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Rebecca Svensson Neufert

LUND
UNIVERSITY

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Abstract

Background

Rectal washout (RW) is performed to eliminate intraluminal cancer cells and thereby reducing the risk of local recurrence (LR). The overall aim of this thesis was to investigate the importance of RW in rectal cancer surgery.

Method

Paper I: Survey of the current practice of RW among Swedish colorectal units.

Paper II: The association between RW and 30-day postoperative complications after anterior resection (AR) for rectal cancer was analysed using data from the Swedish Colorectal Cancer Registry (SCRCR).

Paper III: The impact of RW on the 5-year oncological outcome after abdominoperineal resection (APR) for rectal cancer was analysed using data from the SCRCR.

Paper IV: The impact of RW on the 3- and 5-year oncological outcome after AR for rectal cancer was analysed using data from the SCRCR.

Paper V: Patients undergoing transanal total mesorectal excision (taTME) for rectal cancer were assessed for the presence of intraluminal cancer cells during RW.

Results

Paper I: RW was reported to be routinely performed in open and minimally invasive rectal cancer surgery, most often using sterile water or an alcohol-based solution with a minimum volume of 100-<500 ml.

Paper II: The RW group had fewer overall and surgical complications. RW was not a risk factor for overall complications (odds ratio (OR) 0.73, 95% confidence interval (CI) 0.60-0.90, p=0.002) or for surgical complications (OR 0.62, 95% CI 0.50-0.78, p<0.001).

Paper III: There were no differences between the RW and no RW group in rates of LR (10/265 (3.8%) vs. 87/2160 (4.0%), p=0.839), distant metastasis (51/265 (19.2%) vs. 476/2160 (22.0%), p=0.293) and overall recurrence (53/265 (20.0%) vs. 505/2160 (23.4%), p=0.213) at 5-year follow up.

Paper IV: RW in AR did not impact the 3-year oncological outcome. A decreased 5-year risk of LR was observed after RW in multivariable analysis (hazard ratio 0.53, 95% CI 0.31-0.90, p=0.018).

Paper V: Only three of 21 patients had washout samples positive for cancer cells and all samples were negative after 500 ml of RW.

Conclusion

This thesis contributes to increased knowledge about RW and investigates the importance of RW in rectal cancer surgery. Swedish practice of RW is described. RW in AR for rectal cancer seems to be a safe technique with no evidence of increased 30-day postoperative complications. Routine RW in APR for rectal cancer to improve the 5-year oncological outcome is not supported. RW in AR for rectal cancer does not appear to impact the 3-year oncological outcome. However, RW was associated with decreased 5-year risk of LR, justifying continued practice of RW in AR for rectal cancer. Even if intraluminal cancer cells were rare during RW in taTME for rectal cancer, 500 ml of RW is probably needed to ensure elimination of intraluminal cancer cells.

Key words Rectal washout, rectal cancer surgery, anterior resection, abdominoperineal resection, transanal total mesorectal excision, local recurrence

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To my mother

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Original papers

I. **Svensson Neufert R**, Teurneau-Hermansson K, Lydrup M-L, Jörgren F, Buchwald P. Rectal washout in rectal cancer surgery: A survey of Swedish Practice-Questionnaire. Int J Surg Open. 2018;15:32-6. doi: 10.1016/j.ijso.2018.10.003.

II. Teurneau-Hermansson K, **Svensson Neufert R**, Buchwald P, Jörgren F. Rectal washout does not increase the complication risk after anterior resection for rectal cancer. World J Surg Oncol. 2021;19(1):82. doi: 10.1186/s12957-021-02193-7.

III. **Svensson Neufert R**, Jörgren F, Buchwald P. Rectal washout during abdominoperineal resection for rectal cancer has no impact on the oncological outcome. Colorectal Dis. 2022;24(3):284-91. doi: 10.1111/codi.15977.

IV. **Svensson Neufert R**, Jörgren F, Buchwald P. Impact of rectal washout on recurrence and survival after anterior resection for rectal cancer. BJS Open. 2022;6(6):zrac150. doi: 10.1093/bjsopen/zrac150.

V. Perdawood SK, **Neufert RS**, Kroeigaard J, Maina PJ, Eiholm S, Jörgren F, Buchwald P. Low presence of intraluminal cancer cells in rectal washout during transanal total mesorectal excision. Br J Surg. 2021;108(10):e338-9. doi: 10.1093/bjs/znab256.

Abbreviations

AL	Anastomotic Leakage
APR	Abdominoperineal Resection
AR	Anterior Resection
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CHT	Chemotherapy
CI	Confidence Interval
CRM	Circumferential Resection Margin
CT	Computed Tomography
DM	Distant Metastasis
dMMR	Mismatch Repair Deficiency
DRM	Distal Resection Margin
EMVI	Extramural Venous Invasion
ESD	Endoscopic Submucosal Dissection
FIT	Faecal Immunochemical Test
HAR	High Anterior Resection
HP	Hartmann's Procedure
HR	Hazard Ratio
LAR	Low Anterior Resection
LE	Local Excision
LR	Local Recurrence
MDT	Multidisciplinary Team
MIS	Minimally Invasive Surgery
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
OAR	Overall Recurrence
OR	Odds Ratio
PME	Partial Mesorectal Excision
R	Residual
RCT	Randomised Controlled Trial
RT	Radiotherapy
RW	Rectal Washout
SCRCR	Swedish Colorectal Cancer Registry
taTME	Transanal Total Mesorectal Excision
TEM	Transanal Endoscopic Microsurgery
TME	Total Mesorectal Excision
TNM	Tumour Node Metastasis

Populärvetenskaplig sammanfattning

I Sverige drabbas årligen ca 2000 individer av ändtarmscancer och tillsammans med tjocktarmscancer är det den tredje vanligaste cancerformen i världen. Något fler män än kvinnor drabbas av sjukdomen och den är vanligare bland individer över 70 års ålder. Symptom vid debut kan vara ändrade avföringsvanor, blod i avföringen, viktnedgång och blodbrist.

I de flesta fall krävs kirurgi för att uppnå bot. Ofta kombineras kirurgin med strålbehandling och kemoterapi. Det finns tre typoperationer vid ändtarmscancer, vilka samtliga innebär att den del av tarmen som tumören är belägen i opereras bort. Främre resektion innebär att större delen av ändtarmen opereras bort och att en koppling görs mellan tjocktarmen och kvarvarande nedre delen av ändtarmen. Abdominoperineal resektion utförs vid tumörer belägna nära ändtarmsmynningen och innebär att hela ändtarmen tillsammans med analkanalen opereras bort samt att patienten erhåller en permanent stomi. Vid Hartmanns operation opereras ändtarmen bort på samma vis som vid främre resektion, men man avstår från koppling och anlägger i stället en permanent stomi.

Operation vid ändtarmscancer kan utföras med titthåls- eller öppen teknik. Titthålsteknik blir allt vanligare, och står idag för över 70 % av alla ändtarmscanceroperationer som utförs i Sverige.

År 1995 bildades Svenska Kolorektalcancerregistret (SCRCR) med syfte att öka kvaliteten på omhändertagandet av patienter med ändtarmscancer. Alla nydiagnostiserade patienter med ändtarmscancer i Sverige registreras i SCRCR med uppgifter om operationen, komplikationer, tilläggsbehandling, tumöråterfall och död.

Lokalrecidiv (lokalt tumöråterfall i lilla bäckenet) kan vara svårt att bota och orsaka stort lidande för patienten. Lyckligtvis har stora framsteg i omhändertagandet av patienter med ändtarmscancer medfört att färre drabbas av lokalrecidiv. Förbättrad kirurgisk teknik och tillägg av strålbehandling samt kemoterapi har medfört att färre än var tjugonde patient idag drabbas av lokalrecidiv i Sverige.

Förekomst av fria cancerceller i tarmen har påvisats vid ändtarmscancerkirurgi. Dessa cancerceller tros kunna bidra till uppkomst av lokalrecidiv. För att eliminera dessa celler och därigenom försöka minska risken för lokalrecidiv sköljs tarmen vid operation för ändtarmscancer. Detta kallas rektalsköljning. Sköljningen görs med tarmen avstängd nedom tumören men ovanför där tarmen senare ska delas. Det saknas emellertid säkra bevis på att rektalsköljning minskar risken för lokalrecidiv då tidigare studieresultat varit motstridiga. Olika sköljvätskor och volymer används över världen och det är osäkert vilka som är mest effektiva för att motverka lokalrecidiv. En studie baserad på patienter från SCRCR som genomgått främre resektion för ändtarmscancer mellan åren 1995 och 2002 visade att andelen

lokalrecidiv var 6 % efter rektalsköljning jämfört med 10 % utan rektalsköljning, men det är svårt att utesluta om andra faktorer påverkade utfallen. Rektalsköljning vid Hartmanns operation för ändtarmscancer har också studerats, men någon påvisbar skillnad i andel lokalrecidiv hittades inte. Värdet av rektalsköljning vid abdominoperineal resektion har inte studerats. Sammanfattningsvis är kunskapsläget generellt bristfälligt vad gäller värdet av rektalsköljning för att minska risken för lokalrecidiv och värdet vid de enskilda operationerna, titthåls- respektive öppen teknik samt vilka sköljvätskor och volymer som är mest effektiva. Det är heller inte studerat om proceduren kan medföra komplikationer. Enligt gällande nationellt vårdprogram för tjock- och ändtarmscancer i Sverige rekommenderas rektalsköljning vid främre resektion och kan eventuellt utföras vid abdominoperineal resektion. För Hartmanns operation ges inga rekommendationer. I en enkätstudie utförd i Storbritannien uppgav kirurger att de utförde rektalsköljning i mindre utsträckning vid titthålsoperation än vid öppen operation för ändtarmscancer. Detta kan möjligen bero på att sköljningen blir tekniskt svårare att utföra.

Det övergripande syftet med denna avhandling var att kartlägga rektalsköljningens roll vid ändtarmscancerkirurgi för att bidra till ökad kunskap kring proceduren. Den första studien är en nationell enkätundersökning om rådande rutiner för rektalsköljning vid ändtarmscancerkirurgi i Sverige. Enligt enkätsvaren utfördes rektalsköljning rutinmässigt i olika grad beroende på operationstyp. Fyrtio procent av de svarande enheterna hade ett PM för rektalsköljning, och de svarande uppgav oftast att sterilt vatten eller en alkoholbaserad lösning användes som sköljvätska.

I de tre följande studierna användes registeruppgifter från SCRCR. I den andra studien baserad på patienter opererade för ändtarmscancer med främre resektion förelåg en lägre andel totala komplikationer samt kirurgiska komplikationer bland patienterna som genomgått rektalsköljning jämfört med de patienter som inte genomgått rektalsköljning. Resultaten antyder att rektalsköljning är en säker procedur som inte ökar risken för komplikationer på kort sikt efter operationen främre resektion för ändtarmscancer.

De två efterföljande registerstudierna undersökte hur rektalsköljning påverkar risken att drabbas av lokalrecidiv, fjärrmetastaser (tumöråterfall i andra organ utanför lilla bäckenet) och överlevnad vid abdominoperineal resektion respektive främre resektion. I den senare studien undersöktes även om rektalsköljning har samma betydelse vid titthåls- som vid öppen teknik. Vid abdominoperineal resektion kunde ingen nytta påvisas av rektalsköljning för att minska risken för lokalrecidiv och inte heller för de andra undersökta utfallen. Vid främre resektion påverkade rektalsköljning inte andelen lokalrecidiv inom tre år från operation, men risken att drabbas av lokalrecidiv inom fem år från operation var lägre om rektalsköljning utförts. Det är emellertid svårt att avgöra om denna effekt enbart kan tillskrivas rektalsköljning.

I den sista studien undersöktes förekomst av cancerceller i prover från sköljvätska vid transanal total mesorektal excision för ändtarmscancer där rektalsköljning utförts med sterilt vatten. Transanal total mesorektal excision är en operationsmetod som innebär att en del av ändtarmen opereras bort från tarmens insida efter förslutning av tarmen nedom tumören utan att tumören vidrörs. Operationerna utfördes vid Slagelse Sjukhus i Danmark och studien var ett samarbetsprojekt med detta sjukhus. Hos endast tre av 21 patienter sågs cancerceller i sköljvätskeproverna, och efter rektalsköljning med totalt 500 ml sterilt vatten återfanns inga cancerceller hos någon av patienterna. Studien var en pilotstudie och är begränsad i sitt omfång. För att bekräfta resultaten behövs en större studie genomföras med fler patienter.

Denna avhandling bidrar till ökad kunskap kring rektalsköljning vid kirurgi för ändtarmscancer och dess fynd kan ligga till grund för framtida forskning.

Introduction

Rectal cancer

Colorectal cancer has the third highest cancer incidence worldwide and is the second most common cause of cancer death[1, 2]. Rectal cancer is an adenocarcinoma within 15 cm from the anal verge and is subdivided into low (0-5 cm), mid (6-10 cm) and high (11-15)[2]. In Sweden, approximately 2000 patients are diagnosed with rectal cancer annually and the median age at diagnosis is 72 years[2-4]. However, the incidence of colorectal cancer in patients under the age of 50 has increased in high-income countries[5-8]. More men than women are affected[4]. Symptoms of rectal cancer can be rectal bleeding, anaemia, change in bowel habits, urgency to defecation and sensation of incomplete defecation.

Western lifestyle with high intake of processed meat and increased body mass index (BMI) are risk factors for colorectal cancer, reflected in the rising incidence in developing countries[9-13]. An increased risk of colorectal cancer has also been found in patients with type 2 diabetes[14, 15]. Other risk factors are high alcohol intake, cigarette smoking and inflammatory bowel disease[13, 16-20]. Moreover, bacteraemia from certain microbes has been associated to colorectal cancer [21]. Calcium supplements, whole grains, dietary fibre and dairy products reduce risk[13].

Most cases of colorectal cancer arise from adenomas over a 10-15 year period and the greater the size of the adenoma, the higher the risk of cancer[2, 22]. About 20-25% of colorectal cancer cases are hereditary and the most common hereditary conditions are Lynch syndrome, familial adenomatous polyposis and MUTYH-associated polyposis[2, 23].

Diagnosis and testing

Digital rectal examination can detect tumours in the distal part of the rectum. Diagnosis is verified by endoscopic examination with biopsy. Rigid sigmoidoscopy is used to divide the tumour into low, mid or high rectal cancer by measuring the distance to the tumour from the anal verge. Colonoscopy is performed to rule out synchronous tumours or polyps. Pelvic Magnetic Resonance Imaging (MRI) is used for locoregional staging. Computed Tomography (CT) of the thorax and abdomen

assess presence of distant metastasis (DM) and can be complemented with MRI of the liver. If a potentially curative or strictly palliative disease cannot be distinguished, fluorodeoxyglucose positron emission tomography-CT is performed. Occasionally transrectal ultrasound is performed. Multidisciplinary team (MDT) conferences pre- and postoperatively are recommended. At the MDT conference each patient is discussed individually, to optimise treatment and ensure quality, as well as to decide on follow-up[2, 24, 25]. Surgeons, oncologists, radiologist, pathologists and specialist nurses take part at the MDT conference.

Screening for colorectal cancer can be carried out by faecal testing, endoscopic examination or CT colonography[26, 27]. Screening reduces the risk of colorectal cancer death[27, 28]. The European Union recommended the introduction of screening for colorectal cancer in 2003[29]. In Sweden, the National Board of Health and Welfare recommend screening individuals between ages 60 and 74 with faecal immunochemical test (FIT) for occult blood every second year[30]. Screening is operating in all Swedish regions since the fall of 2022. A positive FIT should be followed by a colonoscopy.

Staging

The patient is staged according to the 8th edition of the Tumour Node Metastasis (TNM) Classification of Malignant Tumours by the Union for International Cancer Control (Table 1 and 2)[2, 31]. T stages are illustrated in Figure 1. The TNM classification is an important tool for prognosis, and to select and evaluate treatment. The classification can be accompanied with a prefix where cTNM denotes the clinical classification before treatment is given, and pTNM includes additional information postoperatively together with the pathological examination. An additional y is used for TNM classification following preoperative therapy. The Residual (R) classification defines residual tumour status posttreatment (Table 3)[2, 31].

Apart from contributing to TNM staging, the histopathological examination gives information about several prognostic factors including circumferential resection margin (CRM) and distal resection margin (DRM) (Figure 2), differentiation grade, tumour deposits, tumour budding, lymphovascular invasion, perineural invasion and extramural venous invasion (EMVI)[2]. Mismatch repair deficiency (dMMR)/microsatellite instability (MSI) testing is recommended as well as mutational analysis including KRAS, NRAS and BRAF[2, 32]. The quality of total mesorectal excision (TME) specimen is also macroscopically graded according to criteria by Quirke[2, 33].

Table 1 Summary of TNM classification in rectal cancer

TNM classification	Stage	Definition
T	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	Tis	Carcinoma in situ
	T1	Invasion of submucosa
	T2	Invasion of muscularis propria
	T3	Invasion through muscularis propria into perirectal tissues
	T4a-b	Penetration of visceral peritoneum (a) and/or other organs or structures (b)
N	X	Regional lymph nodes cannot be assessed
	0	No regional lymph node metastasis
	1a-c	Metastasis in 1 (a), 2-3 (b) regional lymph nodes or tumour deposits (c)
	2a-b	Metastasis in 4-6 (a) or ≥7 (b) regional lymph nodes
M	0	No distant mestastasis
	1a-c	Distant metastasis in 1 (a), multiple (b) organs or sites, or peritoneum (c)

The 8th edition by the Union for International Cancer Control

Table 2 Summary of TNM stages in rectal cancer

TNM classification	Stage
Tis N0 M0	Stage 0
T1-2 N0 M0	Stage I
T3-4 N0 M0	Stage II
T1-4 N1-2 M0	Stage III
T1-4 N0-2 M1	Stage IV

The 8th edition by the Union for International Cancer Control

Table 3 Summary of residual tumour (R) classification in rectal cancer

R category	Definition
RX	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

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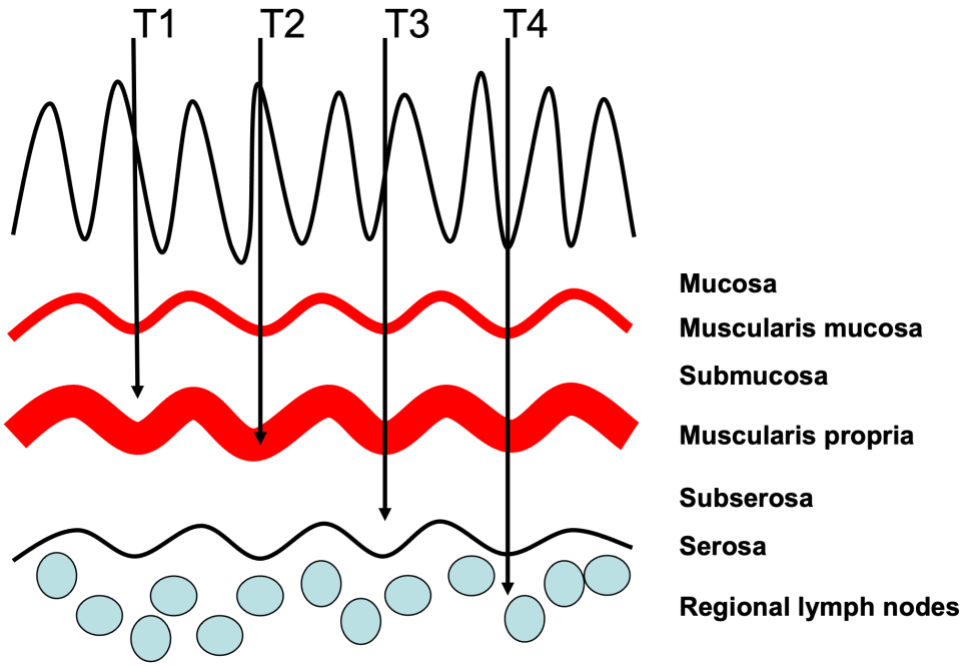

Figure 1 Illustration of the T stages
Illustration by Fredrik Jörgren, reprinted with permission

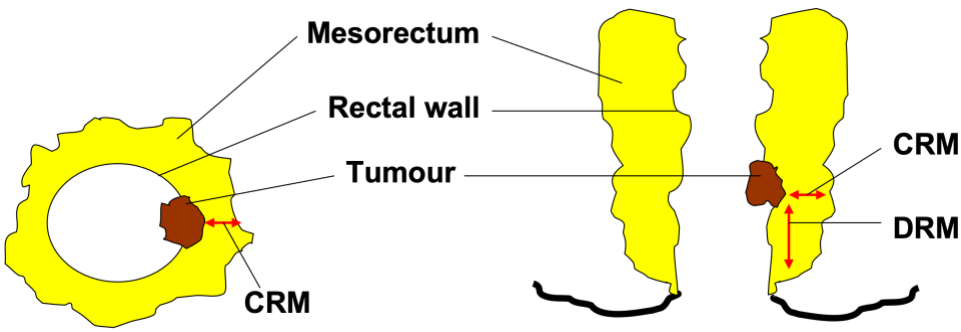

Figure 2 Illustration of resection margins, horisontal section (left), frontal section (right)
Illustration by Fredrik Jörgren, adapted with permission
CRM, circumferential resection margin; DRM, distal resection margin

Survival

The survival of patients with rectal cancer has continued to improve during the 21st century. The 3-year relative survival in Sweden for resected M0 rectal cancer patients is currently above 90%[3]. Overall and relative survival for all patients diagnosed with rectal cancer divided by gender from the SCRCR is presented below in Figure 3.

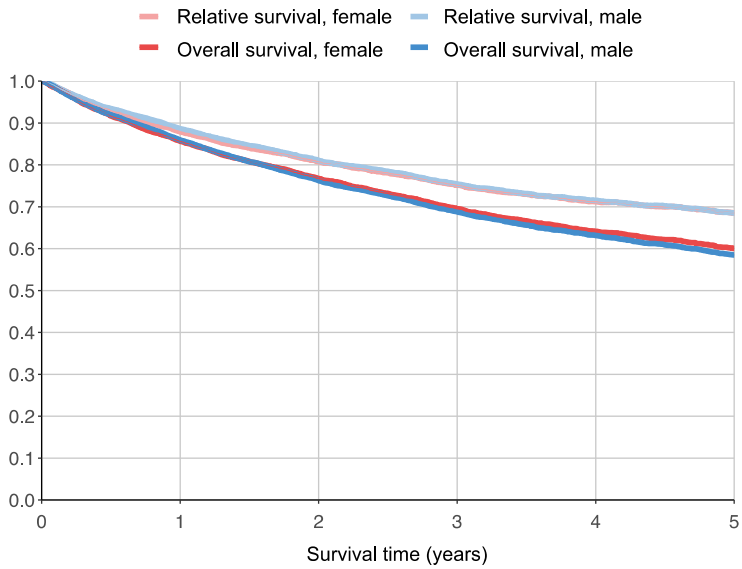

Figure 3 Overall and relative survival, all patients diagnosed with rectal cancer in the Swedish Colorectal Cancer Registry between 2015 to 2021
Adapted with permission from the Swedish Colorectal Cancer Registry

Surgery

Primary treatment of rectal cancer is surgery. The surgical procedures recommended for rectal cancer according to the Swedish national guidelines for colorectal cancer care are presented below and in Figure 4[2, 4].

Minimally invasive surgery

Minimally invasive surgery (MIS) comprises conventional laparoscopic surgery and robotic-assisted surgery. Today, over 70% of rectal cancer resections are performed with MIS in Sweden, and robotic-assisted surgery alone accounts for roughly 50%[3]. Laparoscopic and open surgery have similar oncological outcomes[34-37]. Patients who undergo laparoscopic surgery have a faster recovery, shorter length of hospital stay, and less need of analgesics[38, 39]. Robotic-assisted surgery have short-term results comparable to laparoscopic surgery[40, 41]. However, more data on short- and long-term results are awaited.

Total mesorectal excision

The mesorectum is a fatty lymphovascular tissue that surrounds the lateral and posterior parts of the rectum[42]. TME includes en bloc removal of the tumour bearing section of the rectum with a DRM of at least 1 cm, together with the intact mesorectum performed with precise dissection outside of the mesorectal fascia down to the pelvic floor. The technique was described in the early 1980s by Heald *et al* and was later introduced nationally in Sweden with several workshops and training programmes[43-46]. TME is considered as gold standard in rectal cancer surgery. An alternative for rectal cancer in the upper third of the rectum is partial mesorectal excision (PME) if a distal margin of at least 5 cm can be safely achieved, meaning that the mesorectum is divided and the distal part left behind[2, 47].

Anterior resection

Anterior resection (AR) is a sphincter-sparing procedure. The rectum is resected, and bowel continuity is accomplished with an anastomosis. AR is commonly performed for rectal cancer in the two upper thirds of the rectum. For tumours situated in the mid rectum, a low AR (LAR) with TME is typically performed. The remaining rectal stump is often short and therefore, a colonic reservoir or side-to-end anastomosis is constructed with double stapling technique. If necessary, a defunctioning loop ileostomy is created. The stoma has advantages if a possible anastomotic leakage (AL) occurs but can cause high output related complications, such as dehydration and kidney failure[48, 49]. A high AR (HAR) with PME can be an alternative for high rectal cancers.

Hartmann's procedure

Rectal cancer patients that cannot tolerate AL, e.g., patients with comorbidities or at risk of bad functional outcomes because of sphincteric dysfunction or faecal incontinence, can be considered for a Hartmann's procedure (HP). In HP, the rectum

is resected and the distal end is closed and left behind. The patient receives a permanent sigmoidostomy. The procedure carries a risk of developing pelvic abscess[50].

Abdominoperineal resection

The mesorectum ends in the most distal part of the rectum and instead the levator ani muscles are located directly outside the bowel wall. For cases of low rectal cancer (0-5 cm), an abdominoperineal resection (APR) can be performed. As the name indicates the procedure involves an abdominal part as the previously described for AR, and a perineal part where the anus is closed with a purse-string suture and removed together with the rectum and the pelvic floor to a varying extent. A permanent stoma is formatted.

Local recurrence (LR) rates are higher after APR than LAR, as are the risk of intraoperative perforation and CRM involvement[51-55]. For more advanced tumours or invasion of the levator, an extralevator abdominoperineal excision (ELAPE) allows more extended resection and involves the removal of the levator muscles[56]. Reconstruction of the perineal area is performed with musculocutaneous flap repair from gluteus maximus, vertical rectus abdominis muscle or biologic mesh.

In intersphincteric APR the perineal part of the surgery involves an intersphincteric resection of the anal canal and the procedure is an alternative to HP for tumour located above 5 cm. Results of the completed randomised controlled trial (RCT) HAPIrect comparing HP with intersphincteric APR regarding postoperative surgical morbidity and quality of life is awaited[57]. In addition, oncological outcomes are followed for up to five years.

Transanal total mesorectal excision

Transanal TME (taTME) is a new surgical technique. A purse-string suture is placed to close the rectum below the tumour and the most distal dissection of the TME procedure is performed with transanal MIS from the bottom-up[58-61]. The procedure seems to decrease the rate of CRM involvement and reduce the conversion rate compared to laparoscopic TME[62-65]. However, the procedure is technically demanding with a long learning curve and high rates of multifocal LR have been reported[66, 67]. The Swedish national guidelines recommend caution and that taTME should only be performed by colorectal surgeons with extensive experience in MIS with adequate education in taTME[68-71]. Patients can be registered in the international database LOREC[72]. More data on short- and long-term outcomes and results from the multicentre RCT named COLOR III are warranted[73].

Local excision

Endoscopic submucosal dissection (ESD), transanal endoscopic microsurgery (TEM) and transanal resection are surgical techniques known as local excisions (LE). These methods are used in the treatment of benign adenomas. ESD and TEM are also acceptable options for curative intentions of rectal tumours that only invade the submucosa (T1) with less than 1 mm, without lymphovascular invasion or tumour budding[2, 74]. The two procedures have equal oncological outcomes[75]. Additionally, LE is an option for palliative situations and elderly patients with comorbidities.

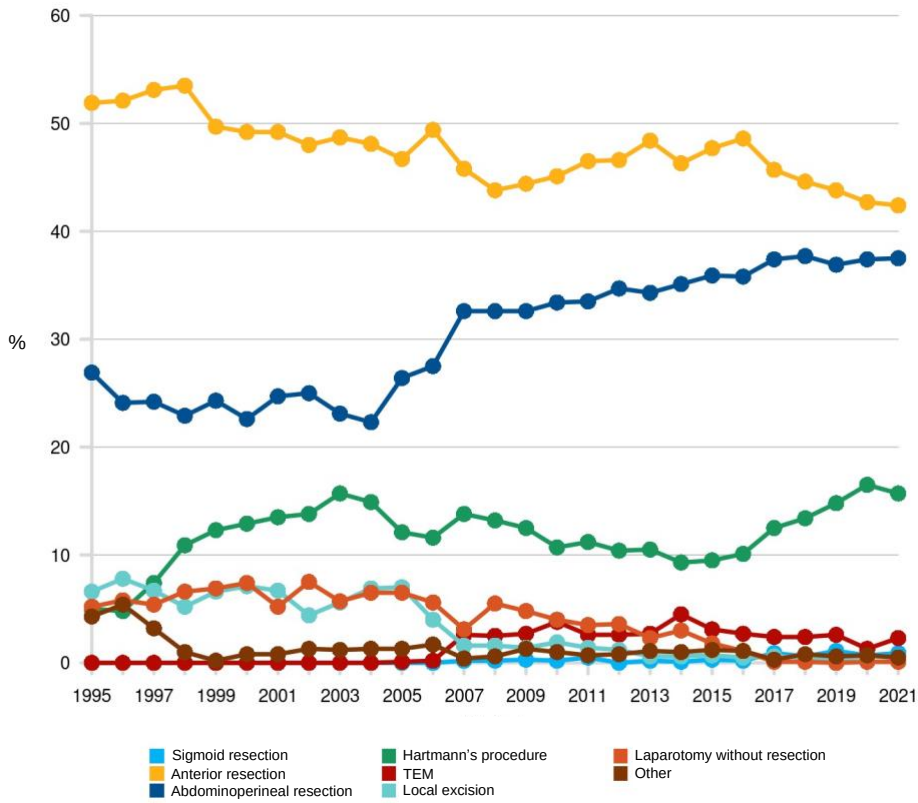

Figure 4 Distribution of surgical procedures, all patients with rectal cancer who had surgery in the Swedish Colorectal Cancer Registry
Adapted with permission from the Swedish Colorectal Cancer Registry
TEM, Transanal endoscopic mircosurgery

Postoperative complications

Postoperative complications are common after rectal cancer surgery. The Swedish Colorectal Cancer Registry (SCRCR) reports a complication rate of 30-50% whereof around 10% are graded as a severe complication (Clavien-Dindo 3b-5), in line with international rates[4, 76-80]. Postoperative complications are divided into infectious, cardiovascular, neurological, surgical and other complications in the SCRCR[3]. Common postoperative surgical complications are wound infection, AL, intraabdominal abscess, ileus and bleeding[78, 81].

Oncological therapy

Neoadjuvant therapy

Radiotherapy (RT) decreases the relative risk of LR of rectal cancer by 50-70%[82-87]. Today, around 50% of rectal cancer patients in Sweden receive preoperative RT[4]. RT comes with associated possible short- and long-term complications[88, 89]. Because of this, adequate selection of patients is essential and the inclusion criteria for RT in Sweden have recently been modified[2].

Patients assessed to be at low risk of LR (less than 6-8%) based on clinical and radiological examination are treated with surgery alone. Patients considered to be at a higher risk of LR, are recommended preoperative RT 5×5 Gy. Surgery can be performed either immediately (within 2-4 days) or delayed (4-8 weeks)[90].

For patients with locally advanced rectal cancer, the aim of neoadjuvant therapy is to improve local control to enable and facilitate surgery, as well as to reduce the risk of DM[91, 92]. This is currently performed with preoperative RT 5x5 Gy followed by 12-18 weeks of chemotherapy (CHT). An alternative in cases of fragile and elderly patients, RT 5x5 Gy with delayed surgery can be given. The standard of care used to be neoadjuvant chemoradiotherapy and is still an option in some cases, but since neoadjuvant CHT has been the focus of several studies lately, the Swedish national guidelines for colorectal cancer care have changed[2]. The RAPIDO trial compared short-course RT 5x5 Gy followed by preoperative CHT with preoperative standard of care chemoradiotherapy, i.e., 1.8-2.0x25-28 Gy with concomitant capecitabine and optional adjuvant CHT[93]. The first mentioned group had a lower 3-year probability of both disease-related treatment failure (23.7% vs. 30.4%) and DM (20.0% vs. 26.8%). However, recently published data from the 5-year follow-up revealed a higher rate of LR in the experimental treatment group compared to the standard of care group (10.2% vs. 6.1%)[94].

In cases of neoadjuvant therapy and delayed surgery, the patient needs to undergo a new clinical examination including flexible sigmoidoscopy and be discussed at a new MDT conference. If complete response is achieved after neoadjuvant therapy, the patient can be considered for a non-operative watch and wait approach with tight follow-up[2, 95].

Adjuvant therapy

High-evidence recommendations on adjuvant therapy for rectal cancer are lacking. Patients in TNM stage III or TNM stage II with high-risk features for recurrence (Table 4) might be candidates for adjuvant CHT[2, 96]. MSI-high/dMMR is associated with more favourable prognosis and are also taken into consideration[2, 97, 98].

Table 4 High-risk features for colorectal cancer recurrence

High-risk features
pT4 tumour
Lymph nodes retrieved <12
Poorly differentiated tumour
Vascular or lymphatic or perineural invasion
Tumour perforation
Emergency surgery
CRM involvement
Postoperative CEA >5ng/ml

CEA, carcinoembryonic antigen; CRM, circumferential resection margin

Follow-up

Colorectal cancer follow-up aims to detect curable recurrences as well as metachronous tumours. Additionally, primary treatment can be evaluated and information, rehabilitation and support for the patient are acknowledged. The recommended follow-up in Sweden after radical surgery for colorectal cancer is chest and abdominal CT and serum carcinoembryonic antigen testing after one and three years[2]. Patients who had AR or HP performed for rectal cancer should also be examined with digital rectal examination and endoscopic examination of the anastomosis or rectal stump. Colonoscopy should be performed after three years and thereafter every fifth year. Deviations from these guidelines may arise since the patient is asked to report any new symptoms that can be related to recurrence, such as weight loss, fatigue or blood in the stool.

Distant metastasis

Twenty percent of rectal cancer patients have synchronous DM and up to 20% develop metachronous DM within five years[4, 99-101]. Liver and lungs are the most common sites of DM[100, 102]. The risk of DM increases with higher TNM stage, poor differentiation grade, tumour budding, tumour deposits and EMVI[100-105]. BRAF and KRAS mutations are associated with an increased risk of recurrence[106, 107]. Selected patients with liver and lung metastases can be treated with surgical resection with a 5-year survival of 20-45%[108]. Metastases in the peritoneum is potentially curable and hyperthermic intraperitoneal CHT can be considered. The treatment involves macroscopically radical surgery, also known as cytoreductive surgery, combined with intraperitoneal CHT[109]. Moreover, angiogenesis inhibitors, epithelial growth factor receptor inhibitors, tyrosine kinase inhibitors and check point inhibitors are available treatment options for metastatic rectal cancer[2, 108].

Local recurrence

The rate of LR following rectal cancer surgery has previously been high, up to 20-40%[110-112]. Refined surgery with the TME technique and neoadjuvant RT have led to decreasing LR rates as well as a prolonged time to develop LR[44, 46, 82, 83, 85, 113-117]. Today, the LR rate within five years postoperative in Sweden is 4%[3, 4]. Within three to five years, up to 85% of LR have developed[118, 119]. Lymph nodes located outside of the mesorectum and along the internal iliac and obturator vessels are called lateral lymph nodes[120, 121]. Patients with tumour invasion of lateral lymph nodes are at risk of developing LR. Other risk factors for LR are mainly related to non-radical surgery, CRM involvement, intraoperative bowel perforation, location of the primary tumour and TNM stage[100, 119, 122-128]. Intraoperative adverse events are also an independent risk factor[129]. Moreover, implantation of exfoliated intraluminal cancer cells is considered to contribute to LR after AR if left behind during rectal cancer surgery[130-134]. Symptoms related to LR can be pain from the pelvic area, urogenital or perianal problems and bleeding[135, 136]. The condition is often incurable or in need of extensive treatment, such as pelvic exenterations[136-138]. Median overall survival following R0 pelvic exenteration is 36 months[138]. In patients with locally recurrent rectal cancer that undergo resection with curative intent, R0-resection is accomplished in about 50% with 5-year overall survival of 43%[136, 139]. Reirradiation is another treatment alternative[140].

Exfoliated intraluminal cancer cells

As early as in the year of 1907, the implantation of exfoliated cancer cells was suggested as a possible cause of cancer recurrence and its role in rectal cancer surgery was speculated early on[141, 142]. The presence of exfoliated cancer cells during rectal cancer surgery has been demonstrated from intraluminal fluid samples as well as on surgical staple instruments and doughnuts from stapled anastomoses[143-153]. The viability of these cells and their proliferative potential in immune deprived mice has been studied[130-132, 145, 154]. Exfoliated intraluminal cancer cells are suggested to be capable of implantation and therefore a potential source for LR when stapling the anastomosis or by pelvic seeding from intraluminal leakage[132, 145, 152, 154, 155]. Exfoliated intraperitoneal cancer cells have also been detected[156].

Rectal washout

To eliminate exfoliated intraluminal cancer cells and thus potentially prevent the development of LR, rectal washout (RW) is performed during rectal cancer surgery[2, 143, 144, 151, 153, 157]. RW denotes transanal irrigation of the lumen of the rectal stump and the intended line of transection with the rectum cross-clamped distal to the tumour, performed before transection (Figure 5). The washout is an integrated part of the TME technique[46, 158].

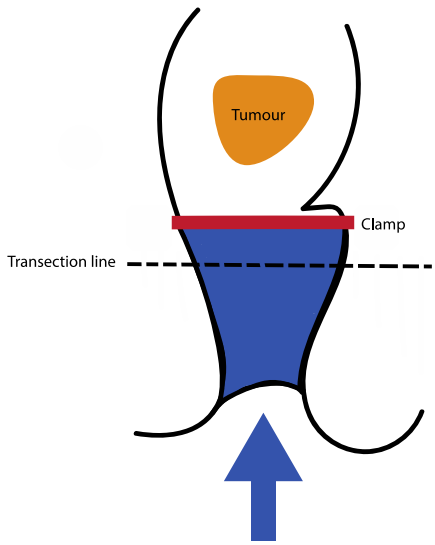

Figure 5 The rectal washout procedure
Illustration by Sofia Bredin, reprinted with permission

Even though RW decreases the presence of exfoliated cancer cells[143, 144, 146, 147, 151, 153, 157], the true impact of RW on LR risk is still debatable. Results from conducted studies comparing patients regarding RW have been inconsistent, and the cohorts have been heterogenous regarding patient characteristics, surgical procedures and washout routines. While some studies did not find any difference in LR rates after RW, others report the opposite[129, 146, 159-170]. The largest study consisted of 4677 patients from the SCRCR treated with AR for rectal cancer between 1995 to 2002[162]. The LR rate was 6.0% among the patients where RW was performed, compared to 10.2% in patients who did not have RW performed. A meta-analysis from 2021 including four studies, whereof one was the above mentioned study by Kodeda *et al*, found a benefit of RW on LR risk[171]. When the study of Kodeda *et al* was excluded, the effect of RW did not reach significance. I n an even more recent systematic review and meta-analysis including eight studies published between 1989 to 2018, the results were similar[172]. The relative risk reduction was 36.9% and the number needed to treat to prevent one LR at five years was calculated to 29. The study of Kodeda *et al* had again most of the weightage, together with Jörgren *et al*[162, 172, 173].

Despite no clear evidence from observational studies and that no RCT has been conducted of the impact of RW on LR risk, the procedure is widely accepted and routinely performed in rectal cancer surgery[42, 151, 161, 163, 164, 170, 172, 174, 175]. A RCT would require the inclusion of up to 2000 patients according to previous power calculations[162, 164, 172]. The American Society for Colon and Rectal Surgeons states RW during TME as a weak recommendation[176]. The Swedish national guidelines for colorectal cancer care recommend RW in AR and a washout of the rectum is also proposed to be performed in APR before the placement of the purse-string suture[2]. No recommendation about RW is given regarding HP, and the impact of RW when performing HP has not showed any oncological benefits[173].

RW is often described as a risk-free and fast procedure, and thus recommended for continued practice despite the absence of robust evidence for a LR reducing effect[42, 143, 160-162, 164, 169]. Still a possible association between postoperative complications and RW has not been explored. A median time of three minutes to perform RW has been documented with no associated problems[143]. Two case reports describe incidents of RW causing anaphylaxis and instability in blood pressure with cardiac ischemia, respectively[177, 178].

The routine practice of RW has also been challenged by the increasing use of MIS. Surgeons in the UK have reported to not perform RW to the same extent in laparoscopic rectal cancer surgery compared to open resections[179]. Laparoscopic resections can make RW more technically challenging and require more manipulation of the rectum, yet this does at least not seem to alter the risk of intraperitoneal spillage of cancer cells[180].

Fluid, volume and technique

Although RW is continuously a part of routine practice in rectal cancer surgery, there is a lack of evidence on what washout fluid and volume are the most effective in preventing LR. Few details are given regarding what instruments to use when cross-clamping the bowel and for irrigation. Different washout fluids and volumes are used in the studies included in conducted meta-analyses, making it difficult to conclude the most effective practice[160, 163, 164, 169, 171, 172]. The RW procedure varies greatly with both international and national differences[157, 179, 181, 182]. RW is performed to a lesser extent by surgeons in the United States[181]. In Sweden, reduced regional differences has been observed together with improvement of the quality of rectal cancer management, including increased performance of RW[183]. Different washout fluids and combinations are mentioned in the literature. While saline might perform a mechanical elimination of cells, sterile water destroys the cells by lysis[46, 143, 144, 146, 151, 157, 159-161, 184, 185]. Early studies mention the use of mercuric chloride[157, 186, 187]. Other fluids alone or as mixtures include ethanol, formalin and, occasionally associated with complications, povidone-iodine, cetrimide and chlorhexidine[134, 153, 157, 165-168, 177-179, 188-190]. The efficacy of various fluids has been investigated with less cytotoxic effect in vivo compared to in vitro[155, 157, 188, 191]. A study of the viability of different cancer cell lines including colorectal cancer, found water to cause lysis of all cells[192]. Saline had a slower lytic effect and after three hours, approximately half of the studied colorectal cancer cells were still viable. Other studies found lysis of over 95% of colorectal cancer cells after water exposure in vitro within 14 and 15 minutes respectively[185, 193]. Dafnis *et al* performed RW with 1000 ml of sterile water together with 1000 ml of 70 % ethanol, and out of 33 patients with prewashout sample containing cancer cells, 30 had negative cytology in the final sample[153].

Volume recommendations for a sufficient RW varies from 500 to >2000 ml[143, 144, 146, 147, 153, 159, 160, 184]. Higher tumour location has been associated to the need of greater washout volume, although the opposite has also been suggested[143, 144]. Visually clear effluents are neither a safe indicator since two thirds of studied fluid samples still revealed cancer cells[143].

Clamps, staplers, ligatures, tapes or a piece of tubing from an intravenous line are described as occlusive devices[144, 151, 167, 168, 179, 184, 187, 194]. A triple stapling technique can be performed where a line of staples is placed to occlude the bowel below the tumour before RW is performed[158]. The irrigation can be performed with catheters, syringes and rectal tubes[146, 151, 153, 179]. Furthermore, devices constructed especially for RW are available[143, 179]. RW including the tumour, with the bowel clamped proximally to the tumour, has also been described in patients with low rectal cancer[147, 195].

The Swedish Colorectal Cancer Registry

The SCRCR is a national population-based registry for quality assurance. Moreover, data from the SCRCR are used for research[2, 3]. The SCRCR is divided in a rectal cancer registry founded in 1995, and a colon cancer registry founded in 2007. The registry is continually evolved. Currently the SCRCR contains almost 1000 variables. The registry includes colorectal cancer that are adenocarcinomas. Colorectal cancer diagnosed at autopsy are not included. The completeness of rectal cancer cases in Sweden in the SCRCR was 97.7% in 2021. Information about investigation, surgical and oncological management, pathological outcomes and short- and long-term follow-up are registered. Primary data are reported 30 days postoperatively or at diagnosis for patients where no surgery is performed. Long-term follow-up including long-term complications, recurrences and survival are registered at three and five years with a completeness at 85.8% and 89.8% in 2021 respectively.

Approvals from the board of the SCRCR and from the Swedish Ethical Review Authority are required for data extraction. An annual quality report is published by the SCRCR and interactive reports can be accessed online to tailor national and regional data to specific parameters[4].

Overview of papers

Overview of the five papers in this thesis

	Paper I	Paper II	Paper III	Paper IV	Paper V
Design	Survey-based study	Observational registry study	Observational registry study	Observational registry study	Explorative study
Population	Swedish surgical departments performing rectal cancer surgery	All Swedish patients who underwent anterior resection for rectal cancer	All Swedish patients who underwent elective R0 abdominoperineal resection for rectal cancer (TNM Stage I-III)	All Swedish patients who underwent elective R0 anterior resection for rectal cancer (TNM Stage I-III)	Patients who underwent transanal total mesorectal excision for rectal cancer at Slagelse Hospital, Denmark
Ethical approval	2014/332	2014/332	2018/1040	2020-02227/2021-00753	SJ-817
Included (n)	35	4821	2425	6186	21
Study period	October 2016 to February 2017	January 2007 to December 2013	January 2007 to December 2013	January 2007 to December 2017	March 2020 to January 2021
Database	N/A	Swedish Colorectal Cancer Registry	Swedish Colorectal Cancer Registry	Swedish Colorectal Cancer Registry	N/A
Statitical methods	Descpritive statistics	Logistic regression	Cox regression	Cox regression	Descpritive statistics
Primary outcome	Current practice of rectal washout	Postoperative complications	Local recurrence	Local recurrence	Presence of cancer cells in fluid samples from rectal washout
Conclusion	Rectal washout was reported to be routinely performed in open and minimally invasive rectal cancer surgery, most often using sterile water or an alcohol-based solution with a minimum volume of 100-<500 ml	Rectal washout in anterior resection seems to be a safe technique with no evidence of increased 30-day postoperative complications	Routine rectal washout in abdominoperineal resection to improve the 5-year risk of local recurrence or other investigated oncological outcomes is not supported	Rectal washout in anterior resection does not appear to impact the 3-year oncological outcome, but at 5-year follow-up, the local recurrence risk was decreased after rectal washout	No cancer cells were observed after 500 ml of rectal washout

Aims

This thesis aims to increase the knowledge about RW and investigates the importance of RW in rectal cancer surgery.

Specific aims

Paper I To describe the current practice of RW in Swedish surgical departments performing rectal cancer surgery.

Paper II To evaluate the safety of RW in AR for rectal cancer by investigating the impact of RW on 30-day postoperative complications with a focus on surgical complications.

Paper III To assess the impact of RW on the oncological outcome in terms of LR, DM, overall recurrence (OAR), overall survival and relative survival after APR for rectal cancer.

Paper IV To investigate the impact of RW on the oncological outcome in terms of LR, DM, OAR, overall survival and relative survival after AR for rectal cancer.

Paper V To examine the presence of intraluminal cancer cells during taTME in fluid samples from RW and to determine what fluid volume is needed to eliminate these cells.

Methods

Study population

In Paper I, anonymous questionnaires reviewed by five colorectal surgeons at two different hospitals were used for data collection (Supplementary material 1). The questionnaires were distributed to the local data providers of the SCRCR at 44 surgical departments between October 2016 and February 2017. The responders were asked to answer on behalf of their unit. Submitted surveys were considered as consent to participate. Free text answers were interpreted and categorised.

Baseline and follow-up data from the SCRCR were used in Paper II-IV. Patients registered in the SCRCR between 2007 and 2013 who underwent AR for rectal cancer and had available data on RW were included in Paper II. In Paper III, patients registered in the SCRCR who underwent elective R0 APR for rectal cancer (TNM stage I-III) between 2007 and 2013 with available data on RW and 5-year follow-up were included. For Paper IV, the inclusion period was expanded to gather more MIS cases, including patients between 2007 and 2017. Patients registered in the SCRCR who underwent elective R0 AR for rectal cancer (TNM stage I-III) with available data on RW and 3-year follow-up were included. Patients with recurrence or death within 90 days postoperatively were excluded in Paper III and IV.

Paper V was performed at Slagelse Hospital, Denmark, between March 2020 and January 2021 and constitutes of 21 patients how underwent taTME for rectal cancer. Patient and tumour characteristics, operative details, and cytopathology were prospectively registered at a local database.

SCRCR

The SCRCR constitutes a useful source for quality assurance and research. The validity of the registry has been assessed in previous publications[117, 126, 183, 196-199]. The registry is dynamic and continues to constantly evolve. Definitions of variables changed, and new variables were added during the different study periods. From the beginning, the surgeon was responsible for all the registrations. This is gradually changing, and the current aim is that the pathology, oncology, and radiology departments are responsible for reporting their own data.

The SCRCR data may include random registration errors, but this can be compensated by the large sample sizes the registry offers. Another problem with registry research is missing data caused by incomplete registrations. The rates of missing data of the each studied variable were stated in the papers but excluded in the analyses since patients with missing data could not be grouped for comparison.

In 2008, a separate form for neoadjuvant and adjuvant oncological therapy was introduced to the SCRCR. Because of missing data, the oncological therapy was reported according to the previous variables reported by the surgeon in Paper III. For Paper IV, primarily the new variables from the oncology form were used, and if missing, the variables reported by the surgeon were used.

In Paper IV, if the patient had synchronous rectal tumours, i.e., tumours with the same date of diagnosis and/or surgery, only one tumour with the highest T stage was reported.

Definitions

Rectal cancer is defined as an adenocarcinoma that is completely or partly located within 15 cm from the anal verge measured with rigid sigmoidoscope during withdrawal. This definition is used in the SCRCR.

Intraoperative RW is conducted by cross-clamping of the bowel distal to the tumour but proximal to the intended line of transection, and transanal irrigation of the rectal stump before resection. A variable describing if RW was performed or not is available in the SCRCR. No details about the washout procedure are registered, e.g., washout fluid, volume, instruments used and if the bowel was cross-clamped above or below the tumour. In addition, the reason for omission of RW is not specified.

Hospital volume refers to the annual number of rectal cancer resections performed and is defined as low (1-10), medium (11-25) and high (≥26) according to definitions of the SCRCR.

Surgical competence is reported as the highest surgical competence present when the resection was performed. A colorectal surgeon is defined as an accredited colorectal surgeon or a surgeon with special interest in colorectal surgery trained in the TME technique.

R0 is defined as a locally radical procedure with neither macroscopic tumour tissue left behind according to the surgeon nor microscopic tumour tissue at the resection margins according to the pathologist.

Thirty-day postoperative complication is any complication that occurred during the hospital stay or within 30 days postoperatively.

The definition of an intraoperative perforation is an unintentional perforation of the rectum that occurs during surgery.

LR is defined as the presence of tumour tissue below the level of the promontory related to the primary rectal cancer diagnosed more than 90 days after primary surgery by clinical, radiological, pathological or endoscopic examination.

DM is defined as the presence of tumour tissue in the ovary, liver, peritoneum, bone, lung, brain or any other organ as well as in any lymph node located outside the pelvis diagnosed more than 90 days after primary surgery by clinical, radiological, pathological or endoscopic examination.

OAR is defined as any type of recurrences, either isolated LR or DM, or both LR and DM.

Bowel clamp represents any non-invasive instruments used to cross-clamp the bowel.

Minimum washout volumes were grouped into intervals of <100, 100-<500, 500-<1000 and ≥1000 ml based on the lowest specified value.

TaTME consists of an abdominal approach and a transanal part where a purse-string suture is applied below the tumour to close the lumen distally. RW is then performed. Detailed descriptions of the procedure can be read in previous publications[200, 201].

Outcomes of interest

Paper I: Current Swedish practice of RW in rectal cancer surgery with details about washout fluid, volume and technique.

Paper II: Overall and surgical 30-day postoperative complications were the primary studied outcomes. The latter included the subgroups wound infections, intraabdominal infections, wound dehiscence, intraabdominal bleedings, AL and stoma complications. Secondary, the following complications were explored: 30-day mortality, reoperations, and infectious, cardiovascular and neurological complications.

Paper IV: The primary outcome of interest was LR at 5-year follow-up. DM, OAR, overall survival and relative survival at 5-year follow-up were analysed as secondary aims.

Paper IV: The primary outcome of interest was LR at 3- and 5-year follow-up. DM, OAR, overall survival and relative survival at 3- and 5-year follow-up were analysed as secondary aims.

Paper V: Presence of cancer cells in fluid samples from RW was the primary outcome. A secondary outcome was at what volume the sample had negative cytology.

Statistical analysis

Statistical methods and analysis were planned and discussed with statisticians to ensure correct reporting and interpretation of results. All statistical analyses in Paper I-V were performed with IBM SPSS Statistics (IBM Corp. Released 2015/2016/2017. IBM SPSS Statistics for Macintosh/Windows, Version 23.0/24.0/25.0. Armonk, NY: IBM Corp.), except from when relative survival was calculated in Paper III and IV, please see below. Categorical variables are presented as numbers with percentages, and the Chi-square test and Fisher's exact test were used for group comparison when appropriate. Continuous variables are presented as median with range or interquartile range, and when comparing groups, the independent sample t test was used. A p-value of <0.05 was considered as statistically significant and all tests were two-sided.

For survival analysis in Paper III and IV, Kaplan-Meier curves with log-rank test and Cox regression were used. Relative survival in Paper III was calculated in R version 4.0.1 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.) with the R package relsurv and the Andersen multiplicative model[202]. Population life tables from the Human Life-Table Database available at http://www.lifetable.de were used[203]. In Paper IV, relative survival was calculated in Stata 16.1 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) with Poisson regression and the Ederer II method for estimating expected survival[204]. Population mortality rates were obtain from the Human Mortality Database[205].

Uni- and multivariable logistic regression analyses were performed to investigate the association of RW on 30-day postoperative complications in Paper II. In Paper III and IV when taking account for time to event, i.e., oncological outcomes at 3- and 5-year follow-up, uni- and multivariable Cox regression analyses were performed. When the proportional hazards assumption was violated, the hazard ratio (HR) was interpreted as an average HR over time. Potential confounders adjusted for in multivariable analysis were identified by clinical consideration, specified in each paper.

Sample procedure and cytology in Paper V

The RW sampling procedure was initiated immediately after the purse-string suture was placed. RW was performed with five portions of 100 ml of sterile water. After every portion, fluid samples were collected by instilling 50 ml of saline using a syringe. A sixth sample was collected from the presacral space following the retrieval of the specimen, using a suction device to collect the fluid sample in a test tube.

All samples were analysed by a gastrointestinal pathologist (S.E.). After the sample had been centrifuged at 4000 rpm for eight minutes, the supernatant was poured off and an artificial clot was prepared by adding human plasma and mixing with a pipette. Next, 1-2 drops of bovine thrombin were added for the solution to coagulate. The coagulated clot was packed in a tissue tray and placed in a capsule. The clot was fixed in neutral buffered formalin and cast into a paraffin block. The paraffin block was sectioned into three slides and put on a glass microscope slide, stained with haematoxylin and eosin. Cytological examination of the presence of cancer cells was performed using a microscope at x10 and x40 magnification.

Ethical considerations

The Declaration of Helsinki has been developed by the World Medical Association[206]. The declaration provides ethical principles for medical research involving human subjects. All presented studies in this thesis were granted with ethical approval. Paper I-IV was approved by the Swedish Ethical Review Authority with the following registration numbers (Dnr):

- Paper I and II: 2014/332
- Paper III: 2018/1040
- Paper IV: 2020-02227/2021-00753

Paper II-IV use registry data, and before data extraction, approval was also obtained from the board of the SCRCR. The purpose of the SCRCR is quality assurance of colorectal cancer care, research and statistics. All patients or their next of kin are informed that participation in the SCRCR is voluntary and does not impact the care that the patient receives. The patient has the right to deny that data are registered and to have the data deleted.

Paper V was approved by the local Scientific Committee of Zealand Region in Denmark (Approval ID: SJ-817) and was registered at www.clinicaltrials.gov (NCT04730102). Written informed consent was obtained from each patient. Patient data were registered in a local database, approved by The Danish Data Protection Agency (approval number: REG-202-2019).

The conducted studies do not directly benefit the included patients, but neither are any expected risk identified.

Results

Paper I

Thirty-five surveys were analysed whereof all reported to perform open rectal cancer surgery, 32/35 (91.4%) performed MIS and 26/35 (74.3%) performed LE (TEM, TAR). Among all the analysed surveys, 31/35 (88.6%) were high volume hospitals and 4/35 (11.4%) were medium volume hospitals. Overall, 14/35 (40.0%) of the units reported to have a procedure protocol on RW for rectal cancer surgery at their department.

RW was reported to be routinely performed in open and minimally invasive LAR and HAR to a high extent, while it was not frequently performed in APR (Table 5). All units used the same washout fluid and minimum volume for RW in open and MIS. RW was reported to be routinely performed in LE at the unit by 7/26 (26.9%) responders.

Sterile water was the most common washout fluid, reported by 16/35 units (45.7%). Seventeen out of 34 responders (50.0%) used a minimum volume of 100-<500 ml when performing RW at their unit. List of the individual responses regarding minimum volume in RW is presented in Table 6. All 34 responders reported that the bowel was cross-clamped prior to RW.

Table 5 Reported routine use of RW in open and minimally invasive rectal cancer surgery

	Units performing open surgery (*n*=35)	Units performing MIS (*n*=32)
RW in LAR	34 (97.1)	30 (93.8)
RW in HAR	33 (94.3)	31 (96.9)
RW in HP	28 (80.0)	27 (84.4)
RW in APR	2 (5.7)	5 (15.6)

Values in parentheses are percentages

APR, abdominoperineal resection; HAR, high anterior resection; HP, Hartmann's procedure; LAR, low anterior resection; MIS, minimally invasive surgery; RW, rectal washout

Table 6 List of reported minimum volumes in rectal washout

Assigned category	Minimum volume (ml)	Responders (*n*=34)
<100 ml	40	2
	60	1
100-<500 ml	100	5
	150	1
	200	9
	300	2
500-<1000 ml	500	6
≥1000 ml	1000	4
	2000	1
Until the effluent is clear	Until the effluent is clear	3

Paper II

Between 2007 and 2013, 11 617 patients with rectal cancer were registered in the SCRCR. AR was performed in 4826/11 617 (41.5%) patients, and after exclusion of patients with missing data on RW, 4821 patients were included for analysis in Paper II. The included cohort consisted of 4317/4821 (89.5%) patients where RW was performed during AR, and 504/4821 (10.5%) patients where RW was not performed. The rates of overall complications (1578/4317 (36.6%) vs. 208/504 (41.3%), p=0.039) and surgical complications (879/4317 (20.4%) vs. 140/504 (27.8%), p<0.001) were not increased in the RW group compared to the no RW group (Table 7).

Multivariable analysis is presented in Table 8. RW was neither a risk factor for overall complications (odds ratio (OR) 0.73, 95% confidence interval (CI) 0.60-0.90, p=0.002), nor for surgical complications (OR 0.62, 95% CI 0.50-0.78, p<0.001).

Table 7 Data on 30-day postoperative complications after anterior resection for rectal cancer in Sweden between 2007 and 2013

Complications	All patients (*n*=4821)	RW (*n*=4317)	No RW (*n*=504)	*p*
Overall	1786 (37.0)	1578 (36.6)	208 (41.3)	0.039
Missing data	3 (0.1)	3 (0.1)	0	
30-day mortality	62 (1.3)	50 (1.2)	12 (2.4)	0.020
Missing data	6 (0.1)	3 (0.1)	3 (0.6)	
Reoperation	495 (10.3)	419 (9.7)	76 (15.1)	<0.001
Missing data	22 (0.5)	17 (0.4)	5 (1.0)	
Infectious	287 (6.0)	256 (5.9)	31 (6.2)	0.843
Cardiovascular	159 (3.3)	139 (3.2)	20 (4.0)	0.373
Neurological	11 (0.2)	10 (0.2)	1 (0.2)	1.000
Other	537 (11.1)	488 (11.3)	49 (9.7)	0.285
Surgical	1019 (21.1)	879 (20.4)	140 (27.8)	<0.001
Wound infection	211 (4.4)	182 (4.2)	29 (5.8)	0.110
Intraabdominal infection	171 (3.5)	152 (3.5)	19 (3.8)	0.775
Wound dehiscence	88 (1.8)	73 (1.7)	15 (3.0)	0.041
Intraabdominal bleeding	43 (0.9)	36 (0.8)	7 (1.4)	0.210
Anastomotic leakage	405 (8.4)	345 (8.0)	60 (11.9)	0.003
Stoma complication	89 (1.8)	74 (1.7)	15 (3.0)	0.010
Other surgical	54 (1.1)	46 (1.1)	8 (1.6)	0.292

Values in parentheses are percentages

RW, Rectal washout

Table 8 Univariable and multivariable logistic regression analysis of impact of rectal washout on 30-day postoperative complications after anterior resection for rectal cancer in Sweden between 2007 and 2013

	Univariable analysis		Multivariable analysis	
	Odds ratio	*p*	Odds ratio	*p*
Overall	0.82 (0.68-0.99)	0.039	0.73 (0.60-0.90)	0.002
30-day mortality*	0.48 (0.25–0.90)	0.023	0.55 (0.27–1.13)	0.105
Surgical	0.67 (0.54–0.82)	<0.001	0.62 (0.50–0.78)	<0.001
Anastomotic leakage	0.64 (0.48–0.86)	0.003	0.59 (0.43–0.80)	0.001
Reoperation	0.60 (0.46–0.78)	<0.001	0.61 (0.46–0.81)	0.001
Cardiovascular†	0.81 (0.50–1.30)	0.374	0.79 (0.47–1.33)	0.378
Infectious	0.96 (0.66–1.41)	0.843	0.92 (0.61–1.39)	0.688
Other	1.18 (0.87–1.61)	0.286	0.98 (0.71–1.37)	0.911

Values in parentheses are 95% confidence intervals

Adjusted for age, gender, ASA-class, BMI, hospital volume, tumour height, radiotherapy, temporary stoma, perforation, TNM stage, residual tumour, colorectal surgeon and laparoscopic procedure unless indicated otherwise

*Adjusted for age, gender, ASA-class, BMI, hospital volume, tumour height, radiotherapy, temporary stoma, perforation, TNM stage and laparoscopic procedure

†Adjusted for age, gender, ASA-class, BMI, hospital volume, tumour height, radiotherapy, temporary stoma, perforation, TNM stage, colorectal surgeon and laparoscopic procedure

ASA, American Society of Anesthesiologists; BMI, body mass index

Paper III

The cohort of patients with TNM stage I-III rectal cancer who underwent elective R0 APR between 2007 and 2013 with a 5-year follow-up and available data on RW consisted of 2425 and was included for analysis in Paper III. In this study, 265/2425 (10.9%) patients had RW performed, and 2160/2425 (89.1%) patients had no RW. The rates of LR within five years did not differ between the RW and no RW patients (10/265 (3.8%) vs. 87/2160 (4.0%), *p*=0.839). Moreover, no differences were shown in DM rates (51/265 (19.2%) vs. 476/2160 (22.0%), *p*=0.293) and OAR rates (53/265 (20.0%) vs. 505/2160 (23.4%), *p*=0.213) between the groups. In multivariable analysis, RW had no impact on the 5-year risk of LR (HR 0.80, 95% CI 0.40-1.62, *p*=0.544) or the other investigated oncological outcomes (Table 9).

Table 9 Univariable and multivariable Cox regression analysis of impact of rectal washout on 5-year recurrence and survival after elective R0 abdominoperineal resection for TNM stage I-III rectal cancer in Sweden between 2007 and 2013

	Univariable analysis		Multivariable analysis	
	Hazard ratio	***p***	**Hazard ratio**	***p***
Local recurrence	0.97 (0.50-1.87)	0.925	0.80 (0.40-1.62)	0.544
Distant metastasis	0.87 (0.65-1.16)	0.353	0.79 (0.58-1.06)	0.116
Overall recurrence	0.86 (0.65-1.14)	0.299	0.77 (0.57-1.03)	0.079
Overall survival	1.00 (0.79-1.27)	0.996	0.87 (0.67-1.11)	0.257
Relative survival	0.95 (0.75-1.21)	0.675	0.87 (0.68-1.12)	0.271

Values in parentheses are 95% confidence intervals

Adjusted for age, gender, TNM stage, tumour height, neoadjuvant radiotherapy, neoadjuvant chemotherapy, intraoperative perforation, adjuvant chemotherapy

Subgroup analysis was performed on the 1828 patients with low tumours (0-5 cm) as well as the 133 patients with intraoperative perforation with respect to LR, DM and OAR without differences between the RW and no RW group.

Paper IV

A total of 6186 patients who underwent elective R0 AR for TNM stage I-III rectal cancer between 2007 and 2017 had a valid 3-year follow-up and available data on RW. RW was performed in 5706/6186 (92.2%) of the patients.

The 3-year LR rate was 97/5706 (1.7%) in the RW group compared to 12/480 (2.5%) in the no RW group (*p*=0.203). RW did not impact the 3-year risk of LR in multivariable analysis adjusted for age, gender, TNM stage, tumour height, neoadjuvant RT, neoadjuvant CHT, MIS, intraoperative perforation, and adjuvant CHT (HR 0.57, 95% CI 0.31-1.05, *p*=0.073).

MIS was performed in 1410/6186 (22.8%) patients. Recurrence data of this subgroup are shown in Table 10, with no differences in LR, DM and OAR rates between the RW and no RW group. RW was performed in 1263/1410 (89.6%) of these patients, and 590/1410 (41.8%) had robotic-assisted surgery.

Table 10 Three-year recurrence data after elective R0 minimally invasive anterior resection for TNM stage I-III rectal cancer in Sweden between 2007 and 2017

		All patients (*n*=1410)	RW (*n*=1263)	No RW (*n*=147)	*p*
Local recurrence	No	1384 (98.2)	1240 (98.2)	144 (98.0)	0.732
	Yes	24 (1.7)	21 (1.7)	3 (2.0)	
	Missing data	2 (0.1)	2 (0.2)	0	
Distant metastasis	No	1240 (87.9)	1108 (87.7)	132 (89.8)	0.480
	Yes	169 (12.0)	154 (12.2)	15 (10.2)	
	Missing data	1 (0.1)	1 (0.1)	0	
Overall recurrence	No	1225 (86.9)	1095 (86.7)	130 (88.4)	0.570
	Yes	184 (13.0)	167 (13.2)	17 (11.6)	
	Missing data	1 (0.1)	1 (0.1)	0	

Values in parentheses are percentages

RW, rectal washout

The 4991 patients who underwent elective R0 AR for TNM stage I-III rectal cancer between 2007 and 2015 with available 5-year follow-up were also analysed. Baseline characteristics of this cohort is presented in Table 11 and recurrence data is demonstrated in Table 12. The LR rate within 5 years was lower in the RW group compared to the no RW group (104/4583 (2.3%) vs. 16/408 (3.9%), p=0.037). The were no differences in secondary investigated oncological outcomes.

Kaplan-Meier curves with log rank test of 5-year overall and relative survival are presented in Figure 6. The 5-year overall survival in the RW group was 0.83 compared to 0.81 in the no RW group (p=0.204). The 5-year relative survival in the RW and the no RW group was 0.89 and 0.88, respectively (p=0.408).

In multivariable analysis (Table 13), a decreased 5-year risk of LR was observed after RW (HR 0.53, 95% CI 0.31-0.90, p=0.018).

Table 11 Patient, tumour and treatment characteristics of patients treated with elective R0 anterior resection for TNM stage I-III rectal cancer in Sweden between 2007 and 2015

	All patients (*n*=4991)	RW (*n*=4583)	No RW (*n*=408)	*p*
Age at diagnosis (years)*	67 (14)	67 (14)	68 (15)	0.355
Gender				
M	2937 (58.8)	2706 (59.0)	231 (56.6)	0.340
F	2054 (41.2)	1877 (41.0)	177 (43.4)	
Tumour height (cm)				
Low: 0-5	158 (3.2)	144 (3.1)	14 (3.4)	0.003
Mid: 6-10	2453 (49.1)	2288 (49.9)	165 (40.4)	
High: 11-15	2353 (47.1)	2132 (46.5)	221 (54.2)	
Missing data	27 (0.5)	19 (0.4)	8 (2.0)	
TNM stage				
I	1518 (30.4)	1377 (30.0)	141 (34.6)	0.024
II	1571 (31.5)	1466 (32.0)	105 (25.7)	
III	1902 (38.1)	1740 (38.0)	162 (39.7)	
Neoadjuvant radiotherapy	2870 (57.5)	2683 (58.5)	187 (45.8)	<0.001
Missing data	1 (0.0)	1 (0.0)	0	
Neoadjuvant chemotherapy	620 (12.4)	583 (12.7)	37 (9.1)	0.032
Missing data	1 (0.0)	1 (0.0)	0	
Hospital volume				
Low (1-10)	187 (3.7)	168 (3.7)	19 (4.7)	<0.001
Medium (11-25)	871 (17.5)	771 (16.8)	100 (24.5)	
High (≥26)	3933 (78.8)	3644 (79.5)	289 (70.8)	
Surgical competence				
Colorectal	4931 (98.8)	4532 (98.9)	399 (97.8)	0.012
General	39 (0.8)	31 (0.7)	8 (2.0)	
Missing data	21 (0.4)	20 (0.4)	1 (0.2)	
Minimally invasive surgery	749 (15.0)	648 (14.1)	101 (24.8)	<0.001
Missing data	31 (0.6)	24 (0.5)	7 (1.7)	
Conversion to open surgery	174 (23.2)	154 (23.8)	20 (19.8)	0.380
Postoperative complication	1829 (36.6)	1671 (36.5)	158 (38.7)	0.363
Surgical complication	1036 (20.8)	925 (20.2)	111 (27.2)	<0.001
Intraoperative perforation	90 (1.8)	76 (1.7)	14 (3.4)	0.009
Missing data	30 (0.6)	26 (0.6)	4 (1.0)	
Adjuvant chemotherapy	1330 (26.6)	1211 (26.4)	119 (29.2)	0.228
Missing data	11 (0.2)	10 (0.2)	1 (0.2)	

Values in parentheses are percentages unless indicated otherwise

*Values are median (interquartile range)

RW, rectal washout

Table 12 Five-year recurrence data after elective R0 anterior resection for TNM stage I-III rectal cancer in Sweden between 2007 and 2015

		All patients (*n*=4991)	RW (*n*=4583)	No RW (*n*=408)	*p*
Local recurrence	No	4863 (97.4)	4471 (97.6)	392 (96.1)	0.037
	Yes	120 (2.4)	104 (2.3)	16 (3.9)	
	Missing data	8 (0.2)	8 (0.2)	0	
Distant metastasis	No	4134 (82.8)	3790 (82.7)	344 (84.3)	0.449
	Yes	849 (17.0)	785 (17.1)	64 (15.7)	
	Missing data	8 (0.2)	8 (0.2)	0	
Overall recurrence	No	4078 (81.7)	3744 (81.7)	334 (81.9)	0.989
	Yes	905 (18.1)	831 (18.1)	74 (18.1)	
	Missing data	8 (0.2)	8 (0.2)	0	

Values in parentheses are percentages

RW, rectal washout

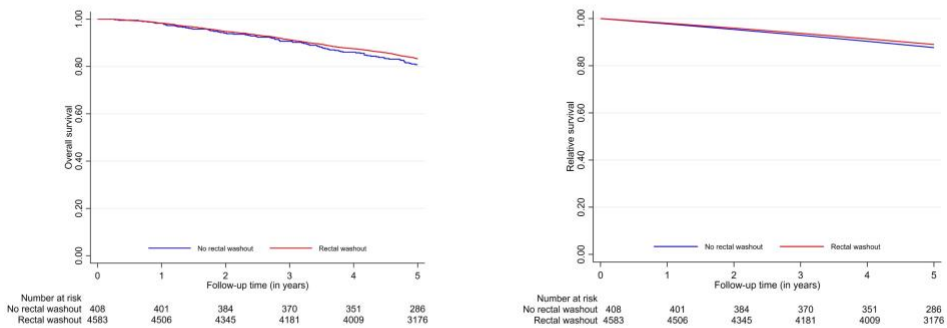

Figure 6 Five-year overall and relative survival after elective R0 anterior resection for TNM stage I-III rectal cancer in Sweden between 2007 and 2015
Overall survival, *p*=0.204; relative survival, *p*=0.408 (log rank test)

Table 13 Univariable and multivariable Cox regression analysis of impact of rectal washout on 5-year recurrence and survival after elective R0 anterior resection for TNM stage I-III rectal cancer in Sweden between 2007 and 2015

	Univariable analysis		Multivariable analysis	
	Hazard ratio	***p***	**Hazard ratio**	***P***
Local recurrence	0.57 (0.33-0.96)	0.034	0.53 (0.31-0.90)	0.018
Distant metastasis	1.08 (0.84-1.39)	0.552	1.04 (0.80-1.35)	0.779
Overall recurrence	0.99 (0.78-1.25)	0.912	0.94 (0.74-1.19)	0.601
Overall survival*	0.86 (0.68-1.09)	0.204	0.88 (0.69-1.13)	0.314
Relative survival*	0.78 (0.44-1.40)	0.408	1.15 (0.52-2.53)	0.734

Values in parentheses are 95% confidence intervals

Adjusted for age, gender, TNM stage, tumour height, neoadjuvant radiotherapy, neoadjuvant chemotherapy, minimally invasive surgery, intraoperative perforation and adjuvant chemotherapy unless indicated otherwise

*Adjusted for age, gender, TNM stage, tumour height, neoadjuvant radiotherapy, neoadjuvant chemotherapy, hospital volume, minimally invasive surgery, intraoperative perforation, postoperative complication and adjuvant chemotherapy

Paper V

Baseline data of the 21 participating patients are presented in Table 14. Data from the pathological examination are demonstrated in Table 15. A complete specimen was shown in 18/21 cases (85.7%) and a nearly complete in the remaining 3/21 (14.3%) according to criteria by Quirke at pathological examination[207, 208]. CRM and DRM were negative in all cases.

Cancer cells were detected in 3/21 (14.3%) patients (Table 16). All patients had negative samples after 500 ml of RW with sterile water.

All samples from the presacral space had negative cytology for cancer cells.

Table 14 Baseline characteristics and intraoperative outcomes of patients treated with transanal total mesorectal excision for rectal cancer

	All patients (*n*=21)
Gender	
M	13 (61.9)
F	8 (38.1)
BMI (kg/m²)*	24 (19-35)
Age (years)*	62 (37-86)
ASA classification	
ASA I	7 (33.3)
ASA II	14 (66.7)
Tumour distance from anal verge (cm)*	8 (5-11)
cT category	
T2	9 (42.9)
T3	9 (42.9)
T4	3 (14.3)
cN category	
N0	6 (28.6)
N1	6 (28.6)
N2	9 (42.9)
cM category	
M0	20 (95.2)
M1	1 (4.8)
Neoadjuvant therapy	5 (23.8)
Surgical procedure	
Low anterior resection	19 (90.5)
Hartmann's procedure	2 (9.5)
Blood loss (ml)*	50 (50-500)
Specimen extraction	
Transabdominal	4 (19.0)
Transanal	17 (81.0)
Operative time (min)*	269 (168-378)

Values in parentheses are percentages unless indicated otherwise

*Values are median (range)

ASA, American Society of Anesthesiologists; BMI, body mass index

Table 15 Pathological outcomes of patients treated with transanal total mesorectal excision for rectal cancer

	All patients (*n*=21)
Specimen grade	
Mesorectal	18 (85.7)
Intramesorectal	3 (14.3)
CRM	
Positive	0
DRM	
Positive	0
Resection margin (mm)*	
CRM	8 (2-20)
DRM	21 (8-50)
Retrieved lymph nodes*	21 (11-50)
pT category	
T2	8 (38.1)
T3	12 (57.1)
T4	1 (4.8)
pN category	
N0	15 (71.4)
N1	4 (19.0)
N2	2 (9.5)

Values in parentheses are percentages unless indicated otherwise

*Values are median (range)

CRM, circumferential resection margin; DRM, distal resection margin

Table 16 Cytological examination and characteristics of patients treated with transanal total mesorectal excision for rectal cancer with positive washout sample

Patients	Gender	Tumour height (cm)	Specimen grade	CRM (mm)	DRM (mm)	pT category	S 1	S 2	S 3	S 4	S 5	S 6
Patient 1	F	7	Intramesorectal	3	11	T3	-	-	+	+	-	-
Patient 2	M	9	Mesorectal	6	17	T3	-	-	+	-	-	-
Patient 3	M	11	Mesorectal	9	30	T3	+	-	-	-	-	-

CRM, circumferential resection margin; DRM, distal resection margin; S1-5, sample from rectal washout; S6, sample from presacral space

Discussion

This thesis consists of five papers with the aim to increase knowledge and investigate the importance of RW in rectal cancer surgery. The papers have different study designs starting off with Paper I as a descriptive survey, Paper II-IV which use registry data and finally an explorative study as Paper V.

Based on the survey of Paper I, RW is routinely performed in Swedish rectal cancer surgery, often with sterile water or an alcohol-based solution and a minimum volume of 100-<500 ml. This in spite of that more than half of the responders reported not having a procedure protocol for RW at their unit, and that the national guidelines for colorectal cancer care do not suggest course of action[2]. RW was reported to be routinely performed in both open and minimally invasive procedures, and abandonment of RW in MIS was not as profound as in a survey from the UK[179].

The results of Paper I cannot be generalised globally since it describes the current practice at colorectal units performing rectal cancer surgery in Sweden at that time. The data are best presented as descriptive statistics and are not primarily suitable for statistical analysis as in the published version.

The responders of a self-reported survey might be more prone to agree to the research statement and answer according to guidelines instead of the true practice at the unit, resulting in different types of response biases[209]. Social desirability bias means that the responders report the socially desirable behaviour, i.e., in the case of our survey, following the national guidelines. Interviewer bias can occur if the responders report what they believe the interviewer wants to hear.

The survey measures what one surgeon report is performed at their unit, which might not translate into what is actually practised. At units with no procedure protocol, washout fluid and volume are chosen at the discretion of the surgeon. Even at units with established protocols, these may not always be followed. Since the approach is of the surgeon's choice, the practice may vary if surgeons resign or new surgeons begin practise at the units, and how the residents are educated and affected by senior colleagues. A larger and perhaps more valid study design could have been to investigate the current practice of individual surgeons instead of units, an approach used in other surveys[179, 181]. Yet, another obstacle would be to identify all individual colorectal surgeons in Sweden since there is no reliable record of them. Another alternative data acquisition could have been a medical record review of operative reports.

The responders were not obligated to answer all questions. Free text answers and multiple answers were possible. As a result, the response rate differed, and answers had to be interpreted and categorised, introducing a risk of information bias. Digital surveys could have allowed for more control over this. Telephone interviews would have allowed supplementary questions and to sort out any misconceptions. On the other hand, this would have resulted in less standardisation of the questioning.

Paper I forms a basis for the other papers and for further discussion about standardisation of RW. The description of the current practice of RW can be applied to the results of Paper II-IV. It also highlights the inconsistency in the practice of RW in Sweden, and the knowledge gap that exists regarding which washout fluid and volume are the most effective in preventing LR. Several different washout fluids and volumes are also used internationally when performing RW[134]. Large international multicentre studies, preferably RCTs, would be required to achieve detailed evidence-based guidelines on RW, including the most effective washout fluid and volume in terms of eliminating exfoliated cancer cells and thereby reducing the LR risk. Another possible way to find out more about the RW procedure could be to add variables to the SCRCR about washout fluid and volume used along with explicit definitions. Yet, this could also result in various combinations that would be hard to compare.

Guidelines can improve clinical practice and outcome for colorectal cancer patients[210, 211]. The Swedish national guidelines for colorectal cancer care are electronically available which can potentially improve adherence[212]. The annual quality reports of the SCRCR evaluate to what extent the guidelines are followed, functioning as a motivation to adherence. Observational studies comparing groups where RW was performed and not performed are at risk of selection bias. The recommendation to perform RW in AR is followed to a large extent, causing the group of patients where RW is not performed to be small in Paper II and IV. The performance of RW in AR is possibly a surrogate marker for adherence to overall current guidelines and surgical quality, for example the proportion of temporary stomas were higher in the RW group in Paper II and a colorectal surgeon were more often present in the RW group in both Paper II and IV. On the other hand, the Swedish guidelines state that RW can possibly be performed in APR, yet only a small portion of these patients had RW performed, as presented in Paper III. The reason for omission of RW is not registered in the SCRCR. No clear contraindications of RW exist, but adverse intraoperative events might have contributed to the decision to perform RW or not. The rates of surgical complications and intraoperative perforations were higher among the patients in the no RW group in both Paper II and IV. On the contrary, in Paper III, intraoperative perforation was a more common event in the RW group. An intraoperative perforation could possibly have promoted a decision to convert an initially planned AR to APR after RW was performed, thus allocating the patient to the RW group. Another possible reason for conversion from AR to APR could be that the surgeon

assessed the cancer to be more locally advanced or at a lower tumour height than expected.

RW is probably not an independent protective factor for reducing postoperative complication rates. However, the results of Paper II show no indications of any harm of performing RW. Occasional case reports in the subject have been published[177, 178]. The operative time was longer in the RW group in both Paper II and IV. These differences could have several explanations, e.g., tumour height, TNM stage, or higher grade of fibrosis after neoadjuvant RT. A median time of approximately three minutes to perform RW have previously been reported[143]. The performance of RW requires the patient to be placed in the lithotomy position, which may add more time.

The 5-year oncological outcome after APR did not differ between the RW group and no RW group in Paper III. This was also the case after RW in HP[173]. The hypothesis in Paper III was that RW in APR eliminates intraluminal cancer cells before a possible leakage from the purse-string suture or an intraoperative perforation, and thereby decreasing the risk of LR. Based on Paper III, routine RW in APR to improve the oncological outcome is not supported. However, the events of intraoperative perforation were rare and other possible benefits of RW in APR patients were not investigated, e.g., reduced perineal infections or improved wound healing[213].

Even though RW did not appear to impact the 3-year oncological outcome after AR in Paper IV, a decreased risk of LR at 5-year follow-up was observed after RW. A study found that the registration of recurrences was less accurate in patients with shorter follow-up than five years in the SCRCR[198]. TME and neoadjuvant therapy have reduced LR rates and prolonged time to LR[2, 46, 82, 113, 114]. For these reasons, a possible difference in LR rates after RW might not be detected at the 3-year follow-up.

In the previous Swedish study on RW and association to LR by Kodeda *et al*, multivariable analysis was repeated on parts of the study cohort until it only consisted of patients with a curative procedure that was judged as locally radical, and without intraoperative perforation or AL[162]. The results still favoured RW. In Paper III and IV, R1- and R2-resections were excluded. As mentioned before, conducted meta-analyses of RW and LR risk were greatly impacted by the study by Kodeda *et al* and a meta-analysis from 2008, before the publication of Kodeda *et al*, could not either prove a LR reducing effect of RW[162, 169, 171, 172].

RCTs are considered the gold standard when studying causality[214]. The papers of this thesis cannot prove causal relationship but associations. Since RW is an integrated part of the TME technique, and without evidence to be harmful, it can be difficult to motivate randomisation to refrain from RW. RCTs can be time-consuming and impractical to conduct if there are few events of the studied outcome and large sample sizes are needed to demonstrate a significant difference.

Population-based cancer registries have become more widely used in cancer research[215]. Although data analysis of Paper II-IV is retrospective, the data collection in the SCRCR is prospective. The registry data of Paper II-IV provide a large national cohort of patients. Some of the included patients might have been excluded from an RCT due to high age, comorbidities or performance status. On the other hand, observational data are at risk of bias and confounding. The non-randomised nature of the registry data result in groups that differ in size and characteristics. Multivariable analysis was performed in Paper II-IV to determine if RW was an independent factor of importance for the investigated primary outcomes, i.e., postoperative complications and LR. Variables adjusted for were risk factors assessed as clinically relevant. All confounders cannot be adjusted for since all confounding factors are not known. To further improve the selection of confounders in Paper II-IV, directed acyclic graphs could have been used[216]. However, some of the statistically significant differences in the papers were small and may not be clinically important differences[217]. For example, in Paper IV there was a statistically significant difference in surgical competence between the groups, where 35/5706 (0.6%) patients in the RW group had a general surgeon who performed the procedure, compared to 8/480 (1.7%) in the no RW group.

Another difficulty when studying LR of rectal cancer is that the event is rare, which restricted the number of confounders that could be adjusted for in multivariable analysis of the impact of RW on LR risk in Paper III and IV. The one in ten rule describes the rule of thumb for having a minimum of ten events per confounder in multivariable analysis, however this have been suggested to be too strict in some cases[218]. An alternative method to control confounding in observational studies is to use propensity score[219]. However the results does not always seem to differ between the two methods[220, 221]. Regression analysis may be more appropriate in studies with many events per confounder as in Paper II[222]. In situations where there are fewer than eight events per confounder, propensity score are superior to logistic regression, and the reverse is applied when there are at least eight events per confounder[223].

Patients excluded in Paper II-IV due to missing data on RW were few (<0.5%). Certain variables of interest were introduced in the SCRCR during or after the study periods and thus not available for all patients, e.g., specimen quality according to the classification by Quirke, TME, tumour deposits and EMVI. Missing data in the papers could have been diminished by data imputation or by reviewing medical records.

The rate of MIS in Sweden has continued to increase every year[3]. This fast development might limit the generalisability of the results of this thesis. In Paper II-IV, MIS was more common in the no RW group. The performance of RW can be more technically challenging in conventional laparoscopic surgery compared to in open surgery. Unfortunately, the MIS group in Paper IV was too small for

multivariable analysis, but the LR rate did not differ between the RW and no RW group.

The SCRCR data in Paper II-IV are unvalidated, but several other validation reports have been published[117, 126, 183, 196-199]. Moberger *et al* have assessed the SCRCR and found the average agreement of the variables to be 90%[197]. The validity was examined by reabstraction of cases from the year of 2008. The RW variable among other variables in the SCRCR was investigated and an 84% exact agreement was found between the original and reabstracted data. The postoperative course was also assessed, represented as 28 selected variables, with a median agreement of 96%. In the case of objective variables based on international definitions, the person entering the data needs to be familiar with the definitions and up-to-date about any possible changes, for example an updated edition of the TNM classification. Some variables, for example radicality as assessed by the surgeon, does leave room for risk of subjective estimations. This is not suspected to differ between the RW and no RW group in Paper II-IV. The SCRCR does not include any variables describing technical details of the RW procedure, e.g., if the bowel was cross-clamped or not, and no variable exist for washout of the abdominal cavity. Therefore, there might be a risk that any kind of intraoperative washout is registered as RW. A way to reduce random errors in the SCRCR would be to eliminate any intermediate hosts during the registration and that the data were transferred directly from the medical records. This process would however be complicated, both regarding technical aspects as well as from an ethical point of view. Nevertheless, it may be possible in the future with new electronic chart systems. An alternative method for Paper II-IV would be to review medical records. This would be a time-consuming process and the data collection would have been retrospective with a risk of misinterpretation and miscoding of data.

Cancer-specific survival and relative survival are two common methods used to evaluate cancer patient survival. In Paper III and IV, relative survival is presented instead of cancer-specific survival. Relative survival can be the preferred choice when using registry data, and for colorectal cancer, the two methods provide similar results[224].

In Paper V, RW was performed with sterile water during taTME, and none of the patients had fluid samples positive for cancer cells after 500 ml of RW. Cancer cells have previously been found in the fluid samples after RW of 500-2000 ml of saline in AR for rectal cancer[143, 144]. Dafnis *et al* found cancer cells in three of 60 patients during LAR and HP for rectal cancer after RW of 2000 ml with sterile water and 70% ethanol[153]. RW is an integrated part of the TME procedure as well as the taTME procedure. The technical demanding procedure of taTME requires that the surgeon have extensive experience of MIS and is familiar with the anatomy seen from below. A study comparing long-term outcomes including LR and survival after taTME for rectal cancer would be of interest, especially since alarming multifocal LR have been reported during the learning curve[2, 67]. The results of Paper V suggest that the

risk of intraabdominal wound contamination with cancer cells is small during taTME, since none of the patients had a positive sample from the presacral space. Nevertheless, Paper V is a pilot study, and a larger sample size is needed to validate the results. Another limitation is the absence of a control group with no RW performed, or with a different washout fluid.

Conclusions

Paper I

- RW was reported to be routinely performed in open and minimally invasive rectal cancer surgery by Swedish colorectal units, most often using sterile water or an alcohol-based solution with a minimum volume of 100-<500 ml.
- Most Swedish colorectal units did not have a procedure protocol for RW during the study period.

Paper II

- RW in AR for rectal cancer seems to be a safe technique with no evidence of increased 30-day postoperative complications.

Paper III

- Routine RW in APR for rectal cancer to improve the 5-year oncological outcome is not supported.

Paper IV

- RW in AR for rectal cancer does not appear to impact the 3-year oncological outcome.
- RW was associated with decreased 5-year risk of LR, justifying continued practice of RW in AR for rectal cancer.

Paper V

- Intraluminal cancer cells were rare after 500 ml of RW in taTME for rectal cancer. Further studies are needed to validate the results.

Future perspectives

This thesis investigates the importance of RW in rectal cancer surgery. The papers add new details about current practice of RW in Sweden and the use of RW in taTME. Moreover, the RW procedure seems to be safe to perform in AR and beneficial for decreasing LR risk after AR. Any impact of RW on the oncological outcome after APR was not supported. However, it is possible that RW in APR has other unexplored benefits, e.g., enhancing perineal wound healing or decreasing the risk of postoperative infection.

Rectal cancer management has developed during recent years, with improvements in the surgical technique, i.e., TME and MIS, and in the oncological treatment. Neoadjuvant short-course RT followed by CHT has replaced chemoradiotherapy in the Swedish national guidelines due to the RAPIDO trial. TaTME is currently not performed in Sweden for rectal cancer but for benign disease. Furthermore, screening for colorectal cancer is currently being introduced in Sweden. Considering these ongoing advances, it would be unwise to change standards regarding RW. A difficulty in evaluating the impact of RW on LR risk is that conclusions are limited by few events of the outcome.

One of the research questions that remains to be addressed is which washout fluid and volume are the most effective in preventing LR. Fluid, volume and technique used in RW varies greatly both nationally and internationally, which complicates comparison. Further work is needed to establish the effect of the various washout methods used to keep optimising the management of rectal cancer patients. As addressed in the Declaration of Helsinki, negative and inconclusive results should also be published, and can be important clues to contribute to a better understanding of this field[206]. Adding variables to the SCRCR that describes the washout fluid and volume used in RW could facilitate further registry studies. International multicentre collaborations for prospective studies comparing different RW methods, preferably by randomisation to one treatment or the other, are desirable to be able to provide evidence-based guidelines containing specific details on the performance of RW.

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Supplementary material

Supplementary material 1

SKÖLJNING VID REKTALCANCEROPERATION – KARTLÄGGNING AV SVENSK PRAXIS

Vi ämnar utföra en studie för att studera förekomst av eventuella komplikationer till sköljning av rektum vid rektalcanceroperation. Som ett led i denna studie vill vi undersöka vilken praxis som finns på de svenska kirurgkliniker som opererar rektalcancer. Etiskt godkännande har sökts och beviljats. Vi vore tacksamma för svar senast 161201, använd medsänt svarskuvert.

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Var god ange antal rektalcanceroperationer som utförs på din klinik per år:	_____ /år
Finns ett PM för sköljning av rektum vid rektalcanceroperation på din klinik?	Ja ☐ Nej ☐
Anger detta PM vilket tillvägagångssätt som skall användas? (Teknik, sköljvätska, volym etc.)	Ja ☐ Nej ☐
Sköljs rutinmässigt öppen låg främre resektion?	Ja ☐ Nej ☐
Sköljs rutinmässigt öppen hög främre resektion?	Ja ☐ Nej ☐
Sköljs rutinmässigt öppen Hartman's operation?	Ja ☐ Nej ☐

Sköljs rutinmässigt öppen abdominell perineal resektion?	Ja ☐ Nej ☐
Vilken sköljvätska används?	Vatten ☐ Natriumklorid 0,9% ☐ Alkohol ☐ 50% vatten / 50% alkohol ☐ Annan ☐ Om annan, vilken? _____
Vilken är minsta använda volym sköljvätska?	_____ ml
Stängs tarmen inför sköljning?	Ja ☐ Nej ☐
Vilken metod används för avstängning av tarmen?	Dubbelstapling ☐ Tarmklämma ☐ Annan ☐ Om annan, vilken? _____
Utförs sköljning före eller efter avstapling av rektum?	Före ☐ Efter ☐
Sköljningen utförs med:	Rektalsond ☐ Sårspruta ☐ Annat ☐
Sköljes även bukhålan?	Ja ☐ Nej ☐ Om ja, vilken volym? _____ ml
Om ja på frågan ovan, vilken vätska används?	Samma som i rektum ☐ Annan ☐ Om annan, vilken? _____
Utförs laparoskopisk och/eller robotassisterad rektalcancerkirurgi vid din enhet?	Ja ☐ Nej ☐

REGION SKÅNE

Om ja på frågan ovan, utförs sköljning av rektum rutinmässigt vid laparoskopisk och/eller robotassisterad operation?	Ja ☐ Nej ☐
Om ja på frågan ovan, • Vilken metod används för avstängning av tarmen vid laparoskopisk och/eller robotassisterad operation?	Dubbelstapling ☐ Tarmklämma ☐ Annan ☐ Om annan, vilken? _____
• Används samma typ av sköljvätska vid sköljning av rektum vid laparoskopisk och/eller robotassisterad operation som vid öppen operation?	Ja ☐ Nej ☐
• Används samma minsta volym av sköljvätska vid sköljning av rektum vid laparoskopisk och/eller robotassisterad operation som vid öppen operation?	Ja ☐ Nej ☐
Utförs sköljning av rektum rutinmässigt vid laparoskopisk och/eller robotassisterad	
• Låg främre resektion?	Ja ☐ Nej ☐
• Hög främre resektion?	Ja ☐ Nej ☐
• Hartman's operation?	Ja ☐ Nej ☐
• Abdominell perineal resektion?	Ja ☐ Nej ☐
Utförs lokal excision (TEM, TAR) vid din enhet?	Ja ☐ Nej ☐
Om ja på frågan ovan, utförs sköljning av rektum rutinmässigt vid lokal excision?	Ja ☐ Nej ☐

Tack för din medverkan!

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