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Loop-ileostomies and anastomotic leakage in anterior resections for rectal cancer

Munshi, Eihab Adil

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PO Box 117
221 00 Lund
+46 46-222 00 00

Loop-ileostomies and anastomotic leakage in anterior resections for rectal cancer

Eihab Adil Munshi



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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 18th of September at 13:00 in lokal Vallmon, ing 38, Skånes Universitetssjukhus Malmö.

Faculty opponent

Mima Abraham-Nordling, M.D., PhD, Associate Professor of Surgery,
Karolinska Institute, Sweden

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Abstract:

Background: Defunctioning loop ileostomy (DLI) is frequently used to mitigate the consequences of anastomotic leakage (AL) following anterior resection (AR) for rectal cancer. However, its routine use has been increasingly questioned due to its associated complications, low reversal rates, and impact on quality of life. This thesis examines outcomes of DLI-related dehydration under active surveillance, the impact of routine DLI use on AL rates, the efficacy of endoscopic vacuum therapy (EVT) for AL, and the influence of stoma reversal (SR) timing on postoperative complications.

Aim: This series of studies investigates the effect of active surveillance on DLI-related dehydration, national trends in DLI construction and AL occurrence, the comparative efficacy of EVT versus traditional drainage (TD) for AL, and the impact of time to SR on postoperative complications.

Methods: Four original studies utilized prospective and retrospective cohort data from medical records and the Swedish Colorectal Cancer Registry (SCRCR). Outcomes related to DLI complications, AL incidence, treatment modalities, and SR timing were analyzed using comparative and multivariable statistical methods.

Results: A surveillance program for DLI (n=87) between 2013 and 2015 reduced symptomatic dehydration (11% vs. 29%, $p < 0.05$) but did not significantly lower overall dehydration or readmission rates (Study I). Nationally, DLI use in AR increased from 71.6% to 76.7% between 2007-2009 and 2016-2018 ($p < 0.001$), yet the AL rate remained unchanged (9.2% vs. 8.2%), suggesting a limited effect of routine DLI on AL prevention (Study II). Among patients with AL (n=39) between 2009-2018, EVT (n=14) showed no superiority over TD (n=17) in clinical success (78.6% vs. 88.2%, $p=0.64$) or bowel continuity (50% vs. 64.7%, $p=0.28$) (Study III). In a cohort of 638 patients who underwent SR after AR, a longer time to SR was associated with higher rates of postoperative complications (median 10.2 vs. 7.3 months, $p<0.001$) and reoperations (11.1 vs. 7.6 months, $p=0.002$) (Study IV).

Conclusion: Active surveillance reduces symptomatic DLI-related dehydration but not overall dehydration or readmissions. Increasing routine DLI use did not reduce national AL rates. EVT and TD yield comparable outcomes concerning AL management. Delayed SR is independently associated with increased complications and reoperations, underscoring the importance of timely reversal when feasible.

Key words: Rectal cancer, anterior resection, anastomotic leak, defunctioning loop ileostomy, stoma reversal, complications, surveillance, endoscopic vacuum therapy

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*To those who endure unseen struggles with quiet courage and
unwavering patience. May their strength be recognized, even
when their burdens are not.*

This work is dedicated to them.

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Abbreviations

AJCC	American Joint Committee on Cancer
AKI	Acute kidney injury
AL	Anastomotic leakage
APR	Abdominoperineal resection
AR	Anterior resection
ASA	American Society of Anesthesiologists
BMI	Body mass index
BRAF	B-Raf proto-oncogene
CCI	Charlson Comorbidity Index
CI	Confidence interval
CRC	Colorectal cancer
CRM	Circumferential resection margin
CT	Computed tomography
DFS	Disease-free survival
DLI	Defunctioning loop ileostomy
DS	Defunctioning stoma
EMVI	Extramural vascular invasion
EORTC	European Organisation for Research and Treatment of Cancer
ESD	Endoscopic submucosal dissection
ESMO	European Society for Medical Oncology
EVT	Endoscopic vacuum therapy
FAP	Familial adenomatous polyposis
HOS	High-output stoma
HR	Hazard ratio
IBD	Inflammatory bowel disease
IQR	Interquartile range
ISREC	International Study Group of Rectal Cancer
KDIGO	Kidney Disease: Improving Global Outcomes

KRAS	Kirsten rat sarcoma viral proto-oncogene
LAR	Low anterior resection
LARC	Locally advanced rectal cancer
LARS	Low anterior resection syndrome
LCCRT	Long-course chemoradiotherapy
LR	Local recurrence
MDT	Multidisciplinary team
MMR	Mismatch repair
MRF	Mesorectal fascia
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NCCN	National Comprehensive Cancer Network
OR	Odds ratio
OS	Overall survival
pCR	Pathological complete response
PET	Positron emission tomography
PME	Partial mesorectal excision
RAPIDO	Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation
RCT	Randomised controlled trial
SCRCR	Swedish Colorectal Cancer Registry
SCRT	Short-course radiotherapy
SPSS	Statistical Package for the Social Sciences
SR	Stoma reversal
TAMIS	Transanal minimally invasive surgery
TME	Total mesorectal excision
TNM	Tumor, Node, Metastasis
TNT	Total neoadjuvant therapy

List of Papers

Paper I

Munshi E, Bengtsson E, Blomberg K, Syk I, Buchwald P. *Interventions to reduce dehydration related to defunctioning loop ileostomy after low anterior resection in rectal cancer: a prospective cohort study*. ANZ Journal of Surgery. 2020. doi:10.1111/ans.16258

Paper II

Munshi E, Lydrup ML, Buchwald P. *Defunctioning stoma in anterior resection for rectal cancer does not impact anastomotic leakage: a national population-based cohort study*. BMC Surgery. 2023;23:167. doi:10.1186/s12893-023-01998-5

Paper III

Munshi E, Dahlbäck C, Johansson S, Lydrup ML, Jutesten H, Buchwald P. *Long-term outcomes of endoscopic vacuum therapy and transanal drainage for anastomotic leakage after anterior resection*. In Vivo. 2022;36:2275–2278. doi:10.21873/invivo.12956

Paper IV

Munshi E, Segelman J, Matthiessen P, Park J, Rutegård M, Sjöström O, Jutesten H, Lydrup ML, Buchwald P; on behalf of the RectoLeak Study Group. *Increased risk of postoperative complications after delayed stoma reversal: a multicenter retrospective cohort study on patients undergoing anterior resection for rectal cancer*. International Journal of Colorectal Disease. 2025;40:36. doi:10.1007/s00384-025-04831-y

Abstract

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Introduction

Global and national epidemiology of rectal cancer

Colorectal cancer (CRC) represents a significant global health burden, characterized by high incidence and mortality rates, with distinct patterns in disease presentation. Globally, approximately 60–65% of CRC cases are diagnosed at local or regional stages (Stage I–III), while 20–25% present with metastatic disease (Stage IV), contributing to substantial mortality (1). While rectal cancer can present acutely as an emergency (e.g., due to acute malignant obstruction or perforation), emergency resection is rarely performed. Instead, standard clinical practice prioritizes acute stabilizing maneuvers to allow for formal staging and multidisciplinary optimization before definitive oncological surgery, as immediate emergency resections are associated with significantly higher postoperative morbidity and mortality (2).

Historically, CRC predominantly affects individuals aged 50 or older. According to GLOBOCAN estimates, CRC accounted for over 1.9 million new cases and approximately 935,000 deaths worldwide in 2020, with rectal cancer contributing roughly 730,000 new cases and over 340,000 deaths by 2022 (1,3). In Sweden, national registry data from 2006 to 2016 reveal a slight decline in overall CRC incidence (−0.55% per year). However, an increase in rectal cancer among adults younger than 50 years has emerged, with over 60% of these cases diagnosed at advanced stages (Stage III or IV), highlighting a shift in disease demographics (4). This rise in early-onset rectal cancer is mirrored in other Western countries, potentially driven by lifestyle factors such as poor diet, physical inactivity, and obesity (5).

In contrast, CRC incidence has historically been lower in Asia than in Western nations. However, recent decades have shown a notable increase in Asian countries, particularly in rapidly developing regions, which is speculated to result from the adoption of Westernized lifestyles, including high-fat diets and reduced physical activity (6). Tailored early detection strategies and optimized treatment pathways are critical to improving outcomes. Understanding these global and regional epidemiological trends is vital for shaping public health policies and advancing rectal cancer research.

Molecular pathogenesis and genetic risk

The pathogenesis of rectal cancer involves a series of molecular alterations that disrupt normal cell regulation, leading to uncontrolled proliferation and malignancy. While rectal and colonic tumors share many features, identifying specific molecular mechanisms is critical for clinical decision-making and therapeutic targeting.

The adenoma–carcinoma sequence, first proposed by Fearon and Vogelstein, remains the cornerstone model of colorectal carcinogenesis. It describes a stepwise accumulation of genetic mutations transforming normal epithelium into carcinoma, primarily driven by chromosomal instability (CIN) (7). CIN is characterized by widespread genomic alterations, including aneuploidy, deletions, and translocations.

One of the earliest events in this sequence is the inactivation of the adenomatous polyposis coli (APC) gene, a tumor suppressor. Loss of APC function deregulates the Wnt/ β -catenin signaling pathway, promoting cellular proliferation and resistance to apoptosis (8). Inherited APC mutations are the hallmark of familial adenomatous polyposis (FAP), a hereditary syndrome significantly increasing CRC risk.

Subsequent mutations often involve the KRAS oncogene, present in approximately 40% of CRCs. KRAS mutations lead to constitutive activation of signaling pathways, such as MAPK and PI3K, which enhance tumor growth and survival (9). These mutations also confer resistance to anti-Epidermal growth factor receptor monoclonal antibodies, making KRAS genotyping essential for treatment planning in metastatic CRC.

Later in the carcinogenic process, TP53 mutations typically occur. Known as the "guardian of the genome," TP53 is crucial for DNA repair and apoptosis. Its inactivation allows survival of genomically unstable cells, contributing to tumor progression and poor prognosis (10).

While CIN accounts for most CRCs, approximately 15% arise from microsatellite instability (MSI) caused by defects in the DNA mismatch repair (dMMR) system. Loss of MMR function leads to replication errors in microsatellite regions, resulting in a hypermutated phenotype (11). MSI-high tumors exhibit distinct biological behavior, with better prognosis in early stages and increased sensitivity to immune checkpoint inhibitors due to elevated neo-antigen levels.

Hereditary cancer syndromes

Though most rectal cancers are sporadic, familial clustering occurs in up to 20% of cases. However, well-characterized hereditary syndromes account for less than 5% of all CRCs. All patients with early-onset colorectal cancer or a suggestive family

history should undergo genetic counseling and multigene panel testing to identify hereditary syndromes. The two most significant syndromes are Lynch syndrome and FAP (12,13).

Lynch syndrome, the most common hereditary CRC syndrome, is caused by germline mutations in MMR genes (MLH1, MSH2, MSH6, PMS2). Affected individuals face a markedly increased lifetime risk of CRC, often developing tumors at a younger age, along with elevated risks for endometrial, gastric, urothelial, and ovarian cancers(12). FAP, in contrast, results from germline APC mutations, leading to the early development of hundreds to thousands of adenomatous polyps in the colon and rectum. Without prophylactic colectomy, nearly all patients develop CRC by mid-adulthood(13). Other less common hereditary syndromes include MUTYH-associated polyposis, Juvenile polyposis syndrome, and Peutz-Jeghers syndrome(13). These syndromes, though rare, contribute to CRC risk through distinct genetic mechanisms, necessitating targeted screening and management strategies.

Recognizing these hereditary syndromes is critical for implementing tailored surveillance protocols, risk-reducing surgery, and genetic counseling for family members. Integrating molecular diagnostics into routine care enhances personalized risk assessment and supports precision medicine in the management of CRC.

Environmental and lifestyle risk factors

Although inherited predispositions explain a portion of rectal cancer cases, much of the risk is shaped by everyday exposures. Diet, physical activity, body weight, and habits like smoking or alcohol use can strongly influence disease development. These factors, unlike genetics, are modifiable, and targeting them offers real potential for prevention. Often, they work together with genetic traits to either amplify or reduce risk.

Diet and nutrition

Among environmental exposures, diet is one of the most closely studied. High consumption of red and processed meats—such as beef, pork, sausages, or deli meats—has been consistently linked to a higher risk of colorectal cancer (14). This may be due to the formation of carcinogenic compounds like heterocyclic amines or N-nitroso compounds during cooking, especially at high temperatures. Heme iron, abundant in red meat, may also promote oxidative damage in the bowel lining (15).

On the other hand, eating more fruits, vegetables, and whole grains appears to lower the risk (16). Dietary fiber supports healthy bowel movements, reduces exposure to potential carcinogens, and nourishes beneficial gut bacteria. These findings support public health guidance that emphasizes a plant-based, fiber-rich diet for cancer prevention.

Physical activity and anthropometric

A sedentary lifestyle is another well-established risk factor. People who engage in regular physical activity tend to have a lower risk of CRC, regardless of their weight. The protective effect may be attributed to improved blood sugar regulation, reduced inflammation, enhanced immune surveillance, and faster gut transit time (17).

Obesity, particularly when fat is concentrated around the abdomen, is also associated with a higher risk. This is thought to be linked to chronic inflammation, hormone imbalances, and insulin resistance, all of which may encourage cancer development (18). Adult height has also been associated with an increased risk of colorectal cancer, with meta-analytic data showing that each 10-cm increase in adult height is associated with an approximately 14% higher CRC risk (19).

Alcohol and smoking

Alcohol, heavy, long-term use, is another modifiable risk factor. Alcohol breaks down into acetaldehyde, a toxic substance that can damage DNA. It also disrupts folate metabolism, which is important for cell repair and replication (20).

Smoking is commonly tied to lung disease, but its effect on CRC should not be underestimated. Chemicals from tobacco can reach the colon through the bloodstream, damaging cells and promoting mutations. Risk increases with both the amount and duration of smoking (21).

Inflammatory bowel disease (IBD)

Patients with chronic inflammatory conditions, such as IBD, face an elevated risk of CRC, particularly with long disease duration, extensive colonic involvement, sustained inflammatory activity, and coexisting primary sclerosing cholangitis (22). Chronic mucosal inflammation contributes to inflammation-associated carcinogenesis through repeated epithelial injury, dysplasia, and genomic instability (22). Notably, CRC associated with IBD tends to develop at a younger age (median 46–66 years vs. 67–72 years for sporadic CRC) and is often associated with poorer outcomes, including lower survival rates due to aggressive histological features and reduced curative resection rates (23). Consequently, patients with colonic IBD

undergo regular colonoscopy surveillance with biopsies to detect precancerous dysplasia early, guided by evidence-based protocols (24).

The gut microbiome

In recent years, scientists have begun to explore how the bacteria living in our intestines may play a role in CRC. An imbalance in these microbes, known as dysbiosis, can lead to inflammation, the production of harmful compounds, and changes in the immune system that may favor cancer growth (25).

Although research is ongoing, the microbiome may one day become a target for both prevention and treatment, through diet, probiotics, or other interventions.

Overall, the development of rectal cancer is rarely due to a single factor. It's the accumulation and sometimes the combination of environmental, lifestyle, and genetic influences that shape a person's risk. While no one can change their genetic background, changes in diet, activity, and other behaviors offer a real chance to reduce the burden of disease.

Diagnostic and staging strategies

Accurate diagnosis and staging are critical for effective rectal cancer treatment, guiding decisions from surgery to chemotherapy and directly influencing outcomes. Most patients present with rectal bleeding, altered bowel habits, or persistent abdominal discomfort, while others are identified through CRC screening. Early detection via screening using fecal immunochemical testing followed by colonoscopy when indicated is associated with lower-stage disease and improved survival. In Sweden, a national FIT-based screening program was introduced in 2019, offering biennial testing to all individuals aged 60-74 years (26).

Confirming the diagnosis

Patients with symptoms raising suspicion of CRC, such as visible rectal bleeding, are initially assessed according to the SVF pathway with history, rectal palpation, and primarily rectoscopy. Colonoscopy is subsequently used to confirm the diagnosis, obtain a biopsy, and assess the remaining colon for synchronous lesions (27). A biopsy confirms malignancy and provides information on tumor grade, enabling testing of molecular markers (MSI, KRAS, BRAF, PIK3CA) that may have implications for treatment (28). Advances in next-generation sequencing (NGS) have further expanded the scope of molecular profiling, allowing comprehensive tumor characterization to guide personalized treatment strategies

(29). Full colonoscopy is also essential for detecting synchronous lesions, which occur in approximately 3–5% of cases (30). For rectal cancer, it is essential to perform a rigid sigmoidoscopy to determine tumor height (31). Digital rectal examination is also important to evaluate sphincter function and possible involvement of other organs (32).

The role of MRI

Once the diagnosis is confirmed, the next step is to determine how far the rectal cancer has spread within the pelvis. Pelvic MRI is the imaging method of choice for this. It provides detailed anatomical views, helping clinicians plan the most appropriate treatment. MRI gives key information such as: tumor depth (T-stage), how far the tumor has grown into or through the rectal wall, mesorectal fascia involvement (CRM), and whether the tumor threatens the surgical margin, extramural vascular invasion (EMVI), cancer within blood vessels, associated with a poorer prognosis, tumor deposits, discrete tumor nodules in perirectal fat, linked to increased recurrence risk, regional lymph node status, involvement of mesorectal or lateral nodes.

These details help identify tumors that may benefit from neoadjuvant treatment before surgery. In particular, MRI's ability to predict involvement of CRM has led to more tailored, evidence-based planning (33).

Systemic staging: Computed tomography (CT), and Positron Emission Tomography (PET)

To assess for spread beyond the pelvis, chest, and abdominal CT scans are performed. The liver, lungs, and para-aortal lymph nodes are common sites for metastases. Identifying distant disease is critical, as it distinguishes patients with oligometastatic and potentially curable disease (e.g., single liver metastasis) from those with widespread metastases, where treatment proceeds with palliative intent (32). In certain situations, particularly when findings are uncertain or there are high-risk features, a Positron Emission Tomography and CT (PET-CT) scan may be added. However, due to its limitations in detecting small lesions and the cost involved, it's not used routinely. Liver MRI may be added to further characterize indeterminate liver lesions on CT or when liver metastases appear potentially resectable (34).

Multidisciplinary team (MDT) meetings

After staging, all patients are reviewed in a multidisciplinary team meeting. These sessions include input from colorectal surgeons, oncologists, radiologists, and

pathologists. The purpose is to pool expertise and agree on the most suitable treatment plan. The MDT approach is now standard in rectal cancer care, as it has shown significant improvement in overall survival for CRC patients, especially those with stage III and IV disease (35). It allows for personalized decisions whether the patient undergoes surgery directly, receives chemoradiotherapy, or follows a total neoadjuvant therapy strategy (34).

TNM system and post-treatment staging

The TNM classification by the AJCC is a cornerstone for staging, categorizing disease based on tumor size and depth (T), lymph node involvement (N), and distant metastases (M) (36). Clinical TNM (cTNM) relies on pre-treatment imaging assessments, including pelvic MRI for local staging and CT for distant staging. Endoscopy primarily confirms the diagnosis and excludes synchronous lesions, while endoscopic ultrasound may contribute to local staging in selected cases. Pathological TNM (pTNM), based on surgical specimen analysis, provides the most accurate stage for prognosis and treatment planning. Post-neoadjuvant therapy staging uses the yTNM prefix to reflect tumor response (e.g., ypT0N0 indicates a complete pathological response with excellent outcomes). Less commonly, rTNM denotes staging for recurrent tumors, and aTNM is used for autopsy findings, but these are rarely applied in routine management (36). The definitions of the T, N, and M categories are summarized in Table 1A, while the corresponding AJCC stage groupings are presented in Table 1B.

Table 1. TNM Classification of Rectal Cancer (AJCC 8th Edition, 2017) (36)**Part A: TNM Category Definitions**

Category	Stage	Description
T – Primary Tumor	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ: intramucosal (involvement of lamina propria only)
	T1	Tumor invades submucosa
	T2	Tumor invades muscularis propria
	T3	Tumor invades through muscularis propria into pericorectal tissues
	T4a	Tumor penetrates to the surface of the visceral peritoneum
	T4b	Tumor directly invades or is adherent to other organs or structures
N – Regional Lymph Nodes	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1a	Metastasis in 1 regional lymph node
	N1b	Metastasis in 2–3 regional lymph nodes
	N1c	Tumor deposit(s) in subserosa, mesentery, or non-peritonealized pericolic/perirectal tissues without regional nodal metastasis
	N2a	Metastasis in 4–6 regional lymph nodes
M – Distant Metastasis	N2b	Metastasis in 7 or more regional lymph nodes
	M0	No distant metastasis
	M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, non-regional lymph node)
	M1b	Metastasis in more than one organ/site or the peritoneum
	M1c	Metastasis to the peritoneal surface alone or with other site/organ metastases

Part B: Anatomic Stage/Prognostic Groups

Stage	T	N	M
0	Tis	N0	M0
I	T1–T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1–T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3–T4a	N1/N1c	M0
	T2–T3	N2a	M0
IIIC	T1–T2	N2b	M0
	T4a	N2a	M0
	T3–T4a	N2b	M0
	T4b	N1–N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

Abbreviations: T, tumor; N, node; M, metastasis; Tis, tumor in situ.

Neoadjuvant therapy in rectal cancer

Over the past two decades, neoadjuvant therapy has become a cornerstone in the treatment of locally advanced rectal cancer (LARC). Although definitions vary, LARC generally includes tumors with high-risk features such as T3–4 tumors, nodal involvement, EMVI, mesorectal fascia involvement (MRF+), or low tumors requiring sphincter preservation (32). While early-stage rectal cancers (T1–2, N0) are generally managed with surgery alone, high-risk tumors may benefit from neoadjuvant therapy by reducing local and distant recurrence and, in selected cases, improving the possibility of radical resection or sphincter preservation (32,37,38).

Long-course chemoradiotherapy (LCCRT): the traditional route

Historically, long-course chemoradiotherapy has been the standard preoperative treatment for locally advanced rectal cancer. It typically involves 50–50.4 Gy delivered in 25–28 fractions (1.8–2 Gy per fraction) over 5–6 weeks, with concurrent capecitabine or 5-fluorouracil (5-FU) to enhance radiosensitivity, followed by total mesorectal excision (TME) 4–8 weeks after completion to allow for tumor regression (32,37). LCCRT reduces local recurrence (LR) rates and achieves a pathological complete response (pCR) in 15–20% of patients, a strong prognostic marker for long-term survival (37,39,40). LCCRT is generally well tolerated with manageable toxicity profiles, though common side effects include fatigue, diarrhea, and skin irritation, with potential long-term effects such as bowel or sexual dysfunction impacting quality of life (32,37).

Short-course radiotherapy (SCRT): an alternative

An alternative strategy, SCRT (25 Gy in 5 fractions over 5 consecutive days), achieves local control and overall oncological outcomes comparable to those of long-course chemoradiotherapy, while significantly reducing treatment duration (41). It may be followed by either immediate surgery within approximately 1 week after completion of radiotherapy or delayed surgery, generally performed after an interval of 4–8 weeks to allow for tumor regression (42). More recently, SCRT followed by systemic consolidation chemotherapy has become an important platform for total neoadjuvant therapy (TNT), as discussed in the following section (43,44).

Total neoadjuvant therapy (TNT): changing the sequence

TNT has transformed rectal cancer management by delivering all planned chemotherapy and radiotherapy before surgery, enhancing treatment completion

rates and addressing micro metastases early (38,43). The RAPIDO trial employed SCRT (25 Gy in 5x5 Gy fractions) followed by six cycles of CAPOX or nine cycles of FOLFOX4, then TME, demonstrating higher pCR rates (28% vs. 14%) and reduced distant metastases (20% vs. 27%) compared to standard LCCRT, with improved DFS OR 0.75 (95% CI 0.58–0.97; $p=0.034$) (43). Long-term follow-up revealed a higher LR rate (10% vs. 7%) and surgical challenges in the experimental arm, such as increased fibrosis, with non-responders facing poor outcomes (median survival 1.6 years post-local failure), underscoring the need for careful patient selection and early identification of non-responders (45). The PRODIGE 23 trial used induction FOLFIRINOX (six cycles) followed by LCCRT (50 Gy with capecitabine) and TME, nearly doubling pCR rates (28% vs. 12%) and improving DFS (HR 0.75) compared to LCCRT alone (38). In Sweden, the LARCT-US trial established SCRT (5x5 Gy) followed by four cycles of CAPOX as the standard neoadjuvant protocol, achieving pCR rates of 20–25% and improved DFS, aligning with RAPIDO's benefits but tailored to Swedish practice (44). The sequence of TNT, whether induction (chemotherapy first), particularly when metastatic disease is prominent to address systemic spread early, or consolidation (chemotherapy after radiotherapy), remains under investigation, with ongoing trials like NRG-GI002 exploring immunotherapy integration (e.g., pembrolizumab) to enhance cCR rates (46–48).

Guidelines and clinical use

International guidelines, including European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN), recommend TNT as a preferred strategy for patients with high-risk locally advanced rectal cancer, particularly when features such as threatened mesorectal fascia, extramural vascular invasion, extensive nodal disease (cN2), or lateral lymph node enlargement are present (46,49). In Sweden, the national care program similarly endorses TNT in this setting. The sequencing of TNT remains an area of active investigation, with current evidence not demonstrating clear superiority of either approach; the choice is therefore individualized based on tumor response, patient tolerance, and institutional experience (50).

Regarding adjuvant chemotherapy, the Swedish national care program recommends a selective and individualized approach. Patients who have undergone surgery without neoadjuvant treatment, or after SCRT alone, may be considered for adjuvant chemotherapy using criteria like those applied in colon cancer. In contrast, patients who have completed TNT are not recommended adjuvant chemotherapy, as the full systemic treatment effect is considered to have been achieved preoperatively (50).

Watch-and-Wait: Organ preservation

Organ preservation is an evolving strategy in rectal cancer management, aiming to maintain rectal function and quality of life without compromising oncologic outcomes (51). It can be pursued as an upfront intentional strategy or as an opportunistic response to unexpected clinical complete response (cCR) after neoadjuvant therapy. Patients achieving cCR may be offered a watch-and-wait approach, involving close surveillance instead of immediate surgery (51). The OPERA trial compared TNT with a contact X-ray brachytherapy boost to standard LCCRT, achieving cCR in 36% vs. 21% of patients, supporting organ preservation in responders (52). The GRECCAR-2 trial evaluated standard LCCRT vs. intensified LCCRT to induce cCR, with 20% of patients achieving organ preservation, though no significant difference in cCR rates was observed between arms (53).

Surveillance protocols typically include digital rectal examination, endoscopy, and MRI scans to monitor for tumor regrowth (54,55). Risks include distant metastasis (~10%) and local regrowth (15–25%), with higher regrowth rates in initial T3-4 tumors. Salvage surgery for regrowth achieves R0 resection in approximately 90% of cases, ensuring oncologic safety (54). For patients with early-stage rectal cancer in whom organ preservation is planned from the outset as an intentional strategy, structured programs such as the STAR-TREC trial provide a defined surveillance framework (56). In Sweden, the prospective WoW study has characterized outcomes in patients with opportunistic watch-and-wait following clinical complete response to neoadjuvant therapy (57), and Watch-and-wait approaches are carried out within study protocols (50).

Impact on surgery

The move toward more intensive neoadjuvant treatment has also shifted the surgical landscape. Surgeons now frequently face questions about the best timing for resection, whether to create a protective stoma, and how aggressive the dissection should be during total mesorectal excision. Greater tumor regression also opens more opportunities to preserve the sphincter and avoid a permanent colostomy. The involvement of a multidisciplinary team is critical in shaping these decisions. Choosing the best neoadjuvant strategy depends not just on the tumor and its staging, but also on the patient's preferences and the institution's capabilities. With ongoing trials and refinements in treatment protocols, this remains one of the most dynamic and evolving aspects of rectal cancer care.

The timeline of rectal cancer surgery techniques

Early twentieth century: The Miles revolution (1908-1940s)

Despite significant advancements in chemoradiation therapy and its increasingly promising outcomes, radical tumor resection remains central to improving oncological outcomes in rectal cancer (58). Over time, rectal cancer surgery has evolved from procedures focused mainly on achieving complete tumor resection toward approaches that integrate oncological radicality with preservation of anal function, sphincter integrity, autonomic nerves, and quality of life (59).

At the dawn of the twentieth century, William Ernest Miles revolutionized rectal cancer surgery by introducing abdominoperineal resection (APR). This technique represented a significant advancement over the perineal and sacral resections practiced during the late eighteenth century (59). The APR procedure involves en bloc removal of the rectum, anus, a portion of the sigmoid colon, and associated mesentery through combined abdominal and perineal incisions. This approach was informed by Miles' astute observations from autopsy examinations, which revealed that tumor recurrence typically follows a radial spreading pattern through the lymph nodes and peritoneum surrounding the primary lesion. Consequently, the APR technique was designed to achieve en bloc resection of both the tumor and surrounding lymphatic structures, effectively addressing what Miles conceptualized as cylindrical tumor spread. Nevertheless, while this extensive resection strategy enhanced oncological outcomes, it inevitably disrupts bowel continuity and necessitates a permanent colostomy.

Mid-twentieth century: The quest for sphincter preservation (1940s-1970s)

Throughout the mid-20th century, surgical innovation increasingly focused on developing sphincter-preservation procedures, particularly for tumors in the upper and middle thirds of the rectum, where AR was theoretically feasible while maintaining the integrity of the anal sphincter complex (59). This progressive strategy was supported by an evolving understanding of rectal cancer lymphatic spread patterns, which challenged Miles' original cylindrical concept. Pathological investigations revealed that the predominant lymphatic drainage occurs in a proximal and parallel direction relative to the primary tumor, rather than following the previously assumed radial distribution pattern (60).

Following studies demonstrated that reduced distal resection margins of 2 cm yielded comparable local control rates and long-term survival outcomes to the traditionally advocated 5 cm margins, thereby expanding the technical feasibility of sphincter-preserving procedures (61). The introduction of stapling devices revolutionized anastomotic techniques in the deep pelvis and lower rectum. The implementation of mechanical bowel preparation and prophylactic antibiotic regimens enhanced perioperative safety profiles (62). The convergence of these

pathological insights with technological advances enabled surgeons to perform low colorectal and coloanal anastomoses in cases that would have previously been considered appropriate only for APR.

The TME era: anatomical and oncological precision

The seminal contribution of Richard Heald marked a revolutionary advancement in achieving substantial oncological outcomes. The principles of total mesorectal excision (TME), which appeared in the early 1980s, represented a profound understanding of rectal cancer embryology and anatomy, emphasizing sharp dissection along embryological fascial planes to achieve complete removal of the rectum and its surrounding mesorectal envelope intact (63). With TME, the LR rate significantly decreased approximately 6% in the Stockholm TME project, thereby establishing a new gold standard for oncologic precision in rectal cancer surgery (64).

Nerve-sparing

The functional comorbidity associated with radical pelvic surgery prompted the development of nerve-sparing techniques during the late 1980s and early 1990s. Pioneering work by Hojo and colleagues, followed by Moriya and colleagues, addressed and validated the meticulous technique for identifying and preserving pelvic autonomic nerves during TME, which reduces postoperative sexual and urinary dysfunction without compromising oncological outcomes (65,66). Nerve-sparing TME and pelvic autonomic nerve preservation were introduced to reduce urinary and sexual morbidity without compromising the oncological principles of mesorectal excision. Early functional studies reported relative preservation of voiding function and postoperative erectile capacity in selected male patients, although validated scores still showed measurable declines in sexual and urinary function (67,68).

The arrival of minimally invasive access

The laparoscopic era commenced in the early 1990s, offering reduced operative morbidity and enhanced recovery. Oncological equivalence with open surgery was demonstrated by the COLOR II trial, with 3-year LR rates of 5.0% in both groups (69). Robotic surgery was subsequently introduced to overcome the technical limitations of laparoscopic access in the confined pelvic space. Although the landmark ROLARR trial did not demonstrate a statistically significant reduction in conversion rates (8.1% vs. 12.2%; $p=0.16$), a growing body of evidence from meta-analyses has consistently shown that robotic surgery reduces conversion rates and intraoperative blood loss, albeit with longer operative times and higher costs (70,71). More recently, the REAL randomized trial reported a significantly lower 3-year LR rate (1.6% vs. 4.0%; HR 0.39; $p=0.03$) and improved disease-free survival

(87.2% vs. 84.3%; HR 0.67; $p=0.04$) with robotic surgery, though overall survival did not differ significantly (72).

Contemporary innovations and challenges

The advent of transanal total mesorectal excision (TaTME) in the 2010s addressed the challenges of operating on bulky low rectal tumors, particularly in patients with a narrow male pelvis, where laparoscopic dissection proves technically demanding. Early reports demonstrated promising specimen quality with high rates of complete TME (>90%) and negative CRM, leading to international adoption of the technique (73). However, reports of atypical multifocal LR patterns and increased urethral injury rates led several major centers to pause or critically reevaluate their TaTME programs (74). Although recent long-term data demonstrate comparable 3-year disease-free survival rates (82.1% versus 79.4%, in TaTME and Laparoscopic TME groups, respectively), these findings underscore the critical need for rigorous case selection and standardized training to maintain oncological safety (75).

Beyond radical resection, this era is increasingly defined by the pursuit of organ preservation, aiming to avoid the morbidity of TME while maintaining oncologic safety. This has led to the refinement of established transanal local excision techniques. Platforms such as Transanal Endoscopic Microsurgery and the more accessible Transanal Minimally Invasive Surgery (TAMIS) have been optimized for precise local excision of early-stage (cT1) rectal cancers with favorable histology (76). Endoscopic submucosal dissection (ESD) is a modality for superficial rectal neoplasms (Tis and cT1a), offering en bloc resection with R0 rates exceeding 90% in experienced centers (77). Comparative data suggest that ESD achieves oncological adequate resection with a favorable morbidity profile relative to surgical alternatives, though its application requires careful patient selection based on lesion depth, differentiation, and the absence of lymph vascular invasion (78).

Furthermore, these techniques are now being explored for patients with a significant response to neoadjuvant therapy. For tumors that achieve a good clinical response after treatment, local excision can serve as a definitive "surgical biopsy" to confirm a pathological complete response (ypT0). This strategy, explored in landmark trials like the ACOSOG Z6041, offers a middle ground between radical surgery and a "watch-and-wait" approach. The ACOSOG Z6041 trial reported that among patients who had a good clinical response and underwent local excision, 44% achieved a pathological complete response (ypT0) and could avoid TME (79). However, this approach requires careful patient selection. If residual cancer (ypT1-2) is found in the specimen, the 5-year risk of LR can be high (10-17%), often necessitating completion of TME (80).

Anastomotic leakage in rectal cancer surgery

AL stands as the most critical and extensively studied complication following AR for rectal cancer, fundamentally influencing both immediate and long-term patient outcomes. The occurrence of AL is a major determinant of short-term morbidity and mortality while exerting profound effects on long-term oncological outcomes, including LR rates, as well as functional outcomes such as bowel function and quality of life (81–83). Despite significant improvements in surgical techniques and perioperative care protocols over the decades, the overall incidence of AL has shown only modest improvements, remaining a persistent clinical challenge (84). Reported rates still range from 3% to over 20% in some series, with most large studies citing rates between 8% and 12% (85).

These figures are likely to underestimate the AL rate because they are affected by the duration of postoperative surveillance. Registry-based data from southern Sweden, encompassing a median follow-up of 87 months, demonstrated that late-presenting leakage, defined as AL occurring after hospital discharge, accounted for 51% of all AL cases (86). Corroborating this, a large single-center cohort study similarly reported that late AL, defined as onset beyond 30 days, comprised 48% of all AL cases, with 24% diagnosed more than one year postoperatively (87). Collectively, these findings highlight that studies with short follow-up underestimate the true burden of anastomotic leakage.

Interpretation of reported incidence figures is further complicated by the historical absence of a universally accepted definition. Before 2010, heterogeneous criteria were in use, including those from the Dutch TME trial (88). The landmark proposal by the International Study Group of Rectal Cancer (ISREC) in 2010 addressed this by defining AL as "a defect of the intestinal wall integrity at the colorectal or coloanal anastomotic site leading to a communication between the intra- or extraluminal compartment," and by introducing a three-tier grading system (89). Grade A denotes asymptomatic leakage requiring no active intervention; Grade B encompasses symptomatic leakage managed non-operatively (e.g., percutaneous drainage or endoscopic treatment); and Grade C denotes leakage necessitating surgical re-intervention. This standardized framework has substantially improved the consistency of reporting and the comparability of outcomes across institutions.

Risk factors for anastomotic leakage

Numerous patient-related, tumor-related, and surgery-related factors have been identified as contributing to the risk of AL, with recent evidence providing a refined understanding of their relative importance. Understanding these factors is fundamental to risk stratification and the implementation of preventive measures for AL.

Patient-related factors represent the most significant category of risk determinants, with recent multicentric studies highlighting nutritional status as the predominant predictor. Hypoalbuminemia has emerged as the strongest independent risk factor for AL, with an odds ratio (OR) of 22.2 (95% CI: 11.5-42.9), substantially exceeding the predictive value of other traditional factors (90). Male gender is consistently identified as an independent risk factor across multiple studies, possibly attributed to anatomical differences in the male pelvis and technical challenges associated with narrow pelvic dimensions (91). Advanced age (≥ 65 years) and high comorbidity burden, reflected by American Society of Anesthesiologists (ASA) scores of III or higher, have been confirmed as significant predictors with an OR of 2.48 (95% CI: 1.24-4.97) and an OR of 3.23 (95% CI: 1.10-9.50), respectively (90). Several comorbidities, such as diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease, contribute to the development of AL, in part by being reflected in a higher ASA score (92). Obesity continues to be associated with increased technical difficulty, compromised tissue perfusion, and heightened inflammatory response (91). Active smoking and alcohol abuse remain well-established risk factors that impair microcirculation and immune function (93).

Tumor-related factors significantly influence AL risk by affecting surgical complexity and tissue characteristics. Low tumor height, particularly those located closer to the anal verge, necessitates lower anastomosis construction, which presents increased technical challenges and is associated with higher leakage rates (around 4 - 6.5-fold higher in ≤ 5 cm from the anal verge) due to the narrower pelvic dimensions and compromised vascular supply in the distal rectum (94,95). Advanced tumor stage, particularly clinical stage III-IV disease, has been confirmed as an independent risk factor with an odds ratio of 2.71 (95% CI: 1.34-5.48), likely reflecting the increased surgical complexity and tissue manipulation required for adequate oncological resection (90). Larger tumors and those with deeper invasion (T3/T4) may necessitate more extensive dissection, thereby increasing the risk of tissue damage and ischemic complications that compromise anastomotic healing (90,96). Neoadjuvant chemoradiotherapy, although beneficial for tumor downstaging, remains recognized as a risk factor due to its potential to induce tissue fibrosis and impair local vascularity, thereby compromising anastomotic healing (97).

Surgery-related factors have gained increased recognition in recent literature, with operative characteristics emerging as significant predictors of anastomotic complications. Prolonged operative time has been identified as a crucial risk factor in recent studies, with patients experiencing AL demonstrating significantly longer surgical duration (349.0 versus 232.9 minutes, $p=0.024$) (98). Intraoperative blood loss represents another critical surgical factor, with recent evidence showing markedly higher blood loss in patients who develop AL (800.0 versus 198.6 mL, $p < 0.001$), often necessitating blood transfusions, which themselves are associated with increased inflammatory responses and impaired tissue oxygenation (98).

Diagnosis of anastomotic leakage

Diagnosing AL after rectal cancer surgery is challenging due to its often subtle and non-specific presentation, which can mimic other postoperative complications such as ileus or infection. Early and accurate diagnosis is critical to prevent severe complications like sepsis, peritonitis, or chronic fistulas, which significantly impact morbidity and mortality (93). Clinical suspicion, based on a combination of symptoms, physical examination, laboratory findings, and imaging, guides the diagnostic process.

Clinical assessment remains the cornerstone of AL diagnosis. Common signs include fever, abdominal or pelvic pain, purulent or feculent discharge per anus or from drains, tachycardia, or altered bowel habits (e.g., prolonged ileus or diarrhea) (32). Physical examination may reveal localized or diffuse abdominal tenderness, peritonitis, or systemic signs of sepsis, though these are non-specific and require confirmation with additional tests (32). The timing of symptom onset is critical for raising suspicion, as early leaks may present within 48 hours, whereas most clinically evident leaks occur within the first 5–10 postoperative days. However, late leaks can occur beyond 30 days, and in patients with a DLI, AL may present later or be detected after discharge, with some cases identified at or beyond 90 postoperative days (86,99).

Laboratory tests support clinical suspicion but lack specificity. Elevated C-reactive protein (CRP) levels, particularly above 100–150 mg/L on postoperative days 3–5, are a sensitive marker for AL, with studies reporting a sensitivity of 70–80% and specificity of 60–70% (99). Elevation of the white blood cell count (WBC) is less reliable but is often accompanied by infection or inflammation. Procalcitonin levels are emerging as a complementary biomarker, with higher specificity for bacterial infection in AL, though routine use is not yet standard (100).

Imaging is the mainstay for confirming AL and assessing its extent. Contrast-enhanced CT with rectal water-soluble contrast is the gold standard, with a sensitivity of 85–95% and specificity of 90–95% for detecting AL, extraluminal contrast, or associated collections such as abscesses (101). Typical CT findings include perianastomotic fluid collections, free air, or contrast extravasation. Magnetic resonance imaging (MRI) is rarely used acutely but can help assess chronic leaks or fistulas (32).

Flexible endoscopy provides direct visualization of the anastomosis, identifying defects, dehiscence, or fistulas (102). It may be used as an initial investigation or in conjunction with other diagnostic modalities. In uncertain cases, repeated assessment using flexible endoscopy together with complementary investigations, such as CT imaging, may provide a more comprehensive evaluation. For low rectal anastomoses accessible to the examining finger, digital rectal examination is a simple, practical first-line assessment that allows direct palpation of anastomotic integrity. Endoscopy and digital rectal examination have been shown

to be the most accurate clinical tools for anastomotic assessment, outperforming contrast enema in methodologically robust studies (103). Anastomotic configuration is an additional determinant of diagnostic yield: end-to-end anastomoses are generally the most straightforward to assess, whereas end-to-side anastomoses and reservoir configurations, such as the colonic J-pouch, create a blind end that is difficult to assess by digital rectal examination and may require endoscopic or radiological evaluation.

To synthesize these variables into a more objective assessment, several early detection scores have been developed, including the early warning score, which uses CRP thresholds to flag at-risk patients (104). The Dutch Leakage score combines clinical and laboratory parameters, including CRP levels, respiratory rate, and abdominal pain to generate a daily risk estimate, with higher scores prompting earlier imaging or intervention (105). These scores are promising in research settings but remain impractical for routine clinical use and have not been implemented nationally in Sweden.

Management of anastomotic leakage

The management of AL after rectal cancer surgery is tailored to a combination of factors: the leak's severity, as classified by the ISREC grading system; the patient's overall clinical condition; and their physiological ability to tolerate further intervention, which is heavily influenced by their age and comorbidities (89). A collaborative approach involving surgeons and radiologists is essential to optimize outcomes and minimize morbidity and mortality, which can exceed 10% in severe cases (106). Early diagnosis is paramount. It not only guides timely intervention to prevent life-threatening complications, such as sepsis and mortality, but is also the cornerstone of successful anastomotic preservation. A direct link between timely diagnosis and the ability to save the anastomosis, with one study showing that early detection significantly increased the rate of anastomotic salvage from 43% to 71% (111), as described previously, guides timely intervention to prevent complications such as sepsis or chronic fistulas (107).

Grade A (asymptomatic): Grade A leaks are small, contained defects identified radiologically (e.g., minor contrast extravasation on CT) without clinical symptoms such as fever, pain, or altered bowel habits (89). These leaks typically lack walled-off, enhancing collections or abscesses and do not impact the patient's clinical condition, often resolving spontaneously without intervention (108). Management involves close observation with serial clinical assessments, laboratory monitoring (e.g., CRP), and repeat imaging as needed to confirm resolution. Antibiotics may be considered in select cases to prevent progression, though evidence for their efficacy is limited (32). Regular follow-up ensures early detection of escalation to symptomatic grades.

Grade B (symptomatic, non-surgical intervention): Grade B leaks present with symptoms (e.g., fever, pelvic pain, or discharge) but are managed non-operatively to preserve the anastomosis and avoid surgery. Management differs based on the location of the leak: intraperitoneal or extraperitoneal. Intraperitoneal leaks, often associated with pelvic or perianastomotic abscesses, are effectively treated with CT- or ultrasound-guided percutaneous drainage, achieving resolution in 70–80% of cases (109). Broad-spectrum antibiotics, guided by culture results, are routinely used to manage associated infections. Extraperitoneal leaks, common in low rectal anastomoses, are amenable to endoscopic interventions. EVT involves placing a sponge in the anastomotic defect to promote granulation and closure, with success rates (leak closure) of 80–90% in selected patients (110). A 2021 meta-analysis by Kühn et al. reported an 85% closure rate with EVT for extraperitoneal AL, with low complication rates, making it a preferred option for low rectal leaks (110). Other endoscopic approaches, such as stent placement or clip closure, are less common due to variable efficacy (50–70% success) but may be considered for smaller defects. TD with catheters is an alternative, particularly for smaller extraperitoneal leaks, though less studied (109). Non-operative management requires close surveillance with imaging and endoscopy to monitor progress and detect complications like chronic sinuses.

Grade C (symptomatic, surgical Intervention): Grade C leaks, characterized by diffuse peritonitis, sepsis, or large anastomotic dehiscence, necessitate urgent reoperation. Surgical options include creating a DS (e.g., loop ileostomy) if not previously created during the index operation to divert the fecal stream and control sepsis (111). Direct repair of the anastomosis is feasible in less than 10% of cases due to tissue friability and inflammation. In severe cases, takedown of the anastomosis with creation of an end colostomy (Hartmann's procedure or APR, depending on anastomotic height) is often required, resulting in permanent stoma rates of 22–56% after symptomatic AL. SCRCR data, however, demonstrate substantially higher rates, with 65% of patients experiencing a permanent stoma after anastomotic leakage (111,112), particularly in those aged ≥ 70 years or requiring re-laparotomy [102]. Reoperation is associated with significant morbidity (30–50%) and mortality (5–15%), highlighting the need for early intervention and collaborative decision-making (106). DSs created during the initial surgery reduce AL severity and reoperation rates, though they do not prevent leaks (106).

Guidelines from the European Society of Coloproctology and ESMO recommend individualized management, prioritizing non-operative strategies for Grade B leaks when feasible to preserve anorectal function and quality of life (49,106). Ongoing research focuses on optimizing non-operative techniques, such as EVT and novel endoscopic tools, to improve closure rates and reduce permanent stoma rates (110). Patient factors (e.g., comorbidities, nutritional status) and institutional expertise significantly influence treatment choices.

Defunctioning stoma (DS)

Defunctioning stomas (DS), particularly loop ileostomies, are integral to colorectal surgery, especially in low anterior resection (LAR) for rectal cancer. Their primary role is to divert the fecal stream from a newly created anastomosis, reducing the severity of AL, a serious complication associated with significant morbidity and mortality. While DS has been a cornerstone of surgical practice, its optimal management remains a topic of ongoing research. This section examines the historical evolution, types, indications, and role of DS, offering a comprehensive overview of its application in contemporary rectal cancer management.

History and background of DS

Fecal diversion to manage distal bowel pathology or protect anastomoses has historical roots dating back to the 18th century, initially used for the treatment of obstruction or peritonitis (113). The modern use of DS in colorectal surgery emerged in the mid-20th century, driven by advancements in anastomotic techniques and the rise of LAR with TME for rectal cancer. TME and neoadjuvant therapy increase AL risk due to low pelvic anastomoses and tissue fibrosis, prompting prophylactic DS use (114). Initially, colostomies were common, but loop ileostomies became preferred due to their ease of construction, lower complication rates, and easier reversal (115). Research continues to refine DS indications and outcomes.

Types of DS

DS primarily includes loop ileostomies and loop colostomies, each with distinct anatomical, physiological, and clinical implications. The choice depends on surgical preference, patient factors, and clinical context. The table (Table 2) below summarizes their characteristics (116–122).

Table 2. Comparing two types of DS characteristics: loop ileostomies and loop colostomies

Characteristic	Loop ileostomy	Loop colostomy
Anatomical location	Created from the distal ileum, typically in the right lower quadrant. A loop is exteriorized, creating proximal (effluent) and distal (diverting) openings.	Formed from the transverse or left colon, exteriorized to create proximal and distal limbs.
Physiological impact	Produces liquid to semi-liquid effluent, bypassing colonic water absorption, which requires fluid/electrolyte monitoring and dietary adjustments	Produces more formed stool, thereby reducing the risk of dehydration.
Advantages	Lower rates of stoma prolapse (OR 0.10, 95% CI 0.03-0.34) and a trend toward fewer wound infections (OR 0.60, 95% CI 0.26-1.41). Easier to create and reverse; enhances fecal stream diversion.	Less irritating effluent minimizes skin complications.
Disadvantages	Higher dehydration risk (6-20% readmission rates within 30 days), and peristomal skin complications (36-73%).	Higher complication rates, including stoma prolapse and incisional hernias, are technically challenging to create and reverse.

Loop ileostomies are preferred over loop colostomies for anastomosis protection post-anterior resection in rectal surgery, owing to a reduced risk of serious complications (OR 0.75, 95% CI 0.62–0.91), simpler creation and reversal, and superior fecal diversion, which is crucial for low pelvic anastomoses. However, it carries increased risks of dehydration and skin irritation, requiring vigilant patient care (106,118,119).

Indications and role of DS in rectal cancer surgery and anastomotic leakage

The decision to create a DS in rectal cancer surgery balances anastomotic protection against stoma-related morbidity. DS is primarily indicated to mitigate AL consequences after LAR, particularly for high-risk cases (32).

Primary indications:

The primary intention of a DS in rectal cancer surgery is not to prevent the occurrence of (AL itself, but to mitigate its clinical consequences. By defunctioning the fecal stream, a DS significantly reduces the risk of a symptomatic leak (i.e., causing peritonitis or sepsis), thereby lowering the need for urgent re-operations and improving recovery from non-severe AL by minimizing complications.

Contemporary evidence demonstrates the protective effects of DS through multiple lines of investigation. A protective effect has been demonstrated in a meta-analysis of 9 randomized controlled trials. DS significantly reduced AL (OR 0.362, 95% CI 0.236-0.555), overall complications (OR 0.61, 95% CI 0.461-0.828), and reoperation rates (OR 0.352, 95% CI 0.222-0.559) compared to non-diverted patients (123). Recent meta-analysis shows that patients with DLI experience significantly lower AL rates compared to those without diversion (3.8% vs. 8.5%, p

< 0.001), with diverted patients requiring less invasive interventions when leakage occurs (124). SCRCR data further reveal that DS provides protection against early AL within 30 days (adjusted HR 0.47, 95% CI 0.28–0.77), though late leakage rates after 30 days may be higher in patients with stomas (125). This suggests that DSs may delay rather than prevent some leakages, converting them from early symptomatic events to later, often subclinical occurrences. It is debated whether this reflects a true reduction in leak incidence or merely converts clinical leaks into subclinical events, often detected via imaging (e.g., CT).

Given the morbidity associated with DS, modern practice advocates selective use rather than routine implementation. The decision to create DS is guided by a comprehensive risk assessment that considers the cumulative effects of patient, tumor, and surgical risk factors, as detailed previously (see Section 1.5.4, Risk Factors). Factors such as a low anastomosis, neoadjuvant therapy, and poor patient condition often interact synergistically, strengthening the indication for DS (126). The decision is further informed by intraoperative findings, such as a positive air-leak test or visible signs of poor anastomotic perfusion, which may prompt DS creation even in lower-risk patients, as well as in anastomosis situated above the peritoneal reflection (127). Reinforcing this selective strategy, emerging evidence indicates that the absence of DS itself is an independent risk factor for AL ($P = 0.0092$), particularly in low-situated anastomoses (128). This nuanced approach ensures DS is reserved for patients most likely to benefit, balancing the goal of safeguarding the anastomosis against the burden of stoma-related complications.

Mechanism of action:

DS mitigates AL by several mechanisms. By defunctioning fecal content, stomas minimize bacterial contamination at the anastomotic site, reducing the risk of infection-related complications (108). In elective colorectal surgery, perioperative bowel preparation remains an important component of surgical care. Current clinical practice guidelines recommend the combination of mechanical bowel preparation and oral antibiotics before elective colorectal resection and have associated this strategy with reduced rates of surgical site infection and anastomotic leakage (129). Additionally, they decrease intraluminal pressure, alleviating mechanical stress on healing tissues, which supports anastomotic integrity (130). This reduction in pressure and contamination fosters a favorable environment for tissue repair by attenuating local inflammation, thereby promoting optimal healing conditions.

Temporal Swedish trends in DS usage

The adoption of DS in Swedish rectal cancer surgery underwent a dramatic transformation following the landmark RECTODES trial, which involved 11 Swedish centers and established new paradigms for DS indications in AR (115).

This paradigm shift is clearly documented through temporal usage patterns. At Ersta Hospital, DS stoma usage increased from 15% (2002–2006) to 91% (2007–2011),

representing a six-fold increase coinciding precisely with RECTODES publication (131). This pattern was replicated nationally, SCRCR data demonstrate sustained high usage rates of 78.9% (2007-2016) (132), with continued high utilization increasing from 71.6% (2007-2009) to 76.7% (2016-2018) [Paper III] (133). Despite substantial increases in DS utilization, overall AL incidence remained stable (9.2% vs. 8.2%). This apparent paradox suggests that the primary benefit lies in converting symptomatic leaks into less severe, manageable complications rather than preventing their occurrence.

Complications of DS

DS is frequently employed to safeguard distal anastomoses in rectal cancer surgery, yet it is associated with several short-term complications within 30 days post-operation. High-output stoma (HOS) leading to dehydration and electrolyte imbalances poses a significant risk, with dehydration prevalence ranging from 0.8% to 72% across studies, and dehydration-related readmissions reported at 6% (95% CI 4–9%) and all-cause readmissions at 20% (95% CI 18–23%) (121,134,135). Beyond hydration, DS was associated with an increased risk of acute kidney injury (HR 3, 95% CI 1.6–5.6) compared with non-diverted patients. No significant association with chronic kidney disease was observed, and the excess risk declined following stoma reversal. These findings underscore the importance of proactive perioperative fluid management and early identification of patients at risk during the period of stoma function (136).

Peristomal skin irritation, manifesting as erythema, papules, erosions, and ulcers due to exposure to liquid effluent, affects an estimated 36.3–73.4% of DS patients, with studies consistently showing higher rates in ileostomy patients than in colostomy patients, negatively impacting quality of life and escalating healthcare costs (117,120). Postoperative ileus, affecting 4–13% of patients and associated with increased risk in DS (OR 2.23, 95% CI 1.12–4.43), has been hypothesized to be partly related to alterations in the gut microbiota induced by fecal stream diversion, which alters the gut microbiota and potentially worsens malabsorption and inflammation (116–118).

DS impact on long-term outcomes

While DS provides significant short-term benefits in reducing AL severity, its long-term implications extend beyond immediate perioperative outcomes, affecting oncological treatment, quality of life, and bowel function. A significant concern with DS is the risk of non-reversal, with contemporary studies reporting permanent stoma rates of 18-25% of patients initially intended for temporary diversion (137). Risk factors for non-reversal include anastomotic leakage, advanced cancer stage, patient comorbidities, and treatment-related complications that preclude safe closure. SCRCR consistently demonstrates these elevated permanent stoma rates across multiple healthcare regions (112).

The creation of DS after rectal cancer surgery significantly impacts adjuvant chemotherapy timing and delivery. Large-scale cohort studies have demonstrated that patients with DS experience delayed chemotherapy initiation compared to those without stomas, with a reduced likelihood of receiving treatment within the first two months postoperatively (138). Although cumulative chemotherapy doses and 12-month completion rates remain comparable between groups, the timing delay can affect treatment optimization. These complications, including dehydration and acute kidney injury, impair chemotherapy tolerability and are associated with worse overall survival when leading to incomplete treatment or delayed stoma reversal (139,140).

DSs are associated with impaired long-term bowel function, particularly an increased risk of major Low Anterior Resection Syndrome (LARS). Patients with DS have significantly higher odds of major LARS than those without stomas (adjusted OR 2.43, 95% CI 1.14-5.20), encompassing symptoms such as incontinence of flatus and liquid stools, increased frequency, clustering, and urgency (141). This negative impact on bowel function appears independent of stoma reversal timing, with prolonged stoma duration, especially with ileostomy, associated with greater postoperative functional disturbance (142,143).

Patient-reported outcomes demonstrate specific impacts on quality of life during the stoma period. A multicenter longitudinal study of 120 patients revealed that while global quality of life remained stable, several functional and gastrointestinal scales were markedly impaired after stoma creation. Physical functioning (e.g., mobility and self-care) and role functioning (e.g., daily activities and work limitations) recovered to near-baseline levels following stoma closure; however, social functioning (e.g., interpersonal relationships and social activities) remained significantly impaired even 6 months post-reversal, likely due to persistent bowel symptoms like urgency and incontinence. (144).

Reversal of DS

Reversal of DS aims to restore bowel continuity after anastomotic healing, typically planned 8–12 weeks post-low anterior resection to balance healing with minimizing stoma-related morbidity (145). Stoma reversal can be performed when anastomotic integrity has been confirmed through contrast enema or endoscopy, ensuring no strictures or leaks are present (146). For patients planned for adjuvant therapy, reversal is typically delayed until after completion of treatment, as temporary loop ileostomy closure following rectal cancer surgery is usually delayed until completion of adjuvant chemotherapy (147).

Contemporary evidence demonstrates that delayed stoma reversal increases postoperative complications. Supporting evidence from a study of 170 DS demonstrated that 50% had delayed closure beyond 6 months, which was associated

with increased risk of complications and longer hospital stays following reversal ($P < 0.05$) (148). Delaying stoma closure continues to expose patients to various stoma complications, including poor stoma site, dehydration, acute renal failure, need for parenteral nutrition, and peristomal dermatitis, with rates up to 71% reported in delayed cases (149).

The optimal timing for stoma closure remains a subject of ongoing clinical debate, with emerging evidence exploring very early closure strategies. A meta-analysis of 4 randomized controlled trials involving 446 patients demonstrated that very early closure within 2 weeks of the index procedure was feasible and associated with outcomes comparable to those of conventional delayed closure. Specifically, very early closure showed similar anastomotic leak rates (RR 0.37, 95% CI 0.10-1.42) and overall complication rates (RR 0.75, 95% CI 0.48-1.16), suggesting this aggressive approach may be safe in carefully selected patients (150). However, more recent systematic review evidence indicates that early closure strategies may be associated with higher morbidity rates (25.5% vs. 21.6%) and increased reoperation rates (8.4% vs. 4.2%), emphasizing the importance of individualized patient assessment and multidisciplinary decision-making (121).

Complications of the reversal of DS

Reversal of DS, while restoring bowel continuity, introduces risks that can prolong recovery and increase healthcare utilization. AL at the reversal site, though rare, poses a risk of sepsis or abscess, often due to poor perfusion or technical errors during surgery (151). Small bowel obstruction occurs in approximately 15% of reversals and is typically due to adhesions or strictures. While it is often managed conservatively, it may necessitate reoperation (152,153). Wound infections, occurring in 10% of cases, range from superficial to deep abscesses and contribute to extended hospital stays (154). These complications, reported in 17.3–20.0% of reversals, underscore the need for meticulous surgical technique and timely intervention to minimize morbidity (155). Risk factors for stoma reversal complications include male sex (OR 1.584, 95% CI 1.068-2.347), longer operative time (OR 1.004, 95% CI 1.001-1.007), chronic obstructive pulmonary disease (OR 2.959, 95% CI 1.153-7.591), and dyspnea (OR 2.431, 95% CI 1.139-5.094), while successful reversal is more likely with shorter operative times, absence of comorbidities, and optimal nutritional status (156). Furthermore, among patients with DSs, delayed closure beyond 1 year is associated with increased risk of major LARS (OR 3.7, 95% CI 1.1–13.1) and worse functional outcomes (157,158).

New approaches to DS

Emerging strategies in DS management aim to reduce reliance on stomas, minimize morbidity, and enhance anastomotic protection through personalized risk-based approaches. Selective DS use, guided by validated risk-stratification models that incorporate factors such as male gender, BMI >30, and preoperative radiotherapy,

helps avoid unnecessary stomas in low-risk patients. The SELSA study protocol demonstrates this approach, using an anastomotic risk score with a negative predictive value of 94.7%, thereby potentially reducing DS use by 20% without increasing AL rates (159,160).

A ghost ileostomy represents a promising alternative technique in which a prefabricated loop ileostomy is brought to the abdominal wall but is not matured unless AL is suspected or confirmed. Recent randomized controlled trials demonstrate that ghost ileostomy is a viable and safe option for selective ileostomy creation in LAR, with complication indices and anastomotic leakage rates comparable to those of conventional loop ileostomy. However, conversion to conventional ileostomy occurs in approximately 40% of cases, highlighting the importance of careful patient selection (161,162).

Completely diverted tube ileostomy offers an innovative approach to fecal diversion without creating a traditional cutaneous stoma. This technique involves insertion of a cuffed endotracheal tube into the ileum 20 cm proximal to the ileocecal valve, with balloon occlusion of the intestinal lumen and external fixation via a rubber strip passed through the mesentery and secured to the abdominal wall. The diverted intestinal contents are collected through the tube system connected to an external drainage bag. Clinical studies demonstrate significantly superior outcomes compared to conventional loop ileostomy, including reduced complication rates (15% vs 65%), shorter median duration of diversion (21 vs 270 days), and the avoidance of the need for formal stoma reversal surgery, as the system can be removed non-surgically once anastomotic healing is confirmed. Upon removal of the rubber strip and tube, the small bowel opening spontaneously closes, avoiding the morbidity associated with formal stoma reversal surgery (163,164).

These evidence-based approaches, combined with improved patient selection criteria and validated risk stratification models, hold significant promise for optimizing DS outcomes while reducing unnecessary stoma-related morbidity.

Aim of the thesis

The main aim of the thesis is to study the outcomes and complications associated with DLI in rectal cancer patients undergoing AR, with a focus on reducing dehydration, mitigating anastomotic leakage, improving treatment outcomes for leakage-related interventions, and optimizing the timing of stoma reversal to minimize postoperative morbidity. The specific objectives are:

Specific aims

1. Evaluating the outcome of a post-operative surveillance program on reducing the incidence of dehydration and readmissions related to a DLI following LAR in rectal cancer patients.
2. To investigate whether the increased use of DLI has reduced the incidence of AL in AR for rectal cancer, and to identify risk factors for AL in a national population-based cohort.
3. To compare the clinical success rates and long-term bowel continuity outcomes of EVT versus TD for treating AL after AL in rectal cancer patients.
4. To assess the association between the elapsed time from AR to SR and the risk of postoperative 90-day complications in rectal cancer patients, and to identify factors associated with delayed stoma reversal.

Material and Methods

Data Source

Paper I

Patients who underwent LAR and DLI at Skåne University Hospital (Malmö) and Helsingborg Hospital between 2015 and 2017 were identified and included consecutively. Following identification, electronic medical records were thoroughly reviewed to retrieve clinical variables and intervention details, including pre- and post-follow-up program documentation. A historical control group (2013–2015) was identified retrospectively from a previously conducted descriptive study at the same institutions. The electronic medical records encompassed all participants from southern Swedish hospitals, including Malmö and Helsingborg (the primary intervention sites), ensuring comprehensive coverage.

Paper II

Patients undergoing AR for rectal cancer were identified from SCRCR, a nationwide registry established in 1995 with high validity and >99% coverage of rectal cancer cases in Sweden (165). Clinical variables were retrieved directly from SCRCR entries, including AL detected within 30 days of index surgery and DS, with registration of DS variable commencing in 2007.

Paper III

Patients diagnosed with AL after AR for rectal cancer at Skåne University Hospital between 2009 and 2018 were identified via SCRCR. Electronic medical records of patients with AL were reviewed to confirm the diagnosis and to collect data on treatment modality, including EVT and (TD). For patients subsequently considered candidates for restoration of bowel continuity, additional data on further management and long-term outcomes were collected. Two primary outcomes were assessed: clinical success, defined as successful treatment of AL at the treating physician's discretion; and restoration of bowel continuity, defined as the absence of a permanent stoma at 24 months following index surgery.

Paper IV

Rectal cancer patients who underwent AR with DS were identified from hospital operation lists, with data collected through SCRCR and medical chart review. Stoma status was monitored via the electronic medical records, including reviews for complications of stoma reversal.

Definitions

Symptomatic dehydration: A clinical condition characterized by signs and symptoms of fluid loss (e.g., fatigue, high output stoma, or reduced urine output) with or without laboratory derangements, such as those indicating acute kidney injury (AKI) per KDIGO criteria (e.g., serum creatinine increase ≥ 0.3 mg/dL within 48 hours or ≥ 1.5 times baseline within 7 days)(166).

Asymptomatic dehydration: Mild fluid deficit without overt clinical symptoms or signs, identified solely through laboratory derangements (e.g., elevated blood urea nitrogen, creatinine, or electrolyte imbalances suggestive of AKI per KDIGO).

Overall dehydration: Encompasses both symptomatic and asymptomatic forms, defined as a net loss of body water exceeding intake, leading to impaired physiological function.

Anastomotic leak: In AR for rectal cancer, AL is characterized by a breach allowing communication between the intra- and extraluminal spaces, evident as a defect at the anastomotic site (staple or suture line), a presacral abscess, or a rectovaginal fistula, as outlined by ISREC (167).

Defunctioning loop ileostomy/defunctioning stoma (DLI/DS): A surgical procedure that creates a temporary, manageable stoma to redirect the fecal stream away from a distal anastomosis, thereby mitigating the potential complications associated with anastomotic leak in rectal cancer surgery (168).

Endoscopic Vacuum Therapy (EVT): A minimally invasive endoscopic technique employing negative pressure via sponge systems to promote granulation tissue formation and healing of extra-peritoneal anastomotic leaks in clinically stable, non-peritonitis patients (169).

Transanal Drainage (TD): A therapeutic procedure involving transanal insertion of drainage tubes into anastomotic leak cavities to facilitate fluid evacuation, reduce septic complications, and promote healing in rectal surgery patients (170).

Stoma Reversal (SR): In this thesis on rectal cancer surgery, the surgical closure of a temporary DS (primarily loop ileostomy, occasionally loop colostomy) to restore bowel continuity, typically 3 months or more post-anterior resection after anastomotic healing confirmation (e.g., contrast enema/endoscopy) and patient

optimization (171). Broader contexts may include non-DS, but here it is limited to temporary defunctioning ones.

Permanent stoma: In this thesis on rectal cancer surgery, a temporary DS remained unreversed >24 months post-creation due to anastomotic complications, comorbidities, or technical factors (172). Primarily encompasses non-SR stomas in restorative procedures; may include end colostomies from anastomotic failure. Broader contexts encompass intentional non-SR.

Study design and Methods

Paper I

This was a prospective interventional study aimed at reducing stoma-related dehydration in patients with DLI following low anterior resection for rectal cancer. The study included rectal cancer patients who underwent low anterior resection with DLI performed from 2015 to 2017 at two teaching hospitals: Skåne University Hospital and Helsingborg Hospital, Sweden. The intervention group was compared to a historical control group from the same institutions who met identical inclusion criteria regarding surgical procedure and patient characteristics. The control group comprised a retrospective cohort of rectal cancer patients who underwent low anterior resection with DLI at the same institutions from January 2007 to June 2009 (173).

In patients meeting the study's inclusion criteria, medical records were reviewed at each hospital to document clinical characteristics, surgical details, postoperative outcomes, and laboratory values. All study patients in the intervention group met with stoma care nurses before and after surgery and received standardized education on fluid management, dietary modifications, self-monitoring protocols, and the use of anti-diarrheal medications with dose adjustments as needed. Post-discharge management included biweekly blood sampling (plasma creatinine, sodium, and potassium) until 8 weeks post-operatively, with continuous access to stoma care nurses for telephone consultation. Additional blood testing and colorectal surgeon consultation were initiated for patients with prolonged HOS, weight loss, or abnormal blood tests. The control group received standard care without these structured interventions.

The primary outcome was overall dehydration, categorized as symptomatic or asymptomatic, as previously defined. Secondary outcomes included stoma-related readmissions due to dehydration during the follow-up period.

Statistical Methods: In the intervention group, clinical characteristics were evaluated and analyzed using univariate analysis for dehydrated and non-dehydrated

patients. A group comparison was conducted between the intervention and historical control groups to assess baseline characteristics and comparability. Univariable analysis was conducted between the intervention and control groups for overall dehydration, symptomatic dehydration, and stoma-related dehydration readmission. Additional descriptive statistics compared admitted and non-admitted dehydrated patients within the intervention group.

Continuous variables were analyzed using the t-test or Mann-Whitney U test when appropriate, and categorical variables were analyzed using the chi-squared test or Fisher's exact test when appropriate. A p-value < 0.05 for a two-tailed test was considered statistically significant. Data are presented as median with interquartile range when appropriate. **Sample size was not based on formal power calculation, as this was a prospective cohort study evaluating intervention feasibility rather than superiority.** Consecutive eligible patients (n=87) were recruited over 2 years (2013–2015) from regional sites, informed by historical data (n=93; ~30% dehydration rate) to detect potential reductions in symptomatic events (target ~10-15% absolute decrease, assuming 80% power, $\alpha=0.05$, and 20-30% event rate). This yielded adequate descriptive power for primary comparisons.

Paper II

This was a retrospective national registry-based cohort study evaluating trends in DLI usage and AL rates in patients undergoing AR for rectal cancer. The study aimed to assess temporal changes in DLI usage and its relationship with AL rates over a decade-long period, comparing cohorts from 2007–2009 and 2016–2018. The primary endpoint was the incidence of AL relative to changes in DLI usage between the two periods. Secondary endpoints included the reoperation rate for AL and the identification of AL risk factors.

Data was obtained from SCRCR. The study encompassed all patients who underwent elective AR during two periods: 2007–2009 and 2016–2018. Patient demographics, tumor characteristics, surgical details, postoperative outcomes, and AL events were extracted from SCRCR for individuals meeting the inclusion criteria. Exclusion criteria comprised age <18 years, emergency procedures, microscopically non-radical resections, and unregistered DLI status. Patients were stratified into two cohorts based on the index surgery date (2007–2009 vs. 2016–2018), with further subgrouping by DLI status (present or absent).

Statistical Methods: Analyses were performed using IBM SPSS version 26 (IBM Corp., Armonk, NY). Demographic and clinical characteristics were presented as medians with interquartile ranges (IQRs) for continuous variables and as frequencies with percentages for categorical variables. Missing data were reported if they exceeded 2% for any variable.

Variables were categorized based on clinical relevance and established risk strata, including age (continuous or grouped as appropriate), American Society of Anesthesiologists (ASA) classification (1–2 vs. 3–4), body mass index (BMI; <30 vs. ≥ 30 kg/m²), and neoadjuvant therapy (yes/no). Tumor height from the anal verge served as a proxy for total mesorectal excision (TME; < 11 cm) versus partial mesorectal excision (PME; ≥ 11 cm).

To evaluate comparability between cohorts, descriptive statistics were compared for patients with DLI across the two periods. The incidence of AL and the use of DLI were then compared between the two periods to assess temporal changes. Additionally, the reoperation rate for AL was compared between the two periods.

Risk factors for AL were assessed via univariate analysis, stratifying the combined cohort by AL status (presence or absence), followed by multivariable logistic regression incorporating variables significant in univariate analysis ($p < 0.05$) or deemed clinically relevant (e.g., DLI status). Additional descriptive statistics compared characteristics of PME and TME patients with and without DLI in the 2007–2009 cohort. Results are reported as odds ratios (OR) with 95% confidence intervals (CI).

Continuous variables were compared using the Mann-Whitney U test (due to non-normal distributions), and categorical variables using the chi-squared test or Fisher's exact test as appropriate. A two-sided p -value < 0.05 was considered statistically significant.

Paper III

This was a retrospective, single-center cohort study that compared long-term outcomes after EVT versus TD following AL after anterior resection for rectal cancer. The primary objective was to compare the clinical success rate of EVT versus TD where clinical success was defined as resolution of AL as judged by the treating surgeon, often confirmed by endoscopy or contrast-enhanced computed tomography. Secondary objectives included the restoration of bowel continuity at least 24 months after index surgery, total duration of AL treatment, and the number of treatments requiring anesthesia.

Patients diagnosed with AL after AR for rectal cancer at Skåne University Hospital between 2009 and 2018 were identified via SCRCR. For AL patients who had initiated treatment for bowel continuity restoration, electronic medical records were reviewed to confirm AL diagnoses and extract treatment and outcome data.

Extracted variables comprised age at operation, American Society of Anesthesiologists (ASA) classification, comorbidities for Charlson Comorbidity Index (CCI) calculation, smoking status, tumor/nodal/metastasis (TNM) stage, tumor height from anal verge, preoperative radiotherapy, surgical approach

(laparoscopic vs. open), DS construction, and anastomotic reconstruction type (side-to-end or end-to-end), leak site (circular anastomosis or blind end), stoma status, time from index surgery to AL diagnosis and treatment initiation, AL treatment modality (EVT or TD), treatment duration, and number of treatments requiring anesthesia were obtained from SCRCR and medical records.

A stoma (ileostomy or colostomy) presents 24 months after index surgery was considered permanent (i.e., no bowel continuity restoration). Follow-up ranged from 2 to 11 years.

All ALs were initially assessed endoscopically. For EVT, polyurethane endosponges (Braun®) were placed endoscopically into the abscess cavity with changes performed two to three times weekly. For TD, the cavity and abscess were drained and washed out in the operating theater, with drain placement and subsequent washouts performed at the surgeon's discretion. Procedures were performed in-hospital under general anesthesia or sedation and were transitioned to outpatient settings when clinically appropriate.

The primary outcome was clinical success, defined as complete resolution of the AL without need for further definitive surgical intervention, confirmed by endoscopy or contrast-enhanced CT. Restoration of bowel continuity was defined as reversal of a DS and absence of stoma at ≥ 24 months. Treatment duration was measured from the first AL-directed intervention to documented radiologic or endoscopic resolution. The number of treatments requiring anesthesia included any endoscopic or surgical procedure performed under sedation or general anesthesia.

Analyses were performed using IBM SPSS Statistics version 25.0.0.1 (IBM Corp., Armonk, NY). Continuous variables were summarized as medians with interquartile ranges (IQRs), and categorical variables as frequencies with percentages. Differences in outcomes between EVT and TD groups were assessed using Fisher's exact test. Patients were analyzed according to intention-to-treat. A two-sided p-value < 0.05 was considered statistically significant.

Paper IV

This multicenter retrospective cohort study across eleven Swedish hospitals evaluated whether time from AR to SR affects the incidence of postoperative 90-day complications after SR among rectal cancer patients who received DS between 2014 and 2018. The primary endpoint was the occurrence of at least one postoperative 90-day complication after SR, including reoperation. Secondary endpoints encompassed independent factors contributing to delayed SR (defined as > 6 months post-AR).

Rectal cancer patients were identified from hospital operation lists, with clinical data retrieved from SCRCR and supplemented by medical chart review. AL after

AR was defined according to ISREC. Patients with no evidence of AL on endoscopic or radiological contrast studies were scheduled for SR unless SR was deferred due to planned adjuvant chemotherapy. Stoma status was monitored for at least 2 years, and post-SR complications within 90 days were captured from medical chart review.

SR complications included mechanical small-bowel obstruction, ileus (>7 days or requiring total parenteral nutrition), bleeding, surgical-site infection, AL, wound dehiscence, incisional hernia, cardiac events (new onset arrhythmia, myocardial infarction, heart failure), and pulmonary events (pneumonia, respiratory aspiration, acute respiratory distress syndrome). Reoperation types and indications were recorded.

Patients with documented AL after AR were excluded from the primary outcome analysis to avoid confounding by established leak-related practices; the entire cohort (including patients with AL) was used for analyses of factors associated with delayed SR.

Statistical Methods: Analyses were performed using SPSS version 28 (SPSS, Chicago, IL, USA). Categorical variables were compared using chi-square or Fisher's exact test and presented as percentages. Continuous variables were analyzed with the Mann-Whitney U test and expressed as medians with interquartile ranges (IQRs). A complete-case approach was used to handle missing data; variables with >2% missingness are flagged in the tables.

Logistic regression models assessed the association between elapsed time to SR and outcomes (postoperative 90-day complications and reoperation after SR). Time to SR was modeled both continuously (months) and dichotomously (>6 months vs ≤6 months). Odds ratios (OR) with 95% confidence intervals (CI) are reported.

Multivariable models included covariates selected on clinical grounds and known risk factors: age (≤65 vs. >65), sex (female vs. male), ASA classification (I/II vs. III/IV), yp/pT stage (0/1/2 vs. 3/4), and yp/pN stage (0 vs. 1/2). All covariates were entered simultaneously into multivariable models.

Univariable and multivariable analyses assessed clinical factors related to delayed SR using the same covariate selection approach. A two-sided p-value <0.05 was considered statistically significant.

Ethical considerations

The papers in the thesis adhered to the ethical principles outlined in the 1975 Declaration of Helsinki. Ethical approvals were obtained prior to the commencement of the studies. Papers I-II received approval from the Regional

Ethical Review Board in Lund, Sweden (Regionala etikprövningsnämnden i Lund). Papers III-IV were approved by the Swedish Ethical Review Authority (Etikprövningsmyndigheten). Patients participating were informed of the option to opt out before the review of medical records and the extraction of registry data. Confidentiality was maintained through comprehensive data protection protocols, including patient de-identification and secure data storage with restricted access to authorized research personnel only

Language editing

The thesis was written entirely by the author, who is responsible for all content, interpretations, and conclusions. Artificial intelligence-based language models (ChatGPT 5.5 and Manus 1.6) were used as supportive tools for language editing, improving clarity and readability, refining the structure and presentation of the text, identifying relevant literature, and assisting in the verification of scientific information. All Artificial intelligence-generated suggestions were reviewed, verified, and revised by the author before inclusion. The use of these tools did not replace independent scientific judgment or influence the study design, data collection, data analysis, interpretation of results, or final conclusions.

Results

Paper I

Intervention to reduce DLI-related dehydration

Main results - primary outcomes

Overall incidence of dehydration: Among the 87 patients in the intervention group, 21 (24%) developed dehydration, which did not differ significantly from the historical control group, in which 27 of 91 patients (29%) experienced dehydration ($p=0.62$).

Symptomatic vs. asymptomatic dehydration: The intervention significantly reduced symptomatic dehydration, affecting 10 (11%) patients in the intervention group compared to 27 (29%) in the control group ($p < 0.005$). Asymptomatic dehydration was detected in 11 of the 21 dehydrated patients (52%) in the intervention group, and they were managed with dietary modifications and anti-diarrheal medications, avoiding hospitalization.

Readmission rates: Readmission rates for dehydration did not differ significantly between groups, with 9 of 21 dehydrated patients (43%) in the intervention group requiring readmission compared to 14 of 27 (52%) in the control group ($p=0.57$).

Secondary results

Factors for dehydration: Within the intervention group, dehydrated patients were significantly older (median 70 years, IQR 66-72) than non-dehydrated patients (median 64 years, IQR 60-70; $p=0.009$) and were more likely to use diuretics (19% vs. 3%, $p=0.028$). No significant differences were observed in gender, ASA classification, diabetes, BMI, pre-operative creatinine ($\mu\text{mol/l}$), neoadjuvant therapy, adjuvant therapy, overall ACEi/ARB use, previous operations, or surgical approach.

The intervention and control groups exhibited similar baseline characteristics in group comparison, including age (median 66 years for both), gender distribution, diabetes prevalence, and BMI. The intervention group had a lower rate of neoadjuvant radiotherapy (49% vs. 75%) and a higher rate of adjuvant therapy (43%

vs. 21%), though no statistical comparisons were performed to assess these differences.

Factors for admission in dehydrated patients: Among dehydrated patients in the intervention group, those requiring admission (n=9) were similar to non-admitted patients (n=12) in most demographics but showed a significantly higher use of ACEi/ARB (66% vs. 17%, $p=0.032$).

Other findings of interest

Safety profile: No patients in the intervention group required admission to the intensive care unit. Hyperkalemia was observed in admitted dehydrated patients (mean potassium 5.7 mmol/L, range 4.9-5.9), but no patients experienced hyperkalemia-related cardiac complications.

Paper II

DLI usage increases and stable AL incidence

Between 2007 and 2009 and 2016 and 2018, 3,948 elective AR procedures for rectal cancer were performed. After excluding 131 patients with non-radical resections, 123 with missing resection margin data, and 6 with unregistered DLI status, 3,688 patients were included in the study cohort. This cohort comprised 1,879 patients from 2007–2009 and 1,809 from 2016–2018.

Main results - primary outcomes

DLI usage increased significantly from 71.6% (1,345/1,879) in 2007–2009 to 76.7% (1,387/1,809) in 2016–2018 ($p < 0.001$), reflecting a 5.1 percentage-point increase over the study period (Table 3). Despite this increase, AL incidence remained stable, with no significant reduction: 9.2% (124/1,879) in 2007–2009 versus 8.2% (114/1,809) in 2016–2018 ($p = 0.35$). Similarly, reoperation rates for AL among patients with DLI showed no significant change: 4.3% (58/1,345) in 2007–2009 versus 3.3% (46/1,387) in 2016–2018 ($p = 0.17$).

Table 3. Incidence of AL related to DLI over a twelve-year period (2007–2009) and (2016–2018).

Outcome	2007–2009 (n = 1,879)	2016–2018 (n = 1,809)	p-value
DLI usage	1,345 (71.6%)	1,387 (76.7%)	< 0.001
AL incidence	124 (9.2%)	114 (8.2%)	0.35
Reoperation for AL (among DLI patients)	58 (4.3%)	46 (3.3%)	0.17

Secondary results

Temporal changes in patient characteristics among those with DLI

Compared with the 2007–2009 group, the 2016–2018 group had a higher proportion of patients classified as ASA 3–4 (19.5% vs. 14.1%, $p < 0.001$) and a higher proportion with a BMI ≥ 30 kg/m² (17.6% vs. 12.3%, $p < 0.001$). Tumors were more frequently high-located (≥ 11 cm from the anal verge; 37.1% vs. 35.2%; $p < 0.001$) and less often low-located (< 5 cm from the anal verge; 1.7% vs. 3.4%; $p < 0.001$). The latter group exhibited less advanced pathological tumor stages (T3–4: 57.9% vs. 60.8%; $p < 0.001$) and fewer clinical metastases (M1: 5.5% vs. 6.0%; $p < 0.001$). Minimally invasive AR was more common (58.8% vs. 5.4%; $p < 0.001$), as was high ligation of the inferior mesenteric artery (55.2% vs. 44.7%; $p < 0.001$). The use of neoadjuvant therapy decreased (63.2% vs. 72.2%; $p < 0.001$), as did the use of adjuvant therapy (16.7% vs. 29.6%; $p < 0.001$). Median hospital stay was longer (8 vs. 7 days; $p < 0.001$).

Risk factors for AL - regression analysis

Univariable analysis identified associations between AL and clinical characteristics like male sex, ASA class, BMI, and neoadjuvant therapy (Table 4). Multivariable logistic regression confirmed male sex, ASA score 3–4, BMI ≥ 30 kg/m², and neoadjuvant therapy as independent risk factors. Neither DLI usage nor operation date influenced AL incidence.

Table 4. Univariable and multivariable analysis for anastomotic leak risk factors

Risk factor	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
DLI	0.89 (0.69–1.14)	0.344	0.84 (0.63–1.13)	0.252
Operation date (2016–2018)	0.84 (0.67–1.05)	0.123	0.82 (0.65–1.04)	0.101
Male sex	1.38 (1.09–1.75)	0.008	1.41 (1.09–1.81)	0.008
ASA 3–4	1.40 (1.05–1.82)	0.021	1.39 (1.05–1.85)	0.024
BMI > 30 kg/m²	1.50 (1.10–1.97)	0.010	1.51 (1.13–2.04)	0.006
Neoadjuvant therapy	1.27 (1.00–1.60)	0.047	1.35 (1.03–1.75)	0.027

TME vs. PME subgroup analysis

In both TME and PME subgroups (2007–2009), AL rates were similar between patients with and without DLI. However, reoperation rates for AL were lower in the

+DLI groups: 4.3% vs. 11.2% ($p = 0.004$) for TME and 4.4% vs. 8.8% ($p = 0.019$) for PME.

Paper III

Between 2009 and 2018, 1,095 patients treated for rectal cancer at Skåne University Hospital were identified through SCRCR. Of these, 361 patients underwent anterior resection, and 733 patients had either abdominoperineal resection, a Hartmann's procedure, or other procedures (e.g., local excision, polypectomy). AL occurred in 39 patients (10.8%), comprising 26 males and 13 females. In 34 patients, DS had been constructed at the primary operation. Seven patients were re-operated with abdominoperineal resection ($n=3$), Hartmann's procedure ($n=3$), or abdominal drainage ($n=1$). One patient was treated with antibiotics alone. The remaining 31 patients were treated for AL with either EVT ($n=14$) or TD ($n=17$).

Main results - primary outcomes

The clinical success rate was 78.6% (11/14) in patients treated with EVT and 88.2% (15/17) in patients treated with TD ($p=0.64$). At long-term follow-up (ranging 2-11 years), bowel continuity was restored in 50.0% (7/14) of the EVT group compared with 64.7% (11/17) of the TD group ($p=0.28$).

In the EVT group, treatment failures included: one patient who stopped due to pain and risks associated with anesthesia, one who required emergency re-laparotomy due to bowel obstruction, and one due to lack of improvement. In the TD group, one patient abandoned treatment due to failure to progress. Additionally, one patient who initially received TD switched to EVT.

Patient and tumor characteristics

Patient and tumor characteristics were similar between the EVT and TD groups, with no significant differences, except that patients treated with EVT were more likely to undergo laparoscopic AR 6/14 (62.9%) vs. 1/17 (5.9%), $p = 0.028$ (Table 5).

Table 5. Patient and tumor characteristics of patients treated with TD and EVT.

Characteristic	Endoscopic Vacuum Therapy (n=14)	Transanal Drainage (n=17)
Age (years), median (IQR)	68 (52.8-71)	67 (58.5-71)
Sex (male), n (%)	10 (71.4)	11 (64.7)
BMI (kg/m ²), median (IQR)	26.5 (24.2-31.0)	26.6 (24.8-28.2)
ASA classification, n (%)		
1	2 (11.8)	1 (7.1)
2	13 (76.5)	9 (64.2)
3	2 (11.8)	3 (21.4)
CCI score, median (IQR)	4.5 (3-7)	4 (3.5-5)
Smoking status (yes), n (%)	5 (36)	4 (24)
Tumor height (cm), median (IQR)	10 (9-12)	9 (7.27-10)
Tumor stage, n (%)		
T1	1 (7.1)	3 (17.6)
T2	4 (28.6)	3 (17.6)
T3	8 (57.1)	10 (58.8)
T4	1 (7.1)	1 (5.9)
Preoperative radiotherapy, n (%)	9 (64.3)	12 (70.6)
Laparoscopic approach, n (%)	6 (42.9)	1 (5.9)
Anastomosis type, n (%)		
Side to end with a reservoir	7 (50)	10 (58.8)
End-to-end without a reservoir	7 (50)	7 (41.2)
DS, n (%)	13 (92.9)	16 (94.1)
Leak location (anastomotic ring), n (%)	11 (78.6)	12 (70.6)
Leak location (Blind end), n (%)	2 (14.3)	5 (29.4)

Anastomotic leak characteristics and treatment

Anastomosis types included side-to-end with a reservoir in 7 (50%) EVT patients and 10 (58.8%) TD patients, and end-to-end without a reservoir in 7 (50%) EVT patients and 7 (41.2%) TD patients (Table 5). The AL location was predominantly at the anastomotic ring, with 11 (78.6%) cases in the EVT group and 12 (70.6%) in the TD group, while the rest (EVT 2 (14.3%) and TD 5 (29.4%)) were leaks at the blind end. One patient in the EVT group had missing data for the location of the leak. DS was present in 13 (92.9%) of the EVT patients and 16 (94.1%) of the TD patients.

Treatment factors and outcomes

Treatment factors differed between the groups (Table 6). The median time from index surgery to AL diagnosis was shorter in the EVT group (10.5 days, IQR=7.7-18) compared to the TD group (22 days, IQR=14-28). Similarly, time to treatment start was 11.5 days (IQR=8.7-18.8) for EVT versus 23 days (IQR=15-31.5) for TD.

Patients in the EVT group underwent more treatments overall (median 7.5, IQR=4-9.7 vs. 3, IQR=1-5.7) and more treatments requiring anesthesia (median 4, IQR=1.7-

6.2 vs. 0, IQR=0-1). However, the total treatment duration was shorter for EVT (median 24.5 days, IQR=11-36) than for TD (median 37 days, IQR=17-50.5).

Table 6. Treatment factors and outcome for patients treated with TD and EVT.

Treatment factor	Endoscopic Vacuum Therapy (n=14)	Transanal Drainage (n=17)
Time to AL diagnosis (days), median (IQR)	10.5 (7.7-18)	22 (14-28)
Time to treatment start (days), median (IQR)	11.5 (8.7-18.8)	23 (15-31.5)
Number of treatments, median (IQR)	7.5 (4-9.7)	3 (1-5.7)
Number of treatments in anesthesia, median (IQR)	4 (1.7-6.2)	0 (0-1)
Treatment time (days), median (IQR)	24.5 (11-36)	37 (17-50.5)
Clinical success rate, n (%)	11 (78.6)	15 (88.2)
Bowel continuity after at least 24 months follow-up, n (%)	7 (50.0)	11 (64.7)

Days from index procedure.

Paper VI

Between 2014 and 2018, 1,126 rectal cancer patients underwent AR at 11 hospitals in Sweden. Of these, 905 (80.4%) received DS and were included in this study. The primary endpoint analysis excluded patients with AL (n = 201) or who did not undergo SR (n = 64), resulting in a cohort of 638 patients. The median follow-up period was 4.1 years, with 64 (9%) patients retaining their DS permanently. The patient cohort is detailed in the flowchart below (Figure 1).

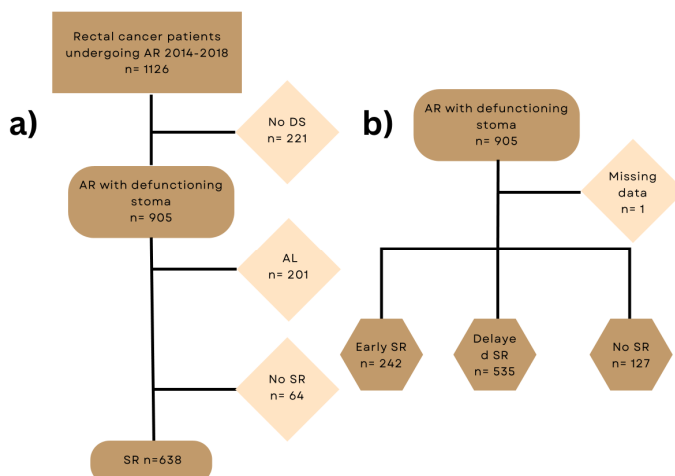


Figure 1. Flowcharts of patients who underwent anterior resection for rectal cancer between 2014 and 2018. A. The elapsed time to stoma reversal and postoperative 90-day complications (primary endpoint) were studied. b. Analysis of the clinical factors associated with delayed stoma reversal (secondary endpoint). AR, anterior resection; DS, defunctioning stoma; AL, anastomotic leak; SR, stoma reversal

Main results - postoperative 90-day complications and reoperations

A total of 116 (18.2%) patients experienced at least one postoperative 90-day complication after SR. The median time from AR to SR was significantly longer in this group compared to the non-complication group (10.2 months [IQR 6.5–15.2] vs. 7.3 months [IQR 4.8–11.7], $p<0.001$). A smaller proportion of patients (39, 6.1%) required reoperation after SR. The median time to SR was also longer in the reoperation group than in the non-reoperation group (11.1 months [IQR 7.8–15] vs. 7.6 months [IQR 4.9–12], $p=0.002$).

Patients were allocated to two groups: 209 (32.8%) patients had SR within 6 months of AR, and 428 (67.2%) patients had delayed SR (>6 months). Univariable analysis revealed a significant relationship between delayed SR (>6 months) and both postoperative 90-day complications ($p=0.009$) and reoperation after SR ($p=0.021$).

Multivariable analysis results

When analyzed as a continuous variable (in months), elapsed time from AR to SR was significantly associated with postoperative 90-day complications (OR 1.02; 95% CI, 1.00-1.04; $p=0.049$), but not with reoperations. When analyzed as a binary variable (6 months), delayed SR was independently associated with an increased risk of postoperative 90-day complications (OR 1.73; 95% CI, 1.04-2.86; $p=0.034$) and reoperation after SR (OR 2.66; 95% CI, 1.06-6.68; $p=0.038$).

Secondary results: patient and tumor characteristics

Patients who did not undergo SR were significantly older (median 70 vs. 66 years), were more frequently classified as ASA III–IV (26.6% vs. 15%), had a higher proportion of advanced tumors (T3-4: 60.9% vs. 56.0% and N1-2: 56.3% vs. 35.9%), and had a higher rate of distant recurrence (28.1% vs. 15.5%) compared to those who underwent SR. Notably, over a third of both the SR and non-SR groups presented with high-lying tumors (38.6% vs. 42.2%), located 11-15 cm from the anal verge. This observation aligns with the findings reported in *Paper II*. The clinical characteristics of the stoma reversal and non-reversed stoma groups are detailed in Table 7.

Table 7. Clinical characteristics of stoma reversal compared with the non-reversed stoma, where patients with anastomotic leak are excluded.

Characteristics	Stoma reversal (N=638)	Non-reversed stoma (N=64)
Age (years)	66 (59-72)	70 (64-74)
Sex (male), n (%)	391 (61.3)	33 (51.6)
BMI (kg/m ²)	25.4 (23.2-28.1)	25.6 (23.4-28.4)
Smoking, n (%)	41 (6.8)	4 (7.4)
ASA class, n (%)		
I	146 (23.1)	7 (10.9)
II	391 (61.9)	40 (62.5)
III-IV	95 (15)	17 (26.6)
CCI group, n (%)		
0	437 (68.5)	38 (59.4)
1	116 (18.2)	15 (23.4)
2	56 (8.8)	5 (7.8)
3+	29 (4.5)	6 (9.4)
Tumor distance, cm		
High (11-15)	246 (38.6)	27 (42.2)
Middle (6-10)	378 (59.3)	36 (56.3)
Low <5	13 (2.0)	1 (1.6)
Neoadjuvant therapy, n (%)		
Radiotherapy	216 (33.9)	23 (35.9)
RCT	108 (16.9)	15 (23.4)
None	314 (49.2)	26 (40.6)
pCR	9 (1.4)	3 (4.7)
Operation time, min	272 (200-362)	263 (197-352)
Surgical approach, n (%)		
Open/converted	343 (53.8)	42 (65.6)
Laparoscopy	108 (17.0)	10 (15.6)
Robotic	186 (29.2)	12 (18.8)
Anastomosis type, n (%)		
End-end	155 (24.3)	14 (21.9)
Side-end/J-pouch	453 (71.0)	44 (68.8)
Missing	30 (4.7)	6 (9.4)
TME	566 (88.7)	57 (89.1)
PME	72 (11.3)	7 (10.9)
Intraoperative complications, n (%)		
Bleeding > 500ml	66 (10.3)	8 (12.5)
Serosal tear	11 (1.7)	2 (3.1)
Bowel perforation	10 (1.6)	2 (3.1)
Ureteric injury	2 (0.3)	0
Tumor stage, n (%)		
T0	12 (1.9)	4 (6.3)
T1-2	261 (41.5)	21 (32.8)
T3-4	353 (56.0)	39 (60.9)
Tx	4 (0.6)	0
yp/pN, n (%)		
N0	401 (63.8)	28 (43.8)
N1-2	226 (35.9)	36 (56.3)
Nx	2 (0.3)	0
M, n (%)		
M0	603 (94.5)	58 (92.1)
M1	19 (3.0)	5 (7.9)
Adjuvant chemotherapy, n (%)	217 (34.0)	28 (43.8)
Local recurrence, n (%)	12 (1.9)	1 (1.6)
Distant recurrence, n (%)	99 (15.5)	18 (28.1)
Follow-up, years	4.8 (3.6-6)	4.6 (3.5-5.8)

Treatment characteristics and surgical approach

In the SR group, 46% of patients underwent minimally invasive procedures, including robotic-assisted procedures in 29%. Patients who received adjuvant chemotherapy had a significantly longer elapsed time to SR than those who did not (11.4 months vs. 6.4 months).

Factors associated with delayed stoma reversal

Univariable and multivariable analyses were performed to identify factors independently contributing to a delayed SR (> 6 months). These analyses revealed that both AL and nodal disease (N1-2) were independently associated with a delayed SR.

Anastomotic leakage: Patients with AL had 2.3 times higher odds of delayed SR (OR 2.30; 95% CI, 1.41-3.75; $p < 0.001$).

Nodal disease (N1-2): Patients with nodal disease had 4.15 times higher odds of delayed SR (OR 4.15; 95% CI, 2.73-6.31; $p < 0.001$).

No significant association was found for age, sex, ASA class, AL grade, or T or M stage.

Complication types and reoperation indications

The most frequent postoperative complications after SR were ileus (5.2%), surgical-site infection (2.7%), and mechanical small-bowel obstruction (4.7%). The full breakdown of all complication types is presented in the following table (Table 8). A total of 39 patients (6%) required reoperation after stoma reversal. The most common indications were small-bowel obstruction (2.7%), bowel resection (1.4%), and new stoma creation (1.3%). Other reasons for reoperation are detailed in Table 8.

Table 8. List of postoperative 90-day complications and reoperations following stoma reversal (SR)

Complications post-SR	n (%)	Indications for reoperation	n (%)
Ileus	33 (5.2)	Small bowel obstruction	17 (2.7)
Small bowel obstruction	30 (4.7)	Bowel resection	9 (1.4)
Surgical site infection	17 (2.7)	New stoma creation	8 (1.3)
Leak	14 (2.2)	Negative laparotomy	7 (1.1)
Other infections than Surgical site infection	23 (3.6)	Small bowel anastomotic leak	6 (0.9)
Incisional hernia	10 (1.6)	Bleeding	4 (0.6)
Wound dehiscence	4 (0.6)	Surgical site infection	4 (0.6)
Bleeding	2 (0.3)	Wound dehiscence	4 (0.6)
Pulmonary complications	4 (0.6)	Other	4 (0.6)
Cardiac complications	3 (0.5)		

Discussion

Paper I

Paper I evaluated a structured surveillance program intended to reduce dehydration and dehydration-related readmissions among patients with DLI after low anterior resection for rectal cancer. While the intervention failed to lower overall dehydration or readmission rates compared to historical controls, it successfully reduced the incidence of symptomatic dehydration. This finding indicates that early detection of electrolyte disturbances and timely outpatient management (dietary counseling and anti-diarrheal therapy) can avert progression to clinically significant dehydration and potentially prevent hospitalization.

Older age and chronic diuretic use emerged as important risk factors for dehydration in Paper I. These associations are consistent with a prior large-scale systematic review and meta-analysis encompassing over 27,000 patients showing that both age ≥ 65 years and regular diuretic use are significant independent predictors of dehydration-related readmission (174). Paper I also noted a non-significant trend towards higher ACE inhibitor/ARB use among admitted dehydrated patients, a finding also described by other investigators who reported an increase of 13 times the odds for dehydration-related readmission in patients receiving these medications (175,176).

While Paper I did not find an association between adjuvant chemotherapy and dehydration, this may be due to its short 8-week follow-up period. Other work has identified adjuvant chemotherapy as an independent factor for HOS and increased ileostomy complications (177), suggesting that differences in follow-up duration and the timing of chemotherapy relative to stoma formation may explain the discrepant findings. It is worth noting that the increasing adoption of total neoadjuvant therapy (TNT) is likely to reduce the proportion of patients receiving adjuvant chemotherapy in contemporary practice, potentially minimizing the relevance of adjuvant chemotherapy as a postoperative risk factor over time. Whether this shift toward TNT influences postoperative stoma output through cumulative preoperative bowel toxicity remains uncertain. To our knowledge, no studies have specifically evaluated the relationship between TNT and DLI-related HOS, which remains an area for future prospective investigation.

The dehydration and readmission rates observed in Paper I fall within the wide range reported across the literature. However, recent interventional studies suggest that different strategies may yield substantial outcomes. For example, Ozata et al. introduced a comprehensive prevention bundle, achieving a reduction in dehydration-related readmissions from 22% to 2% ($p = 0.002$) (178). Their bundle incorporated structured telephonic follow-up, monitoring of ileostomy output and dehydration symptoms, dietary modification, oral rehydration, and stepwise pharmacological escalation. Subsequent analysis identified a mean stoma output of 877.5 mL/day before discharge as a strong predictor of dehydration-related readmission. The primary endpoint, dehydration-related readmissions, was shared with earlier efforts by Nagle et al. and Shaffer et al (179,180). In contrast, Paper I sought to mitigate both the overall incidence of dehydration and associated readmissions. A shared element among these three interventions was active home-based support; Nagle et al.'s "Ileostomy Pathway" incorporated post-discharge visits from the Visiting Nurse Association, resulting in a 0% readmission rate for dehydration (from a pre-intervention baseline of 15.5%). Likewise, Shaffer et al. implemented an intensive 4-week post-discharge protocol with home health agency involvement, featuring scheduled home visits, phone calls, and predefined clinical triggers (e.g., heart rate >100 bpm or ileostomy output >1200 mL/day), which facilitated diversion from emergency departments and yielded a 58% reduction in readmissions (from 20.8% to 8.7%) alongside notable cost savings.

Comparative interpretation must account for methodological and population differences. Prior intervention studies often included heterogeneous patient populations rather than exclusively rectal cancer patients, used small convenience samples, and lacked concurrent randomized controls. Paper I's exclusive focus on rectal cancer patients preserves internal consistency but limits direct comparability to broader series.

Compared with previously described studies, the results in Paper I may appear modest; however, given differences in targeted outcomes and study designs, the findings retain clinical implications and provide supportive evidence for structured follow-up programs.

Limitations of Paper I include its non-randomized design with historical controls and a short 8-week follow-up period, which introduce several potential sources of bias. The non-randomized approach and use of historical controls from 2007–2009, compared to the 2015–2017 intervention period, may lead to selection bias due to differences in patient characteristics or evolving care practices, such as changes in surgical techniques, stoma care, or adjuvant therapies, which could potentially confound the intervention's apparent effect. The Hawthorne effect, where awareness of observation alters participant behavior, potentially inflating compliance and perceived intervention benefits, in the prospective arm, could exaggerate the overall dehydration by heightening vigilance toward subtle symptoms, leading to earlier reporting/detection of mild cases (181). Regarding

statistical risks, the sample size falls short of the a priori estimate of approximately 100 patients needed for 80% power (one-tailed $p < 0.05$) to detect differences in dehydration rates. This raises concerns about type 2 error (false negative), particularly for non-significant outcomes like overall dehydration and readmissions, where a true effect may have been missed due to inadequate power. A formal power analysis could have refined the sample size; however, the prospective cohort design with historical controls was chosen for feasibility, leveraging existing data to avoid the ethical concerns of withholding surveillance from a concurrent control group and addressing resource constraints at the participating hospitals.

Future trials should test multi-component prevention bundles in randomized, adequately powered designs, stratify or enrich for high-risk subgroups (older adults, chronic diuretic chemotherapy-related morbidity), and incorporate health-economic evaluations and implementation metrics.

Paper II

Paper II examined the impact of increased DLI usage on AL incidence in anterior resection for rectal cancer. Despite a marked rise in DLI utilization between study periods, the overall incidence of AL remained unchanged. Reoperation rates for AL were stable overall, but among diverted patients in the earlier cohort, fewer reoperations occurred in both TME and PME subgroups. These findings suggest that DLI reduces the need for surgical intervention and moderates the clinical severity of AL, rather than preventing AL.

The literature reports heterogeneous effects of diversion: some trials and meta-analyses indicate reduced AL incidence with DLI, whereas others show that diversion primarily decreases AL-related morbidity and reoperation rates. (123,182,183).

Recent meta-analytic evidence supports the protective role of DLI, demonstrating significantly lower odds of both complications and AL in diverted patients across nine randomized controlled trials (123). Their analysis revealed that DLI reduced AL occurrence by 64% compared to non-diverted patients. Specific risk factors for AL in the absence of diversion were identified, including higher BMI, ASA score ≥ 3 , lower tumor height, neoadjuvant therapy, open surgical approach, end-to-end anastomosis, and prolonged operative time. Similarly, Hrebinko et al. demonstrated a 54% reduction in AL risk among diverted patients, with substantial differences in subsequent surgical interventions when AL occurred, including reduced rates of colostomy creation, completion proctectomy, and pelvic washout procedures (182).

Of note, in the minimally invasive surgery era, AL following minimally invasive LAR was diagnosed earlier, and the majority of patients (78%) requiring reoperation

were managed laparoscopically, compared with none in the open surgery group (184). These findings suggest that minimally invasive LAR may reduce adhesion burden and preserve the feasibility of laparoscopic re-intervention, potentially extending the window for safe operative management of AL beyond the traditional 14-day threshold described in open surgery.

However, conflicting evidence challenges the notion that DLI offers a universal benefit. Niu et al. found no significant difference in AL rates between patients with and without diverting ileostomy, even in high-risk subgroups receiving neoadjuvant radiotherapy (183). Their multivariate analysis identified diabetes and anastomotic height as the primary predictors of AL, rather than diversion status. Similarly, Paper II confirmed that male gender, ASA class 3-4, BMI ≥ 30 , and neoadjuvant therapy were significant risk factors for AL, while DLI status showed no protective effect. Notably, most patients in the latter cohort presented with mid-level (6-10 cm) and higher-located tumors (11-15 cm from the anal verge), fewer T3-4 tumors, and fewer received both neoadjuvant and adjuvant therapy characteristics that do not typically constitute a high-risk profile for AL. This unselective cohort composition reflects real-world clinical practice, where DLI usage may not be optimally targeted to patients most likely to benefit from diversion.

Differences between randomized trials and registry-based practice likely explain divergent findings. Randomized controlled trials often apply strict inclusion criteria and standardized perioperative protocols that amplify measurable efficacy (efficacy in optimal conditions), whereas registry cohorts capture broader practice heterogeneity and temporal changes in patient selection, technique, and perioperative care (effectiveness in routine practice). In such real-world settings, routine or unselective use of DLI may fail to reduce population-level AL incidence but still attenuate clinical severity when leaks occur.

Modern practice is moving towards selective DLI usage guided by risk stratification and may reflect growing recognition that routine diversion may not benefit all patients undergoing AR. The development of predictive models incorporating multiple risk factors represents a significant advancement from earlier practices of routine diversion for all LARs. Recent initiatives, including the Swedish SELSA study and the GRECCAR 17 trial are investigating tailored approaches to DS use, incorporating anastomotic risk scores to guide decision-making (159,185). The SELSA study employs a validated risk score that integrates patient and technical variables to identify candidates for selective diversion, while the GRECCAR 17 compares tailored versus systematic DLI after TME, with quality of life at 12 months as the endpoint. These models typically integrate patient factors, including age, gender, BMI, and comorbidities, with technical variables such as anastomotic height, surgical approach, and intraoperative assessment of anastomotic integrity. The goal is to identify patients who are most likely to benefit from diversion while avoiding unnecessary stoma creation in low-risk cases.

Machine learning algorithms and artificial intelligence applications are emerging as potential tools for enhanced risk prediction (186). These approaches may identify complex interactions between risk factors that traditional statistical models cannot capture, potentially improving patient selection for DLI. However, external validation and clinical implementation of these advanced prediction tools remain areas of active investigation.

Several limitations must be acknowledged when interpreting the findings of Paper II. The retrospective nature of registry-based analysis inherently limits causal inference, as unmeasured confounders may influence both DLI usage patterns and AL outcomes. The extended study interval spans eras of evolving surgical technique, perioperative care, and oncologic practice, introducing temporal confounding.

One of the most significant limitations is the absence of crucial variables in SCRCR that are known to influence AL risk. Anastomotic height from the anal verge, a well-established predictor of AL, is not recorded in the registry, limiting the ability to control for this important confounding factor. Additionally, the PME variable was recorded only in 2022, after study completion, necessitating the use of tumor height as a proxy for mesorectal excision type. This approach may introduce misclassification bias, as tumor location does not perfectly correlate with the extent of mesorectal excision performed.

The definition and detection of AL may vary across institutions and time periods and may lack a clear definition when registered as SCRCR, potentially affecting the accuracy of reported incidence rates and introducing potential misclassification. Furthermore, interinstitutional and temporal variability in AL definitions and diagnostic intensity may have led to underreporting of subclinical leaks. Additionally, the study's focus on reoperation rates as a primary outcome may not fully capture the spectrum of AL severity or the impact of conservative management strategies.

In summary, Paper II indicates that, in routine clinical practice, DLI primarily attenuates the clinical severity and downstream consequences of anastomotic leak rather than preventing leak occurrence. Targeted use of DLI should be considered for rectal cancer patients at elevated risk of AL, because selective diversion can reduce subsequent morbidity; therefore, individualized risk stratification is essential to optimize the trade-off between protecting against severe leaks and avoiding unnecessary stoma formation, particularly in vulnerable patients for whom diversion may convert a life-threatening septic event into a more contained and manageable complication.

Future research should focus on developing robust prediction models to identify patients most likely to benefit from DLI. Prospective randomized trials comparing selective versus routine diversion strategies, such as the ongoing SELSA study, will provide crucial evidence for evidence-based guidelines (159).

Paper III

In Paper III, EVT treatment had comparable outcomes with TD in AL management after AR for rectal cancer. The results showed no superior success of AL treatment or bowel continuity in patients who underwent EVT versus TD. While EVT facilitates a cleaner wound environment, promotes granulation tissue formation, and reduces cavity size through negative pressure application (187), EVT achieves similar outcomes to conventional approaches, as shown in Paper III, in resolving AL and restoring intestinal continuity.

The results align with another retrospective Swedish study by Weréen et al., which compared 14 patients treated with EVT to 34 receiving transanal irrigation for AL after AR (188). At a median follow-up of 5.9 years, bowel continuity was achieved in 43% of the EVT group and 50% of the irrigation group ($p = 0.75$). Systematic reviews and meta-analyses offer a more comprehensive view of EVT's efficacy by comparing it with conventional management, including drainage, antibiotics, and surgical revision. A meta-analysis by Dhindsa et al. reported clinical success of 84.99% for EVT in AL after AR, with adverse events in 7.7% (189). A subsequent systematic review by Kühn et al. of colorectal leaks found an overall clinical success rate of 81.4% for EVT and a stoma reversal rate of 66.7% (190). A recent systematic review by Luo et al. showed EVT's superiority over traditional treatment in closure rates (RR 1.18, 95% CI 1.03–1.35, $p=0.02$) and shorter treatment duration (mean difference -30.6 days, 95% CI -43.5 to -17.7 days, $p<0.001$) (187). However, the Luo analysis showed no significant difference in restoration of bowel continuity (RR 1.20, 95% CI 0.83–1.73, $p=0.34$), hospital stay (mean difference 1.7 days, 95% CI -4.2 to 7.7, $p=0.57$), or treatment-related complications (RR 1.17, 95% CI 0.52–2.80, $p=0.71$).

The clinical success rates reported in Paper III are comparable to those reported in meta-analyses (81–85%), indicating similar leak-resolution rates. However, the bowel continuity rate in the EVT group is lower than Kühn et al.'s pooled rate (66.7%) but aligns with Weréen et al.'s EVT rate (43%). Notably, the TD group's bowel continuity rate matches the meta-analysis (66.7%), and Luo et al. found no significant difference in bowel continuity restoration between EVT and standard care (187,190). This difference in the EVT group likely reflects long-term follow-up capturing real-world outcomes, study heterogeneity, and publication bias in meta-analyses, patient selection factors (Kühn noted high success applies to selected patients with extraperitoneal defects; Luo noted potential severity differences between groups) (187,190). Additionally, the high proportion of patients receiving neoadjuvant radiotherapy may affect long-term anastomotic function. These systematic reviews demonstrate heterogeneous study designs ranging from single-arm case series to comparative studies, with varying patient populations, treatment protocols, and outcome definitions across the included studies. This methodological diversity limits the ability to draw definitive conclusions about the superiority of

EVT over specific conventional treatments. These findings emphasize the need for realistic expectations and careful patient selection for EVT.

The timing of treatment initiation has emerged as a critical factor in the successful management of anastomotic leaks. Although various cut-off points for treatment initiating have been suggested by different authors, early intervention is commonly reported as vital for a successful outcome. The French GRECCAR Group multicenter study demonstrated that EVT initiation within 15 days of AL diagnosis resulted in significantly higher success rates compared to delayed treatment (72.4% vs. 27.8%, $p = 0.003$) (191). Furthermore, primary EVT implementation achieved superior outcomes compared to salvage therapy (patients who underwent previous AL management procedures), 73% vs. 33%, $p = 0.006$, emphasizing the importance of early decision-making in treatment algorithms. These findings are corroborated by Talboom et al., who reported that early endoscopic vacuum-assisted surgical closure (EVASC) initiation (≤ 21 days) yielded substantially higher rates of healed anastomosis (87% vs. 59%, OR 4.43, $p < 0.05$) and functional anastomosis (80% vs. 56%, OR 3.11, $p < 0.05$) compared to late initiation (192). The median interval from AL diagnosis to treatment initiation was significantly shorter in the early group (11 days vs. 70 days, $p < 0.001$), with permanent stoma rates dramatically reduced (7% vs. 28%, OR 0.18, $p < 0.05$). Similarly, van Koperen et al. found in their Dutch multicenter study that EVT initiated within 6 weeks of initial surgery (median, 24 days post-surgery) resulted in higher cavity closure rates compared to later initiation (75% vs. 38%, $p = 0.315$), although the difference did not reach statistical significance (193).

Neoadjuvant therapy is another factor possibly influencing EVT treatment. In our study, the proportion of patients who received neoadjuvant radiotherapy was comparable between the EVT and TD groups (64.3% vs. 70.6%), but no subgroup analysis of neoadjuvant-treated patients was performed. However, the literature consistently shows that neoadjuvant treatment affects the duration of AL treatment. Von Bernstorff et al. reported that healing took considerably longer in patients receiving neoadjuvant treatment (31.6 days) than in those without (12.3 days; $p < 0.001$) (194). This extension is attributed to radiation-induced tissue atrophy, fibrosis, and vascular damage, which delay the formation of effective granulation tissue and wound closure. In a large cohort study of various colorectal defects (AL and rectal stump leak), including a majority with AL (77%), it was found that while previous chemo-radiation was associated with a significantly longer duration of EVT ($p = 0.006$), it was not linked to outright EVT failure in the entire cohort. A prolonged treatment time was specifically noted in the subgroup of patients treated for AL ($p = 0.013$) (195).

Despite the potential of EVT in managing AL, treatment failures remain a notable concern. In Paper III, failures included three cases of abandoned treatment. These findings align with the literature, indicating a failure rate of approximately 16.3%, often associated with procedure-related complications in 11.8% of cases, such as

progressive pelvic sepsis and persistent sinus (190). Other complications were bleeding, severe pain, and lack of compliance.

The main limitations of Paper III stem from its retrospective observational design, which introduces risks of bias and precludes strong causal inferences. The small sample size further limits statistical power and generalizability of the findings. Additionally, the non-randomized treatment assignment, determined by surgeon preference, raises the potential for selection bias (as evidenced by the higher rate of laparoscopic resection among EVT patients, even though baseline patient and tumor characteristics were comparable). Finally, the upfront exclusion of the most severe AL cases likely skewed the cohort toward less complex leaks, potentially underestimating EVT's true challenges in high-risk clinical scenarios.

EVT should be integrated into AL management algorithms after AR with caution. Meta-analyses report high success rates for EVT in selected populations, supporting its role as a minimally invasive option for stable, contained leaks. However, EVT is resource- and labor-intensive owing to the need for repeated device exchanges, often performed under sedation or anesthesia, and is associated with increased material costs. For patients with proximal diversion who are clinically stable, TD or conservative management remains a reasonable and often preferable strategy because they demand fewer resources. EVT may improve functional outcomes by facilitating sphincter preservation and reducing stoma duration, but current evidence does not justify routine replacement of TD with EVT in all diverted, stable patients.

The landscape of AL management with EVT is evolving, and several modifications of the technique have been described by various authors. One such approach involves pre-treatment with EVT, followed by early transanal suturing of the anastomotic defect, as demonstrated in the CLEAN study, a prospective multicenter feasibility study by Borstlap et al. involving 30 patients with rectal cancer post TME. In that study, anastomotic healing was achieved in 70% of cases at a median follow-up of 14 months. Bowel continuity was restored in 67% of patients, and 73% received preoperative radiotherapy. Better outcomes were observed when treatment was started within three weeks of the index operation (196). There are ongoing and planned studies aiming to provide high-quality evidence from randomized controlled trials that is currently lacking. The SEVTAR trial is a multi-European center RCT, evaluating prophylactic EVT for 5 days to reduce AL rates after low anterior resection for rectal cancer with DSs and low anastomoses (197). Additionally, Heiss et al. reported early experience with the VACStent device, a self-expanding nitinol stent covered with a silicone membrane and encased in a polyurethane sponge cylinder. In their pilot study of 12 patients, the device showed successful AL healing without major complications other than stent dislodgement, suggesting a potential role in treating anastomotic leaks while maintaining fecal passage and avoiding stoma creation (198).

In conclusion, this study demonstrates equivalent outcomes between traditionally performed EVT and TD for managing AL after AR in patients with DSs, thereby challenging the assumption of EVT's routine superiority. These findings suggest that in stable, diverted patients with contained leaks, the choice between EVT and TD should be individualized based on institutional expertise, resource availability, and patient-specific factors. Institutions should develop standardized protocols for patient selection, device management, exchange intervals, complication surveillance, and predefined criteria for escalation to operative management, and should prioritize patient enrollment in randomized studies to strengthen the evidence base.

Paper IV

Delays in SR after AR for rectal cancer present a clinically important trade-off between quality of life and the morbidity of a second operation. Understanding the temporal relationship between AR and SR is essential for perioperative planning and risk stratification. Delayed stoma reversal, particularly beyond six months, emerged as an independent risk factor for 90-day postoperative complications and reoperation.

A plausible physiological mechanism for this association is a prolonged non-functional state of the diverted bowel segment, which can suffer from smooth muscle atrophy and loss of contractility (199). Such changes may predispose to immediate postoperative complications after restoration of continuity, notably postoperative ileus and small bowel obstruction, and can thereby increase the risk of subsequent interventions (155). These findings strongly emphasize that the elapsed time to SR is not a benign factor but a crucial independent determinant of postoperative morbidity.

This aligns with several investigations on delayed SR in rectal cancer patients. Studies demonstrate a clear association: delays in ileostomy reversal beyond six months are linked to increased postoperative complications and longer hospital stays (148,200,201). Common causes of these delays include the need for adjuvant therapy and complications like anastomotic leaks following index surgery. Specifically, these studies reported a reversal rate averaging approximately 75%, with median reversal times ranging from 5.6 to 10.3 months. Post-reversal complication rates, including ileus, wound infections, and pseudomembranous colitis, ranged from 26% to 40%. Statistically significant associations included a higher risk of complications with delays exceeding six months and neoadjuvant radiotherapy as a predictor of non-reversal (148,200,201).

A more recent retrospective cohort study by Turner et al. supports the previous findings; the overall complication rate was 21.5%, with rates strongly associated

with the time to ileostomy closure (202). Complication rates approximately doubled with each stepwise increase in delay when closed; within 90 days (8%), between 90-360 days (20%), between 360-720 days (28%), and after 720 days (54%). An additional finding was a 6% increase in the risk of complications for each additional 30 days a patient spends waiting for closure (RR 1.06, 95% CI [1.02-1.10]). The median length of stay also increased with stoma duration, rising from 4 days (up to 180 days) to 7 days (longer than 720 days). Similarly, a retrospective study by Hacim et al. found the likelihood of postoperative complications escalated when the elapsed time after index surgery to stoma closure was divided into three intervals: less than 3 months, 3–6 months, and greater than 6 months (203). Their analysis identified ileostomy duration as the primary independent predictor of postoperative complications. By using the < 3 months group as the reference, the odds ratios were 4.5 (95% CI 1.2–16.7, $P=0.023$) for the 3–6 months group and 15.2 (95% CI 3.1–75.2, $P=0.001$) for the >6 months group.

In contrast, Zhen et al.'s 2017 prospective non-randomized study [11] compared early closure (~1 month) versus late closure (~6 months) in 161 rectal cancer patients, revealing that late closure patients received more adjuvant chemotherapy cycles (4.35 vs. 2.99, $P=0.01$) but had comparable post-closure complication rates (18.6% vs. 20.9%), including wound infections and ileus (204). Quality-of-life assessments using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CR38 and the Fecal Incontinence Quality of Life scale showed similar overall outcomes, although patients with early closure experienced more micturition problems ($P < 0.05$). Additionally, neoadjuvant therapy was more prevalent in late closure (48.6% vs. 28.6%, $P = 0.009$). This contrasts with Paper IV's increased risk of complications associated with delays of more than 6 months, suggesting that later closure may facilitate completion of adjuvant therapy without substantially increasing severe outcomes.

Multiple population-based studies have consistently identified adjuvant chemotherapy as the predominant health-related factor contributing to delayed stoma reversal. Gadan et al. reported that adjuvant therapy was the leading cause of delay in 38% of cases in a Swedish population-based cohort. The underlying basis for impaired adjuvant therapy tolerance in patients with diverting ileostomies involves high-output complications, leading to dehydration, electrolyte imbalances, and subsequent dose reductions (177).

The existing literature demonstrates a complex, bidirectional relationship between DSs and adjuvant chemotherapy, with significant implications for both treatment tolerance and the timing of stoma reversal. Recently, Yagyu et al. conducted a comparative analysis of 107 rectal cancer patients and reported equivalent chemotherapy completion rates and relative dose intensity between DLI and non-DLI cohorts (139). However, the DLI group demonstrated significantly higher rates of grade 3 or higher adverse events, predominantly during the first three cycles of treatment (18.2% vs. 4.1%, $P = 0.015$).

The findings of Paper IV, while significant, must be interpreted in light of its limitations. The retrospective design introduces a potential for selection bias, as the reasons for delayed stoma reversal may not be fully captured in the registry data. For instance, patients with a prolonged recovery from index surgery or those with poor nutritional status may have had their stoma reversal intentionally delayed, confounding the association between timing and complications. Furthermore, the study's reliance on registry data meant that a standardized complication grading system, such as the Clavien-Dindo classification, was not used, potentially limiting the accuracy of complication reporting and hampering direct comparisons with other studies. The exclusion of patients with ALs of all grades from the primary analysis, while intended to create a more homogeneous cohort, may also have introduced selection bias by potentially excluding patients at higher risk of complications. Finally, the lack of detailed data on the timing and completion of adjuvant chemotherapy limits the ability to draw firm conclusions about the interplay between chemotherapy and complications of stoma reversal.

Despite these limitations, Paper IV's principal finding remains clinically significant: delaying stoma reversal beyond six months independently increases the risk of early postoperative morbidity and reoperation. This challenges traditional delays and supports earlier closure where feasible. The EASY trial demonstrated that very early closure (8–13 days) is safe, cost-effective, and reduces complications/permanent stomas in highly selected patients, although it did not assess timing relative to adjuvant chemotherapy (205). Ongoing randomized trials such as CoCStom (early: 8–10 days pre-adjuvant; late: ~26 weeks post) and STOMAD (early: 30–40 days during adjuvant; late: post-adjuvant) directly address this gap by testing whether early closure improves chemotherapy completeness and patient outcomes versus conventional late reversal (206,207).

The presence of nodal disease, which necessitates adjuvant chemotherapy, is a key predictor of delayed reversal and highlights this therapy's central role in timing decisions, creating a clinical dilemma: prolonged diversion increases stoma-related morbidity and may impair chemotherapy tolerance, while incomplete adjuvant therapy compromises oncological outcomes (208). Multidisciplinary assessment should individualize timing by integrating surgical recovery, nutritional status, stoma function, and the oncological schedule. Where oncologically and clinically appropriate, clinicians should prioritize strategies that avoid excessively late reversal targeting closure within six months when feasible while ensuring completion of systemic therapy.

Future randomized trials must integrate perioperative outcomes with chemotherapy metrics (completion, dose intensity) and long-term oncological endpoints, using standardized complication grading and patient-reported quality-of-life measures to resolve these competing risks.

The central clinical implication of Paper IV is therefore that prolonged delay to SR should be avoided when surgical recovery, anastomotic integrity, and oncological treatment planning allow earlier closure. Pending the results of randomized trials, clinicians should prioritize timely reversal in clinically stable patients, carefully coordinating surgical and oncological care to optimize both short- and long-term outcomes.

Future Perspective

Despite substantial advances in rectal cancer surgery and perioperative care, AL remains one of the most challenging complications following anterior resection. Future research should focus on improving the selective use of DLI by accurately predicting AL risk. Individualized risk stratification models incorporating patient characteristics, tumor factors, surgical variables, and emerging technologies such as real-time tissue perfusion assessment using indocyanine green fluorescence angiography and microbiome profiling may facilitate more tailored decision-making.

The findings of this thesis also highlight the need for structured surveillance programs for patients living with a DLI. Such initiatives should be regarded as a healthcare priority, particularly for elderly, frail, and multimorbid patients who may require enhanced support after hospital discharge. Future studies should evaluate whether intensified follow-up pathways, digital monitoring tools, and multidisciplinary stoma care can reduce dehydration, readmissions, and DLI-related morbidity.

As treatment options for AL continue to evolve, future clinical trials should aim to standardize treatment protocols, establish clear indications for individual treatment modalities, and evaluate long-term outcomes beyond leak healing alone. Particular emphasis should be placed on restoration of bowel continuity, functional outcomes including LARS, and overall quality of life. Furthermore, future studies should seek to identify the optimal treatment strategy for specific leakage characteristics and patient populations.

Finally, the association between delayed SR and increased postoperative morbidity underscores the need to identify and overcome barriers to timely reversal. Future prospective studies should clarify the relationship between adjuvant chemotherapy and SR timing, including the safety and feasibility of performing SR during or shortly after systemic treatment. Optimizing SR pathways may reduce postoperative complications while preserving oncological outcomes and improving overall patient recovery.

Populärvetenskaplig sammanfattning

Rektalcancer är en vanlig cancersjukdom i Sverige och utgör en betydande andel av all tjock- och ändtarmscancer. För många patienter är kirurgi den viktigaste behandlingen och syftar till att avlägsna tumören och samtidigt bevara normal tarmfunktion. En vanlig operationsmetod är främre resektion, där den del av ändtarmen som innehåller tumören opereras bort och tarmen därefter kopplas samman igen.

En av de allvarligaste komplikationerna efter denna operation är att tarmskarven inte läker som planerat. Detta kallas anastomosläckage och innebär att tarminnehåll kan läcka ut genom en defekt i skarven. Komplikationen kan leda till infektioner, behov av nya operationer, långvariga besvär och i vissa fall permanent stomi.

För att minska konsekvenserna av ett eventuellt läckage anläggs ofta en tillfällig avlastande stomi, vanligen en loop-ileostomi. En sådan stomi leder ut tarminnehållet till en påse på magen och minskar belastningen på den nyanlagda tarmskarven. Även om en avlastande stomi kan skydda patienten mot de allvarligaste följderna av ett läckage är den inte problemfri. Många patienter drabbas av komplikationer som uttorkning, påverkan på livskvaliteten och ibland fördröjd eller utebliven återställning av stomin.

Denna avhandling undersöker olika aspekter av avlastande stomier och anastomosläckage efter kirurgi för rektalcancer.

I den första studien undersöktes om ett särskilt uppföljningsprogram kunde minska risken för uttorkning hos patienter med avlastande stomi. Patienterna följdes noggrant under de första veckorna efter operationen genom regelbunden kontakt med sjukvården. Resultaten visade att fler patienter med symtom på uttorkning upptäcktes tidigt och fick medicinsk bedömning och behandling. Studien visar att strukturerad uppföljning kan bidra till säkrare vård efter utskrivning från sjukhuset.

I den andra studien användes data från Svenska Kolorektalcancerregistret för att undersöka sambandet mellan användningen av avlastande stomier och förekomsten av anastomosläckage efter operation för rektalcancer. Studien visade att allt fler patienter fick en avlastande stomi i samband med operation för rektalcancer. Trots detta sågs ingen tydlig minskning av förekomsten av anastomosläckage. Resultaten väcker frågor om den rutinmässiga användningen av avlastande stomier och belyser behovet av ett mer individuellt anpassat beslutsfattande.

Den tredje studien fokuserade på behandling av anastomosläckage. Endoskopisk vakuumterapi jämfördes med traditionell dräneringsbehandling. Båda metoderna syftar till att kontrollera infektion och skapa förutsättningar för läkning av tarmskarven. Resultaten visade inga tydliga skillnader mellan metoderna när det gäller möjligheten att bevara tarmkontinuiteten eller uppnå läkning. Studien tyder på att båda behandlingsmetoderna kan vara effektiva och att valet av behandling bör anpassas till den enskilda patientens situation.

I den fjärde studien undersöktes betydelsen av när en avlastande stomi återställs. Många patienter får vänta länge innan stomin kan läggas ned och tarmkontinuiteten återställas. Studien visade att längre tid med stomi var förknippad med en ökad risk för komplikationer efter stominedläggningen. Resultaten belyser vikten av att undvika onödiga förseningar och att återställa stomin när patientens medicinska situation tillåter det.

Sammantaget visar denna avhandling att avlastande stomier både kan vara till nytta och medföra betydande nackdelar. Resultaten understryker vikten av noggrann patientselektion, strukturerad uppföljning och väl avvägda beslut kring både anläggning och nedläggning av stomi. Resultaten bidrar till ökad kunskap om hur komplikationer efter kirurgi för rektalcancer kan förebyggas och behandlas, med målet att förbättra vården och de långsiktiga resultaten för patienterna.

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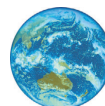
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Paper I





Interventions to reduce dehydration related to defunctioning loop ileostomy after low anterior resection in rectal cancer: a prospective cohort study

Eihab Munshi,*† Eva Bengtsson,‡ Karin Blomberg,* Ingvar Syk* and Pamela Buchwald*

*Colorectal Unit, Department of Surgery, Skåne University Hospital, Malmö, Sweden

†Department of Surgery, University of Jeddah, Jeddah, Saudi Arabia and

‡Department of Surgery, Helsingborg Hospital, Helsingborg, Sweden

Key words

defunctioning loop ileostomy, dehydration, high-output stoma, hospitalization, rectal cancer, surveillance.

Correspondence

Dr Eihab Munshi, Department of Surgery, Skåne University Hospital, 205 02 Malmö, Sweden.
Email: eihab.munshi@gmail.com

E. Munshi MD; **E. Bengtsson** RN;
K. Blomberg RN; **I. Syk** MD; **P. Buchwald** MD.

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Abstract

Background: Defunctioning loop ileostomy (DLI) in low anterior resection (LAR) in rectal cancer patients reduces the morbidity of anastomotic leakages. In our previous study, 30% of patients developed dehydration due to DLI, mostly during the first 6 weeks. This interventional study aimed to reduce these figures by establishing a surveillance programme.

Methods: An interventional study of rectal cancer patients undergoing LAR and DLI between 2013 and 2015 was carried out. A historical study group was used as control. Stoma care nurses educated the intervention group about high-output stoma. Blood tests, including creatinine and electrolytes, were taken every second week until 8 weeks post-operatively and an additional control in case of subjective high-output stoma.

Results: Eighty-seven patients underwent LAR and DLI during the study period. Twenty-one (24%) developed dehydration episodes, and nine (43%) of them required readmission. There was no difference compared to the control group, where 29% developed dehydration, and about half (52%) needed readmission ($P = 0.62$ and $P = 0.57$, respectively). However, when explicitly examining patients demonstrating symptomatic dehydration, there was a significant difference, that is 10 (11%) versus 27 (29%) ($P < 0.005$). Overall, the dehydrated group was older and more likely to take diuretics compared to the non-dehydrated group.

Conclusion: Our results indicate that reducing dehydration episodes and readmission after DLI is a challenging process. The proposed surveillance was only effective in preventing symptomatic dehydration. Subjects taking diuretics and the elderly are at risk of dehydration and should be followed cautiously.

Introduction

Defunctioning loop ileostomy (DLI) is an established method to protect from the consequences of anastomotic leakage (AL) in rectal cancer patients treated with low anterior resection (LAR). The risk of AL is reported to be about 15% after total mesorectal excision and neoadjuvant chemoradiotherapy.^{1–6} However, DLI is not a complication-free procedure and may result in skin irritation, parastomal hernia, gastrointestinal bleeding, stoma stenosis, obstruction and dehydration.⁷ Furthermore, these morbidities have been demonstrated to be related to time with a DLI, and therefore, some surgeons advocate an early DLI reversal.^{8,9} Dehydration following DLI, defined as high-output stoma (HOS) >1.5 L/day for one to three consecutive days, is a common complication with a frequency

of 0.8–72%.^{7,10–14} The consequences of dehydration may result in high readmission rates.¹⁵ We have previously shown that dehydration usually has an early onset, that is within 6 weeks post-operatively.⁷ Dehydration constitutes a significant economic and physiological burden, especially in the elderly population.¹⁶ Furthermore, dehydration is considered an independent factor for mortality; studies have reported up to a 47% risk of in-hospital mortality in patients with hyponatraemia.¹⁶ Dehydration ranges from mild, which can be managed in an outpatient setting, to severe, which requires hospital admission and sometimes even treatment in the intensive care unit. Besides, some risk factors have been identified such as previous operation, intake of diuretics, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker.^{14,17} These data raise the question of whether dehydration could be preventable.

In this prospective interventional study, we studied the outcomes of a post-operative surveillance programme in patients that had been subjected to DLI after LAR for rectal cancer. The hypothesis was that interventions could reduce dehydration and hospital admissions in this patient group.

Methods

All patients who underwent LAR and DLI at two teaching hospitals, Skåne University Hospital, and Helsingborg Hospital Sweden, between 2015 and 2017, were included in the study. Post-operative care was performed using an enhanced recovery after surgery programme. Patients receiving a DLI for any diagnosis other than rectal cancer and patients who succumbed within 30 days post-operatively were excluded.

All study patients met the stoma care nurses before and after the surgical procedure and were informed about proper fluid intake (2 L/day minimal), diet impact on stoma output, self-weighing if HOS on two consecutive days and compensating for fluid and electrolyte loss by the usage of anti-diarrhoeal medications when needed: loperamide 2 mg three times a day (TID), 30–60 min before meals and sterculia (Inolaxol, BGP Products AB, Stockholm, Sweden) one sachet TID. Dosages were increased to a maximum of 4 mg TID (loperamide) and two sachets TID (sterculia) when appropriate.

After discharge, blood samples (plasma creatinine, plasma sodium and plasma potassium) were tested biweekly until 8 weeks post-operatively. Simultaneously, all patients had access to stoma care nurses by phone for advice, and in case of subjective HOS for more than 2 days, weight loss or impaired routine blood tests, an additional blood test was taken and a colorectal surgeon was contacted for further management. Dehydration was defined as HOS (>1.5 L) for 1–3 days and electrolyte imbalance as plasma sodium <130 mmol/L or serum creatinine >125 µmol/L or serum creatinine >1.5 times baseline (pre-operative serum creatinine).

The following data were prospectively collected: age, gender, height, weight, American Society of Anesthesiologists (ASA) score, diagnosis of diabetes, medication at admission, neoadjuvant and adjuvant therapy, operation date, discharge date, anti-diarrhoeal medications at discharge, blood tests values (plasma sodium, plasma potassium and serum creatinine post-operatively week 2, 4, 6 and 8), date of DLI reversal, if dehydration happened during the study period, visits to the stoma care nurse and details for readmission related to dehydration. A predefined treatment protocol was created before the start of the study. As a control group, we used a previously described group of patients from a descriptive study on DLI-related dehydration in rectal cancer patients.⁷ The Strengthening the Reporting of Observational studies in Epidemiology guidance for reporting of observational studies was followed.

The data were analysed with Statistical Package for the Social Sciences using the chi-squared test, Mann–Whitney *U*-test and Fischer's exact test when appropriate. The power calculation showed that just above 100 patients were needed for 80% power. A *P*-value <0.05 for a one-tailed test was considered statistically significant. Data are presented as median with interquartile range when appropriate.

The regional ethical review board committee in Lund, Sweden, approved the study (Dnr 2013/733).

Results

Among 115 patients who received a DLI during the study period, 87 patients had DLI due to LAR for rectal cancer, all of whom were included in the study and comprised the intervention group. Sixty-two (71%) out of 87 patients were operated on with an open procedure, five (6%) with minimally invasive surgery laparoscopically and 20 (23%) robot-assisted entry. None of the patients underwent DLI reversal during the study period, all but six patients had DLI reversal eventually. The demographic and clinical characteristics of the dehydrated and the non-dehydrated groups are shown in Table 1. The dehydrated group was older, that is 70 years (66–72) compared to the non-dehydrated group at 64 years (60–70) (*P* = 0.009), and among medication at admission, the usage of diuretics was more likely (*P* = 0.028).

Overall, 21 (24%) out of 87 patients in the study group developed dehydration during the 8 weeks of follow-up, of which 10 patients were symptomatic. The remaining 11 patients were asymptomatic but demonstrated electrolyte disturbances during the surveillance and were managed conservatively with increasing dosages of loperamide or sterculia (Inlaxol) and adjusted oral intake according to the treatment protocol. Laboratory tests returned to normal after repeated blood tests.

In comparison to the control group, a demographic comparison between the cohort and the control group is displayed in Table 2. The surveillance protocol did not decrease the dehydration episodes compared to the controls, 21/87 (24%) versus 27/91 (29%), respectively (*P* = 0.62). However, when examining patients demonstrating symptomatic dehydration, there was a significant difference with 10/87 (11%) versus 27/91 (29%) (*P* < 0.05). Nine (43%) out of 21 patients in this study group were hospitalized during the study period, compared to 14/27 (52%) in the control group (*P* = 0.57). There was no admission to the intensive care unit. Of the admitted patients, two suffered an AL, one had influenza and one had a non-mechanical obstruction. Besides, the two groups (admitted dehydrated patients and non-admitted dehydrated patients) were clinically similar, except for the intake of angiotensin-converting enzyme inhibitor, as shown in Appendix S1. Among the admitted dehydrated group, the mean potassium value was 5.7 (4.9–5.9), and none of the patients had any cardiac complications related to hyperkalaemia.

Discussion

The present study could overall not demonstrate a reduced frequency of dehydration episodes or decreased readmission rates despite a surveillance programme, including predefined information. The intervention was only effective on symptomatic dehydration, which may have been identified without surveillance. Although DLI has been shown to protect from the consequences of AL, it is an eventful procedure associated with several morbidities, including dehydration, which has a high frequency and

Table 1 Patient demography of the dehydrated and non-dehydrated groups

	Dehydration, n = 21	No dehydration, n = 66	P-value
Age (years), median (IQR)	70 (66–72)	64 (60–70)	0.009*
Gender (male/female), n (%)	15 (71)/6 (29)	39 (59)/27 (41)	0.440**
ASA category, n (%)			
1	2 (9.5)	22 (33)	0.102***
2	17 (81)	40 (61)	
3	2 (9.5)	4 (6)	
Diabetes, n (%)	1 (5)	3 (5)	1.000**
BMI (kg/m ²), median (IQR)	25 (23–27)	26 (23–27)	0.435*
Pre-operative creatinine (μmol/L), median (IQR)	80 (70–91)	73 (63–84)	0.177*
Neoadjuvant radiotherapy, n (%)	9 (43)	34 (52)	0.617**
5 × 5 Gy	7 (78)	29 (85)	0.624**
Long course	2 (22)	5 (15)	
Adjuvant therapy, n (%)	8 (38)	29 (44)	0.801**
ACE inhibitor/ARB, n (%)	8 (38)	16 (24)	0.265**
Diuretics, n (%)	4 (19)	2 (3)	0.028**
Previously operated (previous operation), n (%)	8 (38)	7 (11)	0.799**
Surgical entry, n (%)			
Open	16 (76)	46 (70)	0.849***
Laparoscopic	1 (5)	4 (6)	
Robot-assisted laparoscopic	4 (19)	16 (24)	

*Mann-Whitney U-test.

**Fisher's exact test.

***Chi-squared test.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, American Society of Anesthesiologists score; BMI, body mass index; IQR, interquartile range.

Table 2 Comparison between the cohort and control group demographic characteristics

	Control group, n = 91	Study cohort, n = 87
Age (years), median (IQR)	66 (59–74)	66 (61–72)
Gender (male/female), n (%)	54 (59)/37 (41)	54 (62%)/33 (38)
ASA category, n (%)		
1	38 (42)	24 (28)
2	41 (45)	57 (65)
3	12 (13)	6 (7)
Diabetes, n (%)	5 (5)	4 (5)
BMI (kg/m ²), median (IQR)	25 (24–26)	26 (23–27)
Neoadjuvant radiotherapy, n (%)	68 (75)	43 (49)
5 × 5 Gy	45 (66)	36 (84)
Long course	23 (34)	7 (16)
Adjuvant therapy, n (%)	19 (21)	37 (43)

ASA, American Society of Anesthesiologists score; BMI, body mass index; IQR, interquartile range.

is potentially lethal.^{7,13} This prospective study introduced a surveillance programme in patients with DLI after LAR for rectal cancer following a previous retrospective study at the same hospitals.

A significant number of the patients in the dehydrated group (11/21) were asymptomatic with deranged electrolytes or acute kidney injury according to the Kidney Disease Improving Global Outcomes clinical practice guideline.¹⁸ Adding these asymptomatic patients to the dehydration group may constitute an overdiagnosis compared to our previous study since the patients, which were assessed retrospectively, were all symptomatic and needed readmission. Furthermore, definitions of dehydration and HOS

post-DLI vary in earlier studies, and some authors have implied that dehydration should be objectively addressed by interventions needed. Using the acute kidney injury criteria from the Kidney Disease Improving Global Outcomes guideline is one way to standardize the definition.¹³

Readmission for fluid support and correcting electrolytes has a median cost of 4261 American dollars¹⁹ and causes severe patient suffering. Nagle *et al.* have shown readmission rates due to dehydration drop to zero when patients were followed up by a visiting nurse who checked the intake and output records.¹⁵ In another study by Shaffer *et al.*, regular home visits by nurses for 4 weeks post-operatively led to decreased readmission rates from 20.8% to 8.7% and lowered readmission costs from \$4520 to \$508, attributed to early diagnosis and treatment.²⁰ However, these studies recorded only readmission to their hospital, and patients who had outpatient management of dehydration were not included in the data. Furthermore, the study populations were heterogeneous, including rectal cancer, diverticulitis and inflammatory bowel disease, and had a lower median age than our study. In the present study, the protocol failed to reduce dehydration episodes in rectal cancer patients with DLI or decrease readmission. However, the study managed to underline that elderly frailer patients and those who are on diuretics are at risk.

Data regarding adjuvant chemotherapy and DLI have been conflicting. This study does not demonstrate a significant correlation between adjuvant chemotherapy, neither on dehydration nor readmission rates. However, since the blood tests and close surveillance were only performed during the first 8 weeks post-operatively, most patients may just have started their adjuvant chemotherapy. Robertson *et al.* showed that adjuvant chemotherapy was an independent factor for HOS, and there are

indications that high output ileostomy morbidity increases during chemotherapy and may require chemotherapy modification or omission.²¹

Although DLI is associated with less morbidity if AL occurs, the stoma itself has been related to substantial morbidities.^{6,22} Moreover, 26% of the intended DLI never get reversed for various reasons.²³ Even if surveillance could reduce dehydration, some high-risk rectal cancer patients could be better off with a permanent sigmoid ostomy upfront. Although there is no clear relationship between AL and DLI complications, there are certain overlapping risk factors.

This study has some limitations. First, this study was not a randomized controlled trial but a prospective study with a retrospective control group. The proposed surveillance detects both symptomatic and asymptomatic patients, where the control group accounted for symptomatic patients only. However, we have no reason to believe that the indications for LARs changed or any other major shift in the treatment of rectal cancer was introduced during the study period. Second, the study population is small with a risk for type II error, and we only carried out close surveillance during the first 8 weeks. Furthermore, the control group received information from the stoma nurses, although not in a structured manner, and the blood tests themselves may not have been enough. However, we are not aware that any of the patients required in-patient care at a later stage. The present study was performed at the same hospitals as the previous study, and the study population is homogenous, which should be considered as strengths.

Future studies may further explore whether a defunctioning stoma may be avoided in LARs or may be only be offered to high-risk patients. There could be individual patients where a permanent sigmoid ostomy would be a more suitable option. Furthermore, identifying early predictors and presentations of dehydration may improve treatment. Randomized controlled trials on interventions are also needed.

Conclusion

Dehydration associated with DLI carries a spectrum of health burdens, especially in rectal cancer patients. The implementation of post-operative surveillance did not significantly decrease dehydration episodes and did not reduce readmission rates.

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Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Patient demography of the admitted dehydrated and non-admitted dehydrated groups. All data are presented as median with IQR when appropriate.

Paper II



RESEARCH

Open Access



Defunctioning stoma in anterior resection for rectal cancer does not impact anastomotic leakage: a national population-based cohort study

Eihab Munshi^{1,2,4*} , Marie-Louise Lydrup^{1,3*} and Pamela Buchwald^{1,3}

Abstract

Background Anterior resection (AR) is considered the gold standard for curative cancer treatment in the middle and upper rectum. The goal of the sphincter-preserving procedure, such as AR, is vulnerable to anastomotic leak (AL) complications. Defunctioning stoma (DS) became the protective measure against AL. Often a defunctioning loop-ileostomy is used, which is associated with substantial morbidity. However, not much is known if the routine use of DS reduces the overall incidence of AL.

Methods Elective patients subjected to AR in 2007–2009 and 2016–18 were recruited from the Swedish colorectal cancer registry (SCRCR). Patient characteristics, including DS status and occurrence of AL, were analyzed. In addition, independent risk factors for AL were investigated by multivariable regression.

Results The statistical increase of DS from 71.6% in 2007–2009 to 76.7% in 2016–2018 did not impact the incidence of AL (9.2% and 8.2%), respectively. DLI was constructed in more than 35% of high-located tumors ≥ 11 cm from the anal verge. Multivariable analysis showed that male gender, ASA 3–4, BMI > 30 kg/m², and neoadjuvant therapy were independent risk factors for AL.

Conclusion Routine DS did not decrease overall AL after AR. A selective decision algorithm for DS construction is needed to protect from AL and mitigate DS morbidities.

Keywords Rectal cancer, Defunctioning stoma, Defunctioning loop-ileostomy, Anastomotic leakage, Anterior resection

*Correspondence:

Eihab Munshi
eihab.munshi@gmail.com
Marie-Louise Lydrup
marie-louise.lydrup@skane.se

¹Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

²Department of Surgery, University of Jeddah, Jeddah, Saudi Arabia

³Department of Surgery, Skåne University Hospital, Malmö, Sweden

⁴Department of Surgery, Samsung Medical Center, Seoul, South Korea



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Introduction

Anterior resection (AR) is considered the gold standard for the curative treatment of cancer in the middle and upper rectum [1]. The widespread use of total mesorectal excision (TME) and neoadjuvant therapy have improved oncological outcomes and survival [2]. Anastomotic leakage (AL) is a dreaded complication affecting 4–20% of patients undergoing AR [2, 3]. Several risk factors for AL have been described, e.g., male gender, smoking, excess alcohol, overweight, advanced ASA class, diabetes mellitus, pulmonary, renal, vascular diseases, tumor size, neoadjuvant therapy, and anastomotic height from the anal verge [3–5]. Meta-analysis and randomized controlled trials have shown a risk reduction of symptomatic AL after low anterior resection and the need for reoperation in patients with a defunctioning stoma (DS) [6, 7]. Following studies detected a mitigating role of DS in AL complications rather than a decline in overall AL incidence [2, 8]. DS is frequently fashioned as a defunctioning loop-ileostomy (DLI) and more seldom as a loop colostomy [6, 7]. Around 70–80% of AR patients are protected with DS in the UK and Holland, respectively [9, 10]. According to the Swedish colorectal cancer registry (SCRCR), around 600 ARs are performed annually in Sweden [11]. Since most DS are fashioned as DLI, DS will hereafter be named DLI [12, 13].

DLI becomes permanent in about 25% of the cases. The local and systemic physiological changes due to DLI can vary from minor symptoms of skin irritation and leakage (59%) to significant issues like dehydration, obstruction, and parastomal hernia (25%) [14]. One-third of DLI patients risk dehydration in the first six weeks, and half of them require admission for electrolytes correction, possibly putting adjuvant chemotherapy at stake [15]. DLI also impairs health-related quality of life [16]. Delayed DLI closure has been associated with impaired bowel function and major low anterior resection syndrome (LARS) [17, 18]. In addition, about 40% of patients encounter surgical complications, most commonly small bowel obstruction and wound sepsis, during the DLI reversal procedure [14, 19].

This study aimed to evaluate whether the frequency of AL has decreased as the usage of DLI has increased and, as a secondary outcome, investigate risk factors for AL. We hypothesized that the lack of clear indications for DLI leads to increased DLI usage without reducing AL.

Materials and methods

This study is a population-based retrospective cohort study of patients subjected to rectal cancer surgery in Sweden. The SCRCR is a nationwide registry including rectal cancer patients since 1995 in Sweden with high validity and coverage [20]. We encompassed all rectal cancer patients undergoing AR during two intervals,

2007–2009 and 2016–2018. The criteria for exclusion were age < 18-year-old, emergency surgery, microscopically non-radical resection, and unregistered DLI status. Eligible patients were divided into two groups based on the time for index surgery. We expected patients in the latter group (2016–2018) to be more exposed to DLI than the early cohort (2007–2009) since RECTODES trial results were released in August 2007. Thus, the latter group would be more protected against AL. Each group was further divided into having DLI at the index surgery or not. To be noted, the variable DLI was firstly introduced in the registry in 2007. Patients were discussed at a multidisciplinary team conference.

Definitions

Rectal cancer was defined as adenocarcinoma within ≤ 15 cm from the anal verge measured with rigid sigmoidoscopy.

According to the International Study Group of Rectal Cancer (ISREC), AL after AR for rectal cancer is defined as a communication between the two cavities (intra- and extraluminal compartments) manifested as a defect in the anastomosis (anastomotic staple or suture line), the presence of a presacral pelvic abscess or a rectovaginal fistula [21] and divided into three grades. AL was reported by different colorectal surgeons in the SCRCR; hence, the validity of the AL definition may vary. In addition, all grades of AL are represented.

DLI is an ileostomy that diverts bowel contents and protects the newly reconstructed colorectal anastomosis applied during the elective AR.

The partial mesorectal excision (PME) variable will be registered in 2022 after the study is completed and the colorectal anastomosis level is not enlisted in SCRCR. Tumor height from the anal verge is employed as a proxy for PME, with PME operations defined as tumors located 11 cm or higher from the anal verge.

Ethics

Ethical approval was obtained via the Swedish Ethical Review Authority (Diary number 2020–01082).

Statistical analysis

Statistical analyses were made using IBM SPSS version 26. Demographic characteristics were reported as medians with first and third interquartile range (IQR) when continuous and categorical variables as numbers and percentages. Mann-Whitney U test was applied for continuous variables, Fisher's Exact or Chi-square tests for categorical variables. A two-sided p -value < 0.05 was considered statistically significant. Missing data were reported when exceeding 2% in a variable.

Risk factors for AL were identified using a binary logistic regression model for a univariable and multivariable

analysis, including significant univariable variables and other clinically essential indicators like DLI, and index operation date.

Results

Study cohort

A total of 3948 AR procedures for rectal cancer were performed during 2007 to 2009 and 2016 to 2018. One hundred thirty-one patients were non-radically resected, 123 patients had missing data regarding resection margins, and six with unregistered DLI status were excluded resulting in 3688 included patients in the study cohort, Fig. 1.

DLI patient characteristics and demographics are displayed in Table 1. Noteworthy, patients in the latter cohort (2016–2018) had more commonly high-located rectal tumor (≥ 11 cm from the anal verge) than the earlier cohort (37% vs. 35%; $p < 0.001$), and less low-located tumor (< 5 cm from the anal verge) (1.7 vs. 3.4%;

$p < 0.001$). Additionally, less advanced tumor stage and less distant metastasis were found in the latter cohort.

Compared to the former cohort, patients in the latter group comprised more patients with ASA 3–4 (19.5% vs. 14.1%; $p < 0.001$), BMI > 30 (17.6% vs. 12.3%; $p < 0.001$), and had a longer hospital stay (8 vs. 7 days; $p < 0.001$). Throughout the research period, the neoadjuvant therapy was either a short course of 5×5 Gy or radio-chemotherapy 2×25 Gy with radiosensitizing capecitabine, with the latter group receiving less neoadjuvant therapy (63% vs. 72%; $p < 0.001$). Moreover, fewer patients in the latter group were treated with adjuvant therapy (17% compared to 39%; $p < 0.001$). Perioperatively, the latter cohort more frequently underwent minimally invasive anterior resection and high ligation of the inferior mesenteric artery. The characteristics of the PME and TME groups are shown in Supplement Tables 1 and 2.

Defunctioning loop-ileostomy, anastomotic leakage, and risk factors

Although more than two-thirds of the patients, 71.6% (1345/1879), were diverted by DLI (2007–2009), the diversion rate increased further to 76.7% (1387/1809) ($p < 0.001$) in the latter group (2016–2018), shown in Table 2.

There was no significant reduction in AL incidence over 11 years despite the expansion in DLI usage (9.2% (124/1879) in 2007–2009 compared to 8.2% (114/1809) in 2016–2018) ($p = 0.35$). The number of reoperations for AL was unchanged (4% (58/1345) vs. 3% (46/1387), respectively). Comparisons between +/-DLI in the subgroups TME and PME are shown in supplement Tables 1 and 2. The AL rate did not differ between +DLI and -DLI; however, the non-stoma groups needed more reoperations for AL than the +DLI group. This was not significant in the TME group in the latter cohort due to few cases.

The study cohort was divided into +/-AL, and AL risk factors were analyzed (Table 3). Patients with AL had as many DLI as patients without AL (72% compared to 74%, $p = 0.36$). In a univariable analysis, AL was significantly related to the male sex, ASA class, BMI, and neoadjuvant therapy.

Male gender, ASA class 3–4, BMI 30 or above, and neoadjuvant therapy remained risk factors for AL in the multivariable analysis (Table 3). DLI and surgery date, on the other hand, had no influence on the incidence of AL.

Discussion

This study demonstrated a 5% increase in DLI construction between 2007 and 2009 and 2016–2018. Surprisingly, a high number of DLI (71.6%) was registered from 2007 to 2009, although RECTODES-trial was not reported until 2007 [6]. The increased usage of DLI did

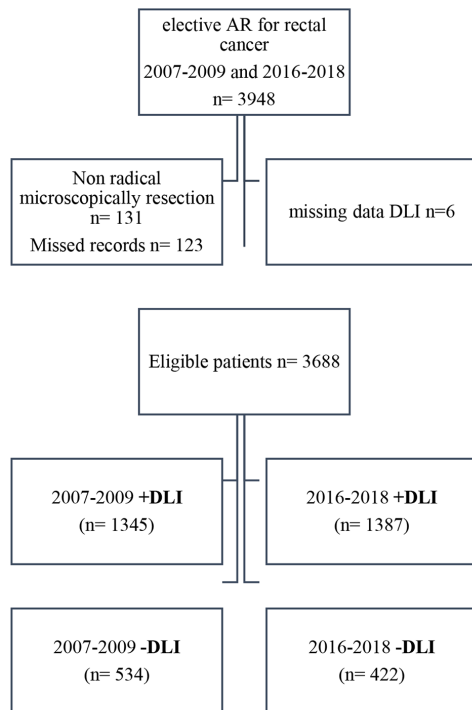


Fig. 1 Rectal cancer patients undergoing AR (2007–09) and (2016–2018) retrieved from SCRCR and divided into +/-DLI
SCRCR, Swedish Colorectal Cancer Registry, AR, anterior resection, DLI, de-functioning loop-ileostomy

Table 1 Comparison of patient characteristics with DLI after AR grouped according to the time (2007–2009) and (2016–2018)

	2007–2009 n = 1345	2016–2018 n = 1387	p-value
Age (years)	66 (60–73)	67 (60–73)	0.38 ¹
Gender (male)	854 (63.5)	852 (61.4)	0.27 ²
ASA			0.001 ²
ASA1-2	1128 (83.9)	1092 (78.7)	
ASA3-4	189 (14.1)	271 (19.5)	
BMI (kg/m ²)			0.001 ²
<30	1063 (79)	1127 (81.3)	
≥30	165 (12.3)	244 (17.6)	
Missing data	117 (8.7)	16 (1.2)	
Tumor location*			0.001 ³
11–15 cm	474 (35.2)	515 (37.1)	
6–10 cm	799 (59.4)	842 (60.7)	
0–5 cm	64 (3.4)	23 (1.7)	
pTumor stage			0.001 ³
T0	35 (2.6)	29 (2.1)	
T1-2	479 (35.6)	554 (39.9)	
T3-4	818 (60.8)	803 (57.9)	
Tx	11 (0.8)	0	
pN stage			0.17 ³
N0	810 (60.2)	857 (61.8)	
N1-N2	522 (38.8)	523 (37.7)	
Nx	12 (0.9)	5 (0.4)	
cM stage			0.001 ³
M0	1229 (91.4)	1220 (90.7)	
M1	81 (6)	74 (5.5)	
Mx	33 (2.5)	0	
Missing data	2 (0.1)	93 (6.9)	
Neoadjuvant therapy	971 (72.2)	876 (63.2)	0.001 ²
Laparoscopic index AR	73 (5.4)	815 (58.8)	0.001 ²
High ligation of IMA	601 (44.7)	766 (55.2)	0.001 ²
Intraoperative perforation	28 (2.1)	28 (2)	0.953 ²
Hospital stay (days)	7 (6–11)	8 (6–13)	0.001 ¹
Adjuvant therapy	398 (29.6)	232 (16.7)	0.001 ²
Missing data	22 (1.6)	709 (51.1)	

¹Mann-Whitney U²Fisher's exact test³Chi-squared test

*cm for anal verge

ASA, American society of anesthesiologists, BMI, body mass index, pT, pathological tumor stage, pN, pathological lymph node stage, cM, clinical metastasis, IMA, inferior mesenteric artery

Values are shown in numbers and percentages in parentheses for categorical variables. Continuous variables are expressed as median and interquartile ranges

Table 2 Incidence of AL related to DLI over twelve year-period (2007–2009) and (2016–2018)

	AR 2007–2009 (n = 1879)	AR 2016–2018 (n = 1809)	P- value
DLI	1345 (71.6)	1387 (76.7)	0.001
AL	124 (9.2)	114 (8.2)	0.35
Reoperation for AL	58 (4.3)	46 (3.3)	0.17

Fisher's Exact Test was used

AR, anterior resection, DLI, defunctioning loop-ileostomy, AL, anastomotic leakage

not reduce AL incidence nor reoperations due to AL. More than one-third of the DLI-patients in both periods had tumors located ≥ 11 cm from the anal verge.

AL is deemed one of the most feared surgical complications after sphincter-preserving surgery. Significant efforts to preclude its occurrence are conducted by minimizing modifiable risk factors and implementing protective measures, including DS. There are inconsistent results on how DS affects AL rates despite well-conducted randomized controlled trials, prospective multicentre studies, and meta-analyses [22, 23].

Table 3 Univariable and multivariable analysis for anastomotic leakage risk factors

	Univariable analysis			Multivariable Analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
DLI	0.89	0.69–1.14	0.344	0.84	0.63–1.13	0.252
Operation date (2016–2018)	0.84	0.67–1.05	0.123	0.82	0.65–1.04	0.101
Male sex	1.38	1.09–1.75	0.008	1.41	1.09–1.81	0.008
ASA 3–4 ²	1.4	1.05–1.82	0.021	1.39	1.05–1.85	0.024
BMI (> 30 kg/m ²)	1.5	1.1–1.97	0.01	1.51	1.13–2.04	0.006
Neoadjuvant therapy	1.27	1–1.6	0.047	1.35	1.03–1.75	0.027

ASA, American society of anesthesiologists, BMI, body mass index, pT, pathological tumor stage

The present national study indicates that too many AR patients receive a DLI without a beneficial effect on AL, suggesting that the selection process is too blunt. Similarly, a comparison of the Dutch TME-trial in 1996–1999 to the Dutch Surgical Colorectal Audit in 2010 demonstrated significantly increased defunctioning rates from 57 to 70%, albeit AL remained stable (12% vs. 11%) [9].

Additionally, a Swedish regional study found an increase in DS construction from 15% (2002–2006) to 91% (2007–2011), while AL lingered around 10% [24]. The continuing RECTODES trial may have had an impact on clinical practice in both participating and non-participating hospitals. This impact might be attributed to many assumptions, such as DLI structure providing ultimate protection for AL or more frail patients being evaluated for operational care than previously. However, surgeons' decision-making strategies vary widely, which is a subject for future survey studies. Moreover, the increase in DLI construction would raise the question if some patients would be better off with a permanent colostomy during index surgery and whether some low-risk patients should not be defunctioned, considering comorbidities-related DLI.

The interpretation of the results from RCTs advocating the protective role of DS must consider the circumstances that entail DS construction. In the case of the RECTODES trial, several detrimental factors were considered. More than two-thirds of AR patients were not accepted for randomization. In our opinion, the most critical exclusion criterion was anastomosis level > 7 cm above the anal verge or resection with a PME procedure. However, in Sweden, a high proportion (25%) of AR patients have high-located tumors (≥ 11 cm from the anal verge), and about 34% subjected to PME were diverted with DLI in Sweden [24, 25]. This high proportion of PME is consistent with our findings which detected a diverting rate of 35% (2007–2009) and 37% (2016–2018).

Furthermore, the most frequent exclusion factor was intraoperative technical difficulties or intraoperative adverse events, which would create a selection bias and, consequently, decrease the external validity.

Blok RD et al. suggested a shift from routine to a highly selective defunctioning ileostomy (HS-DI) after

laparoscopic and transanal TME. With a diversion rate of 8% compared to 90% in a historical group, the incidence of AL at 30 days and one year was similar in both groups [26]. Recently, the protocol of the first prospective randomized trial to assess a tailored policy in DS after TME has been presented using an Anastomotic Failure Observed Risk Score (AFOR score) [27].

The short- and long-term stoma-related morbidities for a DS are not negligible. The few weeks after hospital discharge carry a high risk of readmission (17%) due to dehydration by high-output stoma [28]. Moreover, the risk for chronic kidney injury (CKD) accompanying DLI is also time-related, as the incidence of severe CKD injury is higher during the first six months [29]. Stoma reversal is another eventful step that conveys a high rate of 18–40% complications which might require reoperation in 3–8% [30, 31]. Two Swedish population-based cohort studies have investigated the permanent stoma rate, and up to 26% of AR patients would have a permanent stoma. Although AL is one of the most prominent risk factors for the permanent stoma, constructing a defunctioning stoma has no more than negligible effect on maintaining a permanent one [25, 32].

This observational study is strengthened by a large sample representing the national population of this patient group and thus enhances its generalizability and external validity. It was unbiased in selecting all consecutive patients from two periods. However, this registry-based study is limited by unavailable variables. The possibility to explore the effect of DLI on attenuating AL severity and delaying its presentation is hampered by the lack in SCRCR of details on AL presentation and management such as diagnosis date, type of treatment (conservative, antibiotics, drainage, Endoscopic vacuum therapy), details on reoperation, stoma reversal, PME definition and missing data on adjuvant therapy. Another limitation is the unavailability of neoadjuvant treatment toxicity. Neoadjuvant toxicity could be studied for its potential effect on anastomotic healing.

Conclusion

This population-based study demonstrates an inefficient DLI role in diminishing the risk of AL in routine

AR use. Other preventive measures are being studied, including ghost ileostomies, HS-DI, an AL-check list, and scheduled postoperative AL surveillance, including sigmoidoscopy, labs, and rectography. Thereby, an urge for a decision algorithm regarding selective criteria for DLI is called for to spare DLI usage in this complex patient group with multiple risk factors for AL. Noteworthy, there is a significant shift from open to laparoscopic approach in TME-procedure. Therefore, new studies should explore the protective role of DLI specifically in the current surgical practice of laparoscopic and trans-anal TME procedures.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12893-023-01998-5>.

Supplementary Material 1

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Author contributions

This original research is a part of doctoral studies for EM, who wrote the main manuscript with the figure and tables. The project is supervised and guided by PB (supervisor) and M-LL (Co-supervisor), who contributed to designing the project, then reviewing and editing the manuscript.

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Data Availability

The data that support the findings of this study are available from SCRCR, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of SCRCR.

Declarations

Ethical approval and consent

The Swedish ethical review authority (Etikprövningsmyndigheten) provided the ethical approval for the study (Diary number 2020–01082), and it waived the informed consent owing to retrieving the data from the national registry. Additionally, the study was conducted following the relevant ethical considerations according to the Helsinki declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Paper III



Long-term Outcomes of Endoscopic Vacuum Therapy and Transanal Drainage for Anastomotic Leakage After Anterior Resection

EIHAB MUNSHI^{1,2}, CECILIA DAHLBÄCK^{1,2}, SALLE JOHANSSON^{1,2},
MARIE-LOUISE LYDRUP^{1,2}, HENRIK JUTESTEN^{1,2} and PAMELA BUCHWALD^{1,2}

¹Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden;

²Department of Surgery, Skåne University Hospital, Malmö, Sweden

Abstract. *Background/Aim:* Anastomotic leakage (AL) after anterior resection for rectal cancer occurs in up to 26% of patients. In the last decade, endoscopic vacuum therapy (EVT) has gained interest as a treatment option for AL. This study aimed to compare the clinical success rate of EVT versus transanal drainage (TD) in AL treatment and investigate whether the frequency of bowel continuity differed. *Patients and Methods:* Patients treated for rectal cancer at the Skåne University Hospital, Sweden between 2009-2018 were identified through the Swedish Colorectal Cancer Registry (SCRCR). Patient characteristics, operative and AL data were retrieved by SCRCR and chart review. *Results:* Out of 1,095 patients subjected to rectal cancer surgery, 361 patients had undergone anterior resection. AL occurred in 39 patients, of these 14 patients were treated with EVT and 17 with TD. Bowel continuity was achieved in 50% of patients treated with EVT and 65% of patients treated with TD ($p=0.28$). The patients were under treatment for a median period of 24.5 days (IQR=11-36 days) when treated with EVT and 37 days (IQR=17-51 days) with TD. *Conclusion:* No superiority of EVT treatment could be shown in restoring bowel continuity. This questions the role of EVT in AL treatment after anterior resection.

Anastomotic leakage (AL) is a dreaded complication after anterior resection and can be diagnosed in near proximity to

surgery or in the later course. AL is defined as “communication between the intra- and extraluminal compartments owing to a defect of the integrity of the intestinal wall at the anastomosis between the colon and rectum or the colon and anus” according to The International Study Group of Rectal Cancer (ISREC) (1). AL incidence rates differ between studies and ranges from 15 to 28% after low anterior resection in large cohorts (2-4).

Depending on the severity of the leakage, treatments may include antibiotics, drainage, and reoperation (2). In 2008, treatment of AL with endoscopic vacuum therapy (EVT) was first described by Weidenhagen *et al.* (5). In the last decade, this treatment option for AL has gained interest. EVT may reduce necrotic tissue and fibrin in the cavity by stimulating granulation tissue formation possibly resulting in quicker healing. Further studies have shown promising results, with high rates of technical and clinical success rates and few adverse effects (6).

As EVT often requires anaesthesia or sedation, at least for the initial treatments, and the endosponge must be replaced every 48-72 hours the method is quite laborious and costly. Therefore, it is necessary to study if EVT is superior to more conventional therapies.

The aim of the study was to investigate the outcomes after EVT compared to transanal drainage (TD) and antibiotics. We hypothesized that EVT would lead to higher extent of bowel continuity compared to conventional treatment.

Patient and Methods

Patients treated for rectal cancer at the Skåne University Hospital between 2009 and 2018 were identified through the Swedish Colorectal Cancer Registry (SCRCR), a national quality registry with high validity (7, 8), into which it is mandatory to register all diagnosed rectal adenocarcinomas. Over 99% of patients in Sweden diagnosed with rectal cancer are included in SCRCR (9).

The study population comprised patients who were diagnosed with AL after anterior resection. Only patients deemed to have an AL considered candidates for bowel continuity were included. To affirm

Correspondence to: Pamela Buchwald, Department of Surgery, Skåne University Hospital, SE-205 02 Malmö, Sweden. Tel: +46 (0)40331000, e-mail: pamelabuchwald@med.lu.se

Key Words: Rectal cancer, anterior resection, anastomotic leakage, endoscopic vacuum therapy, transanal drainage.



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the diagnosis of AL, medical records were revised to make sure that the diagnoses of AL were correct according to the classification made by ISREC. Data on age at time of operation, American Society of Anaesthesiologists (ASA) classification, tumour/nodal/metastases (TNM) stage, tumour height from anal verge, preoperative radiotherapy, laparoscopic *versus* open surgical approach, construction of a diverting stoma, and type of anastomotic reconstruction (side-end or end-end) were retrieved from the SCRCR.

Data on comorbidities relevant to calculating Charlson Comorbidity Index (CCI), smoking status, site of leakage in the anastomosis (circular anastomosis or blind end), stoma status, time from index surgery to AL diagnosis, time from index operation to initiation of AL treatment, AL treatment modality (ETV or TD), treatment duration and number of AL treatments requiring anaesthesia, were retrieved from medical records. A stoma, irrespective of ileostomy or colostomy, 24 months after index surgery was regarded as permanent *i.e.* not restored bowel continuity. Follow-up time ranged 2-11 years.

The first assessment of all ALs was performed endoscopically. In cases where ETV was chosen endosponges (Braun®) were fitted and placed endoscopically via a plastic tube into the deepest point of the abscess cavity and changed 2-3 times/week. When THD was used the cavity and any abscess were drained and washout in the operating theatre. Drain placement $\pm$ further washout was at the discretion of the surgeon. All primary procedures were performed in-hospital $\pm$ sedation and gradually altered to outpatient clinics when possible.

Clinical success rate was defined as successful treatment of AL at the discretion of treating physician often with confirmation via endoscopy or contrast enhanced computed tomography imaging.

Statistics. Statistical analysis was performed using IBM Software (IBM SPSS Statistics v. 25.0.0.1). Results are presented as median value and interquartile range. Differences in outcomes were calculated with Fisher's exact test. Patients were analysed according to intention to treat.

Ethical approval. Ethical approval was obtained by the Ethical review board of Lund Sweden Dnr2019/123.

Results

In all, 1,095 patients were identified through the SCRCR (Figure 1). These patients had undergone anterior resection (n=362), abdominoperineal resection (n=450), Hartmann's procedure (n=181), or other procedure *i.e.*, local excision, polypectomy *etc.* (n=102).

Of the 361 patients who had undergone anterior resection, AL occurred in 39 patients (26 males/13 females), comprising the study population. In 34 patients, a diverting stoma had been constructed at the primary operation. Seven patients were re-operated with abdominoperineal resection (n=3), Hartmann's procedure (n=3), or with abdominal drainage (n=1). One was treated with antibiotics alone. Fourteen patients were treated with EVT and 17 patients with TD.

Patient and tumour characteristics along with treatment factors for the patients treated with TD and EVT are presented in Table I. Patient and tumour characteristics were very similar between the two groups. Regarding treatment factors, it could

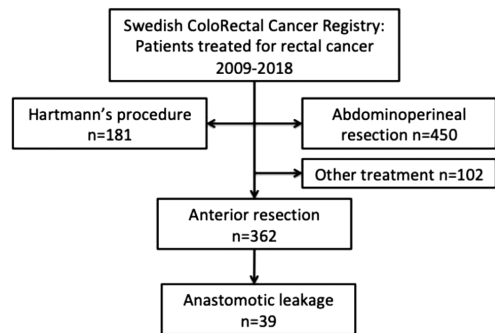


Figure 1. Flow-chart.

be noted that patients treated with EVT had more often undergone laparoscopic anterior resection ($p=0.028$).

Clinical success rate was 78.6% and 88.2% for EVT and TD respectively ($p=0.64$). In the EVT group, one patient stopped treatment due to pain and risks associated with full anaesthesia. Another patient needed emergency re-laparotomy due to bowel obstruction. Treatment was abandoned for one patient in each treatment group due to lack of improvement. One patient primarily treated with TD changed treatment approach to EVT.

At long-term follow-up 50% of EVT treated group had bowel continuity in contrast to 64.7% in the TD group ($p=0.28$).

Discussion

In this study, no superior effect of EVT over TD could be found in the treatment of AL after anterior resection for rectal cancer.

The results of the present study are in accordance with another recent study from Stockholm, Sweden, by Weren *et al.* (10), in which 14 patients with AL after anterior resection treated with EVT were compared to 34 patients receiving transanal irrigation. At the end of the median 5.9 years follow-up, 43% of EVT-treated patients had bowel continuity compared to 50% of those treated with transanal irrigation.

Dhindsa *et al.* recently published a systematic review and meta-analysis of 17 studies (14 manuscripts and 3 abstracts) investigating EVT in the treatment of AL after anterior resection. It was shown that technical success rates were high (99.9%) and clinical success was achieved in 85.0%. Adverse effects were reported in 7.7%, recurrent abscesses and bleeding being most frequent (11). However, the studies generally consisted of small study populations and very few have compared EVT to other treatment options.

Table I. Patient and tumour characteristics, treatment factors and outcome for patients treated with transanal drainage and endoscopic vacuum therapy.

	Endoscopic vacuum therapy n=14	Transanal drainage n=17
Age (years)	68 (52.8-71)	67 (58.5-71)
Sex (male)	10 (71.4)	11 (64.7)
BMI (kg/m ²)	26.5 (24.2-31.0)	26.6 (24.8-28.2)
ASA classification		
1	2 (11.8)	1 (7.1)
2	13 (76.5)	9 (64.2)
3	2 (11.8)	3 (21.4)
CCI score	4.5 (3-7)	4 (3.5-5)
Smoking status (yes)	5 (36)	4 (24)
Tumour height (cm)	10 (9-12)	9 (7.27-10)
Tumour stage		
T1	1 (7.1)	3 (17.6)
T2	4 (28.6)	3 (17.6)
T3	8 (57.1)	10 (58.8)
T4	1 (7.1)	1 (5.9)
Preoperative radiotherapy	9 (64.3)	12 (70.6)
Laparoscopic approach	6 (42.9)	1 (5.9)
Anastomosis type (side-end)	7 (50.0)	10 (58.9)
Diverting stoma	13 (92.9)	16 (94.1)
Leakage location (anastomotic ring)	11 (78.6)	12 (70.6)
Time to AL diagnosis (days)*	10.5 (7.7-18)	22 (14-28)
Time to treatment start (days)*	11.5 (8.7-18.8)	23 (15-31.5)
Number of treatments	7.5 (4-9.7)	3 (1-5.7)
Number of treatments in anaesthesia	4 (1.7-6.2)	0 (0-1)
Treatment time (days)	24.5 (11-36)	37 (17-50.5)
Clinical success rate	11 (78.6)	15 (88.2)
Bowel continuity after at least 24 months follow-up	7 (50.0)	11 (64.7)

Continuous variables are presented as the median with an interquartile range, and categorical data are described using frequencies of counts with associated percentages. *Days from index procedure. BMI: Body mass index; ASA: American Society of Anaesthesiologists; CCI: Charlson Comorbidity Index; AL: anastomotic leakage.

The first published study on EVT by Weidenhagen *et al.* showed that definitive healing was achieved in 28 of 29 treated patients (5). However, the study population had been diagnosed with AL shortly after surgery (between the 3rd and 17th postoperative day) and only one third of patients had received preoperative radiotherapy. Others have shown a higher clinical success rate if AL was diagnosed within 15 days (72.4% *versus* 27.8%) (12). In the current study, the median time to detection of AL as well as to treatment was longer for the patients treated with TD. Despite this, EVT could not be shown to improve healing.

The CLEAN study investigated the efficacy of early transanal closure of AL after pre-treatment with EVT. The study included 30 patients and demonstrated anastomotic integrity in 53% and 70% after six months and median follow-up 14 months respectively. Bowel continuity was restored in 67%. In this study, 73% had received preoperative radiotherapy (13).

The strength of the study is a diligent review of a retrospective consecutive patient series of AL at a high volume rectal cancer referral centre where treatment algorithms have

rather been uniformed. There are several limitations to our study. It was a retrospective observational study with a small study population and no uniform measuring of the AL cavity. Given that the choice of treatment was not randomized but at the discretion of the surgeon, there is a risk of selection bias. However, when comparing patient and tumour characteristics between the two groups, they were similar. Regarding treatment factors, patients who had been subjected to EVT had undergone laparoscopic anterior resection more frequently. We may speculate that surgeons comfortable with laparoscopic techniques are more prone to test new methods such as EVT. If this would be the case, the treatment choice would mostly rely on the surgeons' attitude towards EVT, and the risk of selection bias on AL severity would be low. Moreover, seven patients were treated with laparotomy upfront thus the most severe AL were excluded.

Even when taking these limitations into consideration, the results indicate that EVT might not be superior to TD, a treatment not requiring costly equipment, anaesthesia or mandatory repeated interventions at a minimum of every third day.

As AL is a highly versatile complication, with differing clinical manifestations, it is likely that EVT has a place in treatment for selected patients. Further studies are needed to elucidate which patients would benefit from this treatment and if functional results differ.

Conclusion

In this retrospective study of rectal cancer patients treated with either EVT or TD for AL after anterior resection, no benefit of EVT could be shown. Before EVT can be recommended routinely in clinical practice its usefulness should be more thoroughly investigated in randomized trials.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

P.B. conceived the study, E.M. and S.J. performed data collection, E.M. and C.D. wrote the paper and M.L.L., H.J., and P.B. provided scientific advice and revised the paper.

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Paper IV





Increased risk of postoperative complications after delayed stoma reversal: a multicenter retrospective cohort study on patients undergoing anterior resection for rectal cancer

Eihab Munshi^{1,2} · Josefin Segelman³ · Peter Matthiessen⁴ · Jennifer Park⁵ · Martin Rutegård⁶ · Olle Sjöström⁶ · Henrik Jutesten¹ · Marie-Louise Lydrup¹ · Pamela Buchwald¹ on behalf of the RectoLeak Study group

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Abstract

Purpose Defunctioning stoma (DS) has been suggested to mitigate the consequences of anastomotic leak (AL) after low anterior resection. Stoma reversal (SR) is commonly delayed for nonmedical reasons in many healthcare systems. This study investigated the impact of the elapsed time from AR to SR on postoperative 90-day complications. The secondary aim was to explore the independent factors associated with a delayed SR.

M&M This multicenter retrospective cohort study included rectal cancer patients who underwent anterior resection (AR) and DS between 2014 and 2018. Multivariable logistic regression was used to evaluate the influence of the elapsed time from AR to SR on postoperative complications within 90 days.

Results Out of 905 patients subjected to AR with DS, 116 (18%) patients experienced at least one postoperative 90-day complication after SR. Multivariable analysis revealed an association between the elapsed time to SR and complications within 90 days from SR (OR 1.02; 95% CI, 1.00–1.04). The association with SR complications was further highlighted in patients who experienced delayed SR > 6 months after AR (OR 1.73; 95% CI, 1.04–2.86). AL after AR and nodal disease were both related to delayed SR.

Conclusion This study demonstrated that postoperative 90-day complications are associated with the time elapsed to SR. These findings emphasize the importance of early SR, preferably within 6 months, to prevent complications.

Keywords Defunctioning stoma · Stoma reversal time · Anterior resection · Anastomotic leak · Postoperative complications · Stoma reversal complications

✉ Eihab Munshi
eihab.munshi@gmail.com

¹ Department of Surgery, Skåne University Hospital, Lund University, Malmö, Sweden

² Department of Surgery, University of Jeddah, Jeddah, Saudi Arabia

³ Department of Molecular Medicine and Surgery, Karolinska Institutet, and Department of Surgery, Ersta Hospital, Stockholm, Sweden

⁴ Department of Surgery, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

⁵ Department of Surgery, Scandinavian Surgical Outcomes Research Group (SSORG), Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

⁶ Department of Diagnostics and Intervention, Surgery, Umeå University, Umeå, Sweden

Introduction

After sphincter-preserving surgery, a defunctioning stoma (DS) temporarily diverts the fecal stream. Typically, DS is a defunctioning loop ileostomy. A DS mitigates the severity of clinically relevant anastomotic leak (AL) and reduces the incidence of reoperation for AL [1–4]. However, the DS has several drawbacks [5]. Early defunctioning loop ileostomy morbidity includes high-flow dehydration and renal injury [6, 7]. The long-term presence of DS may lead to stoma prolapse, parastomal hernia, and reduced anorectal function, often known as low anterior resection syndrome (LARS) [8, 9]. These stoma-related morbidities can result in increased costs and hospitalization [10, 11]. Moreover, one of the four defunctioning loop ileostomy procedures may become permanent because patient frailty, tumor progression, or pelvic inflammation following AL hinder the restoration of bowel

continuity, resulting in the need for permanent maintenance or conversion to end colostomy [12, 13].

Since symptomatic AL most often manifests within 2 weeks following surgery, while stoma-related complications may occur continuously until stoma reversal (SR), experts recommend the reversal of DS between 8 and 12 weeks following the initial surgery [6, 14]. Previous studies have indicated that the reversal of a DS after 6 months may lead to a higher complication rate and longer hospital stays and nearly quadruples the risk of long-term bowel dysfunction [15, 16]. Stoma reversal is generally straightforward but has a 3–40% complication rate [17]. Despite its role as the second step in oncological surgery, approximately one-third of SRs are delayed due to low priority [11, 18].

The primary objective of this study was to investigate the relationship between the elapsed time to SR and postoperative 90-day complications post-SR. The secondary aim was to explore the independent factors associated with a delayed SR. We hypothesize that postponing SR will increase the likelihood of postoperative 90-day complications.

Materials and methods

This project stems from the RectoLeak project, which involved eleven hospitals from Sweden, consisting of patients subjected to anterior resection (AR) for rectal cancer in the years 2014–2018, described in detail elsewhere [19]. Patients were identified from hospital operation lists, and data were collected via the Swedish ColoRectal Cancer Registry (SCRCR) and medical chart review. The SCRCR comprises nearly all rectal cancer patients (98.8%) in Sweden and has high validity [20]. This study was approved by the Swedish Ethical Review Authority (Dnr 2020–02285).

Following the planned AR, patients were followed up at outpatient clinics for symptoms and signs of adverse surgical events, including AL. Anastomotic leak after AR was defined as a defect in the intestinal wall at the site of the anastomosis (where the staple or suture line is located) that results in communication between the intraluminal and extraluminal compartments, which was proposed by the International Study Group of Rectal Cancer (ISREC) [21]. Patients without any signs of AL at endoscopic or radiological contrast examinations were scheduled for SR if not planned for adjuvant chemotherapy. Patients indicated for adjuvant chemotherapy received treatment before SR. Stomas that reversed over 6 months after the index surgery were classified as delayed SR. This specific cutoff time was related to increased postoperative complications after SR [15, 22]. The stoma status was followed for at least 2 years. Following SR, medical charts were reviewed for medical

and surgical complications, including reoperations, within 90 days.

SR complications included mechanical small-bowel obstruction, ileus (paralytic ileus lasting more than 7 days or requiring total parenteral nutrition), bleeding, surgical-site infection (SSI), AL, wound dehiscence, incisional hernia, cardiac (new onset arrhythmia, myocardial infarction, and heart failure), and pulmonary events (pneumonia, respiratory aspiration, and acute respiratory distress syndrome). The type of reoperation after SR and the indications for the procedures were recorded.

Data analysis

The correlation of the elapsed time from AR to SR (exposure) with postoperative 90-day complications after SR (outcome) was assessed. Elapsed time was defined as a continuous variable (in months) as well as a binary variable (> 6 months, i.e., delayed SR). The outcome was specified as SR complications or reoperations within 90 days from the time of SR.

To ensure a more consistent group for analysis, we excluded patients with AL from the primary outcome evaluation. This decision was impacted by the potential risk associated with Grade C AL, which can lead to the closure of the diverting stoma while performing an end colostomy [21].

However, while evaluating delayed SR-associated clinical factors, we investigated factors that are clinically relevant for determining the timing of SR, including age, sex, American Society of Anesthesiologists (ASA) physical score, AL grade, and TNM stage, in the entire cohort.

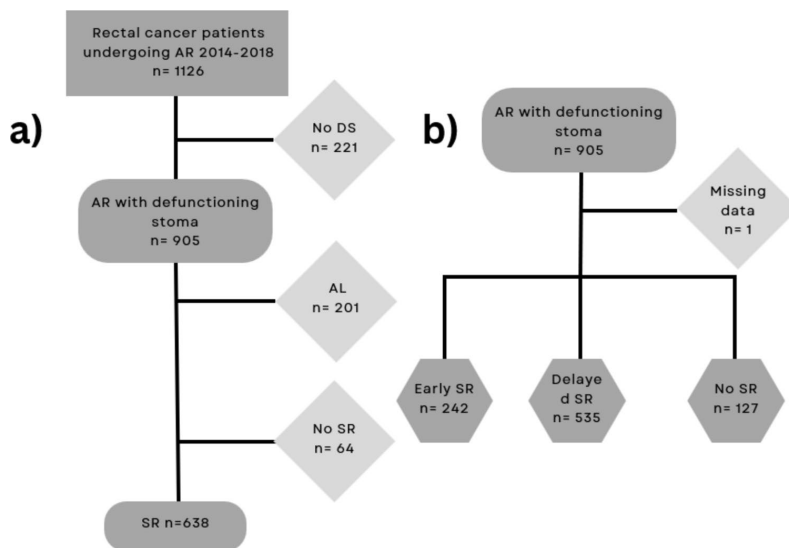
Statistical methods

Categorical variables were compared via the chi-square test and Fisher's exact test and are presented as percentages. The Mann–Whitney *U* test was used to analyze continuous variables, expressed as medians with interquartile ranges (IQRs).

Logistic regression was used to analyze the correlation between the elapsed time to SR and the outcome (postoperative 90-day complications and reoperation after SR). Elapsed time was defined as a continuous variable (in months) and as a binary variable (> 6 months, i.e., delayed SR). The following factors were included in the multivariable logistic regression to adjust for confounding variables: age (≤ 65 and > 65), sex (female and male), ASA (I, II and III, IV), *yp/pT* stage (0, 1, 2 and 3, 4), and *yp/pN* stage (0 and 1, 2). The confounders were chosen based on clinical reasoning, suggesting an influence on the timing of the SR procedure and the occurrence of complications.

Univariable and multivariable analyses assessed the clinical factors related to delayed SR. A two-sided *p* value of $< 5\%$ was considered significant.

Fig. 1 Flowcharts of patients who underwent anterior resection for rectal cancer between 2014 and 2018. **a** The elapsed time to stoma reversal and postoperative 90-day complications (primary endpoint) were studied. **b** Analysis of the clinical factors associated with delayed stoma reversal (secondary endpoint). AR, anterior resection; DS, defunctioning stoma; AL, anastomotic leak; SR, stoma reversal



A complete case analysis was performed when data were missing, and > 2% of the missing data are reported in the tables. SPSS 28 software was used (SPSS, Chicago, IL, USA).

Results

Patient demographic and clinical characteristics

Between 2014 and 2018, 11 hospitals in Sweden performed 1126 AR procedures for rectal cancer. The 905 patients who received a DS (898 defunctioning loop ileostomy, 99%) in conjunction with AR were included in the current study (Fig. 1). In total, 201 (22%) patients had AL. Table 1 displays the characteristics of patients without AL who had an SR or did not have one. Two hundred ninety-four (46%) patients underwent minimally invasive procedures, and 186 (29%) underwent robotic-assisted operations. After a mean follow-up of 4.1 years, 64 (9%) patients retained their DS. In the non-SR group, patients were older, more frequently classified as ASA III–IV, had more advanced tumors in terms of T and N stages, and a greater proportion had distant recurrence. In the SR group, half of the patients received neoadjuvant therapy—either radiotherapy, 216 (34%), or radiochemotherapy, 108 (17%)—while one-third received adjuvant chemotherapy, 217 (34%). Those who underwent adjuvant chemotherapy had a longer elapsed time to SR than those in the non-adjuvant group (11.4 vs. 6.4 months). Supplementary Table 1 compares the characteristics of the entire study group, including patients with AL.

Elapsed time to stoma reversal and postoperative 90-day complications

After patients who had AL ($n = 201$ (22%)) or did not undergo SR ($n = 64$ (7%)) were excluded, 638 remained in the main analysis regarding time to SR. One hundred sixteen (18%) patients experienced at least one postoperative 90-day complication after SR, and 39 (6%) patients underwent reoperation after SR (Suppl Table 2). The median time from AR to SR was longer in the postoperative 90-day complications group than in the non-complication group (10.2 (IQR 6.5–15.2) months vs. 7.3 (IQR 4.8–11.7) months ($p < 0.001$)). Similarly, the median time to SR was longer in the reoperation after SR group than in the non-reoperation group (11.1 (IQR 7.8–15) vs. 7.6 (IQR 4.9–12) months ($p = 0.002$)).

Patients were allocated to two groups: 209 (33%) patients had SR within 6 months of AR, and 428 (67%) patients had delayed SR (> 6 months). The univariable analysis revealed a relationship between delayed SR and postoperative 90-day complications and reoperation after SR ($p = 0.009$ and $p = 0.021$, respectively).

Supplementary Table 2 details the indications for and types of reoperations and overall complications.

The results of the multivariable analyses exploring the associations between time (continuous variable) from AR to SR and the main outcome of 90-day complications, as well as reoperations following SR, are presented in Table 2. After adjustment for clinical and pathological factors, a significant association was found between time and postoperative 90-day complications (OR 1.02 (95%

Table 1 Clinical characteristics of stoma reversal compared with the non-reversed stoma, where patients with anastomotic leak are excluded

	Stoma reversal <i>N</i> = 638	Non-reversed stoma <i>N</i> = 64
Age in years (IQR)	66 (59–72)	70 (64–74)
Sex (male)	391 (61.3)	33 (51.6)
BMI (kg/m ²) (IQR)	25.4 (23.2–28.1)	25.6 (23.4–28.4)
Smoking		
Missing	33 (5.2)	10 (15.6)
ASA class		
I	146 (23.1)	7 (10.9)
II	391 (61.9)	40 (62.5)
III–IV	95 (15)	17 (26.6)
CCI group		
0	437 (68.5)	38 (59.4)
1	116 (18.2)	15 (23.4)
2	56 (8.8)	5 (7.8)
3+	29 (4.5)	6 (9.4)
Tumor distance*		
High (11–15)	246 (38.6)	27 (42.2)
Middle (6–10)	378 (59.3)	36 (56.3)
Low ≤ 5	13 (2)	1 (1.6)
Neoadjuvant therapy		
Radiotherapy	216 (33.9)	23 (35.9)
RCT	108 (16.9)	15 (23.4)
None	314 (49.2)	26 (40.6)
pCR	9 (1.4)	3 (4.7)
Operation time, minutes (IQR)	272 (200–362)	263 (197–352)
Surgical approach		
Open/converted	343 (53.8)	42 (65.6)
Laparoscopy	108 (17)	10 (15.6)
Robotic	186 (29.2)	12 (18.8)
Anastomosis type		
End-end	155 (24.3)	14 (21.9)
Side-end/J-pouch	453 (71)	44 (68.8)
Missing	30 (4.7)	6 (9.4)
Mesorectal excision type		
TME	566 (88.7)	57 (89.1)
PME	72 (11.3)	7 (10.9)
Intraoperative complications		
Significant bleeding > 500 ml	66 (10.3)	8 (12.5)
Serosal tear	11 (1.7)	2 (3.1)
Bowel perforation	10 (1.6)	2 (3.1)
Ureteric injury	2 (0.3)	0
Tumor stage		
<i>yp/pT</i>		
T0	12 (1.9)	4 (6.3)
T1–2	261 (41.5)	21 (32.8)
T3–4	353 (56)	39 (60.9)

Table 1 (continued)

	Stoma reversal <i>N</i> = 638	Non-reversed stoma <i>N</i> = 64
Tx	4 (0.6)	0
<i>yp/pN</i>		
N0	401 (63.8)	28 (43.8)
N1–2	226 (35.9)	36 (56.3)
Nx	2 (0.3)	0
M		
M0	603 (94.5)	58 (92.1)
M1	19 (3)	5 (7.9)
Adjuvant chemotherapy	217 (34)	28 (43.8)
Local recurrence	12 (1.9)	1 (1.6)
Distant recurrence	99 (15.5)	18 (28.1)
Follow-up (years)	4.8 (3.6–6)	4.6 (3.5–5.8)
Stoma reversal time		
≤ 6 months	209 (32.8)	NA
> 6 months	428 (67)	NA

Values in parentheses are percentages if not stated otherwise

BMI body mass index, *ASA* American Society of Anesthesiologists, *CCI* Charlson Comorbidity Index, *RCT* radiochemotherapy, *pCR* complete pathological response, *MIS* minimally invasive surgery, *IMA* inferior mesenteric artery, *ICG* indocyanine green, *TME* total mesorectal excision, *PME* partial mesorectal excision, *yp/pT* neoadjuvant/pathological tumor stage, *yp/pN* neoadjuvant/pathological lymph node stage, *NA* not applicable

*cm from the anal verge

¹Mann-Whitney *U*

²Fisher's exact test

³Chi-squared test

Table 2 Logistic regression relating elapsed time (per month) from AR to stoma reversal and overall postoperative complications and reoperation post-SR

Overall postoperative complications			
Unadjusted		Adjusted*	
OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
1.02 (1.00–1.04)	0.023	1.02 (1.00–1.04)	0.049
Reoperation			
Unadjusted		Adjusted*	
OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
1.01 (0.99–1.04)	0.346	1.01 (0.98–1.04)	0.510

*Adjusted for age, sex, ASA, T stage, and N stage

CI, 1.00–1.04, *p* = 0.049)) but not with reoperations. In addition, delayed SR (SR > 6 months) was associated with an increased risk of postoperative 90-day complications (OR 1.73 (95% CI, 1.04–2.86, *p* = 0.034) (Table 3)) as well as reoperation after SR (OR 2.66 (95% CI, 1.06–6.68, *p* = 0.038)).

Table 3 Logistic regression relating elapsed time (> 6 months) from AR to stoma reversal and overall postoperative complications and reoperation post-SR

Overall postoperative complications			
Unadjusted		Adjusted*	
OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
1.86 (1.17–2.97)	0.009	1.73 (1.04–2.86)	0.034
Reoperation			
Unadjusted		Adjusted*	
OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
2.96 (1.22–7.17)	0.017	2.66 (1.06–6.68)	0.038

*Adjusted for age, sex, ASA, T stage, and N stage

Clinical factors related to delayed defunctioning stoma reversal

Table 4 presents the uni- and multivariable analyses of the potential associations between clinical factors and a delayed SR (SR > 6 months). The analyses identified AL and N1–2 disease as independent factors related to delayed SR. No discernible influence was observed for age, sex, ASA class, AL grade, or T or M stage.

Discussion

This study demonstrates an association between the time elapsed from AR to SR and postoperative 90-day complications after SR. Furthermore, patients with delayed SR (> 6 months) had a 1.7-fold increased likelihood of postoperative 90-day complications and a 2.7-fold increased likelihood of reoperation after SR. Nodal disease and AL post-AR impacted the timing of SR and were associated with its delay. For nodal disease, adjuvant chemotherapy is recommended, which may delay SR. When managing

AL complications, an extended period for management and recovery is often needed before SR can be considered. Although the SR procedure is relatively straightforward, the SR timing could be crucial for obtaining preferable results.

Recently, Hacim et al. reported similar results in a cohort of 133 patients with defunctioning loop ileostomy, where the time until SR was classified into < 3, 3–6, and > 6 months [22]. The time to SR was found to be the primary determinant of complications related to defunctioning loop ileostomy, with complication rates of up to 62.5% in the latter group. These findings were consistent following stratification for complication type (ileostomy site-related, anastomosis-related, and metabolic) and severity [22]. Other prior studies have indicated that complication rates following SR vary between 13 and 40%, and the elapsed time to SR has been suggested as an independent risk factor for complications. Specifically, any SR delay of 6 months or more puts the patient at risk of experiencing complications [17, 23, 24]. A large retrospective cohort study reported a 6% increase in post-SR complications per month of delay [25]. However, some studies have reported that delaying SR has no effect on postoperative complications but have reported increased risks of postoperative complications among patients over 80 years of age, males, and those who experienced surgical site infection following AR [26, 27]. The conflicting results may be attributed to the studies' limited reporting of 30-day follow-up after SR, possibly underestimating the influence of elapsed time.

A systemic review and meta-analysis investigated early SR (within 2 weeks post-AR) and concluded it is safe and feasible. Despite not increasing the incidence of AL or overall complications, early SR is still associated with a higher incidence of significant complications and reoperation [18]. Early SR accounts for barely more than 2% of the SR patients in our cohort and is outside the scope of the current study.

Table 4 Logistic regression was used to analyze patients' clinical factors related to delayed stoma reversal (> 6 months from anterior resection)

Variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age > 65	1.07	0.79–1.45	0.696	0.99	0.72–1.39	0.956
Sex (male)	1.34	0.98–1.83	0.075	1.36	0.96–1.91	0.082
ASA class (III–V)	1.26	0.81–1.96	0.329	1.12	0.70–1.81	0.629
Anastomotic leak	2.11	1.41–3.53	< 0.001	2.30	1.41–3.75	< 0.001
AL grade (B–C)	0.93	0.32–2.73	1			
Tumor stage						
yp/pT (T3–4)	1.86	1.36–2.54	< 0.001	1.21	0.86–1.71	0.272
yp/pN (N1–2)	4.15	2.83–6.23	< 0.001	4.15	2.73–6.31	< 0.001
M	2.03	0.68–6.05	0.245			

ASA American Society of Anesthesiologists physical status classification, AL anastomotic leak, yp/pT neoadjuvant/pathological tumor stage, yp/pN neoadjuvant/pathological lymph node stage

Patients with DS who require adjuvant chemotherapy (one-third of our cohort) face a complex decision of whether to prioritize the initiation of adjuvant chemotherapy over SR. The effectiveness of adjuvant therapy diminishes when it is initiated after 8 weeks [28]. The presence of DS during chemotherapy exacerbates chemotherapy-induced diarrhea and gastrointestinal toxicity, potentially affecting treatment completion, dosing, and subsequently disease-free survival [29]. In our study, the non-SR group received more adjuvant chemotherapy (44% vs. 34% in the SR group). Therefore, novel treatment approaches with neoadjuvant chemotherapy may be beneficial in terms of timely SR [30]. Nationwide research by Hoshino et al. revealed no difference in total adjuvant chemotherapy doses between patients with and without DS but did find a dose reduction in DS patients and patients with early SR (≤ 6 months after LAR) compared with those with late SR (7–12 months) [31]. A meta-analysis examining the SR during or after adjuvant chemotherapy revealed no significant differences in overall perioperative complications, AL, SSI, ileus, or length of hospital stay between the two groups [32]. However, these studies did not explore the effect of SR on chemotherapy completion or dosage modification. Presently, the results of the German CoCStom study are awaited, assessing adjuvant chemotherapy completion early (8–10 days following tumor resection and before commencing adjuvant) vs. delayed SR (26 weeks after tumor resection and adjuvant therapy completion) [33, 34].

Strengths and limitations

The study's limitations include its retrospective design, which introduces a risk of selection bias. In some patients, SR may be intentionally delayed for unregistered reasons, such as a need for a longer recovery time from AR and chemotherapy or poor nutritional status, making earlier SR disadvantageous in terms of risk of postoperative complications. Residual confounding may be present due to unknown predictors or missing information regarding the ex-anastomotic technique (stapled or handsewn) or if laparotomy is performed. The complications were not classified via a grading system, such as the Clavien-Dindo score, which may have hampered comparisons across studies. To create homogeneous comparable groups, patients with AL of all grades were excluded since a Grade C AL can mandate early closure of the DS and the creation of an end colostomy. On the other hand, this restriction may have introduced a selection of patients with a lower risk of surgical complications in general, underestimating the actual risk of complications to SR. Furthermore, the time interval between AR and adjuvant chemotherapy and the completion of adjuvant chemotherapy and the SR were not recorded. Nevertheless, the study benefits from an adequate sample size, encompassing data from

11 centers (county as well as university hospitals), enhancing its representativeness and generalizability.

Conclusion

While timely SR is advocated to alleviate patient suffering, our findings hold relevance in the context of today's overstretched healthcare systems. This study highlights the importance of seeking early SR to minimize the risk of post-operative 90-day complications.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00384-025-04831-y>.

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Author contribution This original research is a part of doctoral studies for EM, who wrote the main manuscript with figures and tables. The project is supervised and guided by PB (supervisor), M-LL, HJ (co-supervisors), JS, PM, JP, MR, and OS, who contributed to designing the project and then reviewed and edited the manuscript.

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Data availability The data supporting this study's findings are available from Svenska Kolorektalcancerregistret (SCRCR). Nevertheless, restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of SCRCR. SCRCR can be contacted via rcnorr.statistiker@regionvasterbotten.se.

Declarations

Ethical approval The Swedish ethical review authority provided ethical approval for the study (Diary number 2020–02285), and it waived informed consent owing to the need to retrieve the data from the national registry. Additionally, the study was conducted in accordance with the relevant ethical considerations of the Helsinki Declaration.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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