UiT The Arctic University of Norway

Faculty of Health Sciences

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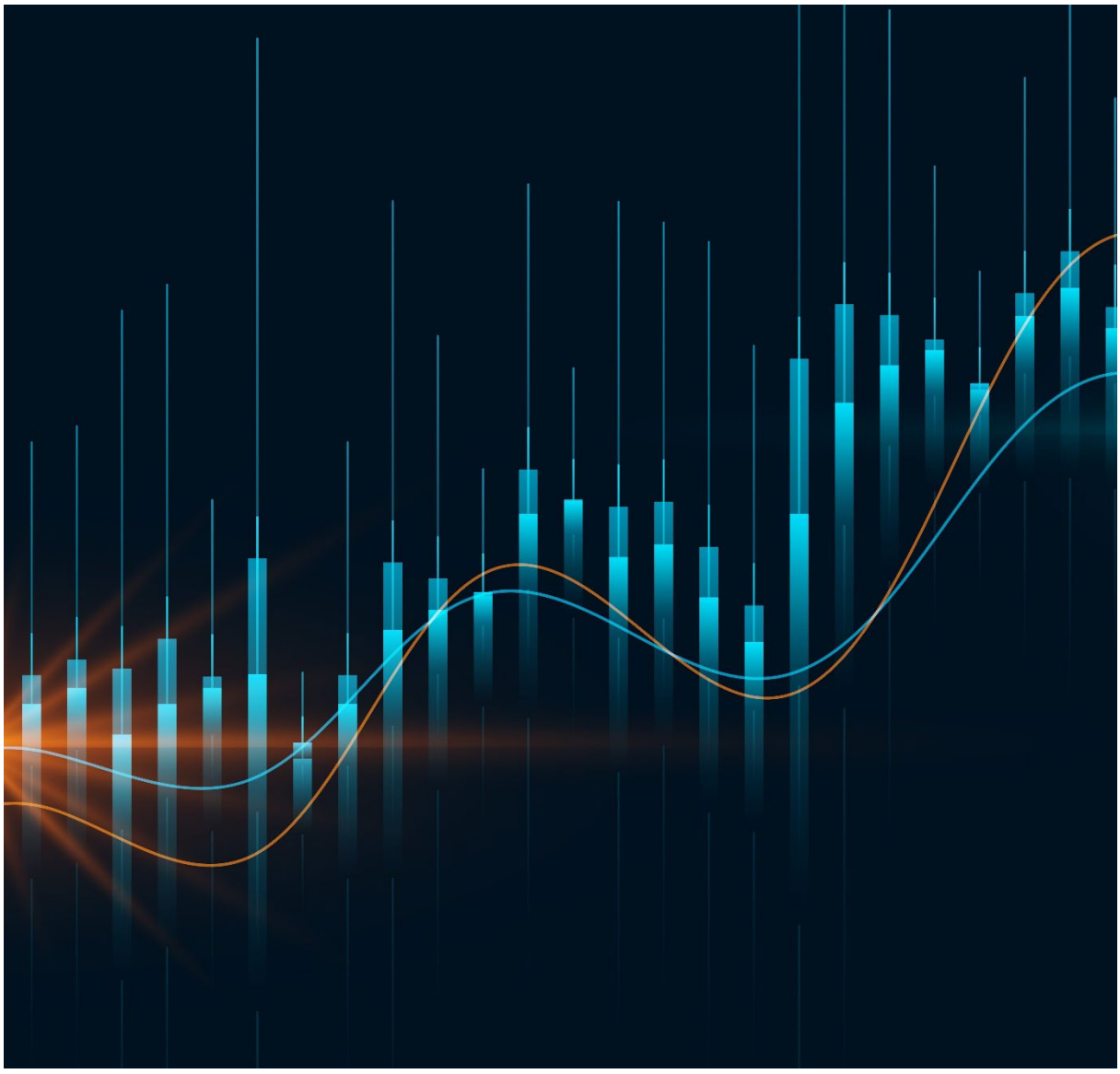
Results after surgical treatment of rectal cancer in Norway

A prospective study of outcome after different surgical approaches.

Elisabeth Myrseth

A dissertation for the degree of Philosophiae Doctor [June 2023]



Front page illustration: Big data statistics, image from Freepik.com

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Elisabeth Myrseth, June 2023

Summary

Colorectal cancer is the third most common cancer worldwide with 1.9 million new cases in 2020, and rectal carcinoma represents about 25% of the cases. Surgical resection of the tumor bearing part is the standard curative treatment, and during the last decades the survival rates have improved through both better surgical methods and the introduction of radiochemotherapy. Minimally invasive surgical approach is increasing in rectal cancer treatment. Studies so far comparing minimally invasive and open techniques have showed diverging results regarding both short-term and long-term results including survival rates and local recurrence rates, and for laparoscopic surgery studies have showed high conversion rates with many operations needed to learn the procedure.

The Norwegian Registry of Gastrointestinal Surgery (NORGAST) is a national quality register established in 2014 which aims to survey the rate, kind and severity of short-term complications following gastrointestinal surgery. The long-term results including survival and recurrence of disease after cancer treatment are important measures, and for rectal cancer this is monitored by the Norwegian Colorectal Cancer Registry.

The aims of this study were to assess the surgical and oncological outcomes after surgical treatment for rectal cancer in a 5-year national cohort, utilizing prospectively registered data from the two quality registries mentioned above. We wanted to investigate differences in short-term outcomes between standard laparoscopic and robotic assisted laparoscopic approach, and to investigate differences in short-term and long-term outcomes between laparoscopic and open access. Based on this patient cohort we also wanted to explore one of the major complications following this treatment; anastomotic leak, and whether diverting stomas has a protective effect or not.

The study cohort were comprised of 1796 patients with rectal adenocarcinoma, operated between January 2014 and December 2018. We found that robotic assisted laparoscopic approach significantly reduced the risk of conversion to open access surgery compared to standard laparoscopic approach, with conversion rates of 2.1% and 9.6% respectively ($p<0.001$). Other short-term outcomes did not differ between the two procedures. Complication rates were higher following conversion to open access, and with longer hospital stay. Diverting stomas were protective against reoperation for anastomotic leak within 30 days, with leak rates of 2.3% for patients with diverting stomas vs 7.8% for patients without

($p<0.001$). However, patients with diverting stomas were reoperated to the same degree but for other reasons than anastomotic leak, and overall morbidity and mortality were the same. Reoperations were associated with higher mortality rates (aOR 12.24, $p=0.004$) regardless the reason for reoperation. Diverting stomas were not associated with increased risk for reoperation, morbidity or mortality. We also found that long-term results in regards of 5-year survival rates and 5-year local recurrence rates following laparoscopic rectal cancer surgery were equivalent to open access surgery.

In conclusion, short- and long-term outcomes following laparoscopic surgery are similar to open access surgery. Robotic assisted laparoscopic surgery reduces the risk of conversion to open access surgery, and conversion to open access is associated with higher complication rates and longer hospital stay. Laparoscopic approach should be chosen over open access if no specific reason to choose otherwise exists.
Diverting stomas protect against reoperation for anastomotic leak within the first 30 postoperative days, but do not reduce reoperation rates, complication rates or mortality rates following low anterior resection. Further research is needed to analyze if diverting stomas protect against late diagnosed leaks and to assess the severity of these leaks.

List of papers

The thesis is based upon three papers, referred to in the text by their Roman numerals (I-III).

I. Myrseth E, Nymo LS, Gjessing PG, Kørner H, Kvaløy JT, Norderval S.

Lower conversion rates with robotic assisted rectal resections compared with conventional laparoscopy; a national cohort study.

Surg Endosc. Volume 36, Issue 5, August 2021, 3574-3584 (https://link.springer.com/article/10.1007/s00464-021-08681-x)

II. Myrseth E, Nymo LS, Gjessing PG, Norderval S.

Diverting stomas reduce reoperation rates for anastomotic leak but not overall reoperation rates within 30 days after anterior rectal resection: a national cohort study

Int J of Col. Dis, Volume 37, Issue 7, June 2022, 1681-1688 (https://link.springer.com/article/10.1007/s00384-022-04205-8)

III. Myrseth E, Gjessing PG, Nymo LS, Kørner H, Kvaløy JT, Norderval S. Laparoscopic rectal cancer resection results in non-inferior clinical and oncological outcomes with shorter hospital stay compared to open access; a five-year national cohort.

Submitted for publication June 2023

Abbreviations

TME	Total mesorectal excision
NORGAST	The Norwegian Registry for Gastrointestinal Surgery
BMI	Body Mass Index
ECOG	Eastern Cooperative Oncology Group performance status
LAR	Low anterior resection
APR	Abdominoperineal resection
NCSP	NOMESCO Classification of Surgical Procedures
ICD	International Classification of Disease
TaTME	Transanal Total Mesorectal Excision
ASA	American Society of Anaesthesiologists physical status classification
FEV1	Forced expiratory volume during the first second
NYHA	New York Heart Association Functional Classification
RR	Robotic assisted laparoscopic resection
LR	Standard laparoscopic resection
ORR	Open rectal resection
LRR	Laparoscopic rectal resection, including robotic assisted resections
OR	Odds ratio
aOR	Adjusted odds ratio
c.i.	Confidence interval
CRM	Circumferential resection margin
DRM	Distal resection margin

1 Introduction

1.1 Rectal cancer and total mesorectal excision

1.1.1 Epidemiology

Colorectal cancer is the third most common cancer worldwide, with 1.9 million new cases in 2020 (1).

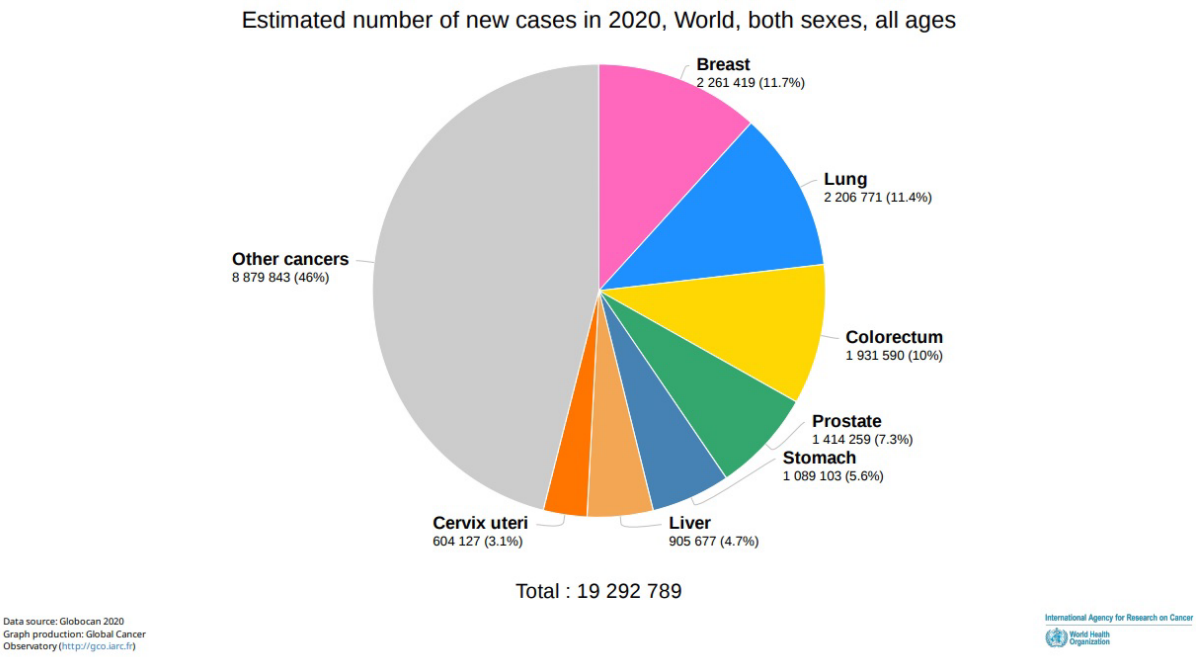
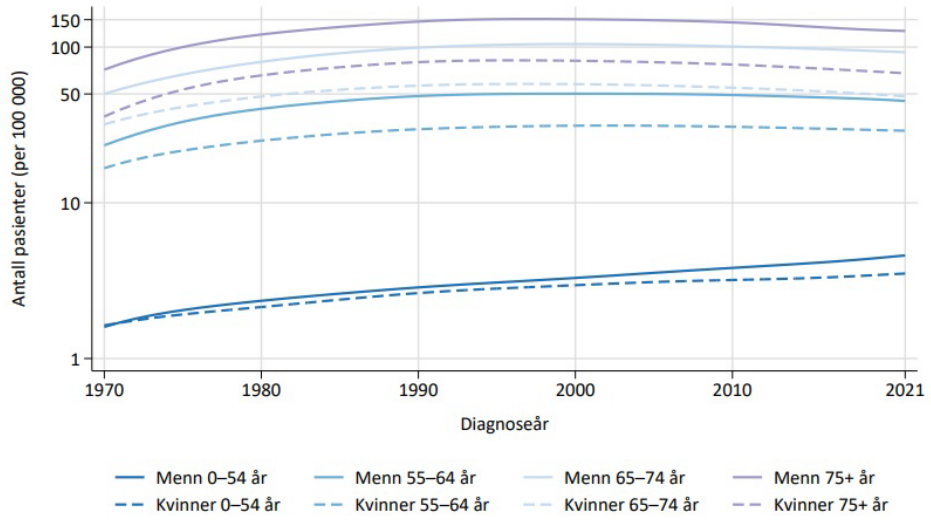


Figure 1: New cases of cancer worldwide 2021, stratified by type. Figure from WHO Global Cancer Observatory

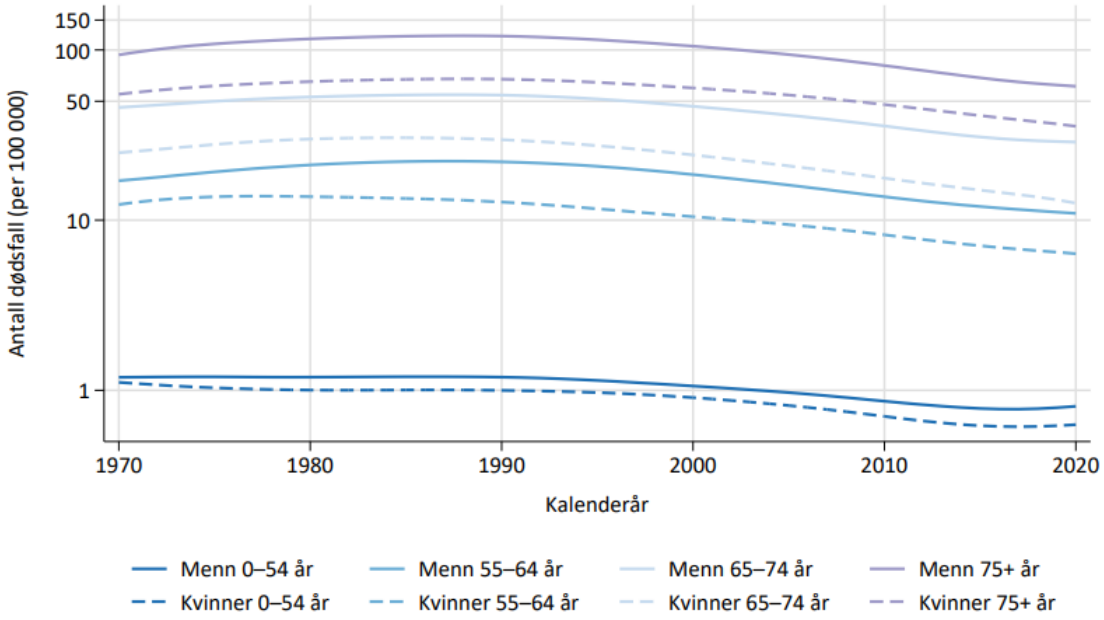
Rectal carcinoma represents about one fourth of the cases, and the incidence is approximately 1300 persons per year in Norway (2). The Norwegian Colorectal Cancer Registry (3) surveys the epidemiology, treatment quality and the results after treatment in Norway, and aims to standardize treatment and improve the quality of initial assessments, treatments given and follow-up. The registry publishes annual reports overviewing the current epidemiology, and in the 2021 report a slight increase in incidence for the younger age groups (both sexes) was seen, whereas the incidence decreased for the older population (rate per 100 000) (2).



Figur 3.26: Forekomst (insidens) i rater - endetarmskreft

Figure 2: Incidence of rectal cancer in Norway 1970-2020, figure from the Colorectal Cancer Registry 2021 annual report

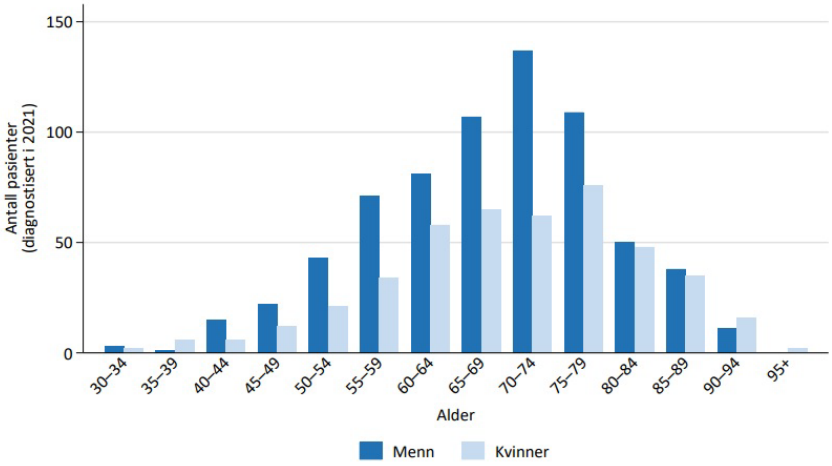
Mortality rates were slightly decreasing for all age groups (rate per 100 000) (2):



Figur 3.27: Dødelighetsrater - endetarmskreft

Figure 3: Rectal cancer mortality rates in Norway 1970-2020, figure from the Colorectal Cancer Registry 2021 annual report

Incidences were higher amongst men, and median age when diagnosed was 70.0 years for men and 71.0 years for women (2):



Figur 3.28: Kjønn og alder – endetarmskreft

Figure 4: Age- and sex-stratified incidence of rectal cancer in 2021 in Norway, figure from the Colorectal Cancer Registry 2021 annual report

1.1.2 A brief history of rectal cancer surgery

"*All carcinomas of the lower sigmoid and upper rectum are tabooed by all practical surgeons on account of their anatomical inaccessibility. All are abandoned without hope to linger on for a few months until death relieves them of their loathsome condition."* H. W. Maunsell, The Lancet, 1892.

William Ernest Miles was the first surgeon to describe rectal excision through an abdominal incision (4) in 1908, and previous standards had been perineal proctectomy. Miles defined what was later named the mesorectum; pelvic tissue containing lymphatic tissue and mesorectal nodes, which he called "zones of upward spread". Local recurrence rates were extremely high in this time period, and Miles reported recurrence rates dropping from nearly 100% to 30% after implementing abdominoperineal rectal resection with removal of mesorectum (4,5).

In 1982 Professor Richard John Heald introduced total mesorectal excision (6,7), where he describes the importance of precise dissection in a defined surgical plane surrounding both the rectum and mesorectal tissue. In this way lymphatic tissue draining rectum with the tumor can

be removed. He defined this plane as “the holy plane”; the avascular space between the presacral and mesorectal fascia. Total mesorectal excision is still today the standard surgical procedure for low and mid rectal cancers, while for cancers in the upper rectum partial mesorectal excision with removal of only the upper parts of the rectum and mesorectal tissue is sometimes adequate (8).

The standard curative treatment for rectal cancer is surgical removal of the tumor. After the introduction of total mesorectal excision (TME), and later neoadjuvant radiochemotherapy for more advanced loco-regional disease, the survival rate has improved, and 5-year local recurrence rate has dropped from above 20% to 4% (9–12).

1.1.3 Modern rectal cancer management

The preoperative assessment of rectal cancer patients is important to determine the clinical cancer stage, and to determine the further treatment strategy. Exact diagnostics requires proctoscopy with measures of distance from tumor to the anal verge, and biopsy from tumor. For superficial tumors endorectal ultrasound can be a useful diagnostic imaging tool (13), while MRI is important for exact grading of tumor stage, lymph node involvement, vessel involvement, involvement of the mesorectal fascia and of neighboring organs. A CT-scan of the thorax, abdomen and pelvic area is performed to determine the presence of distant metastases. The cancer is then graded according to the TNM classification (14)

Table 1: TNM-classification of rectal cancer

T - primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues
T4	Tumor directly invades other organs or structures and/or perforates visceral peritoneum
N - Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
M - distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

After initial assessments the patient is referred to a multidisciplinary team consisting of radiologists, gastrointestinal surgeons, oncologists, and pathologists, where strategy of treatment is planned.

The treatment strategies depend on several measures from the diagnostics; tumor level, infiltration depth, expected distance from tumor to circumferential resection margin (comprised by the mesorectal fascia, vagina/uterus for women and prostate gland for men, musculus levator ani and musculus puborectalis), pathological lymph nodes and tumor deposits, signs of extramural vascular vessel involvement and distant metastasis (15). Curative strategies will be available for cases were tumor is technically resectable and were distant metastasis are resectable. Distance from tumor, tumor deposit or pathological lymph node to the mesorectal fascia (MRF) have in studies shown correlation with clear resection margins in the final specimen (16–18). According to Norwegian guidelines, preoperative radiochemotherapy is used to downstage tumors if distance from MRF to tumor or tumor deposit is $\leq$2 mm, or $\leq$1 mm from pathological lymph node. For low tumors mesorectal tissue anatomically narrows, and margins to planned resection margin may be even shorter. For this reason, radiochemotherapy may be indicated more often in low tumors. In total, 37% of the patients who underwent rectal resection in Norway received neoadjuvant radiation therapy in 2021 (2).

Neoadjuvant treatment in Norway has to great extent been based on risk of involvement of CRM. Patients with T4b-tumors, short distance to MRF ($\leq$2 mm) or suspected pathological lymph nodes on the lateral pelvic wall should be considered for neoadjuvant treatment. The recommended treatment in Norway is 1.8-2 Gy x 25 combined with capecitabine (19,20), both to downstage tumor and to lower risk of local and distant recurrence. For patients without pathological lymph nodes or vessel involvement radiation therapy alone with 5x5 Gy could be an option for downstaging tumor (20,21). The regime with radiation therapy alone can also be an alternative for older patients or patients that cannot receive chemotherapy for other reasons. The Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) (22) study is a multicenter RCT that enrolled patients from 54 countries, were effect of short-course radiotherapy (5x5 Gy) followed by either 6 cycles of CAPOX or 9 cycles of FOLFOX4 chemotherapy followed by operation was compared to the traditional long-course treatment with concomitant capecitabine. The aim was to explore if

this treatment could lower systemic disease burden without compromising locoregional control for patients with locally advanced tumors, and results showed significantly reduced disease related treatment failure with the RAPIDO-regime compared to standard treatment regime. The RAPIDO regime is now offered to some high-risk patients in Norway. Evaluation of the treatment effect is done to determine further strategy; urgent operation in case of poor response to the treatment and technically resectable tumor or wait for further response in case of good response. In some patients a complete clinical response is observed, where there is no visible tumor after neoadjuvant treatment, assessed by palpation, radiology and endoscopy. Several studies have evaluated if radiochemotherapy alone could be an option to TME, by a "watch-and-wait-regime" were the patients are monitored closely without surgery after the treatment (23–25).

After downstaging tumor with neoadjuvant radiochemotherapy surgical resection of the tumor is normally planned. If the patient has distant metastasis, treatment of the metastasis is often planned for after treatment of the primary tumor.

1.1.4 Total mesorectal excision

The rectum is located in the pelvic region, and anatomically different from the remaining colon by the loss of teniae coli and appendices epiploicae which normally happens at 15 cm proximally to the anal verge (26,27). Further, the rectum is often defined into three areas; low, mid and upper rectum, with the mesorectum enveloped by the mesorectal fascia extending down towards the anorectal junction where the anal intersphincteric space begins (27). In close proximity to rectum and mesorectum in the pelvic area are the bladder, ureters and urethra, reproductive organs as well as pelvic and sacral nerves and blood vessels. For rectal resection and total mesorectal excision the dissection must be made within the plane of the mesorectal fascia; sparing other organs and tissue while making sure that rectal lymphatic tissue is resected (6,27,28).

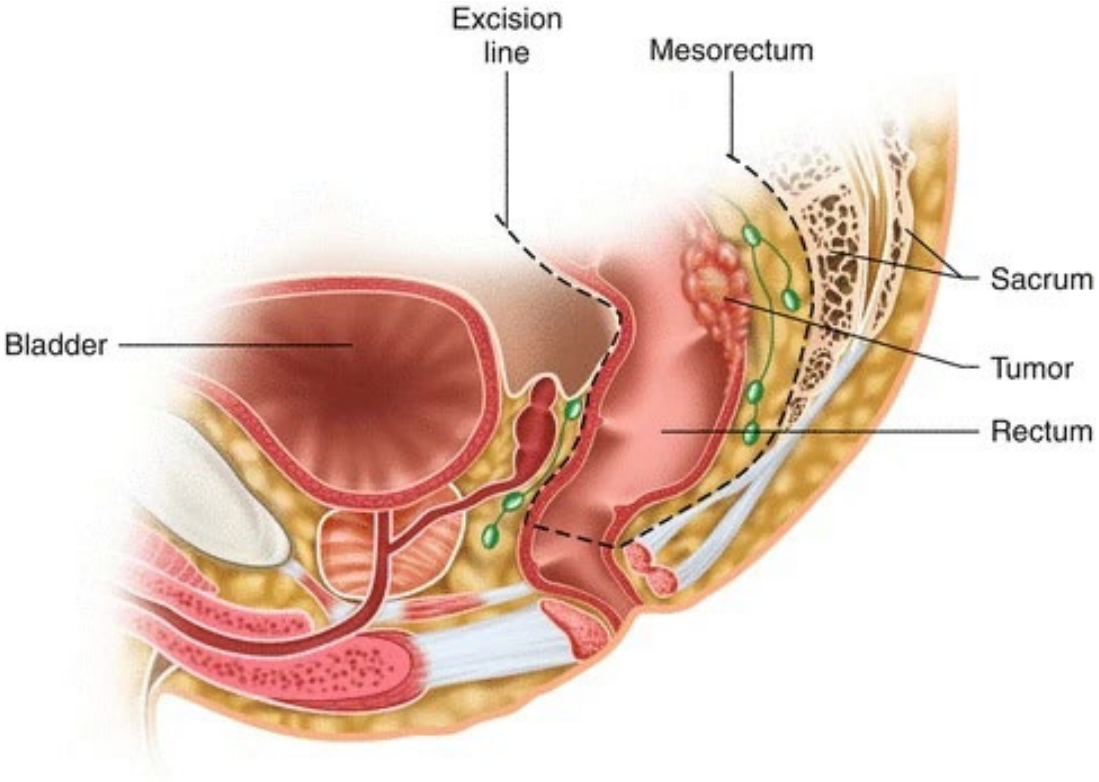


Figure 5: Sketch showing the rectum and mesorectum with its position in the pelvic area, and the plane of dissection for TME. Figure from Hakiman et.al Total Mesorectal Exicion with autonomic nerve preservation "optimized Surgery"(29)

Low anterior resection with total mesorectal excision is normally followed by an anastomosis between the proximal colon sigmoid and the distal remaining rectum or anal canal. Norwegian guidelines recommend a distal resection margin from tumor of minimum 1 cm (15,30,31), meaning the bowel needs to be divided 1 cm distal to the tumor. An anastomosis can be performed after TME where the bowel is divided as low as at the pelvic floor, but for lower tumors abdominoperineal resection with complete removal of the anal canal and closure of the perineal opening with formation of an end colostomy is recommended. For some patients an anastomosis is not recommendable (high risk of anastomotic leak, or they cannot tolerate the burden of anastomotic leak complication), and a TME is performed with formation of an end colostomy (Hartmann's operation).

Locally advanced tumors (T4 cancer) with growth into neighboring organs demands major surgical undertaking. When curative treatment is intended, it involves en bloc resection of rectum and all involved organs after downstaging neoadjuvant radiochemotherapy.

1.2 Minimally invasive surgery

Minimally invasive surgery has been introduced in rectal cancer treatment the last decades, and in Norway 84% of the rectal cancer operations were laparoscopic in 2021 (2). Several studies have shown favorable outcomes with laparoscopic approach compared to open for colon cancer surgery (32–34), but for rectal cancer surgery results have not been unambiguously positive.

Some studies comparing laparoscopic access to open access for rectal cancer have reported inferior histopathological results following laparoscopic resection, which could reflect a more difficult dissection around the tumor. The CLASICC trial (34) was the first RCT comparing open and laparoscopic resection for rectal cancer, and the trial reported higher positive CRM (circumferential resection margins, $\leq$1 mm distance from tumor to resection margin) (12%) after laparoscopic resection compared open resection (6%) for patients that underwent low anterior resection, although the difference was not statistically significant (34). The ALaCaRT multicenter RCT (35) reported higher rates of positive CRM after laparoscopic surgery compared to open as well as inferior rates on mesorectum completeness, although the difference was not statistically significant. The conversion rates have been a concern, and the CLASICC study showed inferior results in terms of increased complication rates and even worsened survival rates following conversion from laparoscopy to open access. The conversion was as high as 34% for rectal procedures in the CLASSIC study. Conversion rates were high also in the large COLORII study (17%), but there were no presented subgroup analyses on results for the converted procedures.

Laparoscopic rectal cancer surgery is technically difficult due to the narrow space in the pelvis, and studies have shown high conversion rates with many operations needed to learn the procedure (36). Hopes have been that the introduction of robotic assistance with better instrument articulation and a stable three-dimensional camera could reduce some of the difficulties associated with laparoscopic surgery in the pelvic region. Some recent studies have shown that robotic assistance lower conversion rates in laparoscopic rectal resection (37,38), but the large multicenter ROLARR RCT trial (39) where conversion rate was the primary end point could not prove non-inferiority with the use of robotic assistance regarding conversion rates.

Transanal TME (TaTME) was introduced as a promising mini-invasive technique for treating low rectal cancers in 2010 (40), where the distal part of the total mesorectal excision is

performed via transanal access. The method aimed to offer better visibility, access to the dissection planes and safe anastomotic techniques, especially for patients with expected technical difficulties such as males (narrow pelvis) and obesity. Some meta-analyses have shown comparable short-term outcomes and oncological results when comparing TaTME with RR or LR (41,42), and a recent meta-analysis concluded with non-inferior survival rates compared to ORR, RR and LR (43). The technique is currently used in many countries. A multicenter study from Norway showed higher rate of local recurrence following TaTME (11.6%) compared to national data (from NORGAST and the Colorectal Cancer Registry) (2.4% $p<0.001$) which included standard operative techniques (open/laparoscopic TME), and the technique is now abandoned in Norway (44).

1.3 Postoperative complications

One can only imagine the morbidity that followed surgical treatment of rectal cancer in the early stages when perineal proctectomy with nearly 100% local recurrence rates and high mortality rates were standard of care. The introduction of abdominoperineal rectal excision by Ernest Miles (4) and later formation of a terminal colostomy as introduced by Henri Hartmann in 1921 (45) improved both survival and morbidity. Techniques for establishing intestinal continuity with a colorectal/coloanal anastomosis was described by dr. Claude Dixon in the 40's (46), and in the 70's the development of surgical staplers (especially circular) made anastomosis technically possible and widely used.

Excessive bleeding, sepsis and mortality was common in the early stages of rectal cancer surgery. Incontinence and sexual dysfunction were not addressed in the early papers but was probably significant. After anastomotic techniques were introduced and intestinal continuity established, complications like fistula and peritonitis, intestinal obstruction, anastomotic stricture, loss of sphincter control and sexual function was addressed in Dixon's study cohort (46), but not to great extent.

In modern rectal cancer surgery sexual dysfunction, bladder dysfunction (47,48) and Low Anterior Resection Syndrome (LARS) with varying degree of bowel dysfunction (49) are some of the known long-term complications. Important short-term complications explored by the first RCT (34) comparing laparoscopic rectal resection to open rectal resection were bleeding, injury to bowel, ureter or bladder, wound infection and anastomotic leak. Anastomotic leak is still one of the most devastating and feared complications following modern rectal cancer surgery.

1.3.1 Anastomotic leak

For patients where an anastomosis is formed between the colon and the remaining rectum or anal canal after rectal resection a leak in this anastomosis may occur. An anastomotic leak should be defined as a communication between the intra- and extraluminal compartments due to a defect in the anastomosis (50), and the clinical presentation varies between asymptomatic patients with an anastomotic leak detected radiologically or at endoscopic evaluation, to patients with septicemia and peritonitis.

Anastomotic leaks may be discovered early in the postoperative course, others may be detected later, sometimes by the development of a fistula or a pelvic abscess. Rahbari et.al graded anastomotic leaks following rectal resection (50), according to what type of intervention the leak requires. The authors defined three categories of leaks where grade A leaks do not require any intervention, grade B leaks require active intervention but without relaparoscopy/relaparotomy, and grade C leaks require relaparoscopy or relaparotomy (50). In most cases an anastomotic leak leads to increased morbidity, prolonged hospital stay, additional interventions and increases mortality (51–53). The long-term functional result may also deteriorate, leading to lifelong implications for the patient (54).
The formation of a temporary diverting stoma is common following low anterior resection to prevent anastomotic leak, and two recent meta-analyses have shown lower leak rates in patients receiving diverting stomas (55,56). Norwegian guidelines recommend diverting ileostomy in case of anastomosis $\leq$ 7 cm from anal verge based on results from research in The Norwegian Colorectal Cancer Registry (15). Stoma-related morbidity and complications do though represent a significant problem (57–59), and patient selection is important. There is an ongoing debate on whether diverting stomas only mask unavoidable leaks and delay the diagnosis, as well as stoma-related morbidity and complications that warrants selection of patients that could benefit from a diverting stoma.

1.4 National quality registers

1.4.1 The Colorectal Cancer Registry

The long-term results after cancer treatment are surveyed by The Norwegian Colorectal Cancer Registry (3). The registry is a subdivision of The Cancer Registry in Norway, and it was established in 2007 as an expansion of the existing Rectal Cancer Registry (existing since 1993). All hospitals in Norway are obliged to report, and reports from clinical departments, pathology departments as well as death certificates is compulsory. The registry aims to strengthen and improve the quality of treatment for colorectal cancer, evaluate whether national guidelines are being followed, as well as monitor the epidemiology of the disease. The register publishes annual reports on epidemiological data.

1.4.2 The Norwegian Registry for Gastrointestinal Surgery (NORGAST)

The Norwegian Registry for Gastrointestinal Surgery (NORGAST) is a national quality registry established in 2014 which aims to survey the rate, kind and severity of complications following gastrointestinal surgery, and all hospitals in Norway performing gastrointestinal resection surgery are obliged to report. The registry records selected factors that might affect a surgical outcome such as weight loss, BMI, ECOG-status, known severe pulmonary and cardiac disease, as well as postoperative outcome measures such as complication rates, length of hospital stay, mortality rates, reoperation rates, readmission rates to mention some. Research on surgical cancer treatment has traditionally been focused on survival and recurrence of disease. The degree of morbidity associated with the treatment, where sometimes severe and fatal complications occur, is less known. Data from this registry gives thus a unique opportunity to assess the outcomes after surgical treatment for rectal cancer and adjust for various factors like patient comorbidity and surgical technique.

1.5 Purpose of this thesis

Although morbidity, local recurrence and mortality have decreased substantially since surgical resection became an option, modern rectal cancer surgery is still a technically difficult procedure with significant complications influencing quality of life for the patient, and with questions to be answered on which surgical method offers the best short-term, oncological, and long-term results.

The aims of this study were to assess the outcomes after surgical treatment for rectal cancer in a 5-year national cohort. We wanted to investigate if there were any differences in short-term and long-term outcomes between laparoscopic and open access resection for rectal cancer, and if there were any differences between robotic assisted resections and standard laparoscopic resections. We also wanted to investigate the protective effect of diverting stomas after low anterior resection regarding reoperation for anastomotic leak and morbidity rates.

2 Aims

2.1 Aims paper I

The aim was to assess short term outcomes after standard laparoscopic versus robotic assisted laparoscopic resections for rectal cancer. Primary end point was conversion rates and secondary end points were postoperative complications within the first 30 days and histopathological results.

2.2 Aims paper II

The aims were to assess the anastomotic leak rates and overall complication rates after LAR with and without a diverting stoma. Primary end point was reoperation for anastomotic leak within 30 days after LAR with and without diverting stomas. Secondary endpoints were overall complication rates including reoperation of any cause.

2.3 Aims paper III

The aims were to assess the short- and long-term results following open and laparoscopic elective major rectal resection for rectal cancer. Primary end point was 5-year overall survival. Secondary end points were 5-year local recurrence rates, oncological resection quality and short-term outcomes measures.

3 Methods

3.1 Study design; observational study

The study was designed as an observational cohort study with prospectively recorded data from two independent national quality registries; the Norwegian Registry of Gastrointestinal Surgery (NORGAST) and the Norwegian Colorectal Cancer Registry. Data for analyses was based mainly on NORGAST data, with supplementary information from the Colorectal Cancer Registry regarding preoperative assessments and histopathological results. In order to minimize the possible effects of confounding, selection bias and information bias, several measures were undertaken in this study and are further explained in this chapter.

3.2 Study population

Patients who underwent elective major resection for rectal cancer from January 1st 2014 to December 31st 2018 were identified via the Norwegian Registry for Gastrointestinal Surgery (NORGAST) (60). Due to some delay in data registration, and also to achieve at least 6 months follow-up, latest date for data extraction was set to December 2018. This national quality registry was established in 2014 and it includes major gastrointestinal and hepatobiliary resections. All Norwegian hospitals performing cancer resections are obliged to report data to NORGAST which records variables that might affect a surgical outcome, such as pre-operative weight loss, BMI, ECOG-status, known severe pulmonary and cardiac disease as well as operative technique and short-term postoperative outcome measures including complications, reoperations, length of hospital stay, readmissions and mortality rates. A detailed presentation of the registry has been published previously (60).

Patients were identified in the NORGAST database based on procedure codes according to the NCSP (NOMESCO Classification Of Surgical Procedures) (61) for rectal resection (JGB00 through JGB07, JGB10 and JGB11, and JGB30 through JGB36). The procedure codes were combined with diagnosis code C20 for cancer $\leq$15 cm from the anal verge assessed with rigid proctoscope according to the International Classification of Diseases version 10 (ICD-10) (62). Some cases registered with cancers located 15 cm or lower measured on rigid proctoscope, but erroneously given the ICD-code C19 for rectosigmoid cancer at discharge, were also included. Patients with tumors other than adenocarcinoma were excluded. Emergency procedures and TaTME procedures were also excluded.

Data from NORGAST were combined with data from the Norwegian Colorectal Cancer Registry based on the patient's social security numbers and an individual project identification number. This added information on preoperative work-up, neoadjuvant treatment, final histopathological results, survival rates, and rates of local recurrence and metastasis during follow-up.

3.3 Data quality

The coverage rate in NORGAST was 75% in 2018 (63), increasing from approximately 20% on a national level in 2014. Low coverage rates the first years were due to few participating hospitals, but in-hospital coverage among participating hospitals was high. The Norwegian Colorectal Cancer Registry has a coverage rate higher than 90% (2). Variable completeness varies, with almost 100% completeness in NORGAST compared to 70% for some variables in the Norwegian Colorectal Cancer Registry. This registry holds data from various sources; clinical reports from diagnostics, treatment and histopathological reports. In cases where some sources have missing reports there are some variable incompleteness. However, as both registries overlap on several core variables, data linking results in an overall high degree of variable completeness. Patients with missing values were excluded from the specific analysis were data was missing.

3.4 Categorization of variables

Age was recoded from a continuous to a categorical variable, and further categorized into three groups (low < 65 years, mid 65-80 years and high >80 years). ASA-scores were grouped into low ASA-scores (scores 1-2) and high ASA-scores (scores 3-4). ECOG-scores were dichotomized into low ECOG-scores (0-1) and high ECOG-scores (2-4). Severe pulmonary disease was defined as having FEV1 <50% or a vital capacity <60% of predicted values. Severe cardiac disease was defined as NYHA classification 3-4, or severe arrythmia requiring mechanical support. Major complications were defined as Accordion (64) grade of 3 or higher. Briefly, Accordion grade 3 is defined as any percutaneous, angiographic or endoscopic intervention, Accordion 4 is defined as intervention in general anesthesia or single-organ failure, Accordion 5 is defined as intervention in general anesthesia plus single-organ or multi-organ failure. Accordion 6 is death within 30 days postoperatively. Anastomotic leak was defined as a leak requiring relaparoscopy or relaparotomy (grade C leaks) (50), and anastomotic leak rate was only calculated for patients that received an

anastomosis. Weight was classified by body mass index (BMI), and the scale was recoded from a continuous variable to a categorical variable. Patients were grouped into 4 BMI-classes (65); [<18.5] [18.5-25] [25-30] [>30].

Cancer stage was derived from the variables tumor-stage, number of pathological lymph nodes, and the presence of distant metastasis. For survival analyses clinical cancer stage with pre-treatment staging of tumor and suspected lymph nodes was used. Pathological cancer stage with information from the pathological reports postoperatively was also reported.

During the work with paper II, further recategorization of one of the variables was done. In NORGAST, a large number of the reoperations were coded with main finding "miscellaneous" at reoperation. As a part of a registry quality review the electronical medical records for all patients coded with "miscellaneous" as main finding at reoperation were investigated and recategorized into more granular main findings.

3.5 Statistical analyses

Data were analyzed with SPSS version 26 (IBM, Armonk, New York, USA). Differences between groups were assessed with Pearson's Chi square test for categorical data, and two-sided T-test or Mann Whitney U-test for continuous data. Confidence interval (c.i.) standard deviations or inter quartile range/quartiles were calculated when appropriate. Univariable binary logistic regression was used to calculate unadjusted odd ratios (OR). Multivariable logistic regression models were used to calculate adjusted odds ratios (aOR) to further analyze the relations between different outcomes and predictor variables. Variables with a p-value of <0.2 in univariable analyses were included in multivariable analysis. Stepwise backward selection was used to suggest the final multivariable model. A final significance level of $p< 0.05$ was used in all tests. There were missing data in some of the variables. Little`s test (66) of whether data were missing completely at random was performed for the different datasets used in papers I and III. The test had a non-significant p-value indicating that missing values were missing completely at random. This allowed patients with missing data in variables included for subgroup analyses to be excluded from these analyses.

In paper I, separate analyses on lymph nodes were made in a linear regression model. The continuous variable "lymph nodes" was the dependent variable, RR or LR was fixed factors and hospitals performing RR was covariate.

To address potential treatment assignment bias in paper I, a propensity score matching was performed by including all available baseline variables. The matched sets were included in a new set of regression analyses. Match tolerance was set to 0.01, and sampling was done without replacement. Robotic assistance was used as group indicator, and baseline characteristics (age, gender, BMI, severe cardiac and pulmonary disease, diabetes, ASA-score, ECOG-score and diabetes) were used as predictors.

In paper III, survival data and local recurrence rates were illustrated with Kaplan-Meier curves, and the log-rank test was used to test for differences between the groups using an intention-to-treat factor approach. To adjust for possible confounders, 5-year survival and local recurrence rates were further explored with Cox multivariable regression analyses adjusting for relevant covariates.'

4 Summary of results

4.1 Population

Out of 2302 patients recorded in NORGAST with an NCSP procedural code for rectal resection in the study period, some 1796 patients had undergone elective resection for rectal adenocarcinoma and were included in the study. A total of 909 patients had a standard laparoscopic operation (LR) and 375 had a robotic assisted laparoscopic operation (RR) and were included for analyses in paper I. Sixteen hospitals contributed data, of which 7 performed both RR and LR. As for paper II, a total of 1018 patients who had undergone low anterior resection with primary anastomosis were included for analyses after excluding 778 Hartmann and APR-resections from the initial 1796 patients. For paper III, a total of 512 open rectal resections (ORR) and 1284 laparoscopic rectal resections, including robotic assisted resections (LRR), were included for analyses. The included patients are presented in the flowchart below (figure 6):

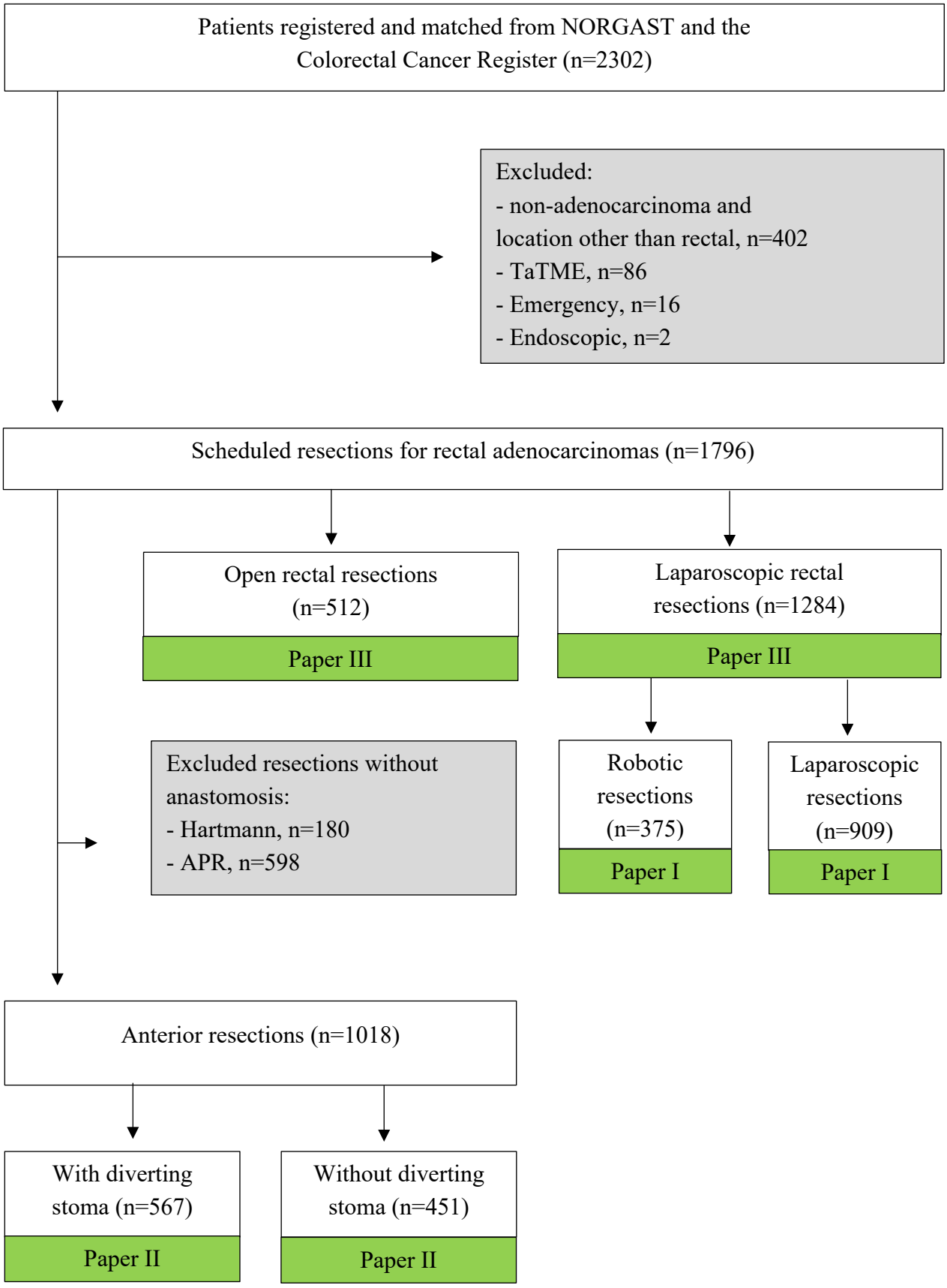


Figure 6: Flowchart

Some baseline differences were observed between all the different study groups. Baseline differences are presented in tables for all study groups in papers I-III. Characteristics for the overall study cohort are shown in the table below (table 2):

Table 2: Baseline characteristics of the study cohort

Baseline characteristics		Total	Laparoscopic		Open access		p-value
		n= 1796	n= 1284		n= 512		
Gender							
	Male	1108	782	(61.0)	326	(64.0)	0.276
	Female	688	502	(39.0)	186	(36.0)	
Age (mean) *(std.dev*)*		67.3 *(11.7)*	67.5	*(11.4)*	66.6	*(12.6)*	0.997
BMI							
	<18.5	40	25	(2.0)	15	(3.1)	0.354
	18-25	730	518	(41.1)	212	(43.6)	
	25-30	678	496	(39.4)	182	(37.4)	
	>30	297	220	(17.5)	77	(15.8)	
Pulmonary disease		83	48	(3.7)	35	(6.8)	0.005
Heart disease		119	73	(5.7)	46	(9.0)	0.011
Diabetes		182	134	(10.4)	48	(9.4)	0.501
ASA-score							
	Low (1-2)	1204	871	(67.8)	413	(69.9)	0.278
	High (3-4)	591	413	(32.2)	178	(34.8)	
ECOG-score							
	Low (0-1)	1667	1210	(72.6)	457	(59.3)	0.002
	High (2-4)	111	67	(27.4)	46	(40.7)	
Radio(chemo)therapy		588	375	(29.2)	213	(41.6)	<0.001
Operative technique							
	LAR	1018	742	(57.8)	276	(53.7)	0.005
	APR	598	432	(33.6)	166	(32.6)	
	Hartmann	180	110	(8.6)	70	(13.7)	
pStage**	1	333	262	(54.7)	71	(40.3)	<0.001
	2	211	159	(33.2)	52	(29.5)	
	3	38	20	(4.2)	18	(10.2)	
	4	73	38	(7.9)	35	(19.9)	
cStage***	1	303	246	(28.3)	57	(18.1)	
	2	323	239	(27.8)	84	(26.7)	
	3	399	288	(33.5)	111	(35.2)	
	4	149	86	(10.0)	63	(20.0)	

Numbers in parenthesis; percentages if not specified otherwise
There are missing values in the following variables:
BMI: 51, ASA-score: 1, ECOG-score: 16, pStage: 1141, cStage: 622
**std.dev: Standard deviations*
*** pStage: Pathological cancer stage, after pathological report*
**** cStage: Clinical cancer stage, after diagnostics before treatment*
LAR; Low anterior resection APR; Abdominoperineal resection

4.2 Short term outcomes

In paper I the primary aim was to assess conversion rates as well as the other short-term outcomes.

4.2.1 Conversion rates, paper I

The overall conversion rate was 95 out of 1284 patients (7.4%). A significantly lower conversion rate was observed for patients that underwent RR with 8 out of 375 (2.1%) compared to 87 out of 909 (9.6%) for patients that underwent LR ($p<0.001$). To investigate if this difference could be related to surgeon or hospital factors, with different conditions in hospitals offering robotic surgery than in those hospitals that do not, a separate analysis was done to investigate the conversion rates for LR only. Conversion rate for LR performed in hospitals using both operative techniques was 51 out of 464 (11.0%) compared to 36 out of 445 (8.1%) in hospitals using laparoscopic technique only ($p=0.137$). In multivariable analyses, RR was associated with reduced risk for conversion with an aOR of 0.21 (95% c.i. 0.09-0.43) compared to LR (table 3). In addition, male gender (aOR 1.86, 95% c.i. 1.14-3.06), BMI> 30 (aOR 2.64, 95% c.i. 1.51-4.61) and severe cardiac disease (aOR 2.16, 95% c.i. 1.08-4.31) were independent predictors for conversion (table 3). The Hartmann procedure was associated with a higher conversion rate (aOR 2.88, 95% c.i. 1.35-6.13) than low anterior resections (LAR), with abdominoperineal resections (APR) as reference. Results from regression analyses are presented in the following table (table 3):

Table 3: Regression analyses of risk factors for conversion paper I

		Conversion rate (%)	Univariable OR (95% c.i.)	*p-value*	Multivariable aOR (95% c.i.)	*p-value*
All patients		95/1284 (7.4)				
Age group						
	<65	37/503 (7.4)	Ref	0.411		
	65-80	43/631 (6.8)	0.91 (0.58-4.45)			
	>80	15/150 (10.0)	1.40 (0.75-2.63)			
Gender						
	Female	24/502 (4.8)	Ref	0.014	Ref	0.014
	Male	71/782 (9.1)	1.98 (1.23-3.21)		1.86 (1.14-3.06)	
WHO ECOG-score						
	0,1	89/1210 (7.4)	Ref	0.974		
	2, 3, 4	5/67 (7.5)	1.02 (0.39-2.59)			
ASA classification						
	1-2	63/871 (7.2)	Ref	0.742		
	3-4	32/413 (7.7)	1.08 (0.69-1.68)			
Severe pulmonary disease						
	No	93/1236 (7.5)	Ref	0.391		
	Yes	2/48 (4.2)	0.53 (0.29-2.34)			
Severe cardiac disease						
	No	83/1211 (6.9)	Ref	0.003	Ref	0.029
	Yes	12/73 (16.4)	2.67 (1.39-5.16)		2.16 (1.08-4.31)	
Diabetes						
	No	79/1150 (6.9)	Ref	0.036		
	Yes	16/134 (11.9)	1.84 (1.04-3.25)			
Weight class (BMI)						
	<18.5	1/24 (4.2)	0.72 (0.09-5.54)	0.007	0.87 (0.12-6.89)	0.002
	18.5-25	29/511 (5.7)	Ref		Ref	
	25-30	32/496 (6.5)	1.15 (0.68-1.93)		1.08 (0.63-1.83)	
	>30	29/228 (12.7)	2.42 (1.41-4.16)		2.64 (1.51-4.61)	
Radio(chemo)therapy						
	No	71/909 (7.8)	Ref	0.381		
	Yes	24/375 (6.4)	0.81 (0.50-1.30)			
Operative technique						
	LAR*	60/743 (8.0)	1.72 (1.03-2.87)	0.012	1.66 (0.97-2.84)	0.021
	Hartmann	14/109 (14.3)	2.88 (1.42-5.88)		2.88 (1.35-6.13)	
	APR**	21/432 (4.8)	Ref		Ref	
Robotic assistance						
	No	87/909 (9.6)	Ref	<0.001	Ref	<0.001
	Yes	8/375 (2.1)	0.21 (0.09-0.43)		0.22(0.10-0.46)	

*LAR; Low anterior resection **APR; Abdominoperineal resection

A total of 730 patients were included after propensity score matching, with 65 exact matches and 289 fuzzy matches. After propensity score matching, RR compared to LR (aOR 0.19, 95% c.i. 0.09-0.42) as well as male gender (aOR 2.44, 95% c.i. 1.14-5.19) remained significant predictors for conversion.

4.2.2 Other short-term outcomes, paper I

There were no significant differences in major complications, 30-day mortality rates and reoperation rates or anastomotic leak rate between the LR and RR group (table 4). Multivariable regression analyses were done in paper I for the outcomes major complications, 30-day mortality rates, reoperation rates and anastomotic leak rates. Robotic assistance was not a predictor for any of these outcomes. Separate analyses were performed for patients that underwent conversion, and we observed higher rates of major complications and reoperations following converted procedures compared to procedures completed laparoscopically, with complication rates of 20 out of 95 (21.1%) vs 135 out of 1189 (11.4%) (p=0.005) and reoperation rates of 13 out of 95 (13.7%) vs 93 out of 1189 (7.8%) (p=0.046). Conversion was also an independent predictor of major complications in multivariable regression analyses (aOR 1.85, 95% c.i. 1.07-3.23, p=0.029).

Table 4: Postoperative complications and histopathological results paper I

	LR	RR	p-values*	CC**	CL***	p-values *
30-day mortality	3 (0.3)	2 (0.2)	0.592	1 (1.1)	4 (0.3)	0.280
90-day mortality	11 (1.2)	5 (1.3)	0.856	3 (3.2)	13 (1.1)	0.081
Major complications	112 (12.3)	43 (11.5)	0.669	20 (21.2)	135 (11.4)	0.005
Conversion rate	87 (9.6)	8 (2.1)	<0.001			
Anastomotic leak	27 (4.9)	14 (7.7)	0.203	5 (8.3)	36 (5.3)	0.319
Reoperation	71 (7.8)	35 (9.3)	0.367	13 (12.3)	93 (7.8)	0.046
Tumor perforation	5 (0.6)	2 (0.6)	0.988	3 (3.8)	4 (0.4)	<0.001
LOS[1] median (IQR)	6 *(4-9)*	5 *(3-7)*	0.001	*8 (6-12)*	6 *(4-8)*	0.001
Single organ failure	22 (2.4)	5 (1.3)	0.217	3 (3.2)	24 (2.0)	0.456
Multi-organ failure	3 (0.3)	2 (0.5)	0.595	2 (2.1)	3 (0.3)	0.005
Histopathological results	LR	RR	p-values	CC	CL	p-values
Positive CRM[2]	35 (4.6)	16 (4.8)	0.885	9 (10.2)	42 (4.2)	0.010
Positive DRM[3]	6 (0.8)	1 (0.3)	0.376	1 (1.1)	6 (0.6)	0.547
N. l.nodes median *(IQR)*	16 *(12-21)*	13 *(11-17)*	0.001	16 *(13-22)*	15 *(12-20)*	0.505
pStage[4] 1	196 (41.4)	66 (36.1)	0.167	14 (28.6)	248 (40.8)	0.063
2	121 (25.5)	38 (20.8)	0.196	11 (22.5)	148 (24.3)	0.692
3	108 (22.8)	54 (29.5)	0.070	14 (28.6)	148 (24.3)	0.927
4	49 (10.3)	25 (13.7)	0.407	10 (20.4)	64 (10.5)	0.051

Values in parentheses are percentages unless indicated otherwise.
LR, laparoscopic resections. RR, robotic resections. N.L.nodes; number of lymph nodes
** Chi square analyses*
*** Converted cases*
**** Completed laparoscopically*
[1]LOS, length of stay
[2]Circumferential resection margin. Missing values in this variable n=194
[3]Distal resection margin. Missing values in this variable n= 209
[4]Missing values in this variable n= 627. Pathological cancer stage, after pathological reports

4.2.3 Histopathological results, paper I

The overall rates of positive CRM and DRM (distal resection margin) were 51 out of 1090 (4.7%) and 7 out of 1075 (0.7%) and there was no significant difference between the RR and LR groups (table 4). The rate of positive CRM was higher (9 out of 88, 10.2%) following converted procedures compared to procedures completed laparoscopically (42 out of 1002, 4.2%, p= 0.010). A higher proportion of positive CRM was seen following APR compared with other operative techniques (APR 33 out of 357, 9.2%, LAR 12 out of 636, 1.9% and

Hartmann 6 out of 97, 6.2%, p <0.001). Further, surgery for low tumors (0-5 cm above anal verge) was associated with higher rates of positive CRM compared with intermediate (5-10 cm) and high (10-15 cm) tumors, with 23 out of 206 (11.2%), 9 out of 297 (3.0%) and 5 out of 250 (2.0%), respectively (p <0.001). Tumor diameter and tumor stage were not associated with higher rates of positive CRM.

A mean number of 14 lymph nodes were retrieved from the specimen in the RR group compared 18 in the LR group (p=0.001). In hospitals performing both LR and RR there were no differences in lymph node retrieval between the two groups, except for one hospital where LR resulted in fewer lymph nodes as compared to RR (table 5). ANCOVA analysis comparing mean number of lymph nodes between the RR group and the LR group correcting for hospital showed no differences between the two methods (p= 0.550).

Table 5: Lymph nodes retrieved with LR and RR in hospitals performing both techniques paper I

			RR		LR		*p value*
Center number	*n total*	*n RR*	Mean n. lymphnodes	*(std.dev)*	Mean n. lymphnodes	*(std.dev)*	
1	*158*	*6*	26.5	*(12.5)*	21.1	*(11)*	0.339
2	*118*	*60*	13.7	*(5.8)*	15.1	*(4.8)*	0.148
3	*75*	*58*	15.2	*(5.8)*	16.1	*(5.9)*	0.564
4	*123*	*4*	20.8	*(3.3)*	15.7	*(7.7)*	**0.044**
5	*32*	*19*	20.7	*(7.8)*	26.6	*(13.5)*	0.174
6	*64*	*34*	15.9	*(5.9)*	16.9	*(4.8)*	0.482
7	*269*	*194*	12.6	*(4.9)*	13.0	*(5.2)*	0.562

RR, robotic resection
LR, laparoscopic resection
std.dev, standard deviations

4.2.4 Reoperation for anastomotic leak, paper II

A total of 1018 patients underwent low anterior resection (LAR) and was included for analyses in paper II. The overall leak rate was 48 out of 1018 (4.7%) with stratified rates for patients with and without a diverting stoma of 13 out of 567 (2.3%) and 35 out of 451 (7.8%) (p<0.001), respectively. Short-term results including anastomotic leak rates are presented in table 6:

Table 6: Results after anterior resection with or without diverting stoma paper II

Results	Diverting stoma					
	Total	With		Without		P-value
Anastomotic leaks						
Open (276)	*16/276 (5.8%)*	4/183	(2.2%)	12/93	(12.9%)	<0.001
Laparoscopy (742)	*32/742 (4.3%)*	9/384	(3.1%)	23/358	(6.4%)	0.006
Tumor level						
0-11.9 cm*	*22/493 (4.5%)*	12/364	(3.3%)	10/129	(7.8%)	0.035
12.0-15.0 cm*	*17/319 (5.3%)*	0/94	(0%)	17/225	(7.6%)	0.006
Reoperations	*102/1018 (10.0%)*	53/567	(9.3%)	49/451	(10.9%)	0.423
Finding at reoperation**						
Anastomotic leak	*49/97 (50.5%)*	13/50	(26.0%)	36/47	(76.6%)	<0.001
Miscellanous	*1/97 (1.0%)*	0	(0%)	1/47	(2.1%)	
Bleeding	*7/97 (7.2%)*	4/50	(8.0%)	3/47	(6.4%)	
Deep infection	*1/97 (1.0%)*	0/50	(0.0%)	1/47	(2.1%)	
Wound dehiscence	*6/97 (6.2%)*	4/50	(8.0%)	2/47	(4.3%)	
Bowel obstruction	*12/97 (12.4%)*	9/50	(18.0%)	3/47	(6.4%)	
Bowel perforation	*3/97 (3.1%)*	2/50	(4.0%)	1/47	(2.1%)	
Stoma-related	*18/97 (18.6%)*	18/50	(36.0%)	-		
Lenght of stay, median (inter-quartile range)	*6 (4-9)*	7 (5-10)		5 (4-8)		<0.001
Major complications	*146/1018 (14.3%)*	87	(15.3%)	59	(13.1%)	0.306
90-day mortality	*14/1018 (1.4%)*	5	(0.9%)	9	(2.0%)	0.130
30-day mortality	*7/1018 (0.7%)*	4	(0.7%)	3	(0.7%)	0.938
Single-organ-failure	*25/1018 (2.5%)*	13	(2.3%)	12	(2.7%)	0.706
Multi-organ-failure	*6/1018 (0.6%)*	4	(0.7%)	2	(0.4%)	0.587

* Missing values=206

** Missing values=5

Leak rate was significantly lower with diverting stomas regardless of tumor level, and tumor level was not a significant predictor for anastomotic leak in univariable regression analyses. In multivariable regression analyses absence of diverting stoma was associated with an increased risk of reoperation for anastomotic leak with an aOR of 3.77 (c.i. 1.97-7.24, p<0.001) compared to anterior resection with a diverting stoma (table 7).

Table 7: Results from multivariable regression analyses paper II*

Outcome measure	Significant variables			Multivariable analyses	
	Variable		*Rate (%)*	aOR (95% c.i.)	p-value
Anastomotic leak	Gender				
		Female	*11/398 (2.8)*	Ref	0.012
		Male	*37/620 (6.0)*	2.43 (1.22-4.85)	
	Diverting stoma				
		Yes	*13/567 (2.3)*	Ref	<0.001
		No	*35/451 (7.8)*	3.77 (1.97-7.24)	
Reoperation	Gender				
		Female	*27/398 (6.8)*	Ref	0.009
		Male	*75/620 (12.1)*	1.85 (1.17-2.94)	
	Severe pulmonary disease				
		No	*90/973 (9.2)*	Ref	<0.001
		Yes	*12/45 (26.7)*	3.44 (1.71-6.94)	
30 days mortality	Age group				
		<65	*1/469 (0.2)*	Ref	0.013
		65-80	*3/477 (0.6)*	2.13 (0.20-22.32)	
		>80	*3/72 (4.2)*	19.99 (1.84-217.18)	
	Severe pulmonary disease				
		No	*4/973 (0.4)*	Ref	0.013
		Yes	*3/45 (6.7)*	8.41 (1.56-45.24)	
	Reoperation				
		Yes	*4/102 (3.9)*	12.42 (2.74-56.31)	0.004
		No	*3/916 (0.3)*	Ref	

*Variables included in univariable analyses: Age group, gender, WHO ECOG-score, ASA classification, severe pulmonary disease, severe cardiac disease, diabetes, weight class (BMI), operative access (open/laparoscopy), tumor level (TME/PME), preoperative radio(chemo)therapy, diverting stoma, anastomotic leak (not for analyses on anastomotic leak) and reoperation (not for analyses on reoperation).

4.2.5 Complication rates, paper II

The overall reoperation rate was 102 out of 1018 (10.0%). There was no difference in reoperation rates between the groups with and without diverting stomas, but the findings at reoperation differed. For patients without a diverting stoma the main finding at reoperation was anastomotic leak in 35 out of 47 (76.6%) patients, while anastomotic leak was the main finding at reoperation in 13 out of 51 (26.0%) patients with a diverting stoma (figure 7). Male gender (aOR 1.85) and severe pulmonary disease (aOR 3.44) were associated with increased risk of reoperation for any reason (table 7). In NORGAST, patients with a diverting stoma

were coded with main finding "miscellaneous" at reoperation in 58.8% of the cases in contrast to 12.8% of reoperations in patients without stoma. As a part of a registry quality review the electronical medical records for all patients coded with "miscellaneous" as main finding at reoperation were investigated and recategorized into more granular main findings. The review revealed that patients with a diverting stoma was reoperated due to stoma-related problems in 36.0% of the cases. Furthermore, bowel obstruction was the reason for reoperation in 18.0% of the patients with a diverting stoma compared to 6.4% in patients without diverting stomas (figure 7).

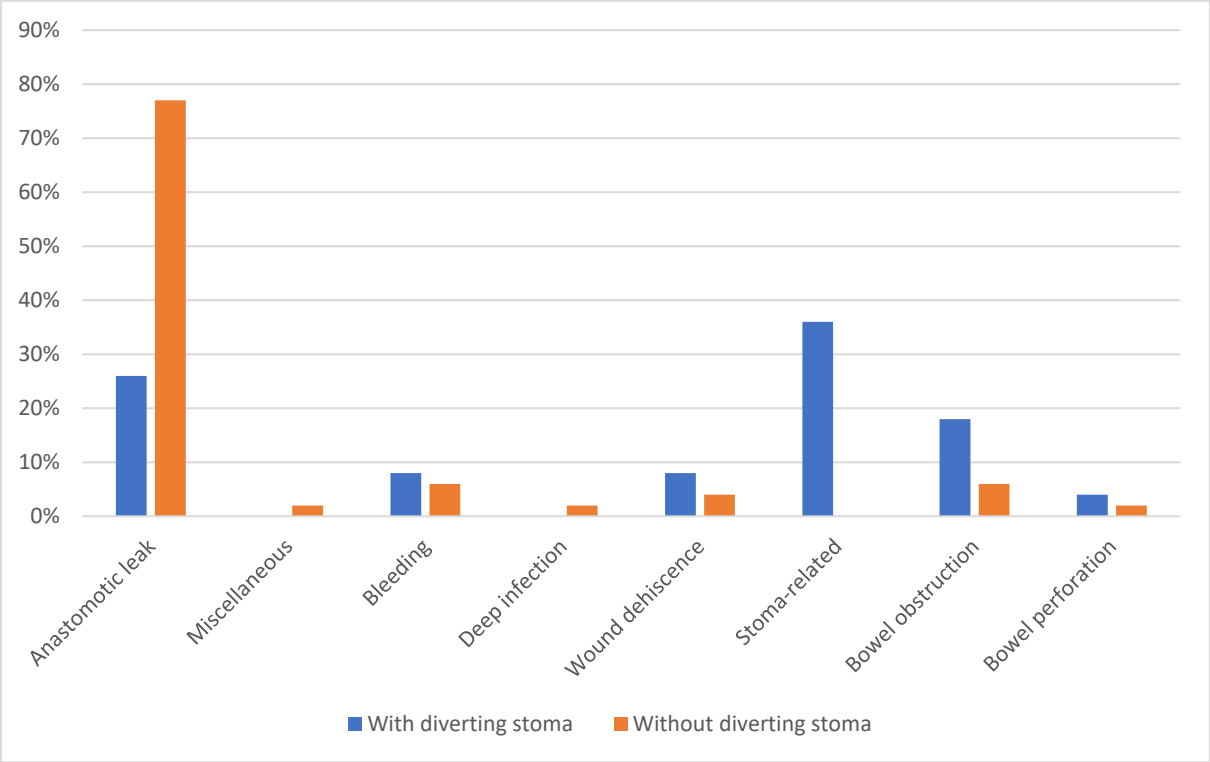


Figure 6: Main finding (%) at reoperation after anterior resection, with and without diverting stoma, paper II

The overall major complication rates, 30-day and 90-day mortality rates and rates of single organ and multi organ failure did not differ between the two groups (table 6). Median LOS was 7 days in the group with diverting stoma compared to 5 days in the group without diverting stoma ($p<0.001$).

In multivariable regression analyses, increasing age (65-80 years aOR 2.13 and >80 years aOR 19.99), severe pulmonary disease (aOR 8.41) as well as reoperation (aOR 11.36) were associated with increased 30-day mortality risk (table 7).

4.2.6 Short-term outcomes, paper III

Length of hospital stay was median 6.0 (quartiles 4.0-8.0) days following LRR (laparoscopic rectal resection including robotic assisted resections) compared to 8.0 (quartiles 7.0-13.0) days following ORR (open rectal resection) (p<0.001). There were no other significant differences in short term outcomes between the groups (table 8).

Table 8: Short-term outcomes paper III

Complications within 30 days	*All*	Laparoscopic, n= 1284	Open, n=512	p-value
30- days mortality	*10*	5 (0.4)	5 (1.0)	0.131
Accordion ≥3	*237*	155 (12.1)	82 (16.0)	0.026
Anastomotic leak*	*48 [1019]*	32[742] (4.3)	16[277] (5.8)	0.327
Reoperation	*144*	97 (7.6)	47 (9.2)	0.252
Length of stay median (quartiles)		6.0 (4.0-8.0)	8.0 (7.0-13.0)	**<0.001**
Single organ failure	*44*	27 (2.1)	17 (3.3)	0.132
Multi organ failure	*9*	5 (0.4)	4 (0.8)	0.288
Histopathological results				
CRM+**	*83*	51 (4.7)	32 (6.9)	0.079
DRM+***	*9*	7 (0.7)	2 (0.4)	0.619
N. lymph nodes median (quartiles)		15.0 (12.0-20.0)	14.0 (12.0-19.0)	0.164

* Anastomotic leak rate calculated only for patients with anastomosis. Number of patients having received anastomosis in brackets.

** Circumferential resection margin. Missing values in this variable: 240

*** Distal resection margin. Missing values in this variable: 265

Numbers in parenthesis: percentages unless specified otherwise

Multivariable regression analyses did not reveal any difference in risk of major complications, reoperations or 30-day mortality between LRR or ORR (table 9). Male gender, severe pulmonary disease, severe cardiac disease and BMI >30 was associated with increased risk of major complications (table 9). Age >80 years and ECOG-score 2-4 was associated with increased 30-day mortality risk (table 9). Male gender and severe pulmonary disease were associated with increased risk of reoperation within 30 days whereas APR compared to LAR and Hartmann lowered the risk of reoperation (table 9).

Table 9: Results from multivariable regression analyses paper III*

Outcome measure	Significant variables			Multivariable analyses	
	Variable		*Rate (%)*	aOR (95% c.i.)	p-value
Major complications					
	Intention-to-treat				
		Open access	*82/512 (16.0)*	1.27 (0.93-1.72)	0.134
		Laparoscopy	*155/1284 (12.1)*	Ref	
	Gender				
		Female	*63/688 (9.2)*	Ref	<0.001
		Male	*174/1108 (15.7)*	1.75 (1.27-2.41)	
	Severe pulmonary disease				
		Yes	*28/237 (11.8)*	2.91 (1.73-4.90)	<0.001
		No	*209/1559 (3.5)*	Ref	
	Severe cardiac disease				
		Yes	*33/237 (13.9)*	1.98 (1.23-3.18)	0.005
		No	*86/1559 (5.5)*	Ref	
	Weight (BMI)				
		<18.5	*4/40 (10.0)*	1.04 (0.35-3.11)	0.014
		18.5-25	*73/730 (10.0)*	Ref	
		25-30	*96/678 (14.2)*	1.38 (0.99-1.92)	
		>30	*54/297 (18.2)*	1.88 (1.27-2.78)	
Reoperations					
	Intention-to-treat				
		Open access	*47/512 (9.2)*	1.17 (0.80-1.69)	0.252
		Laparoscopy	*97/1284 (7.6)*	Ref	
	Gender				
		Female	*36/688 (5.2)*	Ref	<0.001
		Male	*108/1108 (9.7)*	1.95 (1.32-2.89)	
	Severe pulmonary disease				
		Yes	*19/144 (13.2)*	3.68 (2.11-6.42)	<0.001
		No	*64/1652 (3.9)*	Ref	
	Operative technique				
		LAR**	*102/1017 (10.0)*	Ref	<0.001
		Hartmann	*13/180 (7.2)*	0.14 (0.34-1.16)	
		APR***	*29/599 (4.8)*	0.45 (0.29-0.69)	
30-day mortality					
	Intention-to-treat				
		Open access	*5/512 (1.0)*	1.89 (0.49-7.25)	0.131
		Laparoscopy	*5/1284 (0.4)*	Ref	
	Age group				
		<65	*1/714 (0.1)*	Ref	<0.001
		65-80	*4/866 (0.5)*	2.16 (0.22-20.99)	
		>80	*5/216 (2.3)*	10.50 (1.15-96.06)	
	WHO-ECOG				
		0-1	*6/1667 (0.4)*	Ref	<0.001
		2-4	*4/113 (3.5)*	7.29 (1.18-29.29)	

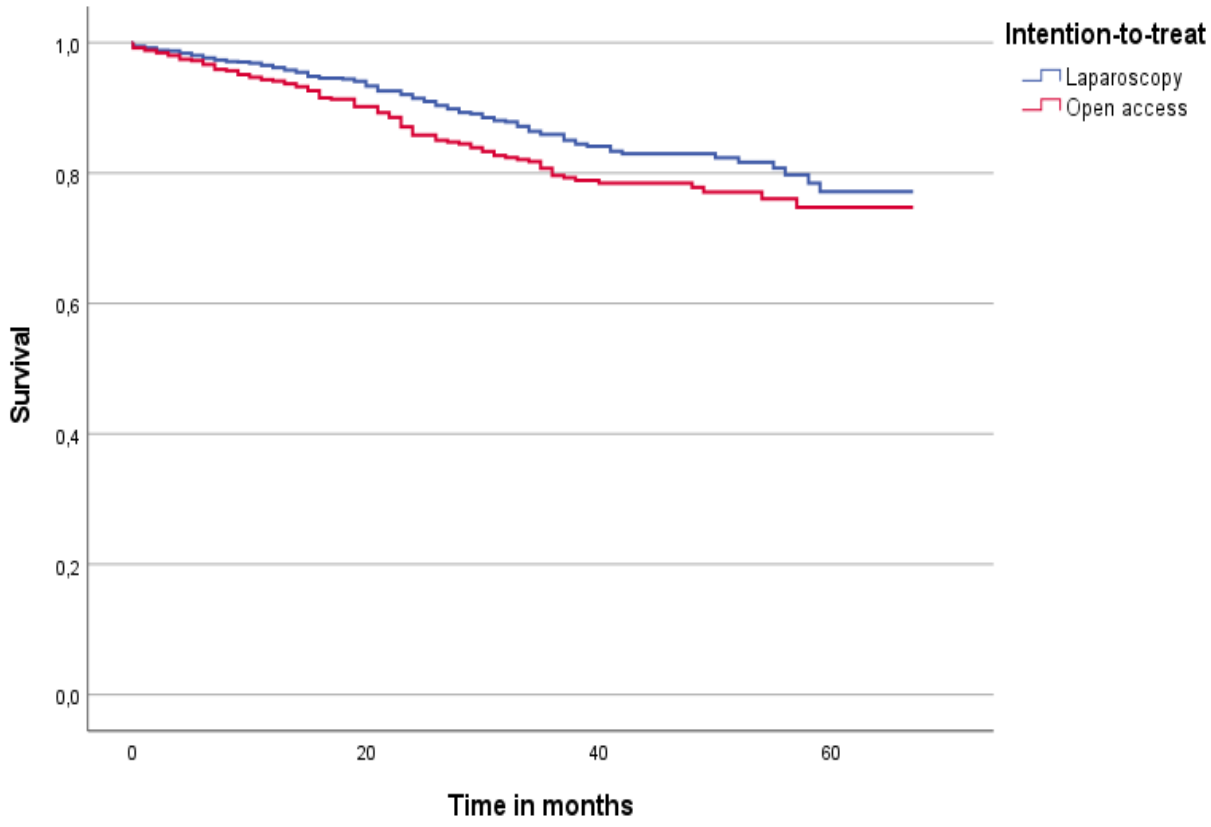
* Variables included in univariable analyses: Age group, gender, WHO ECOG score, ASA classification, severe pulmonary disease, severe cardiac disease, diabetes, weight class (BMI), operative technique, access (laparoscopy/open access), tumor level measured by rigid proctoscope (low, mid-level and high tumors) and preoperative radiochemotherapy.
**LAR; Low anterior resection
** APR: Abdominoperineal resection

4.2.7 Histopathological results, paper II

No group difference in rates of positive circumferential and distal resection margin nor in the number of harvested lymph nodes were found (table 8).

4.3 Long-term overall survival, paper III

The unadjusted overall 5-year survival was 77.1% following LRR compared to 74.8% following ORR, with a significantly lower survival after comparing the two with the log rank test (p=0.015) (figure 8). For stage 1-3 the 5-year survival was 80% following LRR compared to 83% following ORR, and there was no difference with the log rank test (p=0.670). Multivariable Cox regression analyses including clinical cancer stage, gender and age as covariates showed however no significant difference in HR between LRR and ORR (p=0.175). Cancer stage 3 and 4 (aHR 1.70, 95% c.i. 1.02-3.12 and aHR 5.77, 95% c.i. 3.32-10.04 respectively, p<0.001) as well as increasing age (age >80 years compared to <65 years aHR 5.37, 95% c.i. 3.39-8.50, p<0.001) were associated with increased long term mortality hazard.



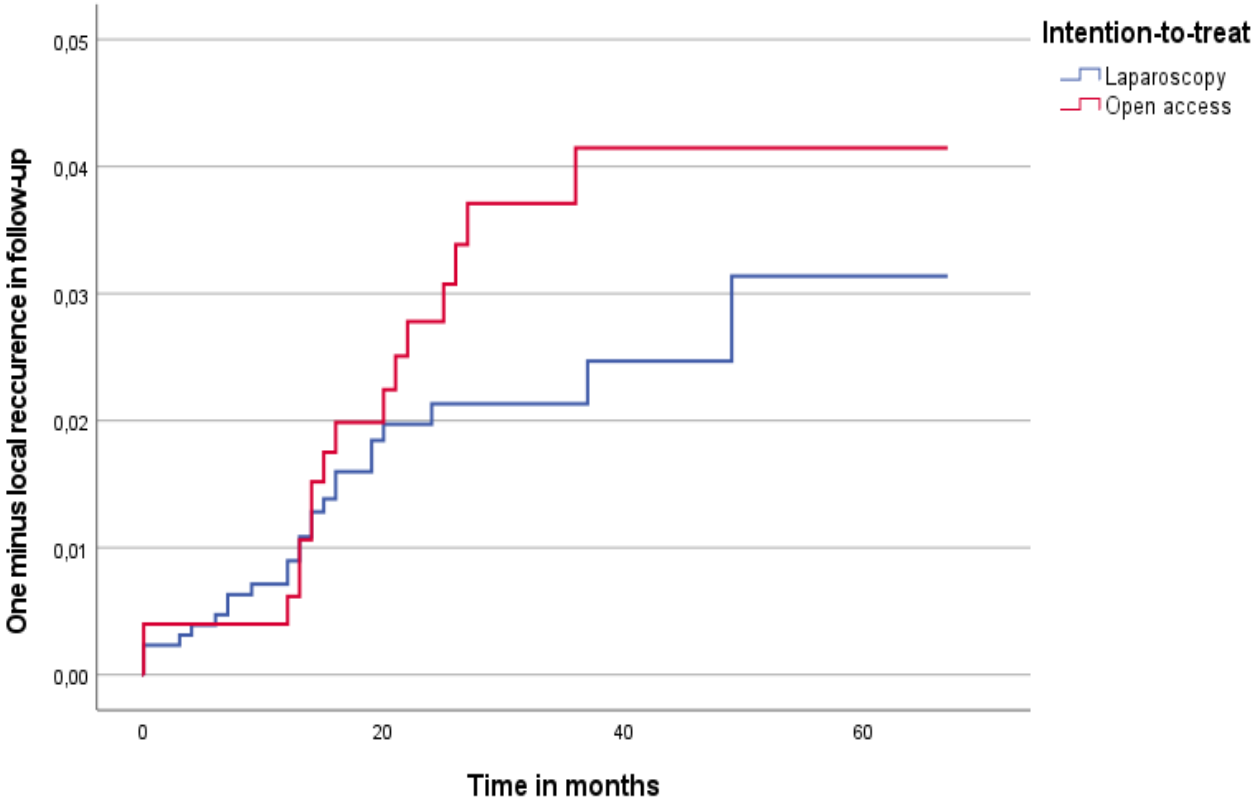
Numbers at risk:

Laparoscopy:	1284	1178	779	439	240	135	53
Open access:	512	477	390	284	180	102	40

Figur 7: Kaplan Meier 5-year survival curves

4.4 Local recurrence rates, paper III

The 5-year rates of local recurrence were 3.1% following LRR and 4.1% following ORR, and there was no difference with the log rank test (p=0.249) (figure 9). Multivariable Cox regression analyses with cancer stage, age and gender as covariate revealed no significant difference between the two groups for any of the covariates.



Numbers at risk:

Laparoscopy:	1280	1169	764	431	236	134	53
Open access:	500	467	378	274	175	98	38

Figur 8: Kaplan Meier analyses estimates of local recurrence probability curves

5 Discussion

5.1 Summary of results

This study is based on compound data from two national quality registries covering the surgical and oncological quality of rectal cancer treatment in an unselected patient population, and reflects national daily practice and true long-term results following rectal resection outside the strict frame of an RCT. The results demonstrate non-inferior results regarding overall survival, local recurrence of disease, oncological quality and short-term outcomes as well as shorter hospital stay after laparoscopic compared to open rectal resection. Conversion rate was lower with robotic assistance compared to standard laparoscopy, and conversion to open access surgery was associated with higher rates of major complications, longer hospital stay and unfavorable histopathological results. Further, reoperation for anastomotic leak was less frequent in patients with a diverting stoma. However, diverting stomas did not affect the overall reoperation rate, mortality or morbidity within the first 30 postoperative days. The latter result has to the authors knowledge not been shown in previous studies.

5.2 Study results and previous research

Rectal cancer surgery has undergone significant changes during the last decades from the introduction of TME to minimally invasive surgery with laparoscopy, robotic assisted surgery and other approaches such as TaTME. The development in treatment options has led to significantly increased survival, as well as mitigating the morbidity following the treatment. Introduction of minimal invasive surgery has improved postoperative outcome regarding complications such as surgical site infections (67), postoperative pain, development of incisional hernias and scarring is more frequent following open than laparoscopic surgery (68–70). Laparoscopic rectal cancer surgery has been implemented widespread throughout the world, however there is still a debate on whether the oncological quality, long-term survival and recurrence after laparoscopic rectal resections is comparable to open resections. Multiple studies have been conducted to assess the results, but nevertheless a recent review (71) summarizing important studies concluded that the non-inferiority of laparoscopic as opposed to open resection in terms of pathological outcomes, local recurrence rates and other long-term outcomes remains to be proven.

5.2.1 Short-term results

Rates of major complications, 30-day mortality, reoperations and anastomotic leak did not differ between the study groups ORR/LRR or RR/LR, which is in line with other large studies

(33,34,38,39,72,73). While some studies have used standardized complication scores like Accordion grading score (74) or Clavien-Dindo score (75), other studies recorded complications according to custom definitions which vary greatly and make direct comparison difficult. A review of 8 studies including 592 patients undergoing laparoscopic or robotic assisted LAR showed that the overall complication rate was significantly lower in the RR group compared to LR (76); however, the definition of complications differed between the included studies. In comparison, there were no differences in complication rates between RR and LR in the ROLARR trial comprising 461 patients (39). The overall rate of major complications in the present study was low, as almost 9 out of 10 patients went through elective rectal cancer surgery without any major complication.

Conversion to open access was followed by higher rates of major complications, reoperations, longer LOS, higher rates of positive CRM and tumor-near bowel-perforation. Higher rates of complications have been associated with conversion of laparoscopic colon cancer resections in several studies (32,33,75,77,78). In a study with prospectively collected data of 470 patients who underwent laparoscopic colorectal resections including 192 rectal resections, postoperative complication rates were significantly higher for patients who experienced conversion to open access, with a rate of 56.1% versus 16.8% when resections were completed laparoscopically (72). This finding is supported by the present study, although the difference in complication rates was less profound.

5.2.2 Conversion

The conversion rate of LRR has been a concern, as the CLASICC study showed inferior results in terms of increased complication rates and even worsened survival rates (34,79). While the conversion rate in some older studies were above 15% (33,34,80), the more recent studies report conversion rates between 1 and 12% (39,81,82). As the intention-to-treat analysis presented in paper III in the present study failed to show any inferior results following LRR as opposed to ORR, the risk of conversion should not be used as an argument against laparoscopic access for rectal cancer surgery. Results from paper I in this study demonstrates that RR lowers conversion rates compared to LR. The latter results are corroborated by data from a recent meta-analysis of RCTs and propensity score matched studies (37) as well as a large single center study on 600 patients (38), both showing lower conversion rates with robotic assistance compared to conventional laparoscopy in rectal cancer patients (37,38). In contrast, the large international multi-center ROLARR trial found

no difference in conversion rates between RR and LR (39). However, according to a post hoc multi-level logistic regression analysis taking into account the participating surgeon's experience with robotic surgery, the lack of difference in conversion rates between the two techniques in this multi-center trial could be explained by a learning effect (83).

A conversion rate of 2.1% with RR and 9.6% with LR is generally low compared to other large studies on both laparoscopic and robotic rectal resections, where reported rates vary between 5.0 and 8.1% for RR and 12.2 and 15.4% for LR (37–39). This could indicate that the operating surgeons in the present study had a high level of experience with both robotic assisted and laparoscopic techniques.

In paper I male gender, BMI>30 and severe cardiac disease were identified as risk factors associated with conversion to open surgery, which is in line with other studies (38,84,85). In a study by Crippa et al (38), robotic surgery was associated with lower conversion rate in obese patients. From paper I in the present study, the conversion rate was especially high for males with BMI>30 who underwent LR, and the risk for conversion in this group was significantly lower with robotic assistance. This indicates that robotic assistance aids in completing surgery laparoscopically especially in the more challenging obese patients combined with a narrow male pelvis. The finding of severe cardiac disease as an independent risk factor for conversion has to our knowledge not been addressed in the literature. The data available for this study do not provide further information to elaborate this finding.

5.2.3 Oncological quality

Histopathological assessment included CRM, DRM and number of retrieved lymph nodes in the specimen. Unfortunately, there was no available information in data received from The Colorectal Cancer Registry on completeness of mesorectal dissection, which is a key quality measure for assessing the histopathological result following rectal cancer surgery. Total number of lymph nodes is also an important histopathological result following colorectal surgery (86). Results from paper I in the present study showed significantly lower numbers of harvested lymph nodes in the RR group compared with the LR group. However, subgroup analysis indicated that this was related to local hospital or laboratory differences rather than between RR and LR, as there was no difference in number of retrieved lymph nodes after LR and RR in hospitals operating with both methods. Large differences between pathology laboratories in lymph node retrieval have previously been shown in other studies (87,88). In the ROLARR trial, mean number of lymph nodes retrieved by robotic resections were 24.1

compared to 23.2 for laparoscopic resections (39). In the COLORII trial the median number of lymph nodes retrieved was 13 for the laparoscopic resections (33), which compares well with the present study.

The overall positive CRM was 4.6% in the present study, which is lower than both the COLORII trial (33) (10.0% for LRR and 10.0% for ORR) and the ROLARR trial (39) (6.3% for LR and 5.1% for RR). In paper I, positive CRM was more frequent in converted cases, with low tumors and if APR was performed. Despite a higher proportion of APR and lower tumors in the RR group, no difference was seen regarding positive CRM between RR and LR. This could indicate that robotic assistance reduces the risk for involved CRM in patients operated with APR. In the present study the reason for conversion was not recorded. In a review (89) of 18 studies on colorectal cancer patients, 3 studies on rectal cancer patients stated that the most common reasons for conversion were advanced tumors, obesity, narrow pelvis and adhesions. The higher rates of positive CRM in specimens from converted procedures could reflect difficult laparoscopic dissection where conversion to open access enabled to finalize the procedure but could not undo the damage caused by suboptimal dissection.

5.2.4 Diverting stomas

The current evidence of the benefits of diverting stomas following rectal resection is unclear, and studies report diverging results. Paper II in this study demonstrated that reoperation for anastomotic leak within 30 days after anterior resection was significantly less frequent in patients with a diverting stoma. However, stoma diversion did not affect the overall reoperation rate, mortality or morbidity. Reoperation was associated with increased mortality irrespective of intraoperative finding, and the total burden of morbidity and mortality within 30 days were similar for patients with and without a diverting stoma.

A recent meta-analysis (56) showed lower anastomotic leak rates and reoperation rates with diverting stomas compared to no stomas, but the diagnostic criteria of leak and time to diagnosis varied in the included studies. A Swedish registry study (54) of 1442 patients who underwent anterior resection showed that late presenting leaks were associated with diverting stomas, and that stoma formation did not alter the overall leak rate. As many as 50% of the leaks were diagnosed after discharge, and about half of these patients needed relaparotomy. A Dutch multicenter study showed that half of the late diagnosed never heal (90). Several studies suggest that diverting stomas do not have a protective effect on late diagnosed leaks,

and reoperation rate and permanent stoma rate seems to be high also after late diagnosed leaks (54,90,91). The functional results following anastomotic leak are inferior (51,53), but it is not known whether the severity of dysfunction differs after early and late discovered leaks. A Japanese study on 1903 patients who underwent LAR showed that formation of a diverting stoma did not protect against late diagnosed leaks, and that permanent stoma rate was higher among patients with late diagnosed leaks compared to those with early diagnosed leaks (92).

Although diverting stomas apparently have a protective effect against early diagnosed leaks, several studies highlight the less favorable consequences of stoma formation (57–59). A temporary stoma will in most cases lead to longer hospital stay and require a second operation and hospital stay for stoma closure. Additionally, patients may experience stoma leak, parastomal hernias, skin problems, dehydration, kidney failure and electrolyte deficiency which may require additional hospital visits.

The results from paper II in the present study emphasize the question whether patients undergoing anterior resection derive any benefit from formation of a diverting stoma and if so, how to select these patients. As low tumor level did not represent a significant risk factor for anastomotic leak, the recommendation of diverting stoma formation for anastomosis level <7 cm from anal verge can be challenged. To explore this issue further a long-term study on outcomes after anterior resection with and without diverting stomas is warranted, assessing both early and late diagnosed anastomotic leaks, long-term overall complication rates, permanent stoma rates and total length of hospital stay. A Norwegian multicenter trial, the Norwegian Stoma Trial (93), exploring some of these issues has recently started enrolling patients. Furthermore, the ongoing Dutch IMARI multicenter trial will explore the one-year anastomotic integrity rate before and after the introduction of a multi-interventional program aiming to reduce anastomotic leak rate (94). In this study, the impact of diverting stomas will also be accounted for.

5.2.5 Long-term results

Only a few previous studies have explored long-term survival, oncological results and complication rates following laparoscopic and open resection for rectal cancer. The CLASICC (79) trial was the first RCT comparing laparoscopic to open resection in 794 colorectal cancer patients, of whom more than half of the patients underwent surgery for rectal cancer. No difference in 5-year survival between open and laparoscopic rectal resections was found in intention-to-treat analysis, but patients who underwent conversion to

open surgery had significantly reduced overall 5-year survival (79). Patients that underwent anterior resection had higher rates of CRM positivity following LRR with 12% compared to 6% in the ORR group, although not statistically significant. Both 5-year local recurrence rate (10.1%) and distant recurrence rate (20.9%) did not differ between the groups. However, the conversion rate for rectal procedures was as high as 34%, and the CLASICC study has been criticized for being performed by many surgeons inexperienced with laparoscopic technique, as the only requirement was that participating surgeons should have had undertaken at least 20 laparoscopic colorectal resections prior to the study. This is supported by the steady decline in overall conversions from initially 38% to 16% at the end of the inclusion period (34), indicating that the results from the CLASICC study may be affected by surgeons' learning curve in laparoscopic surgery.

The later COLORII study (73), a randomized controlled trial with 1044 included rectal cancer patients, showed comparable survival rates for LRR compared to ORR and with a local recurrence rate of 5.0% in both groups. In this study conversion rate was 17% (33), but with no presented subgroup analysis on outcome after conversion. Nevertheless, intention-to-treat analysis revealed no difference in complication rates, completeness of mesorectum, number of harvested lymph nodes or CRM positivity between the groups (33). Also, in the COREAN (81) trial which included 340 patients who had undergone neoadjuvant radiochemotherapy, no difference in CRM positivity or completeness of mesorectum was found between LRR or ORR, and with similar 3-year survival. The 10-year results have recently been published, still with no difference in neither disease-free nor overall survival, and the authors concluded that laparoscopic procedure was non-inferior to open procedure.

In contrast the ALaCaRT study (35), a randomized multi-center study including 575 patients with T1-T3 rectal cancer, failed to establish non-inferiority for LRR regarding completeness of mesorectum, CRM and DRM, although there were no significant differences between the open and laparoscopic group. At a median follow-up of two years there were no difference in disease-free survival or local recurrence between LRR and ORR (95). Similar results were found in the American ACOSOG-study (82,96), which also concluded that non-inferiority for LRR could not be established.

Despite some studies have been unable to prove non-inferiority for laparoscopic rectal resections compared to open, a recent meta-analysis (97) of 12 randomized controlled trials comparing LRR and ORR in 3709 patients showed similar 5-year disease-free survival but

significantly better overall survival after LRR. The present study supports the findings of non-inferiority of LRR compared to ORR.

5.3 Limitations

There are some limitations to this study. The completeness of the mesorectal fascia is an important histopathological quality measure (98,99), but this variable was not available from the Norwegian Colorectal Cancer Registry. Another limitation is that NORGAST is a newly established registry with low national coverage rates during the first years of inclusion, however in-hospital coverage was high with low risk for in-hospital selection bias. During the study period total coverage in NORGAST compared to The Colorectal Cancer Registry was above 60%, which is acceptable.

Furthermore, it is possible that surgeons performing robotic rectal resections are those who previously had developed high surgical skills in conventional laparoscopy. However, rectal cancer surgery in Norway has been centralized before the introduction of conventional laparoscopic rectal resection, and the same surgeons are performing LR and RR at centers offering both techniques. The higher conversion rate in LR also in these centers makes this bias unlikely.

As with all observational studies, variables that were not registered could have confounding effects. Some baseline differences were observed between the study groups, and various methods were used to adjust for possible bias. Regression analyses with multivariable regression modelling was performed to address potential bias from baseline differences. Stratified analyses on hospital level were done in paper I to detect whether conversion rate was dependent on robot system accessibility, and results showed significantly higher conversion rates with LR also in hospitals with access to such operating systems. Furthermore, propensity score matching was also performed to address potential treatment assignment bias in paper I. Cox regression analyses was used to adjust survival rates for important study group differences such as cancer stage, age and gender. Some of the variables included for analyses had missing values that potentially could induce confounding effects. Missing values was addressed by MCAR analyses (missing completely at random), and results showed that the missing values were missing completely at random hence the variable was fit to include for further analyses. In paper I and paper II missing values was not included in baseline characteristics tables, this has been included in paper III and in the thesis.

5.4 Methodological challenges

5.4.1 Observational studies

Observational studies from big data often provide large sample sizes, is cost-effective and not very time consuming compared to designing an interventional study. With observational study designs there are limitations that needs to be addressed. The benefits of randomization to allocate risk factors evenly through the study groups are missing, and causal inference and effects are difficult to prove. Possible effects of confounding and bias must be accounted for. The major challenges with cohort studies would be the following:

1) Selection bias – there is some systematic difference between the study groups that might affect the outcome

2) Confounding – possible factors that differs between the groups and that might affect the outcome. A big issue is that there might be "hidden" factors that we have not been able to control

3) Loss-to-follow-up – bias introduced due to loss-to-follow-up, in this study non-random missing data

The lack of randomization makes causal inference and finding of a causal relationship between the treatment/exposure and the observed outcomes difficult. In randomized controlled trials the random allocation of subjects to different study groups ensures that factors (confounders) that might influence study outcomes are evenly distributed throughout the study groups. In this case a direct causal relationship between the outcome and intervention can be found, as the outcome should not be influenced by confounding factors.

Randomized controlled trials are not always possible to conduct. For the problem to be studied or question asked, there might be ethical issues that complicates the RCT as a study design, the RCT might not be feasible to conduct (very rare condition, very expensive trial etc.), or it might be a factor of time (the question asked needs some quick answers). In this case large databases can offer information for observational studies, either retrospective or prospective. If the data quality is good and the data is managed correctly, the observational study might be fitted to answer questions of causality. Observational studies can also show clear associations between exposures and outcomes, forming hypotheses and foundation for RCTs aimed at answering causality.

Target trial emulation is the application of design principles from randomized trials to the analysis of observational data, and the process is explained by Hernan and Robins in 2016(100). Target trial emulation will then improve the data and make causal inference possible. An outline of a target trial protocol published in New England Journal of Medicine(101) suggests 7 important components in the target trial, and how the observational study data can be as close to an RCT as possible. The treatment assignment is one important component. To emulate random assignment all possible confounders need to be adjusted for, and possible strategies are matching, stratification, regression, standardization or inverse probability weighting(100). Other components in the protocol are;

1) Eligibility criteria: The same criteria should apply for the observational study as for an RCT. This means there needs to be clear inclusion and exclusion criteria for the study

2) Treatment strategies: There needs to be a clear definition of what intervention the study group(s) will receive, together with a date of therapy initiation

3) Treatment assignment: Described above

4) Outcomes: What outcome will be compared among the intervention groups? How will this be measured, and when?

5) Follow-up: How long will eligible persons in the study be followed.? Loss to follow-up needs to be registered.

6) Causal estimand/causal contrast of interest: The causal effect of interest needs to be defined, and in an RCT this is often the intention-to-treat-effect or per-protocol-effect. This should be the effect of interest also in the observational target trial.

7) Statistical analysis: How will the causal contrast be estimated? Often this is done by intention-to-treat analyses, and by adjusting for preassignment and postassignment confounders.

In our study all of the above components have been implemented in the study design, and following would be the outline of a target-trial protocol for our study:

Protocol component	Description
Eligibility criteria	Patients operated for rectal adenocarcinoma between January 1st 2014 and December 31st 2018
Treatment strategies	1. Open access rectal resection 2. Laparoscopic rectal resection 3. Robotic assisted laparoscopic rectal resection
Treatment assignment	Eligible persons will be assigned to one strategy, and they will be aware of which strategy they are assigned to. Random treatment assignment will be emulated through adjusting for confounders by regression analyses and propensity score matching
Outcomes	5-year survival rates, 5-year local recurrence rates, anastomotic leak rates, 30-day postoperative complication rates, histopathological results
Follow-up	Eligible persons will be followed from treatment assignment until death, loss-to-follow-up or administrative end of follow-up, whichever comes first. Loss-to-follow-up would be that the person no longer is to be found in the register (missing value).
Causal estimand	We are interested in intention-to-treat effects
Statistical analysis	The intention-to-treat-effects are measured by intention-to-treat analyses. To adjust for confounding multivariable regression analyses are done, and to adjust for possible treatment assignment bias propensity score matching is done.

5.4.2 Data quality

The data used for observational studies needs to have a certain quality, and there are clear measures defined for assessment. Several data quality dimensions have been described for evaluating big data, and in a recent review(102) 14 data quality dimensions was identified. In Norway the medical national quality registers needs to meet criteria set by the Directory of Health and they are managed by the National Service center for Medical Quality Registries.

This center is responsible for evaluating the registry quality, including data quality which is measured by the following data dimensions; relevance, correctness, completeness, reliability, actuality, and comparability.

NORGAST was accepted as a national quality registry in 2015, and the registry produces an annual report that includes an assessment of the data quality. For 2018(63) the registry reported that 30 of all 32 eligible hospitals reported to the register, with varying degree of completeness. Completeness is assessed with comparison to data from NPR (Norwegian Patient Record), which is the most accurate patient registry in Norway. For colorectal resection the registry reports that 63.3% of the resections were registered, and for rectal resections 73.9% of the resections were registered. The correctness and reliability of variables in NORGAST is high, much due to the digital reporting system in which certain limitations and warnings for unusual combinations exist. The Colorectal Cancer Registry has varying degree of completeness, but with many overlapping variables with NORGAST. In this way correctness and reliability could be controlled. For a few cases there was inconsistency, and for some of these cases there was sometimes possible to find the correct variable input by further analyzing other variables, and in other cases the variable was regarded missing. The registries do not comment actuality and comparability, but data is registered consecutively, and summaries are available for all participating hospitals for quality control.

In the present study, specific analyses were performed to assess whether missing data was missing at random, or if there was systematic data missing. The analysis showed that the missing data was missing completely at random, and missing values could then be excluded from analyses were there was missing data.

The overall quality of the data used in this study is considered to be good although good the completeness in some of the included years was low. This could lead to selection bias, treatment assignment bias and confounding. For that reason, propensity score matching and regression analyses were done in order to minimize this type of bias.

5.4.3 Confounding

Confounding is one of the major threats to observational studies. Confounding variables/factors are variables other than the exposure/intervention that can affect the outcome, and they can be related to the exposure/intervention. In this study confounders would be variables or factors with the patients that affect the postoperative outcomes *other* than what type of operation they receive. The presence of confounders can, if not accounted for, introduce bias and false conclusions.
Several strategies for dealing with confounding have been used in observational studies. Jepsen et. al. reviewed in 2004(103) challenges with observational studies and some of the common strategies for handling bias and confounding. There are two main ways to reduce confounding; 1) to prevent it during the design phase by restriction or matching or 2) adjustments in the statistical analyses by stratification or multivariable techniques. These methods require that the confounders are known and measured. Following is a brief summary of different techniques for dealing with confounding in observational studies:

• Restriction: By this method confounding is reduced by restricting the study population according to the confounding variable. This means if age seems to affect the outcome, the study population could be restricted to only a defined age group. Results from a restricted study population would not be generalizable to the population that were not part of the study.
• Matching: With this strategy, subjects from the study groups with similar confounder values are matched for comparison. With increasing number of confounder variables to match, this process can be demanding. It is commonly used for case-control studies.
• Stratified analyses: Stratification means to divide the study subjects into subgroups/strata which share a specific characteristic, and the intervention effect is estimated in each strata. The Mantel-Haenszel formula is commonly used in stratification to calculate stratum-specific risk ratio or odds ratio, and this can be compared with the unstratified risk ratio or odds ratio. The limitation with stratification comes when there is more than one confounder, and it also requires a relatively large study population.
• Multivariable modelling: Multivariable models have the possibility to adjust for multiple confounders and estimate the effect of each one. Multivariable regression models are commonly used in observational studies, and examples are linear regression, logistic regression and cox proportion hazard models. With these models all baseline characteristics

can be entered and the model will statistically control for confounders. One of the challenges is to identify, measure and include all possible confounders.

• Propensity score: The propensity score is the probability of treatment or exposure assignment due to baseline characteristics, which includes all confounders. There are different propensity score techniques to minimize confounding, and matching is commonly used. With propensity score matching, study subjects in each group are given a score (probability to receive the treatment/exposure given their measured baseline characteristics), and they are matched to a subject from the other group with a similar score. Analyses can be performed on the matched groups.

In the present study differences in some of the baseline characteristics within the study groups were observed. Several characteristics were measured; age, gender, BMI, ASA-score, ECOG-score, severe pulmonary disease, severe cardiac disease, diabetes, preoperative radio(chemo)therapy and tumor level in rectum (low, mid and high rectal cancers) to mention some. We also had available information on operative technique, and several postoperative outcome measures. To minimize confounding from the baseline variables a multivariable regression model was build. Univariable binary logistic analyses was done on all baseline variables, and all variables with a p-value <0,2 were included in the final multivariable analysis model. To minimize the effect of treatment assignment bias we did propensity score matching including all available baseline characteristics. For paper 3 a multivariable Cox regression model was build including variables that were likely to affect the outcome based on a clinical perspective.

Several measures have been undertaken to address possible bias in this study. The study cohort is comprised of data from two national quality registries with overall good data quality, and the cohort is large. Although causal relationships cannot be proven, the results from this study demonstrates associations which are corroborated by other large studies. The study demonstrates that both long-term and short-term results following laparoscopic rectal resection is non-inferior to open rectal resection, with shorter hospital stay. Robotic assistance ameliorates the conversion rates with laparoscopic resection, and conversion is associated with higher complication rates and inferior histopathological results. Diverting stomas do not lower overall reoperation rates, morbidity or mortality rates within the first 30 days postoperatively, but rates of reoperation for anastomotic leaks are lower with diverting stomas. It seems that the latter issue needs further exploration to investigate the possible

benefits of diverting stomas weighed against the burden of complications and need for a second operation.

6 Final conclusions

▪ Laparoscopic resection for rectal cancer can be performed with non-inferior short- and long-term results as compared to open access

▪ Robotic assistance lowers the conversion rates compared to standard laparoscopy in rectal cancer surgery

▪ Conversion to open access is associated with higher complication rates and inferior histopathological results in rectal cancer surgery

▪ Diverting stoma after low anterior resection for cancer reduces reoperation rates for anastomotic leak within the first 30 postoperative days, but does not lower overall reoperation rates, overall morbidity or mortality

7 Future perspectives

▪ Further research is needed to explore the total effects of diverting stomas on morbidity and permanent stoma rates, and to identify which patients (if any) could benefit from diverting stomas

▪ After establishing non-inferiority of laparoscopic and robotic surgery for rectal cancer in regards of short-term outcomes and long-term survival, it is of interest to further assess if these mini-invasive techniques affect postoperative outcomes such as sexual function, bowel function (Low Anterior Rectal Syndrom, LARS), bladder function and quality of life.

8 Errata

While working on the thesis some type errors was discovered in tables in paper II. These type-errors are corrected in tables in the thesis. Following is a list of corrected errors:

- Table 2: Laparoscopy with stoma, corrected to 9/384 (2.3%) from (3.1)
- Table 2: Tumor level 12.0-15.0 cm, without diverting stoma corrected to 225 from 22
- Table 2: Tumor level 0-11.9 cm, Total corrected to 22/493 (4.5%) from 1/11 (9.1%)
- Table 2: Tumor level 12.0-15.0 cm, Total corrected to 17/319 (5.3%) from 16/394 (4.1%)
- Table 2: Bowel perforation, total corrected to 3/93 (3.1%) from 7/97 (2.1%)
- Table 2: Finding at reoperation, stoma-related, with stoma: corrected to 18/50 (36.0%)
- Table 3: Female corrected to 11/398 from 11/389
- Table 3: Reoperation, severe pulmonary: Yes/no category switched, but numbers are correct
- Table 3: 30 days mortality, severe pulmonary disease: Yes/no category switched, but numbers are correct

None of these type-errors had any effects on the results.

Figures and Tables

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Paper I

Surgical Endoscopy
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Lower conversion rate with robotic assisted rectal resections compared with conventional laparoscopy; a national cohort study

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Abstract

Background Conversion from laparoscopic to open access colorectal surgery is associated with a poorer postoperative outcome. The aim of this study was to assess conversion rates and outcomes after standard laparoscopic rectal resection (LR) and robotic laparoscopic rectal resection (RR).

Methods A national 5-year cohort study utilizing prospectively recorded data on patients who underwent elective major laparoscopic resection for rectal cancer. Data were retrieved from the Norwegian Registry for Gastrointestinal Surgery and from the Norwegian Colorectal Cancer Registry. Primary end point was conversion rate. Secondary end points were postoperative complications within 30 days and histopathological results. Chi-square test, two-sided *T* test, and Mann–Whitney *U* test were used for univariable analyses. Both univariable and multivariable logistic regression analyses were used to analyze the relations between different predictors and outcomes, and propensity score matching was performed to address potential treatment assignment bias.

Results A total of 1284 patients were included, of whom 375 underwent RR and 909 LR. Conversion rate was 8 out of 375 (2.1%) for RR compared with 87 out of 909 (9.6%) for LR ($p < 0.001$). RR was associated with reduced risk for conversion compared with LR (aOR 0.22, 95% CI 0.10–0.46). There were no other outcome differences between RR and LR. Factors associated with increased risk for conversion were male gender, severe cardiac disease and BMI > 30. Conversion was associated with higher rates of major complications (20 out of 95 (21.2%) vs 135 out of 1189 (11.4%) $p = 0.005$), reoperations (13 out of 95 (13.7%) vs 93 out of 1189 (7.1%) $p = 0.020$), and longer hospital stay (median 8 days vs 6 days, $p = 0.001$).

Conclusion Conversion rate was lower with robotic assisted rectal resections compared with conventional laparoscopy. Conversions were associated with higher rates of postoperative complications.

Keywords Robotic · Rectal resection · Conversion · Laparoscopy · Complications

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Over the last 10 years, laparoscopic rectal resection has become the preferred approach in many countries [1, 2]. While several studies have shown favorable outcomes after laparoscopic surgery for colon cancer [3–7] with reduced rates of postoperative complications, 30-day mortality, and long-term results equal to open access surgery [8–10], the results after laparoscopic rectal cancer surgery have not been unambiguously positive. Although studies demonstrate similar short- and long-term results compared to open access surgery [11, 12], unfavorable histopathological outcomes with higher rates of positive circumferential resection margins, and lower rates of complete excision of mesorectum after TME have been reported [13, 14].

Due to a narrow operative field in the pelvis and limited instrument mobility, laparoscopic surgery for rectal cancer is

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technically demanding. Studies have shown conversion rates between 12 and 30% [15–18], and a need of about 150 operations to flatten the learning curve [19]. These disadvantages may be overcome with robotic assisted laparoscopic access which offers a three-dimensional view with a stable camera, better ergonomic conditions, enhanced dexterity, and instrument articulation. This might facilitate a more precise dissection with improved specimen quality. In particular, it may also reduce the need for conversion, which is associated with higher complication rates [3, 15, 20]. While several studies have shown lower conversion rates with robotic assisted laparoscopy compared to conventional laparoscopy [16, 21, 22], this could not be confirmed in the large randomized ROLARR trial [23].

The aim of this study was to assess conversion rates after standard laparoscopic versus robotic assisted laparoscopic resections for rectal cancer, as well as postoperative complications within the first 30 days and histopathological results in a national cohort from the Norwegian registry for gastrointestinal surgery (NoRGast) [24] supplied with data from the Norwegian Colorectal Cancer Registry [25].

Materials and methods

Study population

Patients who underwent elective major resection for rectal cancer from January 1st 2014 to December 31st 2018 were identified via the Norwegian Registry for Gastrointestinal Surgery (NoRGast) [24]. Due to some delay in data registry, and also to achieve at least 6 months follow-up, latest operation date for data extraction was set to December 2018. This national quality registry was established in 2014, and includes major gastrointestinal and hepatobiliary resections. All Norwegian hospitals performing cancer resections are obliged to report data to NoRGast which records variables that might affect surgical outcome, such as pre-operative weight loss, BMI, ECOG-status, known severe pulmonary and cardiac disease as well as operative technique, and short-term postoperative outcome measures including complications, reoperations, length of hospital stay, readmissions, and mortality rates. A detailed presentation of the registry has been published previously [24].

Patients were identified in the NoRGast database based on procedure codes according to the NCSP (NOMESCO Classification Of Surgical Procedures) [26] for rectal resection with formation of anastomosis (JGB00 through JGB07), rectal resection with end colostomy (codes JGB10 and JGB11), and abdominoperineal resections (codes JGB30 through JGB36). The procedure codes were combined with diagnosis code C20 for cancer < 15 cm from the anal verge assessed with rigid proctoscope according to the International Classification of Diseases version 10 (ICD-10) [27]. Some cases were registered with cancers located from 15 cm or lower measured on rigid proctoscope, but erroneously had received the ICD-10 code C19 for rectosigmoid cancer at discharge, and these were also included. Patients with tumors other than adenocarcinoma were excluded. Emergency procedures and all procedures commenced by open access, as well as transanal total mesorectal excisions (taTME) were also excluded.

Data were linked to the Norwegian Colorectal Cancer Registry [25] for information on preoperative work-up, oncologic treatment upfront surgery, histopathology of the surgical specimen, and 90 days mortality rate based on the patients' individual social security numbers.

Data quality

The coverage rate in NoRGast has increased during the study period from approximately 20% in 2014 to 75% in 2018 [28]. Variable completeness is 98–100%, much due to its web-based registration system. The Norwegian Colorectal Cancer Registry includes annually more than 90% of all patients surgically treated for rectal cancer [29]. However, this registry includes data from various sources, such as clinical reports on diagnosis and treatment, and histopathological reports. This results in some variations in variable completeness with missing data in up to 30% for some clinical variables, while variables from the histopathological reports have up to 90% completeness. However, as both registries overlap on a number of core variables, data linking results in an overall high degree of variable completeness. Patients with missing data in any variables included for analysis in this study were excluded, and number of missing values are documented in the attached tables. The manuscript was drafted in accordance to the STROBE guidelines for observational studies [30].

Statistical analysis

Data were analyzed with SPSS version 26, (IBM, Armonk, New York, USA). For univariable analyses Pearson's Chi-square test was used for categorical data, and two-sided *T* test or Mann–Whitney *U* test for continuous data. Confidence interval (CI), standard deviation or inter quartile range (IQR) were calculated as appropriate. Univariable binary logistic regression was used to calculate unadjusted odds ratios (OR) for conversion rates, major complications, reoperations, 30 days mortality, and anastomotic leaks. A stepwise backward multivariable logistic regression model was used to further analyze the relations between different predictors and outcomes, and adjusted odds ratios were reported for the final fitted models. Variables with a p value < 0.2 in univariable analyses were included in the multivariable

analyses. All significant variables were tested for two-way interaction, and significant interactions were included in further multivariable analyses. The significance level was set to $p < 0.05$.

A linear regression model was made with the continuous variable as dependent variable, RR or LR as fixed factors and hospitals performing RR as covariate.

To address potential treatment assignment bias, a propensity score matching was performed by including all available baseline variables. The matched sets were included in a new set of regression analyses. Match tolerance was set to 0.01, and sampling was done without replacement. Robotic assistance was used as group indicator, and baseline characteristics (age, gender, BMI, severe cardiac and pulmonary disease, diabetes, ASA-score, ECOG-score, and diabetes) were used as predictors.

Age was categorized into three groups (low < 65, mid 65–80, and high > 80). ASA-scores were grouped into low ASA-scores (scores 1–2) and high ASA-scores (scores 3–4). ECOG-scores were dichotomized into low ECOG-score (0–1) and high ECOG-score (2–4). Severe pulmonary disease was defined as having FEV1 < 50% or a vital capacity < 60% of predicted values. Severe cardiac disease was defined as NYHA classification 3–4, or severe arrythmia requiring mechanical support. Complications were recorded according to the Accordion grading system [31]. Major complications were defined as Accordion grade of 3 or higher. Briefly, Accordion grade 3 is defined as any percutaneous, angiographic or endoscopic intervention, Accordion 4 is defined as intervention in general anesthesia or single-organ failure, Accordion 5 is defined as intervention in general anesthesia plus single- or multi-organ failure. Accordion 6 is death within 30 days postoperatively. Anastomotic leak was defined as a leak requiring reoperation (grade C leaks) [32]. Only resections with formation of an anastomosis were included in analysis of anastomotic leak. Weight was classified by body mass index (BMI), and patients were grouped into 4 BMI-classes [33]; [< 18.5] [18.5–25] [25–30] [> 30]. Positive circumferential resection margin (positive CRM) was defined as CRM ≤ 1 mm, and positive distal resection margin (positive DRM) as DRM ≤ 1 mm.

Results

Patients

A total of 2302 patients were recorded in NoRGast with an NCSP procedural code for rectal resection in the study period. After excluding patients with other tumors than adenocarcinoma, those undergoing taTME, endoscopic or emergency procedures a total of 1796 patients were identified. Some 1284 had a laparoscopic procedure, of whom 909 had a conventional laparoscopic resection and 375 had a robotic assisted resection (Fig. 1). Sixteen hospitals contributed data, of which 7 performed both RR and LR. Demographical and clinical characteristics are presented in Table 1.

Conversion rates

The overall conversion rate was 95 out of 1284 patients (7.4%). In the RR group conversion rate was significantly lower as compared to the LR group, with 8 out of 375 (2.1%) and 87 out of 909 (9.6%), respectively ($p < 0.001$). Conversion rate for LR performed in hospitals using both operative techniques was 51 out of 464 (11.0%) compared to 36 out of 445 (8.1%) in hospitals using laparoscopic technique only ($p = 0.137$). In multivariable analyses, RR was associated with reduced risk for conversion with an aOR of 0.21 (95% CI 0.09–0.43) compared to LR. In addition, male gender (aOR 1.86, 95% CI. 1.14–3.06), BMI > 30 (aOR 2.64, 95% CI 1.51–4.61), and severe cardiac disease (aOR 2.16, 95% CI 1.08–4.31) were independent predictors for conversion (Table 2). The Hartmann procedure was associated with a higher conversion rate (aOR 2.88, 95% CI 1.35–6.13) than

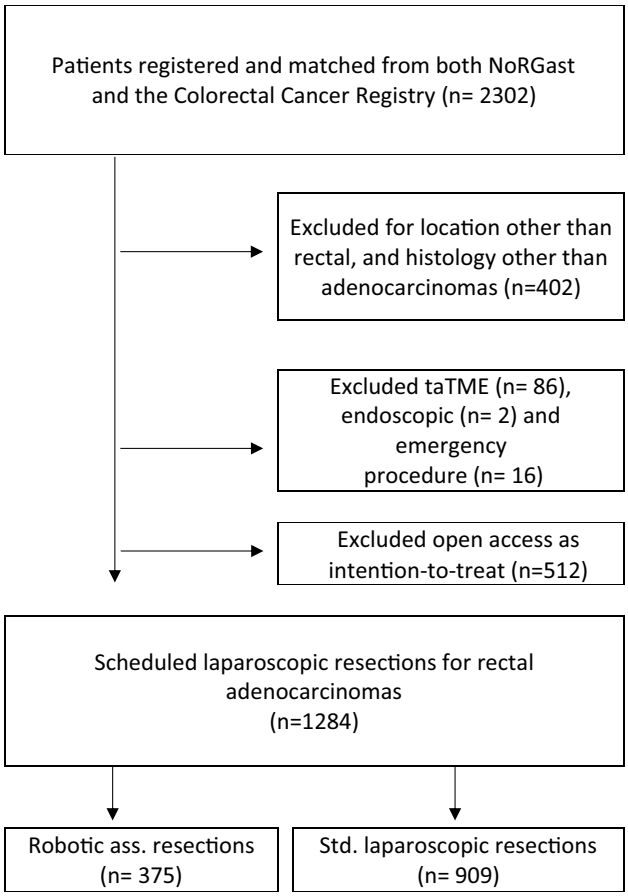

Fig. 1 Flowchart

Table 1 Baseline characteristics

	Total $n=1284$	LR $n=909$	RR $n=375$	p value*
Sex				
Male	782	551 (61)	231 (62)	0.743
Female	502	358 (39)	144 (38)	
Age, median (IQR)	69 (60–76)	69 (60–76)	69 (60–75)	0.760
BMI				
< 18.5	24	18 (2)	6 (1.7)	0.067
18.8–25	511	380 (42.4)	131 (36.1)	
25–30	496	350 (39.1)	146 (40.2)	
> 30	228	148 (16.5)	80 (22.0)	
ASA-score				
Low (1–2)	871	640 (70.4)	231 (61.6)	0.002
High (3–4)	413	269 (29.6)	144 (38.4)	
ECOG-class				
Low (0–1)	1210	854 (94.1)	356 (96.5)	0.078
High (2–4)	67	54 (5.9)	13 (3.6)	
Diabetes	134	92 (10.1)	42 (11.2)	0.565
Pulmonary disease	48	44 (4.8)	4 (1.1)	0.001
Cardiac disease	73	65 (7.2)	8 (2.1)	< 0.001
Radio(chemo) therapy	375	323 (25.5)	143 (38.1)	< 0.001
Tumor level[a]				
Low (0–5 cm)	244	159 (26.6)	85 (35.0)	0.045
Mid (5–10 cm)	332	224 (37.5)	108 (40.6)	
High (10–15 cm)	287	214 (35.8)	73 (27.3)	
Operative technique				
LAR[b]	743	552 (60.7)	191 (50.9)	0.003
APR[c]	432	280 (30.8)	152 (40.5)	
Hartmann	109	77 (8.5)	32 (8.5)	

Values in parentheses are percentages unless indicated otherwise

LR laparoscopic resections, *RR* robotic resections

*Chi-square analyses

[a]Cm from anal verge measured with rigid proctoscope

[b]Low anterior resection

[c]Abdominoperineal resection

low anterior resections (LAR), with abdominoperineal resections (APR) as reference (Table 2).

A separate analysis on the risk factors gender and BMI revealed an especially high conversion rate for male patients with BMI > 30 in the LR group (Table 3). The OR for conversion in male patients with BMI > 30 was 0.23 (95% CI 0.07–0.83) for RR with LR as reference. A total of 730 patients were included after propensity score matching, with 65 exact matches and 289 fuzzy matches. After propensity score matching, RR compared to LR (aOR 0.19, 95% CI 0.09–0.42) as well as male gender (aOR 2.44, 95% CI 1.14–5.19) remained significant predictors for conversion.

Postoperative complications

Major complications, 30-day mortality rates and reoperation rates did not differ between the LR and RR group (Table 4). The overall anastomotic leak rate was 41 out of 743 (5.5%) and did not differ between LR and RR. Rates of major complications and reoperations were higher following converted procedures compared to procedures completed laparoscopically, with complication rates of 20 out of 95 (21.1%) vs 135 out of 1189 (11.4%) ($p=0.005$) and reoperation rates of 13 out of 95 (13.7%) vs 93 out of 1189 (7.8%) ($p=0.046$).

Conversion, male gender, severe pulmonary or cardiac disease, and BMI > 30 were independent predictors for major complications in multivariable regression analysis (Table 5). After propensity score matching only male gender, severe cardiac disease, and BMI > 30 remained significant. In multivariable regression analysis of 30-day mortality only ECOG-score > 2 was found to be an independent predictor (aOR 21.10, 95% CI 3.27–136.26) $p=0.001$). For reoperation, male gender (aOR 2.25, 95% CI 1.41–3.59, $p=0.001$), severe pulmonary disease (aOR 2.74, 95% CI 1.26–5.93, $p=0.011$), and LAR as operative technique with APR as reference (aOR 2.72, 95% CI 1.64–4.53, $p<0.001$) were independent predictors in multivariable regression analyses. For anastomotic leak, only male gender was a predictor (aOR 2.44, 95% CI 1.15–5.19, $p=0.020$). All predictors from initial multivariable logistic regression analysis remained significant in propensity score matched analysis for 30-day mortality rates, reoperations, and anastomotic leak.

Length of in-hospital stay (LOS) was shorter in the RR group compared to LR; median 5 vs 6 days ($p=0.001$). Patients who underwent conversion to open access had a median LOS of 8 days compared to 6 days after procedures completed laparoscopically ($p=0.001$) (Table 4). There were, however, no differences in LOS between LR and RR in hospitals operating with both techniques.

Histopathological results

The overall rates of positive CRM and DRM were 51 out of 1090 (4.7%) and 7 out of 1075 (0.7%) and were similar in the RR and LR group (Table 4). The rate of positive CRM was higher (9 out of 88, 10.2%) following converted procedures compared to procedures completed laparoscopically (42 out of 1002, 4.2%, $p=0.010$). A higher proportion of positive CRM was seen following APR compared with other operative techniques (APR 33 out of 357, 9.2%, LAR 12 out of 636, 1.9% and Hartmann 6 out of 97, 6.2%, $p<0.001$). Further, surgery for low tumors (0–5 cm above anal verge) resulted in higher rates of positive CRM compared with

Table 2 Regression analyses of risk factors for conversion

	Conversion rate (per cent)	Univariable OR (95% CI)	*p* value	Multivariable aOR (95% CI)	*p* value
All patients	95/1284 (7.4)				
Age group					
< 65	37/503 (7.4)	Ref	0.411		
65–80	43/631 (6.8)	0.91 (0.58–4.45)			
> 80	15/150 (10.0)	1.40 (0.75–2.63)			
Sex					
Female	24/502 (4.8)	Ref	0.014	Ref	0.014
Male	71/782 (9.1)	1.98 (1.23–3.21)		1.86 (1.14–3.06)	
WHO ECOG-score					
0, 1	89/1210 (7.4)	Ref	0.974		
2, 3, 4	5/67 (7.5)	1.02 (0.39–2.59)			
ASA classification					
1–2	63/871 (7.2)	Ref	0.742		
3–4	32/413 (7.7)	1.08 (0.69–1.68)			
Severe pulmonary disease					
No	93/1236 (7.5)	Ref	0.391		
Yes	2/48 (4.2)	0.53 (0.29–2.34)			
Severe cardiac disease					
No	83/1211 (6.9)	Ref	0.003	Ref	0.029
Yes	12/73 (16.4)	2.67 (1.39–5.16)		2.16 (1.08–4.31)	
Med. Diabetes					
No	79/1150 (6.9)	Ref	0.036		
Yes	16/134 (11.9)	1.84 (1.04–3.25)			
Weight class (BMI)					
< 18.5	1/24 (4.2)	0.72 (0.09–5.54)	0.007	0.87 (0.12–6.89)	0.002
18.5–25	29/511 (5.7)	Ref		Ref	
25–30	32/496 (6.5)	1.15 (0.68–1.93)		1.08 (0.63–1.83)	
> 30	29/228 (12.7)	2.42 (1.41–4.16)		2.64 (1.51–4.61)	
Radio(chemo)therapy					
No	71/909 (7.8)	Ref	0.381		
Yes	24/375 (6.4)	0.81 (0.50–1.30)			
Operative technique					
LAR	60/743 (8.0)	1.72 (1.03–2.87)	0.012	1.66 (0.97–2.84)	0.021
Hartmann	14/109 (14.3)	2.88 (1.42–5.88)		2.88 (1.35–6.13)	
APR	21/432 (4.8)	Ref		Ref	
Robotic assistance					
No	87/909 (9.6)	Ref	< 0.001	Ref	< 0.001
Yes	8/375 (2.1)	0.21 (0.09–0.43)		0.22 (0.10–0.46)	

intermediate (5–10 cm) and high (10–15 cm) tumors, with 23 out of 206 (11.2%), 9 out of 297 (3.0%), and 5 out of 250 (2.0%), respectively ($p < 0.001$). Tumor diameter and tumor stage were not associated with higher rates of positive CRM.

A mean number of 14 lymph nodes were retrieved from the specimen in the RR group compared 18 in the LR group ($p = 0.001$). In hospitals performing both LR and RR there were no differences in lymph node retrieval between the two groups, except for one hospital where LR resulted in fewer lymph nodes as compared to RR (Table 6). ANCOVA analysis comparing mean number of lymph nodes between the RR group and the LR group correcting for hospital showed no differences between the two methods ($p = 0.550$).

Discussion

This study on a national cohort of patients who underwent laparoscopic resections for rectal cancer demonstrates that conversion rate was lower with robotic assistance compared

Table 3 Rate of conversion stratified by sex and BMI

	Conversion rate		
	RR	LR	OR[a] (95% CI)
Male (all cases)	6 out of 231 (2.6)	65 out of 551 (11.8)	$p < 0.001$*
Male, BMI > 30	3 out of 52 (5.77)	19 out of 91 (20.88)	0.23 (0.07–0.83) $p = 0.024$
Male, BMI < 30	3 out of 172 (1.74)	42 out of 451 (9.31)	0.17 (0.06–0.57) $p = 0.004$
Female (all cases)	2 out of 114 (1.4)	22 out of 358 (6.1)	$p = 0.024$*
Female, BMI > 30	0 out of 28 (0.00)	7 out of 57 (12.28)	0.12 (0.01–2.15) $p = 0.149$
Female, BMI < 30	2 out of 111 (1.80)	15 out of 297 (5.05)	0.36 (0.08–1.53) $p = 0.162$

Values in parentheses are percentages unless indicated otherwise

RR robotic resection, *LR* laparoscopic resection

[a]OR for conversion in RR with LR as reference

*Chi-square analysis

Table 4 Postoperative complications and histopathological results

	LR	RR	*p* values*	CC**	CL***	*p* values*
30-day mortality	3 (0.3)	2 (0.2)	0.592	1 (1.1)	4 (0.3)	0.280
90-day mortality	11 (1.2)	5 (1.3)	0.856	3 (3.2)	13 (1.1)	0.081
Major complications	112 (12.3)	43 (11.5)	0.669	20 (21.2)	135 (11.4)	0.005
Conversion rate	87 (9.6)	8 (2.1)	< 0.001			
Anastomotic leak	27 (4.9)	14 (7.7)	0.203	5 (8.3)	36 (5.3)	0.319
Reoperation	71 (7.8)	35 (9.3)	0.367	13 (12.3)	93 (7.8)	0.046
Tumor perforation	5 (0.6)	2 (0.6)	0.988	3 (3.8)	4 (0.4)	< 0.001
LOS[a] median (IQR)	6 (4–9)	5 (3–7)	0.001	*8* (6–12)	6 (4–8)	0.001
Single-organ failure	22 (2.4)	5 (1.3)	0.217	3 (3.2)	24 (2.0)	0.456
Multi-organ failure	3 (0.3)	2 (0.5)	0.595	2 (2.1)	3 (0.3)	0.005
Histopathological results						
	LR	RR	*p* values	CC	CL	*p* values
Positive CRM[b]	35 (4.6)	16 (4.8)	0.885	9 (10.2)	42 (4.2)	0.010
Positive DRM[c]	6 (0.8)	1 (0.3)	0.376	1 (1.1)	6 (0.6)	0.547
Median DRM[c] (IQR)	3.0 (1.8–4.0)	3.5 (2.0–4.5)	0.002	2.6 (2.0–4.0)	3.0 (2.0–4.4)	0.367
Median PRM[d] (IQR)	15.0 (11.0–20.0)	13.5 (10.0–17.0)	0.001	18.0 (12.0–23.0)	14.0 (10.3–19.0)	0.001
L.node[e] median (IQR)	16 (12–21)	13 (11–17)	0.001	16 (13–22)	15 (12–20)	0.505
Stage[f]						
1	196 (41.4)	66 (36.1)	0.486	14 (28.6)	248 (40.8)	0.135
2	121 (25.5)	38 (20.8)		11 (22.5)	148 (24.3)	
3	108 (22.8)	54 (29.5)		14 (28.6)	148 (24.3)	
4	49 (10.3)	25 (13.7)		10 (20.4)	64 (10.5)	

Values in parentheses are percentages unless indicated otherwise

LR laparoscopic resections, *RR* robotic resections

*Chi-square analyses

**Converted cases

***Completed laparoscopically

[a]LOS, In-hospital length of stay

[b]Circumferential resection margin. Missing values in this variable $n = 194$

[c]Distal resection margin, measured in centimeters. Missing values in this variable $n = 209$

[d]Proximal resection margin, measured in centimeters. Missing values in this variable $n = 280$

[e]Lymph nodes yielded

[f]Missing values in this variable $n = 627$

Table 5 Regression analyses of risk factors for major complications

	Rate (%)	Univariable		Multivariable	
		OR (95% CI)	*p* value	aOR (95% CI)	*p* value
All patients	155/1284 (12.1)				
Age group					
< 65	68/503 (13.5)	Ref	0.192		
65–80	75/631 (11.9)	0.86 (0.61–1.23)			
> 80	12/150 (8.0)	0.56 (0.29–1.06)			
Sex					
Female	43/502 (8.6)	Ref	0.002	Ref	0.009
Male	112/782 (14.3)	1.78 (1.23–2.59)		1.67 (1.14–2.44)	
WHO ECOG-score					
0, 1	148/1210 (12.2)	Ref	0.664		
2, 3, 4	7/67 (10.4)	0.84 (0.38–1.87)			
Severe pulmonary disease					
No	139/1236 (11.2)	Ref	< 0.001	Ref	< 0.001
Yes	16/48 (33.3)	3.95 (2.11–7.48)		3.34 (1.72–6.46)	
Severe cardiac disease					
No	131/1211 (10.8)	Ref	< 0.001	Ref	< 0.001
Yes	24/73 (32.9)	4.04 (2.39–6.79)		3.42 (1.97 (5.94)	
Weight class (BMI)					
< 18.5	2/24 (8.3)	0.98 (0.23–4.35)	0.007		
18.5–25	43/511 (8.4)	Ref			
25–30	70/496 (14.1)	1.79 (1.19–2.67)			
> 30	37/228 (16.2)	2.11 (1.32–3.38)			
Med. Diabetes					
No	135/1150 (10.5)	Ref	0.285		
Yes	20/134 (14.9)	1.32 (0.79–2.19)			
ASA classification					
1–2	102/871 (11.7)	Ref	0.564		
3–4	53/413 (12.8)	1.11 (0.79–1.58)			
Operative technique					
LAR	105/743 (14.1)	Ref	0.020	Ref	0.010
Hartmann	7/109 (6.4)	0.42 (0.19–0.92		0.36 (0.16–0.81)	
APR	43/432 (10.0)	0.67 (0.46–0.78)		0.66 (0.45–0.97)	
Robotic assistance					
No	112/909 (12.3)		0.669		
Yes	43/375 (11.5)	0.92 (0.63–1.34)			
Conversion					
Yes	20/95 (21.1)	2.09 (1.23–5.52)	0.006	1.85 (1.07–3.23)	0.029
No	135/1189 (11.4)	Ref		Ref	

to standard laparoscopy. Further, conversion to open access surgery was associated with higher rates of major complications, longer hospital stay, and unfavorable histopathological results.

These results are corroborated by data from a recent meta-analysis of RCTs and propensity score matched studies [17] as well as a large single center study on 600 patients [16], both showing lower conversion rates with robotic assistance compared to conventional laparoscopy in rectal cancer patients, [16, 17]. In contrast, the large international multi-center ROLARR trial found no difference in conversion rates between RR and LR [18]. However, according to a post hoc multi-level logistic regression analysis taking into account the participating surgeon's experience with robotic surgery, the lack of difference in conversion rates between the two techniques in this multi-center trial could be explained by a learning effect [34].

A conversion rate of 2.1% with RR and 9.6% with LR is generally low compared to other large studies on both laparoscopic and robotic rectal resections, where reported rates

Table 6 Lymph nodes retrieved with LR and RR in hospitals performing both techniques

Center number	*n* total	*n* RR	RR Mean *n*. lymphnodes (Std.dev)	LR Mean *n*. lymphnodes (Std.dev)	*p* value
1	158	6	26.5 (12.5)	21.1 (11.1)	0.339
2	118	60	13.7 (5.8)	15.1 (4.8)	0.148
3	75	58	15.2 (5.8)	16.1 (5.9)	0.564
4	123	4	20.8 (3.3)	15.7 (7.7)	**0.044**
5	32	19	20.7 (7.8)	26.6 (13.5)	0.174
6	64	34	15.9 (5.9)	16.9 (4.8)	0.482
7	269	194	12.6 (4.9)	13.0 (5.2)	0.562

Significant values ($p < 0.05$) are marked in bold

RR robotic resection, *LR* laparoscopic resection

vary between 5.0 and 8.1% for RR and 12.2 and 15.4% for LR [16–18]. This could indicate that the operating surgeons had a high level of experience with both robotic assisted and laparoscopic techniques.

Male gender, BMI > 30, and severe cardiac disease were identified as risk factors associated with conversion to open surgery, which is in line with other studies [16, 35, 36]. In a study by Crippa et al., robotic surgery was associated with lower conversion rate in obese patients [14]. In the present study, the conversion rate was especially high for males with BMI > 30 who underwent LR, and the risk for conversion in this group was significantly lower with robotic assistance (Table 3). This indicates that robotic assistance aids in completing surgery laparoscopically especially in the more challenging obese patients combined with a narrow male pelvis. The finding of severe cardiac disease as an independent risk factor for conversion has to our knowledge not been addressed in the literature. The data available for this study do not provide further information to elaborate this finding.

Rates of major complications, 30 day mortality, reoperations, and anastomotic leak did not differ between RR and LR, which is in line with other large studies [7, 16, 18, 37]. While some studies have used standardized complication scores like Accordion grading score [38] or Clavien-Dindo score [5], other studies recorded complications according to custom definitions which vary greatly and make direct comparison difficult. A review of 8 studies including 592 patients undergoing laparoscopic or robotic assisted LAR showed that the overall complication rate was significantly lower in the RR group compared to LR [39]; however, the definition of complications differed between the included studies. In comparison, there were no differences in complication rates between RR and LR in the ROLARR trial comprising 461 patients [18]. The overall rate of major complications in the present study was low, as almost 9 out of 10 patients went through elective rectal cancer surgery without any major complication.

Conversion to open access was followed by higher rates of major complications, reoperations, longer LOS, higher rates of positive CRM, and tumor-near bowel-perforation. Higher rates of complications have been associated with conversion of laparoscopic colon cancer resections in several studies [3–7]. In a study with prospectively collected data of 470 patients who underwent laparoscopic colorectal resections including 192 rectal resections, postoperative complication rates were significantly higher for patients who experienced conversion to open access, with a rate of 56.1% versus 16.8% when resections were completed laparoscopically [37]. This finding is supported by the present study, although the difference in complication rates was less profound.

Histopathological assessment included CRM/DRM and number of retrieved lymph nodes in the specimen. Total number of lymph nodes is one of the key quality measures for assessing the histopathological result following colorectal surgery [40]. The present study showed significantly lower numbers of harvested lymph nodes in the RR group compared with the LR group. However, subgroup analysis indicated that this was related to local hospital or laboratory differences rather than between RR and LR, as there was no difference in number of retrieved lymph nodes after LR and RR in hospitals operating with both methods. Large differences between pathology laboratories in lymph node retrieval have previously been shown in other studies [41, 42]. In the present study, the proportion of patients with neoadjuvant treatment was significantly higher in the RR group. This was probably related to a larger share of low tumors in the RR group which more often meet the criteria for neoadjuvant treatment. Neoadjuvant treatment is well known to be associated with a lower number of specimen lymph nodes. In the ROLARR trial, mean number of lymph nodes retrieved by robotic resections were 24.1, compared to 23.2 for laparoscopic resections [18]. In the COLORII trial the median number of lymph nodes retrieved was 13 for the laparoscopic resections [7], which compares well with the present study.

The overall positive CRM was 4.7% in the present study, which is lower than both the COLORII trial [7] (7.05% for LR) and the ROLARR trial [18] (6.3% for LR and 5.1% for RR). In the present study, positive CRM was more frequent in converted cases, low tumors and tumors resected by APR. Despite a higher proportion of APR and lower tumors in the RR group, no difference was seen regarding positive CRM. This could indicate that robotic assistance reduces the risk for involved CRM in patients operated with APR. In this study however, the reason for conversion was not recorded. In a review [43] of 18 studies on colorectal cancer patients, 3 studies on rectal cancer patients stated that the most common reasons for conversion were advanced tumors, obesity, narrow pelvis, and adhesions. The higher rates of positive CRM in specimens from converted procedures could reflect difficult laparoscopic dissection where conversion to open access enabled to finalize the procedure but could not undo the damage caused by suboptimal dissection.

There are some limitations to this study. The completeness of the mesorectal fascia is an important histopathological quality measure [44, 45], but this variable was not available from the Norwegian Colorectal Cancer Registry. Another limitation is that NoRGast is a newly established registry with low coverage rates during the first years of inclusion. Furthermore, it is possible that surgeons performing robotic rectal resections are those who previously had developed high surgical skills in conventional laparoscopy. However, rectal cancer surgery in Norway has been centralized before the introduction of conventional laparoscopic rectal resection, and the same surgeons are performing LR and RR at centers offering both techniques. The higher conversion rate in LR also in these centers makes this bias unlikely.

Moreover, the present study is an observational study, and the low conversion rate associated with robotic resection could be a result of confounders which were not recorded as variables in the registries. However, separate analyses on hospital level to detect whether conversion rate was dependent on robot system accessibility, showed significantly higher conversion rates with LR also in hospitals with access to such operating systems. Furthermore, propensity score matching was also performed to eliminate bias otherwise only accounted for by an RCT.

This study is based on compound data from two national quality registries covering the surgical and oncological quality of surgical treatment of rectal cancer and shows real time results from treatment outside the strict frames of an RCT. Mandatory inclusion of patients from all hospitals performing rectal cancer surgery enables the possibility to obtain a large dataset of unselected patient population suited for research using advanced statistical methods to minimize bias and confounding. This approach offers results that reflect national daily practice. The degree of external validity would depend on a similar homogenous population and healthcare provision.

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Declarations

Disclosures Drs Elisabeth Myrseth, Linn Såve Nymo, Petter Fosse Gjessing, Hartwig Kørner, Jan Terje Kvaløy and Stig Norderval have no conflicts of interest or financial ties to disclosure.

Ethical approval The study was approved by The Regional Committee for Medical and Health Research Ethics (Approval Number 2018/2274) and by the Data Protection Officer at the University Hospital of North Norway.

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Paper II

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RESEARCH

Diverting stomas reduce reoperation rates for anastomotic leak but not overall reoperation rates within 30 days after anterior rectal resection: a national cohort study

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Abstract

Purpose A diverting stoma is commonly formed to reduce the rate of anastomotic leak following anterior resection with anastomosis, although some studies question this strategy. The aim of this study was to assess the leak rates and overall complication burden after anterior resection with and without a diverting stoma.

Methods A 5-year national cohort with prospectively registered data of patients who underwent elective anterior resection for rectal cancer located < 15 cm from the anal verge. Data were retrieved from the Norwegian Registry for Gastrointestinal Surgery and the Norwegian Colorectal Cancer Registry. Primary end point was relaparotomy or relaparoscopy for anastomotic leak within 30 days from index surgery. Secondary endpoints were postoperative complications including reoperation for any cause.

Results Some 1018 patients were included of whom 567 had a diverting stoma and 451 had not. Rate of reoperation for anastomotic leak was 13 out of 567 (2.3%) for patients with diverting stoma and 35 out of 451 (7.8%) ($p > 0.001$) for patients without. In multivariable analyses not having a diverting stoma (aOR 3.77, c.i 1.97–7.24, $p < 0.001$) was associated with increased risk for anastomotic leak. However, there were no differences in overall reoperation rates following anterior resection with or without diverting stoma (9.3% vs 10.9%, $p = 0.423$), and overall complication rates were similar. Reoperation was associated with increased mortality irrespective of the main intraoperative finding.

Conclusion Diverting stoma formation after anterior resection is protective against reoperation for anastomotic leak but does not affect overall rates of reoperation or complications within 30 days.

Keywords Stoma · Anterior resection · Anastomotic leak · Rectal cancer

Introduction

Anastomotic leak following anterior resection for rectal cancer is a major complication, leading to increased morbidity, prolonged hospital stay, additional interventions and in some cases death [1, 2]. Even if the anastomosis can be rescued for some patients, leaks are associated with inferior functional results with lifelong implications for the patient [3–5]. The reported leak rate after anterior resections varies between 6.5% and 13.6% [6–9], and one reason for this variation might be differences in definition and grading of severity of anastomotic leaks. Rabhari et al. [10] proposed in 2010 criteria for standardized definitions. The authors defined three categories of leaks where grade A leaks do not require any intervention, grade B leaks require active intervention but without relaparotomy, and grade C leaks require relaparotomy or relaparoscopy.

In order to prevent anastomotic leak, formation of a temporary diverting stoma is common following resections with low anastomoses, and two recent meta-analyses have shown lower leak rates in patients receiving diverting stomas [11, 12]. Norwegian guidelines [13] recommend diverting ileostomy in case of anastomosis < 7 cm from anal verge based on results from the Norwegian Colorectal Cancer Registry [14]. Consideration of a diverting stoma following low anterior

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resection (LAR) is also recommended by the Association of Coloproctology of Great Britain and Ireland [15], but the recommendation does not define a specific group of patients for which stomas should be considered. Nevertheless, stoma-related morbidity and complications represent a significant problem [16–18], and this should warrant selection of patients at risk for anastomotic leak before diverting stoma is considered. Furthermore, there is an ongoing debate whether diverting stomas only mask possible anastomotic leak and further delay the diagnosis. A Swedish multicenter trial showed that only 60% of the leaks after LAR were diagnosed during the initial hospital stay [19], and a Dutch multicenter study showed that half of the late diagnosed leaks never heal [20].

The aim of this study was to assess the anastomotic leak rates and overall complication rates after anterior resection with and without a diverting stoma in a national cohort from the Norwegian Registry for Gastrointestinal Surgery (NoRGast) [21] linked with data from the Norwegian Colorectal Cancer Registry [22]. Primary endpoint was reoperation for anastomotic leak within 30 days after anterior resection with and without diverting stomas. The dataset did not allow for exploration of anastomotic leak or stoma rate later than 30 days after index surgery. Secondary endpoints were overall complication rates including reoperation of any cause.

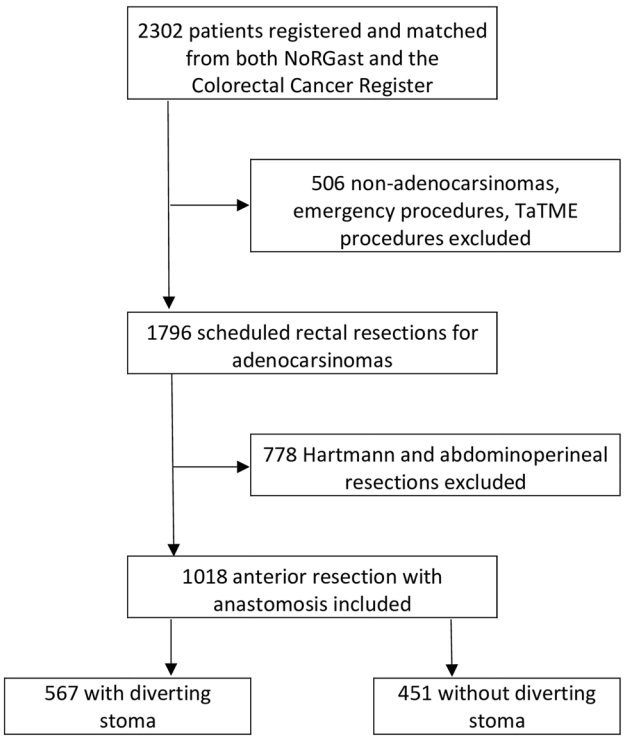

Fig. 1 Flowchart

Methods

Study population

Patients who underwent elective major resection for rectal cancer from January 1st 2014 to December 31st 2018 were identified via NoRGast based on procedure codes according to NCSP (NOMESCO Classification Of Surgical Procedures) [23] for rectal resections, and diagnosis code C20 for cancer according to the International Classification of Diseases version 10 (ICD-10) [24]. Tumors other than adenocarcinomas as well as endoscopic and TaTME procedures were excluded (Fig. 1). NoRGast is a national quality registry established in 2014 and records complications within 30 days after surgery. All Norwegian hospitals performing cancer resections are obliged to report data to NoRGast, and a detailed presentation of the registry has previously been published [21]. Data from NoRGast were linked via the patient's individual social security numbers to the Norwegian Colorectal Cancer Registry [22] for information on preoperative work-up, neoadjuvant treatment and final histopathological results.

Data quality

The national coverage rate in NoRGast has increased during the study period from 20% in 2014 to 75% in 2018 [25]. The low national coverage rate in 2014 was due to a limited number of participating hospitals the first year, although the coverage rates among the participating hospitals were high. The Norwegian Colorectal Cancer Registry has a coverage rate higher than 90% [26]. Variable completeness varies, with almost 100% completeness in NoRGast compared to 70% for some variables in the Norwegian Colorectal Cancer Registry. However, as both registries overlap on several core variables, data linking resulted in an overall high degree of variable completeness in the studied dataset. The correctness and reliability of variables in NoRGast is high much due to the digital reporting system, in which certain limitations and warnings for unusual combinations exist. The records are manually checked by local registrars 30 days postoperatively to increase validity. The manuscript was drafted in accordance to the STROBE guidelines for observational studies [27].

Anastomotic leak definition

According to NoRGast, anastomotic leak was defined as a leak that required relaparotomy or relaparoscopy (grade C leak) [10] within 30 days after the index operation. The registry holds no data on less severe leaks (grade A or grade B leaks).

Categorization of variables

There was no variable available in the register of whether a total mesorectal excision (TME) or a partial mesorectal excision

(PME) had been performed. This is however closely related to tumor level. Hence tumor level was used as a proxy for TME and PME, respectively. Tumor level was measured preoperatively with a rigid proctoscope, and categorized into TME (tumor ≤ 12 cm from anal verge) and PME (tumor > 12 cm from anal verge). Age was categorized into three groups (low < 65 years, mid 65–80 years and high > 80 years). ASA-scores were grouped into low ASA-scores (scores 1–2), and high ASA-scores (scores 3–4). WHO ECOG-scores were dichotomized into low ECOG-score (0–1) and high ECOG-score (2–4). Severe pulmonary disease was defined as having FEV1 < 50 per cent or a vital capacity < 60 per cent of predicted values. Severe cardiac disease was defined as NYHA classification 3–4 or severe arrhythmia requiring mechanical support. Complications were registered according to the Accordion grading system [28], and major complications were defined as Accordion grade 3 or higher. The NoRGast registry categorized finding at reoperation as anastomotic leak, bleeding, deep infection without proof of leak, wound dehiscence and miscellaneous. Weight was classified by body mass index (BMI), and patients were grouped into 4 BMI-classes [29]; [< 18.5] [18.5–25] [25–30] [> 30]. Data were analyzed with SPSS version 26, (IBM, Armonk, New York, USA).

Statistical analyses

For univariable analyses Pearson's Chi-square test was used for categorical data, and two-sided T-test or Mann–Whitney U test for continuous data. Confidence interval (c.i.) or interquartile range (IQR) was calculated when appropriate. Univariable binary logistic regression was used to calculate unadjusted odds ratios (OR). To address and minimize the effects of possible bias resulting from differences in baseline characteristics between patient groups, a stepwise backwards multivariable logistic regression model with adjusted odds ratios (aOR) was used to further analyze the relations between different predictors and outcomes. Variables significant in univariable analyses at a level of $p < 0.2$ were included in multivariable analysis, and final significance level after multivariable analysis was set to $p < 0.05$. Relevant variables were tested for significant two-way interactions, and if interactions were found, they were further accounted for in the analyses. Little's test [30] of whether data were missing completely at random was performed with all variables included for analyses in the test. The test had a Chi-square of 19.44, degrees of freedom = 13 and a non-significant $p = 0.110$ indicating that missing values were missing completely at random. This allowed patients with missing data in variables included for subgroup analyses to be excluded from these analyses.

The study was approved by The Regional Committee for Medical and Health Research Ethics (approval number 2018/2274) and by the Data Protection Officer at the University Hospital of North Norway.

Results

Patients

A total of 2302 patients were recorded in NoRGast with an NCSP procedural code for rectal resection during the study time frame. After excluding non-adenocarcinomas, TaTME, endoscopic and emergency procedures, a total of 1796 patients were identified, of whom 1018 patients underwent anterior resection with primary anastomosis. Some 742 of these 1018 operations were laparoscopic procedures including 191 robotic assisted procedures, and 276 were open access procedures (Fig. 1). Baseline characteristics for the included patients are presented in Table 1.

Anastomotic leak rates

The overall leak rate was 48 out of 1018 (4.7%) with stratified rates for patients with and without a diverting stoma of 13 out of 567 (2.3%) and 35 out of 451 (7.8%) ($p < 0.001$), respectively. Leak rate was significantly lower with diverting stomas regardless of tumor level, and tumor level was not a significant predictor for anastomotic leak in univariable regression analyses. In multivariable regression analyses, absence of diverting stoma was associated with an increased risk of reoperation for anastomotic leak with an aOR of 3.77 (c.i. 1.97–7.24, $p < 0.001$) compared to anterior resection with a diverting stoma (Table 3).

Complication rates

The overall reoperation rate was 102 out of 1018 (10.0%). There was no difference in reoperation rates between the groups with and without diverting stomas (Table 2), but the findings at reoperation differed. For patients without a diverting stoma, the main finding at reoperation was anastomotic leak in 35 out of 47 (74.5%) patients, while anastomotic leak was the main finding at reoperation in 13 out of 51 (25.5%) patients with a diverting stoma (Fig. 2). Male gender (aOR 1.85) and severe pulmonary disease (aOR 3.44) were associated with increased risk of reoperation for any reason (Table 3). In NoRGast, patients with a diverting stoma were coded with main finding "miscellaneous" at reoperation in 58.8% of the cases in contrast to 12.8% of reoperations in patients without stoma. As a part of a registry quality review the electronical medical records for all patients coded with "miscellaneous" as main finding at reoperation were investigated and recategorized into more granular main findings. The review revealed that patients with a diverting stoma was reoperated due to stoma-related problems in 30.0% of the cases. Furthermore, bowel obstruction was the reason for reoperation in 18.0% of the patients with a diverting stoma compared to 6.4% in patients without diverting stomas (Table 2; Fig. 2).

Table 1 Baseline characteristics, patients operated with anterior resection

Characteristics			Diverting stoma		
		Total	With	Without	P-value
Gender (F/M)		*398/620*	208/359	190/261	0.077
Age	< 65	*469*	284 (50.1%)	185 (41.0%)	< 0.001
	65–80	*477*	257 (45.3%)	220 (48.8%)	
	> 80	*72*	26 (4.6%)	46 (10.2%)	
BMI	< 18.5	*22*	10 (1.8%)	12 (2.7%)	0.385
	18.5–25	*393*	230 (41.8%)	163 (37.1%)	
	25–30	*405*	221 (40.2%)	184 (41.9%)	
	> 30	*169*	89 (16.2%)	80 (18.2%)	
ASA	1,2	*754*	422 (74.4%)	332 (73.8%)	0.814
	3,4	*263*	145 (25.6%)	118 (26.2%)	
ECOG	0,1	*958*	530 (94.6%)	428 (96.0%)	0.329
	2,3,4	*48*	30 (5.4%)	18 (4.0%)	
Pulmonary disease		*45*	23 (4.1%)	22 (4.9%)	0.526
Heart disease		*58*	32 (5.6%)	26 (5.8%)	0.934
Diabetes		*87*	54 (9.5%)	33 (7.3)	0.211
Access					
	Open	*276*	183 (66.3%)	93 (33.7%)	< 0.001
	Lap	*742*	384 (51.8%)	358 (48.2%)	
Tumor level					
	0–11,9 cm	*493*	364 (73.8%)	129 (26.2%)	< 0.001
	12,0–15,0 cm	*319*	94 (29.5%)	225 (70.5%)	
Radiochemotherapy		*239*	208 (87.0%)	31 (13.0%)	< 0.001

The overall major complication rates, 30-day and 90-day mortality rates and rates of single-organ and multi-organ failure did not differ between the two groups (Table 2). Median LOS was 7 days in the group with diverting stoma compared to 5 days in the group without diverting stoma ($p < 0.001$).

There were no major differences in mortality or morbidity between patients reoperated for anastomotic leaks and

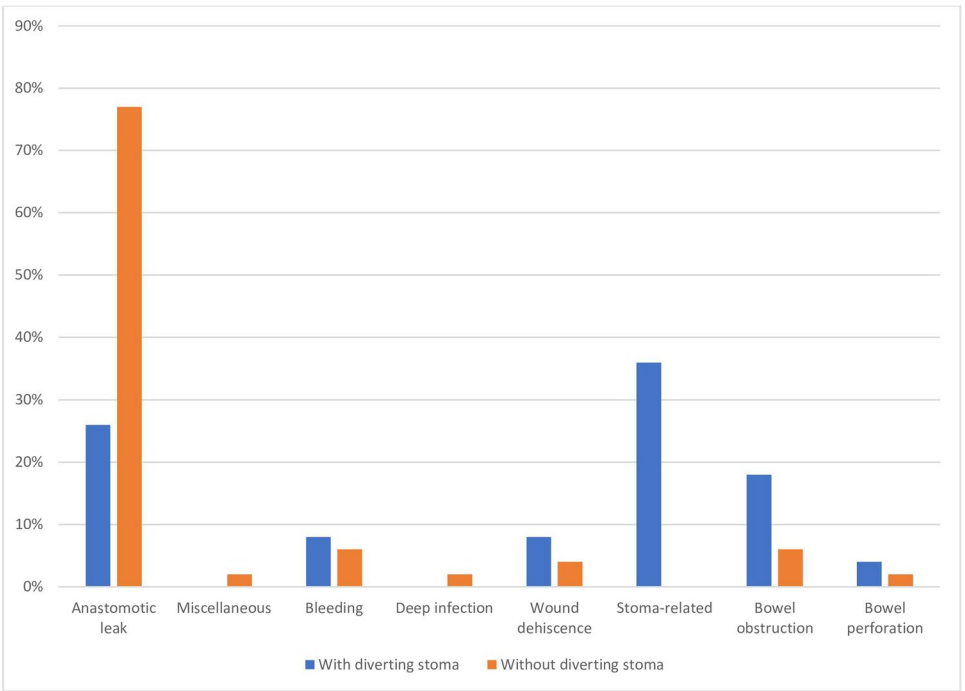

Fig. 2 Main finding (%) at reoperation after anterior resection, with and without diverting stoma

Table 2 Results after anterior resection with or without diverting stoma

Results		Diverting stoma		
	Total	With	Without	P-value
Anastomotic leaks				
Open (276)	*16/276 (5.8%)*	4/183 (2.2%)	12/93 (12.9%)	< 0.001
Laparoscopy (742)	*32/742 (4.3%)*	9/384 (3.1%)	23/358 (6.4%)	0.006
Tumor level				
0–11,9 cm*	*1/11 (9.1%)*	12/364 (3.3%)	10/129 (7.8%)	0.035
12,0–15,0 cm*	*16/394 (4.1%)*	0/94 (0%)	17/22 (7.6%)	0.006
Reoperations	*102/1018 (10.0%)*	53/567 (9.3%)	49/451 (10.9%)	0.423
Finding at reoperation**				
Anastomotic leak	*49/97 (50.5%)*	13/50 (26.0%)	36/47 (76.6%)	< 0.001
Miscellaneous	*1/97 (1.0%)*	0 (0%)	1/47 (2.1%)	
Bleeding	*7/97 (7.2%)*	4/50 (8.0%)	3/47 (6.4%)	
Deep infection	*1/97 (1.0%)*	0/50 (0.0%)	1/47 (2.1%)	
Wound dehiscence	*6/97 (6.2%)*	4/50 (8.0%)	2/47 (4.3%)	
Bowel obstruction	*12/97 (12.4%)*	9/50 (18.0%)	3/47 (6.4%)	
Bowel perforation	*2/97 (2.1%)*	2/50 (4.0%)	1/47 (2.1%)	
Stoma-related	*18/97 (18.6%)*	15/50 (30.0%)	-	
Length of stay, median (IQR)	*6 (4–9)*	7 (5–10)	5 (4–8)	< 0.001
Major complications	*146/1018 (14.3%)*	87 (15.3%)	59 (13.1%)	0.306
90-day mortality	*14/1018 (1.4%)*	5 (0.9%)	9 (2.0%)	0.130
30-day mortality	*7/1018 (0.7%)*	4 (0.7%)	3 (0.7%)	0.938
Single-organ-failure	*25/1018 (2.5%)*	13 (2.3%)	12 (2.7%)	0.706
Multi-organ-failure	*6/1018 (0.6%)*	4 (0.7%)	2 (0.4%)	0.587

* Missing values = 206; ** Missing values = 2

patients reoperated for other reasons (Table 4), but LOS was longer following anastomotic leak (Table 4). In multivariable regression analyses, increasing age (65–80 years aOR 2.13 and > 80 years aOR 19.99), severe pulmonary disease (aOR 8.41) as well as reoperation (aOR 11.36) were associated with increased 30-day mortality risk (Table 3).

Discussion

In the present study, reoperation for anastomotic leak within 30 days after anterior resection was significantly less frequent in patients with a diverting stoma. However, stoma diversion did not affect the overall reoperation rate, mortality or morbidity. This has to the authors knowledge not been shown in previous studies. Reoperation was associated with increased mortality irrespective of intraoperative finding, and the total burden of morbidity and mortality within 30 days were similar for patients with and without a diverting stoma.

The current evidence of the benefits of diverting stomas following anterior resection is unclear, and studies report diverging results. A recent meta-analysis showed lower anastomotic leak rates and reoperation rates with diverting stomas compared to no stomas [31], but the diagnostic criteria of leak and time to diagnosis varied in the included studies. A Swedish registry study of 1442 patients who underwent anterior resection showed that late presenting leaks were associated with diverting stomas, and that stoma formation did not alter the overall leak rate [32]. As many as 50% of the leaks were diagnosed after discharge, and about half of these patients needed relaparotomy. A Dutch multicenter study showed that half of the late diagnosed leaks never heal [20]. Several studies suggest that diverting stomas do not have any protective effect on late diagnosed leaks, and reoperation rate and permanent stoma rate seems to be high also after late diagnosed leaks [20, 32–34]. The functional results following anastomotic leak are inferior [35], but it is not known whether the severity of dysfunction differs after early and late discovered leaks. A Japanese study on 1903 patients who underwent LAR showed that formation of a diverting stoma did not protect against late diagnosed anastomotic leaks, and that permanent stoma rate was higher among patients with late diagnosed leaks compared to those with early diagnosed leaks [33].

Although diverting stomas apparently have a protective effect against early diagnosed leaks, several studies highlight

Table 3 Results from multivariable regression analyses*

Outcome measure	Significant variables			Multivariable analyses	
	Variable		*Rate (%)*	aOR (95%CI)	p-value
Anastomotic leak	Gender				
		Female	*11/389 (2.8)*	Ref	0.012
		Male	*37/620 (6.0)*	2.43 (1.22–4.85)	
	Diverting stoma				
		Yes	*13/567 (2.3)*	Ref	< 0.001
		No	*35/451 (7.8)*	3.77 (1.97–7.24)	
Reoperation	Gender				
		Female	*27/398 (6.8)*	Ref	0.009
		Male	*75/620 (12.1)*	1.85 (1.17–2.94)	
	Severe pulmonary disease				
		Yes	*90/973 (9.2)*	Ref	< 0.001
		No	*12/45 (26.7)*	3.44 (1.71–6.94)	
30-day mortality	Age group				
		< 65	*1/469 (0.2)*	Ref	0.013
		65–80	*3/477 (0.6)*	2.13 (0.20–22.32)	
		> 80	*3/72 (4.2)*	19.99 (1.84–217.18)	
	Severe pulmonary disease				
		Yes	*4/973 (0.4)*	Ref	0.013
		No	*3/45 (6.7)*	8.41 (1.56–45.24)	
	Reoperation				
		Yes	*4/102 (3.9)*	12.42 (2.74–56.31)	0.004
		No	*3/916 (0.3)*	Ref	

*Variables included in univariable analyses: Age group, gender, WHO ECOG-score, ASA classification, severe pulmonary disease, severe cardiac disease, diabetes, weight class (BMI), operative access (open/laparoscopy), tumor level (TME/PME), preoperative radio(chemo)therapy, diverting stoma, anastomotic leak (not for analyses on anastomotic leak) and reoperation (not for analyses on reoperation)

the less favorable consequences of stoma formation [16–18]. A temporary stoma will in most cases lead to longer hospital stay and require a second operation and hospital stay for stoma closure. Additionally, patients may experience stoma leak, parastomal hernias, skin problems, dehydration, kidney failure and electrolyte deficiency which may require additional hospital visits.

In the present cohort diverting stomas did not lower morbidity, mortality or reoperation rates within the first 30 postoperative days. Reoperation for bleeding, deep infection and wound dehiscence was performed to the same extent regardless of whether the patient had received a diverting stoma or not. The patients who received a diverting stoma were also reoperated more frequently due to bowel obstruction, and 30% of the reoperations were directly stoma-related. In support of this notion, formation of diverting stomas has been shown to increase short-term complications including stoma related reoperations after anterior resection [16]. Furthermore, some studies report delayed stoma reversal, and that creation of a diverting stoma might increase risk of permanent stoma on long term [36, 37]

The results of the present study emphasize the question whether patients undergoing anterior resection derive any benefit from formation of a diverting stoma and if so, how to select these patients. As low tumor level did not represent a significant risk factor for anastomotic leak, the recommendation of diverting stoma formation

Table 4 Postoperative complications following reoperation for anastomotic leak and reoperation for other reason

	Anastomotic leak	Reoperation for other reasons	p-value
Length of hospital stay	Median 20 (IQR 14–27)	Median 17 (IQR 13–21)	0.039
90-day mortality	3/49 (6.1%)	2/48 (4.2%)	0.663
30-day mortality	2/49 (4.4%)	2/48 (4.2%)	0.983
Single-organ failure	6/49 (12.6%)	9/48 (18.8%)	0.376
Multi-organ failure	0/49 (0.0%)	3/48 (6.3%)	0.075

for anastomosis level < 7 cm from anal verge can be challenged. To explore this issue further a long-term study on outcomes after anterior resection with and without diverting stomas is warranted, assessing both early and late diagnosed anastomotic leaks, long-term overall complication rates, permanent stoma rates and total length of hospital stay. A Norwegian multicenter trial, the Norwegian Stoma Trial, exploring some of these issues is planned for commencement in 2022 [38]. Furthermore, the ongoing Dutch IMARI [39] multicenter trial will explore the one-year anastomotic integrity rate before and after the introduction of a multi-interventional program aiming to reduce anastomotic leak rate. In this study, the impact of diverting stomas will also be accounted for.

This study has some limitations. NoRGast is a newly established register with low coverage rates during the first years of inclusion. As already described, causality between stoma related problems and indication for reoperation cannot be established due to the nature of the study. The present study is an observational registry study and it is possible that there are variables not registered that could have a confounding effect, and that there are factors not registered and hence accounted for that could lead to selection bias. Nevertheless, our findings add to the question whether the benefits of a diverting stoma following anterior resection is outweighed by the overall complication rate.

Authors contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Elisabeth Myrseth. The first draft of the manuscript was written by Elisabeth Myrseth and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflicts of interest/competing interests The authors have no relevant financial or non-financial interests to disclose.

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Paper III

Laparoscopic rectal cancer resection results in non-inferior clinical and oncological outcomes with shorter hospital stay compared to open access; a five-year national cohort.

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Original article, observational study

Abstract

Purpose: Although widely applied, the non-inferiority of laparoscopic rectal resection (LRR) for cancer compared to open rectal resection (ORR) is still being questioned. The aim of this study was to assess clinical short- and long-term results as well as oncological resection quality following LRR and ORR for cancer in a five-year national cohort.

Methods: Data from The Norwegian Registry for Gastrointestinal Surgery and the Norwegian Colorectal Cancer Registry were retrieved from January 2014 to December 2018 for patients who underwent elective resection for rectal cancer. Primary end point was 5-year overall survival. Secondary end points were local recurrence rates within 5 years, oncological resection quality and short-term outcome measures.

Results: A total of 1796 patients were included, of whom 1284 had undergone LRR and 512 ORR. The 5-year survival was 77.1% following LRR compared to 74.8% following ORR ($p=0.015$). After adjusting for cancer stage there was no difference in survival between the groups. The 5-year rates of local recurrence were 3.1% following LRR and 4.1% following ORR ($p=0.249$). Length of hospital stay was median 6.0 (quartiles 4.0-8.0) days after laparoscopic procedures compared to 8.0 (quartiles 7.0-13.0) days after open access procedures ($p<0.001$). Rates of positive resection margins and number of harvested lymph nodes were similar. There were no other significant differences in short term outcomes between the groups.

Conclusion: Laparoscopic rectal cancer resection was performed with non-inferior clinical and oncological outcomes, but with shorter hospital stay compared to open access surgery.

Keywords: Rectal cancer, survival, laparoscopic, outcome

Statements and Declarations

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Elisabeth Myrseth, Stig Norderval, and Jan Terje Kvaløy. The first draft of the manuscript was written by Elisabeth Myrseth and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Introduction

Colorectal cancer is the third most frequent cancer worldwide with 1.9 million new cases in 2020[1], and rectal carcinoma represents about one fourth of the cases. Survival has improved with the introduction of total mesorectal excision (TME) in the early 90's, and later neoadjuvant chemoradiotherapy for more advanced loco-regional disease, and 5-year local recurrence rate has dropped from above 20 to 4%[2–4].

Laparoscopy has eventually become the preferred surgical approach for rectal cancer in many countries[5,6], although the oncological safety has been a subject for debate. Several studies have shown favorable outcomes after laparoscopic surgery for colon cancer[7–11] with reduced rates of complications and 30-day mortality, and long-term results equal to open access surgery. For rectal cancer the results are divergent. Some studies have shown favorable or similar short- and long-term results comparing laparoscopic rectal resection (LRR) and open rectal resection (ORR)[12–14], while other studies have reported inferior oncological results following laparoscopy with higher rates of positive circumferential resection margins (CRM) and lower rates of complete excision of mesorectum after TME[15,16] compared to open access. Only a few studies have explored difference in long term survival rates and local recurrence rates[17–20].

The long-term results after rectal cancer surgery in Norway are surveyed by The Norwegian Colorectal Cancer Registry. This national quality registry holds data concerning diagnostics, treatment and follow up of colorectal cancer patients, and all Norwegian hospitals are obliged to report. The registry has, however, limited information regarding comorbidity, operative and postoperative details. The national quality registry NORGAST (The Norwegian Registry for Gastrointestinal Surgery) was established in 2014, aiming to survey the rate, kind and severity of complications following major gastrointestinal and hepatobiliary surgery. The registry records selected factors that might affect a surgical outcome such as weight loss, BMI, ECOG-status, preexisting severe pulmonary and cardiac disease as well as operative technique. In addition, short-term postoperative outcome measures including complications, reoperations, length of hospital stay, readmissions and mortality rates are registered. A detailed presentation of the registry has been published previously[21]. Data from NORGAST combined with data from The Norwegian Colorectal Cancer Registry enables assessment of both short- and long-term outcomes following rectal cancer surgery adjusting for factors like operative technique, comorbidity, and cancer stage.

The aim of this study was to assess the short- and long-term results following elective major rectal resection for rectal cancer based on data from NORGAST and The Norwegian

Colorectal Cancer Registry. Primary end point was 5-year overall survival. Secondary end points were local recurrence rates within 5 years, oncological resection quality and short-term outcome measures.

Methods

Study population

Patients who underwent elective major resection for rectal cancer from January 1st 2014 to December 31st 2018 were identified in the NORGAST registry based on the combination of a NSCP (NOMESCO Classification of Surgical Procedures)[22] procedure code for rectal resection, and diagnosis code C20 for rectal cancer according to the International Classification of Diseases version 10 (ICD-10)[23]. Due to some delay in data registration, and also to achieve at least 6 months follow-up, latest operation date was set to December 31st 2018. Tumors other than adenocarcinomas as well as transanal total mesorectal excision (TaTME) procedures were excluded. Data from NORGAST were linked via the patient's individual social security numbers to the Norwegian Colorectal Cancer Registry[24] for information on preoperative work-up, oncological treatment upfront surgery and final histopathological results.

Data quality

The coverage rate in NORGAST was 75% in 2018, increasing from approximately 20% on a national level in 2014[25]. Low national coverage rates the first years of implementation were due to few participating hospitals, but in-hospital coverage among participating hospitals was high. The Norwegian Colorectal Cancer Registry has a coverage rate higher than 90%[26]. Variable completeness varies, with almost 100% completeness in NORGAST compared to 70% for some variables in the Norwegian Colorectal Cancer Registry. The latter registry includes data from various sources, such as clinical reports on diagnosis, treatment and histopathological reports. However, as both registries overlap on a number of core variables, data linking results in an overall high degree of variable completeness. Patients with missing values were excluded from the specific analysis where data were missing. The manuscript was drafted in accordance with the STROBE guidelines for observational studies[27].

Statistical analyses

Data were analyzed with SPSS version 26, (IBM, Armonk, New York, USA). Differences between groups were assessed with Pearson's chi square test for categorical data, and two-sided T-test or Mann Whitney U-test for continuous data. Confidence interval (c.i.), standard deviations or quartiles were calculated as appropriate. Univariable binary logistic regression was used to calculate unadjusted odds ratios (OR). Multivariable logistic regression models were used to calculate adjusted odds ratios (aOR) to further analyze the relations between different outcomes and predictor variables. Variables with a p-value <0.2 in univariable analyses were included in the multivariable analyses. Stepwise backward selection was used to suggest the final multivariable model. A final significance level of $p < 0.05$ was used in all tests. There were some missing data in variables included for analyses. Little's test[28] of whether data were missing completely at random was performed. The test had a non-significant p-value of 0.167 indicating that missing values were missing completely at random. This allowed patients with missing data in variables included for subgroup analyses to be excluded from these analyses. Survival as well as local recurrence were illustrated by Kaplan-Meier curves, and the log-rank test was used to test for difference between groups using an intention-to-treat factor approach. To adjust for possible confounders, 5-year survival rates and local recurrence rates were further explored with Cox multivariable regression analyses adjusting for relevant covariates.

Age was categorized into three groups (<65 years, 65-80 years and > 80 years). ASA-scores were grouped into low (scores 1-2), and high (scores 3-4). WHO ECOG-scores were dichotomized into low (scores 0-1) and high (scores 2-4). Severe pulmonary disease was defined as having FEV1 <50% or a vital capacity < 60% of predicted values. Severe cardiac disease was defined as NYHA classification 3-4, or severe arrythmia requiring mechanical support. Complications were registered according to the Accordion grading system[29], and major complications were defined as Accordion grade 3 or higher. Anastomotic leak was defined as a leak requiring relaparoscopy/relaparotomy (grade C leak)[30]. Weight was classified by body mass index (BMI), and patients were grouped into 4 BMI-classes[31]; [<18.5] [18.5-25] [25-30] [>30].

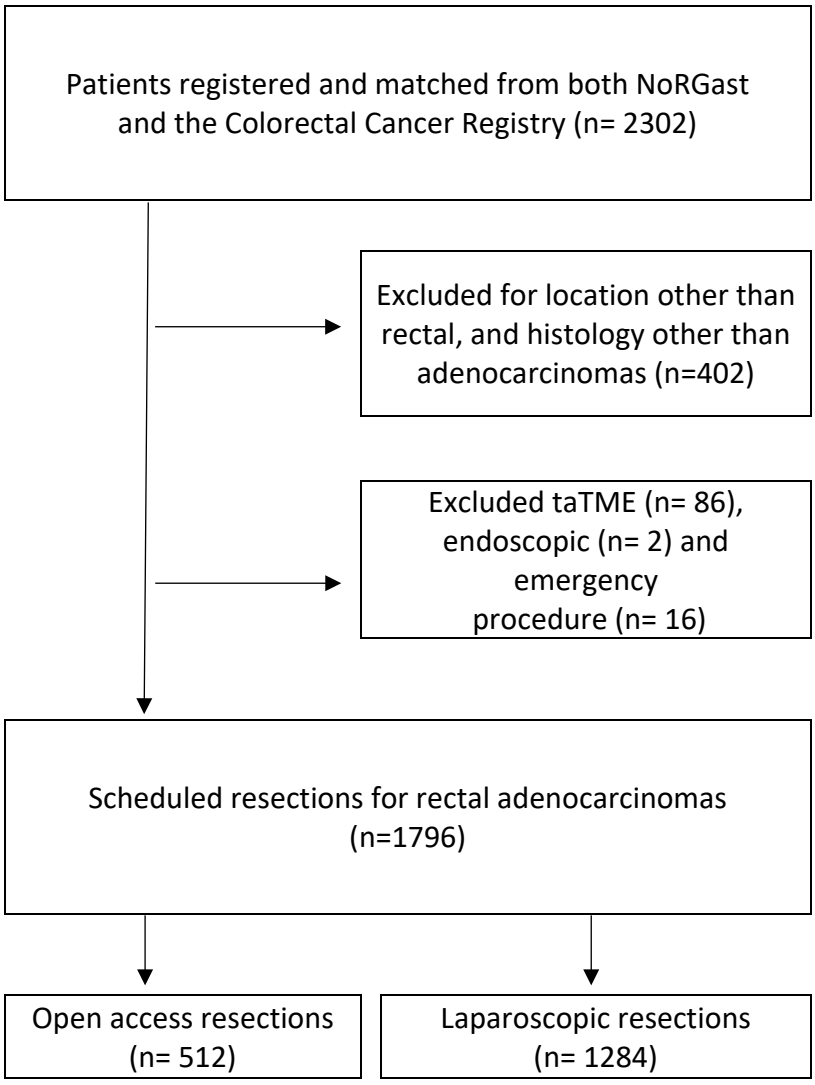


Figure 1: Flowchart

Results

From January 1st 2014 to December 31st 2018 a total of 2302 patients were recorded in NORGAST with rectal cancer and NCSP procedural code for rectal resection. During the same time frame a total of 3694 patients were recorded in the Colorectal Cancer Registry[26] with a major resection for rectal cancer, giving an overall coverage rate in NORGAST of 62%. After excluding patients with tumors other than adenocarcinoma, TaTME endoscopic and emergency procedures, a total of 1796 patients were included in this study. A total of 1284 patients had undergone LRR including 375 robotic assisted procedures, and 512 had undergone ORR (figure 1). Conversion rate following laparoscopic procedures was 95/1284, 7.4%. A steadily increase in laparoscopic procedures was observed during the study time frame, from 56% of the registered procedures registered in 2014 to 86% of the procedures in

2018. There were some baseline differences between the groups; the patients receiving ORR had higher ECOG-scores, higher rates of severe pulmonary and cardiac disease (table 1).

Table 1: Baseline characteristics

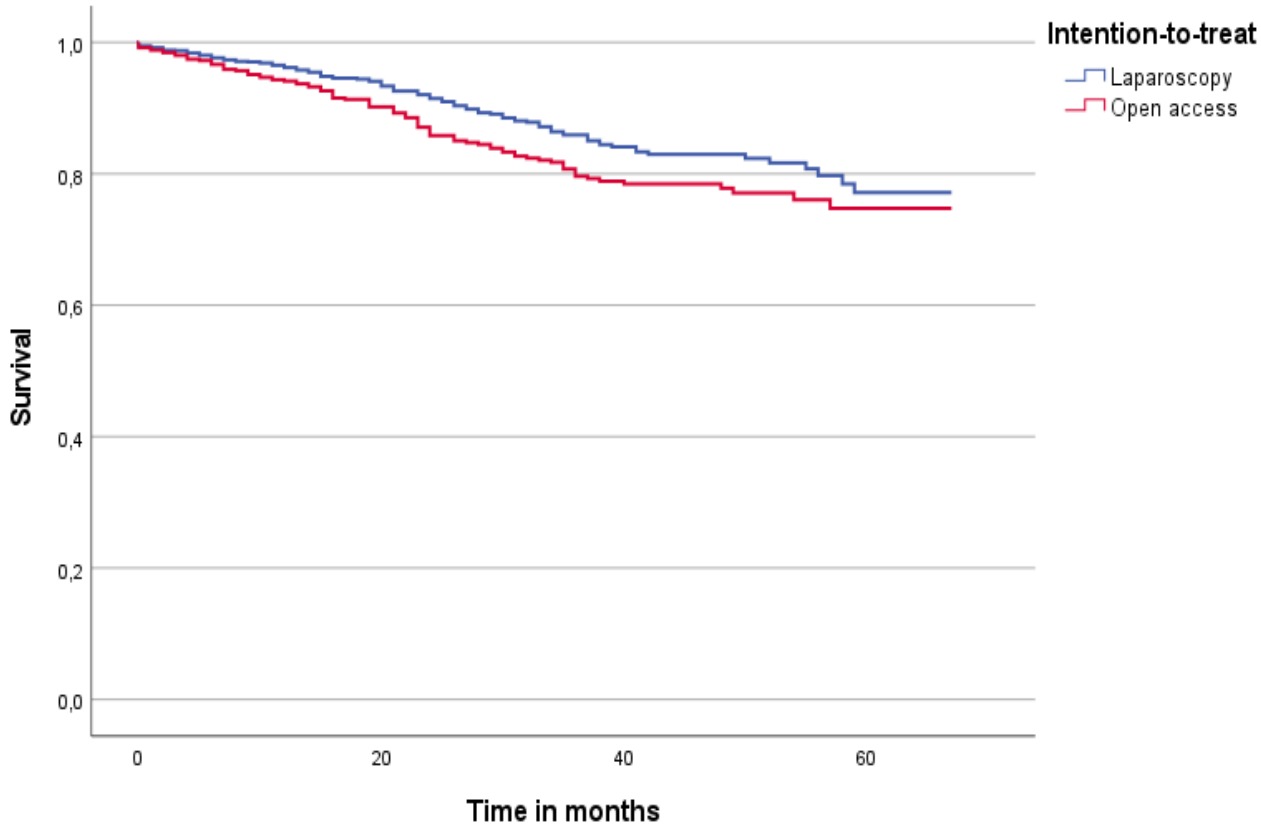
Baseline characteristics		Total	Laparoscopic		Open access		p-value
		n= 1796	n= 1284 (percentage)		n= 512		
Gender							
	Male	1108	782	(61.0)	326	(64.0)	0.276
	Female	688	502	(39.0)	186	(36.0)	
Age (avg) *(std.dev)*		67.3 *(11.7)*	67.5	*(11.4)*	66.6	*(12.6)*	0.997
BMI							
	<18.5	40	25	(2.0)	15	(3.1)	0.354
	18-25	730	518	(41.1)	212	(43.6)	
	25-30	678	496	(39.4)	182	(37.4)	
	>30	297	220	(17.5)	77	(15.8)	
Pulmonary disease		83	48	(3.7)	35	(6.8)	0.005
Heart disease		119	73	(5.7)	46	(9.0)	0.011
Diabetes		182	134	(10.4)	48	(9.4)	0.501
ASA-score							
	Low (1-2)	1204	871	(67.8)	413	(69.9)	0.278
	High (3-4)	591	413	(32.2)	178	(34.8)	
ECOG-score							
	Low (0-1)	1667	1210	(72.6)	457	(59.3)	0.002
	High (2-4)	111	67	(27.4)	46	(40.7)	
Radio(chemo)therapy		588	375	(29.2)	213	(41.6)	<0.001
Operative technique							
	LAR	1017	742	(57.8)	275	(53.7)	0.005
	APR	599	432	(33.6)	167	(32.6)	
	Hartmann	180	110	(8.6)	70	(13.7)	
cStage	1	303	246	(28.6)	57	(18.1)	<0.001
	2	323	239	(27.8)	84	(26.7)	
	3	399	288	(33.5)	111	(35.2)	
	4	149	86	(10.0)	63	(20.0)	
cTumor	x	10	8	(0.6)	2	(0.2)	<0.001
	1	368	299	(23.9)	69	(5.5)	
	2	304	473	(37.7)	163	(13.0)	
	3	636	82	(6.5)	74	(5.9)	
	4	158	68	(5.3)	17	(1.4)	

There are missing values in some of the variables, listed under:
BMI: 51, ASA-score: 1, ECOG-score: 16, cStage: 622, cTumor: 320

Long-term survival

The unadjusted overall 5-year survival was 77.1% after LRR compared to 74.8% after ORR (p=0.015, log rank test) (figure 2). For cancer stage 1-3 the 5-year survival was 80.0% following LRR compared to 83.0% following ORR (p=0.670, log rank test). Multivariable Cox regression analyses including clinical cancer stage, gender and age as covariates showed however no significant difference in HR between LRR and ORR (p=0.175). Cancer stage 3 and 4 (aHR 3.70, 95% c.i. 1.02-3.12 and aHR 5.77, 95% c.i. 3.32-10.04 respectively, p<0.001) as well as increasing age (age>80 years compared to <65 years aHR 5.37, 95% c.i. 3.39-8.50, p<0.001) was associated with increased long-term mortality hazard.

Figure 2: Kaplan-Meier 5-year survival curves



Numbers at risk:

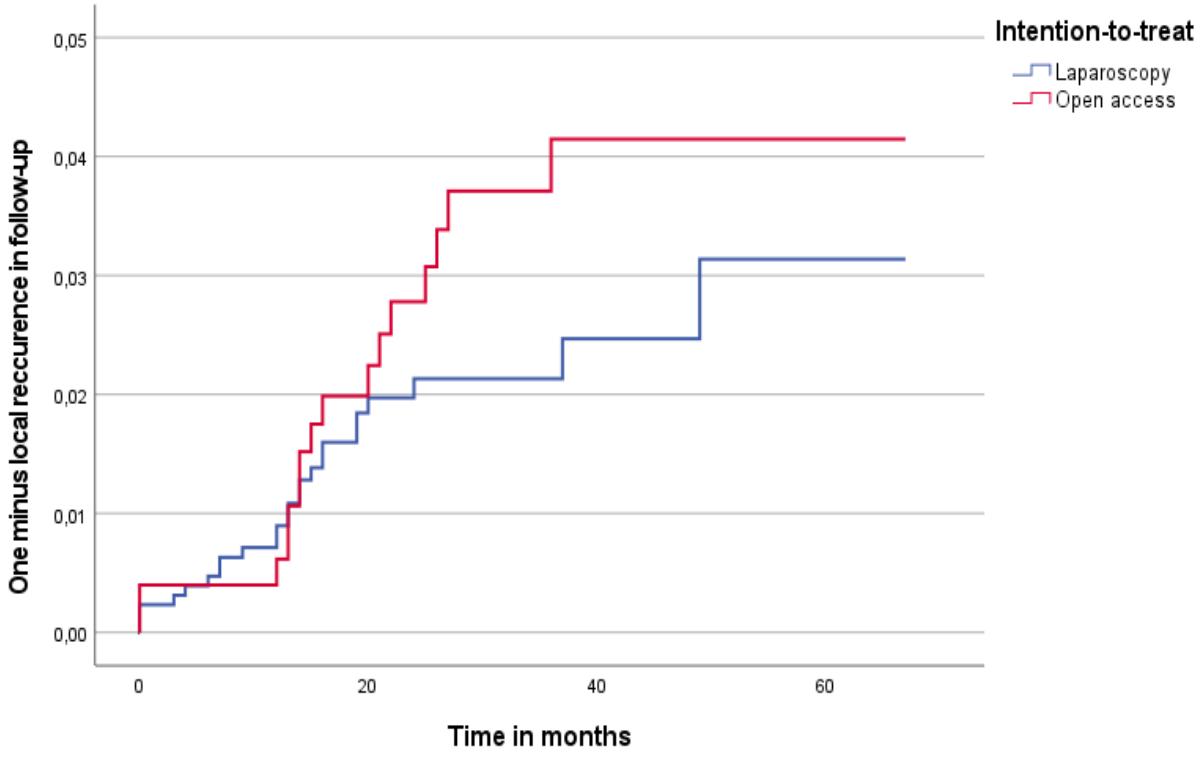
Laparoscopy:	1284	1178	779	439	240	135	53
Open access:	512	477	390	284	180	102	40

Local recurrence rates

The 5-year rates of local recurrence were 3.1% following LRR and 4.1% following ORR (p=0.249, log rank test) (figure 3). Multivariable Cox regression analyses with operative

access, cancer stage, age and gender as covariate revealed no significant difference between the two groups for any covariates.

Figure 3: Kaplan-Meier analyses estimates of local recurrence probalitity curves



Numbers at risk:

Laparoscopy:	1280	1169	764	431	236	134	53
Open access:	500	467	378	274	175	98	38

Short-term outcomes

Length of hospital stay was median 6.0 (quartiles 4.0-8.0) days following LRR compared to 8.0 (quartiles 7.0-13.0) days following ORR ($p<0.001$). There were no other significant differences in short term outcomes between the groups (table 2).

Multivariable regression analyses did not show any difference in risk of major complications, reoperations or 30-day mortality between LRR or ORR. Male gender, severe pulmonary disease, severe cardiac disease and BMI >30 were associated with increased risk of major complications (table 3). Age >80 years and ECOG-score 2-4 was associated with increased 30-day mortality risk (table 3). Male gender and severe pulmonary disease were associated with increased risk of reoperation within 30 days whereas APR compared to LAR and Hartmann lowered the risk of reoperation (table 3).

*Table 3: Results from multivariable logistic regression analyses**

Outcome measure	Significant variables			Multivariable analyses	
	Variable		*Rate (%)*	aOR (95% c.i.)	p-value
Major complications					
	Gender				
		Female	*63/688 (9.2)*	Ref	<0.001
		Male	*174/1108 (15.7)*	1.75 (1.27-2.41)	
	Severe pulmonary disease				
		Yes	*28/237 (11.8)*	2.91 (1.73-4.90)	<0.001
		No	*209/1559 (3.5)*	Ref	
	Severe cardiac disease				
		Yes	*33/237 (13.9)*	1.98 (1.23-3.18)	0.005
		No	*86/1559 (5.5)*	Ref	
	Weight (BMI)				
		<18.5	*4/40 (10.0)*	1.04 (0.35-3.11)	0.014
		18.5-25	*73/730 (10.0)*	Ref	
		25-30	*96/678 (14.2)*	1.38 (0.99-1.92)	
		>30	*54/297 (18.2)*	1.88 (1.27-2.78)	
Reoperations					
	Gender				
		Female	*36/688 (5.2)*	Ref	<0.001
		Male	*108/1108 (9.7)*	1.95 (1.32-2.89)	
	Severe pulmonary disease				
		Yes	*19/144 (13.2)*	3.68 (2.11-6.42)	<0.001
		No	*64/1652 (3.9)*	Ref	
	Operative technique				
		LAR	*102/1017 (10.0)*	Ref	<0.001
		Hartmann	*13/180 (7.2)*	0.14 (0.34-1.16)	
		APR**	*29/599 (4.8)*	0.45 (0.29-0.69)	
30-day mortality					
	Age group				
		<65	*1/714 (0.1)*	Ref	<0.001
		65-80	*4/866 (0.5)*	2.16 (0.22-20.99)	
		>80	*5/216 (2.3)*	10.50 (1.15-96.06)	
	WHO-ECOG				
		0-1	*6/1667 (0.4)*	Ref	<0.001
		2-4	*4/113 (3.5)*	7.29 (1.18-29.29)	

* Variables included in univariable analyses: Age group, gender, WHO ECOG score, ASA classification, severe pulmonary disease, severe cardiac disease, diabetes, weight class (BMI), operative technique, access (laparoscopy/open access), tumor level measured by rigid proctoscope (low, mid-level and high tumors) and preoperative radiochemotherapy.

** APR: Abdominoperineal resection

Histopathological results

There were no differences between the access groups in rates of positive circumferential or distal resection margin nor number of harvested lymph nodes (table 2).

Discussion

The present study is based on compound data from two national quality registries covering the surgical and oncological quality of rectal cancer treatment in an unselected patient population, and reflects national daily practice and true long-term results following rectal resection outside the strict frame of an RCT. The results demonstrate non-inferiority and shorter hospital stay for laparoscopic compared to open rectal resection for cancer.

Rectal cancer surgery has undergone significant changes during the last decades from the introduction of TME to minimal invasive surgery with laparoscopy, robotic assisted surgery and other approaches such as transanal total mesorectal excision. In part this development has led to obvious advantages for the patients as complications such as surgical site infections[32], postoperative pain, development of incisional hernias and scarring is more frequent following open than laparoscopic surgery[33–35]. However, despite widespread clinical implementation of laparoscopic access for rectal cancer surgery and the fact that multiple studies have been conducted to assess the results, a recent review[36] summarizing important studies concluded that the non-inferiority of laparoscopic as opposed to open resection in terms of pathological outcomes, local recurrence rates and other long-term outcomes remains to be proven.

Only a few previous studies have explored long-term survival, oncological results and complication rates following laparoscopic and open resection for rectal cancer. The CLASICC[17] trial was the first RCT comparing laparoscopic to open resection in 794 colorectal cancer patients, of whom more than half of the patients underwent surgery for rectal cancer. No difference in 5-year survival between open and laparoscopic rectal resections was found in intention-to-treat analysis, but patients who underwent conversion to open surgery had significantly reduced overall 5-year survival[17]. Patients that underwent anterior resection had higher rates of CRM positivity following LRR with 12% compared to 6% in the ORR group, although not statistically significant. Both 5-year local recurrence rate (10.1%) and distant recurrence rate (20.9%) did not differ between the groups. However, the

conversion rate for rectal procedures was as high as 34%, and the CLASICC study has been criticized for being performed by many surgeons inexperienced with laparoscopic technique, as the only requirement was that participating surgeons should have had undertaken at least 20 laparoscopic colorectal resections prior to the study, This is supported by the steady decline in overall conversions from initially 38% to 16% at the end of the inclusion period[37], indicating that the results from the CLASICC study may be affected by surgeons' learning curve in laparoscopic surgery.

The later COLORII study[13], a randomized controlled trial with 1044 included rectal cancer patients, showed comparable survival rates for LRR compared to ORR and with a local recurrence rate of 5.0% in both groups. In this study conversion rate was 17%[38], but with no presented subgroup analysis on outcome after conversion. Nevertheless, intention-to-treat analysis revealed no difference in complication rates, completeness of mesorectum, number of harvested lymph nodes or CRM positivity between the groups[38]. Also, in the COREAN[20] trial which included 340 patients who had undergone neoadjuvant chemoradiation therapy, no difference in CRM positivity or completeness of mesorectum was found between LRR or ORR, and with similar 3-year survival. The 10-year results have recently been published, still with no difference in neither disease-free nor overall survival, and the authors concluded that laparoscopic procedure was non-inferior to open procedure.

In contrast the ALaCaRT study[16], a randomized multi-center study including 575 patients with rectal cancer T1-T3, failed to establish non-inferiority for LRR regarding completeness of mesorectum, CRM and distal resection margin, although there were no significant differences between the open and laparoscopic group. At a median follow-up of two years there were no difference in disease-free survival or local recurrence between LRR and ORR[39]. Similar results were found in the American ACOSOG-study[15,40], which also concluded that non-inferiority for LRR could not be established.

Despite some studies unable to prove non-inferiority for laparoscopic rectal resections compared to open, a recent meta-analysis[41] of 12 randomized controlled trials comparing LRR and ORR in 3709 patients showed similar 5-year disease-free survival but significantly better overall survival after LRR. The present study supports the findings of non-inferiority of LRR compared to ORR. The earlier studies[15-17,40] that failed to establish non-inferiority for LRR compared to ORR regarding short- and long-term results could have been affected by a

learning effect of introducing laparoscopy in rectal cancer surgery. The present studywas performed years after laparoscopy was well established nationally for rectal cancer, and the relatively low conversion rate probably reflect that effects of still learning the procedure is minimal

The conversion rate of LRR has been a concern, as the CLASICC study showed inferior results in terms of increased complication rates and even worsened survival rates[17,37]. Accordingly, previously published data from the present study cohort also identified an association between conversion and increased postoperative complication rate[42]. While the conversion rate in some older studies where above 15%[37,38,43], the more recent studies report conversion rates between 1 and 12%[15,20,42,44]. As intention-to-treat analysis have failed to show any inferior results following LRR as opposed to ORR, the risk of conversion can not be used as an argument against laparoscopic access for rectal cancer surgery. Nevertheless, the introduction of robotic assisted laparoscopy seems to further reduce the conversion rate in LRR[42,45].

This study has some limitations. As with all observational studies, variables that were not registered could have had confounding effects. Some baseline differences were observed between the groups, and Cox regression analyses was used to adjust survival rates for important differences such as cancer stage. The variable clinical cancer stage had some missing values (622 out of 1796). Statistical tests show that missing data was missing completely at random meaning this variable is fit to include for further analyses, but results from analyses with this variable should be interpreted with this in mind. There was no information available in the registries on previous abdominal surgery or other reasons for expected adhesions/distorted anatomy that could demand open surgery. Another limitation is that completeness of mesorectum was not available as a variable from the Norwegian Colorectal Cancer Registry. This is an important oncological quality measure of the surgical procedure along with circumferential and distal resection margins and number of lymph nodes harvested.

During the study period total coverage in NORGAST compared to The Colorectal Cancer Register was above 60%, which is acceptable. As a newly established register, the national coverage rates in NORGAST were low during the first years of the study period due to few

participating hospitals. However, in-hospital coverage was high, with low risk for in-hospital selection bias.

The present study is one of the few studies that assesses several of the important aspects following LRR and ORR; long-term survival rate, long-term local recurrence rate, short-term complication rate including hospital length-of-stay, reoperations, anastomotic leak rates, and histopathological results. Results after LRR were non-inferior compared to ORR, but with significantly shorter hospital length-of-stay. Thus, the present study supports the view that laparoscopy should be chosen over open access for rectal cancer resection if no specific reason to choose otherwise exists, such as known adhesions, severe pulmonary disease or stage 4 tumors.

Ethics approval

Approval was obtained from the local Data protection officer at the University hospital of North Norway, as well as the regional North Ethics Committee. Informed consent was obtained from all individual participants included in the study.

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