Long-term outcome, socioeconomic aspects, and postoperative inflammatory response in minimally invasive rectal cancer surgery

He who knows all the answers has not been asked all the questions

Confucius

To my parents Zahra and Mehdi

Örebro Studies in Medicine 286

KAVEH DEHLAGHI JADID

Long-term outcome, socioeconomic aspects, and postoperative inflammatory response in minimally invasive rectal cancer surgery

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ABSTRACT

In Sweden, more than 2,200 individuals are diagnosed with rectal cancer each year and surgical resection is the cornerstone of treatment. Minimally invasive surgery (MIS) was introduced for abdominal rectal cancer resection in the 1990s. Proven advantages of MIS in the short term include less intraoperative bleeding, less postoperative pain, faster postoperative mobilization, and shorter hospital stay. Large randomized studies have also shown that MIS is not inferior to OPEN with regard to the oncological short-term or long-term outcome.

The aim of this thesis was to increase the knowledge of MIS from a Swedish perspective regarding long-term oncological outcome, socioeconomic aspects, and the postoperative inflammatory response in curative abdominal rectal cancer surgery.

Study I included all patients who were diagnosed with clinical stage I–III rectal cancer during 2010–2016. More than 8,300 patients were identified via the Swedish Colorectal Cancer Registry (SCRCR). The study had a so-called non-inferiority design and investigated overall 5-year survival. The results showed that survival was not worse in patients who underwent minimally invasive surgery in comparison to patients who underwent open surgery.

Study II included all patients who were diagnosed with pathological stage I–III cancer of the colon 2010–2016. More than 11,000 patients were identified via the SCRCR. The study was designed in the same way as Study I. The results demonstrated that minimally invasive surgery was not inferior to open surgery.

Study III analysed the potential impact of socioeconomic status, measured as level of education and household income, regarding the likelihood of receiving minimally invasive surgery. All patients who underwent curative abdominal rectal resection surgery during 2010–2016 were included.

More than 8,000 patients were identified. The results showed that patients with the highest level of education and those in the highest income quartile were more likely to be operated on with minimally invasive technique.

Study IV analysed the inflammatory response, measured as serum C-reactive protein during postoperative days 1–5, in all 520 patients undergoing abdominal rectal resection in Örebro between 2011 and 2021. Following exclusions based on postoperative adverse events, 382 patients remained for final analysis. The study demonstrated a trend for a less pronounced inflammatory response in patients operated with robot-assisted laparoscopy compared with conventional laparoscopy.

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ORIGINAL PAPERS

Paper I

Dehlaghi Jadid K, Cao Y, Petersson J, Angenete E, Matthiessen P. Long term oncologic outcomes for laparoscopic versus open surgery for rectal cancer – a population based nationwide noninferiority study. *Colorectal Dis*. 2022;24(11):1308–1317.

Paper II

Dehlaghi Jadid K, Cao Y, Petersson J, Sjövall A, Angenete E, Matthiessen P. Long-term oncological outcomes for minimally invasive surgery versus open surgery for colon cancer – a population-based nationwide study with a non-inferiority design. *Colorectal Dis*. 2023;25(5):954–963.

Paper III

Dehlaghi Jadid K, Gadan S, Wallin G, Nordenvall C, Boman S, Hed Myrberg I, Matthiessen P. Does socio-economic status influence the choice of surgical technique in abdominal rectal cancer surgery? *Submitted*.

Paper IV

Dehlaghi Jadid K, Gadan S, Wallin G, Matthiessen P. Postoperative inflammatory response in patients undergoing laparoscopic and robotic rectal cancer resection. *Manuscript.*

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

Popiolek M, Dehlaghi Jadid K, Gadan S, Baban B, Matthiessen P. Total Mesorectal Excision for Mid-Rectal Cancer without anastomosis: Low Hartmann's operation or intersphincteric Abdomino-perineal excision? *Scand J Surg*. 2019;108(3):233-240

Petersson J, Matthiessen P, Dehlaghi Jadid K, Block D, Angenete E. Short term results in a population based study indicate advantage for laparoscopic colon cancer surgery versus open. *Sci Rep*. 2023;16(13):4335.

Petersson J, Matthiessen P, Dehlaghi Jadid K, Block D, Angenete E. Short term results in a population based study indicate advantage for minimally invasive rectal cancer surgery versus open. *Accepted*

ABBREVIATIONS

ACOSOG	American College of Surgeons Oncology Group
ALaCaRT	Australasian Laparoscopic Cancer of the Rectum study
CI	Confidence interval
CLASICC	Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer study
COLOR	Colon Cancer Laparoscopic or Open Resection study
COLOR II	Colorectal Cancer Laparoscopic or Open Resection study
COREAN	Comparison of Open versus Laparoscopic Surgery for Mid and Low Rectal Cancer After Neoadjuvant Chemo-Radiotherapy study
COST	Clinical Outcome of Surgical Therapy study
CRC	Colorectal cancer
CRCBaSe	Colorectal Cancer Database Sweden
CRP	C-reactive protein
CT	Computed tomography
FAP	Familial adenomatous polyposis
HR	Hazard ratio
IMA	Inferior mesenteric artery
LAP	Conventional laparoscopy
LE	Local excision
MDT	Multidisciplinary team conference
MIS	Minimally invasive surgery
MRI	Magnetic resonance imaging
OPEN	Open surgery
POD	Postoperative day
RCT	Randomized controlled trial
ROBOT	Robot-assisted technique
SCRCR	Swedish Colorectal Cancer Registry
TNM	Tumour-node-metastasis staging system
UC	Ulcerative colitis

INTRODUCTION

Epidemiology

Colorectal cancer (CRC) is the second deadliest cancer and the third most common cancer in the world. Almost 2 million new cases were diagnosed during 2020, and the annual incidence is expected to increase to 3 million by 2040 (Figure 1). [1] Its incidence varies greatly between countries, depending on lifestyle and genetic factors.

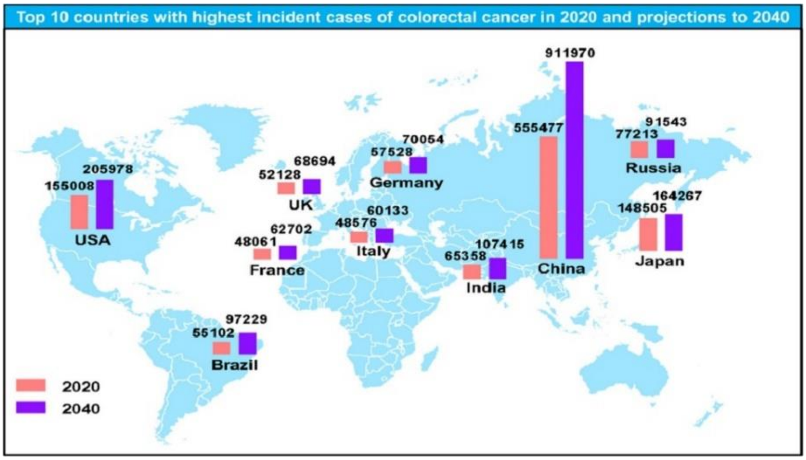

Figure 1. Numbers of new colorectal cancer cases in the 10 countries with the highest annual incidence in 2020, and projections for 2040 [1].

In Sweden, CRC is the second most common type of cancer. Around 7000 patients were diagnosed in 2022, two-thirds of whom had colon cancer and the remaining one-third rectal cancer. The distribution between genders is equal regarding colon cancer, but men have a higher incidence of rectal cancer compared to women; the reasons for this are still unknown. Median age at diagnosis is 70 years for rectal cancer and 74 years for colon cancer. There is a steady increase of cases each year, partly due to an ageing population, but the full explanation remains to be uncovered. [2] Conversely, and fortunately, mortality rates have decreased over time [3] (Figure 2).

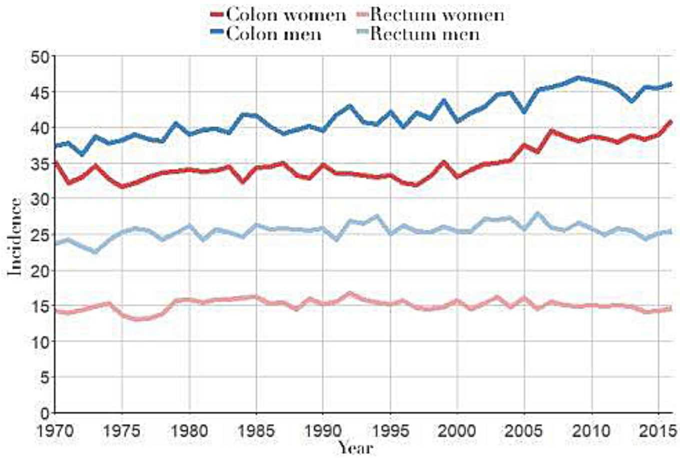

Figure 2. Incidence per 100 000 inhabitants for colon cancer and rectal cancer patients in Sweden, 1970–2016. Used with permission from the Swedish Colorectal Cancer Registry (SCRCR).

Aetiology and risk factors

The rising incidence of CRC in the Western world is believed to be multifactorial, with relevant aspects including age, lifestyle habits, and genetic factors. An ageing population along with improvements in the global average health mean that there is an increased likelihood of an individual developing cancer during their lifetime. [4] Lifestyle factors such as physical inactivity, smoking, alcohol intake, and poor diet including a high intake of processed food and low intake of dietary fibre, as well as personal characteristics such as obesity, are all associated with an increased risk of developing CRC (Figure 3). [5-11]

Regarding genetic factors, there is a group of hereditary colorectal cancer that represents about 10% of all colorectal cancers, the most common being Lynch syndrome and familial adenomatous polyposis (FAP). Both are associated with a higher risk of developing CRC at an early age; for FAP, this usually occurs before the age of 40, while for Lynch syndrome it is usually before the age of 50. [12-14]

Inflammatory bowel disease (IBD) is a risk factor for developing CRC, and both Crohn's disease (CD) and ulcerative colitis (UC) are associated with a higher risk of cancer development. Patients with IBD as well as those at hereditary risk are offered surveillance programs including colonoscopy to facilitate early detection of CRC. [15, 16]

The pathophysiology and development of cancer cells feature a clonal mutation that leads to an increase in mutations, and these cells proliferate and invade other cells. The most common type of CRC is adenocarcinoma, which takes its name from "adeno", meaning "gland", and "carcinoma", which is a type of cancer that grows in the epithelial cells. [17-19]

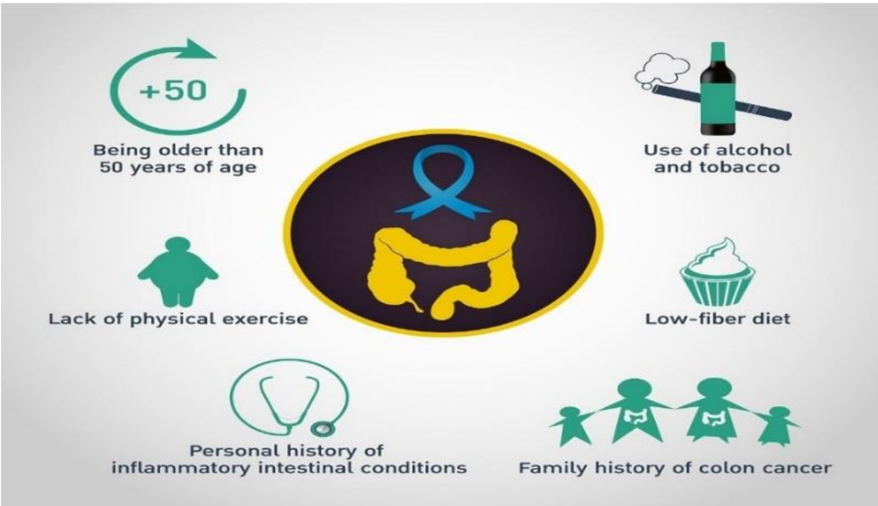

Figure 3. Risk factors associated with colorectal cancer.
From https://noahhelps.org/the-importance-of-colon-cancer-screening

Anatomy

The colon is approximately 100–150 cm long (Figure 4). It begins in the right lower quadrant of the abdomen, with the caecum, which is followed by the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon, and the sigmoid colon. The final part of the colon is the rectum, which begins at the rectosigmoidal junction at the sacral promontory, and ends at the anus. Three bundles of muscle run along the outside of the colon; for most of its length they remain separate, forming the taeniae coli, but in the rectum they spread out and form a continuous layer.

The rectum is investigated with a flexible or rigid rectoscope, and its upper border is considered to exist at 15 cm above the anal verge, as measured with a rigid rectoscope. It is divided into an upper, a middle, and a lower part. The rectum is surrounded by several anatomical structures and fascias, such as the mesorectum, which harbours the blood supply and lymphatic tissue. In women, the lower part of the rectum is separated from the vagina by the rectovaginal fascia; and in men, it is separated from the prostate gland by Denonvilliers' fascia. Posteriorly it is attached to the presacral fascia (Figure 5).

Embryology

The right colon and transverse colon are derived from the midgut and are supplied by the superior mesenteric artery (SMA). The hindgut forms the distal half of the colon, and is supplied by the SMA and the inferior mesenteric artery (IMA). From an embryological point of view, the rectum forms in the hindgut and gets its blood circulation from the IMA.

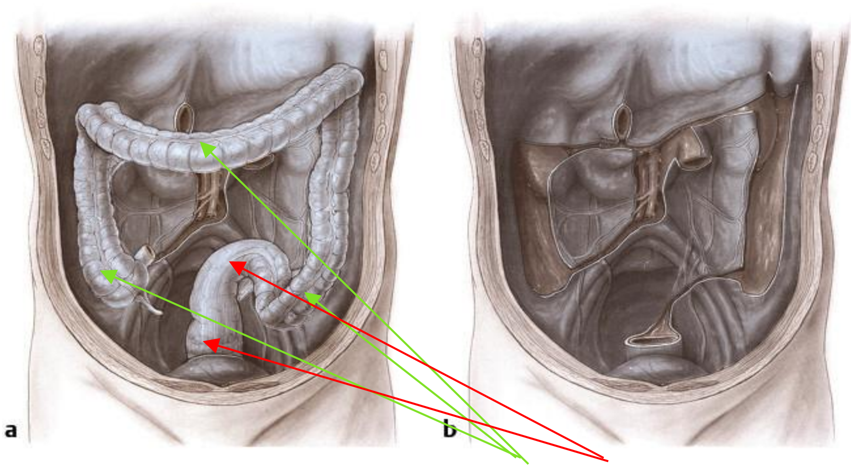

Figure 4. General topography of the large bowel: (a) colon and rectum, (b) peritoneum and adjacent structures. From *Gordon and Nivatvongs' Principles and Practice of Surgery for the Colon, Rectum, and Anus*.

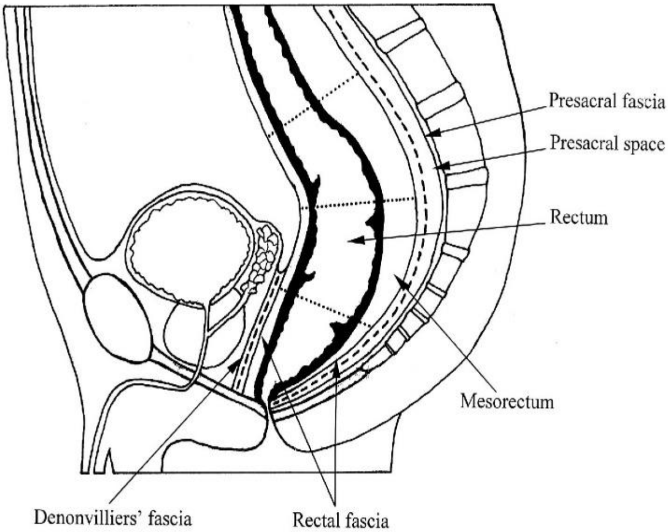

Figure 5. The anatomy of the rectum and its relationship to the fascias. From https://europepmc.org/article/MED/29416206

Symptoms and diagnosis

Colorectal cancer can be asymptomatic in the early stages of the disease. The cardinal symptom is rectal bleeding. Another major symptom is changed bowel habits, which can present as loose stools, constipation, and an incomplete feeling of emptying of the bowel. Weight loss and abdominal pain are usually late signs of more advanced disease. [20-22]

Symptoms

If a patient presents with blood in the stool, anaemia, or changed bowel habits for more than 4 weeks, and is over the age of 50, they should be referred to a colorectal unit for further investigation and examination. Delayed time to diagnosis may have negative consequences such as more locally advanced disease and metastatic spread. In an effort to reduce the time to diagnosis, Sweden has launched the so-called "Standardiserat vårdförlopp" (SVF), which has led to some reduction in the lead time for patients presenting with the symptoms of CRC. [23]

Examination and investigation

Clinical examination is of importance. The rectum is examined with digital palpation and a rigid rectoscope to evaluate tumour height and mobility. [24] A colonoscopy is performed to examine the whole colon, to exclude synchronous tumours, and to give the possibility of taking a biopsy to determine the histopathology of the tumour. [25] Different types of neoplasms can be found in the colon. Adenocarcinoma is the most common type found in CRC, but other types such as neuroendocrine tumour, lymphomas, sarcomas, and in some rare instances melanomas are also seen. [26]

Laboratory tests

Blood sampling to determine haemoglobin and iron levels should be conducted to identify anaemia and to correct low levels before surgery. Intravenous iron infusion may be given preoperatively, usually at outpatient departments, and this has shown positive results regarding intraoperative and postoperative outcome. [27] There are few tumour markers for CRC, but carcinoembryonic antigen (CEA) is useful, and is the most commonly used. [28]

Imaging

Radiology has come far, and there are now a variety of different modalities used to stage the tumour regarding anatomic localisation and morphological information such as spread of tumour, lymph node involvement, and spread to other organs. For colon cancer, a computed tomography (CT) of the abdomen and chest is the standard radiology examination to obtain relevant information regarding the cancer. For rectal cancer, there are additional modalities used that give a better image of the anatomy in the pelvic area. An endoscopic ultrasonography can be used for loco-regional staging, but in Sweden as well as most other countries, it is mandatory to conduct pelvic magnetic resonance imaging (MRI), which is excellent for visualization of the pelvis. In some cases, a positron emission tomography (PET) examination, which combines radioactive isotopes with a CT scan to give further information, is used. [29-32]

Tumour-node-metastasis staging

The system currently used to classify the stages of tumours is the tumour-node-metastasis (TNM) model (Table 1). The first edition of the TNM manual was published in 1987, and the latest edition is the 8th, which was released in 2018. [33, 34]

TNM staging involves both clinical (cTNM) and pathological (pTNM) staging. The clinical stage is the basis for treatment decision, and the pathological stage is the assessment following surgery. Due to the increased use of radiotherapy or radiotherapy and chemotherapy before treatment, a “y” symbol was introduced, which indicates a post-neoadjuvant therapy assessment. Patients can now therefore have a ycTNM stage, which indicates the clinical stage after neoadjuvant treatment, and a ypTNM stage, which represents assessment after neoadjuvant treatment and surgery. [35]

The histopathological report is of major importance, and should include the following information: type of adenocarcinoma, cancer grade (low or high), resection margins, circumferential resection margin (CRM), number of lymph nodes with and without malignant infiltration, tumour deposits, vascular invasion, and perineural invasion. [36] This information is presented and discussed at a multidisciplinary team conference (MDT), and will serve as the basis for deciding further treatment after surgery. [2]

Table 1. Tumour-node-metastasis (TNM) staging (TNM manual, 8th edition).

T – Tumour	
T0	No evidence of primary tumour
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa or non-peritonealized perirectal tissues
T4a	Tumour perforates visceral peritoneum
T4b	Tumour directly invades other organs or structures
N – Regional lymph nodes (Node)	
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumour deposit(s), i.e. satellites in the subserosa, or in non-peritonealized pericolic or perirectal tissue without regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
M – Metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node/nodes) without peritoneal metastases
M1b	Metastasis in more than one organ
M1c	Metastasis to the peritoneum with or without other organ involvement

Multidisciplinary team conference

The multidisciplinary team conference (MDT) was first introduced in England in the 1990s, and arrived in Sweden in the early 2000s. It was applied initially for rectal cancer and later also for colon cancer. [37] The standard CRC MDT in Sweden involves a pathologist, an oncologist, a radiologist, a surgeon, and a dedicated nurse. In principle, all CRC patients are discussed at an MDT before and after surgery and/or oncological treatment.

Depending on the localisation of the tumour and the TNM stage, a decision is made whether the patient should receive radiotherapy or radio-chemotherapy before surgery (neoadjuvant therapy). Some patients will also receive oncological treatment after surgery (adjuvant therapy), depending on the histopathological analysis. There is strong evidence that these MDTs are beneficial for the overall survival and quality of life for patients with CRC. [38, 39]

Oncological treatment

The European Society for Medical Oncology (ESMO) guidelines for rectal and colon cancer include radiotherapy and chemotherapy, which are also labelled as neoadjuvant and adjuvant therapy. [24, 40] Several trials have shown that radiotherapy reduces local recurrence in rectal cancer patients. [41-44] The 5x5 Gray (Gy) regimen is frequently used, and should be followed by surgery within 10 days of the start of the radiotherapy, or after 8–10 weeks. The aim is to sterilize the surrounding tissue, but not to downsize the tumour itself. Conversely, when administering a regimen of 2x25 Gy combined with chemotherapy, called conventional radio-chemotherapy (CRT), the aim is to downsize the tumour in order to facilitate the subsequent surgery. [45] A summary of treatment regimens is given in Table 2.

Radiotherapy combined with chemotherapy preoperatively has demonstrated a very interesting tendency to eliminate all viable tumour. This is called complete pathologic response (pCR), and has been demonstrated both in the RAPIDO trial and in the Swedish protocol LARCTUS. [46, 47] The experimental arm of the RAPIDO protocol, and the LARCTUS protocol, were based on 5x5 Gy followed by chemotherapy (usually Capecitabin and Oxaliplatin). Complete clinical response (cCR) may also occur following conventional radio-therapy and, although infrequently, by 5x5 Gy only. A proportion of patients demonstrate cCR following advanced neoadjuvant treatment. [48, 49] As early as 1998, the Brazilian surgeon Angelita Habr-

Gama [50] suggested a non-operative management for such patients. The risk of so-called regrowth has been calculated to be around 25%, which is considered acceptable if the patient is rigorously followed as stipulated by the protocol. [51-53]

Table 2. Neoadjuvant treatment in rectal cancer (Swedish Regional Cancer Centre 2020).

Tumour height, distance from anal verge in cm	T1–2	T3 a–b	T3 c–d	T4a	T4b	N1	N2	mrf+	Lat.lgl	EMVI
High, 11–15	0	0	5x5	5x5	5x5/CRT	0	5x5	CRT	CRT	5x5
Medium, 6–10	0	5x5	5x5	5x5	5x5/CRT	5x5	5x5	CRT	CRT	5x5
Low, 0–5	5x5	5x5	5x5	-	5x5/CRT	5x5	5x5	CRT	CRT	5x5

5x5 = 5 Gy radiotherapy in 5 fractions; CRT = 1.8 Gy radiotherapy in 28 fractions or 2 Gy in 25 fractions combined with chemotherapy; LARCTUS = 5x5 Gy followed by four cycles of chemotherapy; EMVI = extramural vascular invasion; Lat. lgll = engagement of lymph nodes outside the mesorectal fascia; mrf+ = mesorectal fascia involvement; N = lymph nodes; T = tumour stage.

Endoscopic treatment

Endoscopic treatment may be an alternative for patients with rectal cancer of limited size who would otherwise require major surgery or who have substantial comorbidity which may increase the risk of abdominal surgery. [54]

Transanal endoscopic microsurgery

Transanal endoscopic microsurgery, which was introduced in 1983 by the German surgeon Gerhard Buess, was one of the first complex endoscopic surgical procedures for rectal cancer. [55] Another method is transanal local excision. [56] These methods are employed in selected cases, and generally not in cases with curative intent.

Endoscopic mucosal resection and endoscopic submucosal dissection

Endoscopic mucosal resection (EMR) is the traditional endoscopic method where “hot and cold” snares are used to remove polyps and adenomas. The limitations of this method led to the development of endoscopic submucosal dissection (ESD), [57] which has become a widely used technique for upper gastrointestinal tumours and is now gaining popularity for CRC. ESD is an excellent tool for complete resection of larger colorectal cancers (>20mm), and its use of an endoscopic knife is an excellent alternative when EMR with snares is difficult. [58, 59]

Surgery

The history of surgery dates back to the Mesopotamian empire. Ancient Egyptian scrolls such as the Edwin Smith Papyrus contain instructions for treating infections, use of sutures, and trauma manuals for surgery. [60]
In the 18th century, George Arnaud de Ronsil performed the first right hemicolectomy. [60] The centuries following have been an era of constant surgical development. For example, it is estimated that between 1880 and 1920 more than 300 different methods of bowel anastomoses were introduced. [61]

In 1908, a Lancet article by Sir William Ernest Miles presented a series of patients who underwent abdominoperineal resection for rectal cancer. [62] Of the 57 patients, 54 developed local recurrence within the first six months. Post mortem investigations performed by Miles himself made him realize the importance of complete excision of the mesenteric lymphatic tissue, including the mesorectum, in order to decrease the risk of local recurrence. [63] This novel surgical-anatomical approach was described by Miles in a 1914 publication in the British Journal of Surgery, and is still, in principle, in use after more than 100 years. [64]

The French surgeon Henry Hartmann presented a case series in 1921 describing a two-step procedure for rectal cancer; the first step was the construction of an end colostomy, and the second step, performed about a week later, was excision of the rectum including the tumour, leaving the rectal stump in the low pelvis. [65] He later published an article on a series of rectal cancer patients who underwent this new procedure, reporting a mortality rate of 8.8%, which was astonishingly low for the period. [66]

Surgical staplers

The introduction of surgical stapler devices took colorectal surgery into a new era. Invented in Hungary in 1908 but developed in the former Soviet Union, they caught the eye of the American surgeon Mark Ravitch during a trip to Kiev in 1958. [67] He later developed several prototypes before introducing a functionally reliable stapler device in 1967. [68] These circular mechanical stapler devices enabled the construction of low anastomoses at the pelvic floor, thus reducing the proportion of permanent colostomies. [69]

Total mesorectal excision

A landmark publication by Bill Heald in 1982 suggested a new concept of rectal surgery known as total mesorectal excision. It was initially met with some scepticism, but later gained popularity, and became widespread in Sweden in the late 1990s. [70] The previously commonly used method of blunt surgical technique was associated with high local recurrence rates, while the technique proposed by Heald respected the "holy plane" and included the excision of an intact mesorectum. [71] (Figure 6) Heald was also a proponent of identifying and preserving of the pelvic nerves and neurovascular bundle (Figure 7), and would later report an overall 5-year survival of 80% and a decrease in the local reoccurrence rate from 20% to 4%. [72]

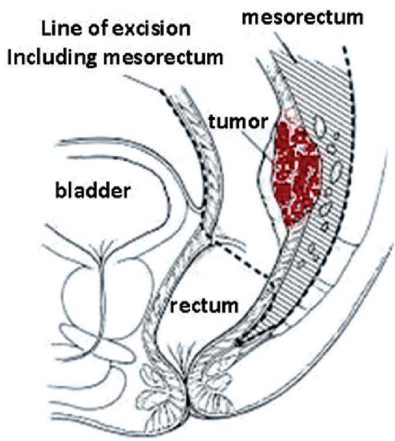

Figure 6. Principles of total mesorectal excision, https://www.researchgate.net/figure/Sketch-showing-the-principles-and-extent-of-Total-Mesorectal-Excision-TME_fig4_305318347

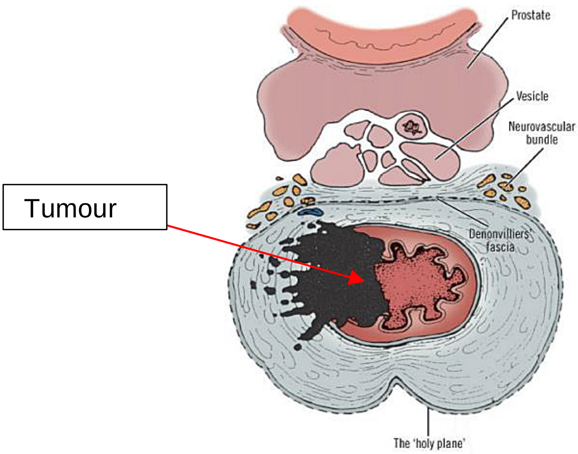

Figure.7 Relations of the neurovascular bundle to the "holy plane". From: https://www.researchgate.net/figure/Illustration-of-the-resection-plane-during-TME-Adapted-from-Skandalakis-Surgical_fig2_228931902

Laparoscopy

George Kelling, a German physician, is recognised as the first to establish pneumoperitoneum in an animal model in 1901. [73] In 1910, Hans Christian Jacobaeus, a Swedish physician, was the first to publish regarding the use in humans of a new technique known as "laparothorakoskopie". [74]

Gynaecological surgeons brought about many breakthroughs in laparoscopic technique during the mid-1960s and 1970s, such as improved instruments for coagulation, better instruments for lighting, and better insufflations for the carbon dioxide to establish pneumoperitoneum. A major improvement was the video laparoscope, which improved vision of the surgical field and made video documentation possible. In the mid-1980s, German and French surgeons started to perform laparoscopic cholecystectomies, which launched a general interest in laparoscopic surgery. [75, 76]

The first reported laparoscopic colectomy was performed in 1991 by Jacob et al. [77] The colorectal community then began to implement this new technique, initially mostly for benign disease. Laparoscopy for colon cancer was performed in the COST trial starting in 1994. [78] Reports of port metastasis after laparoscopic surgery halted the general development for many years, but it was later shown that port site metastases were not more frequent than incisional metastases in open surgery, with a frequency of around 0.5% for both techniques. [79-81] Results from large randomized controlled trials (RCTs) such as the COST, COLOR, and CLASICC trials demonstrated favourable short-term postoperative outcomes for minimally invasive surgery (MIS), such as less blood loss, reduced pain, faster return of bowel function, and shorter hospital stay. [78, 82, 83] Long-term outcomes from these trials demonstrated that oncological results were comparable. [84-86]

Laparoscopic surgery for rectal cancer started later, and its development was initially slower due to concerns regarding the safety of surgical technique and oncological outcome. Several RCTs were conducted to compare laparoscopic to open surgery, such as COLOR II, COREAN, ALaCaRT, and ACOSOG. [87-90] Short-term outcomes showed similar results to the colon cancer trials. A meta-analysis from 2007 covering 27 RCTs on colorectal cancer resection surgery confirmed the safety of laparoscopic colorectal surgery. [91]

In Sweden, the shift towards MIS arrived later than in continental Europe, with the technique starting to become established around 2010.

Robotic surgery

Robot-assisted laparoscopy was first introduced in Germany in 2001. In comparison to conventional laparoscopy, its benefits include ergonomic aspects, the excellent vision provided by advanced optic systems, the absence of impact of possible tremors, and 360-degree dexterity. [92, 93]

Minimally invasive surgery in Sweden

The progress of MIS has been relatively slow-moving in Sweden, with only a handful of hospitals active in the late 1990s. This started to change in the latter part of the 2000s as more hospitals became involved. The proportion of MIS in Sweden remained steady at around 5% during 2007–2009. In 2009, a working party for minimally invasive colorectal surgery in Sweden was formed and supported by the Swedish Society of Colon and Rectal Surgeons (Figure 8 and 9).

Around 2014, the proportion of patients operated on with MIS grew to around 30%. The conversion rate, which is generally regarded as an indicator of the experience and competence of the surgical teams, remained steady at around 20% during this period. This percentage is considered reasonable, as the conversation rate in the multicentre RCT COLOR II [88] was 17%. Robot-assisted surgery for CRC was introduced in one hospital in Sweden during 2010, and thereafter in several other hospitals during 2013–2014. It has been registered in the Swedish Colorectal Cancer Registry (SCRCR) since 2014 (Figure 10 and 11). [94]

The well-established short-term outcomes and the non-inferior long-term results support the continued use of MIS for CRC. It is likely that in the near future, a large majority of the surgical procedures for CRC will be performed with a minimally invasive technique, and subsequently a decreasing proportion by open surgery. This shift will benefit patients, but it also brings the challenge of providing adequate training in open surgery, in order to keep this surgical technique as a high-quality option when needed. [89, 95-96]

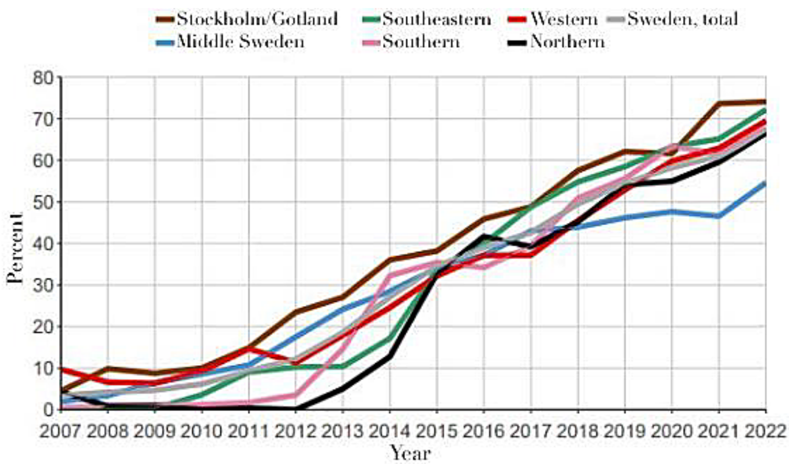

Figure 8. Patients undergoing minimally invasive surgery for colon cancer in Sweden during 2007–2022. Used with permission from Nationell kvalitetsrapport, 2022, the Swedish Colorectal Cancer Registry (SCRCR).

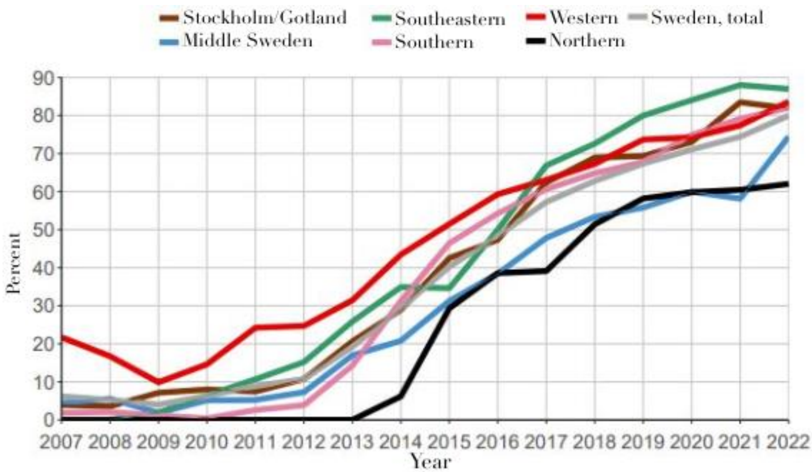

Figure 9. Patients undergoing minimally invasive surgery for rectal cancer in Sweden during 2007–2022. Used with permission from Nationell kvalitetsrapport, 2022, the Swedish Colorectal Cancer Registry (SCRCR).

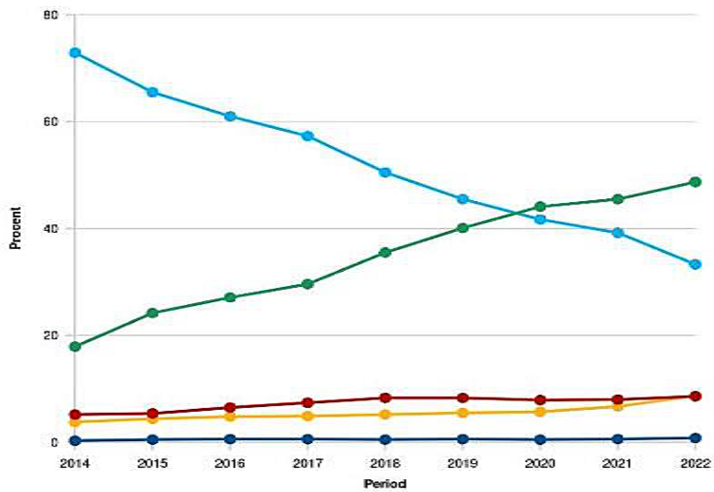

Figure 10. Patients undergoing resection surgery by OPEN, LAP or ROBOT for colon cancer in Sweden during 2014–2022. Blue: Open; Green: Conventional laparoscopy, not converted; Yellow: Robotic, not converted; Red: Conventional laparoscopy, converted; Dark blue: Robotic converted. Used with permission www.scrcr.se (SCRCR).

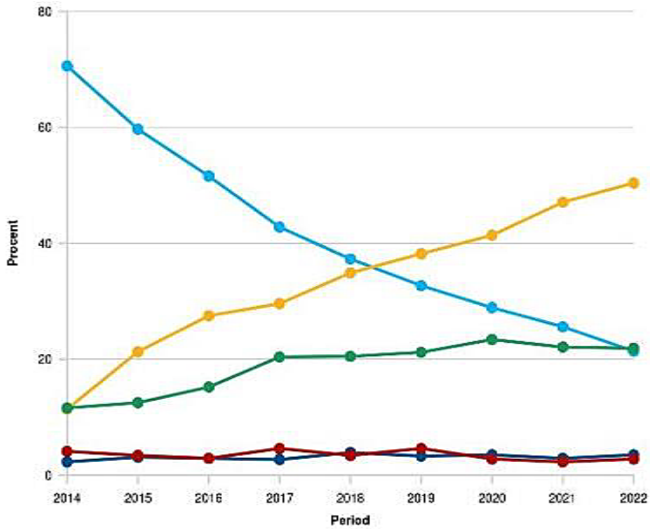

Figure 11. Patients undergoing resection surgery by OPEN, LAP or ROBOT surgery for rectal cancer in Sweden during 2014–2022. Blue: Open; Green: Conventional laparoscopy, not converted; Yellow: Robotic, not converted; Red: Conventional laparoscopy, converted; Dark blue: Robotic converted. Used with permission www.scrcr.se (SCRCR).

AIMS OF THE THESIS

General

The general aim of this thesis was to investigate the impact of minimally invasive surgery in Sweden with regard to long-term outcome, socio-economic aspects, and postoperative inflammatory response.

Aims of the studies

The specific aims of the studies were:

I.
To compare 5-year overall survival in a national cohort of patients undergoing curative abdominal resection for rectal cancer by MIS or open surgery (OPEN).

II.
To compare 5-year overall survival in a national cohort of patients undergoing curative resection for colon cancer in the most common locations, the right colon and sigmoid colon, by MIS or OPEN.

III.
To investigate the possible impact of socioeconomic status or level of education for patients undergoing curative rectal cancer with regard to the likelihood of receiving MIS or OPEN.

IV.
To investigate the postoperative inflammatory response as assessed by postoperative C-reactive protein, comparing open surgery, conventional laparoscopy, and robot-assisted surgery.

METHODS

The study cohorts and methods for Studies I–IV are summarised in Table 3, and patient demographics are given in Table 4.

Study I was a retrospective study using patient data retrieved from the SCRCR. The study population included patients who were diagnosed with clinical stage I–III (cTNM) rectal cancer between 1 January 2010 and 31 December 2016 and subsequently underwent curative abdominal resection surgery. Patients who were diagnosed with cancer stage IV were not included. The cohort was followed until 31 December 2020. The three main abdominal surgical procedures were included: anterior resection, abdominoperineal resection, and Hartmann's procedure. Conventional laparoscopy and robot-assisted laparoscopy were analysed as a single group (MIS). The exposure variable was surgical technique (MIS vs. OPEN), and the main outcome measure was overall survival at 5 years.

Study II was also a retrospective study using patient data retrieved from the SCRCR. The study population included patients who were diagnosed with stage I–III colon cancer between 1 January 2010 and 31 December 2016 and subsequently underwent curative resection surgery. Patients with colon cancer located in the right colon (including the caecum, the ascending colon, and the hepatic flexure) or the sigmoid colon were included. The cohort was followed until 31 December 2020. Patients with cancer stage IV were not included. The surgical procedures included were right hemicolectomy (including extended right hemicolectomy), sigmoid resection, and high anterior resection. Conventional laparoscopy and robot-assisted laparoscopy were analysed as a single group (MIS). The exposure variable was surgical technique (MIS vs. OPEN) and the main outcome measure was overall survival at 5 years.

Study III was a retrospective study including patients diagnosed with rectal cancer and curatively operated between 2010 and 2016. In cooperation with the Colorectal Cancer Database Sweden (CRCBaSe), data from the SCRCR were linked to other Swedish national registries such as the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA), Microdata for folk- and bostadräkning (FoB), the National Board of Health and Welfare (Socialstyrelsen), and Microdata for Analysis of Social Insurance (MIDAS). [97] Exposures were level of education (categorized as 6–9, 10–12, or >12 years) and household income (quartiles 1–4), and outcome was MIS or OPEN.

Study IV was a retrospective study including patients who underwent curative abdominal rectal resection surgery (anterior resection, abdominoperineal resection, or Hartmann's procedure) at the Colorectal Unit, Department of Surgery, Örebro University Hospital, between 2011 and 2021. Three surgical techniques were compared: open surgery (OPEN), conventional laparoscopy (LAP), and robot-assisted laparoscopy (ROBOT). Patient data were retrieved from the SCRCR and copies from the original patient files were assessed regarding patient variables. Inflammatory response, as indicated by C-reactive protein (CRP), was observed both preoperatively and on postoperative days (PODs) 1–5. The exposure was surgical technique and the primary outcome was inflammatory response (CRP) while the secondary outcome was length of hospital stay. The aim was to assess patients without major postoperative adverse events. For this reason, patients with complications classified as Clavien Dindo >2 were excluded, as well as patients with a length of hospital stay exceeding 9 days.

Table 3. Summary of study cohorts and methods for Studies I–IV.

Study	Design	Patients (n)	Year of diagnosis	Exposure	Outcome
I	Retrospective Non-inferiority Registry based	8,410	2010–2016	Surgical technique	Overall 5-year survival
II	Retrospective Non-inferiority Registry based	11,605	2010–2016	Surgical technique	Overall 5-year survival
III	Retrospective Superiority Registry based	7,944	2010–2016	Socio-economic status	MIS or OPEN
IV	Retrospective Superiority Single centre	520	2011–2021	Surgical technique	Postoperative CRP

Table 4. Summary of patient demographics in Studies I–IV.

Study	Age (median)	Female (%)	BMI (median)	ASA class ≥3 (%)
I				
MIS	70	43.6%	25.2	20.8%
OPEN	69	38.5%	25.6	24.9%
II				
MIS	71	46.8%	25.7	27.9%
OPEN	73	52.4%	25.2	33.4%
III				
MIS	70	44.1%	25.2	20.6%
OPEN	69	38.7%	25.6	24.6%
IV				
LAP	71	37.4%	27.0	16.3%
OPEN	72	34.6%	25.0	31.7%
ROBOT	70	36.9%	25.0	21.7%

ASA = American Society of Anesthesiologists; BMI = body mass index; OPEN = open surgery; LAP = conventional laparoscopy; ROBOT = robot-assisted technique; MIS = minimally invasive surgery (LAP + ROBOT)

Statistical analysis

Study I

The primary analysis was a non-inferiority evaluation. In order to estimate an adequate sample size, survival data for all Swedish patients who underwent abdominal surgery for stage I–III rectal cancer between 2010 and 2015 were obtained from the SCRCR via the Swedish Regional Cancer Centre (RCC) website. The 5-year overall survival rates for patients who underwent curative surgery during this period were 75% in the OPEN group and 79% in the MIS group. To establish a non-inferiority setting with a margin of 2%, a statistical power of 90%, and a one-sided type I error of 2.5%, the calculated minimum sample sizes for the OPEN and MIS groups were 1852 and 742, respectively. The actual sample sizes in Study I were 6316 for the OPEN group and 2094 for the MIS group.

Kaplan–Meier curves were used to depict overall mortality in the entire cohort and for each cancer stage individually. Categorical variables were presented as count and percentage, while continuous variables were expressed as median and quartile range (Q25, Q75). The statistical analysis employed the chi-square test, the Wilcoxon rank sum test and the Kruskal Wallis test as appropriate. The association between surgical technique (MIS or OPEN) and postoperative mortality was investigated using multilevel survival regression models. Patients were matched based on propensity score, and adjustments were made for covariates deemed relevant including age, sex, BMI, ASA classification, clinical cancer stage (cTNM), neoadjuvant treatment, tumour level, type of surgical procedure (anterior resection, abdominoperineal resection, Hartmann's procedure), and year of surgery. The propensity scores for receiving OPEN or MIS were estimated using a logistic regression model. In a specific set of statistical models, missing values were addressed through multiple imputation methods. Rubin's rules for synthesis were employed for the outcomes from five imputed datasets.

Study II

The primary analysis was a non-inferiority evaluation. The estimation of an adequate sample was similar to the one in Study I, involving an assessment of the observed survival in all Swedish patients abdominally operated for pathological stage I–III colon cancer during 2010–2015. The data were retrieved from the SCRCR through the RCC website. The observed 5-year overall survival in patients curatively operated between 2010 and 2015 was 64% in the OPEN group and 77% in the MIS group. Based on these findings, in order to demonstrate non-inferiority with a margin of 2%, a statistical power of 90%, and a one-sided type I error of 2.5%, the minimum sizes for the OPEN and MIS groups were 274 and 137, respectively. The actual sizes in Study II were 8308 and 3297, respectively.

The reason for using pathological cancer stage was that, in contrast to Study I, not all patients were preoperatively assessed at an MDT during the relevant study period, while all had a pathological report. A small proportion of patients receiving neoadjuvant chemotherapy were excluded.

Kaplan–Meier curves were used to illustrate all-cause mortality in the entire cohort and for each cancer stage separately. Results are presented as count and percentage for categorical variables, and median and quartile range

(Q25, Q75) for continuous variables, employing the chi-square test, the Wilcoxon rank sum test, and the Kruskal Wallis test as appropriate. The relationship between surgical technique (MIS or OPEN) and postoperative mortality was analysed using multilevel survival regression models. Patients were matched by propensity score, adjusted for the covariates age, sex, BMI, ASA classification, type of surgical procedure (right sided hemicolectomy, sigmoid resection, and high anterior resection), year of surgery, tumour pathological T stage, pathological N stage, and adjuvant therapy. The propensity scores for receiving OPEN or MIS were estimated using a logistic regression model.

Study III

Study III had a superiority design, and was aimed at analysing a number of covariates with regard to the likelihood of receiving MIS. The exposures of primary interest were level of education (categorized as 6–9 years, 10–12 years, and >12 years) and household income (categorized as quartiles 1–4), and the outcome was MIS or OPEN. Descriptive statistics were calculated as frequency and percentage for categorical variables, and median with interquartile range for continuous variables.

Only individuals with non-missing data regarding the regression covariates were included in the regression analyses (n=7,945). The covariates in the multivariable logistic regression model were: age in 5-year increments, sex, country of birth, number of previous abdominal surgical procedures (0, 1, ≥ 2), clinical T stage (cT1–3, cT4), and clinical N stage (cN0, cN1–2). The assumption of linearity between age on the log-odds outcome was evaluated by comparing the Akaike information criterion of a model including age as a linear covariate to models using restricted cubic splines for age. The linearity assumption was found to be adequate. Version 4.2.0 of the statistical software package R was used for all statistical analyses. Statistical tests were two-sided, and statistical significance was set at α=0.05.

Study IV

The exposure of interest was surgical technique according to intention to treat OPEN, LAP, and ROBOT. Primary outcome was CRP on POD 1-5, and secondary outcome was length of hospital stay. Results are presented as count and percentage for categorical variables, and median with interquartile range for continuous variables. When comparing two groups, the chi-squared test and Fisher's exact test were used as appropriate for categorical variables, and the Mann-Whitney U-test and Student's t-test were used for continuous variables. The Kruskal-Wallis one-way ANOVA test was used when comparing more than two groups. Version 29.0 of the SPSS software package (SPSS, Chicago, Illinois, USA) was used for statistical calculations.

Ethical considerations

The four studies included in the present doctoral thesis project were all retrospective. None of the included patients were or will be subjected to any kind of intervention. Since these patients had already undergone surgery, there was no potential benefit or negative impact for them.

Studies I and II: Ethical permission was obtained from the ethical committee of the Uppsala–Örebro healthcare region (refs: 2018/129 and 2019–01787).

Study III: Ethical permission was granted by the Stockholm Regional Ethics Vetting Board (refs: 2014/71-31 and 2018/328-32) and the National Ethical Committee (ref: 2021-00342).

Study IV: Ethical permission was granted by the National Ethical committee (ref: 2023-00232-01)

RESULTS

Study I

A total of 8410 patients met the inclusion criteria: 6316 (74.9%) in the OPEN group and 2094 (24.9%) in the MIS group. The conversion rate in the MIS group was 16.6%. MIS was not found to be inferior to OPEN with regard to overall 5-year survival (Figure 12).

In the secondary analysis, multivariable Cox regression demonstrated that the 5-year overall survival was in fact increased in MIS, with a hazard ratio (HR) of 0.877 (95% CI: 0.775–0.993). Outcome was similar when employing multiple imputation and propensity score matching. When cT4 patients were excluded, there was no statistically significant difference, although the HR was similar (HR: 0.885; 95% CI: 0.790–1.033).

Converted MIS cases had worse 5-year overall survival compared with OPEN (HR: 1.256; 95%CI: 1.004–1.570). At the 5-year follow up, the observed local recurrence rate was comparable between OPEN and MIS (3.6% and 2.9%, respectively; unadjusted p=0.075) (Figure 13), while the rate of observed metastatic disease was higher in OPEN than in MIS (19.6% and 15.6%, respectively; unadjusted p<0.001) (Figure 14).

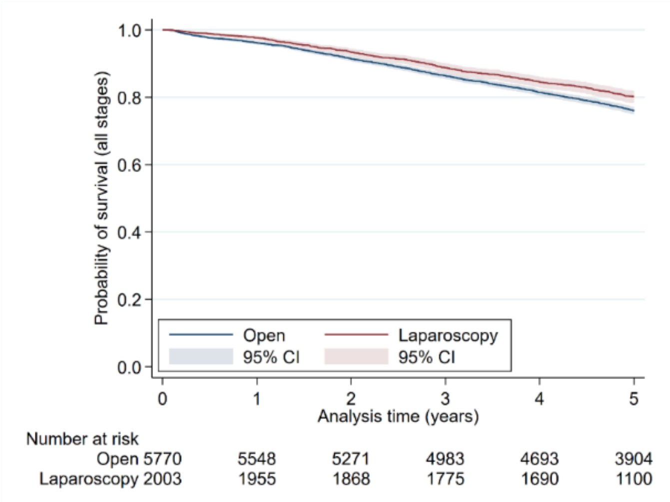

Figure 12. Five-year overall survival in rectal cancer patients in Sweden with preoperatively known cTNM stage I–III cancer diagnosed during 2010–2016 and subsequently undergoing curative laparoscopic or open abdominal resection surgery. Kaplan–Meier curve.

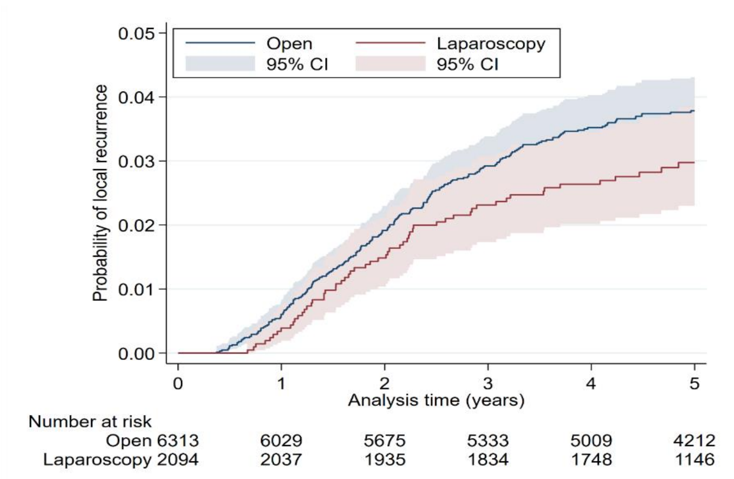

Figure 13. Local recurrence within 5 years of follow up in rectal cancer patients in Sweden with stage I–III cancer diagnosed during 2020–2016 and subsequently undergoing curative laparoscopic or open abdominal resection surgery. Unadjusted data; Kaplan–Meier curve.

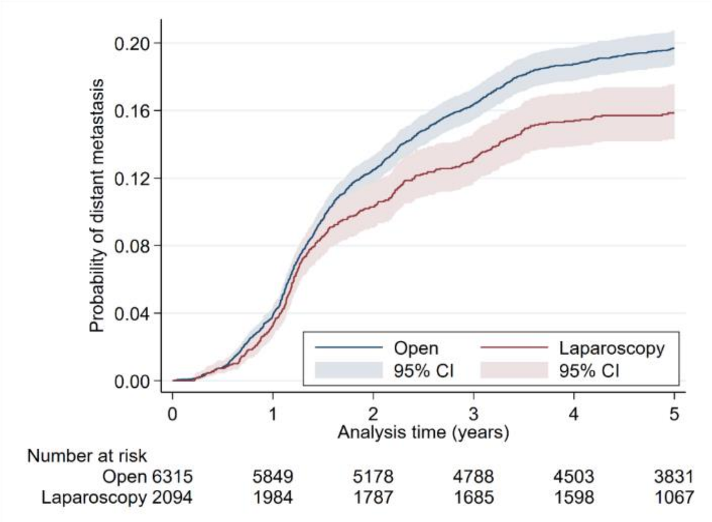

Figure 14. Distant metastasis within 5 years of follow up in rectal cancer patients in Sweden with stage I–III cancer diagnosed during 2010–2016 and subsequently undergoing curative laparoscopic or open abdominal resection surgery. Unadjusted data; Kaplan–Meier curve.

Study II

A total of 11 605 patients with pathological stage I–III colon cancer in the ascending colon or the sigmoid colon were identified, of whom 8308 (71.6%) were in the OPEN group and 3297 (28.4%) were in the MIS group. The conversion rate in the MIS group was 17.1%. MIS was not found to be inferior to OPEN with regard to overall 5-year survival, with the non-inferiority design of the present study, formal superiority was in fact demonstrated (Figure 15).

In the secondary analysis, multivariable Cox regression demonstrated that the 5-year overall survival was higher in MIS than in OPEN (HR: 0.874; 95% CI: 0.791–0.965). Outcome was similar when employing propensity score matching. In a sub-analysis excluding pT4 patients, there was no statistically significant difference (HR: 0.847; 95% CI: 0.756–0.948). There was also no difference found between converted patients and OPEN. At the 5-year follow up, the rate of local recurrence was similar between OPEN and MIS (3.1% and 3.2%, respectively; unadjusted p=0.92) (Figure 16), while the rate of metastatic disease was higher in OPEN than in MIS (17.1% and 14.6%, respectively; unadjusted p<0.001) (Figure 17).

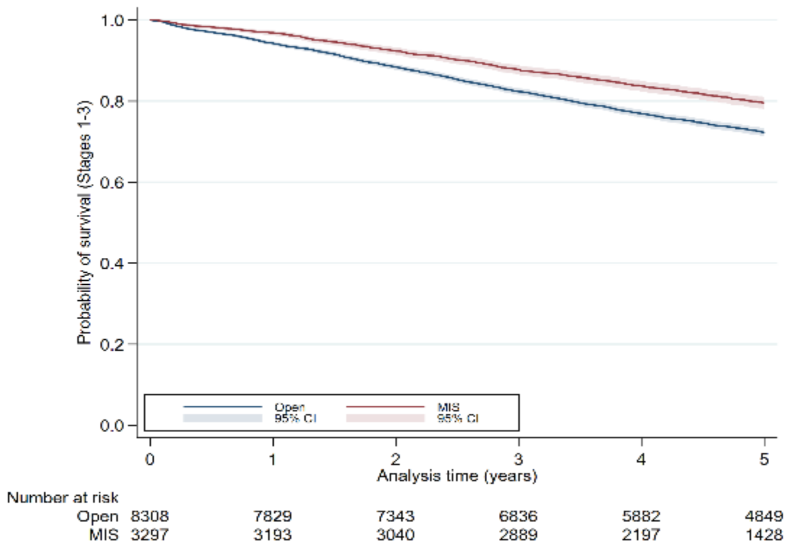

Figure 15. Five-year overall survival in Swedish patients with pathological stage I–III cancer in the ascending colon or sigmoid colon diagnosed during 2010–2016 and subsequently undergoing curative minimally invasive surgery (MIS) or open resection surgery. Kaplan–Meier curve.

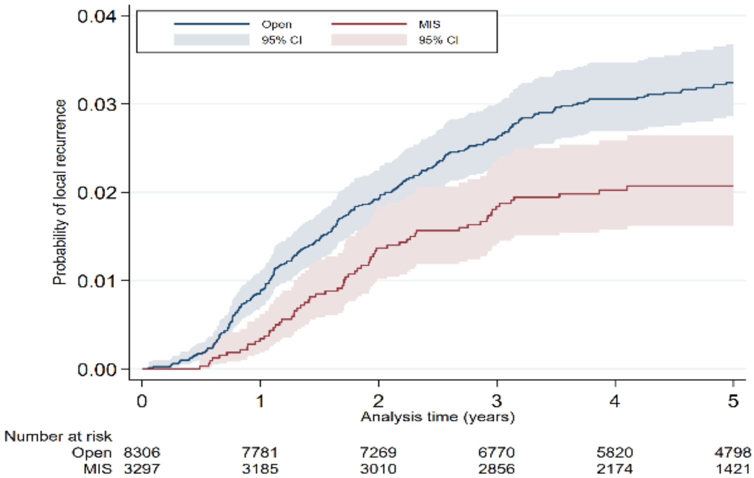

Figure 16. Local recurrence within 5 years of follow-up in Swedish patients with pathological stage I–III cancer in the ascending colon or sigmoid colon (pTNM) diagnosed during 2010–2016 and subsequently undergoing curative minimally invasive (MIS) or open resection surgery. Unadjusted data; Kaplan–Meier curve.

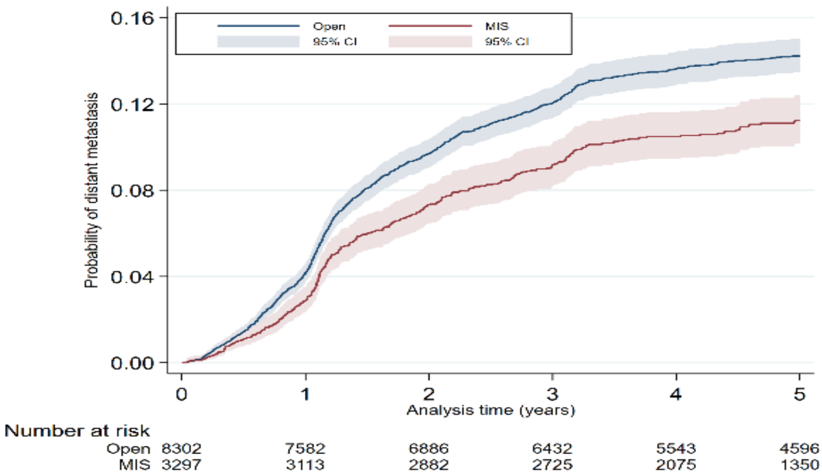

Figure 17. Distant metastasis within 5 years of follow-up in Swedish patients with pathological stage I–III cancer in the ascending colon or sigmoid colon diagnosed during 2010–2016 and subsequently undergoing curative minimally invasive (MIS) or open resection surgery. Unadjusted data; Kaplan–Meier curve.

Study III

A total of 7,945 patients were included, comprising 5960 (75.1%) in the OPEN group and 1985 (24.9%) in the MIS group (Table 5). Patients in the OPEN group had a higher proportion of ASA score ≥3 (24.6% vs. 20.2%), a higher proportion of cT4 (16.5% vs. 10.8%), more often received neoadjuvant treatment (68.2% vs. 62.9%), and were more likely to have had previous abdominal surgery (10.9% vs. 9.1%). Conversely, patients with the highest level of education as compared with the lowest level of education (28.1% vs. 21.8%) and patients within the highest income quartile as compared with the lowest income quartile (34.9% vs. 29.3%) had an increased likelihood of receiving MIS rather than OPEN.

Multivariable logistic regression analysis (Table 6) showed that having the highest level of education and being in the highest income quartile were both associated with an increased probability of receiving MIS (odds ratio [OR]: 1.23; 95% CI: 1.06–1.43 and OR: 1.35; 95% CI: 1.14–1.60, respectively). Female gender was associated with an increased likelihood of receiving MIS (OR: 1.27; 95% CI: 1.14–1.41), and cT4 rectal cancer was associated with a decreased probability of receiving MIS (OR: 0.60; 95% CI: 0.51–0.71).

Table 5. Demographic data of patients undergoing curative resection surgery for rectal cancer in Sweden between 2010 and 2016.

	OPEN (n = 5960)	MIS (n = 1985)
Age, median (Q1; Q3)	69 (61; 76)	70 (62; 75)
Female gender, %	38.7%	44.1%
BMI, median (Q1; Q3)	25.6 (23,1; 28.4)	25.2 (23.0; 27.8)
ASA classification, n (%)		
1	1151 (19.4%)	455 (22.9%)
2	3296 (55.3%)	1120 (56.4%)
3	1392 (23.4%)	383 (19.3%)
4	69 (1.2%)	18 (0.9%)
Missing	48 (0.7%)	9 (0.5%)
Tumour distance from the anal verge, cm		
median (Q1; Q3)	8 (5; 12)	9 (5; 12)
mean (SD)	8.24 (3.83)	8.27 (3.92)
Number of previous abdominal procedures, n (%)		
0	5311 (89.1%)	1805 (90.9%)
1	485 (8.1%)	138 (7.0%)
≥2	164 (2.8%)	42 (2.1%)
Clinical cancer stage, n (%)		
cT1–3	4660 (78.2%)	1702 (85.7%)
cT4	985 (16.5%)	214 (10.8%)
Missing	315	69
Clinical nodal stage, n (%)		
cN0	2505 (42.0%)	881 (44.4%)
cN1–2	3043 (51.1%)	1051 (52.9%)
Missing	412	53
Neoadjuvant therapy, n (%)		
None	1866 (31.3%)	733 (36.9%)
Radiotherapy	2985 (50.1%)	1035 (52.1%)
Chemo-radiotherapy	1084 (18.2%)	214 (10.8%)
Missing	25	3

ASA = American Society of Anaesthesiologists; BMI = body mass index; MIS = minimally invasive surgery; OPEN = open surgery; Q = quartile; SD = standard deviation.

Table 6. Logistic regression analysis of patients undergoing curative resection surgery for rectal cancer in Sweden between 2010 and 2016.

	Multivariable OR (95% CI; p-value)
Duration of education	
6–9 years	1.00 (Ref)
10–12 years	1.01 (0.89–1.15; p=0.86)
>12 years	1.23 (1.06–1.43; p=0.006)
Household income	
Lowest quartile	1.00 (Ref)
Lower middle quartile	0.93 (0.79–1.11; p=0.43)
Upper middle quartile	1.13 (0.96–1.34; p=0.15)
Highest quartile	1.35 (1.14–1.60 p<0.001)
Gender	
Male	1.0 (Ref)
Female	1.27 (1.14–1.41; p<0.001)
Number of previous surgeries	
0	1.00 (Ref)
1	0.86 (0.70–1.05; p=0.14)
≥2	0.81 (0.56–1.17; p=0.26)
Clinical tumour stage	
cT1–T3	1.0 (Ref)
cT4	0.60 (0.51–0.71; p<0.001)

CI = confidence interval; OR = odds ratio.

Study IV

A total of 520 patients were included in the initial analysis, comprising 202 (38.9%) in the OPEN group, 115 (22.1%) in the LAP group and 203 (39.0%) in the ROBOT group. The surgical procedures included anterior resection (32.0% in OPEN, 44.3% in LAP, and 45.3% in ROBOT), abdominoperineal resection (49.0% in OPEN, 45.2% in LAP, and 47.8% in ROBOT), and Hartmann's procedure (19.0% in OPEN, 10,5% in LAP and 6,9% in ROBOT)

The median bleeding was 300 ml in OPEN compared to 150 ml in LAP and 25 ml in ROBOT. The median operative time was 253 min in OPEN, 321 min in LAP, and 278 min in ROBOT. The median length of hospital stay was 7 days for both LAP and ROBOT, and 10 days in OPEN. Table 7.

Median CRP levels on postoperative day 1-5 are given in Table 8. The complication rate within 30 days was 46.0% in LAP, 44.3% in ROBOT, and 53.0% in OPEN. Complications of Clavien-Dindo grade 3a and above were more common in OPEN.

Table 7. Surgical procedures in patients undergoing curative abdominal rectal cancer resection surgery between 2011 and 2021.

Type of surgical procedure	OPEN (n=202)	LAP (n=115)	ROBOT (n=203)
Anterior resection	32,0%	44.3%	45.3%
Abdominoperineal resection	49.0%	45.2%	47.8%
Hartmann's procedure	19.0%	10,5%	6,9%

OPEN = open surgery; LAP = conventional laparoscopy; ROBOT = robot-assisted laparoscopy.

Following exclusion of patients with Clavien Dindo >2 and patients with a hospital stay exceeding 9 days, regardless of Clavien Dindo classification, (n=138), a total of 382 patients remained for final analysis, OPEN (n=139), LAP (n=85) and ROBOT (n=158). Table 8. Figures 18 and 19.

Table 8. Median serum C-reactive protein levels (mg/L) on postoperative day (POD) 1–5 in patients undergoing curative abdominal rectal cancer resection surgery between 2011 and 2021.

	OPEN (n=139)	LAP (n=85)	ROBOT (n=158)
POD 1	92	44	41
POD 2	152	105	87
POD 3	139	112	78
POD 4	90	74	76
POD 5	69	71	63

OPEN = open surgery; LAP = conventional laparoscopy; ROBOT = robot-assisted technique.

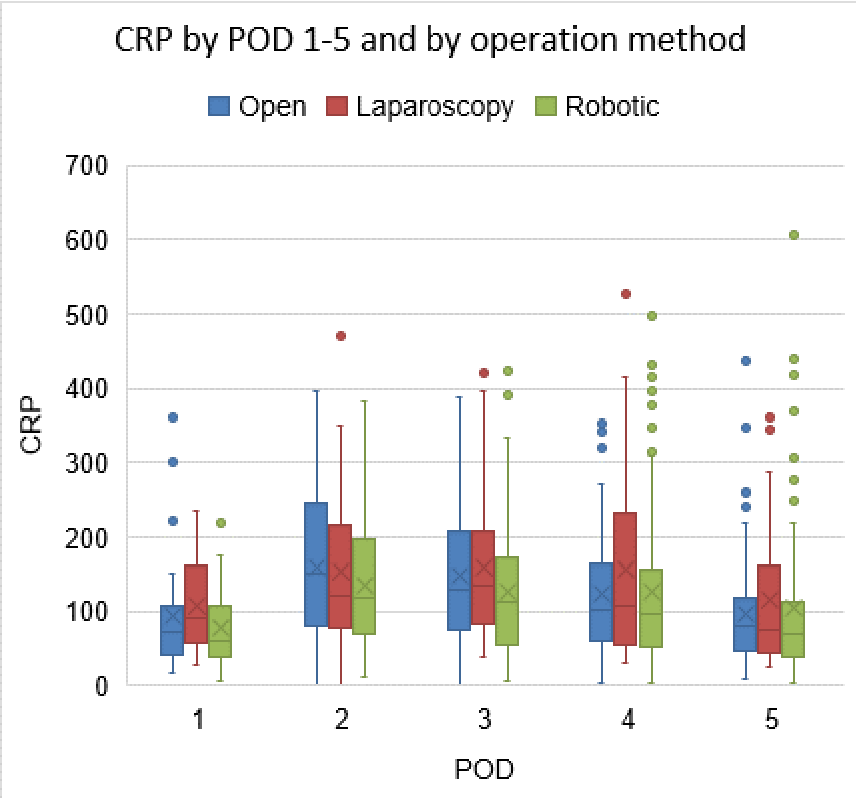

Figure 18. C-reactive protein (CRP) levels measured on postoperative day (POD) 1–5 in patients undergoing curative resection surgery for rectal cancer by open surgery, conventional laparoscopy, or robot-assisted technique between 2011 and 2021 at the Department of Surgery, Örebro University Hospital, Sweden.

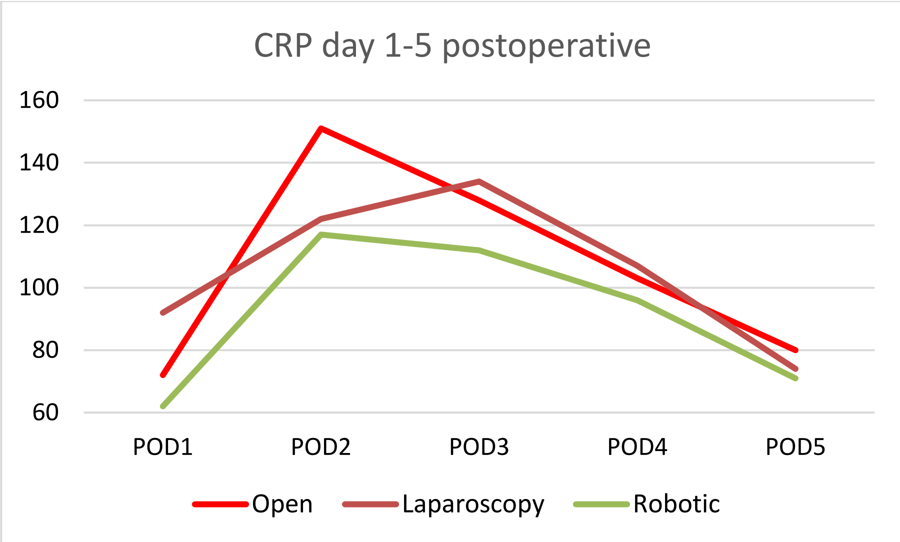

Figure 19. C-reactive protein (CRP) levels measured on postoperative day (POD) 1–5 in patients undergoing curative resection surgery for rectal cancer by open surgery, conventional laparoscopy, or robot-assisted laparoscopy between 2011 and 2021 at the Department of Surgery, Örebro University Hospital, Sweden.

DISCUSSION

Study I

This nationwide study demonstrated that MIS was not inferior to OPEN in term of overall 5-year survival, which was the primary outcome of the non-inferiority design. The secondary outcome was that 5-year overall survival was better for MIS than for OPEN (HR: 0.877; 95% CI: 0.775–0.993). The outcomes were similar when employing multiple imputation and propensity score matching. In subgroup analyses, this was also observed for clinical cancer stage I but not for cancer stages II and III. These analyses included cT4, although patients with this stage were less frequent in MIS. When cT4 was excluded from the analysis, thus restricting the analysis to cT_{1-3} N_{0-2} M_0, the hazard ratio was similar but the difference was no longer statistically significant (HR: 0.885; 95% CI: 0.790–1.033).

Another finding was that the observed rate of metastatic disease within the 5-year follow up was lower for the MIS group than for OPEN (15.6% vs. 19.6%; unadjusted p<0.001). For local recurrence, the observed rates were 2.9% in LAP and 3.6% in OPEN (unadjusted p=0.139)

In a subgroup analysis, converted MIS patients had a statistically significantly worse long-term outcome compared with OPEN (HR: 1.256; 95% CI: 1.004–1.570). This is an interesting finding, as it is in contrast to a recent meta-analysis by Gouvas et al. which did not demonstrate a worse long-term outcome for converted cases. [98]

The proportion of MIS increased substantially over the study period, from 7.3% in 2010 to 49.8% in 2016. A similar increase in proportion was observed in the colon cancer cohort of Study II, from 7.8% in 2010 to 46.2% in 2016. Although there was a substantial increase of MIS in both cohorts, the conversion rate differed considerably. In the rectal cancer cohort of Study I, the conversion rate decreased from 20.5% in 2010 to 12.0% in 2016, whereas the colon cancer cohort of Study II showed a much smaller decrease from 18.4% to 16.6%.

One explanation for this could be the fact that colorectal laparoscopy was introduced rather late in Sweden compared to other countries, and so there may have been a degree of continuous learning curve. Another explanation could be the earlier centralization of hospitals performing rectal cancer surgery as compared with colon surgery. The experience of the surgeons could also play a role, as it may be assumed that surgeons performing rectal cancer surgery will generally be more senior than those performing colon surgery.

Study II

This nationwide study compared all patients diagnosed with pathological stage I–III colon cancer in the ascending or sigmoid colon during 2010–2016 and subsequently undergoing curative resection with MIS or OPEN. The primary outcome was overall survival at the 5-year follow up, and the results confirmed the primary study hypothesis that MIS was not inferior to OPEN. In fact, with the non-inferiority design that was chosen, the study even showed formal superiority. In line with this outcome, the secondary analysis performed with Cox regression models showed that MIS had a better outcome than OPEN.

Another observation in this study was the rate of observed metastatic disease within 5 years, which was lower for MIS than for OPEN (14.6% and 17.1%, respectively; unadjusted p<0.001). The observed rates of local recurrence were similar between OPEN and MIS (3.1% and 3.2%, respectively; unadjusted p=0.92).

In contrast to the findings of Study I, a subgroup analysis showed no difference in long-term overall survival between converted MIS and OPEN (HR: 1.032; 95% CI: 0.857–1.143).

Study III

This study demonstrated that patients diagnosed with cTNM I–III rectal cancer in Sweden during 2010–2016 with the highest level of education (categorized as 6–9, 10–12, >12 years) had an increased likelihood of receiving MIS (OR: 1.23; 95% CI: 1.06–1.43; p=0.006), as did those in the highest income quartile (OR: 1.35; 95% CI: 1.14–1.60; p<0.001). These findings align with previous research from countries such as the USA, where private healthcare systems are more prevalent, demonstrating that level of education, level of income, race, and marital status can influence the selection of medical treatments. [99-101] However, the impact of socioeconomic factors on medical treatments has not been studied in Sweden to the same extent as in some other countries.

These results are somewhat surprising, considering Sweden's tax-based healthcare system. One would expect that in such a healthcare system, socioeconomic factors would not influence the likelihood of receiving MIS or OPEN to the same extent as in healthcare systems largely financed by private insurance. In a tax-based healthcare system, one would expect equal access to healthcare services, but the present findings contradict this view. These findings raise concern about the equality of the Swedish healthcare system, and warrant future investigation.

Another interesting finding was that women were more likely than men to receive MIS (OR: 1.27; 95% CI: 1.14–1.41; p<0.001). One reason for this may be that in comparison to men, women tend to have certain differences in their anatomical features, such as a broader and shallower pelvis, which could be an advantage for surgical teams in the learning phase of MIS.

Study IV

This was a single-centre population based register study including all patients undergoing abdominal rectal cancer surgery at the Department of Surgery, Örebro University Hospital, over an 11-year period. After exclusion of patients with Clavien Dindo classification >2, as well as patients with a hospital stay exceeding 9 days, the results demonstrated a trend, although not a statistically significant difference, for decreased serum levels of CRP in the robot-assisted surgery group compared to the conventional laparoscopic group. Few previous studies have compared the postoperative inflammatory response in LAP and ROBOT, and because of the limited size of such studies, no firm conclusions can be drawn.

Previous studies have demonstrated a shorter hospital stay for ROBOT compared with LAP, but we could not confirm this in the present study. Moreover, patients in the ROBOT group had less bleeding and shorter operation time than those who underwent LAP. These findings could reflect decreased intraoperative tissue damage, which may lead to a reduced inflammatory response expressed as lower serum CRP.

Another interesting finding was the conversation rate, which was 26% in LAP and 11% in ROBOT. This finding is in line with the ROLLAR trial, in which conversion was numerically lower in the group operated by robot-assisted surgery. Previous studies have shown that conversation is an independent risk factor for worse outcome.

General reasons for the lower conversion rates in robot-assisted surgery might include the more advanced visualization and the dexterity of the robot arms and instruments. In the present study, besides the abovementioned qualities of the robot itself, both patient selection and the experience of the individual surgeon may have had an impact on the outcomes. Often, it is the more senior surgeons who perform robotic surgery. Moreover, the substantial economic cost of each robotic procedure may also have impacted on the selection of cases for robotic surgery; less complex cases may have been chosen in order to decrease the risk of conversion.

Finally, the present finding of a less pronounced postoperative inflammatory response in ROBOT might predispose for more favourable short-term outcomes for ROBOT. However, this is speculative, and was not reflected in a shorter hospital stay in the present study. Whether such a finding would affect long-term outcomes remains to be seen.

Limitations and strengths

These studies have some limitations, particularly those associated with registry-based investigations, where residual confounding cannot be completely ruled out and remains a potential challenge. One example is selection bias. The registry does not provide any information regarding the indication for choosing MIS or OPEN for the individual patient. Patient selection was observed in both Studies I and II. In study I patients in OPEN had an increased proportion of cT4, a higher proportion of ASA class ≥3, and were more frequently given neoadjuvant therapy. In study II patients in OPEN had an increased proportion of ASA class ≥3. In study IV, the single center setting is a limitation.

Another example of important information not registered in the Swedish registries is information concerning lifestyle habits such as level of physical fitness, alcohol, and smoking. Moreover, common-law cohabitation is frequently practiced in Sweden, but this is not registered in the national data registries and may have impacted our analyses.

Conversely, these studies have several strengths. First, they had a population-based setting comprising a large number of patients from an entire nation. Second, the SCRCR data had a high completeness rate and included a 5-year follow up for almost all patients. Third, Studies I and II used a non-inferiority hypothesis, which is often used in randomized trials but rarely in observational studies. Moreover, they used a relatively small non-inferiority margin, which is also a strength.

CONCLUSIONS

The aim of this thesis was to investigate long-term outcomes regarding overall survival, socioeconomic aspects, and inflammatory response in patients operated with a minimally invasive technique in colorectal cancer resection.

Study I demonstrated that MIS was not inferior to OPEN regarding overall survival at the 5-year follow up.

Study II showed that MIS for colon cancer was not inferior to OPEN regarding overall 5-year survival.

Study III demonstrated that rectal cancer patients with the highest level of education and the highest household income had an increased probability of receiving MIS.

Study IV showed a tendency for a less pronounced inflammatory response, assessed as postoperative serum CRP levels, in ROBOT compared with LAP in abdominal rectal cancer surgery.

FUTURE PERSPECTIVES

Major advancements are continuously being made in the colorectal cancer field, such as better neoadjuvant and adjuvant treatment therapy, immunotherapy, and organ-sparing treatments labelled as Watch and Wait. Despite these medical advances, surgery is still the primary component of curative treatment for colorectal cancer.

Minimally invasive surgery has long shown superior short-term outcomes such as less pain, faster bowel movement, faster recovery, and shorter hospital stay. Furthermore, previous randomised trials have demonstrated that MIS is not inferior regarding long-term oncological outcome. The regression analyses in Study I demonstrated better overall long-term survival for rectal cancer, and the non-inferiority design in Study II actually demonstrated superiority for long-term overall survival. Given these favourable outcomes, MIS should be considered the gold standard for surgical technique, and should be available to all patients. The use of MIS will continue to increase worldwide due to its well-documented advantages.

Several studies have compared ROBOT and LAP in colorectal cancer surgery, examining factors such as blood loss, conversion rate, and duration of hospital stay. A recent meta-analysis demonstrated results in favour of ROBOT, but it is important to consider the significant cost of ROBOT compared to LAP. [102] Nevertheless, the new competition generated by the recent advent of several new commercially available robotic platforms will lead to substantial cost reduction, which in turn will increase the general availability and further expansion of robot-assisted surgery worldwide. One area that needs further exploration when comparing ROBOT and LAP is the inflammatory response in colorectal cancer. As mentioned earlier, the inflammatory response may be an expression of surgical trauma, which could be related to bleeding, operation time, intraoperative complications, and length of hospital stay.

Finally, there is a need to address the somewhat surprising results of Study III. Sweden has a tax-based healthcare system, which should mean that everyone has the same access to treatment regardless of socioeconomic status. A forthcoming research project will compare the present cohort of 2010–2016 with a more recent cohort from 2017–2021, and it will be of great interest to see whether these findings persist or have changed.

SUMMARY IN SWEDISH

I Sverige får cirka 2200 personer diagnosen rektalcancer årligen. Strålning och cellgifter kan vara del av behandlingen före kirurgi som är den grundläggande botande behandlingsformen. Efter operation kan det vara aktuellt med ytterligare cellgiftsbehandling. Operationsmetod var tidigare enbart öppen teknik (med ett stort buksnitt), men numera opereras majoriteten i Sverige med minimalinvasiv teknik (79% år 2022). Minimalinvasiv teknik inkluderar både traditionell laparoskopisk teknik och robotassisterad teknik. Det är vetenskapligt väl belagt att minimalinvasiv kirurgi har fördelar i det korta perspektivet såsom mindre intraoperativ blödning, mindre smärta efter operationen, snabbare postoperativ mobilisering liksom kortare vårdtid. Stora internationella randomiserade studier har visat att det inte föreligger någon skillnad avseende onkologiska korttids- och långtidsresultat.

Syftet med denna avhandling är att öka kunskapen om minimalinvasiv kirurgi i Sverige, utvärdera det onkologiska långtidsresultatet, undersöka socioekonomiska aspekter, och analysera postoperativ inflammatorisk påverkan vid olika typer av kirurgisk teknik.

I studie I undersöktes samtliga patienter som genomgått kurativt syftande abdominell kirurgi för rektalcancer under perioden 2010-2016. Patienterna identifierades via Svenska Kolorektalcancerregistret (SCRCR) och studien omfattade över 8300 patienter som följdes fram till december 2020. Studien var en så kallad non-inferiority studie, en typ av studie som syftar till att visa att en ny behandling eller intervention inte är sämre än en etablerad behandling. Det som studien undersökte var total 5-årsöverlevnad. Studien visade att minimalinvasivt opererade patienter inte hade sämre överlevnad än patienter som genomgått öppen kirurgi. Regressionsanalyser visade att den minimalinvasivt opererade gruppen hade en bättre total överlevnad.

I studie II undersöktes samtliga patienter som genomgått kurativt syftande abdominell kirurgi för koloncancer. Över 11000 patienter identifierades via SCRCR för perioden 2010-2016. Studien utformades som studie I, således en non-inferiority design, och visade att minimalinvasiv kirurgi inte var sämre än öppen kirurgi. Dessutom utfördes en regressionsanalys som visade bättre total överlevnad för patienter som opererats med minimalinvasiv teknik.

I studie III undersöktes möjlig socio-ekonomisk påverkan på valet av operationsteknik, öppen eller minimalinvasiv teknik, mätt som utbildningsnivå och hushållsinkomst. Ytterligare analyser utfördes med avseende på tidigare abdominell kirurgi, kön, civilstånd och födelseland. Patienter identifierades via SCRCR och samkördes via en nationell registerdatabas, Colorectal Cancer Base (CRCBaSe), som länkar till ett antal andra nationella register. Samtliga patienter som genomgått kurativt syftande abdominell resektionskirurgi 2010-2016 ingick och drygt 8000 patienter identifierades. Resultaten visade att patienter med högst utbildningsnivå samt högst inkomstkvartil hade en större sannolikhet att bli opererade med minimalinvasiv teknik. Detta gällde även för kvinnor generellt. Patienter som tidigare genomgått abdominell kirurgi eller hade en mer lokalt avancerad tumör hade en lägre sannolikhet att få minimalinvasiv kirurgi.

I arbete IV ingick samtliga patienter som opererats abdominellt för rektalcancer på Kirurgiska kliniken, Universitetssjukhuset Örebro, under perioden 2011-2021. Totalt identifierades 520 patienter som genomgått öppen, traditionell laparoskopi eller robotassisterad laparoskopi. Det huvudsakliga syftet var att undersöka om det förelåg någon skillnad mellan konventionell laparoskopi och robotlaparoskopi. Patienterna identifierades via SCRCR och laboratoriedata inhämtades från lokala patientjournaler. Underökningen avsåg postoperativ inflammatorisk reaktion uttryckt via ett blodprov, C-reaktivt protein (CRP), under postoperativ dag 1-5. Patienter med betydande komplikationer eller längre än förväntad vårdtid exkluderades, vilket resulterade i slutlig analays av 382 patienter. Resultaten visade en trend för ett mindre uttalat inflammatoriskt postoperativt påslag hos patienter som opererats med robotlaparoskopisk teknik jämfört med konventionell laparoskopisk teknik.

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