thigh using five monofilaments on four standardised points. Each filament was applied three times at points A-D, comparing the operated and non-operated sides. The sensitivity on the operated side was classified as worse, equal to or better than that of the non-operated side.

Physical tests

The Timed Stands Test (TST) and a stairs test were used to assess lower extremity physical function. For the TST, patients were instructed to sit on a chair with their arms crossed over their chest. Then, they were asked to stand up fully and sit down five times as quickly as possible. Time was recorded from initial movement until the final standing position. The results were thereafter compared to the upper limit of an age- and sex-adjusted control group of healthy individuals (166). The stairs test assessed the patient's ability to climb stairs of different heights, comparing the operated and non-operated sides in patients with gluteal flap reconstructions. Patients who underwent reconstructions with a VRAM flap were included as a reference group to evaluate the performed tests. Patients were also invited to provide free-text comments regarding their perceived mobility after surgery.

Paper III

Several visits were made to the operating theatre to observe and participate in the construction of a GMS flap performed at SUS. Together with a medical illustrator, the surgical method was described using a step-by-step series of illustrations alongside figure legends, creating a manual for the surgical technique. The descriptions were subsequently reviewed by key plastic surgeons developing the method, as well as surgeons performing the reconstructions at our hospital, ensuring accuracy and consistency.

Paper IV

Study cohort

The SCRCR was used to identify patients with primary CRC undergoing surgery with concomitant urinary tract resections between 1 January 2007 and 31 December 2018. Data on patient characteristics, tumour classification, oncological treatment, surgical details, pathological assessment and recurrence were collected. Survival data were obtained using the National Cause of Death Register maintained by the Swedish Board of Health and Welfare on 4 June 2022.

To identify eligible patients, the “A2_ResektAnnatOrgan” variable in the SCRCR was used. This variable indicates whether an organ other than the colorectum was resected (yes/no), followed by a free-text field describing the performed procedure. Patients with documented resections of the urinary bladder and/or ureter were included. To confirm patient inclusion, the results derived from the SCRCR were cross-validated against a local registry of patients with CRC who underwent urinary tract resection.

Study outcomes

Patients were divided based on the performed urinary tract resection: total cystectomy, partial cystectomy and ureter resection. Overall 5-year survival as well as local and distant recurrence were compared among the groups.

To assess potential progress over the study period, the cohort was divided into four equally sized groups based on the year of surgery: quartile 1 (January 2007 to September 2009), quartile 2 (September 2009 to June 2012), quartile 3 (June 2012 to February 2016) and quartile 4 (February 2016 to December 2018). Study outcomes were compared between the quartiles and with patients undergoing CRC surgery without multivisceral resection, providing a broader understanding of the findings.

Paper V

Study cohort

Patients undergoing surgery treating primary and recurrent CRC with concomitant urinary tract resection between 1 January 2007 and 31 December 2020 at SUS, Malmö/Lund and Sahlgrenska University Hospital, Gothenburg were identified using both the SCRCR and local surgery planning program (Orbit and Operätt), with the aid of the assigned surgical codes as per ICD-10. The cohort was divided into three groups depending on the performed urinary tract resections: total cystectomy, partial cystectomy and ureter resection.

Data on patient characteristics, oncological and surgical treatment, the pathological report and recurrence were obtained from the SCRCR and through medical chart reviews at SUS and Sahlgrenska University Hospital. Information regarding postoperative care and complications were collected up to 5 years after surgery using medical chart reviews, with particular attention to urological complications.

Classification of complications

Short-term complications, diagnosed during the first 90 postoperative days, were graded using the Clavien-Dindo classification system; grade $\geq$ II complications were included. The overall burden of complications for each patient was assessed using the CCI, calculated with a validated online tool (<https://www.cci-calculator.com/>).

Long-term complications were defined as events occurring 90 days to 5 years after surgery, or until death if earlier. Clavien-Dindo $\geq$ III complications were reported, excluding complications in patients with recurrence. The need for a decompressive nephrostomy 3 years after surgery was also reported, excluding decompression due to local recurrences.

Urological complications included urinary leakage, ureteral strictures, urostomy complications, urinary fistulas, urinary infection and kidney failure.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate the estimated glomerular filtration rate (eGFR) (167). Kidney function decline was assessed using two eGFR measurements: one calculated from serum creatinine obtained as close as possible to the date of surgery, and a second based on the most recent available serum creatinine value.

Decline in kidney function was defined as a $\geq$ 30% reduction in the eGFR from the preoperative baseline, excluding transient creatinine elevations due to acute illness or dehydration. A postoperative eGFR $\leq$ 30 ml/min/1.73 m² was defined as chronic kidney disease, while kidney failure was defined as an eGFR < 15 ml/min/1.73 m².

Statistics

Descriptive statistics

Throughout the publications (*Papers I-V*), categorical data are presented as the total number with percentages in brackets. For numerical data, the median is presented with the interquartile range in brackets.

Survival analysis

Survival analysis was performed in *Paper IV*, where differences in 5-year overall survival rates among the urinary tract resection groups were compared using Kaplan-Meier analysis and the log-rank test.

Multivariable Cox proportional hazards models were applied to evaluate differences in 5-year overall survival, local recurrence and distant recurrence between the urinary tract resection groups in *Paper IV*. The analyses were adjusted for sex, age at the time of surgery, the ASA score, tumour location (colon or rectum), clinical TNM stage, pathological TN stage, year of surgery and the surgical setting (elective or emergency). Selection of covariates was guided using a directed acyclic graph. Total cystectomy served as the reference group. The results are reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). HRs above 1.0 indicated worse outcomes, whereas HRs below 1.0 indicate improved outcomes relative to the reference group. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA).

Ethics

The principles of the Declaration of Helsinki were followed when conducting the studies.

Papers I and II

Ethical approval was granted by the Ethical board in Lund (2015/715). Written informed consent was provided by all patients participating in *Paper I*.

Paper III

Written informed consent was provided by patients for the use of surgical images.

Paper IV

Ethical approval for this study was granted by the Swedish Ethical Review Authority (2022-00423-01). The general consent for the use of personal data within the SCRCR was the sole informed consent obtained from the patients.

Paper V

Ethical approval was granted by the Swedish Ethical Review Authority (2020-04769 and 2025-00599-02).

Use of AI

This thesis has in part been edited with the assistance of OpenAI. I have processed the generated text and take full responsibility for the content. The AI models were used to correct grammar, find synonyms and receive feedback on content and heading structure.

Results

In the Results and Discussion sections, the papers are presented according to outcome chronology rather than publication order.

Perineal reconstruction: short-term outcomes

A total of 105 patients underwent surgery treating advanced pelvic cancer with perineal flap reconstruction during the study period of *Paper II*. A GM flap was used in 51 patients, while GMS and VRAM flaps were each used in 27 patients.

The majority of patients were treated for rectal cancer and had received neoadjuvant radiotherapy or CRT. The median age was 66 years at time of surgery. PE was performed in 29 (28%) patients, ELAPE in 43 (41%) patients and ELAPE including the posterior vaginal wall in 33 (61%) patients. R0 resection was achieved in 91 (87%) patients.

Overall, 41 (39%) patients experienced at least one complication (Clavien-Dindo $\geq$ II for medical and/or $\geq$ III for surgical complications). Ten (10%) patients required admission to an intensive care unit. One patient died within 90 days postoperatively due to intracerebral haemorrhage.

Approximately one-fourth of the cohort had surgical Clavien-Dindo $\geq$ III complications. The most common surgical complication was abscess formation requiring drainage, either by ultrasound-guided intervention or by surgery. Patients who underwent PE experienced higher complication rates compared with more limited resections (Table 5). Among patients undergoing ELAPE, with or without posterior vaginal wall resection, complication rates were higher after VRAM flap reconstruction (Table 5). Regardless of the surgical procedure, patients who underwent reconstruction with a VRAM flap had longer operative times, greater blood loss and longer hospital stays compared with patients who underwent reconstruction with a gluteal flap.

Flap-specific complications were common, affecting more than half the cohort. Patients who received a VRAM flap showed the highest rates of partial necrosis (Table 6). Two patients (2%) had total dehiscence, and none had total necrosis. Healed flaps were observed in 38 (36%) patients at discharge and in 47 (45%) at outpatient follow-up.

Table 5: Surgical complications based on the surgical procedure

Patients are divided based on the performed resection into ELAPE³, ELAPE with posterior vaginal wall resection and PE.⁵ The total number of patients experiencing surgical complications classified as CD⁴ ≥ III are presented with the percentage in brackets. The total number of pelvic abscesses in each group is presented with the percentage in brackets.

	VRAM ¹	GM/GMS ²
ELAPE	4	39
CD ≥ III	1 (25)	3 (8)
Pelvic abscess	2 (50)	6 (15)
ELAPE with posterior vaginal wall resection	9	24
CD ≥ III	7 (78)	2 (8)
Pelvic abscess	1 (11)	2 (8)
Pelvic exenteration	14	15
CD ≥ III	7 (50)	7 (47)
Pelvic abscess	4 (29)	6 (40)

¹Vertical rectus abdominis musculocutaneous

²Gluteus maximus/gluteus maximus special

³Extended abdominoperineal excision

⁴Clavien-Dindo

⁵Pelvic exenteration

Table 6: Flap-specific complications

The total number of patients with flap dehiscence and/or necrosis are presented with the percentage in brackets. Dehiscence or necrosis affecting less than half of the flap was classified as "partial", whereas involvement of more than half of the flap was classified as "total".

	VRAM ¹	GM ²	GMS ³
Total number	22 (81)	25 (49)	17 (62)
Partial dehiscence	12 (44)	22 (43)	11(41)
Total dehiscence	1 (4)	-	1 (4)
Partial necrosis	9 (33)	3 (6)	5 (19)
Total necrosis	-	-	-

¹Vertical rectus abdominis musculocutaneous

²Gluteus maximus

³Gluteus maximus special

Perineal reconstruction: long-term outcomes

Seventy-one patients were alive at time of inclusion for *Paper I*, of whom 36 consented to participation: 12 underwent reconstruction with a VRAM flap and 24 with a gluteal flap. The majority were female (24 (67%) patients) and were treated for rectal cancer (26 (72%) patients). The median age was 62 years. Neoadjuvant treatment was received by 32 (89%) patients, with R0 resection achieved in 35 (97%) patients. PE was performed in 12 patients, ELAPE in 10 patients and ELAPE including posterior vaginal wall resection in 14 patients.

The EQ-5D showed difficulties in three of the five assessed domains: mobility, pain/discomfort and anxiety/depression. On the QLQ-C30 questionnaire, patients reported high median scores for daily functioning and generally low symptom scores, except for fatigue, which affected 17% of patients. There were high global health scores for both questionnaires.

Of the 21 women who completed the FSFI, all met the criteria for sexual dysfunction. Six women implied they engaged in sexual activity after surgery. Neovaginal measurements showed deeper constructions with GMS flaps compared with VRAM flaps. Severe erectile dysfunction affected 75% of participating men. All men undergoing PE had scores consistent with severe erectile dysfunction. Partner relationships in participating men remained largely unaffected, as reflected by high scores.

Sensitivity testing showed reduced sensation on the operated side in patients who underwent reconstruction with a gluteal flap, most pronounced near the donor site (point A) and improving distally along the posterior thigh (points B-D) (Figure 7). There was no comparable sensory impairment in patients who underwent reconstruction with a VRAM flap. Nineteen (79%) patients who underwent reconstruction with a gluteal flap reported altered sensation.

Based on the TST, there was impaired endurance in patients who underwent reconstruction with a gluteal flap; 11 (46%) patients in the gluteal group and 3 (25%) patients in the VRAM group exceeded the upper time limit of matched healthy controls. The median step height in the stairs test was 45 cm, with no difference between the operated and non-operated sides. All patients reported being able to climb stairs and ride a bicycle in their daily lives. Three patients in each group reported mobility limitations related to stoma. One patient required a walking aid at discharge that had not been needed at admission.

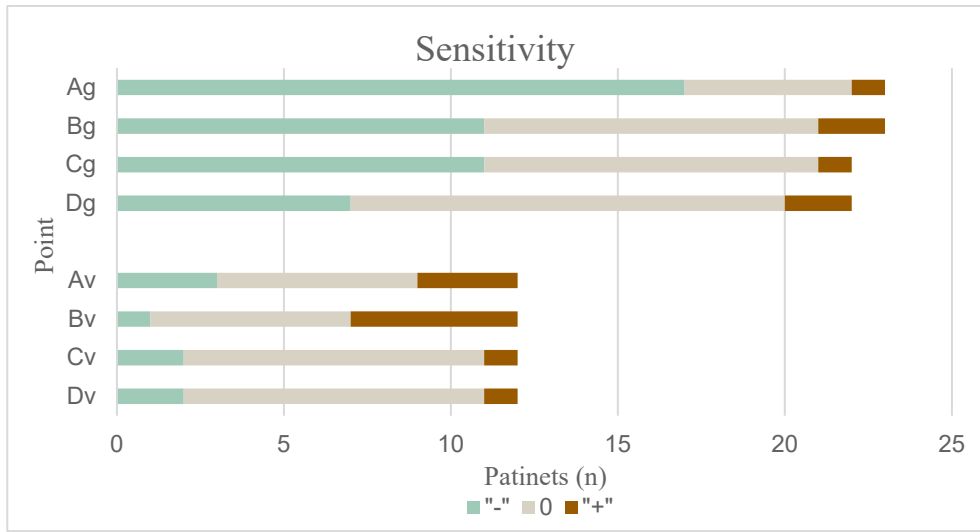


Figure 7: Sensitivity test

Sensitivity in the surgical area of the buttocks and posterior thigh was assessed. Sensitivity on the operated side was classified as worse (-), equal (0) or better (+) compared with the non-operated side in patients who underwent reconstruction with a gluteal flap. Patients who underwent reconstruction with a gluteal flap, marked with "g", reported impaired sensitivity closest to the donor site (point A). Sensory function improved distally along the posterior thigh. Patients who underwent reconstruction with a vertical rectus abdominis myocutaneous flap, marked with "v", did not display the same pattern of sensory impairment.

Gluteus maximus special flap

The construction of a GMS flap is described in *Paper III*. In patients undergoing surgery involving perineal and posterior vaginal wall resection, reconstructive procedures may be required. When the anterior vaginal wall is partially or completely preserved, a GMS flap can be used to reconstruct the perineum and posterior vaginal wall. As illustrated in Figure 8, the GMS technique consists of three components: a fasciocutaneous transposition flap for the posterior vaginal wall, a muscular transposition flap for the deep perineal defect, and a fasciocutaneous rotational flap for the superficial perineal defect.

Figure 8: Construction of a glutes maximus special (GMS) flap

Step 1: The patient is placed in a supine position. The length (A) and width (B) of the anterior vaginal wall are measured and matched to the length (a) and width (b) of the transpositional flap used for posterior vaginal wall reconstruction. Incision lines are drawn cranially in a semicircular fashion, extended caudally reaching the gluteal fold and continued in an arc towards the greater trochanter.

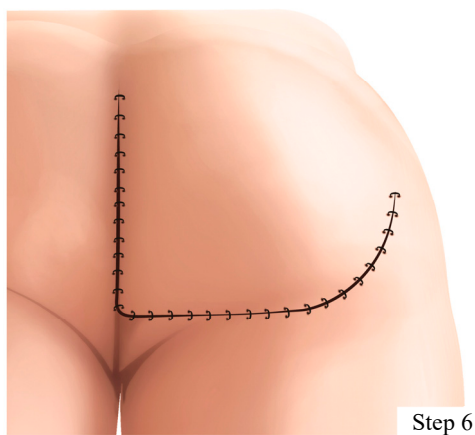
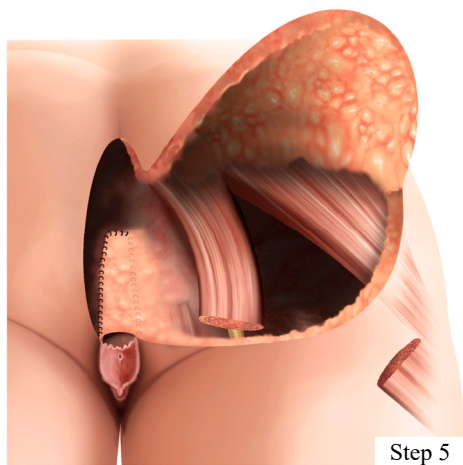
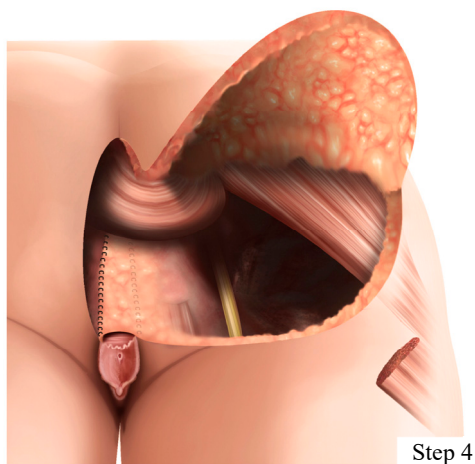
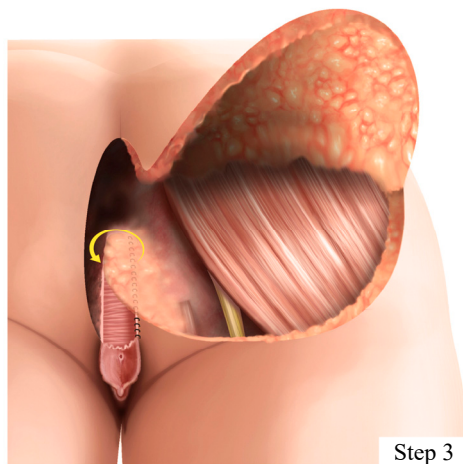
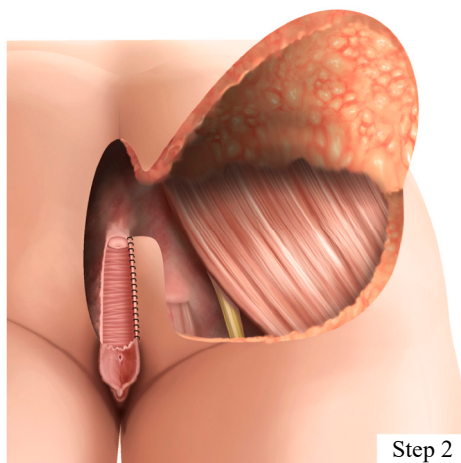
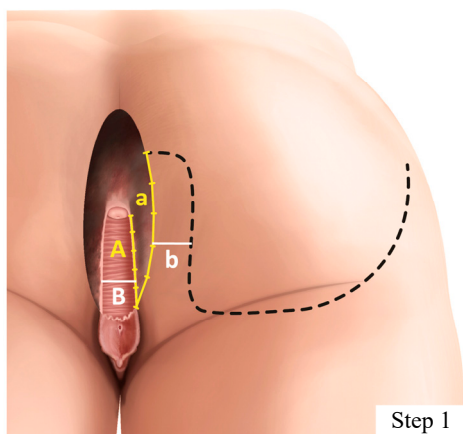
Step 2: An incision is made to elevate the fasciocutaneous transposition flap. The medial edge of the transposition flap is sutured to the ipsilateral portion of the remaining anterior vaginal wall using intravaginal, absorbable sutures.

Step 3: The transposition flap is rotated 180° around its axis to reach the contralateral anterior vaginal wall. This edge is sutured extravaginally using absorbable sutures. To create a fasciocutaneous rotational flap, the fasciocutaneous layer is partially separated from the underlying gluteal muscle. The inferior gluteal artery is preserved in most patients. The inferior cutaneous nerve branches are divided in some patients during flap elevation.

Step 4: Usually, two-thirds of the width of the gluteus maximus is required to fill the pelvic dead space. The muscle is divided close to its origin along the muscle fibres, creating a muscular flap. The muscular transposition flap is used to fill the pelvic dead space and is secured with absorbable sutures.

Step 5: To cover the superficial perineal defect, the fasciocutaneous rotational flap is secured with absorbable sutures along the gluteal incision lines.

Step 6: The final healing results in a scar that mimics the gluteal fold. Postoperatively, patients follow a mobilisation protocol in which sitting is permitted for short periods after day 13 and without restriction after day 21.



Complications after urinary tract resections

Paper V included a total of 373 patients undergoing primary or recurrent CRC surgery with concomitant urinary tract resection: total cystectomy in 192 (51%) patients, partial cystectomy in 120 (32%) patients and ureter resection in 61 (16%) patients.

The baseline patient characteristics were largely comparable between the groups. Patients undergoing total cystectomy more often had rectal cancer and pT4 tumours. The procedure was associated with longer operative times and hospital stays. Colon cancer was more common in the partial cystectomy group. Surgery for recurrent cancer was most frequent in the ureter resection group, which also had the highest rate of distant metastases at diagnosis. R0 resection was achieved in 320 (86%) patients, and the 5-year overall survival rate was 59% (221 patients).

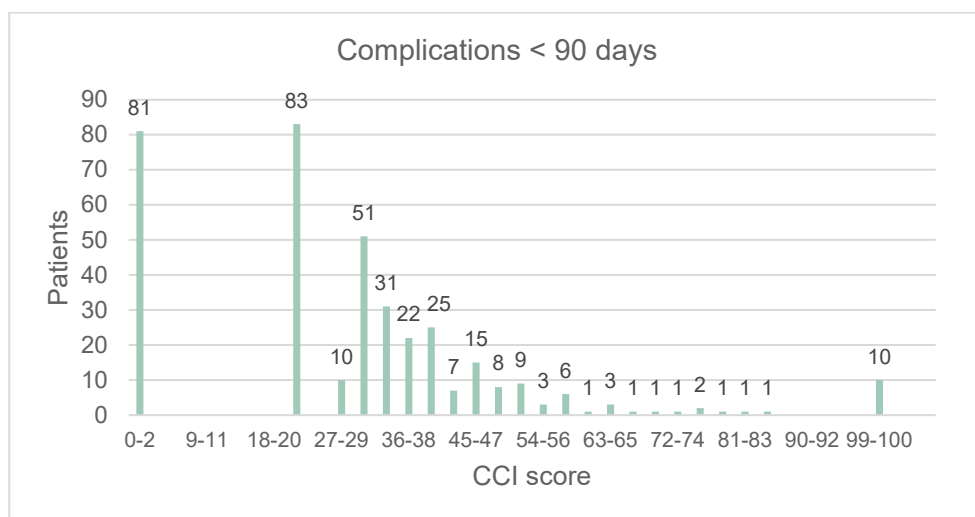


Figure 9: Comprehensive complication index score for short term complications

For each patient a Comprehensive Complication Index (CCI) score was calculated using the Clavien-Dindo classification system. Grade $\geq$ II complication affecting the patient within the first 90 days after surgery were included. A score of 0 indicates no complications while a score of 100 indicates death. The total number of patients is presented on the y-axis.

Short-term complications were common, most frequently presenting as infections, anaemia, ileus and the need for total parenteral nutrition. Based on the CCI scores from the first 90 postoperative days, 81 patients had no complications classified as Clavien-Dindo $\geq$ II and 83 patients had one Clavien-Dindo II complication, collectively representing 44% of the cohort (Figure 9). Nearly one-third of patients had Clavien-Dindo $\geq$ III complications within 90 days, with the highest rates after

total cystectomy. Urinary leakage was the most common urological complication necessitating intervention in the short-term period, often managed with drainage. Intensive care unit treatment was required in 23 (6%) patients. Death was observed in 10 (2%) patients, due to cardiovascular events, infections, surgical complications, respiratory failure and malnutrition.

Table 7: Urological complications: long-term outcome

The total number of patients with urological complications classified as Clavien-Dindo $\geq$ III, diagnosed between 90 days after surgery and 5 years postoperatively, is presented with percentages in brackets. Kidney function decline was defined as a $\geq$ 30% decline when comparing the preoperative estimated glomerular filtration rate (eGFR) to the last recorded value. The median follow-up in years is presented with the IQR¹ in brackets. Chronic kidney disease was defined as an eGFR $\leq$ 30 ml/min/1.73 m² and kidney failure as an eGFR $\leq$ 15 ml/min/1.73 m².

	Total	Total cystectomy	Patial cystectomy	Ureter resection
Number of patients	363	185	118	60
Urological complications				
Clavien-Dindo $\geq$ III	55 (15)	42 (23)	5 (4)	8 (13)
Urinary leakage	3	0	1	2
Ureteral stricture	37	30	3	4
Urinary stoma	4	4	0	0
Urinary fistula	1	0	0	1
Urinary infection	5	4	1	0
Kidney failure	2	2	0	0
Other, urinary	5	3	0	2
Kidney function decline	106 (29)	64 (35)	23 (19)	19 (31)
Median follow-up, years (IQR ¹)	3.4 (1.4-6.7)	4.3 (1.2-7.2)	2.9 (1.4-5.5)	3.8 (1.9-6.2)
Missing	27 (7)	7 (4)	15 (13)	5 (8)
Chronic kidney disease	35 (10)	17 (9)	12 (10)	6 (10)
Kidney failure	8 (2)	3 (2)	2 (2)	3 (5)

¹Interquartile range

A total of 82 (23%) patients had Clavien-Dindo $\geq$ III long-term complications, with a total of 135 performed procedures. Long-term urological complications classified as Clavien-Dindo $\geq$ III affected a total of 55 (15%) patients, most commonly following total cystectomy (Table 7). Ureteral stricture was the most frequent indication for intervention, with 57 procedures in 37 (10%) patients. In patients with ureteral stricture, 17 (46%) patients needed multiple procedures including decompressive nephrostomy, ureteral dilation and ureteral reimplantation.

Postoperative decline in kidney function was observed in 106 (29%) patients, more frequently following total cystectomy (64 patients, 35%), as presented in Table 7. Chronic kidney disease was observed in 35 (10%) patients, of whom 8 (2%) had kidney failure.

Nephrostomy was required in 38 patients (10%) 3 years after surgery, 26 (14%) patients with total cystectomy, 8 (7%) patients with partial cystectomy and 4 (7%) patients with ureter resection. Kidney function decline was observed in 21 (55%) patients with a nephrostomy.

Survival after urinary tract resection

A total of 57 907 patients underwent surgery treating primary CRC from 2007 to 2018. Urinary tract resections were performed in 1 093 patients included in *Paper IV*: 589 total cystectomies, 345 partial cystectomies and 159 ureter resections (Figure 10). Cross-validation demonstrated high agreement between the SCRCR and the local registry.

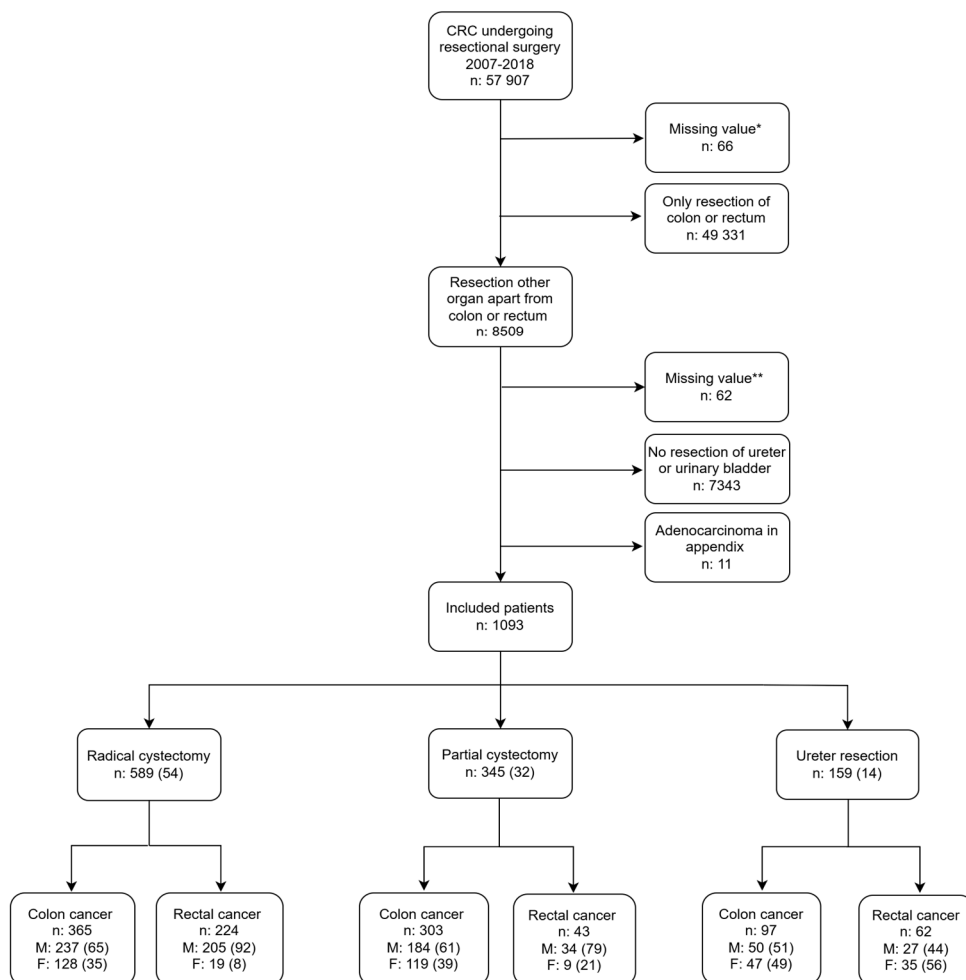


Figure 10: Flowchart of the study cohort

Patients undergoing surgery treating primary colorectal cancer with concomitant resection of the urinary tract organs are included. Neoplasm in the appendix is excluded. Patients are divided into three groups based on the performed urinary tract resection: total cystectomy, partial cystectomy and ureter resection.

Total cystectomy was more common in patients with rectal cancer and T4 tumours. The procedure had the highest median operative time. Partial cystectomy was mainly performed for sigmoid cancer, older patients, in emergency surgeries and for patients for whom there were no MDT discussions. Patients undergoing ureter resections had higher rates of cM1, c/pN+ and right-sided colon cancer; more preoperative blood loss; and longer hospital stays. All groups achieved similar negative resection margins (R0).

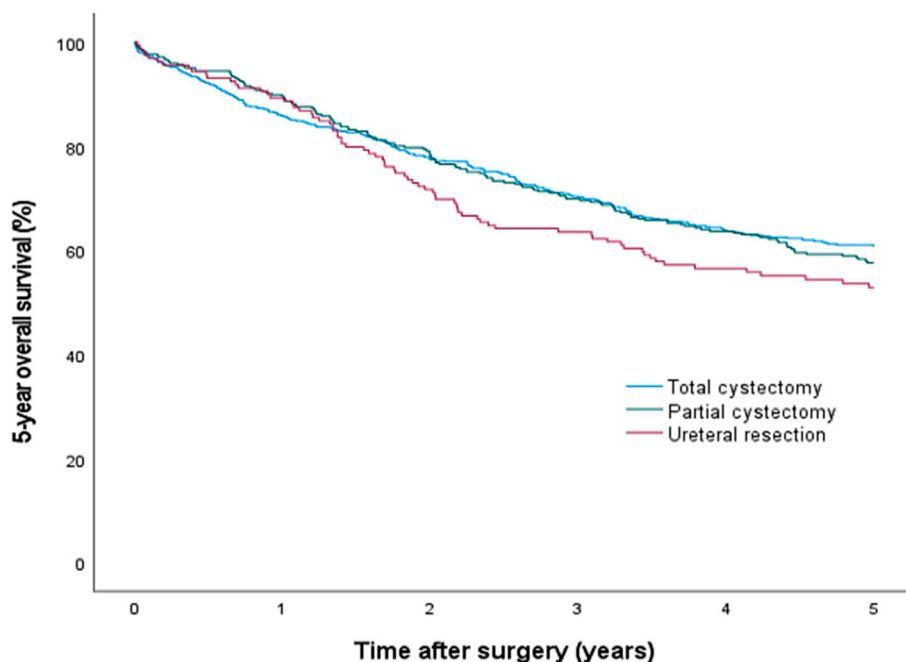


Figure 11: Five-year overall survival

Kaplan-Meier curve showing 5-year overall survival rates, comparing total cystectomy, partial cystectomy and ureter resection. The log rank test was not significant ($p = 0.205$).

Table 8: Number of patients at risk

Year	0	1	2	3	4	5
Total cystectomy	589	504	454	411	353	304
Partial cystectomy	345	309	270	241	210	169
Ureteral resection	159	142	114	101	84	69

Five-year overall survival was highest in patients undergoing total cystectomy (61%), compared with partial cystectomy (58%) and ureter resection (53%). Kaplan-Meier analysis revealed that 5-year overall survival did not differ based on the treatment (log rank test, $p = 0.205$) (Figure 11 and Table 8).

Table 9: Cox regression analysis of death, local recurrence and distant metastases

Cox regression of death, local recurrence and distant metastases were performed, adjusted for age at surgery, American Society of Anesthesiologist classification, tumour localisation (colon or rectum), cTNM, pTN, year of surgery and type of surgery (elective or emergency). Patients who underwent total cystectomy were used as reference. The HR¹ is presented with the CI² and p-value.

		Univariate			Multivariate		
	n	HR	95% CI	p-value	HR	95% CI	p-value
HR of death							
Total cystectomy	228	1	Reference		1	Reference	
Partial cystectomy	144	1.06	0.87-1.32	0.536	1.025	0.78-1.35	0.863
Ureter resection	74	1.27	0.98-1.65	0.076	1.099	0.79-1.54	0.578
HR of local recurrence							
Total cystectomy	42	1	Reference		1	Reference	
Partial cystectomy	21	0.86	0.51-1.45	0.573	1.020	0.51-2.03	0.926
Ureter resection	17	1.65	0.94-2.91	0.080	2.290	1.17-4.50	0.016
HR of distant recurrence							
Total cystectomy	139	1	Reference		1	Reference	
Partial cystectomy	86	1.07	0.81-1.40	0.643	1.242	0.88-1.75	0.212
Ureter resection	44	1.29	0.92-1.82	0.138	1.129	0.75-1.71	0.568

¹Hazard ratio

²Confidence interval

Multivariable Cox regression analysis showed no significant differences in 5-year overall survival rates between the urinary tract resection groups (Table 9). Age > 65 years, ASA class III-IV, metastases at diagnosis, pN+ status, surgery during the early study period, emergency surgery and rectal cancer were significantly associated with poorer 5-year overall survival.

Ureter resections, pN+ status and ASA class III-IV were significantly associated with local recurrence. Distant recurrence was significantly associated with metastatic disease at diagnosis, male sex and rectal cancer.

Improvements in survival and recurrence rates were observed over the study period, despite higher rates of T4 tumours and ASA class III-IV in more recent years. When compared with standard CRC surgery without multivisceral resection, 5-year overall survival was similar, although local and distant recurrences were less frequent after standard CRC surgery. The material enabled comparison of urinary tract resections performed across Sweden. The distribution of surgeries reflected the population base, with slightly higher rates of ureter resection in the Stockholm/Gotland region.

“The wound is the place where the light enters you”

-Rumi



Discussion

Early morbidity, lasting reconstruction

Extensive pelvic surgery necessitating perineal flap reconstruction is associated with low mortality and surgical intervention rates despite significant morbidity, as presented in *Paper II* and supported by earlier publications (8, 132). In our cohort, reconstruction with a VRAM flap was associated with longer operative times, higher complication rates and prolonged hospital stay. This likely reflects a higher proportion of PE, recurrent disease and the need for abdominal wall reconstruction. After adjusting for the performed resection, complications remained higher in patients who underwent reconstruction with a VRAM flap and ELAPE with or without posterior vaginal wall resection. This might be attributed to a higher proportion of anal cancer and associated extensive radiotherapy. VRAM-flap-based vaginal reconstructions were primarily performed early in the study period, with only a few cases after the introduction of GMS flaps in October 2013, also suggesting a potential influence of evolving surgical practice and increasing experience over time.

Flap-related complications were common, regardless of the flap type, as reported in *Paper II*. Flap loss was uncommon, and early morbidity did not appear to predict long-term failure. Importantly, most patients ultimately achieved satisfactory healing. These findings are consistent with previous studies in which dehiscence, infection and partial necrosis are frequently reported with healing typically completed within 12 months (168, 169). This underscores the importance of distinguishing between early postoperative morbidity and long-term reconstructive success when evaluating outcomes.

Interpretation of complication rates, comparing different flap techniques for perineal reconstruction, is inherently challenging. Published cohorts are often small and heterogeneous, with varying tumour types, defect sizes, prior therapy and reconstructive methods. In addition, flap selection is influenced by multiple patient-related factors, introducing confounding by indication. This limits comparability between techniques and should be considered when interpreting results. Multicentre collaboration and exchange of experiences regarding expertise, postsurgical morbidity and QoL outcomes is needed to further address flap-related complications.

Reconstructing life after extensive surgery

Despite the reported limitations in several aspects of life in *Paper I*, the overall QoL score was higher than in patients undergoing conventional CRC surgery and in the general Swedish population (170-172). While some publications have described sustained QoL impairment, especially in non-rectal malignancies, others have reported results in line with our findings (173-175). This variability highlights the heterogeneity in patient populations, treatment strategies, methodological approaches and coping mechanisms (173-175).

At first glance, the high QoL scores appear counterintuitive given the magnitude of surgery and the functional sequelae. This may be explained by *response shift*, whereby patients who survive a life-threatening condition recalibrate their internal standards, values and expectations. Relief from cancer-related symptoms and a sense of having overcome a life-threatening illness may contribute to higher self-reported health, regardless of persistent physical limitations. This could also explain comparable QoL scores after recurrent and primary rectal cancer surgery in previous publications (152).

The methodology in *Paper I* relies on voluntary participation, introducing inherent selection bias. Participating patients tend to be healthier and more resilient (176). Several patients who declined to participate cited cancer recurrence, many hospital visits and long travel distances to SUS, Malmö as reasons. Exclusion analysis demonstrated lower tumour stages and higher R0 resection rates among the included patients, supporting that the cohort represents a subgroup with favourable oncological outcomes.

Furthermore, exclusion analysis showed high participation of women in our study. This finding is consistent with the previous medical literature, demonstrating higher response and participation rates among women in QoL studies (177). This may reflect the fact that women are more willing to discuss health-related issues and engage in seeking health-related information (178). This challenges current clinical practice and highlights the need for targeted strategies to better engage male patients and to improve representativeness. Other factors may also influence participation patterns such as education level and socioeconomic status, variables that were not assessed in our study (179).

To minimise bias, including reporting bias, surgeons did not interact with patients during questionnaire completion. A physiotherapist distributed the questionnaires and assisted when needed.

There are limited options for assessing sexual function, particularly regarding validated instruments with established cut-offs and comparable data from previous publications. The challenging aspects related to the FSFI lie in its construction and definitions. This survey defines sexual activity such as caressing, foreplay,

masturbation and intercourse (penile penetration of the vagina), evaluating the last 4 weeks. The used cut-off defining sexual dysfunction was created using 259 non-operated females with a median age of approximately 40 years (164). In contrast, the median age of our cohort was 62 years. This age mismatch limits the applicability of the instrument in an older surgical cohort.

The FSFI questions rely heavily on penetrative sex, so this instrument may be less applicable to women who are not sexually active or whose sexual practices fall outside the set framework. According to a review, the literature on female sexuality after CRC surgery is of low quality, focusing mainly on heterosexual intercourse and excluding other types of sexual functioning with practically no reporting in lesbian, bisexual, transgender, queer, intersexual and asexual patients (157). Therefore, the results should be interpreted with awareness of the limitations regarding narrow definition of sexuality and time frame.

A recent systematic review on female sexuality after vaginal reconstruction in patients with CRC demonstrated a marked decline in sexual activity. High rates of sexual dysfunction were reported despite satisfactory surgical outcomes, low wound complication rates and few reoperations (157). This is reflected in our cohort, with high rates of sexual dysfunction, even among women whose neovaginal measurements were comparable to those of healthy, non-operated women (180). Anatomical reconstruction did not translate into preserved sexual function, underscoring the complex interplay between body image, sexual desire and functional outcomes.

Male sexual dysfunction is a prevalent and persistent complication, with increased risks in cases of rectal cancer, radiotherapy, stoma formation and extensive pelvic surgery (181). Improvement in erectile dysfunction over time has been reportedly limited (182). Reported high rates of erectile dysfunction after APE are comparable to our findings, highlighting the need for sexual rehabilitation in both sexes (183).

Although the Swedish version of the IIEF-5 offers certain advantages compared with the FSFI, including a longer recall period and items addressing partner-related aspects, it still has limitations. For instance, the instrument may misclassify men who are not sexually active for reasons unrelated to erectile dysfunction, such as absence of a partner or preference for non-penetrative intimacy (184).

Preoperative sexual function is the strongest predictor of postoperative activity in both sexes, underscoring its importance in preoperative assessment and rehabilitation planning (185, 186). Nevertheless, several series have reported that only a minority of patients recalled receiving, or had documented, structured counselling regarding expected postoperative sexual function (186, 187). This indicates potential for improvement in healthcare provision.

Physical function in our cohort was generally acceptable, with a preserved ability to perform daily activities such as climbing stairs and cycling. A subset of patients

experienced reduced lower limb strength and endurance, particularly after reconstruction with a gluteal flap. In several cases, the presence of a double stoma was reported as a contributing factor to mobility limitations.

In our setting, patients are instructed to avoid sitting for 13 days after reconstruction with a flap; they are asked to instead remain lying or to walk. A study comparing early mobilisation with the standard five days of bedrest following perineal flap reconstruction showed improved performance and reduced length of hospital stay without compromising wound healing (188). Additional studies similarly suggest that early mobilisation is safe and may reduce postoperative complications (189). This warrants a review of current practices and an evaluation of the potential benefits of earlier mobilisation.

The retrospective cross-sectional nature of *Papers I* and *II* comes with several limitations. There was no evaluation of preoperative QoL and no longitudinal follow-up. The included patients were operated on over a 10-year period with differences in preoperative treatment and postoperative routines possibly affecting the results. The strength of the papers lies in their unique insights covering several aspects of life after surgery in a sparsely studied patient group.

How to choose the most appropriate flap

The perineal defect left after advanced pelvic surgery can be substantial. Several methods for perineal reconstruction are used internationally, each with its own strengths and limitations. The literature guiding surgeons on when to reconstruct and how to choose the appropriate flap remains limited.

The BIOPEX trials, RCTs conducted at 19 centres in the Netherlands and the United Kingdom including patients with rectal cancer who underwent APE compared primary closure with biological mesh and a gluteal turnover flap. There was no reported difference in perineal wound healing at 30 days. Biological mesh was associated with significantly lower rates of perineal hernia, and gluteal flaps demonstrated lower incidence of presacral abscesses (117, 169). However, the limitations included a relatively short follow-up, restriction to patients with rectal cancer and exclusion of more extensive resections such as PE, limiting generalisability to broader pelvic reconstructive practice.

Local reconstructive preferences vary across centres, further reflecting limited evidence. In our setting, a GM flap is the preferred method for reconstruction in patients with significant perineal defects. A GMS flap is used in women requiring posterior vaginal wall reconstruction, allowing for deeper neovaginal reconstructions compared with a VRAM flap, as demonstrated in *Paper I*. At SUS,

reconstruction using a VRAM flap is reserved for extensive defects, particularly anterior defects, or when the rotational arc of a GM/GMS flap is insufficient.

International practice illustrates similar variability: at Royal Prince Alfred Hospital in Sydney, for example, a PAP flap is the primary option, followed by a gluteal flap and a VRAM flap. At Dresden-Friedrichstadt General Hospital, Germany, bilateral gluteal V-Y flaps are proposed for ELAPE, whereas a VRAM flap is recommended for PE. This approach is supported by a shorter operative time, lower donor-site morbidity and fewer complications (122).

Prasath et al. (190) reported that compared with VRAM and gracilis flaps, gluteal thigh flaps are the most cost-effective first-line reconstruction, supporting the use of local flaps (190). Similarly, a study from Melbourne, Australia, compared inferior gluteal artery myocutaneous flaps with VRAM flaps. The authors reported significantly higher rates of adverse events in the VRAM group, again favouring local flap reconstruction (191). These centre-specific protocols highlight how the reconstructive choice is influenced not only by defect characteristics but also by accumulated institutional experience and available surgical expertise.

Selection of the reconstructive method remains highly variable until further evidence provides clearer guidance. Factors such as defect size, the need for vaginal reconstruction, prior radiotherapy, donor-site availability and patient comorbidities must be considered. Local expertise and established practice are other important variables, particularly in low-volume centres where a limited number of techniques are used to maintain proficiency. The complexity of reconstructive surgery necessitates a multidisciplinary, patient-tailored approach (104, 142).

What the records reveal

In *Papers II* and *V*, a cornerstone of the methodology was the review of medical records. The principal strength of retrospective medical record review is the availability of detailed clinical data in a cost-efficient format. It enables long-term outcome assessment, data validation through cross-validation, and inclusion of a large study population within a shorter time frame than typically feasible in a prospective design. This is particularly relevant in rare and complex surgical procedures where prospective recruitment is challenging. Inherent limitations include incomplete documentation; variability in data quality; a lack of standardised definitions; and the risk of selection, information and confounding biases. Additionally, changes in clinical practice over time and inconsistent follow-up routines introduce further challenges.

It is well recognised that milder complications only requiring medical management are often underreported in clinical records (192). Some studies address this

limitation by including complications graded as Clavien-Dindo $\geq$ III. However, severe medical complications – such as cardiac infarctions treated with thrombolysis – may be managed conservatively and therefore classified as Clavien-Dindo grade II. Consequently, significant morbidity may be underestimated, compromising the overall evaluation of postoperative risk.

Several measures were implemented to mitigate these methodological limitations. To ensure uniform data collection, a predefined protocol was applied in both studies. In *Paper II*, all medical record reviews were conducted by the author, whereas in *Paper V* the reviews were performed in collaboration with one co-author, promoting consistency in data extraction. To enhance comprehensive identification of complications, record review was supplemented by systematic examination of medication lists and relevant radiological reports. Furthermore, validated classification systems (Clavien-Dindo and the CCI) were used to standardise complication grading.

Although registry-based data from the SCRCR provide an alternative source for complication reporting, several limitations reduce its suitability for *Papers II* and *V*. Complication registration was introduced in 2007 and restricted to the first 30 postoperative days, with Clavien-Dindo grading implemented from 2011. In addition, registry-based complication variables have shown lower validity, particularly for milder complications (42).

The story lies in the details

Urological complications were common throughout the postoperative course after CRC surgery with concomitant urinary tract resections, as presented in *Paper V*. In the short-term setting, complications were predominantly mild, mainly urinary tract infections. Even severe urological complications, such as urinary leakage, were frequently treated conservatively through antibiotic therapy and percutaneous drainage. Notably, a substantial proportion of patients experienced either no complications or only a single Clavien-Dindo grade II event, indicating acceptable early postoperative safety. Low overall 90-day mortality rates were reported, comparable to conventional CRC surgery (193).

In contrast, urological complications were the most common indication for intervention in the long-term setting, with ureteral strictures accounting for 42% of all procedures performed. Approximately half of all patients with ureteral strictures required multiple interventions, reflecting the complexity and resource demands of this complication. These findings are in line with previous publications, underscoring the long-standing effects of urinary tract resections in patients with CRC (136, 194, 195).

When comparing complication rates across different types of urinary tract resections in our cohort, total cystectomy was associated with higher overall morbidity than partial cystectomy or ureter resection. Possible explanations include previously reported risk factors such as more extensive surgery, greater blood loss, higher rates of intestinal anastomotic leakage, ileal conduit formation and a larger proportion of rectal cancer (135, 136, 195, 196). Many of these patients also receive neoadjuvant therapy, although the independent impact of radiotherapy remains unclear (137, 138).

Only a limited number of studies have compared complication rates among different types of urinary tract resections in CRC surgery. The existing publications are characterised by heterogeneous inclusion criteria, varying subgroup definitions and differences in how complications are classified. While some studies are consistent with our findings, Bolmstrand et al. (136, 197) reported significantly greater morbidity following ureter resection. This discrepancy may relate to the inclusion of anal cancer cases and to the combined analysis of total and partial cystectomy when compared with ureter resection (136, 197).

Univariable and multivariable analyses were initially performed to explore potential predictors of complications in our study. However, the limited number of events within each urinary tract resection subgroup precluded robust statistical modelling, and these analyses were therefore not pursued further. This highlights the need for larger, collaborative datasets to enable meaningful risk stratification.

Kidney function decline represented a clinically significant long-term outcome in this study, affecting 29% of patients. The highest incidence was observed following total cystectomy (35%). A previous study applying the same definition of kidney function decline reported a 40% decline 5 years after CRC surgery with total cystectomy. In the same study, conduit lengths exceeding 20 cm were associated with greater kidney function deterioration. It is hypothesised that longer conduits increase urinary reabsorption and subsequent metabolic acidosis (141).

Patients undergoing radical cystectomy for urothelial carcinoma commonly experience a decline in their eGFR, comparable to our rates (198). Identified risk factors include advanced age, impaired baseline renal function, diabetes mellitus, hypertension, ureteral stricture and hydronephrosis (198, 199). A study examining trends in kidney function described a rapid decline during the first postoperative year, followed by a gradual continuous decline (200). There are no similar studies in the context of CRC.

Internationally, serum-creatinine-based equations, particularly the CKD-EPI formula, are frequently used to estimate kidney function (167). Alternative methods, such as the Lund-Malmö equation incorporating cystatin C, has been proposed. This formula has superior sensitivity for detecting early renal impairment (201). As the Lund-Malmö equation has limited international adoption, kidney function in the present study was assessed using the CKD-EPI equation.

Regardless of the kidney function assessment model used, there is a clear need for structured long-term monitoring of kidney function in patients undergoing urinary tract resection for CRC. Surveillance should not be limited to patients undergoing total cystectomy, as approximately one-third of patients who underwent ureter resections also experienced kidney function decline. Further understanding of the mechanisms underlying this deterioration and the development of appropriate follow-up strategies are warranted.

Survival beyond the bladder

Long-term survival following partial cystectomy was comparable to total cystectomy, with no significant differences. Likewise, there were no significant differences in the rates of local or distant recurrence between the two approaches. These findings support previous reports suggesting that partial cystectomy may represent an oncologically safe option in selected patients with CRC (202-204). This is particularly relevant given the discrepancy in clinical and pathological overgrowth, higher perioperative morbidity after total cystectomy and the advantage of avoiding urinary diversion (197, 205).

However, these results must be interpreted in the context of the study design and included cohort. Even though the patient characteristics were largely comparable, there were important differences between the groups. Partial cystectomy was predominantly performed in patients with sigmoid colon cancer. In contrast, total cystectomy was more common in rectal cancer and T4 tumours. Rectal cancer often infiltrates the trigonum area while colon cancer, especially sigmoid cancer, affects the dome of the bladder (202, 206, 207). As a result, total cystectomy is more commonly performed in patients with rectal cancer (202, 206). Total cystectomy may also be required when inadequate residual bladder volume or impaired bladder function is anticipated.

Urinary bladder resections were more commonly performed in men than in women, particularly in patients with rectal cancer who underwent total cystectomy, as presented in *Paper IV* and previous publications (203, 207). This likely reflects anatomical differences, as the female reproductive organs provide partial protection against direct tumour invasion of the urinary bladder. However, the influence of sex on surgical decision-making and outcomes warrants further investigation.

Beyond tumour infiltration patterns, the literature provides limited guidance on how to select patients suitable for partial cystectomy. Palma et al. (208) proposed total cystectomy for recurrent disease and partial cystectomy for primary tumours when possible in LARC (208). In patients with microscopic bladder invasion, a higher incidence of urinary bladder recurrence has been reported with exposure of the bladder mucosa to tumour cells, even in R0 resections (202, 205). Intravesical saline

irrigation to reduce recurrence risk is suggested, further underscoring the importance of local factors in disease control (202). Comparable analyses could not be performed in the present study, as all cases in the SCRCR represent primary cancer and the anatomical site of local recurrence is not recorded. This represents an important limitation when interpreting recurrence patterns.

Another important finding was the significantly higher rate of local recurrence following ureter resection. This type of resection was predominantly performed in advanced and technically demanding disease, characterised by longer operative times, increased perioperative bleeding and higher proportions of cN+ and cM1 tumours. Cases of right-sided colon cancer were overrepresented in this group, suggesting potentially different tumour biology, including a possibly higher prevalence of MSI-H tumours. Such biological characteristics may influence responsiveness to systemic therapy and together with the increased surgical complexity, contribute to the observed results.

Over the study period, R0 resection rates increased even though patients presented with higher ASA scores and a greater proportion of T4 tumours. This development aligns with international trends and may reflect centralisation of care and increasing surgical expertise (51). Notably, survival rates in patients with urinary tract resections were comparable to those observed in patients undergoing CRC surgery without multivisceral resection, as presented in *Paper IV*, further underscoring the treatment progress.

For the first time, comprehensive national data are presented on urinary tract resections performed in patients with CRC in Sweden. Regional differences were identified, which are of relevance within the Swedish healthcare system. As expected, the number of performed procedures reflected regional population size, with more extensive surgery undertaken in regions with university hospitals. There were slightly higher rates of ureter resection in the Stockholm/Gotland region, likely reflecting referral routines and a concentration of particularly complex cases.

When selecting the appropriate method for the *Paper IV*, the SCRCR offered sufficient data to address the study aim, with well-established high validity for key categorical variables (71). However, several methodological challenges were encountered. The use of a free-text variable to capture multivisceral resections introduced heterogeneity in reporting, with considerable variation in language, terminology and level of detail. In some cases, anatomical structures inherently included in the primary resection, such as lymph nodes, were reported as separate organ resection. Furthermore, descriptions were not always sufficiently specific. For example, “cystectomy” was sometimes recorded without clarification regarding the location and extent. An additional limitation was the absence of information on the indication for multivisceral resection. Whether resections were due to direct tumour invasion, fibrosis, intraoperative findings or complications is not stated in the

registry. This limits the ability to distinguish oncologically necessary resections from precautionary or technically driven decisions.

Standardised procedure coding could potentially improve reporting quality. For instance, using procedure codes based on ICD-10 to specify performed resections may enhance consistency and facilitate accurate identification of relevant cohorts in future studies. Despite several limitations, the registry provides a valuable reflection of real-world practice and includes a representative population. This can be difficult to achieve in an RCT and is particularly valuable in research settings where alternative study designs may not be justifiable. In some situations, there may already be strong clinical confidence that one treatment is superior, making randomisation ethically challenging.

Conclusion

Extensive surgery for pelvic malignancies with perineal flap reconstruction is associated with high rates of short-term complications, whereas reoperation and mortality rates remain low. Flap-related complications are frequent but usually managed conservatively. Long-term follow-up demonstrates high overall QoL scores, preserved everyday mobility, and neovaginal measurements comparable to those of healthy individuals. However, patients of both sexes report high rates of sexual dysfunction and impaired sensitivity following reconstructions with a gluteal flap.

A GMS flap can be used to reconstruct the posterior vaginal wall in women undergoing perineal surgery. The use of this flap results in deeper neovaginal construction, with favourable cosmetic result and lower complication rates, compared to a VRAM flap.

Patients undergoing surgery for CRC with concomitant urinary tract resection have high rates of urological complications, particularly in the long term. The highest rates of postoperative complications, reoperations and need for nephrostomy and a decline in kidney function occurred following total cystectomy, compared with partial cystectomy and ureter resection.

Long-term survival was achievable through limited urinary tract resection in patients with CRC, with no significant differences in 5-year overall survival among patients undergoing total cystectomy, partial cystectomy or ureter resection. Rates of distant metastasis and local recurrence were also comparable between total and partial cystectomies, supporting the safety of partial resections when oncologically appropriate. There were significantly higher local recurrence rates in patients who underwent ureter resections, highlighting the complexity of these procedures.

Future perspectives

Advanced CRC treatment does not end with an R0 resection. Further progress lies in improving recovery, reducing morbidity and enhancing QoL. Most studies on QoL and functional outcomes rely on validated questionnaires which, despite their strengths, often lack sensitivity to individual experiences and temporal changes, and fail to capture the complexity of recovery. Complementary approaches are therefore needed to better understand recovery, including QoL, sexual dysfunction and functional outcomes.

One strategy is to combine multiple questionnaires covering similar domains, as applied in *Paper I* and previous studies (149). While this may capture different aspects of postoperative function, it also increases participant burden and may negatively affect inclusion and completion rates. Another approach is the use of mixed-method designs, incorporating qualitative data. Flexible interviews allow patients to raise relevant topics, providing deeper insight into lived experiences.

In a mixed-methods study by Rotaru et al. (161), patients undergoing PE described profound changes in identity, social roles, and intimate relationships (161). They simultaneously described a process of psychological adaptation, involving a readjustment of priorities in life and a shift towards valuing survival over physical integrity. These findings support the incorporation of psychological support and individualised preoperative counselling as key elements of care. Given the relatively small patient population in Sweden, qualitative research may represent a valuable contribution. In combination with international multicentre collaborations, such as the PelvEx Collaborative, research regarding QoL can be greatly improved.

Flap selection varies across centres and is influenced by defect size, previous treatments, donor-site availability, patient comorbidities and local expertise. To better define optimal reconstructive strategies, more studies, preferably RCTs, are needed. Such studies should include a range of resections and reconstructive options, also considering the place for using biological mesh and primary closure without reconstruction. Flap complications such as infections, dehiscence and necrosis are common and often managed conservatively. The potential benefit of early surgical debridement and its impact on healing require further investigation. Long-term complications such as perineal hernias, flap loss and recurrence within the flap are uncommon, with limited management experience. Standardised definitions and systematic documentation of complication severity, timing and

management may facilitate comparison between centres and support the development of evidence-based management strategies.

Findings suggest that partial cystectomies should be considered when feasible. However, selecting suitable patients remain challenging, requiring further investigation. Literature on management of urological complications in CRC patients with urinary tract resection remains scarce. Experiences from urothelial malignancy may offer guidance. However, there are differences in the extent of surgery and oncological treatment. Systematic collection of clinical experience is needed to support the development of treatment algorithms, particularly for ureteral strictures, a common indication for reinterventions. Multicentre studies and international registries are needed to identify predictive factors for urological complications. Such datasets should include conduit length and repeated measurements of renal function (141).

The findings suggest that patients may benefit from closer postoperative surveillance of urological complications, including biochemical monitoring. The current national follow-up programme for CRC in Sweden includes blood tests for CEA at 12 and 36 months after surgery (22). Expanding these to include renal function and metabolic parameters, such as creatinine and base excess, may represent a pragmatic step towards improved surveillance. In comparison, patients with urothelial malignancy undergoing radical cystectomy are closely monitored the first postoperative year (209). It is reported that close to half of all ureteral strictures are diagnosed during the first postoperative year (210). During the same period, a substantial decline in kidney function is described (200). It remains unknown whether the same complication pattern exists in our patient group or whether they would benefit from a similar follow-up.

The importance of organ preservation is likely to increase with advances in oncological treatment and surgical technique. Significant tumour downsizing and complete clinical responses may influence surgical planning and follow-up strategies. Therefore, future research should consider how evolving oncological strategies may modify the balance between radical surgery, organ preservation, and functional outcome. In this context, the place of extensive pelvic surgery, including PE, may change.

Improved survival following multimodal treatment may increase the number of patients living with the long-term consequences of extensive surgery. Tools to identify patients who benefit from such surgery remain limited. Further research, preferably through international collaborations, is needed to identify predictors of oncological and functional outcomes, as well as the ability to maintain good QoL. To generate the datasets needed to address these questions, the establishment of international registries is encouraged.

Populärvetenskaplig sammanfattning

Tjock- och ändtarmscancer är den tredje vanligaste cancerformen i Sverige och globalt. Hos vissa patienter växer tumören genom tarmväggen, och kan då spridas till närliggande organ. Detta kallas för lokalt avancerad tumörsjukdom. Behandlingen innefattar ofta en kombination av onkologisk och kirurgisk behandling, där tumören inklusive annan tumörinfiltrerande vävnad avlägsnas. I vissa fall medför detta att flertalet organ bortopereras, exempelvis urinblåsa, livmoder, slida, äggstockar, större blodkärl, delar av korsbenet samt vävnad i bäckenbotten och mellangården.

Efter sådan omfattande kirurgisk behandling behöver både anatomi och funktion återskapas. Majoriteten av patienterna behöver avföringsstomi efter tarmkirurgi. I de fall där urinblåsan avlägsnas behöver patienten även en stomi för urinavledning. Vid stora defekter i bäckenbotten och/eller mellangården kan vävnaden behöva rekonstrueras med hjälp av lambå, det vill säga transplantation av både muskel och hud från en annan del av kroppen. En lambå kan tas från bukväggen eller från sätesmuskeln.

Utvecklingen inom onkologisk förbehandling och kirurgisk teknik har inneburit förbättrad överlevnad hos patienter med avancerad tumörsjukdom. Samtidigt föreligger det fortsatt kunskapsluckor. Rekonstruktion av perineum vid ändtarmscancer är sparsamt studerat avseende komplikationer och livskvalitet. Detta gäller även patienter där urinblåsan eller urinledarna behöver tas bort, då det finns tydliga kunskapsluckor vad gäller överlevnad och komplikationer. Denna avhandling omfattar fem studier som syftar till att öka kunskapen inom dessa områden.

Studie I och II inriktar sig på patienter som till följd av tumörkirurgi behövt en lambå från sätesmuskeln för att återskapa perineum. I *studie I* fick patienterna besvara självskattningssenkäter om livskvalitet och sexuell funktion. Funktionella tester av nedre extremitet genomfördes och känseln undersöktes i operationsområdet efter sätesmuskellambå. Hos patienter där slidan hade återskapats uppmättes längd och vidgning med hjälp av silikonstavar.

Resultatet visade en god övergripande livskvalitet och bevarad funktion att utföra vardagliga aktiviteter. Måttan för rekonstruerad slida var jämförbara med dem hos friska individer. Nedsatt sexuell funktion var vanligt förekommande hos båda

könen. Nedsatt känsel i operationsområdet och på baksidan av låret observerades hos en betydande andel av patienterna med sätesmuskellambå.

I *studie II* samlades data genom journalgranskning om komplikationer inom 90 dagar efter kirurgi hos patienter med avancerad cancer i det lilla bäckenet. En fjärdedel av patienterna drabbades av komplikationer som krävde medicinsk behandling och/eller kirurgisk åtgärd. Andelen patienter som behövde opereras på nytt samt dödligheten var dock låg. Komplikationer var vanligare hos patienter som genomgått mer omfattande kirurgi där flera organ i lilla bäckenet avlägsnats jämfört med mer begränsade ingrepp. Lambårelaterade komplikationer var också vanliga. Majoriteten av komplikationer läkte dock utan behov av ytterligare kirurgi.

Studie III syftade till att beskriva en kirurgisk teknik för en modifierad sätesmuskellambå där den bakre slidväggen återskapas. Tekniken bygger på tre olika lambådeler. Den första delen går ut på att delvis fylla ut den djupa defekten genom att använda sätesmuskeln på ena sidan. Den andra delen återskapar den bakre slidväggen med en mjukdelslambå. Den tredje delen täcker den ytliga defekten med en mjukdelslambå från ena skinkan. Studien innehåller även en illustrationsserie som tydliggör den kirurgiska tekniken.

I *studie IV och V* studerades patienter där operationen för tjock- och ändtarmscancer även inkluderade urinvägarna. *Studie IV* jämför överlevnad och canceråterfall fem år efter kirurgi där hela urinblåsan, delar av urinblåsan eller urinledaren avlägsnats. Data hämtades från Svenska kolorektalcancerregistret, ett nationellt kvalitetsregister där samtliga fall av tjock- och ändtarmscancer i Sverige registreras.

Femårsöverlevnaden var likvärdig mellan grupperna vilket tyder på att det i vissa fall kan vara säkert att endast ta bort en del av urinblåsan. Vad gäller återfall sågs ingen skillnad i förekomsten av fjärrmetastaser mellan grupperna. Däremot hade patienter som genomgått kirurgi av urinledaren en högre andel lokala återfall. Detta speglar sannolikt en kombination av tumörens biologiska egenskaper och den kirurgiska komplexiteten.

Studie V är en samarbetsstudie där data från Skånes universitetssjukhus och Sahlgrenska universitetssjukhuset inkluderades. I studien samlades information om komplikationer upp till fem år efter urinvägskirurgi hos patienter med tjock- och ändtarmscancer, med särskilt fokus på urologiska komplikationer. Urologiska komplikationer var vanliga både på kort och lång sikt. På kort sikt var komplikationerna oftast milda och krävde sällan kirurgisk behandling. På längre sikt var urologiska komplikationer, framför allt förträngning av urinledaren, den vanligaste orsaken till kirurgisk åtgärd. Vidare drabbades en tredjedel av patienterna av en betydande försämring av njurfunktionen efter operationen. Patienter där hela urinblåsan tagits bort hade högre andel komplikationer, behov av ytterligare kirurgi och försämrad njurfunktion, jämfört med patienter som genomgått begränsad urinvägskirurgi.

Sammanfattningsvis tyder denna avhandling på att tumörkirurgi inte nödvändigtvis innebär försämrad livskvalitet eller vardaglig funktionsnivå. Bevarad känsel och god sexuell funktion är däremot inte en självklarhet, varför uppföljning och stöd efter kirurgi är särskilt viktigt för patientgruppen. I de fall där tumörkirurgin inneburit urinvägsengagemang har urologiska komplikationer varit vanligt förekommande. Däremot visar studierna att mer begränsad urinvägskirurgi inte behöver innebära ökad risk för canceråterfall eller försämrad överlevnad för utvalda patienter. Detta ställer därför krav på långsiktig uppföljning anpassad efter den typ av kirurgi patienten genomgått.

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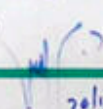
D/D	No.	Loc.	FE. Num.	C.T.	Investig.
Sun.				WHOEVER STANDS UNTIL THE END,	
Mon.				WILL TELL THE STORY WE DID WHAT WE COULD	
Tue.				✳ REMEMBER US ✳	
Wed.				 20/10/2023	

Figure 12: Dr Mahmoud Abu Nujaila's message on the planning whiteboard of the Limb Reconstructive Surgery unit of Al-Awda hospital Gaza, written on 20 October 2023. Source: Médecins Sans Frontières

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